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Title: Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

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ABSTRACT

Background

Comorbid depression is prevalent in people with multiple sclerosis (MS). Depression is commonly untreated or undertreated and there is a need for effective and safe interventions. Guidelines for depression management in people with MS recommend psychological and pharmaceutical interventions, however current research suggests other interventions such as exercise could also be effective. The comparative efficacy and safety between intervention modalities have not been established in the literature.

Objective:

To outline a protocol for a systematic review and network meta-analysis to compare efficacy and safety of psychological, pharmaceutical, physical, and magnetic stimulation interventions for depression in people with MS.

Methods and analysis:

We will search seven key databases using a search strategy developed for this protocol with search terms revolving around three concepts: MS, depression, and randomised controlled trials. Included trials will be randomised controlled trials with depression as the primary outcome, only outcome, or secondary outcome with *a priori* power calculation with a population of people with MS using an aforementioned intervention type will be included. Screening, data extraction, and risk of bias assessment (using the Risk of Bias 2 tool) will be conducted by two independent reviewers. We will generate descriptive statistics and provide a narrative synthesis of the included trials. We will use a frequentist multivariate random effects model in a network meta-analysis where efficacy will be measured using a standardised mean

difference and safety using an odds ratio. If possible, we will provide summary measures including a geometry of the network, surface under the cumulative ranking curve, and a league table. Sub-group analysis will be performed if possible, using pre-planned variables.

Ethics and dissemination:

Ethical approval is not necessary for this type of study. Results of the systematic review and network meta-analysis will be published in a peer reviewed journal.

Review registration:

PROSPERO registration number CRD42020209803.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This will be the first systematic review and network meta-analysis to identify the comparative efficacy, safety, and tolerability of interventions for depression in people with MS.
- Eligibility criteria include randomised controlled trials which are limited to depression as the primary outcome, only outcome, or secondary outcome with a power analysis.
- The review will include multiple intervention types which are used in both clinical and research settings.
- To meet the transitivity assumption, trials including participants with treatment resistant/refractory depression must be excluded.

KEYWORDS: multiple sclerosis, depression, network meta-analysis, systematic review,

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INTRODUCTION:

Multiple Sclerosis (MS) is a chronic, immune mediated and neurodegenerative disease characterised by the formation of destructive lesions predominantly involving myelinated axons within in the central nervous system [1]. There are a broad range of symptoms attributed to the multifocal lesions distinctive of MS including depression, pain, fatigue, impaired gait, incontinence, impaired vision, and spasticity [2]. Depression can be particularly burdensome, and affects up to 50% of people with MS [3]. Depressive symptoms in people with MS are reported to impact adherence to disease modifying therapies [4], increase pain sensitivity [2], and reduce participation in work and poor health related quality of life [5]. Major depressive disorder (MDD), the most commonly diagnosed depressive disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is defined as experiencing a minimum of five symptoms including depressed mood or lack of pleasure, feelings of worthlessness/guilt, fatigue, appetite or weight changes, psychomotor agitation, diminished concentration, feelings of worthlessness/guilt, suicidality and sleep difficulties within a period of two-weeks [6]. Depressive symptoms which do not meet the definition of MDD are even more prevalent in people with MS, and commonly still require treatment [7]. Furthermore, people with MS who have moderate-to-severe depressive symptoms have been reportedly underdiagnosed and undertreated [8 9]. The aetiology of depression and depressive symptoms in people with MS is not yet fully understood but [10] but due to the multitude of effects, safe and effective interventions are required.

Guidelines for treating depression in people with MS suggest that a combination of psychological and pharmaceutical interventions is the most effective two-pronged therapy [11]

[12]. Further, the American Association of Neurology review to inform guidelines in 2014 [13] point out the scarcity of trials to treat depression in people with MS, and therefore a lack of strong evidence. Following this pivotal review [13] a number of studies have sought to address the dearth in literature. Some interventions, such as mindfulness-based interventions [14] and Pilates [15] have not been included in these guidelines. Further, recent systematic reviews reported that exercise [16 17] and mindfulness-based interventions [18], compared to waitlist/usual care, have a moderate effect at reducing depressive symptoms in people with MS. However, it is unclear how these interventions compare in terms of efficacy and safety. Network meta-analysis enables the comparison of multiple interventions by combining the direct and indirect evidence without the need for several analyses [19]. Synthesising the evidence in this manner will enable a comprehensive understanding of how interventions compare, which should greatly enhance evidence-based decision making for people with MS and their clinicians on how best to manage depressive symptoms.

This article outlines the protocol for a systematic review and network meta-analysis to compare the effectiveness and safety of intervention modalities, or combination of modalities, in reducing depressive symptoms in adults with MS. This review is the first stage of a larger project that aims to provide guidance for public health researchers on the design and analysis of network meta-analysis studies in MS.

METHODS

This systematic review protocol is registered with The International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020209803) and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-

Analysis (PRISMA NMA) statement [20], see supplementary file 1 for checklist.

Eligibility criteria

Participants

Adults (aged 18 years or older) of any gender who have been diagnosed with any type of MS.

Interventions

We will include interventions that aim to alleviate depressive symptoms in people with MS, including:

Psychological interventions will be delivered with the intention of treating depressive symptoms, informed by psychological theories or principle(s) and a) implemented by a psychiatrist/psychologist or other mental health clinician or b) manualized, with content developed by a mental health clinician or researcher, e.g. online/app or web-based intervention.

Pharmaceutical interventions will be delivered with the intention involve the use of medication or drugs for the intention of treating depressive symptoms at a therapeutic dose according to the manufacturer guidelines (if available).

Physical interventions including physiotherapy and physical activity (any bodily movement that results in energy expenditure) including exercise, aimed at treating depressive symptoms. Subtypes of physical activity will be included.

Electromagnetic stimulations involve the use of targeted electromagnetic stimulation to stimulate areas of the brain to reduce depressive symptoms. Subtypes include transcranial magnetic stimulation, and transcranial direct current stimulation.

Combinations of the above-mentioned intervention modalities will be included and will form new categories. Any interventions that are specific to people with treatment resistant depression/refractory depression will not be included (e.g. electroconvulsive therapy). This is because participants who have treatment resistant depression will have previously participated in first step methods such as cognitive behavioural therapy and to satisfy the transitivity assumption [19] (i.e., a participant who does not have treatment resistant depression would not be eligible to be randomised to an intervention such as electroconvulsive therapy).

Grouping of interventions will depend on the eligible trials. The four broad categories will be split into smaller sub-categories, e.g. psychological interventions could have a sub-category of mindfulness-based interventions, similarly pharmaceutical interventions could have a sub-category of serotonin reuptake inhibitors.

Comparator

We will consider the following comparators: any intervention modality included in the above list, placebo, wait-list control, treatment as usual, or no treatment. Classification of comparator groups will depend on the type of comparator the author of the RCT has employed. Common types of comparators can include, but not limited to, placebo, wait-list control, treatment as usual, and no treatment control. These comparator groups do not have similar methodology and can influence participant outcome in altering ways. Therefore, for this protocol and

subsequent systematic review and network meta-analysis, we will adopt the recommended framework for classification of comparator groups [21]. The groups will be (1) minimal treatment control, active control, or similar; (2) wait-list control, treatment as usual, or no treatment; and (3) pill placebo.

Outcome

We will include studies which specified that depressive symptoms were the primary (or only) outcome, or as a secondary outcome where an a-priori power calculation was provided. The severity of depressive symptoms must have been measured by a validated self-report questionnaire or by clinician interview. Although depression and depressive symptoms is measured and defined differently across studies [22], we have chosen to accept all types of standardised measures or clinical interviews. To assess the acute efficacy of the intervention, depressive symptoms must be measured within two weeks of completion of the intervention. We will also assess the long-term efficacy of the intervention using studies that have measured depressive symptoms at approximately six months post-intervention (within 4-8 months). Any studies that have measured just one of the aforementioned time points will still be eligible for inclusion.

Safety and tolerability outcomes will include:

- Frequency of serious adverse events (SAEs) defined as an untoward occurrence of a medical event that is fatal, life-threatening, requires hospitalization or prolonging of existing hospitalization and/or persistent disability [23-26].
- Frequency of adverse events (AEs) defined as the occurrence of an undesirable event

occurring during the study duration even if the event was not considered to be related to the intervention [23-26].

- Tolerability of the intervention will be assessed as the frequency of participants who discontinue the study and/or have reduced compliance due to SAE or AEs [23 27].

The events will be measured as dichotomous outcomes during the intervention period and SAE's and AE's might be combined in analysis if they are rare outcomes of the studies.

Types of Studies

We will include randomised controlled trials, including multi-arm randomised trials. Quasi-randomised, cluster and cross-over trials will not be included.

Search strategy

We will search the following seven databases: EMBASE, Ovid (Medline), Cochrane CENTRAL, APA PsycInfo, Web of Science, CINAHL and PEDro. The search strategy was developed in conjunction with a medical librarian at the University of Melbourne, Australia, as well as a clinical physiotherapist (YL) who works with people with MS, and a clinical psychologist (AM). The search terms relate to three main concepts of MS, depression, and randomised controlled trials. Search strategies for all databases are listed in supplementary file 2. Databases will be searched from inception to present. We will also search the reference lists of relevant systematic reviews to identify any randomised trials that might have been missed in the database search. Trials will be limited to those published in English.

