

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Efficacy and acceptability of next step treatment strategies in adults with treatment-resistant major depressive disorder: Protocol for systematic review and network meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056777
Article Type:	Protocol
Date Submitted by the Author:	21-Sep-2021
Complete List of Authors:	Muit, Jan; Radboud University Nijmegen, Department of Psychiatry van Eijndhoven, Philip FP; Radboud University Nijmegen, Department of Psychiatry Cipriani, Andrea; University of Oxford, Department of Psychiatry; Warneford Hospital Dalhuisen, Iris; Radboud University Nijmegen, Department of Psychiatry van Bronswijk, Suzanne; Maastricht University, Department of Psychiatry and Psychology Furukawa, Toshi; School of Public Health, Departments of Health Promotion and Human Behavior and of Clinical Epidemiology Ruhe, Henricus; Radboud University Nijmegen, Department of Psychiatry
Keywords:	Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts

1
2
3 1 *Efficacy and acceptability of next step treatment strategies in adults with treatment-resistant major*
4
5 2 *depressive disorder: Protocol for systematic review and network meta-analysis*
6
7
8

9 3 Authors

10
11
12 4 Jan J Muit, MD (corresponding author) (ORCID 0000-0002-0353-2905)
13 5 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
14 6 P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
15 7 Tel. +31(0)24 361 35 13
16 8 bob.muit@radboudumc.nl
17 9

18
19 10 Philip FP van Eijndhoven, MD, PhD (ORCID 0000-0003-3474-4326)
20 11 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
21 12 philip.vaneijndhoven@radboudumc.nl
22 13

23 14 Andrea Cipriani, MD, PhD (ORCID 0000-0001-5179-8321)
24 15 Department of Psychiatry, University of Oxford, Oxford, UK
25 16 Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK
26 17 andrea.cipriani@psych.ox.ac.uk
27 18

28
29 19 Iris Dalhuisen, MSc (ORCID 0000-0002-7539-6498)
30 20 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
31 21 iris.dalhuisen@radboudumc.nl
32 22

33 23 Suzanne van Bronswijk, MD, PhD (OCiD 0000-0002-2983-1268)
34 24 Department of Psychiatry and Psychology, University Hospital Maastricht, Netherlands
35 25 School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences,
36 26 Maastricht University, Netherlands
37 27 suzanne.vanbronswijk@maastrichtuniversity.nl
38 28

39
40 29 Toshi A Furukawa, MD, PhD (ORCID 0000-0003-2159-3776)
41 30 Departments of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto
42 31 University Graduate School of Medicine / School of Public Health, Kyoto, Japan
43 32 furukawa@kuhp.kyoto-u.ac.jp
44 33

45 34 Henricus G Ruhe, MD, PhD
46 35 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
47 36 eric.ruhe@radboudumc.nl
48 37

49 37 Abstract

50 38 Introduction

51
52
53
54
55
56 39 For major depression a one-size-fits-all treatment does not exist. Patients enter a 'trial-and-change'
57
58 40 algorithm in which effective therapies are subsequently applied. Unfortunately, an empirically based
59
60

1
2
3 41 order of treatments has not yet been determined. There is a magnitude of different treatment
4
5 42 strategies while clinical trials only compare a small number of these. Network meta-analyses (NMA)
6
7 43 might offer a solution, but so far have been limited in scope and did not account for possible
8
9 44 differences in population characteristics that arise with increasing levels of treatment-resistance,
10
11 45 potentially violating the transitivity assumption. We therefore present a protocol for a systematic
12
13 46 review and network meta-analysis aiming at summarizing and ranking treatments for TRD while
14
15 47 covering a broad range of therapeutic options and accounting for possible differences in population
16
17 48 characteristics at increasing levels of treatment-resistance.

21 49 **Methods and analysis**

22
23
24 50 Randomized controlled trials will be included that compared next-step pharmacological,
25
26 51 neuromodulation or psychological treatments for treatment-resistant depression (TRD; i.e., failure to
27
28 52 respond to ≥ 1 adequate antidepressant drug trial(s) in the current episode) to each other or to a
29
30 53 control condition. Primary outcomes will be the proportion of patients who responded to (efficacy)
31
32 54 and dropped out of (acceptability) the allocated treatment. A random effects NMA will be
33
34 55 conducted, synthesizing the evidence for each outcome and determining the differential efficacy of
35
36 56 treatments. Heterogeneity in treatment nodes will be reduced by considering alternative geometries
37
38 57 of the network structure and by conducting a meta-regression examining different levels of TRD.
39
40 58 Local and global methods will be applied to evaluate consistency. The Cochrane Risk of Bias 2 (RoB2)
41
42 59 tool, Confidence in Network Meta-Analysis (CiNeMA), and the Grading of Recommendations
43
44 60 Assessment, Development and Evaluation (GRADE) framework will be used to assess risk of bias and
45
46 61 certainty.

51 62 **Ethics and dissemination**

52
53
54 63 This review does not require ethical approval.

56 64 **Registration details**

57
58
59 65 PROSPERO registration number: pending.

66 Article summary

67 Strengths and limitations of this study

- 68 • This will be the most up to date and comprehensive network meta-analysis conducted about
69 the next-step treatments of treatment-resistant depression (TRD). Findings of this study will
70 inform treatment decisions and guideline development.
- 71 • We will address the potential heterogeneity arising from different levels of TRD (i.e. the
72 quantity and/or quality of previous treatment steps) which has not been considered before.
- 73 • There is a potential risk of high heterogeneity among studies given the broad range of
74 included interventions. Heterogeneity within treatment nodes will be limited by considering
75 alternative geometries of the network structure.
- 76 • Limitations of primary studies will be assessed using the Cochrane RoB2 tool, CiNeMA, and
77 the GRADE framework.

78 Author contributions

79 HGR is guarantor. JJM, PFPE and HGR devised the study and drafted the protocol. JJM designed the
80 search strategy. All authors contributed to the development of the selection criteria. ID, SB, TAF and
81 AC assisted in drafting the protocol. TAF and AC assisted in designing the study and provided
82 statistical expertise. All authors read, provided feedback and approved the final manuscript.

83 Funding

84 This research received no specific grant from any funding agency in the public, commercial or not-
85 for-profit sectors.

86 Competing interests statement

87 JJM: None to declare. PFPE: reports grants from ZonMW and speaking fees from Janssen outside of
88 the submitted work. AC is supported by the National Institute for Health Research (NIHR) Oxford

1
2
3 89 Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017-08-ST2-
4
5 90 006), by the NIHR Oxford and Thames Valley Applied Research Collaboration and by the NIHR Oxford
6
7 91 Health Biomedical Research Centre (grant BRC-1215-20005). The views expressed are those of the
8
9 92 authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department
10
11 93 of Health; he has received research and consultancy fees from INCiPiT (Italian Network for Paediatric
12
13 94 Trials), CARIPLO Foundation and Angelini Pharma. ID: None to declare. SB: None to declare. TAF: TAF
14
15 95 reports grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD, grants and
16
17 96 personal fees from Shionogi, outside the submitted work; In addition, TAF has a patent 2020-548587
18
19 97 concerning smartphone CBT apps pending, and intellectual properties for Kokoro-app licensed to
20
21 98 Mitsubishi-Tanabe. HGR reports grants from ZonMW, Hersenstichting, EU Horizon 2020 and speaking
22
23 99 fees from Lundbeck and Janssen outside of the submitted work.
24
25
26
27
28

29 100 Keywords

30
31
32 101 "Depressive Disorder, Treatment-Resistant"[Mesh]; "Antidepressive Agents"[Mesh]; "Treatment
33
34 102 Outcome"[Mesh]; "Network Meta-Analysis"[Mesh]; "Randomized Controlled Trials as Topic"[Mesh]
35
36

37 103 Word count

38
39
40
41 104 4017
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

105 Introduction

106 Depression has been one of the leading causes of non-fatal health loss for nearly three decades, with
107 Major Depressive Disorder (MDD) affecting 163 million people worldwide in 2017.¹ No one-size-fits-
108 all treatment exists.^{2 3} Patients enter a 'trial-and-change' algorithm in which evidence-based
109 treatments are subsequently applied.⁴ Unfortunately, there is no empirically based optimal
110 treatment sequence determined yet.

111 In order to consider a depression to be treatment-resistant, several adequate treatment trials of
112 sufficient dosage and length must have been previously applied. Definitions of 'treatment-resistance'
113 range from nonresponse to one antidepressant medication (ADM) (after ≥ 4 weeks of treatment) to a
114 failure to respond to more than 10 adequate trials of different classes of ADM and augmentation
115 strategies, electroconvulsive therapy (ECT) and psychological treatments, taking into account factors
116 such as disease severity, comorbidity, functional impairment and intensity of treatment.^{5 6} However,
117 most recent insights suggest to use a dimensional approach to define levels of treatment-resistant
118 depression (TRD).⁶⁻¹² In addition, TRD is often confused with "pseudo-resistant" depression, a term
119 used to describe non-response to antidepressant trials of inadequate dosage and duration.¹³

120 Common strategies for treatment-resistance to ADM include dose-escalation and switching.¹⁴⁻¹⁷
121 Dose-escalation of the first ADM has extensively been addressed in previous research. It was found
122 that beyond 20 to 40mg fluoxetine equivalents for selective serotonin reuptake inhibitors (SSRI) and
123 above 30mg mirtazapine, efficacy does not increase, leaving limited room for dose-escalation in non-
124 responders to these dosages.¹⁸⁻²⁰ However, it was found that adding or switching to mirtazapine was
125 superior to continuing sertraline among previously untreated patients.²¹ The Sequenced Treatment
126 Alternatives to Relieve Depression (STAR*D) trial aimed to ascertain whether certain treatments
127 were more optimal after one or more failed trials.^{2 22} No differences were found between any of the
128 next-step treatment strategies. However, it was found that patients with higher levels of treatment-
129 resistance showed lower rates of remission, as remission rates dropped after two failed trials

1
2
3 130 (remission rates of 36.8-30.6% after step 1 and 2 versus 13.7-13.0% after step 3 and 4). The authors
4
5 131 hypothesized the steep reduction in remission rates after step 2 occurred due to differences in
6
7 132 population characteristics (e.g. presence of comorbid medical or psychiatric disorders, or degree of
8
9 133 chronicity) and general heterogeneity of MDD. Alternatively, poor monitoring of nortriptyline or
10
11 134 lithium levels and inadequate dosing of MAO-inhibitors might explain the poor responses in step 3
12
13 135 and 4 in STAR*D. Nevertheless, the decreases in response and remission rates after the second ADM
14
15 136 might be related to a selection process of patients that are non-responsive to all types of mono-
16
17 137 aminergic ADM.²³ This could explain the slight advantage of between-class over within-class switches
18
19 138 after a first ADM,^{17 24 25} but it remains to be shown empirically whether this selection effect is indeed
20
21 139 applicable to increasing levels of TRD. Hypothetically, treatments targeting different pathways might
22
23 140 provide better efficacy in these cases.

24
25
26
27
28 141 Several efforts have been undertaken to perform network meta-analysis (NMA) for TRD,²⁶⁻³⁰
29
30 142 however overall conclusions are impeded by various factors. First, these NMAs employed various
31
32 143 definitions of TRD: e.g. two of them also included patients with only one failed adequate trial in the
33
34 144 current episode.^{26 27} Second, these NMAs studied various types of interventions: from only a few
35
36 145 augmentation strategies²⁶ or only neuromodulation strategies³⁰ to several augmentation,
37
38 146 pharmacotherapy switch, and neuromodulation strategies.²⁸ Third, only one study accounted for
39
40 147 differences in dosages.²⁶ Fourth, one study accounted for outcome measures at different points in
41
42 148 time, ranging from 2 to 8 weeks, limiting the number of possible comparisons.²⁸ Fifth, the most
43
44 149 recent study investigating multiple modalities grouped treatments based on the presumed
45
46 150 mechanisms of action, without clear description of considerations regarding the treatment
47
48 151 network.²⁹ Although Wang, et al.³¹ stratified for number of failed ADM in a pairwise meta-analysis,
49
50 152 none of the NMAs²⁶⁻²⁹ were able to account for levels of TRD and possible differences in population
51
52 153 characteristics that might arise with increasing levels of TRD,² which might violate the transitivity
53
54 154 assumption for NMA. Violation of the transitivity assumption would make estimating indirect
55
56 155 comparisons from unobserved head-to-head comparisons invalid.³² Neither were these studies able

1
2
3 156 to evaluate whether higher levels of treatment-resistance respond to more aggressive or invasive
4
5 157 treatments.^{7 29}
6
7

8 158 In summary, current research is affected by several complicating factors. No common consensus on
9
10 159 the definition of TRD exists. A magnitude of different treatment strategies is available while clinical
11
12 160 trials usually only compare a small number of these. NMAs performed so far are limited in scope and
13
14 161 do not account for possible differences in population characteristics that might arise with increasing
15
16 162 levels of TRD, potentially violating the transitivity assumption. Therefore, a more comprehensive
17
18 163 approach to summarize and determine relative efficacy of treatments for TRD is needed.
19
20
21
22

23 164 Objectives

24
25
26 165 The aim of this systematic review and NMA is to evaluate (1) the differential efficacy and
27
28 166 acceptability of treatment strategies when administered after a failed ADM trial in adults with MDD;
29
30 167 (2) whether differential efficacy and acceptability is dependent on the study-level of treatment-
31
32 168 resistance as defined by inclusion criteria used in the trials. These aims can be applied to the
33
34 169 following clinical questions: (1) what are next-step treatment strategies in adult patients with TRD
35
36 170 that are beneficial and/or safe? (2) how do the various treatment strategies compare to each other?
37
38 171 (3) does the level of treatment-resistance affect the differential efficacy of next-step treatment-
39
40 172 strategies?
41
42
43

44 173 In order to answer the first clinical question, absolute and relative efficacy and acceptability of next-
45
46 174 step antidepressant treatments for TRD will be examined using head-to-head and treatment-control
47
48 175 comparisons in pairwise meta-analyses. To answer the second clinical question, relative efficacy and
49
50 176 acceptability of the various next-step treatment strategies will be estimated in an NMA, while
51
52 177 ranking their probabilities of highest efficacy and acceptability to inform the treatment algorithm for
53
54 178 MDD. In order to answer the third clinical question, we will investigate the transitivity assumption by
55
56 179 examining the impact of the study's level of treatment resistance (i.e., the number of failed
57
58
59
60

1
2
3 180 antidepressant trials that studies required as an inclusion criterion) in a network meta-analysis with a
4
5 181 meta-regression.
6
7

