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BMJ Open Antidepressant use and interpersonal violence perpetration: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction There are conflicting perspectives as to whether antidepressant medication increases, decreases or has no effect on violence perpetration, impulsivity and aggressive behaviour. This is an important question given the widespread use of antidepressant medication and the significant medical, social, legal and health consequences of violence. We aim to: (1) systematically identify observational studies and randomised controlled trials that quantify the relationship between antidepressant use and interpersonal violence; (2) assess the quality of studies that quantify the relationship between antidepressant use and interpersonal violence and (3) estimate the pooled prevalence and measure of effect for the relationship between antidepressant use and interpersonal violence.

Methods and analysis We will search MEDLINE, EMBASE, CINAHL, PsycINFO, PubMed and the Cochrane Library for relevant peer-reviewed literature. Our primary outcome is the perpetration of violent acts directed at others. Our secondary outcome is physical, interpersonal aggression measured through validated surveys. We will include randomised controlled trials, cohort studies and case-control studies that examine the association between the use of antidepressants and violence perpetration and/or physical aggression. No restrictions will be placed on the population. We will use the Methodological Standard for Epidemiological Research scale to assess the quality of included studies. We will provide an overview of the included studies and assess heterogeneity and publication bias. If there are sufficient studies, we will conduct meta-analyses to examine the possible association between antidepressants and violence, and undertake meta-regression to examine the effect of antidepressant class, length of follow-up, age of participants and population subgroups on the association between antidepressants and violence.

Ethics and dissemination No ethics approval is required. Our findings will be disseminated through a peer-reviewed journal article and conference presentations.

PROSPERO registration details CRD42020175474.

INTRODUCTION

The use of antidepressants, particularly in high-income countries, has become commonplace.¹⁻³ Between 2000 and 2017, consumption of antidepressants in Organisation for

Strengths and limitations

- The relationship between antidepressants and violence is an important topic with medical, social and legal implications in a conflicting literature that hitherto has not been systematically reviewed.
- This systematic review uses a comprehensive search strategy including six key academic databases and a grey literature search.
- The review will be reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for conducting and reporting systematic reviews.
- The planned analysis will allow for clinically relevant covariates to be examined, if sufficient evidence is found.
- A small number of primary studies, and heterogeneity between study populations and study design, may preclude meta-analysis or direct comparisons between studies.

Economic Co-operation and Development countries doubled.⁴ While this may, in part, reflect higher doses in long-term users of antidepressants due to increasing tolerance, it also likely reflects a growing proportion of the population using antidepressants. In Australia, the United States and England, it is estimated that more than 1 in 10 adults were prescribed an antidepressant in the most recent year that data are available.^{3 5 6} In addition to treating depression, antidepressants are also used for a range of other conditions, such as anxiety disorders, insomnia and pain.⁷

Interpersonal violence is a serious public health concern.⁸ In 2013, the Global Burden of Disease (GBD) study estimated there were approximately 405 000 deaths globally due to interpersonal violence.⁹ In 2017, the GBD estimated there were approximately 4.5 million years lived with disability due to interpersonal violence.¹⁰ Given the profound impacts of violence, societies have consistently attempted to control aggressive behaviour

and prevent violence.⁸ Accordingly, the use of pharmacotherapy to modulate aggressive and violent behaviour has been examined for more than four decades. Neuro-psychiatric agents including lithium,¹¹ benzodiazepines,¹² atypical antipsychotics^{13 14} and antiepileptic drugs¹⁵ have all been examined as potential pharmacotherapies for reducing violent and aggressive behaviour. To date, however, none of these pharmacotherapies have shown long-term effectiveness.¹⁶

Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), have also been identified as potential candidates for violence-prevention medications.^{17 18} The use of serotonergic or noradrenergic antidepressants to reduce violent behaviour has some biological plausibility. Serotonergic dysfunction has been associated with increased aggressive behaviour in animal and human studies.^{19–21} Similarly, the noradrenergic system has been found to modulate aggressive behaviour in animal studies, and a hyperactive noradrenergic system has been correlated with aggressive behaviour in humans.²² Therefore, drugs that regulate the serotonergic or noradrenergic systems may act to reduce aggressive and violent behaviour. Indeed, some research has reported an association between the use of SSRIs and reduced impulsivity and aggressive behaviour.^{18 23–26}