Study selection

Results from the search strategy will be uploaded to Endnote [28] where duplicates will be removed. The remaining citations will be uploaded into the software management system Covidence [29] where any additional duplicates will be removed. Covidence will then be used for title and abstract screening and full text screening by at least two independent reviewers with any conflicts resolved by a third reviewer.

Data Extraction

Data will be extracted using a data extraction tool developed for this review using Excel software by at least two independent reviewers, with conflicts resolved by a third reviewer. If data was missing from the published article the corresponding author will be contacted. We will not look at other sources of citations such as grey literature, clinical trial registries, or protocol papers. The extracted data will relate to the following categories:

- Study characteristics: first author's last name, year of publication, year of baseline recruitment, method of recruitment, method of randomisation, inclusion criteria (e.g. a baseline level of depression cut off for inclusion into study).
- Sample demographics: sample size, number of participants randomised, baseline characteristics such as diagnosis of MS, age (years), sex, years since diagnosis of MS, level of disability, and disability tool.
- Intervention and comparator characteristics: type, frequency of intervention/treatment, duration of intervention/treatment, and dose of intervention/treatment.
- Efficacy outcome data: type of outcome measurement scale, mean and standard deviation of depressive symptom score at baseline, post-intervention, and at six months post-intervention (if available).

- Safety and tolerability data: type and number of all SAEs and AE, number of participants that discontinue due to an SAE or AE or for other reasons during the intervention reported for each trial arm (if time-point data is available, this information will be extracted).
- Data relating to the risk of bias assessment: randomisation process, allocation concealment, deviations from intended treatment, baseline characteristics differences, missing outcome data, appropriateness of outcome measurement, potential influence in outcome assessment, and selectively reporting results.

Risk of bias assessment

We will use the Risk of Bias 2 tool (RoB 2) to assess the risk of bias for each study that meets the eligibility criteria [30]. This tool evaluates the risk of bias in five key domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The RoB 2 tool provides an overall assessment of the risk of bias in the study using three categories: low risk, some concerns or high risk of bias. At least two independent reviewers will assess the risk of bias in each study with any conflicts between judgements resolved by a third reviewer. In this systematic review and network meta-analysis there will be an inherent difference in the overall risk of bias between studies due to the type of intervention. Blinding of the participants to the assigned intervention is difficult in some study designs and interventions. For example, participants in a two-arm randomised trial that compared exercise to wait-list control will be aware of the treatment arm they were allocated in the randomisation process, whereas participants in a pharmaceutical intervention which compared an anti-depressant to placebo have reasonable doubt as to which intervention they were allocated. Blinding of the outcome

assessors can also be difficult in these trials as depressive symptoms are typically measured using self-reported tools. Despite this inherent difference we have chosen not to deviate from the protocol of the RoB 2 tool or alter the tool in any way.

Data synthesis

All analyses will be conducted using Stata version 16.1 using the network package [31].

Characteristics of the included studies

We will generate descriptive statistics for the sample populations to understand the demographics of the review participants across all eligible trials. These descriptive statistics will describe key clinical and methodological characteristics such as age, sex, type of MS, and type of intervention modality.

Outcome data

For this network meta-analysis, we will have two primary and two secondary outcomes.

Primary outcome:

(1) efficacy of intervention(s) at post-intervention using standardised mean difference [32], and

(2) safety of interventions (SAEs, AEs and tolerability) using pooled odds ratios at post-intervention.

Secondary outcome:

(1) efficacy of intervention(s) at post-intervention using standardised mean difference at six months post-intervention (between four and eight months)

(2) safety of interventions (SAEs, AEs and tolerability) using pooled odds ratios at six months post-intervention (between four and eight months)

Geometry of the network

We will generate a network diagram, separately for efficacy and safety, to visualise the network of intervention modalities. The nodes (or intervention modalities) will represent the total number of studies in that group; the larger the size of the node the larger the sample size. The edges of the lines connecting each node will represent the precision of the evidence, i.e., the thicker the line the more precise evidence. Figure 1 shows an example of the possible network structure with the major intervention modalities included.

<insert figure 1 here>

Pairwise Meta-analysis

For each major category of intervention modality (i.e. psychological, pharmaceutical, physical, electromagnetic stimulation therapies or combination) that is informed by 10 or more trials in the category we will fit a random effects pairwise meta-analysis. The random effects model will assume that the underlying intervention effects across the studies are similar but not identical allowing an estimation of the heterogeneity in the model [33]. This will be performed for both the efficacy outcome, using the SMD, and the safety outcome, using odds ratios. Effect sizes will be presented with their corresponding 95% confidence intervals.

Heterogeneity will be estimated using the I^2 statistic giving a percentage of variation across the studies due to heterogeneity [34].

Assessment of transitivity in the network

The transitivity assumption, which underpins the method of a network meta-analysis, states that any participant in one trial could be equally randomised to any other trial in the network [19]. Participant characteristics (for example, age, sex, type of MS, level of disability, and years since diagnosis of MS) might cause the transitivity assumption to be violated [19]. For example, if participants in a trial comparing pharmacological interventions were eligible for recruitment if they had severe mobility disability and they would never be eligible for a trial comparing two physical activity interventions then we would conclude that the transitivity assumption has potentially been violated. To assess transitivity of the network the inclusion criteria for participants recruited into each trial will be assessed. If the transitivity assumption is thought to be violated, we will undertake narrative synthesis of the data (described below) and possibly pair wise meta-analyses (described above). If we find no reason to suggest that violation of the transitivity assumption, we will synthesise the available evidence using network meta-analysis techniques. We will fit a random effects network meta-analysis model in a frequentist framework and assume a common heterogeneity parameter across the eligible trials. The random effects model assumes that the variation between studies could be a result of heterogeneity and not from sampling variation [19 31].

Summary Statistics

We will present the summary SMDs or ORs for all pairwise comparisons in a league table [35]

[36]. We will use a predictive interval plot to show the grouped intervention modality SMD or OR in a future trial [35]. We will then obtain a hierarchy of the intervention modalities using the surface under the cumulative ranking curve (SUCRA). SUCRA uses probabilities to determine which intervention modality is most likely to be the most effective at reducing depressive symptoms in people with MS. A probability of 1 (or 100%) is indicative of the stated intervention modality being the most effective intervention modality, conversely, a probability of 0 (or 0%) is indicative of the stated intervention modality being the least effective [36].

Assessment of inconsistency

Consistency is a measure of the agreement between direct evidence and indirect evidence. If inconsistency occurs in a network it may suggest that there is significant heterogeneity and that the transitivity assumption could be violated [19 33]. Using the network meta-analysis package in Stata a consistency and inconsistency model can be separately applied to assess whether the direct and indirect evidence are in agreement for each outcome. These models can provide information to help ascertain if the direct and indirect evidence are in statistical agreement [37]. If there is evidence of inconsistency in the network, we will use a local method with the side-splitting approach, a technique that divides the evidence within a node and analyses it separately to identify if the evidence agrees with the network, to identify if there is a specific modality of interventions that contribute to inconsistency in the network [31 37]. This will enable us to further investigate the possible sources of inconsistency [38].

Sub-group analysis

We will conduct separate sub-group analyses for the efficacy and the safety outcome if there is substantial heterogeneity and the data allows this.

For the efficacy outcome we will assess whether the following characteristics might explain any of the observed heterogeneity in the model using a sub-group analysis:

- Year of baseline recruitment; to determine if treatments have become more effective over time.
- Severity of depression at baseline (i.e., studies that recruited based on level of depression vs. studies that did not); to identify whether interventions are efficacious when a level of depressive symptoms is present.
- Comparison of self-reported outcome measures vs clinical assessment; to determine if there is a difference in the efficacy of the treatment due to the measurement of the outcome.
- Level of disability at enrolment (e.g., as measured by Patient determined disease steps, Expanded Disability Disease Scale: categorized in mild, moderate severe); to determine if level of disability is associated with the efficacy of the intervention.
- Whether the intervention was conducted in a dose according to guidelines that exist for that type of interventions (e.g., exercise guidelines for people with MS); to determine if a minimum dose is associated with the efficacy of the intervention.

For the safety and tolerability outcome we will assess whether year of baseline recruitment and level of disability at enrolment might explain any of the observed heterogeneity.

Assessment of small study effects

We will use the comparison-adjusted [35] and contour-enhanced [39] funnel plots to investigate

whether results in imprecise trials differ from those in more precise trials. Network meta-regression models will be used to investigate associations between study sample size and effect size [40].

Narrative synthesis

If we are unable to conduct a NMA or meta-analyses we plan to conduct a narrative synthesis to assess which interventions reported the outcomes of interest and if there were any patterns relating to specific interventions, or gaps in the literature.

