

1 Appendix 1. PRISMA-P 2015 checklist³³

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	Y		1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A		
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Y		64, 181-182
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y		4-36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y		77-80
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Y		183-185
Support					
Sources	5a	Indicate sources of financial or other support for the review	Y		85-97
Sponsor	5b	Provide name for the review funder and/or sponsor	Y		85-97
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Y		85-97
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	Y		104-161
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y		163-179
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status)	Y		189-236, 254-270

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		to be used as criteria for eligibility for the review			
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Y		273-287
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y		Appendix 3
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y		289-290, 296-297
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Y		289-294
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y		296-297, 318-321
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Y		298-317
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y		238-252
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y		193-194, 323-334
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Y		352-358
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	Y		337-363, 375-418
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Y		364-373, 424-435

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y		337-338
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Y		420-422
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Y		437-439

2 Appendix 2. Types of interventions.

	<i>Types of next-step treatments</i>		<i>Antidepressant treatments</i>
1	Switching to a different antidepressant medication (ADM) monotherapy	a.	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, (SSRIs)
		b.	desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine (SNRIs)
		c.	amitriptyline, clomipramine, imipramine, nortriptyline (TCAs)
		d.	phenelzine, tranylcypromine (irreversible MAO-Is)
		e.	agomelatine, bupropion, mirtazapine, nefazodone, reboxetine, trazodone, vortioxetine, vilazodone (other)
2	Augmenting ADM with another (mostly mono-aminergic) ADM (i.e. combination treatment)		see (1)
3	Augmenting ADM with another psychopharmacological agent	a.	aripiprazol, brexpiprazole, cariprazine, olanzapine, olanzapine/fluoxetine

			combination (OFC), quetiapine, risperidone, ziprasidone (atypical antipsychotics)
		b.	i. lithium ii. lamotrigine, sodium valproate (mood stabilizers)
		c.	i. esketamine, ketamine ii. d-cycloserine (DCS), minocycline (glutamatergic agents)
		d.	dexamphetamine, methylphenidate (stimulants)
		e.	triiodothyronine (T3) (thyroid hormone)
		f.	buspirone, pindolol, metyrapone (other)
4	Switching to psychedelic therapy or psychedelic-assisted psychotherapy		ayahuasca, dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), psilocybin, mescaline, 3,4-methylenedioxymethamphetamine (MDMA)
5	Switching to neuromodulation treatment	a.	electroconvulsive therapy (ECT) ⁽¹⁾
		b.	deep brain stimulation (DBS)
		c.	magnetic seizure therapy (MST)

		d.	<ul style="list-style-type: none"> i. repetitive transcranial magnetic stimulation (rTMS)⁽²⁾ ii. accelerated transcranial magnetic stimulation (aTMS) iii. deep transcranial magnetic stimulation (dTMS) iv. priming transcranial magnetic stimulation (priming TMS) v. thetaburst stimulation (TBS)⁽³⁾ (transcranial magnetic stimulation)
		e.	<ul style="list-style-type: none"> i. transcranial direct current stimulation (tDCS) ii. transcranial alternating current stimulation (tACS)
		f.	vagus nerve stimulation (VNS)
6	Augmenting ADM with neuromodulation treatment		see (5)
7	Switching to psychological therapy		behavioural cognitive therapy (CBT), cognitive behavioral analysis system of psychotherapy (CBASP), dialectical behavioural therapy (DBT), interpersonal psychotherapy (IPT), intensive short-term dynamic psychotherapy (ISTDP), mindfulness-based cognitive therapy (MBCT) ⁽⁴⁾

8	Augmenting ADM with psychological therapy		see (7)
---	---	--	---------

3 Notes:

4 ⁽¹⁾ Including: Right unilateral ECT (RUL ECT); bilateral ECT (BL ECT).

5 ⁽²⁾ Including: high frequent rTMS of left DLPFC (HF-L rTMS); low frequent rTMS of right DLPFC (LF-R
6 rTMS; bilateral rTMS, protocol comprising both high frequent rTMS of left DLPFC and low frequent
7 rTMS of right DLPFC (BL rTMS).