However, contrasting research findings have also emerged, with some studies reporting an association between the use of antidepressants and *increased* aggression and violence perpetration.^{27–31} For example, a systematic review of clinical study reports found an increased risk of aggression in children and adolescents while using SSRIs but not in adults.²⁷ A second systematic review of randomised control trials (RCTs) examining the association between antidepressants, suicidality and violence in healthy volunteers found that taking antidepressants doubled the occurrence of events, such as anxiety, nervousness and agitation, that may serve as proxy markers for violence.²⁸ Similarly, an expert review argued that clinical trial and pharmacovigilance data suggest that SSRIs are associated with an increased violent behaviour.³⁰

Compounding the conflicting nature of this evidence, the methodology of this research, particularly the published systematic reviews, has been criticised. Concerns include: the use of adverse events and/or proxy measures of violence that are only tangentially related to violence, limitations of the statistical analysis techniques used and inaccuracies in the authors' interpretation of the included studies.^{32–36} Further, most systematic reviews on antidepressants and violence have had a primary focus on violence against self, with limited or no examination of violence against others.^{27 28 37} These limitations have led some researchers to argue that the assertion that there is an association between antidepressant use and increased aggression or violence against others is overstated or misleading.³⁵

Others have argued that weaknesses of the included RCTs may have resulted in an *under-reporting* of violence

perpetration related to antidepressants.²⁷ Measures of violent behaviour, and related adverse events such as aggression and impulsivity, have been poorly recorded in many RCTs.^{27 28 38} Further, the majority of RCTs have little capacity to examine long-term harms such as violence due to short follow-up periods,³⁸ small sample size and strict participant inclusion criteria that may exclude those at high risk of aggression or violence¹⁸ and the relative rarity of violent events. Therefore, there is a reliance on proxy measures for violence such as self-reported aggression or hostility.^{18 28 39} As such, the effectiveness of antidepressants in reducing violent outcomes is uncertain.³⁹

Given the contradicting associations found between studies, concerns raised about prior review methodology and a possibility for bias in individual studies, a comprehensive review of the evidence on the association between antidepressant use and interpersonal violence perpetration is required. This is made more urgent by emerging recommendations for antidepressants to be used as a treatment for violent behaviour.¹⁷ Despite this, to our knowledge, there has been no attempt to systematically and rigorously synthesise both RCTs and observational studies that examine the association between antidepressant use and interpersonal violence.

This study seeks to examine the following key questions: to what extent has the association between antidepressant use and violence against others been investigated, what is the quality of research examining this association and what is the nature of the association (if present) between antidepressant use and violence against others? Therefore, in this study we will: (1) systematically identify RCTs and observational studies that quantify the relationship between antidepressant use and interpersonal violence perpetration; (2) assess the quality of studies that quantify the relationship between antidepressant use and interpersonal violence perpetration and (3) estimate the pooled prevalence and measure of effect for the relationship between antidepressant use and interpersonal violence perpetration.

METHODS AND ANALYSIS

This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols⁴⁰ and has been registered with PROSPERO.

Eligibility criteria

Inclusion and exclusion criteria are outlined in [table 1](#).

Participants

There are no restrictions on the participants of the reviewed studies. We will include studies that focus on the use of antidepressants in children, adults or specific subpopulations such as people with autism spectrum disorder, people with dementia, people with conduct disorder and people with a history of violent crime.