ETHICS AND DISSEMINATION

Ethical approval is not needed for a systematic review and network meta-analysis as this study will use aggregated data from already published RCT's. The dissemination of the results of the systematic review and network meta-analysis will include publishing in a peer reviewed journals to apprise MS researchers and clinicians, and people with MS. The results of the systematic review and network meta-analysis have the potential to inform future treatment guidelines for depression in people with MS. Further, the review may highlight any gaps in the literature and provide recommendations for the conduct and reporting of future randomised controlled trials.

AUTHORS CONTRIBUTIONS

AK and CM conceived the study. AK, CM, JL, SC, YL, AGK and AM contributed to the study design. JL drafted the manuscript and AK, CM, SC, YL edited the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PATIENT AND PUBLIC INVOLVEMENT

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of the research in this article.

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FIGURE LEGEND:

Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

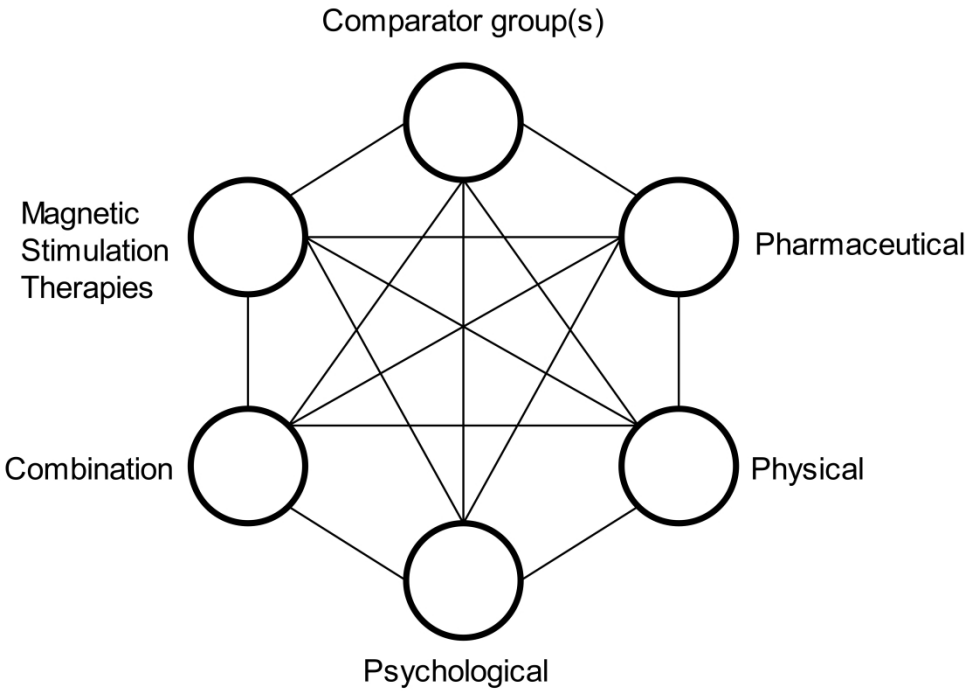

Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

2053x1443mm (72 x 72 DPI)

SUPPLEMENTARY FILE 1:

Table 1: PRISMA-NMA guidelines checklist.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and 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. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	6-9
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.	9
Search	8	Present full electronic search strategy for at least one database,	Supplementary file 2

		including any limits used, such that it could be repeated.	
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).	9-10
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.	10-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	13
Risk of bias within 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.	11-12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	15
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* •*Assessment of model fit.*	12-17
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	15
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).	16-17
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	15-16

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.	NA
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
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.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	NA

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).	NA
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). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			18
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. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this

SUPPLEMENTARY FILE 2:

Complete database search strategy

Table 1: search strategy for databases EMBASE, APA PsycInfo, Ovid MEDLINE, Cochrane CENTRAL.

	Search terms
1	multiple sclerosis.ti,ab.
2	exp multiple sclerosis/
3	1 or 2
4	exp depression/
5	(depress* or mood disorder or despair or misery or unhappiness or dysthymia or dysphor* or seasonal affective disorder or affective disorder or sadness or loss of pleasure).ti,ab.
6	4 or 5
7	exp randomized controlled trial/
8	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*").ti,ab.
9	7 or 8
10	3 AND 6 AND 9

Table 2: search strategy for databases CINAHL and Web of Science.

	Search Term
1	“multiple sclerosis”
2	depress* or “mood disorder*” or despair or misery or unhappiness or dysthymia or dysphor* or “seasonal affective disorder” or “affective disorder” or sadness or “loss of pleasure”
3	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*")
4	1 AND 2 AND 3

Table 3: search strategy for PEDro database.

	Search line
1	"multiple sclerosis" and depress*

BMJ Open

Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055796.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2022
Complete List of Authors:	Lyons, Julia; The University of Melbourne School of Population and Global Health, Disability and Health Unit Campese, Stephanie; The University of Melbourne School of Population and Global Health, Disabiity and Health Unit Learmonth, Yvonne ; Murdoch University, Discipline of Exercise Science & Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute; Perron Institute for Neurological and Translational Science Metse, Alexandra; University of Newcastle, School of Psychology; University of the Sunshine Coast, School of Health and Behavioural Sciences Kermode, Allan; Perron Institute for Neurological and Translational Science; Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute Karahalios, Amalia; The University of Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics Marck, C; The University of Melbourne School of Population and Global Health, Disability and Health Unit
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY

Title: Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

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Word count: 3565

ABSTRACT

Background

Comorbid depression is prevalent in people with multiple sclerosis (MS). Depression is commonly untreated or undertreated and there is a need for effective and safe interventions. Current guidelines recommend psychological and pharmaceutical interventions for the management of depression in people with MS. However, current research suggests other interventions, such as exercise, could also be effective. The comparative efficacy and safety of intervention modalities have not been established in the literature.

We plan to conduct a systematic review and network meta-analysis to compare efficacy and safety of psychological, pharmaceutical, physical, and magnetic stimulation interventions for depression in people with MS.

Methods:

We will search seven key databases with search terms revolving around three concepts: MS, depression, and randomised controlled trials. Included studies will be randomised controlled trials, where the participants are people with MS people that are randomised to receive one of the aforementioned intervention types. For a trial to be included, depression or depressive symptoms will be the primary outcome, only outcome, or secondary outcome with an *a priori* power calculation. Screening of the citations and full text articles, data extraction, and risk of bias assessment (using the Risk of Bias 2 tool - RoB 2) will be conducted by two independent reviewers. We plan to pool the trials using pairwise and network meta-analysis. For the pairwise meta-analyses, we will fit a random effects model. For the network meta-analysis, we

will fit a frequentist multivariate random effects model. For the pairwise and network meta-analysis models, efficacy will be measured using a standardised mean difference, and safety using an odds ratio. If possible, we will provide summary measures including forest plots, a geometry of the network, surface under the cumulative ranking curve, and a league table. Subgroup analysis will be performed if possible, using pre-planned variables.

Review registration:

PROSPERO registration number CRD42020209803.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This will be the first systematic review and network meta-analysis to quantify the comparative efficacy, safety, and tolerability of interventions for depression in people with MS.
- Eligibility criteria include randomised controlled trials which are limited to depression as the primary outcome, only outcome, or secondary outcome with a power analysis.
- The review will aim to simultaneously compare intervention types that are used in both clinical and research settings.
- To meet the transitivity assumption, trials that include participants with treatment resistant/refractory depression will be excluded.

KEYWORDS: multiple sclerosis, depression or depressive symptoms, network meta-analysis, systematic review.

ARTICLE TYPE: protocol

INTRODUCTION:

Multiple Sclerosis (MS) is a chronic, immune mediated and neurodegenerative disease characterised by the formation of destructive lesions predominantly involving myelinated axons within the central nervous system [1]. There are a broad range of symptoms attributed to the multifocal lesions distinctive of MS including depression and depressive symptoms, pain, fatigue, impaired gait, incontinence, impaired vision, and spasticity [2]. Depression can be particularly burdensome, and affects up to 50% of people with MS [3]. Depressive symptoms in people with MS are reported to impact adherence to disease modifying therapies [4], and increase pain sensitivity [2]. Further, reduced participation in work and depressive symptoms are associated with poor health related quality of life [5] in people with MS. Major depressive disorder is the most commonly diagnosed depressive disorder [6]. It is defined as experiencing a minimum of five of the following symptoms within a two-week period: depressed mood or lack of pleasure, feelings of worthlessness/guilt, fatigue, appetite or weight changes, psychomotor agitation, diminished concentration, feelings of worthlessness/guilt, suicidality and sleep difficulties [6]. Depressive symptoms which do not meet the definition of major depressive disorder are even more prevalent in people with MS, and commonly require treatment [7]. Furthermore, people with MS who have moderate-to-severe depressive symptoms have been reportedly underdiagnosed and undertreated [5 8]. The aetiology of depression and depressive symptoms in people with MS is not yet fully understood [9] but due to the multitude of effects, safe and effective interventions are required.