8 9 182 **Methods**

10
11 183 This protocol is submitted with the International Prospective Register of Systematic Reviews
12
13 184 (PROSPERO) on 21-07-2021 (registration pending). We used the Preferred Reporting Items for
14
15 185 Systematic Review and Meta-Analysis Protocols (PRISMA-P),³³ see Appendix 1. In case of protocol
16
17 186 amendments, we will describe the date of each amendment together with a description of the
18
19 187 change and the rationale.
20
21
22

23 24 188 **Eligibility criteria**

25 26 189 **Types of studies**

27
28 190 We include randomized controlled trials (RCT), in which next-step pharmacological, neuromodulation
29
30 191 or psychological treatment strategies are compared to each other or a control condition.
31
32

33 192 Quasi-randomised trials will be excluded, while cluster RCTs will be included when the clustering
34
35 193 effect can be taken into account. For cross-over trials the results from the first randomized treatment
36
37 194 period will be included. We will exclude studies where there was a high risk of bias arising from the
38
39 195 randomization process.
40
41
42

43 44 196 **Types of participants**

45
46 197 We include studies with patients aged ≥ 18 years with unipolar MDD diagnosed by using any
47
48 198 standard operationalised criteria, such as Feighner criteria, Research Diagnostic Criteria, DSM-III,
49
50 199 DSM-III-R, DSM-IV, DSM-5 and ICD-10.
51
52

53 200 We require studies where patients failed to respond to ≥ 1 ADM trial(s) prescribed at least at a
54
55 201 minimally effective dose for ≥ 4 weeks in the current episode.³⁴ We will not exclude studies that
56
57 202 considered intolerance to a previous treatment trial as a failure in their definition of TRD. Although
58
59 203 intolerance to treatment could be considered pseudo-resistance, in clinical practice it might not
60

1
2
3 204 always be possible to distinguish between failure and intolerance as information on previous failed
4
5 205 trials is often based on historical information.
6
7
8 206 Studies in which 20% or more of the participants are suffering from bipolar disorder, peri-partum
9
10 207 depression or psychotic depression will be excluded. We exclude RCTs that have included patients
11
12 208 with a concurrent *primary* diagnosis of another psychiatric or personality disorder. A secondary
13
14 209 diagnosis of another psychiatric disorder will not be considered an exclusion criterion. RCTs focusing
15
16 210 on patients with a concomitant medical illness will be excluded.³⁵ We include studies that allow use
17
18 211 of rescue medications, if these medications were made equally available to all treatment groups.
19
20
21

22 212 Types of interventions

23
24 213 We distinguish 8 types of next-step treatments covering different modalities: 1) Switching to a
25
26 214 different ADM, 2) Combining continued ADM with another ADM, 3) Augmenting ADM with another
27
28 215 psychopharmacological agent, 4) Switching to psychedelic or psychedelic-assisted therapy, 5)
29
30 216 Switching treatment to neuromodulation treatment, 6) Augmenting ADM with neuromodulation
31
32 217 treatment, 7) Switching treatment to psychological therapy, 8) Augmenting ADM with psychological
33
34 218 therapy. For a more detailed overview, see Appendix 2.
35
36
37
38

39 219 We will obtain information about interventions of interest either from head-to-head or controlled
40
41 220 trials. We exclude studies if the intervention is not targeted at the depressive disorder. Studies that
42
43 221 co-initiated multiple interventions of interest will not be excluded and treated as a combined
44
45 222 treatment.
46
47

- 48 223 • Comparator interventions (switching or augmenting)
 - 49 224 ○ Alternative intervention (head-to-head)
 - 50 225 ○ Pill placebo
 - 51 226 ○ Psychological placebo
 - 52 227 ○ Sham neuromodulation
 - 53 228 ○ Continuation of antidepressant treatment

- 1
2
3 229 ○ Treatment as usual (TAU; defined as standard non-protocolized treatment in primary
4
5 230 or secondary care, typically with pharmacotherapy)
6
7 231 ○ No treatment (NT; applies in case TAU involved virtually no intervention, defined as <
8
9 232 50% of patients receiving any antidepressant treatment; patients know they will not
10
11 233 receive active treatment after the trial)
12
13
14 234 ○ Waiting list control (WL; similar to NT, except patients know they will receive active
15
16 235 treatment after the waiting phase)³⁶
17
18

19 236 **Outcome measures**

20
21
22 237 **Primary outcomes:**

- 23
24
25 238 • Response (efficacy as a dichotomous outcome), for patients who did not respond to first-step
26
27 239 treatment strategies but achieved response with next-step treatment strategies.
28
29 240 • All-cause dropout (acceptability as a dichotomous outcome) for patients who left the trial or
30
31 241 stopped the treatment early due to any reason up to the end of study duration.
32
33

34 242 **Secondary outcomes:**

- 35
36
37 243 • Change in severity of symptoms measured on the Hamilton (HDRS) or Montgomery-Asberg
38
39 244 depression rating scales (MADRS) or other depression rating scales. Extraction of continuous
40
41 245 efficacy outcome data will be prioritized as proposed by Furukawa, et al.³⁷ Change scores
42
43 246 will be used when end point scores are not reported.³⁸
44
45
46 247 • Remission, for patients who did not respond or did not achieve remission with first-step
47
48 248 treatment strategies but achieved remission with next-step treatment strategies.
49
50
51 249 • Dropout due to adverse events (tolerability) measured as the proportion of patients who left
52
53 250 the trial early due to any adverse events.
54
55

56 251 We will use the original author's definition of "response" and "remission".
57
58
59
60

252 Trial duration

253 There is no consensus on the appropriate duration of an acute phase trial.^{39 40} Some newer
254 treatments might show effects within one session.⁴¹ Nevertheless, the effect of trials should at least
255 be evaluated after 4 weeks in order to determine stability of antidepressant effects. We define acute
256 treatment as an 8-week treatment. If 8-week data are not available, we will use data as close to 8
257 weeks as possible (ranging between 4 and 12 weeks). If equidistant, we will use the longer outcome.
258 We will exclude studies from the statistical synthesis if no data for the 4–12 weeks period can be
259 provided.³⁷

260 Comparability of dosages

261 We include fixed-dose and flexible-dose designs, and only include arms randomizing patients to
262 pharmacological, neuromodulation and psychological therapies within licensed doses and ranges of
263 approved treatments, and any dosage or range of unapproved treatments. In case of psychotherapy,
264 we require a minimum of 4 sessions, as this has been proposed as a minimally effective dose.⁴²

265 Setting

266 We will not apply restrictions by type of setting.

267 Language

268 We will apply no language restrictions.

269 Search strategy and data management

270 Search strategy

271 We will identify published, unpublished and ongoing RCTs that compared the efficacy and/or
272 acceptability of one treatment strategy to another treatment or to a control condition in the
273 treatment of TRD. The following sources will be searched: MEDLINE (Ovid), Cochrane Central Register
274 of Controlled Trials (CENTRAL), Embase (Ovid), LILACS database, and PsycINFO (Ovid). MEDLINE and
275 Embase will be searched from 2019 onwards, as these are also indexed by CENTRAL. CENTRAL,

1
2
3 276 LILACS and PsycINFO will be searched without date restrictions. Keywords for TRD and the RCT filter
4
5 277 are based on the strategy used by Davies, et al.⁴³ See Appendix 3 for the MEDLINE search strategy,
6
7 278 this strategy will be adapted to syntax and subject headings of other databases. We will search
8
9
10 279 international trial registries (clinicaltrials.gov and WHO International Clinical Trials Registry Platform).
11
12 280 We will contact the National Institute for Clinical Excellence (UK), the Institut für Qualität und
13
14 281 Wirtschaftlichkeit in Gesundheitswesen (Germany), check the websites of pharmaceutical companies
15
16 282 to obtain unpublished information and contact their representatives. In addition, we will search
17
18 283 references lists of included studies and recent systematic reviews.^{26-30 43-50}

20
21 284 Relevant authors will be contacted to supplement published/unpublished studies or incomplete
22
23 285 reporting, and reminded twice.

26 286 Study selection

27
28
29 287 Two investigators will independently review retrieved references and abstracts. Abstracts will be
30
31 288 screened using the Rayyan web-application.⁵¹ A pilot will be conducted to refine screening policy of
32
33 289 both reviewers. If both reviewers agree about a trial not meeting eligibility criteria, it will be
34
35 290 excluded. We will obtain the full text of all remaining articles and use the same eligibility criteria to
36
37 291 determine the final selection. Two independent reviewers will perform the selection and resolve
38
39 292 disagreements via discussion with a third member of the review team.

42 293 Data extraction

43
44 294 Two reviewers will independently extract data and evaluate risk of bias for each selected trial. We
45
46 295 will use a structured data extraction sheet, the use of which will be refined in a pilot period.
47
48 296 Reliability of the data extraction will be checked. Information extracted will include trial
49
50 297 characteristics (such as lead author, journal, publication year, design, inclusion criteria, sponsorship,
51
52 298 number of recruitment centers, whether nonresponse was prospectively or retrospectively assessed,
53
54 299 type and definition of non-response at time of enrollment (non-responder or non-remitter), whether
55
56 300 non-response to psychological therapy was included in the TRD definition (a failed psychotherapy
57
58
59
60

1
2
3 301 trial is classified as a failure to respond to an adequate course of 8 attended sessions of a form of
4
5 302 psychotherapy with demonstrated effectiveness for MDD),⁷ definitions of response and remission),
6
7 303 participant characteristics (such as diagnostic criteria for depression, depression severity threshold,
8
9 304 participant age, gender distribution, setting, number of previously failed treatment trials in the
10
11 305 current episode, length of current depressive episode, number of previous episodes, length of
12
13 306 depressive disorder since age of onset, length of the previous treatment trial(s), depression severity
14
15 307 at baseline, physical or psychiatric comorbidity), outcome measures and intervention details
16
17 308 including co-interventions or continuation treatment. In case of pharmacological strategies we
18
19 309 extract dosing schedule, dose ranges and mean doses of study drugs. For the antidepressant
20
21 310 switching, we distinguish within or between class switches. In case of neuromodulation strategies we
22
23 311 extract data on treatment protocols, mean number of treatment sessions, targeted sites and
24
25 312 stimulation parameters. In case of psychological treatment strategies we extract type of
26
27 313 psychotherapy, mean number of treatment sessions, whether it concerned individual or group
28
29 314 therapy, whether therapy was offered in a blended format or as partially self-guided therapy, and
30
31 315 assessment of treatment integrity.
32
33
34
35
36
37 316 Level of TRD as inclusion criterion will be rated by two independent assessors. Reliability of this
38
39 317 assessment will be quantified. Disagreements in any of the extracted data will be resolved through
40
41 318 discussion with a third member of the review team. We will contact corresponding authors if
42
43 319 necessary, to obtain missing information.
44
45
46

47 320 Risk of Bias Assessment

48
49 321 Risk of bias of included studies will be assessed at outcome level for the two primary outcomes, using
50
51 322 the Risk of Bias 2 tool described in the Cochrane Handbook for Systematic Reviews of Interventions.⁵²
52
53 323 We will assess the following domains: bias arising from the randomization process, bias due to
54
55 324 deviations from intended interventions, bias due to missing outcome data, bias in measurement of the
56
57 325 outcome and bias in selection of the reported result. Two independent raters will perform the
58
59
60

1
2
3 326 assessment. If the raters disagree, the final rating will be made by consensus with the involvement of
4
5 327 another member of the review group. We will contact corresponding authors if necessary, to obtain
6
7 328 missing information. Overall risk of bias of each study will be categorized as follows: studies will be
8
9
10 329 classified as having low risk of bias if all domains were rated at low risk of bias; some concerns if none
11
12 330 were rated as high risk of bias but at least one domain raised some concerns; high risk of bias if at least
13
14 331 one domain was rated at high risk of bias or multiple domains raise some concerns in a way that
15
16 332 substantially lowers confidence in the results.

19 333 **Statistical analysis**

22 334 **Synthesis of results**

23
24 335 We will analyze the data using the meta⁵³ and netmeta⁵⁴ packages in R⁵⁵. Characteristics and findings
25
26 336 of included studies will be presented in text and tables. We will analyze dichotomous outcomes on an
27
28 337 intention-to-treat basis: all dropouts from treatment will be assumed to have had negative outcomes
29
30 338 (i.e. non-response).

34 339 **Pairwise meta-analysis**

35
36 340 In order to answer our three clinical questions (see Objectives), we conduct three main analyses. The
37
38 341 first clinical question relates to whether treating TRD with next-step treatment strategies is beneficial
39
40 342 and/or safe. Via pairwise meta-analysis, we will obtain estimates of efficacy and acceptability of
41
42 343 different treatment strategies, compared to both each other and control conditions. We will perform
43
44 344 a random-effects meta-analysis on the 8 types of next-step treatments as described in Appendix 2.
45
46 345 For each pairwise comparison, we will synthesize data to obtain summary standardized mean
47
48 346 differences (SMD, Hedges' g) for continuous outcomes or ORs for dichotomous outcomes, both with
49
50 347 95% Confidence Intervals (CI).^{56 57}

55 348 **Network meta-analysis**

56
57 349 The second clinical question we aim to answer is how various next-step treatment strategies
58
59 350 compare with each other. We will conduct an NMA to examine comparative efficacy and
60

1
2
3 351 acceptability of the next-step treatment strategies. In line with a previous protocol,³⁷ we assume that
4
5 352 patients who fulfil the inclusion criteria are equally likely to be randomized to any of the treatments
6
7 353 that we plan to compare. If the collected studies appear to be sufficiently homogeneous with respect
8
9
10 354 to distribution of effect modifiers (see Assessment of transitivity assumption section below), we will
11
12 355 conduct a random effects NMA to synthesize all evidence for each outcome, and obtain a
13
14 356 comprehensive ranking of all treatments. We will use arm-level data and the binomial likelihood for
15
16 357 dichotomous outcomes. We will account for correlations induced by possible multiarmed studies by
17
18 358 employing multivariate distributions. We will assume a single heterogeneity parameter for each
19
20 359 network. We will present summary ORs or SMD for all pairwise comparisons in a league table. To
21
22
23 360 rank the various treatments for each outcome, we will use the surface under the cumulative ranking
24
25 361 curve (SUCRA) and the mean ranks.