Exposure measures

We will include studies of antidepressants licensed as such for use by the US Food and Drug Administration (FDA),

Table 1 Summary of inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Participants	No restrictions	N/A
Intervention	Antidepressants (see table 2)	Other psychotropic medications, antidepressant use of less than 1 week
Comparator	Placebo, active comparator or periods of non-use (self-controlled)	No comparison group
Outcome	Primary: acts of physical violence against others Secondary: acts of physical aggression against others measured through validated measure	Verbal aggression, violence against self, self-reported violence where type of violence is not specified, self-reported violence through a non-validated measure, measures of anger and irritability
Study design	Case-control studies, cohort studies and randomised controlled trials	Open-label single-arm trials, case reports, case series, uncontrolled before/after studies, ecological studies and cross-sectional studies

the UK Medicines and Healthcare products Regulatory Agency, the European Union's European Medicines Agency and Australia's Pharmaceutical Benefits Advisory Committee (PBAC) as of January 2020. These regulatory agencies were chosen as they regulate medications in the regions where rates of antidepressant prescribing are highest and have clear procedures for assessing and regulating medications.⁴ A list of included antidepressants is presented in [table 2](#).

We will include studies that compare the risk of violence perpetration between: (1) people exposed to antidepressants and people not exposed to antidepressants, including people exposed to medications other than antidepressants; (2) people exposed to different antidepressants or (3) time periods of exposure to antidepressants versus periods of no exposure, within individual participants. For example, we will include RCTs that use a placebo, an active control of a different antidepressant or other treatment or a crossover design. As antidepressants exert their effect via homeostatic changes that occur with repeated administration, we will require antidepressants to be used for at least 1 week for the study to be included. We will apply the same comparator criteria to RCTs and observational studies. We will exclude studies that examine antidepressant discontinuation, primarily use medication adherence as the exposure and in which the antidepressant medication is used recreationally rather than as prescribed by a health practitioner.

Outcome measures

Our primary outcome will be the perpetration of physical violence (ie, the intentional use of force) directed at others.^{41 42} This will include violent crimes such as homicide, assault, family or intimate partner violence, robbery, sexual assaults and self-reported, familial-reported, friend-reported or clinician-reported violent acts. This may be measured by self-report, administrative data (eg, ambulance, emergency department, hospital or criminal justice system records) or a valid observer rating scale. Consistent with our definition of interpersonal violence, we will exclude outcomes related to self-harm or suicide.

Given the difficulties in measuring violent acts directly,⁴¹ we will include measures of physical aggression ascertained through validated tools as secondary outcomes. There are plausible neurobiological mechanisms through which certain antidepressants may impact the occurrence of violent acts by reducing aggression.¹⁹⁻²¹ While we recognise that violence and aggression are dimensional, our focus is on externalised violent and aggressive physical actions and behaviours towards others, rather than studies which examine emotions, thoughts or verbalised aggression exclusively. As such, we will distinguish between physically aggressive acts towards others and the emotions or feelings that may be associated with such acts, including anger and irritability. Measures of the former will be included, whereas measures of the latter will not. We will exclude studies that use an experimental paradigm of aggression, due to a lack of generalisability.

Study design

We will include case-control studies, cohort studies and RCTs defined according to the Cochrane study design guide.⁴³ Reviewing and synthesising the observational research will address a critical gap in the evidence on the potential association between antidepressant use and violence perpetration. Compared with RCTs, observational research typically allows for longer follow-up time, can include violence as the main study outcome with fewer ethical concerns and can examine the outcomes of a broader participant group under naturalistic (ie, real-world) circumstances. Studies using within-case comparisons (eg, crossover or case-crossover studies and studies using fixed effects analysis of repeated measures data or similar analytic methods—see⁴⁴) will be included. However, due to the possibility of carry-over effects or antidepressant withdrawal obscuring or reversing the observed association between antidepressant exposure and violence perpetration, sensitivity analysis will be used to examine the impact of including such studies. We will exclude open-label single-arm trials, case reports, case series, uncontrolled before/after studies, ecological studies and cross-sectional studies due to difficulties in