8 ⁽³⁾ Including: intermittent thetaburst stimulation (iTBS) of the left DLPFC; bilateral thetaburst
9 stimulation, protocol comprising both iTBS of left DLPFC and cTBS of right DLPFC (BL TBS).

10 ⁽⁴⁾ Psychological therapy is defined as a face-to-face interaction with a therapist, delivered either in a
11 group or individually, in both in- and outpatient settings, possibly in a blended format. Solely e-health
12 interventions will be excluded.⁴⁶

13 Appendix 3. Draft of search strategy

14 Below we present the query for use in MEDLINE (Ovid). The keywords for TRD (see #1) are based on a
15 version used by Davies, et al. ⁴⁵, to which “(depress* and (adjunct* adj5 (treatment or therapy or
16 placebo or antidepress*))).mp.” and “(antidepress* adj3 resistan*).ti,ab,kf.” are added to enhance
17 sensitivity. The RCT filter (see #5 and #6) has also been adapted from Davies, et al. ⁴⁵.

	Search terms
#1	Depressive Disorder, Treatment-Resistant/ OR (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or "re-uptake")) or medication* or psychotropic or treatment* or respon*) adj2 fail*).ti,ab,kf. OR

	<p>(depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or "re-uptake"))) or "psychotropic medication*" or treatment*) adj2 ("no respon*" or "not respon*" or nonrespon* or "non-respon*" or unrespon*))).ti,ab,kf. OR</p> <p>(depress* adj3 (refractor* or resistan* or chronic* or persist*)).ti,ab,kf. OR (depress* adj3 (relaps* or recurr*)).ti,kf. OR</p> <p>(depress* and (augment* or potentiat*)).mp. OR</p> <p>(depress* and (adjunct* adj5 (treatment or therapy or placebo or antidepress*))).mp. OR</p> <p>(antidepress* adj3 resistan*).ti,ab,kf.</p>
#2	<p>antidepressive agents/ or antidepressive agents, second-generation/ or antidepressive agents, tricyclic/ or "serotonin and noradrenaline reuptake inhibitors"/ or serotonin uptake inhibitors/ or monoamine oxidase inhibitors/ or levomilnacipran/ or milnacipran/ or mirtazapine/ or sertraline/ or vilazodone hydrochloride/ or vortioxetine/ or bupropion/ or citalopram/ or fluoxetine/ or fluvoxamine/ or paroxetine/ or trazodone/ or reboxetine/ or desvenlafaxine succinate/ or duloxetine hydrochloride/ or venlafaxine hydrochloride/ or amitriptyline/ or clomipramine/ or imipramine/ or nortriptyline/ or phenelzine/ or tranlycypromine/ or antipsychotic agents/ or aripiprazole/ or olanzapine/ or quetiapine fumarate/ or risperidone/ or ketamine/ or cycloserine/ or minocycline/ or lithium/ or lithium carbonate/ or lithium compounds/ or lithium chloride/ or valproic acid/ or lamotrigine/ or Triiodothyronine/ or pindolol/ or metyrapone/ or hallucinogens/ or lysergic acid diethylamide/ or mescaline/ or n,n-dimethyltryptamine/ or n-methyl-3,4-methylenedioxyamphetamine/ or psilocybin/ or banisteriopsis/ or (SSRI or "selective serotonin reuptake inhibitor*" or TCA or "tricyclic antidepressant*" or SNRI or "serotonin noradrenaline reuptake inhibitor*" or "serotonin norepinephrine reuptake inhibitor*" or MAOI or "Monoamine Oxidase Inhibitor*").ti,ab. OR (agomelatine or bupropion or citalopram or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or levomilnacipran or milnacipran or mirtazapine or paroxetine or reboxetine or sertraline or</p>