28 362 **Meta-regression analysis of treatment resistance**

30
31 363 In order to answer our third clinical question, we will perform meta-regression that evaluates the
32
33 364 impact of different levels of TRD on the primary outcomes. TRD is defined as (i) the number of failed
34
35 365 (antidepressant) treatment-trials (including augmentation and psychotherapy) that were required as
36
37 366 inclusion criterion for the study⁸ or (ii) dichotomized by slightly adapting Conway, et al.⁷: TRD level I
38
39 367 (Failure of 1 or 2 adequate dose-duration antidepressants or psychotherapy from different classes
40
41 368 (either in combination or succession)) or level II (Failure of ≥ 3 adequate antidepressant or
42
43 369 psychotherapy trials from different classes (either in combination or succession)). If sufficient data
44
45
46 370 are available, we aim to use the first, more detailed, grouping of TRD. If this proves unfeasible, we
47
48 371 will employ the second definition.

51 372 **Alternative geometry of treatment network structure**

52
53
54 373 As described in Appendix 2, we aim to group treatments by presumed mechanism of action (e.g.,
55
56 374 SSRI), and whether treatment was given as addition (augmentation) or replacement (switching) of
57
58 375 the previous treatment. Similar to Carter, et al.²⁹, we analyze the so-defined 8 different types of
59
60

1
2
3 376 treatment. Secondly, we aim to make detailed comparisons between individual treatments. We aim
4
5 377 to reduce heterogeneity in treatment nodes as much as possible, depending on how much data will
6
7 378 be available for analysis.⁵⁸ We will not analyze the antidepressants in the 'other' subgroup at the
8
9 379 subgroup level, due to the amount of heterogeneity we expect to arise from and lack of clinical
10
11 380 relevance of grouping together this heterogeneous group of antidepressants (i.e. we either include
12
13 381 them in the general antidepressant group, or as individual antidepressants). In case of atypical
14
15 382 antipsychotics, we account for differences in low or high doses, if possible.^{26,28} In case of
16
17 383 neuromodulation treatment and psychological therapy, if the data does not allow for separate
18
19 384 analysis for both switch strategies and augmentation strategies, these strategies will be (partially)
20
21 385 clustered within a 'mixed' strategy. We will consider clustering the comparator interventions in
22
23 386 'placebo' (i.e. pill placebo, psychological placebo and sham neuromodulation), 'pharmacological
24
25 387 control' (i.e. continuation of treatment and TAU) and 'no treatment' (i.e. NT and WL) groups, if the
26
27 388 groups are sufficiently homogeneous and consistent.

389 Assessment of heterogeneity (pairwise meta-analysis)

390 Comparable to Furukawa, et al.³⁷, in the pairwise meta-analysis, we check the possibility of
391
392 heterogeneity by visually inspecting the forest plots and compare the estimated value for the
393
394 heterogeneity variance with the corresponding empirical distribution.⁵⁹ Moreover, we report the I^2
395
396 statistic with 95% CI,^{60,61} using the proposed thresholds in the Cochrane Handbook for interpretation
397
398 (e.g. 0-40% might not be important, 30-60% might represent moderate heterogeneity, 50-90% might
399
400 represent substantial heterogeneity, 75-100% might represent considerable heterogeneity).⁵² In the
401
402 NMA, we estimate the heterogeneity variance and compare it with the empirical distribution.

403 Assessment of the transitivity assumption (network meta-analysis)

404 We will investigate the distribution of clinical and methodological variables that can act as effect
405
406 modifiers across treatment comparisons. We will examine levels of TRD as a possible violation of the
407
408 transitivity assumption, as higher levels of TRD might be accompanied by differences in population
409
410 characteristics.² Clinical features which moderate efficacy of antidepressants include bipolarity⁶² and

1
2
3 402 psychotic features.⁶³ We assure transitivity regarding these variables by limiting our samples to
4
5 403 participants with non-psychotic, unipolar depression. Other variables that may influence our primary
6
7 404 outcomes include: age, depressive severity at baseline,^{64 65} dosing schedule⁶⁶ and whether inclusion
8
9
10 405 criteria of studies concerned non-response or non-remission. We will investigate whether these
11
12 406 variables are similarly distributed across studies grouped by comparison. In order to account for the
13
14 407 potential of placebo to violate the transitivity assumption, the comparability of placebo-controlled
15
16 408 studies with those providing head-to-head evidence will be examined carefully.^{67 68}

19 409 Assessment of inconsistency

21
22 410 We employ local and global methods to evaluate consistency of the network,⁶⁹ using the node splitting
23
24 411 approach⁷⁰ and design-by-treatment interaction test⁷¹ respectively. We evaluate consistency in the
25
26 412 entire network by calculating the I^2 for network heterogeneity, inconsistency, and for both.^{71 72} Because
27
28 413 tests for inconsistency are known to have low power,⁷³ and 10% of evidence loops published in medical
29
30 414 literature are expected to be inconsistent,⁷⁴ we interpret statistical inference about inconsistency with
31
32 415 caution; possible sources of inconsistency will be explored even in the absence of evidence for
33
34 416 inconsistency.

38 417 Assessment of publication bias and small study effects

40
41 418 We use comparison-adjusted⁷⁵ and contour enhanced⁷⁶ funnel plots to investigate whether results in
42
43 419 imprecise trials differ from those in more precise trials. We will run network meta-regression models
44
45 420 to detect associations between study size and effect size.⁷⁷

48 421 Exploring heterogeneity and sensitivity analyses

50
51 422 We will explore whether treatment effects for the two primary outcomes are robust in subgroup
52
53 423 analyses and network meta-regression using the following characteristics:^{78 79}

- 55 424 (1) level of treatment resistance (see Meta-regression analysis of treatment resistance)
- 57 425 (2) study year
- 59 426 (3) depression severity at baseline

1
2
3 427 (4) proportion of participants to be allocated to placebo
4

5 428 (5) number of recruiting centers (single center vs multicentric studies)
6
7

8 429 Sensitivity of our conclusions for the two primary outcomes will be evaluated by analyzing:
9

10
11 430 (1) only studies with reported SD rather than imputed
12

13 431 (2) only studies that used non-response as inclusion criterion (i.e., we exclude studies that used
14
15 432 non-remission as an inclusion criterion)
16

17
18 433 (3) only studies with a low risk of bias
19

20 434 (4) only studies with a prospective ascertainment of at least one treatment trial failure
21
22

23 435 **GRADE quality assessment**
24

25
26 436 We will assess certainty of evidence contributing to network estimates of the primary outcomes by
27

28 437 using Confidence in Network Meta-Analysis (CiNeMA),⁸⁰ and according to the Grading of
29

30 438 Recommendations Assessment, Development and Evaluation (GRADE) framework.⁶⁹
31
32

33 439 **Patient and public involvement**
34

35
36 440 No patients or members of the public will be involved in conducting this study.
37
38

39 441 **Ethics and dissemination**
40

41
42 442 This review does not require ethical approval. Findings will be submitted for publication in a peer-
43

44 443 reviewed scientific journal. The data set will be made available.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

444 References

1. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1789-858. doi: 10.1016/s0140-6736(18)32279-7 [published Online First: 2018/11/30]
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905 [published Online First: 2006/11/01]
3. Cohen ZD, DeRubeis RJ. Treatment Selection in Depression. *Annual Review of Clinical Psychology* 2018;14(1):209-36. doi: 10.1146/annurev-clinpsy-050817-084746
4. Leuchter AF, Cook IA, Hamilton SP, et al. Biomarkers to predict antidepressant response. *Curr Psychiatry Rep* 2010;12(6):553-62. doi: 10.1007/s11920-010-0160-4 [published Online First: 2010/10/22]
5. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol* 2007;17(11):696-707. doi: 10.1016/j.euroneuro.2007.03.009 [published Online First: 2007/05/25]
6. Peeters FP, Ruhe HG, Wichers M, et al. The Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD): an extension of the Maudsley Staging Method. *J Affect Disord* 2016;205:365-71. doi: 10.1016/j.jad.2016.08.019 [published Online First: 2016/08/29]
7. Conway CR, George MS, Sackeim HA. Toward an Evidence-Based, Operational Definition of Treatment-Resistant Depression: When Enough Is Enough. *JAMA Psychiatry* 2017;74(1):9-10. doi: 10.1001/jamapsychiatry.2016.2586 [published Online First: 2016/10/27]
8. Ruhé HG, van Rooijen G, Spijker J, et al. Staging methods for treatment resistant depression. A systematic review. *J Affect Disord* 2012;137(1-3):35-45. doi: 10.1016/j.jad.2011.02.020 [published Online First: 2011/03/26]
9. van Dijk DA, van den Boogaard TM, Deen ML, et al. Predicting clinical course in major depressive disorder: The association between DM-TRD score and symptom severity over time in 1115 outpatients. *Depress Anxiety* 2019;36(4):345-52. doi: 10.1002/da.22865 [published Online First: 2018/11/27]
10. Fekadu A, Rane LJ, Wooderson SC, et al. Prediction of longer-term outcome of treatment-resistant depression in tertiary care. *Br J Psychiatry* 2012;201(5):369-75. doi: 10.1192/bjp.bp.111.102665 [published Online First: 2012/09/08]
11. Fekadu A, Wooderson SC, Markopoulou K, et al. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin Psychiatry* 2009;70(7):952-7. doi: 10.4088/JCP.08m04728 [published Online First: 2009/05/22]
12. Fekadu A, Wooderson S, Donaldson C, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry* 2009;70(2):177-84. doi: 10.4088/jcp.08m04309 [published Online First: 2009/02/05]
13. Nierenberg AA, Amsterdam JD. Treatment-resistant depression: definition and treatment approaches. *J Clin Psychiatry* 1990;51 Suppl:39-47; discussion 48-50. [published Online First: 1990/06/01]
14. Spijker J, Nolen WA. [The algorithm for the biological treatment of depression in the Dutch multidisciplinary guideline on depression]. *Tijdschr Psychiatr* 2011;53(4):223-33. [published Online First: 2011/04/21]
15. NICE. Depression in adults: recognition and management (NICE Clinical Guidelines No. 90) London: National Institute for Health and Care Excellence (UK); 2009 [Available from: <https://www.ncbi.nlm.nih.gov/books/NBK553259/>].

- 1
2
3 494 16. Fredman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse, and relapse with selective
4 495 serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. *J*
5 496 *Clin Psychiatry* 2000;61(6):403-8. doi: 10.4088/jcp.v61n0602 [published Online First:
6 497 2000/07/20]
- 7
8 498 17. Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression.
9 499 *International Journal of Psychiatry in Clinical Practice* 2017;21(1):13-23. doi:
10 500 10.1080/13651501.2016.1248852
- 11 501 18. Adli M, Baethge C, Heinz A, et al. Is dose escalation of antidepressants a rational strategy after a
12 502 medium-dose treatment has failed? A systematic review. *Eur Arch Psychiatry Clin Neurosci*
13 503 2005;255(6):387-400. doi: 10.1007/s00406-005-0579-5 [published Online First: 2005/05/04]
- 14 504 19. Furukawa TA, Cipriani A, Cowen PJ, et al. Optimal dose of selective serotonin reuptake inhibitors,
15 505 venlafaxine, and mirtazapine in major depression: a systematic review and dose-response
16 506 meta-analysis. *Lancet Psychiatry* 2019;6(7):601-09. doi: 10.1016/s2215-0366(19)30217-2
17 507 [published Online First: 2019/06/11]
- 18 508 20. Ruhe HG, Booij J, van Weert HC, et al. [Dose-escalation of SSRIS in major depressive disorder.
20 509 Should not be recommended in current guidelines]. *Tijdschr Psychiatr* 2010;52(9):615-25.
21 510 [published Online First: 2010/09/24]
- 22 511 21. Kato T, Furukawa TA, Mantani A, et al. Optimising first- and second-line treatment strategies for
23 512 untreated major depressive disorder - the SUN☺D study: a pragmatic, multi-centre,
24 513 assessor-blinded randomised controlled trial. *BMC medicine* 2018;16(1):103-03. doi:
25 514 10.1186/s12916-018-1096-5
- 26 515 22. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression
28 516 (STAR*D) trial: a review. *Can J Psychiatry* 2010;55(3):126-35. doi:
29 517 10.1177/070674371005500303 [published Online First: 2010/04/08]
- 30 518 23. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen*
31 519 *Psychiatry* 2007;64(3):327-37. doi: 10.1001/archpsyc.64.3.327 [published Online First:
32 520 2007/03/07]
- 33 521 24. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure
34 522 of SSRIs for depression. *N Engl J Med* 2006;354(12):1231-42. doi: 10.1056/NEJMoa052963
35 523 [published Online First: 2006/03/24]
- 36 524 25. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis
38 525 comparing within- versus across-class switches. *Biol Psychiatry* 2008;63(7):699-704. doi:
39 526 10.1016/j.biopsych.2007.08.010 [published Online First: 2007/10/09]
- 40 527 26. Zhou X, Keitner GI, Qin B, et al. Atypical Antipsychotic Augmentation for Treatment-Resistant
41 528 Depression: A Systematic Review and Network Meta-Analysis. *Int J Neuropsychopharmacol*
42 529 2015;18(11):pyv060. doi: 10.1093/ijnp/pyv060 [published Online First: 2015/05/28]
- 43 530 27. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of
44 531 augmentation agents in treatment-resistant depression: systematic review and network
45 532 meta-analysis. *J Clin Psychiatry* 2015;76(4):e487-98. doi: 10.4088/JCP.14r09204 [published
46 533 Online First: 2015/04/29]
- 47 534 28. Papadimitropoulou K, Vossen C, Karabis A, et al. Comparative efficacy and tolerability of
48 535 pharmacological and somatic interventions in adult patients with treatment-resistant
49 536 depression: a systematic review and network meta-analysis. *Curr Med Res Opin*
50 537 2017;33(4):701-11. doi: 10.1080/03007995.2016.1277201 [published Online First:
51 538 2016/12/31]
- 52 539 29. Carter B, Strawbridge R, Husain MI, et al. Relative effectiveness of augmentation treatments for
53 540 treatment-resistant depression: a systematic review and network meta-analysis.
54 541 *International Review of Psychiatry* 2020;32(5-6):477-90. doi:
55 542 10.1080/09540261.2020.1765748
- 56 543 30. Li H, Cui L, Li J, et al. Comparative efficacy and acceptability of neuromodulation procedures in
57 544 the treatment of treatment-resistant depression: a network meta-analysis of randomized

