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BMJ Open

Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: Comparison of multiple treatment modalities

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Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: Comparison of multiple treatment modalities

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For peer review only

Abstract:

Introduction: The high placebo response in depression treatment trials is a major contributing factor for randomized control trial (RCT) failure to establish efficacy of novel or repurposed treatments in treatment resistant depression (TRD) and Major Depressive Disorder (MDD) in general. Though there have been a number of meta-analyses and primary research studies evaluating the placebo response in non-TRD depression, placebo response in TRD is poorly understood. It is important to understand the placebo response of TRD as treatments are only moderately effective and up to 1/3 of patients will experience treatment-resistant depression (TRD).

Methods and Analysis: We will conduct a search of electronic databases (MEDLINE and PsychINFO) from inception to January 24th 2020 including randomized, placebo-controlled controlled trials of pharmacological, somatic and psychological interventions for adults with TRD. TRD will be defined as a failure to respond to at least 2 interventions of adequate dose or duration. We will also search reference lists from review articles. We will perform several meta-analyses to quantify the placebo response for each treatment modality. Regression analysis will explore potential contributing demographic and clinical variables to the placebo response. We will utilize Cochrane risk of bias tool (ROB).

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3 **Ethics and dissemination:** There is no research ethics board
4 approval required. The dissemination plan is to publish results
5 in a peer-reviewed academic journal.
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12 Prospero ID: 190465
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17 **Strengths and limitations of this study:**
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21 This analysis will be the first to exclusively study the placebo
22 response in TRD.
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28 We will seek to quantify the placebo response among distinct
29 treatment modalities.
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34 The study will assess a large number of variables that may
35 contribute to the placebo response.
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41 Direct statistical comparison between the placebo response of
42 treatment modalities will not be done given the significant
43 heterogeneity among treatment modalities.
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55 **Introduction:**
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5 The placebo response is the therapeutic effect produced by a
6 placebo intervention that is not due to any inherent properties
7 of the placebo itself. The high placebo response in large
8 depression treatment trials is a major contributing factor for
9 RCT failure to establish efficacy of novel and repurposed
10 treatments (1). There have been several studies attempting to
11 determine patient and study variables contributing to the
12 placebo response in non-TRD depression. Variables found to
13 contribute to the placebo response include year of publication,
14 baseline severity, probability of being allocated to placebo
15 arm, number of clinic centers, dosing schedule, length of trial,
16 the magnitude active response, early score fluctuations, and
17 inflation of baseline severity (2-10). The largest meta-analysis
18 to date (252 studies, pooled n= 26,324) reported that the
19 placebo response rate of anti-depressant medications has been
20 stable over the last thirty years and ranges between 35% and 40%
21 (11). While the placebo response is extensively investigated in
22 non-TRD depression, there is a paucity of research into the
23 magnitude of the placebo response in TRD.

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50 TRD is defined by a lack of response to at least 2 separate
51 treatments and imposes a heavy burden on the individual, their
52 families, and society; through decreased quality of life,
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3 increased morbidity and direct/indirect medical costs (12,13).
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5 It is important to integrate novel treatments into clinical
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7 practice; however, a high placebo response and negative clinical
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9 trials has led to a delay in this regard. To address this gap,
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11 it is important characterize and understand the placebo response
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13 in TRD. Two meta-analyses have explored the placebo response in
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15 repetitive transcranial magnetic stimulation (rTMS) trials,
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17 including TRD and non-TRD patients which reported a large
18
19 placebo response (14,15). To date these are the only studies
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21 attempting the characterize the placebo response in TRD.
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26 Currently, there is not a clear understanding as to what the
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28 placebo response in TRD is, what contributes to it, and how it
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30 may differ across various treatment modalities. Hence, we will
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32 complete a systematic review and meta-analysis of randomized-
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34 placebo-controlled trials in TRD. Our primary objective will be
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36 to characterize the placebo response in TRD across various
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38 treatment modalities. Our exploratory aim will be to determine
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40 any demographic, clinical, and methodological characteristics
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42 contribute to it. Characterizing and understanding what
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44 contributes to the placebo response in TRD is a crucial step
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46 towards the advancement of emerging treatments as well as
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48 potentially harnessing the placebo response for patients.
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55 **Methods and Analysis:**

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5 This protocol will be developed and reported in accordance with
6 PRISMA statement.(16)
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10 11 12 **Eligibility Criteria:**

13 14 ***Participants and Setting:***

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16 We will include RCTs that recruited: TRD patients of any gender
17 and between 18 and 65 years old. Treatment-resistant depression
18 will be defined as patients with MDD as defined by The
19 Diagnostic and Statistical Manual of Mental Disorders (DSM) III,
20 IV, IV-R and 5 or international classification of diseases (ICD)
21 9-10 that are currently in a depressive episode (17-19).