Guidelines for treating depression in people with MS suggest that a combination of psychological and pharmaceutical interventions is the most effective therapy in reducing

levels of depressive symptoms [10 11]. Specifically, these guidelines recommend pharmacotherapies such as antidepressants, psychological treatments such as cognitive behavioural therapy, and, where applicable and safe, exercise-based interventions [11]. However, some interventions, including third wave cognitive and behavioural (psychological) interventions that emphasise the role of mindfulness [12] and specific types of exercise such as Pilates [13], have not been included in these guidelines. The American Association of Neurology review to inform guidelines [14] noted the scarcity of trials to treat depression in people with MS and therefore a lack of strong evidence. Following this review [14], several studies have sought to address the treatment of depressive symptoms in MS. Evidence from systematic reviews reported that exercise [15 16] and mindfulness-based interventions [17] when compared to waitlist/usual care have a moderate effect at reducing depressive symptoms in people with MS. However, it is unclear how these interventions compare in terms of efficacy and safety.

Network meta-analysis enables the comparison of multiple interventions by simultaneously combining direct and indirect evidence [18]. Synthesising the evidence in this manner will enable a comprehensive understanding of how interventions compare (in terms of efficacy and safety), which should greatly enhance evidence-based decision making for people with MS and their clinicians on how best to manage depressive symptoms. The major assumption underpinning network meta-analysis methods ensures that we can compare two interventions via a third (common) intervention and is referred to as transitivity. Transitivity requires that the trials included in the network meta-analysis are considered to be 'jointly randomisable', that the common intervention (comparator) from the different trials is similar enough to be combined, and that the characteristics associated with the effect of the intervention are similar

across the included trials[19 20].

This article outlines the protocol for a systematic review and network meta-analysis to compare the effectiveness and safety of intervention modalities, or combination of modalities, in reducing depressive symptoms in adults with MS. This review is the first stage of a larger project that aims to provide guidance for public health researchers on the design and analysis of systematic reviews with network meta-analysis and future trials in MS.

METHODS

This systematic review protocol is registered with The International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020209803) and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-Analysis (PRISMA NMA) statement [21], see supplementary file 1 for checklist.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, or reporting of the research in this article.

Eligibility criteria

Participants

Adults (aged 18 years or older) of any gender who have been diagnosed with any type of MS.

Interventions

We will include interventions that aim to alleviate depressive symptoms in people with MS, including:

Psychological interventions delivered with the intention of treating depressive symptoms, informed by psychological theories or principle(s) and a) implemented by a psychiatrist/psychologist or other mental health clinician or b) manualized, with content developed by a mental health clinician or researcher, e.g., online/app or web-based intervention.

Pharmaceutical interventions that involve the use of medication or drugs for the intention of treating depressive symptoms at a therapeutic dose according to the manufacturer guidelines (if available).

Physical interventions including physiotherapy and physical activity (any bodily movement that results in energy expenditure) including exercise, aimed at treating depressive symptoms. Subtypes of physical activity will be included.

Electromagnetic stimulations involve the use of targeted electromagnetic stimulation to stimulate areas of the brain to reduce depressive symptoms. Subtypes include transcranial magnetic stimulation, and transcranial direct current stimulation.

Combinations of the above-mentioned intervention modalities will be included and will form new categories. Any interventions that are specific to people with treatment resistant depression/refractory depression will not be included (e.g., electroconvulsive therapy). These treatments will be excluded because they will compromise the transitivity assumption (i.e.,

that all interventions are considered to be 'jointly randomisable'). Treatments for people with treatment resistant depression would not be considered to meet this assumption because they are not considered first line treatments for people with MS [18].

Grouping of interventions will depend on the eligible trials. The four broad categories will be split into smaller sub-categories, e.g., psychological interventions could have a sub-category of mindfulness-based interventions, similarly pharmaceutical interventions could have a sub-category of serotonin reuptake inhibitors.

Comparator

We will consider the following comparators: any intervention modality included in the above list, placebo, wait-list control, treatment as usual, or no treatment. Classification of comparator groups will depend on the type of comparator used in the original randomised trial. Common types of comparators can include, but are not limited to, placebo, wait-list control, treatment as usual, and no treatment control. These comparator groups do not have similar methodology and can influence participant outcome in altering ways. Therefore, for this protocol and subsequent systematic review and network meta-analysis, we will adopt the recommended framework for classification of comparator groups [22]. The groups will be (1) minimal treatment control, active control, or similar; (2) wait-list control, treatment as usual, or no treatment; and (3) pill placebo.

Outcome

We will include trials that specified that depressive symptoms were the primary (or only)

outcome, or as a secondary outcome where an *a-priori* power calculation was provided. The severity of depressive symptoms must have been measured by a validated self-report questionnaire or by clinician interview. Although depression and depressive symptoms are likely to be measured and defined differently across trials [23], we have chosen to accept all types of standardised measures or clinical interviews. To assess the acute efficacy of the intervention, depressive symptoms must be measured within two weeks of completion of the intervention. We will also assess the long-term efficacy of the intervention using trials that have measured depressive symptoms at approximately six months post-intervention (within 4-8 months). To measure long term efficacy and safety of interventions for reducing depressive symptoms we will also extract the relevant data that is measured 12 or more months post-intervention. Any trials that have measured just one of the aforementioned time points will still be eligible for inclusion.

Safety and tolerability outcomes will include:

- Frequency of serious adverse events (SAEs) defined as an untoward occurrence of a medical event that is fatal, life-threatening, requires hospitalisation or prolonging of existing hospitalisation and/or persistent disability [24-27].
- Frequency of adverse events (AEs) defined as the occurrence of an undesirable event occurring during the study duration even if the event was not considered to be related to the intervention [24-27].
- Tolerability of the intervention will be assessed as the number of participants who discontinue the study and/or have reduced compliance due to SAE or AEs [24 28].

The events will be measured as dichotomous outcomes during the intervention period. We

will consider combining the SAE's and AE's if they are rare events in the trials.

Types of Studies

We will include randomised controlled trials, including multi-arm randomised trials. Quasi-randomised, cluster and cross-over trials will not be included.

Search strategy

We will search the following seven databases: EMBASE, Medline, Cochrane CENTRAL, APA PsycInfo, Web of Science, CINAHL and PEDro. Note that EMBASE, Medline, Cochrane CENTRAL and APA PsycInfo will be searched through the Ovid platform. The search strategy was developed in conjunction with a medical librarian at the University of Melbourne, Australia, as well as a clinical physiotherapist (YL) who works with people with MS, and a clinical psychologist (AM). The search terms relate to three main concepts of MS, depression, and randomised controlled trials. Search strategies for all databases are listed in supplementary file 2. All databases were searched from inception to the 11th of July 2020 and the search will be updated to include articles published up to the 31st of December 2021. We will also search the reference lists of relevant systematic reviews to identify any randomised trials that might have been missed in the database search. Trials will be limited to those published in English.

Study selection

Results from the search strategy will be uploaded to Endnote [29] where duplicates will be removed. The remaining citations will be uploaded into the software management system

Covidence [30] where any additional duplicates will be removed. Covidence will then be used for title and abstract screening and full text screening by at least two independent reviewers with any conflicts resolved by a third reviewer.

Data Extraction

Data will be extracted using a data extraction tool developed for this review using Excel software by at least two independent reviewers, with conflicts resolved by a third reviewer. If data were missing from the published article the corresponding author will be contacted. We will not look at other sources of citations such as grey literature, clinical trial registries, or protocol papers. The extracted data will relate to the following categories:

- Study characteristics: first author's last name, year of publication, year of baseline recruitment, method of recruitment, method of randomisation, inclusion criteria (e.g., a baseline level of depression cut off for inclusion into study).
- Sample demographics: sample size, number of participants randomised, baseline characteristics such as diagnosis of MS, age (years), sex, years since diagnosis of MS, level of disability, and disability tool.
- Intervention and comparator characteristics: type, frequency of intervention/treatment, duration of intervention/treatment, and dose of intervention/treatment. We will use TIDieR for clear reporting of the characteristics of the interventions and comparators [31].
- Efficacy outcome data: type of outcome measurement scale, mean and standard deviation of depressive symptom score at baseline, post-intervention, at six months post-intervention, and at 12 months post-intervention (if available).
- Safety and tolerability data: type and number of SAEs and AEs, number of participants that

discontinue participation due to an SAE or AE or discontinue participation for other reasons during the intervention. Safety and tolerability data will be extracted for each trial arm and time point where available.

- Data relating to the risk of bias assessment: randomisation process, allocation concealment, deviations from intended treatment, baseline characteristics differences, missing outcome data, appropriateness of outcome measurement, potential influence in outcome assessment, and selectively reporting results.

Risk of bias assessment

We will use the RoB 2 to assess the risk of bias for each study that meets the eligibility criteria [32]. This tool evaluates the risk of bias in five key domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The RoB 2 tool provides an overall assessment of the risk of bias in the study using three categories: low risk, some concerns or high risk of bias. At least two independent reviewers will assess the risk of bias in each study with any conflicts between judgements resolved by a third reviewer. In this systematic review and network meta-analysis there will be an inherent difference in the overall risk of bias between trials due to the type of intervention. Blinding of the participants to the assigned intervention is difficult in some study designs and interventions. For example, in a trial that randomised participants to exercise and wait-list control, participants will be aware of the treatment arm that they were allocated to. However, in a trial that randomised participants to an anti-depressant and placebo, participants are unlikely to be aware which treatment they were allocated. As well, blinding of the outcome assessors can also be difficult in these trials as depressive symptoms

are typically measured using self-reported tools. Despite this inherent difference we have chosen not to deviate from the protocol of the RoB 2 tool or alter the tool in any way.