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- controlled trials. *Journal of affective disorders* 2021;287:115-24. doi:
<https://dx.doi.org/10.1016/j.jad.2021.03.019>
- 547 31. Wang HR, Woo YS, Ahn HS, et al. Can Atypical Antipsychotic Augmentation Reduce Subsequent
548 Treatment Failure More Effectively Among Depressed Patients with a Higher Degree of
549 Treatment Resistance? A Meta-Analysis of Randomized Controlled Trials. *Int J*
550 *Neuropsychopharmacol* 2015;18(8) doi: 10.1093/ijnp/pyv023 [published Online First:
551 2015/03/15]
- 552 32. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-
553 analysis: many names, many benefits, many concerns for the next generation evidence
554 synthesis tool. *Res Synth Methods* 2012;3(2):80-97. doi: 10.1002/jrsm.1037 [published Online
555 First: 2012/06/01]
- 556 33. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-
557 analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi: 10.1186/2046-4053-4-
558 1 [published Online First: 2015/01/03]
- 559 34. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant
560 nonresponders. *J Clin Psychiatry* 1997;58 Suppl 13:23-9. [published Online First: 1997/01/01]
- 561 35. Sprah L, Dernovsek MZ, Wahlbeck K, et al. Psychiatric readmissions and their association with
562 physical comorbidity: a systematic literature review. *BMC Psychiatry* 2017;17(1):2. doi:
563 10.1186/s12888-016-1172-3 [published Online First: 2017/01/05]
- 564 36. Michopoulos I, Furukawa TA, Noma H, et al. Different control conditions can produce different
565 effect estimates in psychotherapy trials for depression. *J Clin Epidemiol* 2021;132:59-70. doi:
566 10.1016/j.jclinepi.2020.12.012 [published Online First: 2020/12/19]
- 567 37. Furukawa TA, Salanti G, Atkinson LZ, et al. Comparative efficacy and acceptability of first-
568 generation and second-generation antidepressants in the acute treatment of major
569 depression: protocol for a network meta-analysis. *BMJ Open* 2016;6(7):e010919. doi:
570 10.1136/bmjopen-2015-010919 [published Online First: 2016/07/13]
- 571 38. da Costa BR, Nüesch E, Rutjes AW, et al. Combining follow-up and change data is valid in meta-
572 analyses of continuous outcomes: a meta-epidemiological study. *J Clin Epidemiol*
573 2013;66(8):847-55. doi: 10.1016/j.jclinepi.2013.03.009 [published Online First: 2013/06/12]
- 574 39. Uher R, Mors O, Rietschel M, et al. Early and delayed onset of response to antidepressants in
575 individual trajectories of change during treatment of major depression: a secondary analysis
576 of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. *J Clin*
577 *Psychiatry* 2011;72(11):1478-84. doi: 10.4088/JCP.10m06419 [published Online First:
578 2011/12/01]
- 579 40. Quitkin FM, Petkova E, McGrath PJ, et al. When should a trial of fluoxetine for major depression
580 be declared failed? *Am J Psychiatry* 2003;160(4):734-40. doi: 10.1176/appi.ajp.160.4.734
581 [published Online First: 2003/04/02]
- 582 41. Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. The Timing of Antidepressant Effects: A
583 Comparison of Diverse Pharmacological and Somatic Treatments. *Pharmaceuticals (Basel)*
584 2010;3(1):19-41. doi: 10.3390/ph3010019 [published Online First: 2010/01/06]
- 585 42. Robinson L, Delgado J, Kellett S. The dose-response effect in routinely delivered psychological
586 therapies: A systematic review. *Psychother Res* 2020;30(1):79-96. doi:
587 10.1080/10503307.2019.1566676 [published Online First: 2019/01/22]
- 588 43. Davies P, Ijaz S, Williams CJ, et al. Pharmacological interventions for treatment-resistant
589 depression in adults. *Cochrane Database Syst Rev* 2019;12(12):Cd010557. doi:
590 10.1002/14651858.CD010557.pub2 [published Online First: 2019/12/18]
- 591 44. van Bronswijk S, Moopen N, Beijers L, et al. Effectiveness of psychotherapy for treatment-
592 resistant depression: a meta-analysis and meta-regression. *Psychol Med* 2019;49(3):366-79.
593 doi: 10.1017/s003329171800199x [published Online First: 2018/08/25]
- 594 45. Ijaz S, Davies P, Williams CJ, et al. Psychological therapies for treatment-resistant depression in
595 adults. *Cochrane Database Syst Rev* 2018;5(5):Cd010558. doi:
596 10.1002/14651858.CD010558.pub2 [published Online First: 2018/05/16]

- 1
2
3 597 46. Cantù F, Ciappolino V, Enrico P, et al. Augmentation with Atypical Antipsychotics for Treatment-
4 598 Resistant Depression. *J Affect Disord* 2021;280(Pt A):45-53. doi: 10.1016/j.jad.2020.11.006
5 599 [published Online First: 2020/11/18]
6 600 47. Song GM, Tian X, Shuai T, et al. Treatment of Adults With Treatment-Resistant Depression:
7 601 Electroconvulsive Therapy Plus Antidepressant or Electroconvulsive Therapy Alone? Evidence
8 602 From an Indirect Comparison Meta-Analysis. *Medicine (Baltimore)* 2015;94(26):e1052. doi:
9 603 10.1097/md.0000000000001052 [published Online First: 2015/07/02]
10 604 48. Bottomley JM, LeReun C, Diamantopoulos A, et al. Vagus nerve stimulation (VNS) therapy in
11 605 patients with treatment resistant depression: A systematic review and meta-analysis. *Compr*
12 606 *Psychiatry* 2019;98:152156. doi: 10.1016/j.comppsy.2019.152156 [published Online First:
13 607 2020/01/25]
14 608 49. Zhou C, Zhang H, Qin Y, et al. A systematic review and meta-analysis of deep brain stimulation in
15 609 treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;82:224-32.
16 610 doi: 10.1016/j.pnpbp.2017.11.012 [published Online First: 2017/11/18]
17 611 50. Mutz J, Vipulanathan V, Carter B, et al. Comparative efficacy and acceptability of non-surgical
18 612 brain stimulation for the acute treatment of major depressive episodes in adults: systematic
19 613 review and network meta-analysis. *Bmj* 2019;364:l1079. doi: 10.1136/bmj.l1079 [published
20 614 Online First: 2019/03/29]
21 615 51. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic
22 616 reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First:
23 617 2016/12/07]
24 618 52. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of
25 619 Interventions 2021 [version 6.2 (updated February 2021)]:[Available from:
26 620 www.training.cochrane.org/handbook.
27 621 53. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial.
28 622 *Evid Based Ment Health* 2019;22(4):153-60. doi: 10.1136/ebmental-2019-300117 [published
29 623 Online First: 2019/09/30]
30 624 54. Rucker G, Krahn U, König J, et al. netmeta: Network Meta-Analysis using Frequentist Methods.
31 625 2021
32 626 55. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria, 2021.
33 627 56. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth*
34 628 *Methods* 2019;10(3):398-419. doi: 10.1002/jrsm.1347 [published Online First: 2019/03/12]
35 629 57. Doi SA, Furuya-Kanamori L, Xu C, et al. Questionable utility of the relative risk in clinical research:
36 630 a call for change to practice. *J Clin Epidemiol* 2020 doi: 10.1016/j.jclinepi.2020.08.019
37 631 [published Online First: 2020/11/11]
38 632 58. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
39 633 systematic reviews incorporating network meta-analyses of health care interventions:
40 634 checklist and explanations. *Ann Intern Med* 2015;162(11):777-84. doi: 10.7326/m14-2385
41 635 [published Online First: 2015/06/02]
42 636 59. Turner RM, Jackson D, Wei Y, et al. Predictive distributions for between-study heterogeneity and
43 637 simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015;34(6):984-98.
44 638 doi: 10.1002/sim.6381 [published Online First: 2014/12/06]
45 639 60. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
46 640 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]
47 641 61. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-
48 642 analyses. *Bmj* 2007;335(7626):914-6. doi: 10.1136/bmj.39343.408449.80 [published Online
49 643 First: 2007/11/03]
50 644 62. Taylor DM, Cornelius V, Smith L, et al. Comparative efficacy and acceptability of drug treatments
51 645 for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*
52 646 2014;130(6):452-69. doi: 10.1111/acps.12343 [published Online First: 2014/10/07]
53
54
55
56
57
58
59
60

- 1
2
3 647 63. Wijkstra J, Lijmer J, Burger H, et al. Pharmacological treatment for psychotic depression.
4 648 *Cochrane Database Syst Rev* 2015(7):CD004044. doi: 10.1002/14651858.CD004044.pub4
5 649 [published Online First: 2015/08/01]
6 650 64. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a
7 651 patient-level meta-analysis. *Jama* 2010;303(1):47-53. doi: 10.1001/jama.2009.1943
8 652 [published Online First: 2010/01/07]
9 653 65. Gibbons RD, Hur K, Brown CH, et al. Benefits from antidepressants: synthesis of 6-week patient-
10 654 level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and
11 655 venlafaxine. *Arch Gen Psychiatry* 2012;69(6):572-9. doi:
12 656 10.1001/archgenpsychiatry.2011.2044 [published Online First: 2012/03/07]
13 657 66. Khan A, Kolts RL, Thase ME, et al. Research design features and patient characteristics associated
14 658 with the outcome of antidepressant clinical trials. *Am J Psychiatry* 2004;161(11):2045-9. doi:
15 659 10.1176/appi.ajp.161.11.2045 [published Online First: 2004/10/30]
16 660 67. Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome?. The effects of placebo
17 661 control and treatment duration in antidepressant trials. *Psychother Psychosom*
18 662 2009;78(3):172-81. doi: 10.1159/000209348 [published Online First: 2009/03/27]
19 663 68. Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to
20 664 active antidepressant treatment in randomized controlled trials? Results from pooled and
21 665 meta-analyses. *J Clin Psychiatry* 2010;71(3):270-9. doi: 10.4088/JCP.08r04516blu [published
22 666 Online First: 2010/02/04]
23 667 69. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network
24 668 meta-analysis. *PLoS One* 2014;9(7):e99682. doi: 10.1371/journal.pone.0099682 [published
25 669 Online First: 2014/07/06]
26 670 70. Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-
27 671 analysis. *Stat Med* 2010;29(7-8):932-44. doi: 10.1002/sim.3767 [published Online First:
28 672 2010/03/10]
29 673 71. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis:
30 674 concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-110. doi:
31 675 10.1002/jrsm.1044 [published Online First: 2012/06/01]
32 676 72. Jackson D, Barrett JK, Rice S, et al. A design-by-treatment interaction model for network meta-
33 677 analysis with random inconsistency effects. *Stat Med* 2014;33(21):3639-54. doi:
34 678 10.1002/sim.6188 [published Online First: 2014/04/30]
35 679 73. Veroniki AA, Mavridis D, Higgins JP, et al. Characteristics of a loop of evidence that affect
36 680 detection and estimation of inconsistency: a simulation study. *BMC Med Res Methodol*
37 681 2014;14:106. doi: 10.1186/1471-2288-14-106 [published Online First: 2014/09/23]
38 682 74. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of
39 683 interventions. *Int J Epidemiol* 2013;42(1):332-45. doi: 10.1093/ije/dys222 [published Online
40 684 First: 2013/03/20]
41 685 75. Furukawa TA, Miura T, Chaimani A, et al. Using the contribution matrix to evaluate complex study
42 686 limitations in a network meta-analysis: a case study of bipolar maintenance
43 687 pharmacotherapy review. *BMC Res Notes* 2016;9:218. doi: 10.1186/s13104-016-2019-1
44 688 [published Online First: 2016/04/15]
45 689 76. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help
46 690 distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*
47 691 2008;61(10):991-6. doi: 10.1016/j.jclinepi.2007.11.010 [published Online First: 2008/06/10]
48 692 77. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study
49 693 effects in a network of interventions. *Res Synth Methods* 2012;3(2):161-76. doi:
50 694 10.1002/jrsm.57 [published Online First: 2012/06/01]
51 695 78. Greenberg RP, Bornstein RF, Greenberg MD, et al. A meta-analysis of antidepressant outcome
52 696 under "blinder" conditions. *J Consult Clin Psychol* 1992;60(5):664-9; discussion 70-7. doi:
53 697 10.1037//0022-006x.60.5.664 [published Online First: 1992/10/01]
54
55
56
57
58
59
60

- 1
2
3 698 79. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome?
4 699 A meta-regression of double-blind, randomized clinical trials in MDD. *Eur*
5 700 *Neuropsychopharmacol* 2009;19(1):34-40. doi: 10.1016/j.euroneuro.2008.08.009 [published
6 701 Online First: 2008/10/01]
7 702 80. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing
8 703 confidence in the results of a network meta-analysis. *PLoS Med* 2020;17(4):e1003082. doi:
9 704 10.1371/journal.pmed.1003082 [published Online First: 2020/04/04]

10
11 705
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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, 183-184
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		79-82
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		185-187
Support					
Sources	5a	Indicate sources of financial or other support for the review	Y		84-85
Sponsor	5b	Provide name for the review funder and/or sponsor	Y		84-85
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Y		84-85
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	Y		106-163
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y		164-181
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) to be used as criteria for eligibility for the review	Y		190-235, 253-269
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey	Y		271-285

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		literature sources) with planned dates of coverage			
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		287-288, 294-295
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		287-292
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		294-296, 316-319
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		296-315
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		237-251
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		194-195, 321-332
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Y		351-356
	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		328-356, 373-416
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Y		363-371, 422-434
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y		335-336
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Y		418-420
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Y		436-438

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.	bupirone, 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.	i. repetitive transcranial magnetic stimulation (rTMS) ⁽²⁾ ii. accelerated transcranial magnetic stimulation (aTMS) iii. deep transcranial magnetic stimulation (dTMS)

		<ul style="list-style-type: none"> iv. priming transcranial magnetic stimulation (priming TMS) v. thetaburst stimulation (TBS)⁽³⁾ (transcranial magnetic stimulation)
		<ul style="list-style-type: none"> 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)

Notes:

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

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

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

(4) Psychological therapy is defined as a face-to-face interaction with a therapist, delivered either in a group or individually, in both in- and outpatient settings, possibly in a blended format. Solely e-health interventions will be excluded.⁴⁴

Appendix 3. Draft of search strategy

Below we present the query for use in MEDLINE (Ovid). The keywords for TRD (see #1) are based on a version used by Davies, et al.⁴³, to which “(depress* and (adjunct* adj5 (treatment or therapy or placebo or antidepress*))).mp.” and “(antidepress* adj3 resistan*).ti,ab,kf.” are added to enhance sensitivity. The RCT filter (see #5 and #6) has also been adapted from Davies, et al.⁴³.