22
23 Patients must have failed at least two trials of antidepressant
24 medication within the current depressive episode with adequate
25 dose and duration. Within class switches (e.g. 2 selective
26 serotonin reuptake inhibitors (SSRI's) will be included as part
27 of the TRD staging (20). Failed psychotherapy or brain
28 stimulation trials will be included in the TRD staging. If a
29 study reported that they included patients with 2 failed trials,
30 but did not indicate whether this occurred within the current
31 depressive episode, the study will be included as this is the
32 most consistent definition of TRD (21-23). Patients from any
33 setting (i.e. inpatient or outpatient) will be included.
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3 Psychiatric comorbidity will be included, if MDD is the primary
4 psychiatric disorder being treated.
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7 We will exclude: Studies that recruited patients with bipolar
8 depression, unless 15% or less of the patients randomized were
9 bipolar depression. Patients diagnosed with primary psychotic
10 illness or active substance use disorders. Patients with
11 neurological disorders, physical co-morbidities, or medical
12 conditions will only be excluded if these diagnoses are the
13 primary diagnosis (e.g. MDD in patients with diabetes or MDD in
14 patients with multiple sclerosis). Studies with sample sizes
15 less than 10 subjects (24). Studies that utilize a non-inert
16 placebo.
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32 **Interventions:**

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34 We will include pharmacological and somatic therapies that are
35 included in the Maudsley Treatment Inventory (MTI) (25). This
36 inventory is derived from the Maudsley Prescribing Guidelines as
37 well as other standardised guidelines for depression treatment.
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39 We will also include novel and repurposed agents that have
40 multiple meta-analysis supporting their use.
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51 For psychological agents, we will include those from the NICE
52 guidelines which includes computerised or face-to-face CBT,
53 behavioural activation, interpersonal therapy, manualised
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3 psychodynamic therapy, behavioural couples' therapy, cognitive
4 behavioural analysis system of psychotherapy, or mindfulness-
5 based cognitive therapy. (22)
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12 **Comparator:**
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14 Trials that include a placebo arm. Placebo will be defined as an
15 inert oral medication, parental medication, sham device, or sham
16 therapy that does not include any theoretical active property to
17 induce the proposed therapeutic effect. Wait-list or treatment
18 as usual will not be considered a placebo group for therapy
19 trials.
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30 **Study designs and publication types:**
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32 We will only include parallel arm, randomized double-blind
33 placebo-controlled trials. We will include cross-over studies if
34 they report outcomes before the cross-over. Trials must include
35 randomization to at least 1 placebo arm.
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44 **Language and Timeframe:**
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46 Studies to be included will be published in English or
47 Portuguese. Attempts to translate other languages will also be
48 made. Time frame of included studies will be from the date of
49 inception until January 24th 2020.
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Information Source and Search Strategy:

The electronic databases MEDLINE and PsychInfo will be searched. Key terms, notable papers and citation lists will also be reviewed for additional studies. The following search terms will be used in addition to mapping key terms: (depress* OR MDD OR major depress*) AND (resistan* OR refractor* OR non-respon* OR nonrespon* OR un-respon* OR unrespon* OR TRD OR fail* OR inadequate OR difficult OR intractable) AND (Placebo OR sham OR control OR controlled) AND (randomi* OR RCT) AND (treatment OR intervention OR trial).

Study Records:

Study Selection and Data Extraction: Two authors will independently screen the abstracts and full-texts to decide on their inclusion based on predefined inclusion criteria. Any discrepancies of inclusion or extraction will be discussed between the two authors, and a third author will resolve any further conflicts. Two authors will then extract data which will include description of the interventions and control group, demographics, clinical data, and quality assessment.

