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Effects of Electroconvulsive Therapy on Cognitive Functioning in Patients with Depression: Protocol for a Systematic Review and Meta–Analysis.

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ABSTRACT

Introduction: Depression is the leading cause of disability worldwide, affecting approximately 350 million people. Evidence indicates that only 60–70% of persons with major depressive disorder (MDD) who tolerate anti–depressants respond to first–line drug treatment; the remainder become treatment resistant. Electroconvulsive therapy (ECT) is considered an effective therapy in persons with treatment–resistant depression. The use of ECT is controversial due to concerns about temporary cognitive impairment in the acute post–treatment period. We will conduct a meta–analysis to examine the effects of ECT on cognition in persons with depression. **Methods:** This systematic review and meta–analysis has been registered with PROSPERO (registration number: CRD42014009100). We developed our methods following the Preferred Reporting Items for Systematic Reviews and Meta–Analysis (PRISMA) statement. We are searching Medline, PsychINFO, Embase, CINAHL, and Cochrane from the date of database inception to the end of October 2014. We are also searching the reference lists of published reviews and evidence reports for additional citations. Comparative studies (randomized controlled trials, cohort, and case control) published in English will be included in the meta–analysis. Two clinical neuropsychologists will independently group the cognitive tests in each included article into a set of mutually exclusive cognitive sub–domains. The risk of bias of randomized controlled trials will be assessed using the Jadad scale. The risk of bias of cohort and case control studies will be assessed using the Newcastle–Ottawa Scale. We will employ the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the strength of evidence. **Statistical Analysis:** Separate meta–analyses will be conducted for each ECT treatment modality and cognitive sub–domain using Comprehensive Meta–Analysis v2.0.

INTRODUCTION

According to the World Health Organization, depression is the leading cause of disability worldwide. Approximately 350 million people suffer from depression worldwide.[1] Despite the availablity of numerous psychopharmacological treatments, evidence indicates that only 60 to 70% of persons who tolerate anti–depressants will respond to first–line drug therapy for major depressive disorder (MDD).[2] Furthermore, at least one–third of persons with MDD who receive drug therapy will become treatment resistant.[3] Various definitions have been proposed for treatment–resistant depression (TRD). The European Agency for the Evaluation of Medicinal Products has defined TRD

as the failure to respond to two drugs of different classes, provided these drugs are used for a sufficient length of time and at an adequate dose.[4] TRD has also been defined as failing four or more different therapeutic antidepressant regimens, including augmentation, combination, and ECT.[5]

The aetiology of TRD is unclear. Various clinical factors have been associated with treatment non–response and resistance in MDD,[6,7] including non–adherence to treatment, poor tolerability to anti–depressant medications, and medical and psychiatric comorbidity. Researchers have also identified comorbid post–traumatic stress disorder[6] and the presence of early life adversity[7] as important predictors of incomplete treatment response.[6–8]

ECT is considered an effective acute treatment for TRD[9] in either unipolar or bipolar depression.[10] ECT is used primarily when antidepressant medications do not result in adequate response in TRD[11]. Approximately 100,000 persons annually receive ECT in the U.S.[12] However, the use of ECT remains controversial due to concerns about temporary cognitive impairment in persons with depression who receive acute ECT. Indeed, retrograde, and anterograde memory deficits are among the more reliably reported cognitive changes due to ECT.[9] The UK ECT Group also found that differences in ECT treatment modalities (e.g., electrode placement, pulse shape, treatment frequency, and treatment dosage) had a differential impact on the incidence and duration of cognitive impairment in persons with depression.[9]

Semkovska & McLoughlin (2010)[13] examined the issue of cognitive impairment in a recent meta–analysis. They found that cognitive impairment was limited to a post–treatment period of three days. However, the meta–analysis included only observational studies, which are lower on the hierarchy of evidence than randomized controlled trials (RCTs). In addition, this meta–analysis[13] did not assess the risk of bias in reporting, nor did it grade the strength of evidence of the included studies. Finally, results across the included studies were pooled by cognitive test, regardless of the clinical heterogeneity of these studies.

The purpose of the present study is to address these weaknesses in the current literature through a systematic review and meta–analysis of the effects of ECT on cognition in persons with depression. We seek to quantify the effect of different ECT treatment modalities on the occurrence and duration

of cognitive impairment. The present review includes comparative studies only (randomized controlled trials, cohort, and case control), which are among the highest levels of evidence. Additionally, cognitive function as an outcome is reported using standardized neuropsychological tests grouped into mutually exclusive cognitive sub–domains. We also evaluate the risk of bias of included studies and report on the strength of the reported evidence.