	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 (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 (depress* adj3 (refractor* or resistan* or chronic* or persist*).ti,ab,kf. OR (depress* adj3 (relaps* or recurr*).ti,kf. OR (depress* and (augment* or potentiat*).mp. OR (depress* and (adjunct* adj5 (treatment or therapy or placebo or antidepress*))).mp. OR (antidepress* adj3 resistan*).ti,ab,kf.
#2	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

	<p>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 tranylcypromine/ 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 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 dexamethylphenidate).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</p>

	<p>("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 "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.</p>
#5	<p>(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</p>

	"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"

BMJ Open

Efficacy and acceptability of next step treatment strategies in adults with treatment-resistant major depressive disorder: Protocol for systematic review and network meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056777.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2022
Complete List of Authors:	Muit, Jan; Radboud University Nijmegen, Department of Psychiatry van Eijndhoven, Philip FP; Radboud University Nijmegen, Department of Psychiatry Cipriani, Andrea; University of Oxford, Department of Psychiatry; Warneford Hospital Dalhuisen, Iris; Radboud University Nijmegen, Department of Psychiatry van Bronswijk, Suzanne; Maastricht University, Department of Psychiatry and Psychology Furukawa, Toshi; School of Public Health, Departments of Health Promotion and Human Behavior and of Clinical Epidemiology Ruhe, Henricus; Radboud University Nijmegen, Department of Psychiatry
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics, Mental health
Keywords:	Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts

1
2
3 1 *Efficacy and acceptability of next step treatment strategies in adults with treatment-resistant major*
4
5 2 *depressive disorder: Protocol for systematic review and network meta-analysis*
6
7
8

9 3 Authors

10
11
12 4 Jan J Muit, MD (corresponding author) (ORCID 0000-0002-0353-2905)
13 5 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
14 6 P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
15 7 Tel. +31(0)24 361 35 13
16 8 bob.muit@radboudumc.nl
17 9

18
19 10 Philip FP van Eijndhoven, MD, PhD (ORCID 0000-0003-3474-4326)
20 11 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
21 12 philip.vaneijndhoven@radboudumc.nl
22 13

23 14 Andrea Cipriani, MD, PhD (ORCID 0000-0001-5179-8321)
24 15 Department of Psychiatry, University of Oxford, Oxford, UK
25 16 Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK
26 17 andrea.cipriani@psych.ox.ac.uk
27 18

28
29 19 Iris Dalhuisen, MSc (ORCID 0000-0002-7539-6498)
30 20 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
31 21 iris.dalhuisen@radboudumc.nl
32 22

33 23 Suzanne van Bronswijk, MD, PhD (OCiD 0000-0002-2983-1268)
34 24 Department of Psychiatry and Psychology, University Hospital Maastricht, Netherlands
35 25 School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences,
36 26 Maastricht University, Netherlands
37 27 suzanne.vanbronswijk@maastrichtuniversity.nl
38 28

39
40 29 Toshi A Furukawa, MD, PhD (ORCID 0000-0003-2159-3776)
41 30 Departments of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto
42 31 University Graduate School of Medicine / School of Public Health, Kyoto, Japan
43 32 furukawa@kuhp.kyoto-u.ac.jp
44 33

45 34 Henricus G Ruhe, MD, PhD
46 35 Department of Psychiatry, Radboud University, Nijmegen, Netherlands
47 36 eric.ruhe@radboudumc.nl
48 37

49 37 Abstract

50 38 Introduction

51
52
53
54
55
56 39 For major depression a one-size-fits-all treatment does not exist. Patients enter a 'trial-and-change'
57
58 40 algorithm in which effective therapies are subsequently applied. Unfortunately, an empirically based
59
60

1
2
3 41 order of treatments has not yet been determined. There is a magnitude of different treatment
4
5 42 strategies while clinical trials only compare a small number of these. Network meta-analyses (NMA)
6
7 43 might offer a solution, but so far have been limited in scope and did not account for possible
8
9 44 differences in population characteristics that arise with increasing levels of treatment-resistance,
10
11 45 potentially violating the transitivity assumption. We therefore present a protocol for a systematic
12
13 46 review and network meta-analysis aiming at summarizing and ranking treatments for TRD while
14
15 47 covering a broad range of therapeutic options and accounting for possible differences in population
16
17 48 characteristics at increasing levels of treatment-resistance.

21 49 **Methods and analysis**

22
23
24 50 Randomized controlled trials will be included that compared next-step pharmacological,
25
26 51 neuromodulation or psychological treatments for treatment-resistant depression (TRD; i.e., failure to
27
28 52 respond to ≥ 1 adequate antidepressant drug trial(s) in the current episode) to each other or to a
29
30 53 control condition. Primary outcomes will be the proportion of patients who responded to (efficacy)
31
32 54 and dropped out of (acceptability) the allocated treatment. A random effects NMA will be
33
34 55 conducted, synthesizing the evidence for each outcome and determining the differential efficacy of
35
36 56 treatments. Heterogeneity in treatment nodes will be reduced by considering alternative geometries
37
38 57 of the network structure and by conducting a meta-regression examining different levels of TRD.
39
40 58 Local and global methods will be applied to evaluate consistency. The Cochrane Risk of Bias 2 (RoB2)
41
42 59 tool, Confidence in Network Meta-Analysis (CiNeMA), and the Grading of Recommendations
43
44 60 Assessment, Development and Evaluation (GRADE) framework will be used to assess risk of bias and
45
46 61 certainty.

51 62 **Ethics and dissemination**

52
53
54 63 This review does not require ethical approval.

56 64 **Registration details**

57
58
59 65 PROSPERO registration number: pending.

66 Article summary

67 Strengths and limitations of this study

- 68 • The systematic review and meta-analysis will follow the Preferred Reporting Items for
69 Systematic Reviews and Meta-Analyses guidelines.
- 70 • We will address the potential heterogeneity arising from different levels of TRD
- 71 • Heterogeneity within treatment nodes will be limited by considering alternative geometries
72 of the network structure.
- 73 • This study does not address quality of life
- 74 • Limitations of primary studies will be assessed using the Cochrane RoB2 tool, CiNeMA, and
75 the GRADE framework.

76 Author contributions

77 HGR is guarantor. JJM, PFPE and HGR devised the study and drafted the protocol. JJM designed the
78 search strategy. All authors contributed to the development of the selection criteria. ID, SB, TAF and
79 AC assisted in drafting the protocol. TAF and AC assisted in designing the study and provided
80 statistical expertise. All authors read, provided feedback and approved the final manuscript.

81 Funding

82 This research received no specific grant from any funding agency in the public, commercial or not-
83 for-profit sectors.

84 Competing interests statement

85 JJM: None to declare. PFPE: reports grants from ZonMW and speaking fees from Janssen outside of
86 the submitted work. AC is supported by the National Institute for Health Research (NIHR) Oxford
87 Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017-08-ST2-
88 006), by the NIHR Oxford and Thames Valley Applied Research Collaboration and by the NIHR Oxford

1
2
3 89 Health Biomedical Research Centre (grant BRC-1215-20005). The views expressed are those of the
4
5 90 authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department
6
7 91 of Health; he has received research and consultancy fees from INCiPiT (Italian Network for Paediatric
8
9 92 Trials), CARIPLO Foundation and Angelini Pharma. ID: None to declare. SB: None to declare. TAF: TAF
10
11 93 reports grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD, grants and
12
13 94 personal fees from Shionogi, outside the submitted work; In addition, TAF has a patent 2020-548587
14
15 95 concerning smartphone CBT apps pending, and intellectual properties for Kokoro-app licensed to
16
17 96 Mitsubishi-Tanabe. HGR reports grants from ZonMW, Hersenstichting, EU Horizon 2020 and speaking
18
19 97 fees from Lundbeck and Janssen outside of the submitted work.
20
21
22
23

24 98 Keywords

25
26
27 99 "Depressive Disorder, Treatment-Resistant"[Mesh]; "Antidepressive Agents"[Mesh]; "Treatment
28
29 100 Outcome"[Mesh]; "Network Meta-Analysis"[Mesh]; "Randomized Controlled Trials as Topic"[Mesh]
30
31

32 33 101 Word count

34
35
36 102 4062
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

103 Introduction

104 Depression has been one of the leading causes of non-fatal health loss for nearly three decades, with
105 Major Depressive Disorder (MDD) affecting 163 million people worldwide in 2017.¹ No one-size-fits-
106 all treatment exists.^{2 3} Patients enter a ‘trial-and-change’ algorithm in which evidence-based
107 treatments are subsequently applied.⁴ Unfortunately, there is no empirically based optimal
108 treatment sequence determined yet.

109 In order to consider a depression to be treatment-resistant, several adequate treatment trials of
110 sufficient dosage and length must have been previously applied. Definitions of ‘treatment-resistance’
111 range from nonresponse to one antidepressant medication (ADM) (after ≥ 4 weeks of treatment) to a
112 failure to respond to more than 10 adequate trials of different classes of ADM and augmentation
113 strategies, electroconvulsive therapy (ECT) and psychological treatments, taking into account factors
114 such as disease severity, comorbidity, functional impairment and intensity of treatment.^{5 6} However,
115 most recent insights suggest to use a dimensional approach to define levels of treatment-resistant
116 depression (TRD).⁶⁻¹² In addition, TRD is often confused with “pseudo-resistant” depression, a term
117 used to describe non-response to antidepressant trials of inadequate dosage and duration.¹³

118 Common strategies for treatment-resistance to ADM include dose-escalation and switching.¹⁴⁻¹⁷
119 Dose-escalation of the first ADM has extensively been addressed in previous research. It was found
120 that beyond 20 to 40mg fluoxetine equivalents for selective serotonin reuptake inhibitors (SSRI) and
121 above 30mg mirtazapine, efficacy does not increase, leaving limited room for dose-escalation in non-
122 responders to these dosages.¹⁸⁻²⁰ However, it was found that adding or switching to mirtazapine was
123 superior to continuing sertraline among previously untreated patients.²¹ The Sequenced Treatment
124 Alternatives to Relieve Depression (STAR*D) trial aimed to ascertain whether certain treatments
125 were more optimal after one or more failed trials.^{2 22} No differences were found between any of the
126 next-step treatment strategies. However, it was found that patients with higher levels of treatment-
127 resistance showed lower rates of remission, as remission rates dropped after two failed trials

1
2
3 128 (remission rates of 36.8-30.6% after step 1 and 2 versus 13.7-13.0% after step 3 and 4). The authors
4
5 129 hypothesized the steep reduction in remission rates after step 2 occurred due to differences in
6
7 130 population characteristics (e.g. presence of comorbid medical or psychiatric disorders, or degree of
8
9 131 chronicity) and general heterogeneity of MDD. Alternatively, poor monitoring of nortriptyline or
10
11 132 lithium levels and inadequate dosing of MAO-inhibitors might explain the poor responses in step 3
12
13 133 and 4 in STAR*D. Nevertheless, the decreases in response and remission rates after the second ADM
14
15 134 might be related to a selection process of patients that are non-responsive to all types of mono-
16
17 135 aminergic ADM.²³ This could explain the slight advantage of between-class over within-class switches
18
19 136 after a first ADM,^{17 24 25} but it remains to be shown empirically whether this selection effect is indeed
20
21 137 applicable to increasing levels of TRD. Hypothetically, treatments targeting different pathways might
22
23 138 provide better efficacy in these cases.

24
25
26
27
28 139 Several efforts have been undertaken to perform network meta-analysis (NMA) for TRD,²⁶⁻³⁰
29
30 140 however overall conclusions are impeded by various factors. First, these NMAs employed various
31
32 141 definitions of TRD: e.g. two of them also included patients with only one failed adequate trial in the
33
34 142 current episode.^{26 27} Second, these NMAs studied various types of interventions: from only a few
35
36 143 augmentation strategies²⁶ or only neuromodulation strategies³⁰ to several augmentation,
37
38 144 pharmacotherapy switch, and neuromodulation strategies.²⁸ Third, only one study accounted for
39
40 145 differences in dosages.²⁶ Fourth, one study accounted for outcome measures at different points in
41
42 146 time, ranging from 2 to 8 weeks, limiting the number of possible comparisons.²⁸ Fifth, the most
43
44 147 recent study investigating multiple modalities grouped treatments based on the presumed
45
46 148 mechanisms of action, without clear description of considerations regarding the treatment
47
48 149 network.²⁹ Although Wang, et al.³¹ stratified for number of failed ADM in a pairwise meta-analysis,
49
50 150 none of the NMAs²⁶⁻²⁹ were able to account for levels of TRD and possible differences in population
51
52 151 characteristics that might arise with increasing levels of TRD,² which might violate the transitivity
53
54 152 assumption for NMA. Violation of the transitivity assumption would make estimating indirect
55
56 153 comparisons from unobserved head-to-head comparisons invalid.³² Neither were these studies able

1
2
3 154 to evaluate whether higher levels of treatment-resistance respond to more aggressive or invasive
4
5 155 treatments.^{7 29}
6
7

8 156 In summary, current research is affected by several complicating factors. No common consensus on
9
10 157 the definition of TRD exists. A magnitude of different treatment strategies is available while clinical
11
12 158 trials usually only compare a small number of these. NMAs performed so far are limited in scope and
13
14 159 do not account for possible differences in population characteristics that might arise with increasing
15
16 160 levels of TRD, potentially violating the transitivity assumption. Therefore, a more comprehensive
17
18 161 approach to summarize and determine relative efficacy of treatments for TRD is needed.
19
20
21
22

23 162 Objectives

24
25
26 163 The aim of this systematic review and NMA is to evaluate (1) the differential efficacy and
27
28 164 acceptability of treatment strategies when administered after a failed ADM trial in adults with MDD;
29
30 165 (2) whether differential efficacy and acceptability is dependent on the study-level of treatment-
31
32 166 resistance as defined by inclusion criteria used in the trials. These aims can be applied to the
33
34 167 following clinical questions: (1) what are next-step treatment strategies in adult patients with TRD
35
36 168 that are beneficial and/or safe? (2) how do the various treatment strategies compare to each other?
37
38 169 (3) does the level of treatment-resistance affect the differential efficacy of next-step treatment-
39
40 170 strategies?
41
42
43
44

45 171 In order to answer the first clinical question, absolute and relative efficacy and acceptability of next-
46
47 172 step antidepressant treatments for TRD will be examined using head-to-head and treatment-control
48
49 173 comparisons in pairwise meta-analyses. To answer the second clinical question, relative efficacy and
50
51 174 acceptability of the various next-step treatment strategies will be estimated in an NMA, while
52
53 175 ranking their probabilities of highest efficacy and acceptability to inform the treatment algorithm for
54
55 176 MDD. In order to answer the third clinical question, we will investigate the transitivity assumption by
56
57 177 examining the impact of the study's level of treatment resistance (i.e., the number of failed
58
59
60

