Esketamine for Treatment-Resistant Major Depressive Disorder

Research Protocol

January 14, 2019

Institute for Clinical and Economic Review

Table of Contents

Background, Objectives, and Research Questions 2
Background 2
Objectives 3
Research Questions 4
PICOTS Criteria 4
Evidence Review Methods 8
Search Methods and Data Sources 8
Eligibility Criteria 13
Data Extraction Strategy 13
Quality Assessment Criteria 14
Publication Bias Assessment 14
Evidence Synthesis 15
References 17
Appendix A. PRISMA Checklist 19
Appendix B. Data Extraction Summary Table Shell 20

Background, Objectives, and Research Questions

Background

Major depressive disorder (MDD) is a common psychiatric condition, with an estimated 16 million adults, representing 7% of adults in the United States, experiencing at least one major depressive episode in 2016 alone.[1] Symptoms of depression can include persistent sadness, feelings of hopelessness, loss of interest in usual activities, decreased energy, difficulty concentrating or sleeping, change in appetite and thoughts of hurting oneself. Depression can increase the risk of suicide and result in long-term suffering. It impacts all aspects of life including social relationships, ability to work, and is the second leading cause of disability in the United States.[2] Treatment, including medication and psychotherapy, leads to improvement in many individuals, but multiple alterations in the therapeutic regimen may be required to achieve an adequate outcome. Treatment-resistant depression (TRD) refers to a major depressive episode with an inadequate response to therapy of adequate dosing and duration.[3] The failure of two or more trials of antidepressant monotherapies are commonly considered TRD,[4] but the number of trials has not been standardized.[5] Overall, approximately one in three patients with depression are considered "treatment-resistant." Patients with TRD have higher costs of care, decreased work productivity and account for around $64 billion in total costs.[3,6]

A major depressive episode is diagnosed based upon patient-reported symptoms of at least two weeks duration; there is a lack of reliable signs or tests that confirm the diagnosis or predict response to a specific treatment.[7] A diagnosis is typically made and treatment is often initiated by primary care clinicians, and broadly includes a range of different medications and psychological therapies in addition to supportive care such as self-help, relaxation techniques, and exercise. Second generation antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants are commonly used for initial pharmacotherapy in patients with depression.[8,9] However, patients with depression vary in terms of the severity of symptoms, course (episodic or chronic), and associated conditions such as anxiety or substance use disorders. Initial treatment may not work or may cause unacceptable side effects, and switching to a different therapy is common. Since a trial of a therapy may require dose adjustments and 6-12 weeks to assess response, patients may find it difficult to remain on therapy long enough for an adequate trial of the treatment, especially if there are side effects or symptoms that are incapacitating. For this reason, TRD can be difficult to define because it includes not only the number of unique treatments tried, but whether the trials were considered adequate.

In treatment trials, response to therapy is traditionally defined as a 50% or greater decrease in score from baseline on a depression rating scale.[5] However, many responders may continue to

have symptoms and impaired function, and better functional outcomes can lag behind and are only modestly correlated with improved symptoms.[10] Remission, which refers to symptoms below a minimal level, is associated with improved quality of life and lower likelihood of relapse.[11,12] Since initial treatment does not result in response in about one in three patients and remission in about two in three,[11] there is a great need for therapies focused on those individuals with resistant depression. Treatment options for individuals with TRD broadly include modifying antidepressant therapy or augmenting existing therapies with non-antidepressant medications. Modification of antidepressant therapy can take several forms: attempting to optimize existing treatment by maximizing the dose used, switching to a new treatment, or adding on to an existing therapy. There is limited evidence comparing these different strategies.[13] Among those with TRD, there are patients with highly resistant depression with symptoms over long periods of time, with many sequential treatment regimens, and inadequate responses and/or multiple relapses. These patients face chronic disability and account for a disproportionate cost of care.[6]

For these most difficult to treat patients, referred to as having refractory depression, other strategies such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) may be tried.[14,15] ECT has been shown to be useful in those with highly resistant depression.[16] However, ECT requires anesthetic sedation and has side effects including memory loss and cognitive impairment as well as logistical constraints and stigma based upon media portrayals. Though patients can relapse after ECT, it can be administered chronically to maintain remission in certain patients. TMS is another device-based treatment for refractory depression. Repetitive TMS has been shown to improve depressive symptoms but may be less effective than ECT and also has logistical constraints that make long-term therapy difficult.[15,17] If not already tried, psychotherapy may be added to pharmacotherapy, but is generally not considered stand-alone therapy.[18]