Table 2 Antidepressants included in review

Class	Generic drug name
Selective serotonin reuptake inhibitors	Fluoxetine
	Citalopram/escitalopram
	Fluvoxamine
	Sertraline
	Paroxetine
	Vortioxetine
Serotonin and norepinephrine reuptake inhibitors	Venlafaxine
	Desvenlafaxine
	Duloxetine
	Milnacipran/levomilnacipran
Tricyclic antidepressants	Amitriptyline
	Nortriptyline
	Imipramine
	Desipramine
	Doxepin
	Dothiepin
	Protriptyline
	Trimipramine
	Clomipramine
	Amoxapine
	Lofepramine
	Maprotiline
	Monoamine oxidase inhibitors
Phenelzine	
Selegiline	
Isocarboxazid	
Moclobemide	
Other	Agomelatine
	Bupropion
	Nefazodone
	Trazodone
	Mirtazapine
	Ketamine/esketamine
	Mianserin
	Brexanolone/allopregnanolone

determining the direction of association. We will also exclude dissertations, conference abstracts and study registrations. We will not include previous systematic reviews, as not all included studies may meet our inclusion criteria. However, we will identify peer-reviewed studies related to any dissertations, conference abstracts or study registrations, and original studies referenced in related systematic reviews, and include any that met our inclusion criteria but were not identified by our search strategy.

Search strategy and data management

Search strategy

We will search key health and medical databases (MEDLINE, EMBASE, CINAHL, PsycINFO, PubMed and the Cochrane library) for peer-reviewed literature from inception of each database until most-recent available study on the date of conducting our final search. The initial search was performed on the 19 March 2020, and an update will be conducted on the 1 March 2021. We will use Cochrane-recommended search strategies to identify RCTs,⁴⁵ and a version of Ovid's recommended observational study search filter,⁴⁶ adapted for each database, to identify observational studies. The search strategy for MEDLINE (Ovid) is presented in table 3. The search strategy was developed in consultation with a librarian at the Murdoch Children's Research Institute. The reference and citation lists of all eligible studies will be screened to identify any additional relevant studies. Studies will be limited to those conducted on human participants. There will be no restrictions on the year or location of publication. We will only review English language abstracts. However, any full-text papers not in English that were identified via abstract search, grey literature search, reference list review or from author follow-up will be translated into English and reviewed.

To identify relevant trials that may have been conducted in the process of licencing or monitoring medications by national regulatory bodies, the following sources will be searched for grey literature: the FDA (<https://www.fda.gov/home>), the National Institute for Health and Care Excellence (NICE, <https://www.nice.org.uk/>), Pharmac (<https://www.pharmac.govt.nz/>), the PBAC (<http://www.pbs.gov.au/pbs/home>), the Canadian Agency for Drugs and Technologies in Health (CADTH, <https://www.cadth.ca/>) and Google Scholar.

Study selection

Identified studies will be imported into the citation management software Covidence (www.covidence.org) and duplicates will be removed. All titles and abstracts will be independently screened by the lead author (CK) and another member of the research team. After 15% of the papers identified through the search strategy have been double screened, we will reassess our inclusion and exclusion criteria to ensure they are relevant to the studies that have been identified. The reassessment will involve a discussion by two reviewers and an additional third author (JY/GN-H/JK) in which each study that was determined to be eligible for inclusion by at least one reviewer will be discussed, and any disagreements or uncertainty regarding the reasons for inclusion or exclusion will be resolved by consensus. Any changes or clarifications to the inclusion and exclusion criteria as a result of this discussion will be circulated to all members of the research team, and all team members will agree to these changes before screening continues. The updated inclusion and exclusion criteria will be used for the remaining title and abstract screening, which will be independently

Table 3 Search strategy for MEDLINE (Ovid)