1
2
3 178 antidepressant trials that studies required as an inclusion criterion) in a network meta-analysis with a
4
5 179 meta-regression.
6
7

8 9 180 **Methods**

10
11 181 This protocol is submitted with the International Prospective Register of Systematic Reviews
12
13 182 (PROSPERO) on 21-07-2021 (registration pending). We used the Preferred Reporting Items for
14
15 183 Systematic Review and Meta-Analysis Protocols (PRISMA-P),³³ see Appendix 1. In case of protocol
16
17 184 amendments, we will describe the date of each amendment together with a description of the
18
19 185 change and the rationale. We performed a preliminary search in May 2021, and aim to submit the
20
21 186 results in 2024.
22
23
24
25

26 187 **Eligibility criteria**

28 188 **Types of studies**

29
30 189 We include randomized controlled trials (RCT), in which next-step pharmacological, neuromodulation
31
32 190 or psychological treatment strategies are compared to each other or a control condition.
33
34
35

36 191 Quasi-randomised trials will be excluded, while cluster RCTs will be included when the clustering
37
38 192 effect can be taken into account. For cross-over trials the results from the first randomized treatment
39
40 193 period will be included. We will exclude studies where there was a high risk of bias arising from the
41
42 194 randomization process.
43
44
45

46 195 **Types of participants**

47
48 196 We include studies with patients aged ≥ 18 years with unipolar MDD diagnosed by using any
49
50 197 standard operationalised criteria, such as Feighner criteria, Research Diagnostic Criteria, DSM-III,
51
52 198 DSM-III-R, DSM-IV, DSM-5 and ICD-10.
53
54
55

56 199 We require studies where patients failed to respond to ≥ 1 ADM trial(s) prescribed at least at a
57
58 200 minimally effective dose for ≥ 4 weeks in the current episode.³⁴ We will not exclude studies that
59
60 201 considered intolerance to a previous treatment trial as a failure in their definition of TRD. Although

1
2
3 202 intolerance to treatment could be considered pseudo-resistance, in clinical practice it might not
4
5 203 always be possible to distinguish between failure and intolerance as information on previous failed
6
7 204 trials is often based on historical information. We will include studies with both prospectively and
8
9 205 historically assessed treatment failure.
10
11
12 206 Studies in which 20% or more of the participants are suffering from bipolar disorder, peri-partum
13
14 207 depression or psychotic depression will be excluded. We exclude RCTs that have included patients
15
16 208 with a concurrent *primary* diagnosis of another psychiatric or personality disorder. A secondary
17
18 209 diagnosis of another psychiatric disorder will not be considered an exclusion criterion. RCTs focusing
19
20 210 on patients with a concomitant medical illness will be excluded.³⁵ We include studies that allow use
21
22 211 of rescue medications, if these medications were made equally available to all treatment groups.
23
24
25
26

27 212 Types of interventions

28
29 213 We distinguish 8 types of next-step treatments covering different modalities: 1) Switching to a
30
31 214 different ADM, 2) Combining continued ADM with another ADM, 3) Augmenting ADM with another
32
33 215 psychopharmacological agent, 4) Switching to psychedelic or psychedelic-assisted therapy, 5)
34
35 216 Switching treatment to neuromodulation treatment, 6) Augmenting ADM with neuromodulation
36
37 217 treatment, 7) Switching treatment to psychological therapy, 8) Augmenting ADM with psychological
38
39 218 therapy. For a more detailed overview, see Appendix 2.
40
41
42

43 219 We will obtain information about interventions of interest either from head-to-head or controlled
44
45 220 trials. We exclude studies if the intervention is not targeted at the depressive disorder. Studies that
46
47 221 co-initiated multiple interventions of interest will not be excluded and treated as a combined
48
49 222 treatment.
50
51

- 52
53 223 • Comparator interventions (switching or augmenting)
 - 54
55 224 ○ Alternative intervention (head-to-head)
 - 56
57 225 ○ Pill placebo
 - 58
59 226 ○ Psychological placebo

- 1
2
3 227 ○ Sham neuromodulation
4
5 228 ○ Continuation of antidepressant treatment
6
7 229 ○ Treatment as usual (TAU; defined as standard non-protocolized treatment in primary
8
9 or secondary care, typically with pharmacotherapy)
10 230
11
12 231 ○ No treatment (NT; applies in case TAU involved virtually no intervention, defined as <
13
14 232 50% of patients receiving any antidepressant treatment (including pharmacotherapy,
15
16 233 psychological therapy and/or neuromodulation treatment); patients know they will
17
18 234 not receive active treatment after the trial)
19
20
21 235 ○ Waiting list control (WL; similar to NT, except patients know they will receive active
22
23 236 treatment after the waiting phase)³⁶

26 237 Outcome measures

28 238 Primary outcomes:

- 30
31 239 • Response (efficacy as a dichotomous outcome), for patients who did not respond to first-step
32
33 treatment strategies but achieved response with next-step treatment strategies.
34 240
35
36 241 • All-cause dropout (acceptability as a dichotomous outcome) for patients who left the trial or
37
38 242 stopped the treatment early due to any reason up to the end of study duration.

41 243 Secondary outcomes:

- 43
44 244 • Change in severity of symptoms measured on the Hamilton (HDRS) or Montgomery-Asberg
45
46 245 depression rating scales (MADRS) or other depression rating scales. Extraction of continuous
47
48 246 efficacy outcome data will be prioritized as proposed by Furukawa, et al.³⁷ Change scores
49
50 247 will be used when end point scores are not reported.³⁸
51
52
53 248 • Remission, for patients who did not respond or did not achieve remission with first-step
54
55 249 treatment strategies but achieved remission with next-step treatment strategies.
56
57 250 • Dropout due to adverse events (tolerability) measured as the proportion of patients who left
58
59 251 the trial early due to any adverse events.

1
2
3 252 We will use the original author's definition of "response" and "remission".
4
5

6 253 Trial duration 7

8 254 There is no consensus on the appropriate duration of an acute phase trial.^{39 40} Some newer
9
10 255 treatments might show effects within one session.⁴¹ Nevertheless, the effect of trials should at least
11
12 256 be evaluated after 4 weeks in order to determine stability of antidepressant effects. We will use the
13
14 257 original author's primary endpoint, ranging from 4 weeks or longer but less than 6 months, for
15
16 258 analysis of the acute phase outcome data. We address long-term outcomes by additionally analyzing
17
18 259 the primary outcomes at a treatment duration of 6 months or longer, if these data are available.^{42 43}
19
20

21 260 We will exclude studies from the statistical synthesis if no primary endpoint data for the 4+ weeks
22
23 261 period can be provided.³⁷
24
25

26 262 Comparability of dosages 27

28
29 263 We include fixed-dose and flexible-dose designs, and only include arms randomizing patients to
30
31 264 pharmacological, neuromodulation and psychological therapies within licensed doses and ranges of
32
33 265 approved treatments, and any dosage or range of unapproved treatments. In case of psychotherapy,
34
35 266 we require a minimum of 4 sessions, as this has been proposed as a minimally effective dose.⁴⁴
36
37
38

39 267 Setting 40

41 268 We will not apply restrictions by type of setting.
42
43

44 269 Language 45

46 270 We will apply no language restrictions.
47
48
49

50 271 Search strategy and data management 51

52 272 Search strategy 53

54
55 273 We will identify published, unpublished and ongoing RCTs that compared the efficacy and/or
56
57 274 acceptability of one treatment strategy to another treatment or to a control condition in the
58
59 275 treatment of TRD. The following sources will be searched: MEDLINE (Ovid), Cochrane Central Register
60

1
2
3 276 of Controlled Trials (CENTRAL), Embase (Ovid), LILACS database, and PsycINFO (Ovid). MEDLINE and
4
5 277 Embase will be searched from 2019 onwards, as these are also indexed by CENTRAL. CENTRAL,
6
7 278 LILACS and PsycINFO will be searched without date restrictions. Keywords for TRD and the RCT filter
8
9 279 are based on the strategy used by Davies, et al.⁴⁵ See Appendix 3 for the MEDLINE search strategy,
10
11 280 this strategy will be adapted to syntax and subject headings of other databases. We will search
12
13 281 international trial registries (clinicaltrials.gov and WHO International Clinical Trials Registry Platform).
14
15 282 We will contact the National Institute for Clinical Excellence (UK), the Institut für Qualität und
16
17 283 Wirtschaftlichkeit in Gesundheitswesen (Germany), check the websites of pharmaceutical companies
18
19 284 to obtain unpublished information and contact their representatives. In addition, we will search
20
21 285 references lists of included studies and recent systematic reviews.^{26-30 45-52}
22
23
24
25
26 286 Relevant authors will be contacted to supplement published/unpublished studies or incomplete
27
28 287 reporting, and reminded twice.

288 Study selection

289 Two investigators will independently review retrieved references and abstracts. Abstracts will be
30
31 290 screened using the Rayyan web-application.⁵³ A pilot will be conducted to refine screening policy of
32
33 291 both reviewers. If both reviewers agree about a trial not meeting eligibility criteria, it will be
34
35 292 excluded. We will obtain the full text of all remaining articles and use the same eligibility criteria to
36
37 293 determine the final selection. Two independent reviewers will perform the selection and resolve
38
39 294 disagreements via discussion with a third member of the review team.

295 Data extraction

296 Two reviewers will independently extract data and evaluate risk of bias for each selected trial. We
297
298 will use a structured data extraction sheet, the use of which will be refined in a pilot period.
299
300 Reliability of the data extraction will be checked. Information extracted will include trial
301
302 characteristics (such as lead author, journal, publication year, design, inclusion criteria, sponsorship,
303
304 number of recruitment centers, whether nonresponse was prospectively or retrospectively assessed,
305
306

1
2
3 301 type and definition of non-response at time of enrollment (non-responder or non-remitter), whether
4
5 302 non-response to psychological therapy was included in the TRD definition (a failed psychotherapy
6
7 303 trial is classified as a failure to respond to an adequate course of 8 attended sessions of a form of
8
9 304 psychotherapy with demonstrated effectiveness for MDD),⁷ definitions of response and remission),
10
11 305 participant characteristics (such as diagnostic criteria for depression, depression severity threshold,
12
13 306 participant age, gender distribution, setting, number of previously failed treatment trials in the
14
15 307 current episode, length of current depressive episode, number of previous episodes, length of
16
17 308 depressive disorder since age of onset, length of the previous treatment trial(s), depression severity
18
19 309 at baseline, physical or psychiatric comorbidity), outcome measures and intervention details
20
21 310 including co-interventions or continuation treatment. In case of pharmacological strategies we
22
23 311 extract dosing schedule, dose ranges and mean doses of study drugs. For the antidepressant
24
25 312 switching, we distinguish within or between class switches. In case of neuromodulation strategies we
26
27 313 extract data on treatment protocols, mean number of treatment sessions, targeted sites and
28
29 314 stimulation parameters. In case of psychological treatment strategies we extract type of
30
31 315 psychotherapy, mean number of treatment sessions, whether it concerned individual or group
32
33 316 therapy, whether therapy was offered in a blended format or as partially self-guided therapy, and
34
35 317 assessment of treatment integrity.
36
37
38
39
40
41 318 Level of TRD as inclusion criterion will be rated by two independent assessors. Reliability of this
42
43 319 assessment will be quantified. Disagreements in any of the extracted data will be resolved through
44
45 320 discussion with a third member of the review team. We will contact corresponding authors if
46
47 321 necessary, to obtain missing information.
48
49
50

51 322 Risk of Bias Assessment

52
53 323 Risk of bias of included studies will be assessed at outcome level for the two primary outcomes, using
54
55 324 the Risk of Bias 2 tool described in the Cochrane Handbook for Systematic Reviews of Interventions.⁵⁴
56
57 325 We will assess the following domains: bias arising from the randomization process, bias due to
58
59
60

1
2
3 326 deviations from intended interventions, bias due to missing outcome data, bias in measurement of the
4
5 327 outcome and bias in selection of the reported result. Two independent raters will perform the
6
7 328 assessment. If the raters disagree, the final rating will be made by consensus with the involvement of
8
9 329 another member of the review group. We will contact corresponding authors if necessary, to obtain
10
11 330 missing information. Overall risk of bias of each study will be categorized as follows: studies will be
12
13 331 classified as having low risk of bias if all domains were rated at low risk of bias; some concerns if none
14
15 332 were rated as high risk of bias but at least one domain raised some concerns; high risk of bias if at least
16
17 333 one domain was rated at high risk of bias or multiple domains raise some concerns in a way that
18
19 334 substantially lowers confidence in the results.
20
21
22
23

24 335 **Statistical analysis**

26 336 **Synthesis of results**

27
28
29 337 We will analyze the data using the meta⁵⁵ and netmeta⁵⁶ packages in R⁵⁷. Characteristics and findings
30
31 338 of included studies will be presented in text and tables. We will analyze dichotomous outcomes on an
32
33 339 intention-to-treat basis: all dropouts from treatment will be assumed to have had negative outcomes
34
35 340 (i.e. non-response).
36
37

38 341 **Pairwise meta-analysis**

39
40
41 342 In order to answer our three clinical questions (see Objectives), we conduct three main analyses. The
42
43 343 first clinical question relates to whether treating TRD with next-step treatment strategies is beneficial
44
45 344 and/or safe. Via pairwise meta-analysis, we will obtain estimates of efficacy and acceptability of
46
47 345 different treatment strategies, compared to both each other and control conditions. We will perform
48
49 346 a random-effects meta-analysis on the 8 types of next-step treatments as described in Appendix 2.
50
51 347 For each pairwise comparison, we will synthesize data to obtain summary standardized mean
52
53 348 differences (SMD, Hedges' g) for continuous outcomes or ORs for dichotomous outcomes, both with
54
55 349 95% Confidence Intervals (CI).^{58 59}
56
57
58
59
60

350 Network meta-analysis

351 The second clinical question we aim to answer is how various next-step treatment strategies
352 compare with each other. We will conduct an NMA to examine comparative efficacy and
353 acceptability of the next-step treatment strategies. In line with a previous protocol,³⁷ we assume that
354 patients who fulfil the inclusion criteria are equally likely to be randomized to any of the treatments
355 that we plan to compare. If the collected studies appear to be sufficiently homogeneous with respect
356 to distribution of effect modifiers (see Assessment of transitivity assumption section below), we will
357 conduct a random effects NMA to synthesize all evidence for each outcome, and obtain a
358 comprehensive ranking of all treatments. We will use arm-level data and the binomial likelihood for
359 dichotomous outcomes. We will account for correlations induced by possible multiarmed studies by
360 employing multivariate distributions. We will assume a single heterogeneity parameter for each
361 network. We will present summary ORs or SMD for all pairwise comparisons in a league table. To
362 rank the various treatments for each outcome, we will use the surface under the cumulative ranking
363 curve (SUCRA) and the mean ranks.