Despite available treatments, there are many individuals who do not respond to multiple therapies for whom new treatment options are needed. One potential new target for therapy is the N-methyl-D-aspartate (NMDA) receptor.[19] Interest in agents that target this receptor have been driven by the observation that ketamine, an anesthetic, can transiently improve symptoms of depression.[20] Short-term studies have shown benefit, but this drug is usually administered intravenously and has side effects as well as the potential for abuse or diversion. A new agent, esketamine (investigational, Janssen), is under FDA review for patients with TRD. Ketamine is a racemic mixture of two stereoisomers. Esketamine is the S-enantiomer, which binds with greater affinity to the NMDA receptor and is being studied as a nasal spray for the treatment of adults with TRD.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project

will assess both the comparative clinical effectiveness and economic impacts of esketamine for the treatment of TRD. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). Details on the proposed methodology and model structure for the economic evaluation will be presented in a separate document (model analysis plan; to be published on February 5, 2019).

Research Questions

To inform our review of the clinical evidence, we have developed the following research question with input from clinical experts, patients and patient groups:

- In patients with TRD, what is the comparative efficacy, safety, and effectiveness of esketamine versus ketamine, ECT, TMS, oral antidepressants, or augmentation with antipsychotics in terms of treatment response, remission, relapse, quality of life, adverse events, and other key outcomes?
- In patients with TRD, what is the comparative efficacy, safety, and effectiveness of esketamine versus no treatment beyond background antidepressants (i.e. placebo arms of clinical trials) in terms of treatment response, remission, relapse, quality of life, adverse events, and other key outcomes?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The population of focus for this review will be adults ages 18 years and older with major depressive disorder, without psychotic features, and for whom two or more prior antidepressants prescribed at adequate dose and duration during the current episode have failed, termed TRD. As data permit, we will also plan to examine subgroups of patients suggested by patients and clinical experts. These include subgroups defined by:

1. Age: Adults 18 – 64 years; Adults 65 years and older
2. Number of prior treatment failures during the current episode (e.g., 2-3; 3-5; ≥5)

Interventions

The intervention of interest will be esketamine nasal spray plus background antidepressants (continued or new administration). In addition, we will seek clinical evidence on all forms of the product, including the intravenous form.

Comparators

Feedback from clinical experts suggests that esketamine will be used in patients for whom numerous antidepressants have failed. As such, our comparators for this review include treatments commonly used in this setting. These comparators may be used alone or in combination with background antidepressants (continued or new administration):

- Ketamine, an anesthetic agent used off-label for treatment-resistant depression
- ECT
- TMS

In addition, we will seek evidence on the following comparators:

- Other oral antidepressants (plus background antidepressants)
- Augmentation with antipsychotics (plus background antidepressants)
- No additional therapy beyond background antidepressants (i.e. placebo arm of clinical trials)

Outcomes

We will look for evidence on the following outcomes of interest.

Efficacy outcomes:

- Symptom improvement measured on Montgomery–Åsberg depression rating scales (MADRS) or other depression rating scale
- Rate of response
- Rate of remission
- Rate of relapse
- Symptom improvement as assessed by the clinician (Clinical Global Impression of Severity [CGI-S]) and patient (Patient Global Impression of Severity [PGI-S])
- Health-related quality of life assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L)

Safety outcomes:

- Serious adverse events (including suicidality)
- Discontinuation due to adverse events
- Treatment-emergent adverse events (e.g.,)
    - Dissociation
    - Dizziness
    - Headache
    - Fatigue
    - Somnolence
    - Nausea
    - Impaired sense of taste
    - High blood pressure
    - Metabolic changes
    - Substance use disorder
    - Memory loss

Timing

Evidence on intervention effectiveness and safety will be derived from studies of at least fourteen days, as long as they meet the study design criteria set forth above and measure an outcome of interest.