METHODS

This systematic review and meta–analysis was registered with PROSPERO (registration number: CRD42014009100; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009100).[14] We based the methods on the Preferred Reporting Items for Systematic Reviews and Meta–Analysis[15] statement.

Literature Review

We are searching Medline, PsychINFO, Embase, CINAHL, and Cochrane Library from database inception to the end of October 2014. We are basing our literature search on the UK ECT Review Group literature search terms.[9] We consulted a medical librarian to add specific search terms to narrow our focus to the identification of articles about cognitive side effects. The final search terms included: electroconvulsive therapy; electroshock therapy; ECT; shock therapy; convulsive therapy; mood disorders; depression; schizophrenia–and–disorders–with–psychotic–features; personality disorders; delirium–dementia, –amnesic, –cognitive–disorders; bipolar disorder; randomized–controlled–trials; random*; cohort–studies; case–control–studies; double–blind–method; single–blind–method; follow–up–studies; attention; orientation, learn*; memory; concentration; cognit*; mental–process*; executive functioning; visuospatial; language; intelligence; intellectual functioning; motor function; neuropsychology. We are also searching the references of published reviews and health technology assessments related to ECT and cognition.[9,10,13,16–18]

Inclusion/Exclusion Criteria

We are including studies retrieved in the literature search that meet the following criteria:

1) Comparative studies: randomized controlled trials, cohort studies and case control studies;

2) Measurement of outcomes using standardized neuropsychological tests;
3) Diagnosis of subjects with a major depressive episode (DSM III, DSM–III–R, DSM–IV, DSM–IV–TR, RDC, ICD–9, ICD–10) or endogenous depression; and
4) Published in English.

Study Selection and Data Extraction

Two reviewers are independently applying the inclusion and exclusion criteria to the citations retrieved in the literature search. This screening process is divided into two levels and it is guided by standardized instructions. For the first screening level, reviewers are independently evaluating the titles and abstracts. Citations that fulfill the inclusion criteria are advanced to the second screening level. Advancement also occurs if the reviewer does not find sufficient information to determine whether the citation fulfills the inclusion criteria. For the second screening level, the complete scientific paper is read to determine whether the inclusion criteria are met. At both levels, mutual agreement is required from the reviewers to advance a study. Discrepancies are resolved by consensus. When consensus is not attained, a third reviewer independently reviews the study in question and makes a final decision. We will use weighted kappa to measure inter-rater agreement between reviewers at both levels of screening.

Studies that pass the second screening level advance to data extraction. A team of trained reviewers extracts data from the included studies. Standardized forms and training guide the data extraction process. The following information is extracted from each article: study design, mean age, proportion of men and women, diagnosis, co–morbidity, illness duration, illness severity, age of illness onset (in years), number of illness episodes, sample size, ECT description, total number of ECT sessions, comparator group characteristics, length of follow up, treatment modality, and cognitive outcomes. Examples of treatment modalities (less versus more conservative modalities) include bilateral versus unilateral ECT, three times versus twice weekly treatment, ultra–brief versus brief pulse, sine versus pulse, ECT versus pharmacological treatment, ECT versus no treatment, and ECT versus sham. The first author of this protocol (CO) reviews the extracted data to verify the accuracy of the work.

Cognitive Sub–domains

Since cognitive outcomes in ECT studies are reported using a wide range of measurement instruments, we grouped these instruments into cognitive sub–domains to facilitate data extraction, reporting, and analysis. Three experienced clinical neuropsychologists (BL, HM, MCM) independently generated a list of sub–domains by reviewing the included papers, identifying the cognitive instruments, and grouping these instruments into cognitive sub–domains. Disagreements about domain assignment are resolved by consensus. We will use weighted kappa to measure levels of agreement between the neuropsychologists. The cognitive sub–domains are: subjective memory, verbal memory–immediate recall, verbal memory–delayed recall, verbal memory–recognition, non–verbal memory–immediate recall, non–verbal memory–delayed recall, non–verbal memory–recognition, working memory, attention, intellectual ability, executive function, processing speed, spatial problem solving, global cognitive status, language, motor, construction/visuospatial, and emotional/functional.