1	exp *antidepressive agents/ae, tu or *tranquilizing agents/ae, tu
2	exp *Serotonin Uptake Inhibitors/ae, tu
3	*Serotonin Antagonists/ae, tu
4	(antidepressant* or anti-depressant* or antidepressive* or anti-depressive*).tw,kf.
5	(MAOI? or monoamine-oxidase-inhibit* or SSRI? or SNRI? or TCA? or tricyclic? or tetracyclic? or heterocyclic? or psychotropic? or noradrenerg* or antiadrenergic? or anti-adrenergic? or ((serotonin or norepinephrine or noradrenaline or epinephrine or noradrenaline or neurotransmitt* or domamine*) and (uptake or reuptake))).tw,kf.
6	(Fluoxetine or citalopram or escitalopram or sertraline or paroxetine or vortioxetine or vilazodone or venlafaxine or desvenlafaxine or duloxetine or milnacipran or levomilnacipran or amitriptyline or nortriptyline or imipramine or desipramine or doxepin or dothiepin or protriptyline or trimipramine or clomipramine or amoxapine or lofepramine or maprotiline or tranlycypromine or phenelzine or selegiline or isocarboxazid or moclobemide or agomelatine or bupropion or nefazodone or trazodone or mirtazapine or reboxetine or ketamine).tw,kf.
7	or/1–6
8	violence/ or exp domestic violence/ or gender-based violence/ or exp intimate partner violence/ or physical abuse/ or rape/
9	crime/ or homicide/
10	aggression/ or agonistic behavior/ or bullying/
11	exp Anger/
12	(Violen* or crime? or aggressi* or assault* or abuse? or abusive or maltreat* or rape?).tw,kf.
13	(sn or px or de or et or dt).fs.
14	(8 or 9 or 10 or 11 or 12) and 13
15	Exp epidemiologic studies/ or exp case-control studies/ or exp cohort studies/ or exp controlled before-after studies/ or exp pharmacoepidemiology/
16	(Case-crossover or case-cross-over or case-control or observation*).tw,kf.
17	(longterm or long-term or repeat* or serial or longitudinal* or follow-up or followup or cohort? or retrospective* or prospective*).tw,kf.
18	Randomized controlled trial.pt.
19	Controlled clinical trial.pt.
20	Randomi#ed.ab.
21	Placebo.ab.
22	Randomly.ab.
23	Trial.ab.
24	Groups.ab
25	Or/15–24
26	7 and 14 and 25
27	Exp animals/not human*.sh
28	26 not 27

conducted by CK and one other member of the research team. Any uncertainty or disagreement over inclusion for the remaining studies will be resolved by a third author (JY/JK/GNH). The overall inter-rater reliability will be tested using Cohen's kappa statistic.⁴⁷

Full-text articles will be screened by CK and one other member of research team, with a third reviewer resolving any conflicts. Where clarification is needed to determine eligibility, we will contact the original study authors. If multiple included studies use the same dataset (assessed using study titles, author names, locations and dates),

the study using the longest duration of follow-up will be included (ie, the other study(ies) will be excluded).

Data extraction

Data will be extracted by one research team member using standardised, prespecified Excel forms developed by the research team. A second team member will check the extraction and amend any errors. A summary of the data extraction fields is presented in [table 4](#). We will contact study authors for additional information if the required data are missing, incomplete or unclear.

Table 4 Extraction fields

Domain	Extraction fields
Study details	Author(s)
	Year of publication
	Journal name
	Geographic location of study
	Year(s) of study
Methods	Study type
	Population
	Recruitment methods
	Type of antidepressant(s)
	Method(s) of measuring antidepressant use
	Type of comparator(s)
	Method(s) of measurement of comparator(s)
	Definition of violence
	Method of measuring violence
	Definition of aggression
	Method of measuring aggression
	Method of randomisation*
	Methods for avoiding confounding (covariate adjustment, propensity score, etc.)†
	Blinding*
	Allocation procedure*
Statistical analyses	
Results	Number of participants
	Age of participants (average and/or age categories)
	Proportion male and female
	Median length of follow-up (and variance)
	Attrition rates and/or exclusions after entry
	Proportion missing data or loss to follow-up
	Number exposed (total, by sex, by age)
	Duration of antidepressant use and variance (total, by sex, by age)
	Number not exposed (total, by sex, by age)
	Number with outcome (total, by sex, by age)
	Number exposed with outcome (total, by sex, by age)
	Number not exposed with outcome (total, by sex, by age)
	Measure of association (and CI, SE, p value)
	Any treatment deviations, non-compliance or non-adherence
	Funding and conflict of interests
Funding sources (list)	
Conflict of interests declared	
Conflict of interests (list)	

*Relevant to randomised controlled trials.