Data synthesis

Characteristics of the included trials

We will generate descriptive statistics for the sample populations to understand the demographics of the review participants across all eligible trials. These descriptive statistics will describe key clinical and methodological characteristics such as age, sex, type of MS, and type of intervention modality.

Outcome data

We will have two primary and two secondary outcomes.

Primary outcomes:

(1) efficacy of the interventions (reduction of depressive symptoms) measured immediately post-intervention and quantified using standardised mean difference [33], and

(2) safety of the interventions (SAEs, AEs and tolerability) measured immediately post-intervention and quantified using odds ratios.

Secondary outcomes:

(1) efficacy of the interventions (reduction of depressive symptoms) measured immediately six months post-intervention (between four and eight months) and quantified

using standardised mean differences;

(2) safety of the interventions (SAEs, AEs and tolerability) measured six months post intervention (between four and eight months) and quantified using odds ratios;

(3) efficacy of intervention (reduction of depressive symptoms) measured 12 months post-intervention (12 months or longer) and quantified using standardised mean differences;

(4) safety of interventions (SAEs, AEs and tolerability) measured 12 months post-intervention (12 months or longer) and quantified using odds ratios.

Pairwise Meta-analysis

First, we will pool the data that compare the same major category of intervention modality (i.e., psychological, pharmaceutical, physical, electromagnetic stimulation therapies or combination) to each other or to placebo/usual care by fitting a random effects pairwise meta-analysis model and using the restricted maximum likelihood estimator to estimate the between study heterogeneity. The random effects model will assume that the underlying intervention effects across the trials are similar but not identical allowing an estimation of the heterogeneity in the model [34]. This will be performed for both the efficacy outcome, using the standardised mean difference, and the safety outcome, using odds ratios. Effect sizes will be presented with their corresponding 95% confidence intervals. Heterogeneity will be estimated using the I^2 and τ^2 statistics [35].

Network meta-analysis model

We will fit a multivariate meta-analysis contrast-based model within a frequentist framework using the network package in Stata [36]. We will assume common heterogeneity across the

trials.

Geometry of the network

We will generate a network diagram, separately for efficacy and safety, to visualise the network of intervention modalities. The nodes (or intervention modalities) will represent the total number of trials in each treatment group; the larger the size of the node the larger the sample size. The edges of the lines connecting each node will represent the precision of the evidence, i.e., the thicker the line the more precise evidence. Figure 1 shows an example of the possible network structure with the major intervention modalities included.

<insert figure 1 here>

Assessment of transitivity in the network

The transitivity assumption, which underpins the method of a network meta-analysis, requires that the characteristics associated with the effect of the intervention are similar across the included trials [18]. Participant characteristics (for example, age, sex, type of MS, level of disability, and years since diagnosis of MS) could indicate violation of the transitivity assumption [18]. To assess this requirement of the transitivity assumption the characteristics of the participants recruited into each trial will be summarised and compared. If this requirement of the transitivity assumption is thought to be violated, we will undertake narrative synthesis of the data (described below) and possibly pair wise meta-analyses (described above). If we find no reason to suggest that violation of the transitivity assumption, we will synthesise the available evidence using network meta-analysis techniques. We will fit a random effects

network meta-analysis model in a frequentist framework and assume a common heterogeneity parameter across the eligible trials. The random effects model assumes that the variation between trials could be a result of heterogeneity and not from sampling variation [18 36].

Summary Statistics and presentation of results

We will present forest plots that will include pooled estimates from the direct and mixed intervention effects and league tables with the summary standardised mean differences or odds ratios for all pairwise comparisons [37 38]. We will use a predictive interval plot to show the grouped intervention modality standardised mean differences or odds ratios in a future trial [37]. We will then obtain a hierarchy of the intervention modalities using the surface under the cumulative ranking curve (SUCRA). SUCRA uses probabilities to determine which intervention modality is most likely to be the most effective at reducing depressive symptoms in people with MS. A probability of 1 (or 100%) is indicative of the stated intervention modality being the most effective intervention modality, conversely, a probability of 0 (or 0%) is indicative of the stated intervention modality being the least effective [38].

Assessment of inconsistency

Consistency is a measure of the agreement between direct evidence and indirect evidence. If inconsistency occurs in a network it may suggest that there is significant heterogeneity and that the transitivity assumption could be violated [18 34]. Using the network meta-analysis package in Stata [36] a consistency and an inconsistency model can be separately fitted to assess whether the direct and indirect evidence are in agreement for each outcome. These models can provide information to help ascertain if the direct and indirect evidence are in statistical

agreement [39]. If there is evidence of inconsistency in the network, we will use the side-splitting approach to identify if there is a specific modality of interventions that contribute to inconsistency in the network [36 39]. This will enable us to further investigate the possible sources of inconsistency [40].

Subgroup analysis

We will conduct separate subgroup analyses for the efficacy and the safety outcome if there is substantial heterogeneity or inconsistency and the data allows this.

For the efficacy outcome, we will assess the following subgroups:

- Year of baseline recruitment; to determine if treatments have become more effective over time.
- Severity of depression at baseline (i.e., trials that recruited based on level of depression vs trials that did not); to determine whether interventions are efficacious when a level of depressive symptoms is present.
- Comparison of self-reported outcome measures vs clinical assessment; to determine if there is a difference in the efficacy of the treatment due to the measurement of the outcome.
- Level of disability at enrolment (e.g., as measured by Patient determined disease steps, Expanded Disability Disease Scale: categorised in mild, moderate or severe disability); to determine if level of disability is associated with the efficacy of the intervention.
- Whether the intervention was conducted in a dose according to guidelines that

exist for that type of interventions (e.g., exercise guidelines for people with MS); to determine if a minimum dose is associated with the efficacy of the intervention. For the safety and tolerability outcome we will undertake subgroup analyses by year of baseline recruitment and level of disability at enrolment.

Assessment of small study effects

We will use the comparison-adjusted [37] and contour-enhanced [41] funnel plots to investigate whether results in imprecise trials differ from those in more precise trials. Network meta-regression models will be used to investigate associations between study sample size and effect size [42].

Narrative synthesis

If we are unable to conduct a NMA or pairwise meta-analyses we plan to conduct a narrative synthesis to assess which interventions reported the outcomes of interest and if there were any patterns relating to specific interventions, or gaps in the literature.

ETHICS AND DISSEMINATION

Ethical approval is not needed for a systematic review and network meta-analysis as we will use aggregated data from previously published randomised trials. The dissemination of the results of the systematic review and network meta-analysis will include publishing in a peer reviewed journals to apprise MS researchers and clinicians, and people with MS. The results of the systematic review and network meta-analysis have the potential to inform future

treatment guidelines for depression in people with MS. Further, the review may highlight any gaps in the literature and provide recommendations for the conduct and reporting of future randomised trials.

AUTHORS CONTRIBUTIONS

AK and CHM conceived the study. AK, CHM, JL, SC, YL, AGK and AM contributed to the study design. JL drafted the manuscript and AK, CHM, SC, YL edited the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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FIGURE LEGEND:

Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

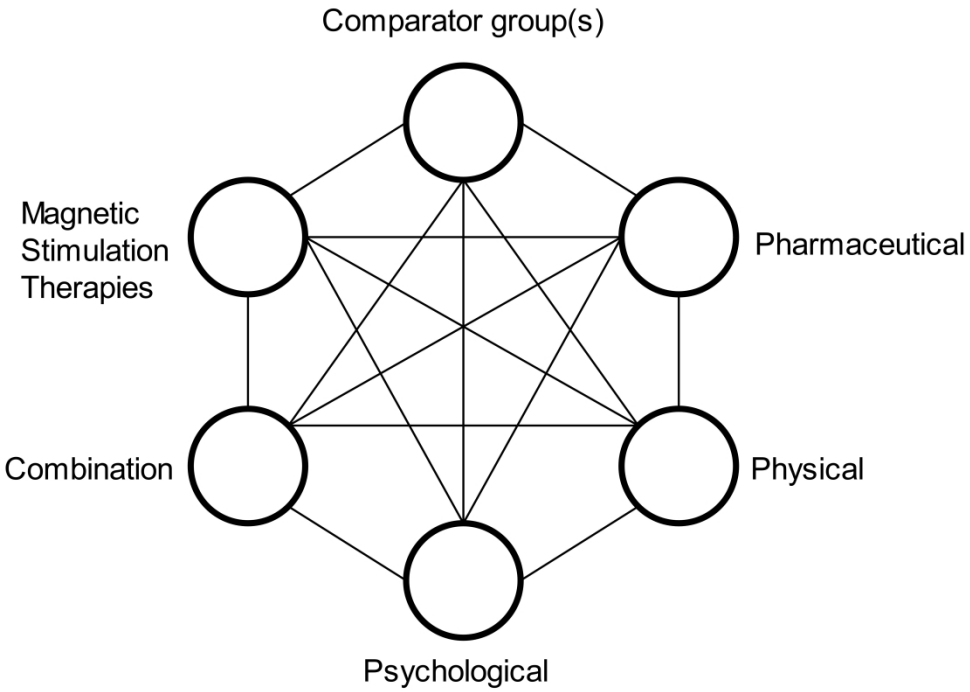

Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

2053x1443mm (72 x 72 DPI)

SUPPLEMENTARY FILE 1:

Table 1: PRISMA-NMA guidelines checklist.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
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. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	6-10
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.	9
Search	8	Present full electronic search strategy for at least one database,	Supplementary file

		including any limits used, such that it could be repeated.	
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).	10-11
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.	11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11-12
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	15
Risk of bias within 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.	12-13
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	16
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* •*Assessment of model fit.*	14-18
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	15-16
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).	18
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	17-18

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.	NA
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
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.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	NA

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).	NA
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). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			19
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. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this

SUPPLEMENTARY FILE 2:

Complete database search strategy

Supplementary Table 1: Search strategy for databases EMBASE, APA PsycInfo, MEDLINE, Cochrane CENTRAL, searched through the Ovid platform.