Assessment of Risk of Bias

Following data extraction, two reviewers will independently assess the risk of bias of each included study. Discrepancies will be resolved by consensus. If consensus is not reached, a third reviewer will decide. The risk of bias of randomized controlled trials (RCTs) will be assessed using the Jadad scale[19] which has six questions comprising the following domains: randomization, double blinding, tracking of withdrawals and adverse effects, appropriate use of statistics, and inclusion and exclusion criteria. One point is awarded for each “yes” response; zero points for “no” responses. Additional points may be added or deducted if the randomization scheme and blinding are appropriate or inappropriate. The maximum score is eight points.

The risk of bias of cohort and case control studies will be assessed using the Newcastle–Ottawa Scale (NOS)[20]. The NOS is divided into two subscales, one for cohort and the other for case control studies. Both subscales assess the following three domains: selection of study groups, comparability of study groups, and ascertainment of exposure or outcome. The NOS has a 'star system' to score studies (maximum score is nine stars).

Grading the Strength of Evidence

In addition to assessing the risk of bias, we will use the BMJ Evidence Centre guidelines for Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[21] GRADE[21] is a means

of rating the existing level of evidence to judge whether new evidence would change the conclusions of our review, or whether new evidence would be unlikely to change these conclusions. We will rate the evidence for each cognitive sub–domain on five categories: type of evidence, quality, consistency, directness, and precision. The ratings will yield an overall GRADE[21] score, with scores of 4 or more indicating a high likelihood that further evidence would be unlikely to change the conclusions of our review. A score of 3 would indicate moderate likelihood, 2 would equate to low likelihood, and less than 2 would mean a very low likelihood.

Statistical analysis

To examine the impact of ECT on cognitive functioning in persons with depression, we will use Comprehensive Meta–Analysis v2.0 software[22] to conduct separate meta–analyses for each ECT treatment modality and cognitive sub–domain. We will enter outcomes as means and standard deviations or, if unavailable, as mean differences. The software will transform all entered data into odds ratios (ORs) for ease of interpretation. We will enter outcome data in such a manner to ensure the ORs represent comparisons of less to more conservative ECT modalities. ORs greater than 1.0 will indicate that persons receiving less conservative modalities had greater odds of developing cognitive impairment than persons receiving more conservative modalities; ORs less than 1.0 will show the reverse; ORs equal to 1.0 will suggest no difference between modalities.

To compute summary OR estimates, we will use a standard inverse–variance, random–effects meta–analysis.[23] We will utilize the I^2 statistic to quantify the degree of between–study heterogeneity.

Authors' Contributions

C. Oremus, M. Oremus, H. McNeely, B. Losier, M. King, G. Hasey, R. Lanius, and M.C. McKinnon conceived and designed the study.

C. Oremus conducted the literature search.

C. Oremus and M. Parlar are selecting studies for inclusion in the review (tittle and abstract and full text screening)

C. Oremus, M. Parlar, G. Fervaha, A. C. Graham, C. Gregory, L. Handford, A. Nazarov, M. Restivo, E. Tatham, W. Truong, G.B.C. Hall are extracting data from the included studies and

they will asses the risk of bias of included studies.

C. Oremus drafted the protocol manuscript.

All authors critically revised and commented the manuscript for important intellectual content.

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Conflict of Interest

None of the authors declare any conflict of interest.

Ethics Committee Approval

We are collecting data from published manuscripts. Therefore, our study is not required to be approved by an ethics committee.

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INTRODUCTION

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depression (TRD). The European Agency for the Evaluation of Medicinal Products has defined TRD as the failure to respond to two drugs of different classes, provided these drugs are used for a sufficient length of time and at an adequate dose.[4] TRD has also been defined as failing four or more different therapeutic antidepressant regimens, including augmentation, combination, and ECT.[5]

The aetiology of TRD is unclear. Various clinical factors have been associated with treatment non–response and resistance in MDD,[6,7] including non–adherence to treatment, poor tolerability to anti–depressant medications, and medical and psychiatric comorbidity. Researchers have also identified comorbid post–traumatic stress disorder[6] and the presence of early life adversity[7] as important predictors of incomplete treatment response.[6–8]

ECT is considered an effective acute treatment for TRD[9] in either unipolar or bipolar depression.[10] ECT is used primarily when antidepressant medications do not result in adequate response in TRD.[11] Approximately 100,000 persons annually receive ECT in the U.S.[12] However, the use of ECT remains controversial due to concerns about temporary cognitive impairment in persons with depression who receive acute ECT. Indeed, retrograde and anterograde memory deficits are among the more reliably reported cognitive changes due to ECT.[9] The UK ECT Group also found that differences in ECT treatment modalities (e.g., electrode placement, pulse shape, treatment frequency, and treatment dosage) had a differential impact on the incidence and duration of cognitive impairment in persons with depression.[9]

Semkovska & McLoughlin (2010)[13] examined the issue of cognitive impairment post–ECT in a recent meta–analysis. After pooling results by cognitive test, these authors found that cognitive impairment was limited to a post–treatment period of three days. Although Semkovska & McLoughlin[13] did assess risk of bias, these results are not reported in the manuscript nor did they report the grading of the strength of evidence.