Outcomes:**Primary outcome:**

The primary outcome will be 'placebo response' as measured by Cohen's d effect size of the change in the primary outcome variable (i.e. depression symptom rating scales) from baseline

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2
3 to primary endpoint. Where multiple outcomes are reported, the
4 primary outcome for inclusion in analyses will be selected in a
5 hierarchical fashion: the most preferable scale will be a
6 clinician-rated assessment of depression severity (HAM-D, MADRS,
7 IDS or validated subscales of these), followed by a patient-
8 rated measure (PHQ-9, IDS or BDI). Where multiple endpoints are
9 reported, this review will consider the acute endpoint as the
10 primary endpoint. If the study only reports a delayed endpoint,
11 this will be recorded and controlled for.
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26 *Secondary outcomes:*

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28 1. Response rate measured by the total number of patients who
29 had a reduction of $\geq 50\%$ of the total score on a standardized
30 rating scale for depression.
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34 2. Remission rates as measured by a standardized rating scale
35 for depression
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41 **Assessment of risk bias:**

42 We will utilize the Cochrane risk of Bias (RoB) tool. This tool
43 assesses bias across five domains five domains (selection,
44 performance, attrition, reporting, and other). A sensitivity
45 analysis will assess the difference in statistical effects
46 between studies with a high and low risk of bias.
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Data Synthesis:

Qualitative data will be analyzed, and sufficiently homogenous studies will be aggregated based upon similarity of patient characteristics, treatment modality, as well as study design. We will conduct a pairwise meta-analysis within each modality.

Placebo effect size will be determined by Hedge's g , which will be calculated based on reported means and standard deviations (SD) from baseline and endpoint of each study. A random-effects model will be used to perform this calculation. When necessary, we will impute SD based on graphs, standard errors, or confidence intervals provided in the published reports. The pooled effect size for each study will be calculated by the inverse variance of each study.

We will perform an explanatory analysis on factors affecting the placebo response using a univariate meta-regression. Several univariate meta-regressions will be performed for each treatment modality. Factors chosen will be dependent on data availability, however, examples include: methodological factors, publication year, number of study sites, study setting, number of treatment arms, industry sponsorship, duration of study, number of times placebo was measured, number of days receiving placebo, dosing (e.g. once daily vs twice daily), presence of a placebo run-in, augmentation vs monotherapy treatment strategy, and study

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3 quality, as well as demographic factors (e.g. age, gender, and
4 race/ethnicity), and clinical factors (e.g. number of failed
5 trials in the current episode, recurrence of illness, age of
6 onset, baseline severity, and effect size of the active group).
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8 For univariate meta-regression analyses, significant values will
9
10 be considered as $p < 0.05$.
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14 We will perform sensitivity analysis, cumulative regression and
15 assess publication bias using Begg-modified funnel plot and
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17 Egger test (26). Heterogeneity will be evaluated with a Chi-
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19 square test.
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25 26 27 28 **Confidence of cumulative evidence:**

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30 The Grading of Recommendations, Assessment, Development and
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32 Evaluations (GRADE) approach will be utilized the rank the
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34 quality of the evidence in making recommendations of what the
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36 placebo response in TRD is.
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39 40 **Patient and Public involvement:**

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42 TRD is a very significant public health concern. As there is no
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44 direct patient involvement in this study, we have decided to not
45
46 include patients and public in the development in the protocol.
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48 49 **Discussion:**

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51 A placebo-controlled clinical trial is the gold-standard for
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53 establishing efficacy of a proposed active treatment. While
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55 there is a well-established understanding of the placebo
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3 response in treatment naive MDD, there is not a clear
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5 understanding of the placebo response in TRD. Furthermore, the
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7 analyses of the placebo response in non-TRD focuses almost
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9 entirely on the placebo response as it relates to oral
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11 medications. This has implications on the transferability of
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13 this knowledge to TRD as this patient population frequently
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15 utilizes somatic and novel treatments. The objective of this
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17 study is to better quantify the placebo response in TRD, its
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19 contributing factors, and how it may differ between treatment
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21 modalities. This knowledge will help clinicians and researchers
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23 interpret past and future studies as well as improve the design
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25 and development of future trials. With an established placebo
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27 response, study designs such a non-inferiority, can be utilized
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29 with improved confidence. Lastly, this knowledge would have
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31 implications of how care can be delivered and improved for
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33 patients with TRD.
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39 **Ethics and dissemination:** There is no research ethics board
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41 approval required. The dissemination plan is to publish results
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43 in a peer-reviewed academic journal.
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7 [.proquest.com/docview/622097738?accountid=14771](http://myaccess.library.utoronto.ca/login?url=https://search.proquest.com/docview/622097738?accountid=14771)
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Patient consent for publication Not required