Setting

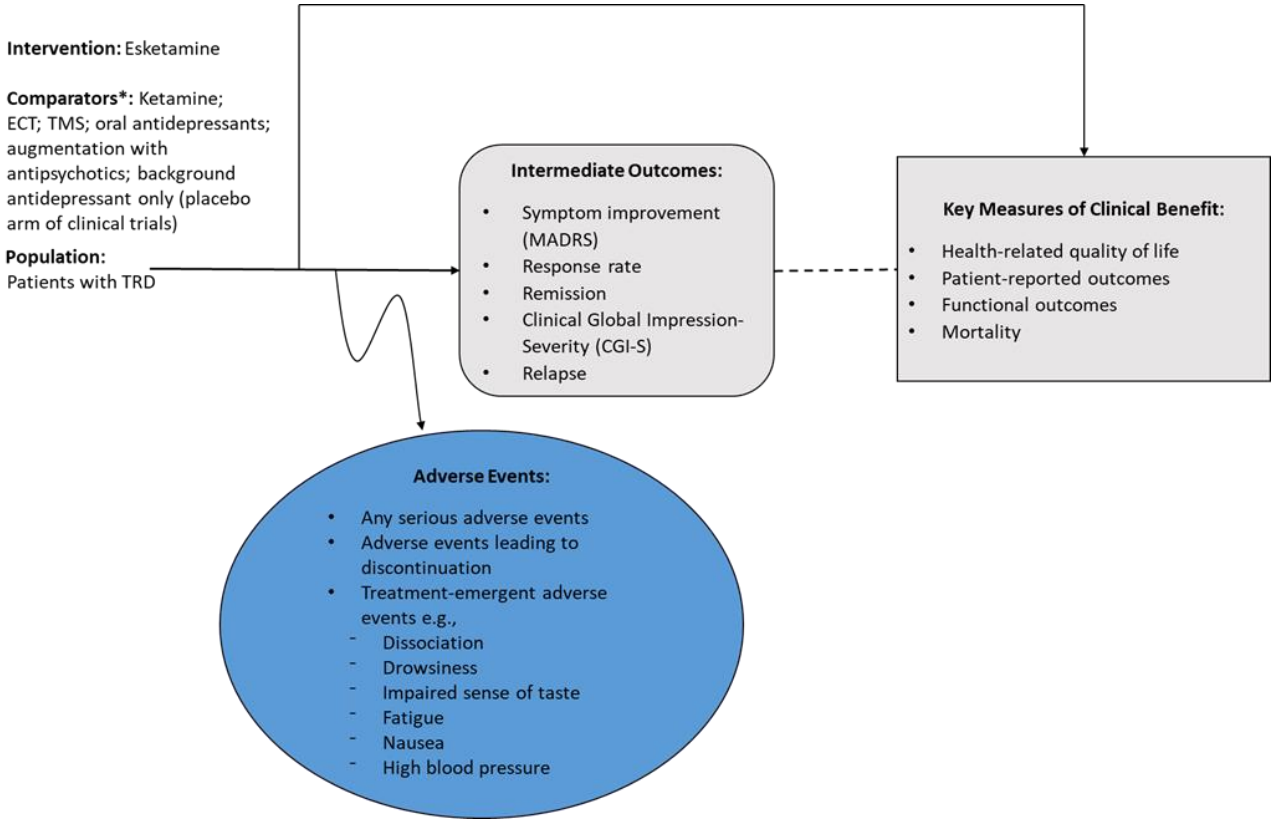
Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Study design

Randomized controlled trials (RCTs) with at least 10 patients will be included. In addition, we will seek evidence on esketamine and ketamine from non-randomized controlled trials and observational studies with at least 20 patients.

Analytic Framework

The proposed analytic framework for this project is depicted below:



ECT: Electroconvulsive therapy; MADRS: Montgomery–Åsberg depression rating scales; TMS: Transcranial Magnetic Stimulation; TRD: Treatment-resistant depression; *Comparators may be used alone or in combination with background antidepressant.

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in blood pressure), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.[21]

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on esketamine for TRD will follow established best methods.[22,23] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We identified a recent systematic review of RCTs of ketamine, ECT, TMS, oral antidepressants, and augmentation for TRD which followed a similar scope to the one planned for ths review, with literature search end date of September 2014.[14] We will identify RCTs of ECT, TMS, oral antidepressants, and augmentation with antipyschotics that meet our criteria from the systematic review, and search for new evidence by conducting an updated systematic literature search.