	Search terms
1	multiple sclerosis.ti,ab.
2	exp multiple sclerosis/
3	1 or 2
4	exp depression/
5	(depress* or mood disorder or despair or misery or unhappiness or dysthymia or dysphor* or seasonal affective disorder or affective disorder or sadness or loss of pleasure).ti,ab.
6	4 or 5
7	exp randomized controlled trial/
8	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*").ti,ab.
9	7 or 8
10	3 AND 6 AND 9

Supplementary Table 2: Search strategy for databases CINAHL through the Scopus platform*, and Web of Science searched through the Web of Science platform*.

	Search Term
1	"multiple sclerosis"
2	depress* or "mood disorder*" or despair or misery or unhappiness or dysthymia or dysphor* or "seasonal affective disorder" or "affective disorder" or sadness or "loss of pleasure"
3	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*")
4	1 AND 2 AND 3

*The search strategy for Scopus platform and Web of Science platform is the same.

Supplementary Table 3: Search strategy for PEDro database.

	Search line
1	"multiple sclerosis" and depress*

BMJ Open

Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055796.R2
Article Type:	Protocol
Date Submitted by the Author:	18-May-2022
Complete List of Authors:	Lyons, Julia; The University of Melbourne School of Population and Global Health, Disability and Health Unit Campese, Stephanie; The University of Melbourne School of Population and Global Health, Disabiity and Health Unit Learmonth, Yvonne ; Murdoch University, Discipline of Exercise Science & Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute; Perron Institute for Neurological and Translational Science Metse, Alexandra; University of Newcastle, School of Psychology; University of the Sunshine Coast, School of Health and Behavioural Sciences Kermode, Allan; Perron Institute for Neurological and Translational Science; Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute Karahalios, Amalia; The University of Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics Marck, C; The University of Melbourne School of Population and Global Health, Disability and Health Unit
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY

Title: Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

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Word count: 3565

ABSTRACT

Background

Comorbid depression is prevalent in people with multiple sclerosis (MS). Depression is commonly untreated or undertreated, thus, there is a need for effective and safe interventions and current guidelines recommend psychological and pharmaceutical interventions for people with MS. However, research suggests that other interventions, such as exercise, could also be effective. The comparative efficacy and safety of intervention modalities have not been quantified.

We plan to conduct a systematic review and network meta-analysis to compare efficacy and safety of psychological, pharmaceutical, physical, and magnetic stimulation interventions for depression in people with MS.

Methods and analysis:

We will search EMBASE, Medline, Cochrane CENTRAL, APA PsycInfo, Web of Science, CINAHL and PEDro from inception to 31/12/2021. Search terms will stem from three concepts: MS, depression, and randomised controlled trials. Included studies will be randomised controlled trials, where participants are people with MS randomised to receive one of the aforementioned intervention types, and depression or depressive symptoms is the primary outcome, only outcome, or secondary outcome with an *a priori* power calculation. Screening, data extraction, and risk of bias assessment (using the Risk of Bias 2 tool) will be conducted independently by two reviewers. If possible, we will synthesise the evidence by fitting a frequentist network meta-analysis model with multivariate random effects, or a pairwise random-effects meta-analysis model. For each model, efficacy will be measured

using a standardised mean difference, and safety using an odds ratio. We plan to provide summary measures including forest plots, a geometry of the network, surface under the cumulative ranking curve, and a league table, and perform subgroup analyses. Otherwise, a narrative review will be provided.

Ethics and dissemination:

Ethics is not required for a systematic review and network meta-analysis. Results will be published in a peer reviewed journal.

Review registration:

PROSPERO registration CRD42020209803.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Advanced network meta-analysis methods together with sensitivity and subgroup analyses will comprehensively quantify the comparative efficacy, safety, and tolerability of several interventions for depression in people with MS.
- This systematic review will use a detailed search strategy and pre-specified eligibility criteria, with all steps of the review process conducted independently by two reviewers.
- Eligibility criteria include randomised controlled trials which are limited to depression as the primary outcome, only outcome, or secondary outcome with a power analysis.
- To meet the transitivity assumption, trials that include participants with treatment resistant/refractory depression will be excluded.

KEYWORDS: multiple sclerosis, depression or depressive symptoms, network meta-analysis, systematic review.

ARTICLE TYPE: protocol

INTRODUCTION:

Multiple Sclerosis (MS) is a chronic, immune mediated and neurodegenerative disease characterised by the formation of destructive lesions predominantly involving myelinated axons within the central nervous system [1]. There are a broad range of symptoms attributed to the multifocal lesions distinctive of MS including depression and depressive symptoms, pain, fatigue, impaired gait, incontinence, impaired vision, and spasticity [2]. Depression can be particularly burdensome, and affects up to 50% of people with MS [3]. Depressive symptoms in people with MS are reported to impact adherence to disease modifying therapies [4], and increase pain sensitivity [2]. Further, reduced participation in work and depressive symptoms are associated with poor health related quality of life [5] in people with MS. Major depressive disorder is the most commonly diagnosed depressive disorder [6]. It is defined as experiencing a minimum of five of the following symptoms within a two-week period: depressed mood or lack of pleasure, feelings of worthlessness/guilt, fatigue, appetite or weight changes, psychomotor agitation, diminished concentration, feelings of worthlessness/guilt, suicidality and sleep difficulties [6]. Depressive symptoms which do not meet the definition of major depressive disorder are even more prevalent in people with MS, and commonly require treatment [7]. Furthermore, people with MS who have moderate-to-severe depressive symptoms have been reportedly underdiagnosed and undertreated [5 8]. The aetiology of depression and depressive symptoms in people with MS is not yet fully understood [9] but due to the multitude of effects, safe and effective interventions are required.

Guidelines for treating depression in people with MS suggest that a combination of psychological and pharmaceutical interventions is the most effective therapy in reducing

levels of depressive symptoms [10 11]. Specifically, these guidelines recommend pharmacotherapies such as antidepressants, psychological treatments such as cognitive behavioural therapy, and, where applicable and safe, exercise-based interventions [11]. However, some interventions, including third wave cognitive and behavioural (psychological) interventions that emphasise the role of mindfulness [12] and specific types of exercise such as Pilates [13], have not been included in these guidelines. The American Association of Neurology review to inform guidelines [14] noted the scarcity of trials to treat depression in people with MS and therefore a lack of strong evidence. Following this review [14], several studies have sought to address the treatment of depressive symptoms in MS. Evidence from systematic reviews reported that exercise [15 16] and mindfulness-based interventions [17] when compared to waitlist/usual care have a moderate effect at reducing depressive symptoms in people with MS. However, it is unclear how these interventions compare in terms of efficacy and safety.

Network meta-analysis enables the comparison of multiple interventions by simultaneously combining direct and indirect evidence [18]. Synthesising the evidence in this manner will enable a comprehensive understanding of how interventions compare (in terms of efficacy and safety), which should greatly enhance evidence-based decision making for people with MS and their clinicians on how best to manage depressive symptoms. The major assumption underpinning network meta-analysis methods ensures that we can compare two interventions via a third (common) intervention and is referred to as transitivity. Transitivity requires that the trials included in the network meta-analysis are considered to be 'jointly randomisable', that the common intervention (comparator) from the different trials is similar enough to be combined, and that the characteristics associated with the effect of the intervention are similar

across the included trials[19 20].

This article outlines the protocol for a systematic review and network meta-analysis to compare the effectiveness and safety of intervention modalities, or combination of modalities, in reducing depressive symptoms in adults with MS. This review is the first stage of a larger project that aims to provide guidance for public health researchers on the design and analysis of systematic reviews with network meta-analysis and future trials in MS.

METHODS

This systematic review protocol is registered with The International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020209803) and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-Analysis (PRISMA NMA) statement [21], see supplementary file 1 for checklist.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, or reporting of the research in this article.

Eligibility criteria

Participants

Adults (aged 18 years or older) of any gender who have been diagnosed with any type of MS.