	<p>venlafaxine or vilazodone or vortioxetine or amitriptyline or clomipramine or nortriptyline or imipramine or trazodone or nefazodone or tranylcypromine or phenelzine).ti,ab. OR (aripiprazole or brexpiprazole or cariprazine or OFC or olanzapine or quetiapine or risperidone).ti,ab. OR (esketamine or ketamine or "d-cycloserine" or cycloserine or DCS or minocycline).ti,ab. OR (lamotrigine or "sodium valproate" or "valproic acid" or lithium).ti,ab. OR (triiodothyronine or T3 or pindolol or Metyrapone).ti,ab. OR (psychedelic* or hallucinogen* or psychotomimetic or psilocybin or ayahuasca or banisteriopsis or LSD or "lysergic acid diethylamide" or MDMA or mescaline or DMT or dimethyltryptamine).ti,ab. OR (dexamphetamine OR methylphenidate OR dexmethylphenidate).ti,ab. OR exp dextroamphetamine OR exp methylphenidate/</p>
#3	<p>Electroconvulsive Therapy/ or Deep Brain Stimulation/ or Transcranial Magnetic Stimulation/ or Vagus Nerve Stimulation/ OR Transcranial Direct Current Stimulation/ OR ("electroconvulsive therap*" OR "convulsive therap*" OR ECT OR "electroshock therap*" OR "shock therap*" OR "electroconvulsive treatment*" OR "convulsive treatment*" OR "electroshock treatment*" OR "shock treatment*" OR "deep brain stimulation*" OR DBS OR "transcranial magnetic stimulation*" OR rTMS OR VNS OR "vagus nerve stimulation*" OR "vagal nerve stimulation*" OR "transcranial direct current stimulation" OR "transcranial alternating current stimulation" OR tDCS OR tACS OR "transcranial electric current stimulation" OR "TES" OR "thetaburst stimulation" OR TBS OR iTBS OR cTBS).ti,ab. OR (TMS or aTMS or dTMS or MST or "magnetic seizure therap*" or "magnetic seizure treatment*").ti,ab.</p>
#4	<p>exp Psychotherapy/ OR ("psychological treatment" OR "psychological therapy" OR psychotherap* OR "behavioural cognitive therap*" OR "behavioral cognitive therap*" OR "cognitive behaviour therap*" OR "cognitive behavior therap*" OR "cognitive behavioural therap*" OR "cognitive behavioral therap*" OR "behavioural cognitive treatment" OR</p>

	"behavioral cognitive treatment" OR "cognitive behaviour treatment" OR "cognitive behavior treatment" OR "cognitive behavioural treatment" OR "cognitive behavioral treatment" OR CBT OR "dialectical behavioural therap*" OR "dialectical behavioral therap*" OR "dialectical behaviour therap*" OR "dialectical behavior therap*" OR "dialectical behavioural treatment" OR "dialectical behavioral treatment" OR "dialectical behaviour treatment" OR "dialectical behavior treatment" OR DBT OR "mindfulness-based cognitive therapy" OR "mindfulness-based cognitive treatment" OR MBCT OR CBASP OR IPT OR ISTDP).ti,ab.
#5	(randomized controlled trial.pt. or exp randomized controlled trial/ or exp Randomized Controlled Trials as Topic/ OR controlled clinical trial.pt. OR (RCT or randomi* or "at random" or (random* adj3 (assign* or allocat* or divide* or division or number*))).ti,ab,kf. OR ((placebo or sham or mock or fake or dummy) and (control* or group*)).ti,ab,kf. OR "double-blind*".ti,ab,kf,hw. OR trial.ti. OR ((cluster or crossover* or "cross-over*") adj3 (random* or trial or study or control* or group*)).ti,ab,kf.) NOT ((letter/ OR editorial/ OR news/ OR exp historical article/ OR Anecdotes as topic/ OR comment/ OR case report/ OR (letter or comment*).ti. OR exp animals/ not humans/ OR exp Animals, Laboratory/ OR exp Animal Experimentation/ not (exp human experimentation/ or humans/) OR exp Models, Animal/ OR exp rodentia/ OR (rat or rats or mouse or mice or rodent*).ti.))
#6	1 AND (2 OR 3 OR 4) AND 5
#7	Limit 6 to yr="2019 -Current"