We will search MEDLINE, PsychINFO and EMBASE for relevant studies. In order to account for delays in indexing, we will overlap the search timeframe for ECT, TMS, oral antidepressants, and augmentation with antipyschotics with that of the previous systematic review, starting from January 2013. However, we will conduct a de novo search for ketamine and esketamine without a time restriction. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and recent systematic reviews of the intervention and individual comparators and also invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1: Search Strategy of Medline* and PsychINFO via Ovid

1	exp depressive disorder, treatment-resistant/
2	exp treatment-resistant depression/
3	depress*.ti,ab.
4	(treatment-resist* or treatment-resist* or therapy-resist* or therapy resist* or refract* or resist* or intractable or nonrespon* or non-respon* or unrespon* or fail* or ((no* or inadequat* or incomplet* or partial* or poor* or sub*) adj2 respon*) or (no* adj2 remi*)).ti,ab.
5	treatment failure/
6	drug resistance/
7	drug resistance, multiple/
8	4 or 5 or 6 or 7
9	3 and 8
10	1 or 2 or 9
11	(esketamine or S-ketamine or S ketamine or Ketanest or Ketanest S).ti,ab.
12	ketamine/
13	(ketamine or Ketaset or Ketalar or CI-581 or CI581 or CI 581 or Calipsol or Kalipsol or Calypsol or ketamin*).ti,ab.
14	(Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Paroxetine or Sertraline or Venlafaxine or Desvenlafaxine or Duloxetine or Milnacipran or Levomilnacipran or Amitriptyline or Amitriptylinoxide or Butriptyline or Clomipramine or Demexiptiline or Desipramine or Dibenzepin or Dimetacrine or Dosulepin or Dothiepin or Imipramine or Imipraminoxide or Lofepramine or Melitracen or Metapramine or Nitroxazepine or Nortriptyline or Noxiptiline or Pipofezine or Propizepine or Protriptyline or Quinupramine or Amineptine or Iprindole or Opipramol or Tianeptine or Trimipramine or Bupropion or Trazodone or Amoxapine or Maprotiline or Mazindol or Mianserin or Setiptiline or Isocarboxazid or Moclobemide or Phenelzine or Pirlindole or Selegiline or Tranylcypromine or Risperidone or Amisulpride or Aripiprazole or Asenapine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Ziprasidone or Zotepine or Symbyax or Mirtazapin$ or Vortioxetine or Agomelatine or Doxepin or Reboxetine or Brexpiprazole or Vilazodone or Nefazodone).ti,ab.
15	Citalopram/ or Fluoxetine/ or Fluvoxamine/ or Paroxetine/ or Sertraline/ or Venlafaxine Hydrochloride/ or Desvenlafaxine Succinate/ or Duloxetine Hydrochloride/ or Milnacipran/ or Levomilnacipran/ or Amitriptyline/ or Clomipramine/ or Desipramine/ or Dothiepin/ or Imipramine/ or Lofepramine/ or Nortriptyline/ or Protriptyline/ or Iprindole/ or Opipramol/ or Trimipramine/ or Bupropion/ or Trazodone/ or Amoxapine/ or Maprotiline/ or Mazindol/ or Mianserin/ or Isocarboxazid/ or Moclobemide/ or Phenelzine/ or Selegiline/ or Tranylcypromine/ or Risperidone/ or Amisulpride/ or Aripiprazole/ or Clozapine/ or Lurasidone Hydrochloride/ or Olanzapine/ or Paliperidone Palmitate/ or Quetiapine Fumarate/ or olanzapine-fluoxetine combination/ or Mirtazapine/ or Vortioxetine/ or Doxepin/ or Reboxetine/ or Vilazodone Hydrochloride/
16	(Celexa or Cipramil or Cipram or Dalsan or Recital or Emocal or Sepram or Seropram or Citox or Cital or Lexapro or Cipralex or Seroplex or Esertia or Depex or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Flutop or Fluctin or Fluox or Lovan or Prodep or Luvox or Fevarin or Faverin or Dumyrox or Favoxil or Movox or Floxyfral or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Deparoc or Zoloft or Lustral or Serlain or Asentra or Tresleen or Effexor or Efexor or Cymbalta or Ariclaim or Xeristar or Yentreve or Duzela or Dulane or Wellbutrin or Budeprion or Prexaton or Elontril or Aplenzin or Risperdal or Parnate or Jatrosom or Tofranil or Tofranil-PM or Elavil or Endep or Vanatrip or Anafranil or Pamelor or Aventyl