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
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 (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3/4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4/5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
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	7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8/9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7/8
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8/9
	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 (such as I^2 , Kendall's τ)	8/9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8/9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: Comparison of multiple treatment modalities

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Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: Comparison of multiple treatment modalities

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For peer review only

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2
3 **Abstract:**
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7 **Introduction:** The high placebo response in depression treatment trials is a major
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9
10 contributing factor for randomized control trial (RCT) failure to establish efficacy of novel
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12
13 or repurposed treatments in treatment resistant depression (TRD) and Major
14
15
16 Depressive Disorder (MDD) in general. Though there have been a number of meta-
17
18
19 analyses and primary research studies evaluating the placebo response in non-TRD
20
21
22 depression, placebo response in TRD is poorly understood. It is important to understand
23
24
25 the placebo response of TRD as treatments are only moderately effective and up to 1/3
26
27
28 of patients will experience treatment-resistant depression (TRD).
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34 **Methods and Analysis:** We will conduct a search of electronic databases (MEDLINE and
35
36
37 PsychINFO) from inception to January 24th 2020 including randomized, placebo-
38
39
40 controlled controlled trials of pharmacological, somatic and psychological interventions
41
42
43 for adults with TRD. TRD will be defined as a failure to respond to at least 2
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45
46 interventions of adequate dose or duration. We will also search reference lists from
47
48
49 review articles. We will perform several meta-analyses to quantify the placebo response
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53 for each treatment modality. Regression analysis will explore potential contributing
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3 demographic and clinical variables to the placebo response. We will utilize Cochrane
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7 risk of bias tool (ROB).
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10 **Ethics and dissemination:** There is no research ethics board approval required. The
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14 dissemination plan is to publish results in a peer-reviewed academic journal.
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21 Prospero ID: 190465
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28 **Strengths and limitations of this study:**
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35 This analysis will be the first to exclusively study the placebo response in TRD.
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42 We will seek to quantify the placebo response among distinct treatment modalities.
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49 The study will assess a large number of variables that may contribute to the placebo
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52 response.
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3 Direct statistical comparison between the placebo response of treatment modalities will
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7 not be done given the significant heterogeneity among treatment modalities.
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21 Introduction:

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28 The placebo response is the therapeutic effect produced by a placebo intervention that
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31 is not due to any inherent properties of the placebo itself. The high placebo response in
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33
34 large depression treatment trials is a major contributing factor for RCT failure to
35
36
37 establish efficacy of novel and repurposed treatments (1). There have been several
38
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41
42 studies attempting to determine patient and study variables contributing to the placebo
43
44
45 response in non-TRD depression. Variables found to contribute to the placebo response
46
47
48 include year of publication, baseline severity, probability of being allocated to placebo
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52 arm, number of clinic centers, dosing schedule, length of trial, the magnitude active
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54
55 response, early score fluctuations, and inflation of baseline severity (2–10). The largest
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3 meta-analysis to date (252 studies, pooled n= 26,324) reported that the placebo
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7 response rate of anti-depressant medications has been stable over the last thirty years
8
9
10 and ranges between 35% and 40% (11). While the placebo response is extensively
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12
13 investigated in non-TRD depression, there is a paucity of research into the magnitude of
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15
16
17 the placebo response in TRD.
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24 TRD is defined by a lack of response to at least 2 separate treatments and imposes a
25
26
27 heavy burden on the individual, their families, and society; through decreased quality of
28
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30
31 life, increased morbidity and direct/indirect medical costs (12,13). It is important to
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33
34 integrate novel treatments into clinical practice; however, a high placebo response and
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37 negative clinical trials has led to a delay in this regard. To address this gap, it is
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39
40
41 important characterize and understand the placebo response in TRD. Two meta-
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43
44
45 analyses have explored the placebo response in repetitive transcranial magnetic
46
47
48 stimulation (rTMS) trials, including TRD and non-TRD patients which reported a large
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51
52 placebo response (14,15). To date these are the only studies attempting the
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55
56 characterize the placebo response in TRD.
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4 Currently, there is not a clear understanding as to what the placebo response in TRD is,
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6
7 what contributes to it, and how it may differ across various treatment modalities. Hence,
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9
10 we will complete a systematic review and meta-analysis of randomized-placebo-
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12
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14 controlled trials in TRD. Our primary objective will be to characterize the placebo
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17 response in TRD across various treatment modalities. Our exploratory aim will be to
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21 determine any demographic, clinical, and methodological characteristics contribute to it.
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23
24 Characterizing and understanding what contributes to the placebo response in TRD is a
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26
27 crucial step towards the advancement of emerging treatments as well as potentially
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31 harnessing the placebo response for patients.
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38 **Methods and Analysis:**