The purpose of the present study is to conduct a systematic review and meta–analysis of the effects of ECT on cognition in persons with depression. We seek to quantify the effect of different ECT treatment modalities on the occurrence and duration of cognitive impairment. The present review includes comparative studies only (randomized controlled trials, cohort, and case control), which are

among the highest levels of evidence. Additionally, the review only includes studies where cognitive function as an outcome is reported using standardized neuropsychological tests or self–report measures that are grouped into mutually exclusive cognitive sub–domains.

In contrast to Semkovska & McLoughlin[13], results in the proposed review are grouped by cognitive sub–domains, rather than cognitive tests. The focus on cognitive sub–domains is a closer reflection of clinical and research practice. In these settings, multiple tests are available to assess performance within individual cognitive domains (e.g., verbal recollective memory). The current literature reflects this heterogeneity, with multiple measures reported across studies to assess key cognitive domains that have become the focus of intense research interest. Inclusion of a wider corpus of measures within common cognitive domains reflects clinical and research practice. In further contrast to Semakovska and McLoughlin, we include studies that actively compare more conservative ECT treatments (e.g., unilateral) to less conservative (e.g., bilateral) ECT treatments. Here, a primary outcome is post–treatment between–group differences in cognition for persons receiving less conservative versus more conservative ECT treatments. By contrast, Semkovska & McLoughlin[13] compared pre– and post–treatment scores on cognitive tests. Although they stratified by some components of treatment modality, the resulting comparisons were within–group differences, rather than between–group (between–treatment) comparisons. From a clinical perspective, it is crucial to determine whether the impact of cognitive impairment differs between treatments. Furthermore, by including studies that measured subjective memory in addition to objective neuropsychological measures of memory, we are able to compare and contrast potential differences in these aspects of memory functioning following treatment. Finally, we provide key data concerning the risk of bias of the included studies and rate the overall strength of evidence.

METHODS

This systematic review and meta–analysis was registered with PROSPERO (registration number: CRD42014009100; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009100).[14] We based the review methods on the Preferred Reporting Items for Systematic Reviews and Meta–Analysis[15] statement.

Literature Review

We are searching Medline, PsychINFO, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials from database inception to the end of October 2014. The literature search mirrors the search employed by the UK ECT Review Group.[9] We consulted a medical librarian to add specific search terms to narrow our focus to the identification of articles about cognitive side effects. The final search terms included: electroconvulsive therapy; electroshock therapy; ECT; shock therapy; convulsive therapy; mood disorders; depression; schizophrenia–and–disorders–with–psychotic–features; personality disorders; delirium–dementia, –amnesic, –cognitive–disorders; bipolar disorder; randomized–controlled–trials; random*; cohort–studies; case–control–studies; double–blind–method; single–blind–method; follow–up–studies; attention; orientation, learn*; memory; concentration; cognit*; mental–process*; executive functioning; visuospatial; language; intelligence; intellectual functioning; motor function; neuropsychology. We are also searching the references of published reviews and health technology assessments related to ECT and cognition.[9,10,13,16–18]

Inclusion/Exclusion Criteria

We are including studies retrieved in the literature search that meet the following criteria:

1) Comparative studies (randomized controlled trials, cohort studies and case control studies) assessing less versus more conservative ECT treatments;
2) Outcomes measured using standardized neuropsychological tests and self–report memory measures with established psychometric properties;
3) Diagnosis of subjects with a major depressive episode (DSM III, DSM–III–R, DSM–IV, DSM–IV–TR, RDC, ICD–9, ICD–10) or endogenous depression; and
4) Published in English.