	Hydrochloride or Desyrel or Oleptro or Beneficat or Deprax or Desirel or Molipaxin or Thombran or Trazorel or Trialodine or Trittico or Mesyrel or Meresa or Bosnyl or Dogmatil or Dolmatil or Eglonyl or Modal or Espiride or Abilify or Saphris or Sycrest or Leponex or Fanapt or Fanapta or Zomaril or Latuda or Zyprexa or Zalasta or Invega or Seroquel or Geodon or Zeldox or Pristiq or Dalcipran or Ixel or Savella or Fetzima or Tryptomer or Elavil or Endep or Amioxid or Ambivalon or Equilibrin or Evadyne or Deparon or Tinora or Norpramin or Pertofane or Noveril or Victoril or Istonil or Istonyl or Miroistonil or Prothiaden or Adapin or Sinequan or Tofranil or Janimine or Praminil or Imiprex or Elepsin or Lomont or Gamanil or Deanxit or Dixeran or Melixeran or Trausabun or Timaxel or Pamelor or Aventyl or Norpress or Agedal or Elronon or Nogedal or Azafen or Azaphen or Vagran or Vivactil or Kevopril or Kinupril or Adeprim or Quinuprine or Survector or Maneon or Directim or Prondol or Galatur or Tetran or Insidon or Pramolan or Ensidon or Oprimol or Stablon or Coaxil or Tatinol or Surmontil or Asendin or Deprilept or Ludiomil or Psymion or Mazanor or Sanorex or Tecipul or Marplan or Aurorix or Manerix or Nardil or Eldepryl or Zelapar or Emsam or Solian or Clozaril or Nipolept or Remergil or Remeron or Zispin or Remergon or Rexer or Promyrtil or Norset or Remeron SolTab or 6-Azamianserin or Mepirzepine or ORG-3770 or Brintellix or Valdoxan or Melitor or Thymanax or Deptran or Sinequan or Edronax or Prolift or OPC-34712 or Viibryd or Serzone).ti,ab.
17	electroconvulsive therapy/
18	(ect or electroconvulsive therapy).ti,ab.
19	transcranial magnetic stimulation/
20	(TMS or rTMS or transcranial magnetic stimulation).ti,ab.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	limit 21 to yr="2013- Current"
23	11 or 12 or 13 or 22
24	10 and 23
25	(animals not (human and animals)).sh.
26	24 not 25
27	limit 26 to english language
28	(addresses OR autobiography OR bibliography OR biography OR case reports OR clinical trial, phase I OR comment OR congresses OR consensus development conference OR duplicate publication OR editorial OR guideline OR interview OR lectures OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video-audio media).pt
29	exp cohort studies/ OR comparative study.pt.
30	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or (clinical trial or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or multicenter study or randomized controlled trial).pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab.
31	29 or 30
32	31 not 28
33	27 and 32
34	remove duplicates from 33