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45 This protocol will be developed and reported in accordance with PRISMA
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49 statement.(16)
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55 **Eligibility Criteria:**

Participants and Setting:

We will include RCTs that recruited: TRD patients of any gender and between 18 and 65 years old. Treatment-resistant depression will be defined as patients with MDD as defined by The Diagnostic and Statistical Manual of Mental Disorders (DSM) III, IV, IV-R and 5 or international classification of diseases (ICD) 9-10 that are currently in a depressive episode (17–19). Patients must have failed at least two trials of antidepressant medication within the current depressive episode with adequate dose and duration. Within class switches (e.g. 2 selective serotonin reuptake inhibitors (SSRI's) will be included as part of the TRD staging (20). Failed psychotherapy or brain stimulation trials will be included in the TRD staging. If a study reported that they included patients with 2 failed trials, but did not indicate whether this occurred within the current depressive episode, the study will be included as this is the most consistent definition of TRD (21–23). Patients from any setting (i.e. inpatient or outpatient) will be included. Psychiatric comorbidity will be included, if MDD is the primary psychiatric disorder being treated.

1
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3 We will exclude: Studies that recruited patients with bipolar depression, unless 15% or
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5
6
7 less of the patients randomized were bipolar depression. Patients diagnosed with
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9
10 primary psychotic illness or active substance use disorders. Patients with neurological
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12
13 disorders, physical co-morbidities, or medical conditions will only be excluded if these
14
15
16 diagnoses are the primary diagnosis (e.g. MDD in patients with diabetes or MDD in
17
18
19 patients with multiple sclerosis). Studies with sample sizes less than 10 subjects (24).
20
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22
23
24 Studies that utilize a non-inert placebo.
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31 ***Interventions:***
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34
35 We will include pharmacological and somatic therapies that are included in the
36
37
38 Maudsley Treatment Inventory (MTI)(25). This inventory is derived from the Maudsley
39
40
41 Prescribing Guidelines as well as other standardised guidelines for depression
42
43
44
45 treatment. We will also include novel and repurposed agents that have multiple meta-
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49 analysis supporting their use.
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3 For psychological agents, we will include those from the NICE guidelines which includes
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6
7 computerised or face-to-face CBT, behavioural activation, interpersonal therapy,
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10 manualised psychodynamic therapy, behavioural couples' therapy, cognitive
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13 behavioural analysis system of psychotherapy, or mindfulness-based cognitive
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15
16
17 therapy.(22)
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24 ***Comparator:***

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27
28 Trials that include a placebo arm. Placebo will be defined as an inert oral medication,
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30
31 parental medication, sham device, or sham therapy that does not include any theoretical
32
33
34 active property to induce the proposed therapeutic effect. Wait-list or treatment as usual
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36
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38 will not be considered a placebo group for therapy trials.
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45 ***Study designs and publication types:***

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48
49 We will only include parallel arm, randomized double-blind placebo-controlled trials. We
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52 will include cross-over studies if they report outcomes before the cross-over. Trials must
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54
55 include randomization to at least 1 placebo arm.
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7 ***Language and Timeframe:***
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10 Studies to be included will be published in English or Portuguese. Attempts to translate
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13 other languages will also be made. Time frame of included studies will be from the date
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17 of inception until January 24th 2020.
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25 **Information Source and Search Strategy:**
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27