Study Selection and Data Extraction

Two reviewers are independently applying the inclusion and exclusion criteria to the citations retrieved in the literature search. This screening process is divided into two levels and it is guided by standardized instructions. For the first screening level, reviewers are independently evaluating the titles and abstracts. Citations that fulfill the inclusion criteria are advanced to the second screening level. Advancement also occurs if the reviewer does not find sufficient information to determine

whether the citation fulfills the inclusion criteria. For the second screening level, the complete scientific paper is read to determine whether the inclusion criteria are met. At both levels, mutual agreement is required from the reviewers to advance a study. Discrepancies are resolved by consensus. When consensus is not attained, a third reviewer independently reviews the study in question and makes a final decision. We will use weighted kappa to measure inter–rater agreement between reviewers at both levels of screening.

Studies that pass the second screening level advance to data extraction. A team of trained reviewers extracts data from the included studies. Standardized forms and training guide the data extraction process. The following information is extracted from each article: study design, mean age, proportion of men and women, diagnosis, co–morbidity, illness duration, illness severity, age of illness onset (in years), number of illness episodes, sample size, ECT description, total number of ECT sessions, comparator group characteristics, length of follow up, treatment modality, and cognitive outcomes. Examples of treatment modalities (less versus more conservative modalities) include bilateral versus unilateral ECT, three times versus twice weekly treatment, ultra–brief versus brief pulse, sine versus pulse, ECT versus pharmacological treatment, ECT versus no treatment, and ECT versus sham. The first author of this protocol (CO) reviews the extracted data to verify the accuracy of the work. We are contacting the authors of included studies to obtain information that may be missing from the published reports.

Cognitive Sub–domains

Since cognitive outcomes in ECT studies are reported using a wide range of measurement instruments that increases the number of variables across and between studies, we grouped these instruments into cognitive sub–domains to facilitate data extraction, reporting, and analysis. Three experienced clinical neuropsychologists (BL, HM, MCM) generated a list of sub–domains by reviewing the included papers, identifying the cognitive instruments, and grouping these instruments into cognitive sub–domains. Disagreements about domain assignment are resolved by consensus. The cognitive sub–domains are: verbal memory–immediate recall, verbal memory–delayed recall, verbal memory–recognition, non–verbal memory–immediate recall, non–verbal memory–delayed recall, non–verbal memory–recognition, working memory, attention, intellectual ability, executive function, processing speed, spatial problem solving, global cognitive status, language, motor, and

construction/visuospatial. In addition, autiobiographical memory and subjective memory as measured by standardized self–report tools are included. Notably, narrative comparison of outcomes assessed by objective and subjective measures is critical, given that patients' subjective report of cognitive performance may differ significantly from that captured by objective measurement.

Assessment of Risk of Bias

Following data extraction, two reviewers will independently assess the risk of bias of each included study. Discrepancies will be resolved by consensus. If consensus is not reached, a third reviewer will decide. The risk of bias of randomized controlled trials (RCTs) will be assessed using the Jadad scale[19] which has six questions comprising the following domains: randomization, double blinding, tracking of withdrawals and adverse effects, appropriate use of statistics, and inclusion and exclusion criteria. We will supplement the questions on the Jadad scale with additional questions (yes/no responses) about the adequacy of allocation concealment, use of intention–to–treat analysis, justification of sample size, reporting of outliers, and selective outcome reporting. Some of these additional questions are based on the Cochrane risk of bias tool[20]; the addition of questions to existing scales has been used in other meta–analyses.[21]

The risk of bias of cohort and case control studies will be assessed using the Newcastle–Ottawa Scale (NOS).[22] The NOS is divided into two subscales, one for cohort and the other for case control studies. Both subscales assess the following three domains: selection of study groups, comparability of study groups, and ascertainment of exposure or outcome.

Using the responses to the aforementioned scales and questions, reviewers will qualitatively assess the risk of bias for each study as 'low', 'unclear', or 'high'. According to the Cochrane Collaboration, 'low' means any bias is unlikely to substantively alter a study's results, 'unclear' means the bias causes doubts about the results, and high means the bias is likely to threaten the validity of the results.[20]

Grading the Strength of Evidence

We will use the BMJ Evidence Centre guidelines for Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[23] to judge the overall quality of evidence for specific sub–

domains. In situations where the group of studies assessing a specific sub–domain has a low quality of evidence, one would hold little confidence in the validity of the results. One would also be hesitant to draw firm conclusions or make clinical recommendations based on these results. Future studies – assuming they present a higher quality of evidence – might provide a stronger basis from which to draw conclusions or make clinical recommendations.