*Medline 1996 to Present with Daily Update

Table 2. Search strategy of EMBASE

1	'treatment-resistant depression'/exp
2	depress*:ti,ab
3	'treatment-resist*':ti,ab OR 'treatment-resist*':ti,ab OR 'therapy resist*':ti,ab OR 'therapy-resist*':ti,ab OR refract*:ti,ab OR resist*:ti,ab OR intractable:ti,ab OR nonrespon*:ti,ab OR 'non-respon*':ti,ab OR fail*:ti,ab OR unrespon*:ti,ab OR (((no* OR inadequat* OR incomplet* OR partial* OR poor* OR sub*) NEAR/2 respon*):ti,ab) OR ((no* NEAR/2 remi*):ti,ab)
4	'treatment failure'/exp
5	'drug resistance'/de
6	'multidrug resistance'/de
7	#3 OR #4 OR #5 OR #6
8	#2 AND #7
9	#1 OR #8
10	'esketamine'/de
11	esketamine:ti,ab OR 's ketamine':ti,ab OR 's-ketamine':ti,ab OR ketanest:ti,ab
12	'ketamine'/de
13	ketamine:ti,ab OR ketaset:ti,ab OR ketalar:ti,ab OR ci581:ti,ab OR 'ci 581':ti,ab OR 'ci-581':ti,ab OR calipsol:ti,ab OR kalipsol:ti,ab OR calypsol:ti,ab or ketamin*:ti,ab
14	#10 OR #11 OR #12 OR #13
15	#9 AND #14
16	'clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk
17	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compared':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab
18	#16 OR #17
19	#15 AND #18
20	'electroconvulsive therapy'/de
21	ect:ti,ab OR 'electroconvulsive therapy':ti,ab
22	'transcranial magnetic stimulation'/exp
23	tms:ti,ab OR rtms:ti,ab OR 'transcranial magnetic stimulation':ti,ab
24	citalopram:ti,ab OR escitalopram:ti,ab OR fluoxetine:ti,ab OR fluvoxamine:ti,ab OR paroxetine:ti,ab OR sertraline:ti,ab OR venlafaxine:ti,ab OR desvenlafaxine:ti,ab OR duloxetine:ti,ab OR milnacipran:ti,ab OR levomilnacipran:ti,ab OR amitriptyline:ti,ab OR amitriptylinoxide:ti,ab OR butriptyline:ti,ab OR clomipramine:ti,ab OR demexiptiline:ti,ab OR desipramine:ti,ab OR dibenzepin:ti,ab OR dimetacrine:ti,ab OR dosulepin:ti,ab OR dothiepin:ti,ab OR imipramine:ti,ab OR imipraminoxide:ti,ab OR lofepramine:ti,ab OR melitracen:ti,ab OR metapramine:ti,ab OR nitroxazepine:ti,ab OR nortriptyline:ti,ab OR noxiptiline:ti,ab OR pipofezine:ti,ab OR propizepine:ti,ab OR protriptyline:ti,ab OR quinupramine:ti,ab OR amineptine:ti,ab OR iprindole:ti,ab OR opipramol:ti,ab OR tianeptine:ti,ab OR trimipramine:ti,ab OR amfebutamone:ti,ab OR bupropion:ti,ab OR trazodone:ti,ab OR amoxapine:ti,ab OR maprotiline:ti,ab OR mazindol:ti,ab OR mianserin:ti,ab OR setiptiline:ti,ab OR teciptiline:ti,ab OR isocarboxazid:ti,ab OR moclobemide:ti,ab OR phenelzine:ti,ab OR pirlindole:ti,ab OR selegiline:ti,ab OR tranylcypromine:ti,ab OR risperidone:ti,ab OR amisulpride:ti,ab OR aripiprazole:ti,ab OR asenapine:ti,ab OR clozapine:ti,ab OR iloperidone:ti,ab OR lurasidone:ti,ab OR olanzapine:ti,ab OR paliperidone:ti,ab OR quetiapine:ti,ab OR ziprasidone:ti,ab OR zotepine:ti,ab OR symbyax:ti,ab OR mirtazapin$:ti,ab OR vortioxetine:ti,ab OR agomelatine:ti,ab OR doxepin:ti,ab OR reboxetine:ti,ab OR brexpiprazole:ti,ab OR vilazodone:ti,ab OR nefazodone:ti,ab