Interventions

We will include interventions that aim to alleviate depressive symptoms in people with MS, including:

Psychological interventions delivered with the intention of treating depressive symptoms, informed by psychological theories or principle(s) and a) implemented by a psychiatrist/psychologist or other mental health clinician or b) manualized, with content developed by a mental health clinician or researcher, e.g., online/app or web-based intervention.

Pharmaceutical interventions that involve the use of medication or drugs for the intention of treating depressive symptoms at a therapeutic dose according to the manufacturer guidelines (if available).

Physical interventions including physiotherapy and physical activity (any bodily movement that results in energy expenditure) including exercise, aimed at treating depressive symptoms. Subtypes of physical activity will be included.

Electromagnetic stimulations involve the use of targeted electromagnetic stimulation to stimulate areas of the brain to reduce depressive symptoms. Subtypes include transcranial magnetic stimulation, and transcranial direct current stimulation.

Combinations of the above-mentioned intervention modalities will be included and will form new categories. Any interventions that are specific to people with treatment resistant depression/refractory depression will not be included (e.g., electroconvulsive therapy). These treatments will be excluded because they will compromise the transitivity assumption (i.e.,

that all interventions are considered to be 'jointly randomisable'). Treatments for people with treatment resistant depression would not be considered to meet this assumption because they are not considered first line treatments for people with MS [18].

Grouping of interventions will depend on the eligible trials. The four broad categories will be split into smaller sub-categories, e.g., psychological interventions could have a sub-category of mindfulness-based interventions, similarly pharmaceutical interventions could have a sub-category of serotonin reuptake inhibitors.

Comparator

We will consider the following comparators: any intervention modality included in the above list, placebo, wait-list control, treatment as usual, or no treatment. Classification of comparator groups will depend on the type of comparator used in the original randomised trial. Common types of comparators can include, but are not limited to, placebo, wait-list control, treatment as usual, and no treatment control. These comparator groups do not have similar methodology and can influence participant outcome in altering ways. Therefore, for this protocol and subsequent systematic review and network meta-analysis, we will adopt the recommended framework for classification of comparator groups [22]. The groups will be (1) minimal treatment control, active control, or similar; (2) wait-list control, treatment as usual, or no treatment; and (3) pill placebo.

Outcome

We will include trials that specified that depressive symptoms were the primary (or only)

outcome, or as a secondary outcome where an *a-priori* power calculation was provided. The severity of depressive symptoms must have been measured by a validated self-report questionnaire or by clinician interview. Although depression and depressive symptoms are likely to be measured and defined differently across trials [23], we have chosen to accept all types of standardised measures or clinical interviews. To assess the acute efficacy of the intervention, depressive symptoms must be measured within two weeks of completion of the intervention. We will also assess the long-term efficacy of the intervention using trials that have measured depressive symptoms at approximately six months post-intervention (within 4-8 months). To measure long term efficacy and safety of interventions for reducing depressive symptoms we will also extract the relevant data that is measured 12 or more months post-intervention. Any trials that have measured just one of the aforementioned time points will still be eligible for inclusion.

Safety and tolerability outcomes will include:

- Frequency of serious adverse events (SAEs) defined as an untoward occurrence of a medical event that is fatal, life-threatening, requires hospitalisation or prolonging of existing hospitalisation and/or persistent disability [24-27].
- Frequency of adverse events (AEs) defined as the occurrence of an undesirable event occurring during the study duration even if the event was not considered to be related to the intervention [24-27].
- Tolerability of the intervention will be assessed as the number of participants who discontinue the study and/or have reduced compliance due to SAE or AEs [24 28].

The events will be measured as dichotomous outcomes during the intervention period. We

will consider combining the SAE's and AE's if they are rare events in the trials.

Types of Studies

We will include randomised controlled trials, including multi-arm randomised trials. Quasi-randomised, cluster and cross-over trials will not be included.

Search strategy

We will search the following seven databases: EMBASE, Medline, Cochrane CENTRAL, APA PsycInfo, Web of Science, CINAHL and PEDro. Note that EMBASE, Medline, Cochrane CENTRAL and APA PsycInfo will be searched through the Ovid platform. The search strategy was developed in conjunction with a medical librarian at the University of Melbourne, Australia, as well as a clinical physiotherapist (YL) who works with people with MS, and a clinical psychologist (AM). The search terms relate to three main concepts of MS, depression, and randomised controlled trials. Search strategies for all databases are listed in supplementary file 2. All databases were searched from inception to the 11th of July 2020 and the search will be updated to include articles published up to the 31st of December 2021. We will also search the reference lists of relevant systematic reviews to identify any randomised trials that might have been missed in the database search. Trials will be limited to those published in English.

Study selection

Results from the search strategy will be uploaded to Endnote [29] where duplicates will be removed. The remaining citations will be uploaded into the software management system

Covidence [30] where any additional duplicates will be removed. Covidence will then be used for title and abstract screening and full text screening by at least two independent reviewers with any conflicts resolved by a third reviewer.

Data Extraction

Data will be extracted using a data extraction tool developed for this review using Excel software by at least two independent reviewers, with conflicts resolved by a third reviewer. If data were missing from the published article the corresponding author will be contacted. We will not look at other sources of citations such as grey literature, clinical trial registries, or protocol papers. The extracted data will relate to the following categories:

- Study characteristics: first author's last name, year of publication, year of baseline recruitment, method of recruitment, method of randomisation, inclusion criteria (e.g., a baseline level of depression cut off for inclusion into study).
- Sample demographics: sample size, number of participants randomised, baseline characteristics such as diagnosis of MS, age (years), sex, years since diagnosis of MS, level of disability, and disability tool.
- Intervention and comparator characteristics: type, frequency of intervention/treatment, duration of intervention/treatment, and dose of intervention/treatment. We will use TIDieR for clear reporting of the characteristics of the interventions and comparators [31].
- Efficacy outcome data: type of outcome measurement scale, mean and standard deviation of depressive symptom score at baseline, post-intervention, at six months post-intervention, and at 12 months post-intervention (if available).
- Safety and tolerability data: type and number of SAEs and AEs, number of participants that

discontinue participation due to an SAE or AE or discontinue participation for other reasons during the intervention. Safety and tolerability data will be extracted for each trial arm and time point where available.

- Data relating to the risk of bias assessment: randomisation process, allocation concealment, deviations from intended treatment, baseline characteristics differences, missing outcome data, appropriateness of outcome measurement, potential influence in outcome assessment, and selectively reporting results.

Risk of bias assessment

We will use the RoB 2 to assess the risk of bias for each study that meets the eligibility criteria [32]. This tool evaluates the risk of bias in five key domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The RoB 2 tool provides an overall assessment of the risk of bias in the study using three categories: low risk, some concerns or high risk of bias. At least two independent reviewers will assess the risk of bias in each study with any conflicts between judgements resolved by a third reviewer. In this systematic review and network meta-analysis there will be an inherent difference in the overall risk of bias between trials due to the type of intervention. Blinding of the participants to the assigned intervention is difficult in some study designs and interventions. For example, in a trial that randomised participants to exercise and wait-list control, participants will be aware of the treatment arm that they were allocated to. However, in a trial that randomised participants to an anti-depressant and placebo, participants are unlikely to be aware which treatment they were allocated. As well, blinding of the outcome assessors can also be difficult in these trials as depressive symptoms

are typically measured using self-reported tools. Despite this inherent difference we have chosen not to deviate from the protocol of the RoB 2 tool or alter the tool in any way.

Data synthesis

Characteristics of the included trials

We will generate descriptive statistics for the sample populations to understand the demographics of the review participants across all eligible trials. These descriptive statistics will describe key clinical and methodological characteristics such as age, sex, type of MS, and type of intervention modality.

Outcome data

We will have two primary and two secondary outcomes.

Primary outcomes:

(1) efficacy of the interventions (reduction of depressive symptoms) measured immediately post-intervention and quantified using standardised mean difference [33], and

(2) safety of the interventions (SAEs, AEs and tolerability) measured immediately post-intervention and quantified using odds ratios.

Secondary outcomes:

(1) efficacy of the interventions (reduction of depressive symptoms) measured immediately six months post-intervention (between four and eight months) and quantified

using standardised mean differences;

(2) safety of the interventions (SAEs, AEs and tolerability) measured six months post intervention (between four and eight months) and quantified using odds ratios;

(3) efficacy of intervention (reduction of depressive symptoms) measured 12 months post-intervention (12 months or longer) and quantified using standardised mean differences;

(4) safety of interventions (SAEs, AEs and tolerability) measured 12 months post-intervention (12 months or longer) and quantified using odds ratios.

Pairwise Meta-analysis

First, we will pool the data that compare the same major category of intervention modality (i.e., psychological, pharmaceutical, physical, electromagnetic stimulation therapies or combination) to each other or to placebo/usual care by fitting a random effects pairwise meta-analysis model and using the restricted maximum likelihood estimator to estimate the between study heterogeneity. The random effects model will assume that the underlying intervention effects across the trials are similar but not identical allowing an estimation of the heterogeneity in the model [34]. This will be performed for both the efficacy outcome, using the standardised mean difference, and the safety outcome, using odds ratios. Effect sizes will be presented with their corresponding 95% confidence intervals. Heterogeneity will be estimated using the I^2 and τ^2 statistics [35].