We will use GRADE to rate the evidence separately for each cognitive sub–domain. We will begin by assigning 4 points to each sub–domain if the evidence is largely based on RCT data, or 2 points if the evidence is largely based on observational study data. We will then assess four other categories, i.e., quality, consistency, directness, and precision, and add or deduct points for each category in accordance with GRADE guidelines.[23] The additions or deductions reflect pre–set criteria for assessing how the components of each category contribute to the overall quality of evidence. The final point total serves as the overall GRADE[23] score: scores of 4 or more indicate high quality of evidence, a score of 3 would indicate moderate quality, 2 would suggest low quality, and less than 2 would indicate very low quality. The level of confidence to make clinical recommendations based on the evidence would be stronger for higher overall scores.

GRADE's 'quality' category will include the risk of bias assessments. The Cochrane guidelines for ascertaining risk of bias across studies will be used to synthesize the risk of bias findings for individual studies.[20] These guidelines classify groups of studies according to low, unclear, or high risk of bias. We will deduct points on the quality category as follows: low risk of bias (-1), unclear risk of bias (-2), high risk of bias (-3).

Statistical analysis

After all data have been extracted from the included studies, the investigators will examine the extraction tables and determine whether meta–analysis is possible. We will only conduct meta–analyses on studies that are relatively homogeneous in terms of participants (e.g., age, sex, co–morbidity). In the event between–study heterogeneity precludes a meta–analysis, or only permits us to conduct a meta–analysis on a subset of studies, we will undertake a narrative synthesis[24] of all of the included studies.

Studies that are sufficiently homogeneous in terms of participants will be meta–analyzed. We will conduct separate meta–analyses for each cognitive sub–domain. Within each sub–domain, we will stratify the analyses by study design (RCT, observational, RCT and observational combined). The summary estimates computed in the meta–analyses will compare the differences in post–ECT cognitive impairment between groups receiving less versus more conservative ECT treatments. Initially, these comparisons will take the form of mean between–group differences in scale score. Differences in scale score are, however, difficult to interpret across disparate scales because of variations in score ranges (e.g., a mean difference of 1.0 is larger on a scale that ranges from 0 to 5 relative to a scale that ranges from 1 to 100). Even standardized mean differences can be difficult to interpret clinically because no threshold exists to mark the minimum important difference in score. Therefore, we will report the study–specific and summary estimates as odds ratios (ORs) in all forest plots. ORs greater than 1.0 will indicate that persons receiving less conservative modalities have greater odds of developing cognitive impairment than persons receiving more conservative modalities. ORs less than 1.0 will show the reverse; ORs equal to 1.0 will suggest no difference between modalities.

We will record all study–specific outcomes as means and standard deviations or, if unavailable, as mean differences. Borenstein et al.'s formulae,[25] implemented through Comprehensive Meta–Analysis v2.0 software,[26] will transform all entered data into ORs and generate forest plots. Forest plots will be computed using a fixed–effects model. We will test statistical heterogeneity for each meta–analysis using the I^2 statistic. If the I^2 value is 50% or higher, then we will re–compute the forest plot using a random–effects model. Comprehensive Meta–Analysis will generate funnel plots to enable the assessment of publication bias.

Authors' Contributions

C. Oremus, M. Oremus, H. McNeely, B. Losier, M. King, G. Hasey, R. Lanius, and M.C. McKinnon conceived and designed the study.

C. Oremus conducted the literature search.

C. Oremus and M. Parlar are selecting studies for inclusion in the review (tittle and abstract and full text screening)

C. Oremus, M. Parlar, G. Fervaha, A. C. Graham, C. Gregory, L. Handford, A. Nazarov, M.

Restivo, E. Tatham, W. Truong, G.B.C. Hall are extracting data from the included studies and they will asses the risk of bias of included studies.

C. Oremus drafted the protocol manuscript.

All authors critically revised and commented the manuscript for important intellectual content.

Role of the Funding Source

This study was funded by a Canadian Institutes of Health Research (CIHR) grant to Drs. Margaret C. McKinnon and Ruth Lanius. The study sponsor plays no role in study design, data collection, data analysis, data interpretation, or report writing. All authors have complete access to all data and the corresponding author had final authority to decide to submit this protocol for publication.

Conflict of Interest

None of the authors declare any conflict of interest.

Ethics Committee Approval

We are collecting data from published manuscripts. Therefore, our study is not required to be approved by an ethics committee.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4, 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9, 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9, 10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9, 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	N/A
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N/A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	N/A
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	N/A
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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