25	'citalopram' OR 'escitalopram' OR 'fluoxetine' OR 'fluvoxamine' OR 'paroxetine' OR 'sertraline' OR 'venlafaxine' OR 'desvenlafaxine' OR 'duloxetine' OR 'milnacipran' OR 'levomilnacipran' OR 'amitriptyline' OR 'amitriptylinoxide' OR 'butriptyline' OR 'clomipramine' OR 'demexiptiline' OR 'desipramine' OR 'dibenzepin' OR 'dimetacrine' OR 'dosulepin' OR 'dothiepin' OR 'imipramine' OR 'imipraminoxide' OR 'lofepramine' OR 'melitracen' OR 'metapramine' OR 'nitroxazepine' OR 'nortriptyline' OR 'noxiptiline' OR 'pipofezine' OR 'propizepine' OR 'protriptyline' OR 'quinupramine' OR 'amineptine' OR 'iprindole' OR 'opipramol' OR 'tianeptine' OR 'trimipramine' OR 'amfebutamone' OR 'bupropion' OR 'trazodone' OR 'amoxapine' OR 'maprotiline' OR 'mazindol' OR 'mianserin' OR 'setiptiline' OR 'teciptiline' OR 'isocarboxazid' OR 'moclobemide' OR 'phenelzine' OR 'pirlindole' OR 'selegiline' OR 'tranylcypromine' OR 'risperidone' OR 'amisulpride' OR 'aripiprazole' OR 'asenapine' OR 'clozapine' OR 'iloperidone' OR 'lurasidone' OR 'olanzapine' OR 'paliperidone' OR 'quetiapine' OR 'ziprasidone' OR 'zotepin' OR 'zotepine' OR 'fluoxetine plus olanzapine' OR 'symbyax' OR 'mirtazapine' OR 'vortioxetine' OR 'agomelatine' OR 'doxepin' OR 'reboxetine' OR 'brexpiprazole' OR 'vilazodone' OR 'nefazodone'
26	celexa:ti,ab OR cipramil:ti,ab OR cipram:ti,ab OR dalsan:ti,ab OR recital:ti,ab OR emocal:ti,ab OR sepram:ti,ab OR seropram:ti,ab OR citox:ti,ab OR cital:ti,ab OR lexapro:ti,ab OR cipralex:ti,ab OR seroplex:ti,ab OR esertia:ti,ab OR depex:ti,ab OR prozac:ti,ab OR fontex:ti,ab OR seromex:ti,ab OR seronil:ti,ab OR sarafem:ti,ab OR ladose:ti,ab OR motivest:ti,ab OR flutop:ti,ab OR fluctin:ti,ab OR fluox:ti,ab OR lovan:ti,ab OR prodep:ti,ab OR luvox:ti,ab OR fevarin:ti,ab OR faverin:ti,ab OR dumyrox:ti,ab OR favoxil:ti,ab OR movox:ti,ab OR floxyfral:ti,ab OR paxil:ti,ab OR seroxat:ti,ab OR sereupin:ti,ab OR aropax:ti,ab OR deroxat:ti,ab OR divarius:ti,ab OR rexetin:ti,ab OR xetanor:ti,ab OR paroxat:ti,ab OR loxamine:ti,ab OR deparoc:ti,ab OR zoloft:ti,ab OR lustral:ti,ab OR serlain:ti,ab OR asentra:ti,ab OR tresleen:ti,ab OR effexor:ti,ab OR efexor:ti,ab OR cymbalta:ti,ab OR ariclaim:ti,ab OR xeristar:ti,ab OR yentreve:ti,ab OR duzela:ti,ab OR dulane:ti,ab OR wellbutrin:ti,ab OR budeprion:ti,ab OR prexaton:ti,ab OR elontril:ti,ab OR aplenzin:ti,ab OR risperdal:ti,ab OR parnate:ti,ab OR jatrosom:ti,ab OR 'tofranil pm':ti,ab OR vanatrip:ti,ab OR anafranil:ti,ab OR 'aventyl hydrochloride':ti,ab OR desyrel:ti,ab OR oleptro:ti,ab OR beneficat:ti,ab OR deprax:ti,ab OR desirel:ti,ab OR molipaxin:ti,ab OR thombran:ti,ab OR trazorel:ti,ab OR trialodine:ti,ab OR trittico:ti,ab OR mesyrel:ti,ab OR meresa:ti,ab OR bosnyl:ti,ab OR dogmatil:ti,ab OR dolmatil:ti,ab OR eglonyl:ti,ab OR modal:ti,ab OR espiride:ti,ab OR abilify:ti,ab OR saphris:ti,ab OR sycrest:ti,ab OR leponex:ti,ab OR fanapt:ti,ab OR fanapta:ti,ab OR zomaril:ti,ab OR latuda:ti,ab OR zyprexa:ti,ab OR zalasta:ti,ab OR invega:ti,ab OR seroquel:ti,ab OR geodon:ti,ab OR zeldox:ti,ab OR pristiq:ti,ab OR dalcipran:ti,ab OR ixel:ti,ab OR savella:ti,ab OR fetzima:ti,ab OR tryptomer:ti,ab OR elavil:ti,ab OR endep:ti,ab OR amioxid:ti,ab OR ambivalon:ti,ab OR equilibrin:ti,ab OR evadyne:ti,ab OR deparon:ti,ab OR tinora:ti,ab OR norpramin:ti,ab OR pertofane:ti,ab OR noveril:ti,ab OR victoril:ti,ab OR istonil:ti,ab OR istonyl:ti,ab OR miroistonil:ti,ab OR prothiaden:ti,ab OR adapin:ti,ab OR tofranil:ti,ab OR janimine:ti,ab OR praminil:ti,ab OR imiprex:ti,ab OR elepsin:ti,ab OR lomont:ti,ab OR gamanil:ti,ab OR deanxit:ti,ab OR dixeran:ti,ab OR melixeran:ti,ab OR trausabun:ti,ab OR timaxel:ti,ab OR pamelor:ti,ab OR aventyl:ti,ab OR norpress:ti,ab OR agedal:ti,ab OR elronon:ti,ab OR nogedal:ti,ab OR azafen:ti,ab OR azaphen:ti,ab OR vagran:ti,ab OR vivactil:ti,ab OR kevopril:ti,ab OR kinupril:ti,ab OR adeprim:ti,ab OR quinuprine:ti,ab OR survector:ti,ab OR maneon:ti,ab OR directim:ti,ab OR prondol:ti,ab OR galatur:ti,ab OR tetran:ti,ab OR insidon:ti,ab OR pramolan:ti,ab OR ensidon:ti,ab OR oprimol:ti,ab OR stablon:ti,ab OR coaxil:ti,ab OR tatinol:ti,ab OR surmontil:ti,ab OR asendin:ti,ab OR deprilept:ti,ab OR ludiomil:ti,ab OR psymion:ti,ab OR mazanor:ti,ab OR sanorex:ti,ab OR tecipul:ti,ab OR marplan:ti,ab OR aurorix:ti,ab OR manerix:ti,ab OR nardil:ti,ab OR eldepryl:ti,ab OR zelapar:ti,ab OR emsam:ti,ab OR solian:ti,ab OR clozaril:ti,ab OR nipolept:ti,ab OR remergil:ti,ab OR remeron:ti,ab OR zispin:ti,ab OR remergon:ti,ab OR rexer:ti,ab OR promyrtil:ti,ab OR norset:ti,ab OR 'remeron soltab':ti,ab OR '6 azamianserin':ti,ab OR mepirzepine:ti,ab OR 'org 3770':ti,ab OR brintellix:ti,ab OR valdoxan:ti,ab OR melitor:ti,ab OR