364 Meta-regression analysis of treatment resistance

365 In order to answer our third clinical question, we will perform meta-regression that evaluates the
366 impact of different levels of TRD on the primary outcomes. TRD is defined as (i) the number of failed
367 (antidepressant) treatment-trials (including augmentation and psychotherapy) that were required as
368 inclusion criterion for the study⁸ or (ii) dichotomized by slightly adapting Conway, et al.⁷: TRD level I
369 (Failure of 1 or 2 adequate dose-duration antidepressants or psychotherapy from different classes
370 (either in combination or succession)) or level II (Failure of ≥ 3 adequate antidepressant or
371 psychotherapy trials from different classes (either in combination or succession)). If sufficient data
372 are available, we aim to use the first, more detailed, grouping of TRD. If this proves unfeasible, we
373 will employ the second definition.

374 Alternative geometry of treatment network structure

375 As described in Appendix 2, we aim to group treatments by presumed mechanism of action (e.g.,
376 SSRI), and whether treatment was given as addition (augmentation) or replacement (switching) of
377 the previous treatment. Similar to Carter, et al.²⁹, we analyze the so-defined 8 different types of
378 treatment. Secondly, we aim to make detailed comparisons between individual treatments. We aim
379 to reduce heterogeneity in treatment nodes as much as possible, depending on how much data will
380 be available for analysis.⁶⁰ We will not analyze the antidepressants in the 'other' subgroup at the
381 subgroup level, due to the amount of heterogeneity we expect to arise from and lack of clinical
382 relevance of grouping together this heterogeneous group of antidepressants (i.e. we either include
383 them in the general antidepressant group, or as individual antidepressants). In case of atypical
384 antipsychotics, we account for differences in low or high doses, if possible.^{26 28} In case of
385 neuromodulation treatment and psychological therapy, if the data does not allow for separate
386 analysis for both switch strategies and augmentation strategies, these strategies will be (partially)
387 clustered within a 'mixed' strategy. We will consider clustering the comparator interventions in
388 'placebo' (i.e. pill placebo, psychological placebo and sham neuromodulation), 'pharmacological
389 control' (i.e. continuation of treatment and TAU) and 'no treatment' (i.e. NT and WL) groups, if the
390 groups are sufficiently homogeneous and consistent.

391 Assessment of heterogeneity (pairwise meta-analysis)

392 Comparable to Furukawa, et al.³⁷, in the pairwise meta-analysis, we check the possibility of
393 heterogeneity by visually inspecting the forest plots and compare the estimated value for the
394 heterogeneity variance with the corresponding empirical distribution.⁶¹ Moreover, we report the I^2
395 statistic with 95% CI,^{62 63} using the proposed thresholds in the Cochrane Handbook for interpretation
396 (e.g. 0-40% might not be important, 30-60% might represent moderate heterogeneity, 50-90% might
397 represent substantial heterogeneity, 75-100% might represent considerable heterogeneity).⁵⁴ In the
398 NMA, we estimate the heterogeneity variance and compare it with the empirical distribution.

399 Assessment of the transitivity assumption (network meta-analysis)

400 We will investigate the distribution of clinical and methodological variables that can act as effect
401 modifiers across treatment comparisons. We will examine levels of TRD as a possible violation of the
402 transitivity assumption, as higher levels of TRD might be accompanied by differences in population
403 characteristics.² Clinical features which moderate efficacy of antidepressants include bipolarity⁶⁴ and
404 psychotic features.⁶⁵ We assure transitivity regarding these variables by limiting our samples to
405 participants with non-psychotic, unipolar depression. Other variables that may influence our primary
406 outcomes include: age, depressive severity at baseline,^{66 67} dosing schedule⁶⁸ and whether inclusion
407 criteria of studies concerned non-response or non-remission. We will investigate whether these
408 variables are similarly distributed across studies grouped by comparison. In order to account for the
409 potential of placebo to violate the transitivity assumption, the comparability of placebo-controlled
410 studies with those providing head-to-head evidence will be examined carefully.^{69 70}

411 Assessment of inconsistency

412 We employ local and global methods to evaluate consistency of the network,⁷¹ using the node splitting
413 approach⁷² and design-by-treatment interaction test⁷³ respectively. We evaluate consistency in the
414 entire network by calculating the I^2 for network heterogeneity, inconsistency, and for both.^{73 74} Because
415 tests for inconsistency are known to have low power,⁷⁵ and 10% of evidence loops published in medical
416 literature are expected to be inconsistent,⁷⁶ we interpret statistical inference about inconsistency with
417 caution; possible sources of inconsistency will be explored even in the absence of evidence for
418 inconsistency.

419 Assessment of publication bias and small study effects

420 We use comparison-adjusted⁷⁷ and contour enhanced⁷⁸ funnel plots to investigate whether results in
421 imprecise trials differ from those in more precise trials. We will run network meta-regression models
422 to detect associations between study size and effect size.⁷⁹

423 Exploring heterogeneity and sensitivity analyses

424 We will explore whether treatment effects for the two primary outcomes are robust in subgroup
425 analyses and network meta-regression using the following characteristics:^{80 81}

426 (1) level of treatment resistance (see Meta-regression analysis of treatment resistance)

427 (2) study year

428 (3) depression severity at baseline

429 (4) proportion of participants to be allocated to placebo

430 (5) number of recruiting centers (single center vs multicentric studies)

431 Sensitivity of our conclusions for the two primary outcomes will be evaluated by analyzing:

432 (1) only studies with reported SD rather than imputed

433 (2) only studies that required at least two treatment trial failures in their definition of TRD

434 (3) only studies with a low risk of bias

435 (4) only studies with a prospective ascertainment of at least one treatment trial failure

436 GRADE quality assessment

437 We will assess certainty of evidence contributing to network estimates of the primary outcomes by
438 using Confidence in Network Meta-Analysis (CiNeMA),⁸² and according to the Grading of
439 Recommendations Assessment, Development and Evaluation (GRADE) framework.⁷¹

440 Patient and public involvement

441 No patients or members of the public will be involved in conducting this study.

442 Ethics and dissemination

443 This review does not require ethical approval. Findings will be submitted for publication in a peer-
444 reviewed scientific journal. The data set will be made available.

445 References

- 446 1. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases
447 and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global
448 Burden of Disease Study 2017. *Lancet* 2018;392(10159):1789-858. doi: 10.1016/s0140-
449 6736(18)32279-7 [published Online First: 2018/11/30]
- 450 2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed
451 outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*
452 2006;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905 [published Online First:
453 2006/11/01]
- 454 3. Cohen ZD, DeRubeis RJ. Treatment Selection in Depression. *Annual Review of Clinical Psychology*
455 2018;14(1):209-36. doi: 10.1146/annurev-clinpsy-050817-084746
- 456 4. Leuchter AF, Cook IA, Hamilton SP, et al. Biomarkers to predict antidepressant response. *Curr*
457 *Psychiatry Rep* 2010;12(6):553-62. doi: 10.1007/s11920-010-0160-4 [published Online First:
458 2010/10/22]
- 459 5. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression
460 (TRD)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol*
461 2007;17(11):696-707. doi: 10.1016/j.euroneuro.2007.03.009 [published Online First:
462 2007/05/25]
- 463 6. Peeters FP, Ruhe HG, Wichers M, et al. The Dutch Measure for quantification of Treatment
464 Resistance in Depression (DM-TRD): an extension of the Maudsley Staging Method. *J Affect*
465 *Disord* 2016;205:365-71. doi: 10.1016/j.jad.2016.08.019 [published Online First: 2016/08/29]
- 466 7. Conway CR, George MS, Sackeim HA. Toward an Evidence-Based, Operational Definition of
467 Treatment-Resistant Depression: When Enough Is Enough. *JAMA Psychiatry* 2017;74(1):9-10.
468 doi: 10.1001/jamapsychiatry.2016.2586 [published Online First: 2016/10/27]
- 469 8. Ruhé HG, van Rooijen G, Spijker J, et al. Staging methods for treatment resistant depression. A
470 systematic review. *J Affect Disord* 2012;137(1-3):35-45. doi: 10.1016/j.jad.2011.02.020
471 [published Online First: 2011/03/26]
- 472 9. van Dijk DA, van den Boogaard TM, Deen ML, et al. Predicting clinical course in major depressive
473 disorder: The association between DM-TRD score and symptom severity over time in 1115
474 outpatients. *Depress Anxiety* 2019;36(4):345-52. doi: 10.1002/da.22865 [published Online
475 First: 2018/11/27]
- 476 10. Fekadu A, Rane LJ, Wooderson SC, et al. Prediction of longer-term outcome of treatment-
477 resistant depression in tertiary care. *Br J Psychiatry* 2012;201(5):369-75. doi:
478 10.1192/bjp.bp.111.102665 [published Online First: 2012/09/08]
- 479 11. Fekadu A, Wooderson SC, Markopoulou K, et al. The Maudsley Staging Method for treatment-
480 resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin*
481 *Psychiatry* 2009;70(7):952-7. doi: 10.4088/JCP.08m04728 [published Online First:
482 2009/05/22]
- 483 12. Fekadu A, Wooderson S, Donaldson C, et al. A multidimensional tool to quantify treatment
484 resistance in depression: the Maudsley staging method. *J Clin Psychiatry* 2009;70(2):177-84.
485 doi: 10.4088/jcp.08m04309 [published Online First: 2009/02/05]
- 486 13. Nierenberg AA, Amsterdam JD. Treatment-resistant depression: definition and treatment
487 approaches. *J Clin Psychiatry* 1990;51 Suppl:39-47; discussion 48-50. [published Online First:
488 1990/06/01]
- 489 14. Spijker J, Nolen WA. [The algorithm for the biological treatment of depression in the Dutch
490 multidisciplinary guideline on depression]. *Tijdschr Psychiatr* 2011;53(4):223-33. [published
491 Online First: 2011/04/21]
- 492 15. NICE. Depression in adults: recognition and management (NICE Clinical Guidelines No. 90)
493 London: National Institute for Health and Care Excellence (UK); 2009 [Available from:
494 <https://www.ncbi.nlm.nih.gov/books/NBK553259/>.

- 1
2
3 495 16. Fredman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse, and relapse with selective
4 496 serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. *J*
5 497 *Clin Psychiatry* 2000;61(6):403-8. doi: 10.4088/jcp.v61n0602 [published Online First:
6 498 2000/07/20]
- 7
8 499 17. Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression.
9 500 *International Journal of Psychiatry in Clinical Practice* 2017;21(1):13-23. doi:
10 501 10.1080/13651501.2016.1248852
- 11 502 18. Adli M, Baethge C, Heinz A, et al. Is dose escalation of antidepressants a rational strategy after a
12 503 medium-dose treatment has failed? A systematic review. *Eur Arch Psychiatry Clin Neurosci*
13 504 2005;255(6):387-400. doi: 10.1007/s00406-005-0579-5 [published Online First: 2005/05/04]
- 14 505 19. Furukawa TA, Cipriani A, Cowen PJ, et al. Optimal dose of selective serotonin reuptake inhibitors,
15 506 venlafaxine, and mirtazapine in major depression: a systematic review and dose-response
16 507 meta-analysis. *Lancet Psychiatry* 2019;6(7):601-09. doi: 10.1016/s2215-0366(19)30217-2
17 508 [published Online First: 2019/06/11]
- 18 509 20. Ruhe HG, Booij J, van Weert HC, et al. [Dose-escalation of SSRIS in major depressive disorder.
20 510 Should not be recommended in current guidelines]. *Tijdschr Psychiatr* 2010;52(9):615-25.
21 511 [published Online First: 2010/09/24]
- 22 512 21. Kato T, Furukawa TA, Mantani A, et al. Optimising first- and second-line treatment strategies for
23 513 untreated major depressive disorder - the SUN☺D study: a pragmatic, multi-centre,
24 514 assessor-blinded randomised controlled trial. *BMC medicine* 2018;16(1):103-03. doi:
25 515 10.1186/s12916-018-1096-5
- 26 516 22. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression
27 517 (STAR*D) trial: a review. *Can J Psychiatry* 2010;55(3):126-35. doi:
28 518 10.1177/070674371005500303 [published Online First: 2010/04/08]
- 29 519 23. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen*
30 520 *Psychiatry* 2007;64(3):327-37. doi: 10.1001/archpsyc.64.3.327 [published Online First:
31 521 2007/03/07]
- 32 522 24. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure
33 523 of SSRIs for depression. *N Engl J Med* 2006;354(12):1231-42. doi: 10.1056/NEJMoa052963
34 524 [published Online First: 2006/03/24]
- 35 525 25. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis
36 526 comparing within- versus across-class switches. *Biol Psychiatry* 2008;63(7):699-704. doi:
37 527 10.1016/j.biopsych.2007.08.010 [published Online First: 2007/10/09]
- 38 528 26. Zhou X, Keitner GI, Qin B, et al. Atypical Antipsychotic Augmentation for Treatment-Resistant
39 529 Depression: A Systematic Review and Network Meta-Analysis. *Int J Neuropsychopharmacol*
40 530 2015;18(11):pyv060. doi: 10.1093/ijnp/pyv060 [published Online First: 2015/05/28]
- 41 531 27. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of
42 532 augmentation agents in treatment-resistant depression: systematic review and network
43 533 meta-analysis. *J Clin Psychiatry* 2015;76(4):e487-98. doi: 10.4088/JCP.14r09204 [published
44 534 Online First: 2015/04/29]
- 45 535 28. Papadimitropoulou K, Vossen C, Karabis A, et al. Comparative efficacy and tolerability of
46 536 pharmacological and somatic interventions in adult patients with treatment-resistant
47 537 depression: a systematic review and network meta-analysis. *Curr Med Res Opin*
48 538 2017;33(4):701-11. doi: 10.1080/03007995.2016.1277201 [published Online First:
49 539 2016/12/31]
- 50 540 29. Carter B, Strawbridge R, Husain MI, et al. Relative effectiveness of augmentation treatments for
51 541 treatment-resistant depression: a systematic review and network meta-analysis.
52 542 *International Review of Psychiatry* 2020;32(5-6):477-90. doi:
53 543 10.1080/09540261.2020.1765748
- 54 544 30. Li H, Cui L, Li J, et al. Comparative efficacy and acceptability of neuromodulation procedures in
55 545 the treatment of treatment-resistant depression: a network meta-analysis of randomized