Network meta-analysis model

We will fit a multivariate meta-analysis contrast-based model within a frequentist framework using the network package in Stata [36]. We will assume common heterogeneity across the

trials.

Geometry of the network

We will generate a network diagram, separately for efficacy and safety, to visualise the network of intervention modalities. The nodes (or intervention modalities) will represent the total number of trials in each treatment group; the larger the size of the node the larger the sample size. The edges of the lines connecting each node will represent the precision of the evidence, i.e., the thicker the line the more precise evidence. Figure 1 shows an example of the possible network structure with the major intervention modalities included.

<insert figure 1 here>

Assessment of transitivity in the network

The transitivity assumption, which underpins the method of a network meta-analysis, requires that the characteristics associated with the effect of the intervention are similar across the included trials [18]. Participant characteristics (for example, age, sex, type of MS, level of disability, and years since diagnosis of MS) could indicate violation of the transitivity assumption [18]. To assess this requirement of the transitivity assumption the characteristics of the participants recruited into each trial will be summarised and compared. If this requirement of the transitivity assumption is thought to be violated, we will undertake narrative synthesis of the data (described below) and possibly pair wise meta-analyses (described above). If we find no reason to suggest that violation of the transitivity assumption, we will synthesise the available evidence using network meta-analysis techniques. We will fit a random effects

network meta-analysis model in a frequentist framework and assume a common heterogeneity parameter across the eligible trials. The random effects model assumes that the variation between trials could be a result of heterogeneity and not from sampling variation [18 36].

Summary Statistics and presentation of results

We will present forest plots that will include pooled estimates from the direct and mixed intervention effects and league tables with the summary standardised mean differences or odds ratios for all pairwise comparisons [37 38]. We will use a predictive interval plot to show the grouped intervention modality standardised mean differences or odds ratios in a future trial [37]. We will then obtain a hierarchy of the intervention modalities using the surface under the cumulative ranking curve (SUCRA). SUCRA uses probabilities to determine which intervention modality is most likely to be the most effective at reducing depressive symptoms in people with MS. A probability of 1 (or 100%) is indicative of the stated intervention modality being the most effective intervention modality, conversely, a probability of 0 (or 0%) is indicative of the stated intervention modality being the least effective [38].

Assessment of inconsistency

Consistency is a measure of the agreement between direct evidence and indirect evidence. If inconsistency occurs in a network it may suggest that there is significant heterogeneity and that the transitivity assumption could be violated [18 34]. Using the network meta-analysis package in Stata [36] a consistency and an inconsistency model can be separately fitted to assess whether the direct and indirect evidence are in agreement for each outcome. These models can provide information to help ascertain if the direct and indirect evidence are in statistical

agreement [39]. If there is evidence of inconsistency in the network, we will use the side-splitting approach to identify if there is a specific modality of interventions that contribute to inconsistency in the network [36 39]. This will enable us to further investigate the possible sources of inconsistency [40].

Subgroup analysis

We will conduct separate subgroup analyses for the efficacy and the safety outcome if there is substantial heterogeneity or inconsistency and the data allows this.

For the efficacy outcome, we will assess the following subgroups:

- Year of baseline recruitment; to determine if treatments have become more effective over time.
- Severity of depression at baseline (i.e., trials that recruited based on level of depression vs trials that did not); to determine whether interventions are efficacious when a level of depressive symptoms is present.
- Comparison of self-reported outcome measures vs clinical assessment; to determine if there is a difference in the efficacy of the treatment due to the measurement of the outcome.
- Level of disability at enrolment (e.g., as measured by Patient determined disease steps, Expanded Disability Disease Scale: categorised in mild, moderate or severe disability); to determine if level of disability is associated with the efficacy of the intervention.
- Whether the intervention was conducted in a dose according to guidelines that

exist for that type of interventions (e.g., exercise guidelines for people with MS); to determine if a minimum dose is associated with the efficacy of the intervention. For the safety and tolerability outcome we will undertake subgroup analyses by year of baseline recruitment and level of disability at enrolment.

Assessment of small study effects

We will use the comparison-adjusted [37] and contour-enhanced [41] funnel plots to investigate whether results in imprecise trials differ from those in more precise trials. Network meta-regression models will be used to investigate associations between study sample size and effect size [42].

Narrative synthesis

If we are unable to conduct a NMA or pairwise meta-analyses we plan to conduct a narrative synthesis to assess which interventions reported the outcomes of interest and if there were any patterns relating to specific interventions, or gaps in the literature.

ETHICS AND DISSEMINATION

Ethical approval is not needed for a systematic review and network meta-analysis as we will use aggregated data from previously published randomised trials. The dissemination of the results of the systematic review and network meta-analysis will include publishing in a peer reviewed journals to apprise MS researchers and clinicians, and people with MS. The results of the systematic review and network meta-analysis have the potential to inform future

treatment guidelines for depression in people with MS. Further, the review may highlight any gaps in the literature and provide recommendations for the conduct and reporting of future randomised trials.

AUTHORS CONTRIBUTIONS

AK and CHM conceived the study. AK, CHM, JL, SC, YL, AGK and AM contributed to the study design. JL drafted the manuscript and AK, CHM, SC, YL edited the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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FIGURE LEGEND:

Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

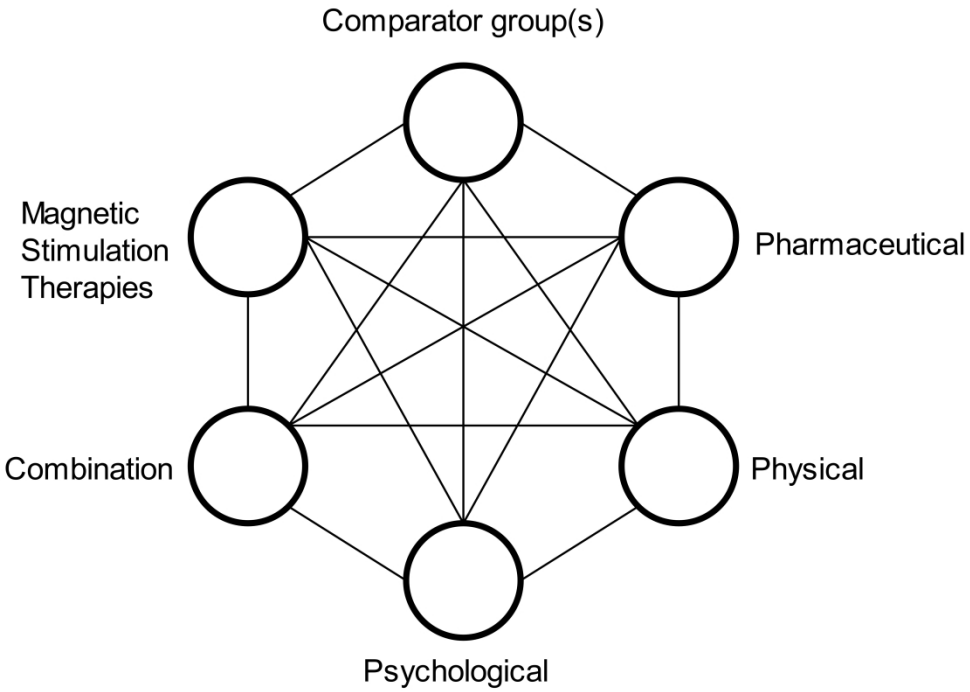

Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

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SUPPLEMENTARY FILE 1:

Table 1: PRISMA-NMA guidelines checklist.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
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. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	6-10
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.	9
Search	8	Present full electronic search strategy for at least one database,	Supplementary file

		including any limits used, such that it could be repeated.	
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).	10-11
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.	11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11-12
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	15
Risk of bias within 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.	12-13
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	16
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* •*Assessment of model fit.*	14-18
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	15-16
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).	18
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	17-18

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.	NA
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
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.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	NA

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).	NA
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). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			19
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. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this

SUPPLEMENTARY FILE 2:

Complete database search strategy

Supplementary Table 1: Search strategy for databases EMBASE, APA PsycInfo, MEDLINE, Cochrane CENTRAL, searched through the Ovid platform.

	Search terms
1	multiple sclerosis.ti,ab.
2	exp multiple sclerosis/
3	1 or 2
4	exp depression/
5	(depress* or mood disorder or despair or misery or unhappiness or dysthymia or dysphor* or seasonal affective disorder or affective disorder or sadness or loss of pleasure).ti,ab.
6	4 or 5
7	exp randomized controlled trial/
8	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*").ti,ab.
9	7 or 8
10	3 AND 6 AND 9

Supplementary Table 2: Search strategy for databases CINAHL through the Scopus platform*, and Web of Science searched through the Web of Science platform*.

	Search Term
1	"multiple sclerosis"
2	depress* or "mood disorder*" or despair or misery or unhappiness or dysthymia or dysphor* or "seasonal affective disorder" or "affective disorder" or sadness or "loss of pleasure"
3	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*")
4	1 AND 2 AND 3

*The search strategy for Scopus platform and Web of Science platform is the same.

Supplementary Table 3: Search strategy for PEDro database.

	Search line
1	"multiple sclerosis" and depress*