†Relevant to observational studies.

Risk of bias assessment

The Methodological Standard for Epidemiological Research (MASTER) scale will be used to assess the quality of the included studies.⁴⁸ The MASTER scale conceptualises quality scores as an indicator of a study's propensity towards bias, rather than an absolute measure of study biases. As such, it creates a means of ranking studies within a review based on their relative probability of bias. This ranking can be used to impute probability of bias variances for meta-analyses, without assuming the ranking is a direct measure of the absolute amount of bias present in any individual study. The MASTER scale uses a generic quality assessment tool across all study designs organised around seven methodological standards (equal recruitment, equal retention, equal ascertainment, equal implementation, equal prognosis, sufficient analysis and temporal precedence) that design-specific bias safeguards aim to fulfil.

The quality of studies and potential risks of bias will be discussed in text, and a quality summary score will be created based on the proportion of bias safeguards achieved in each study. As recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) study group, summary quality scores will not be used to weight analyses but will be used to guide a subgroup analysis of high-quality studies discussed below.⁴⁹

Statistical analysis

We will provide a descriptive overview of characteristics of the included studies, including the quality of the studies, geographic coverage and types of measures used to assess exposure to antidepressants and aggression and violent outcomes.

I^2 calculations will be used to assess heterogeneity. If there are sufficient studies that report measures of effect in a form which can be meta-analysed, a random meta-analysis will be used to estimate a pooled effect size. A random effects model is appropriate as it accounts for unexplained heterogeneity due to the diversity in study designs, treatment types and study populations which will be included in this review.⁵⁰ To test for publication bias, visual inspection of a funnel plot will be performed if a sufficient number of studies is included ($n \sim 10$ or more). An Egger's test statistic will also be calculated.

In order to understand the impact of study design on these pooled effects measures, we will conduct a meta-regression.⁵¹ If the number of included studies is sufficient, we will use meta-regression to investigate variation in effect according to age, sex, antidepressant type and subgroups of interest (including people with autism spectrum disorder, people with dementia, people with conduct disorder and people with a history of violent crime) and to investigate methodological effects including sample size, RCT versus observational design, length of follow-up and comparison condition. If there are differences by sex, antidepressant type or subgroups of interested, we will present analyses stratified by these factors. To examine

the impact of study quality on outcomes, we will conduct a sensitivity analysis which includes only higher-quality papers (papers whose quality assessment score is in the top 30% of included papers).

If the included studies do not have sufficient data to warrant meta-analyses, results will be presented in a harvest plot, examining correlations between study characteristics (such as study design), quality and estimated measure of association⁵² and will be complemented by a narrative description of the included study findings.

Ethics and dissemination

To our knowledge, this review will be the first to systematically synthesise research from RCTs and observational studies on the association between antidepressants and violence perpetration. The findings of this review may be useful to academic researchers, medication prescribers, drug regulatory bodies, and people who have been prescribed antidepressants. We will disseminate our findings by publishing results in a peer-reviewed journal and presenting results at conferences. We will provide our results to relevant professional organisations, stakeholders, and policymakers for dissemination to their members, and publish a plain language summary that links to the main publication.

As this is a review of studies which have already been subject to ethics approval, this study does not require ethics approval.

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Contributors CK and JY developed the original research proposal. CK, JY, JAF, GN-H, MW, SF and JK contributed to the design of the project. CK and MW developed the search strategy with input from JY, JAF, GN-H, MW and JK. CK wrote the initial draft manuscript and JY, JAF, GN-H, MW, SF, RB, JK and SAK contributed significantly to drafting and editing the manuscript. All authors approved the final manuscript.

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