28 The electronic databases MEDLINE and PsychInfo will be searched. Key terms, notable
29
30
31 papers and citation lists will also be reviewed for additional studies. The following
32
33
34
35 search terms will used in addition to mapping key terms: (depress* OR MDD OR major
36
37
38 depress*) AND (resistan* OR refractor* OR non-respon* OR nonrespon* OR un-respon*
39
40
41 OR unrespon* OR TRD OR fail* OR inadequate OR difficult OR intractable) AND
42
43
44
45
46 (Placebo OR sham OR control OR controlled) AND (randomi* OR RCT) AND (treatment
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48
49
50 OR intervention OR trial).
51
52

53 **Study Records:**
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4 ***Study Selection and Data Extraction:*** Two authors will independently screen the
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6
7 abstracts and full-texts to decide on their inclusion based on predefined inclusion
8
9
10 criteria. Any discrepancies of inclusion or extraction will be discussed between the two
11
12
13 authors, and a third author will resolve any further conflicts. Two authors will then
14
15
16 extract data which will include description of the interventions and control group,
17
18
19 demographics, clinical data, and quality assessment.
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21
22

23 24 **Outcomes:**

25 26 27 ***Primary outcome:***

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29
30
31 The primary outcome will be 'placebo response' as measured by Cohen's d effect size
32
33
34 of the change in the primary outcome variable (i.e. depression symptom rating scales)
35
36
37 from baseline to primary endpoint. Where multiple outcomes are reported, the primary
38
39
40 outcome for inclusion in analyses will be selected in a hierarchical fashion: the most
41
42
43 preferable scale will be a clinician-rated assessment of depression severity (HAM-D,
44
45
46 MADRS, IDS or validated subscales of these), followed by a patient-rated measure
47
48
49 (PHQ-9, IDS or BDI). Where multiple endpoints are reported, this review will consider
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3 the acute endpoint as the primary endpoint. If the study only reports a delayed endpoint,
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5
6
7 this will be recorded and controlled for.
8
9

10 11 12 13 14 *Secondary outcomes:*

- 15
16
17 1. Response rate measured by the total number of patients who had a reduction of
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19
20
21 $\geq 50\%$ of the total score on a standardized rating scale for depression.
22
23
- 24 2. Remission rates as measured by a standardized rating scale for depression
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30

31 **Assessment of risk bias:**

32 We will utilize the Cochrane risk of Bias (RoB) tool. This tool assesses bias across five
33
34
35 domains five domains (selection, performance, attrition, reporting, and other). A
36
37
38
39 sensitivity analysis will assess the difference in statistical effects between studies with a
40
41
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43
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45 high and low risk of bias.
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51 52 **Data Synthesis:**

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3 Qualitative data will be analyzed, and sufficiently homogenous studies will be
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5
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7 aggregated based upon similarity of patient characteristics, treatment modality, as well
8
9
10 as study design. We will conduct a pairwise meta-analysis within each modality.
11
12

13
14 Placebo effect size will be determined by Hedge's g , which will be calculated based on
15
16
17 reported means and standard deviations (SD) from baseline and endpoint of each
18
19
20 study. A random-effects model will be used to perform this calculation. When
21
22
23 necessary, we will impute SD based on graphs, standard errors, or confidence intervals
24
25
26 provided in the published reports. The pooled effect size for each study will be
27
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31 calculated by the inverse variance of each study.
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38 We will perform an explanatory analysis on factors affecting the placebo response using
39
40
41 a univariate meta-regression. Several univariate meta-regressions will be performed for
42
43
44 each treatment modality. Factors chosen will be dependent on data availability,
45
46
47 however, examples include: methodological factors, publication year, number of study
48
49
50 sites, study setting, number of treatment arms, industry sponsorship, duration of study,
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53 number of times placebo was measured, number of days receiving placebo, dosing
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3 (e.g. once daily vs twice daily), presence of a placebo run-in, augmentation vs
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7 monotherapy treatment strategy, and study quality, as well as demographic factors (e.g.
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9
10 age, gender, and race/ethnicity), and clinical factors (e.g. number of failed trials in the
11
12
13 current episode, recurrence of illness, age of onset, baseline severity, and effect size of
14
15
16 the active group). For univariate meta-regression analyses, significant values will be
17
18
19 considered as $p < 0.05$.
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24 We will perform sensitivity analysis, cumulative regression and assess publication bias
25
26
27 using Begg-modified funnel plot and Egger test (26). Heterogeneity will be evaluated
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31 with a Chi-square test.
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38 **Confidence of cumulative evidence:**