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- controlled trials. *Journal of affective disorders* 2021;287:115-24. doi: <https://dx.doi.org/10.1016/j.jad.2021.03.019>
- 546
547
548 31. Wang HR, Woo YS, Ahn HS, et al. Can Atypical Antipsychotic Augmentation Reduce Subsequent
549 Treatment Failure More Effectively Among Depressed Patients with a Higher Degree of
550 Treatment Resistance? A Meta-Analysis of Randomized Controlled Trials. *Int J*
551 *Neuropsychopharmacol* 2015;18(8) doi: 10.1093/ijnp/pyv023 [published Online First:
552 2015/03/15]
- 553 32. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-
554 analysis: many names, many benefits, many concerns for the next generation evidence
555 synthesis tool. *Res Synth Methods* 2012;3(2):80-97. doi: 10.1002/jrsm.1037 [published Online
556 First: 2012/06/01]
- 557 33. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-
558 analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi: 10.1186/2046-4053-4-
559 1 [published Online First: 2015/01/03]
- 560 34. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant
561 nonresponders. *J Clin Psychiatry* 1997;58 Suppl 13:23-9. [published Online First: 1997/01/01]
- 562 35. Sprah L, Dernovsek MZ, Wahlbeck K, et al. Psychiatric readmissions and their association with
563 physical comorbidity: a systematic literature review. *BMC Psychiatry* 2017;17(1):2. doi:
564 10.1186/s12888-016-1172-3 [published Online First: 2017/01/05]
- 565 36. Michopoulos I, Furukawa TA, Noma H, et al. Different control conditions can produce different
566 effect estimates in psychotherapy trials for depression. *J Clin Epidemiol* 2021;132:59-70. doi:
567 10.1016/j.jclinepi.2020.12.012 [published Online First: 2020/12/19]
- 568 37. Furukawa TA, Salanti G, Atkinson LZ, et al. Comparative efficacy and acceptability of first-
569 generation and second-generation antidepressants in the acute treatment of major
570 depression: protocol for a network meta-analysis. *BMJ Open* 2016;6(7):e010919. doi:
571 10.1136/bmjopen-2015-010919 [published Online First: 2016/07/13]
- 572 38. da Costa BR, Nüesch E, Rutjes AW, et al. Combining follow-up and change data is valid in meta-
573 analyses of continuous outcomes: a meta-epidemiological study. *J Clin Epidemiol*
574 2013;66(8):847-55. doi: 10.1016/j.jclinepi.2013.03.009 [published Online First: 2013/06/12]
- 575 39. Uher R, Mors O, Rietschel M, et al. Early and delayed onset of response to antidepressants in
576 individual trajectories of change during treatment of major depression: a secondary analysis
577 of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. *J Clin*
578 *Psychiatry* 2011;72(11):1478-84. doi: 10.4088/JCP.10m06419 [published Online First:
579 2011/12/01]
- 580 40. Quitkin FM, Petkova E, McGrath PJ, et al. When should a trial of fluoxetine for major depression
581 be declared failed? *Am J Psychiatry* 2003;160(4):734-40. doi: 10.1176/appi.ajp.160.4.734
582 [published Online First: 2003/04/02]
- 583 41. Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. The Timing of Antidepressant Effects: A
584 Comparison of Diverse Pharmacological and Somatic Treatments. *Pharmaceuticals (Basel)*
585 2010;3(1):19-41. doi: 10.3390/ph3010019 [published Online First: 2010/01/06]
- 586 42. Deshauer D, Moher D, Fergusson D, et al. Selective serotonin reuptake inhibitors for unipolar
587 depression: a systematic review of classic long-term randomized controlled trials. *CMAJ :*
588 *Canadian Medical Association journal = journal de l'Association medicale canadienne*
589 2008;178(10):1293-301. doi: 10.1503/cmaj.071068
- 590 43. Hengartner MP. How effective are antidepressants for depression over the long term? A critical
591 review of relapse prevention trials and the issue of withdrawal confounding. *Ther Adv*
592 *Psychopharmacol* 2020;10:2045125320921694. doi: 10.1177/2045125320921694 [published
593 Online First: 2020/05/22]
- 594 44. Robinson L, Delgado J, Kellett S. The dose-response effect in routinely delivered psychological
595 therapies: A systematic review. *Psychother Res* 2020;30(1):79-96. doi:
596 10.1080/10503307.2019.1566676 [published Online First: 2019/01/22]

- 1
2
3 597 45. Davies P, Ijaz S, Williams CJ, et al. Pharmacological interventions for treatment-resistant
4 598 depression in adults. *Cochrane Database Syst Rev* 2019;12(12):Cd010557. doi:
5 599 10.1002/14651858.CD010557.pub2 [published Online First: 2019/12/18]
6 600 46. van Bronswijk S, Moopen N, Beijers L, et al. Effectiveness of psychotherapy for treatment-
7 601 resistant depression: a meta-analysis and meta-regression. *Psychol Med* 2019;49(3):366-79.
8 602 doi: 10.1017/s003329171800199x [published Online First: 2018/08/25]
9 603 47. Ijaz S, Davies P, Williams CJ, et al. Psychological therapies for treatment-resistant depression in
10 604 adults. *Cochrane Database Syst Rev* 2018;5(5):Cd010558. doi:
11 605 10.1002/14651858.CD010558.pub2 [published Online First: 2018/05/16]
12 606 48. Cantù F, Ciappolino V, Enrico P, et al. Augmentation with Atypical Antipsychotics for Treatment-
13 607 Resistant Depression. *J Affect Disord* 2021;280(Pt A):45-53. doi: 10.1016/j.jad.2020.11.006
14 608 [published Online First: 2020/11/18]
15 609 49. Song GM, Tian X, Shuai T, et al. Treatment of Adults With Treatment-Resistant Depression:
16 610 Electroconvulsive Therapy Plus Antidepressant or Electroconvulsive Therapy Alone? Evidence
17 611 From an Indirect Comparison Meta-Analysis. *Medicine (Baltimore)* 2015;94(26):e1052. doi:
18 612 10.1097/md.0000000000001052 [published Online First: 2015/07/02]
19 613 50. Bottomley JM, LeReun C, Diamantopoulos A, et al. Vagus nerve stimulation (VNS) therapy in
20 614 patients with treatment resistant depression: A systematic review and meta-analysis. *Compr*
21 615 *Psychiatry* 2019;98:152156. doi: 10.1016/j.comppsy.2019.152156 [published Online First:
22 616 2020/01/25]
23 617 51. Zhou C, Zhang H, Qin Y, et al. A systematic review and meta-analysis of deep brain stimulation in
24 618 treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;82:224-32.
25 619 doi: 10.1016/j.pnpbp.2017.11.012 [published Online First: 2017/11/18]
26 620 52. Mutz J, Vipulanathan V, Carter B, et al. Comparative efficacy and acceptability of non-surgical
27 621 brain stimulation for the acute treatment of major depressive episodes in adults: systematic
28 622 review and network meta-analysis. *Bmj* 2019;364:l1079. doi: 10.1136/bmj.l1079 [published
29 623 Online First: 2019/03/29]
30 624 53. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic
31 625 reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First:
32 626 2016/12/07]
33 627 54. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of
34 628 Interventions 2021 [version 6.2 (updated February 2021)]:[Available from:
35 629 www.training.cochrane.org/handbook.
36 630 55. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial.
37 631 *Evid Based Ment Health* 2019;22(4):153-60. doi: 10.1136/ebmental-2019-300117 [published
38 632 Online First: 2019/09/30]
39 633 56. Rucker G, Krahn U, König J, et al. netmeta: Network Meta-Analysis using Frequentist Methods.
40 634 2021
41 635 57. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria, 2021.
42 636 58. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth*
43 637 *Methods* 2019;10(3):398-419. doi: 10.1002/jrsm.1347 [published Online First: 2019/03/12]
44 638 59. Doi SA, Furuya-Kanamori L, Xu C, et al. Questionable utility of the relative risk in clinical research:
45 639 a call for change to practice. *J Clin Epidemiol* 2020 doi: 10.1016/j.jclinepi.2020.08.019
46 640 [published Online First: 2020/11/11]
47 641 60. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
48 642 systematic reviews incorporating network meta-analyses of health care interventions:
49 643 checklist and explanations. *Ann Intern Med* 2015;162(11):777-84. doi: 10.7326/m14-2385
50 644 [published Online First: 2015/06/02]
51 645 61. Turner RM, Jackson D, Wei Y, et al. Predictive distributions for between-study heterogeneity and
52 646 simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015;34(6):984-98.
53 647 doi: 10.1002/sim.6381 [published Online First: 2014/12/06]
54
55
56
57
58
59
60

- 1
2
3 648 62. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
4 649 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]
5 650 63. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-
6 651 analyses. *Bmj* 2007;335(7626):914-6. doi: 10.1136/bmj.39343.408449.80 [published Online
7 652 First: 2007/11/03]
8 653 64. Taylor DM, Cornelius V, Smith L, et al. Comparative efficacy and acceptability of drug treatments
9 654 for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*
10 655 2014;130(6):452-69. doi: 10.1111/acps.12343 [published Online First: 2014/10/07]
11 656 65. Wijkstra J, Lijmer J, Burger H, et al. Pharmacological treatment for psychotic depression.
12 657 *Cochrane Database Syst Rev* 2015(7):CD004044. doi: 10.1002/14651858.CD004044.pub4
13 658 [published Online First: 2015/08/01]
14 659 66. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a
15 660 patient-level meta-analysis. *Jama* 2010;303(1):47-53. doi: 10.1001/jama.2009.1943
16 661 [published Online First: 2010/01/07]
17 662 67. Gibbons RD, Hur K, Brown CH, et al. Benefits from antidepressants: synthesis of 6-week patient-
18 663 level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and
19 664 venlafaxine. *Arch Gen Psychiatry* 2012;69(6):572-9. doi:
20 665 10.1001/archgenpsychiatry.2011.2044 [published Online First: 2012/03/07]
21 666 68. Khan A, Kolts RL, Thase ME, et al. Research design features and patient characteristics associated
22 667 with the outcome of antidepressant clinical trials. *Am J Psychiatry* 2004;161(11):2045-9. doi:
23 668 10.1176/appi.ajp.161.11.2045 [published Online First: 2004/10/30]
24 669 69. Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome?. The effects of placebo
25 670 control and treatment duration in antidepressant trials. *Psychother Psychosom*
26 671 2009;78(3):172-81. doi: 10.1159/000209348 [published Online First: 2009/03/27]
27 672 70. Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to
28 673 active antidepressant treatment in randomized controlled trials? Results from pooled and
29 674 meta-analyses. *J Clin Psychiatry* 2010;71(3):270-9. doi: 10.4088/JCP.08r04516blu [published
30 675 Online First: 2010/02/04]
31 676 71. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network
32 677 meta-analysis. *PLoS One* 2014;9(7):e99682. doi: 10.1371/journal.pone.0099682 [published
33 678 Online First: 2014/07/06]
34 679 72. Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-
35 680 analysis. *Stat Med* 2010;29(7-8):932-44. doi: 10.1002/sim.3767 [published Online First:
36 681 2010/03/10]
37 682 73. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis:
38 683 concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-110. doi:
39 684 10.1002/jrsm.1044 [published Online First: 2012/06/01]
40 685 74. Jackson D, Barrett JK, Rice S, et al. A design-by-treatment interaction model for network meta-
41 686 analysis with random inconsistency effects. *Stat Med* 2014;33(21):3639-54. doi:
42 687 10.1002/sim.6188 [published Online First: 2014/04/30]
43 688 75. Veroniki AA, Mavridis D, Higgins JP, et al. Characteristics of a loop of evidence that affect
44 689 detection and estimation of inconsistency: a simulation study. *BMC Med Res Methodol*
45 690 2014;14:106. doi: 10.1186/1471-2288-14-106 [published Online First: 2014/09/23]
46 691 76. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of
47 692 interventions. *Int J Epidemiol* 2013;42(1):332-45. doi: 10.1093/ije/dys222 [published Online
48 693 First: 2013/03/20]
49 694 77. Furukawa TA, Miura T, Chaimani A, et al. Using the contribution matrix to evaluate complex study
50 695 limitations in a network meta-analysis: a case study of bipolar maintenance
51 696 pharmacotherapy review. *BMC Res Notes* 2016;9:218. doi: 10.1186/s13104-016-2019-1
52 697 [published Online First: 2016/04/15]
53
54
55
56
57
58
59
60

- 1
2
3 698 78. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help
4 699 distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*
5 700 2008;61(10):991-6. doi: 10.1016/j.jclinepi.2007.11.010 [published Online First: 2008/06/10]
6 701
7 702 79. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study
8 703 effects in a network of interventions. *Res Synth Methods* 2012;3(2):161-76. doi:
9 704 10.1002/jrsm.57 [published Online First: 2012/06/01]
10 705 80. Greenberg RP, Bornstein RF, Greenberg MD, et al. A meta-analysis of antidepressant outcome
11 706 under "blinder" conditions. *J Consult Clin Psychol* 1992;60(5):664-9; discussion 70-7. doi:
12 707 10.1037//0022-006x.60.5.664 [published Online First: 1992/10/01]
13 708 81. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome?
14 709 A meta-regression of double-blind, randomized clinical trials in MDD. *Eur*
15 710 *Neuropsychopharmacol* 2009;19(1):34-40. doi: 10.1016/j.euroneuro.2008.08.009 [published
16 711 Online First: 2008/10/01]
17 712 82. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing
18 713 confidence in the results of a network meta-analysis. *PLoS Med* 2020;17(4):e1003082. doi:
19 714 10.1371/journal.pmed.1003082 [published Online First: 2020/04/04]
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.	bupirone, 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)

		<p>d.</p> <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. thetburst stimulation (TBS)⁽³⁾ (transcranial magnetic stimulation) <p>e.</p> <ul style="list-style-type: none"> i. transcranial direct current stimulation (tDCS) ii. transcranial alternating current stimulation (tACS) <p>f. vagus nerve stimulation (VNS)</p>
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)
---	---	--	---------

Notes:

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

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

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

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

Appendix 3. Draft of search strategy

Below we present the query for use in MEDLINE (Ovid). The keywords for TRD (see #1) are based on a version used by Davies, et al.⁴⁵, to which “(depress* and (adjunct* adj5 (treatment or therapy or placebo or antidepress*))) .mp.” and “(antidepress* adj3 resistan*) .ti,ab,kf.” are added to enhance 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"