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40
41 The Grading of Recommendations, Assessment, Development and Evaluations
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43
44 (GRADE) approach will be utilized to rank the quality of the evidence in making
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48 recommendations of what the placebo response in TRD is.
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52 **Patient and Public involvement:**

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3 TRD is a very significant public health concern. As there is no direct patient involvement
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7 in this study, we have decided to not include patients and public in the development in
8
9
10 the protocol.
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13 14 **Discussion:**

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17 A placebo-controlled clinical trial is the gold-standard for establishing efficacy of a
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21 proposed active treatment. While there is a well-established understanding of the
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24 placebo response in treatment naive MDD, there is not a clear understanding of the
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28 placebo response in TRD. Furthermore, the analyses of the placebo response in non-
29
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31 TRD focuses almost entirely on the placebo response as it relates to oral medications.
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34
35 This has implications on the transferability of this knowledge to TRD as this patient
36
37
38 population frequently utilizes somatic and novel treatments. The objective of this study
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41
42 is to better quantify the placebo response in TRD, its contributing factors, and how it
43
44
45 may differ between treatment modalities. This knowledge will help clinicians and
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49 researchers interpret past and future studies as well as improve the design and
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52 development of future trials. With an established placebo response, study designs such
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3 a non-inferiority, can be utilized with improved confidence. Lastly, this knowledge would
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7 have implications of how care can be delivered and improved for patients with TRD.
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10 **Ethics and dissemination:** There is no research ethics board approval required. The
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14 dissemination plan is to publish results in a peer-reviewed academic journal.
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25 **Reference:**
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14 [/622067060?accountid=14771](http://myaccess.library.utoronto.ca/login?url=https://search.proquest.com/docview/622067060?accountid=14771)
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33 [/1970301414?accountid=14771](http://myaccess.library.utoronto.ca/login?url=https://search.proquest.com/docview/1970301414?accountid=14771)
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31 **Authors' contributions:** Brett DM Jones, MD, MSc: made an exceptional contribution to
32 the design/conception of the protocol; wrote the original version of the manuscript; gave
33 final approval of the version published; has agreed to be accountable for all aspects of
34 the work in ensuring that questions related to the accuracy or integrity of any part of the
35 work are appropriately investigated and resolved.
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8 Cory Weissman, MD: made an exceptional contribution to the design/conception of the
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11 protocol; made significant contributions to revisions of the manuscript; gave final
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14 approval of the version published; has agreed to be accountable for all aspects of the
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16 work in ensuring that questions related to the accuracy or integrity of any part of the
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19 work are appropriately investigated and resolved.
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31 Lais B Razza: made an exceptional contribution to the design/conception of the
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34 protocol; made significant contributions to revisions of the manuscript; gave final
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36 approval of the version published; has agreed to be accountable for all aspects of the
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4 Muhammad I. Husain MBBS, MD(Res.), MRCPsych: made an exceptional contribution
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27 Andre R Brunoni, MD PhD: made an exceptional contribution to the design/conception
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30 of the protocol; made significant contributions to revisions of the manuscript; gave final
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33 approval of the version published; has agreed to be accountable for all aspects of the
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36 work in ensuring that questions related to the accuracy or integrity of any part of the
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50 Zafiris J Daskalakis, MD PhD (Corresponding Author): made an exceptional contribution
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53 to the design/conception of the protocol; made significant contributions to revisions of
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7 accountable for all aspects of the work in ensuring that questions related to the
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14
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16
17
18 in the public, commercial or not-for-profit sectors.
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23 **Competing interests' statement:** There are no competing interests to report.
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28 **Patient consent for publication** Not required
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
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 (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3/4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4/5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
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	7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8/9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7/8
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8/9
	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 (such as I^2 , Kendall's τ)	8/9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8/9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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