	thymanax:ti,ab OR deptran:ti,ab OR sinequan:ti,ab OR edronax:ti,ab OR prolift:ti,ab OR 'opc 34712':ti,ab OR viibryd:ti,ab OR serzone:ti,ab
27	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28	#9 AND #27
29	#28 AND [2013-2019]/py
30	#29 AND #16
31	#19 OR #30
32	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
33	#31 NOT #32
34	#33 AND [english]/lim
35	#34 AND [medline]/lim
36	#34 NOT #35
37	#36 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)

Eligibility Criteria

We will exclude studies that do not meet the PICOTS criteria defined above. Studies conducted in patients with treatment-resistant bipolar depression will be excluded. We will only include studies of oral antidepressants and augmentation with antipsychotics if patients in the trial are also receiving background antidepressants.

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Three reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada) and will work to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage,

frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[25]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for this newer treatment, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "esketamine." Alternative drug names will also be used as search terms. We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence table shells are presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

Any analyses to be conducted will reflect the nature and quality of the evidence base. Key considerations for interpreting the results will be specified and described in the Evidence Report.

We also will assess the feasibility of conducting a network meta-analysis (NMA). Studies that are deemed sufficiently similar in terms of the key population, intervention, and outcome measures will be included in NMA. A NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)).[26,27]

NMAs will be conducted using a Bayesian framework. For continuous outcomes (e.g., change from baseline in MADRS), the NMA model corresponds to a generalized linear model with identity link.[28] For binary outcomes (e.g., response rates, remission rates), the NMA model corresponds to a generalized linear model with a logit link.[28] For all analyses, we will include random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) will be assumed constant across all treatment comparisons. We will use noninformative prior distributions for all model parameters. We will initially discard the first 40,000 iterations as "burn-in" and base inferences on an additional 40,000 iterations using 3 chains. Convergence of chains will be assessed with the Gelman-Rubin statistic and visually using trace plots. If the chains do not converge, an additional 10,000 iterations will be run, sequentially, until convergence.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[29] If there is evidence of inconsistency, the results will be presented for the

direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include number of prior antidepressant failures, duration of current depressive episode, and comorbid suicidal ideation. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

All analyses will be conducted in R using the *metaphor* package[30] for pairwise meta-analyses or the *gemtc* package[31] for NMAs. Data included in each analysis along with the corresponding code will be included in an appendix of the Evidence Report. Results for all pairwise comparisons will be presented tabularly in terms of a point estimate and 95% credible intervals.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[24] Additional explanation of each item can be found in Liberati et al. 2009.[32]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shell

Table B1: Study Overview

Drug/Trials	Design	Number of Centers	Location	Prospective Observational Phase (weeks)	Intervention (weeks)	Total Follow-up (weeks)	Concomitant AD	Key Inclusion Criteria	Key Exclusion Criteria

Table B2: Key Baseline Characteristics

Trials	Arm	N	Age, mean (SD) or [range]	Age of MDD diagnosis, mean (SD)	Duration of current episode (years), mean (SD)	No. of prior failed ADs at baseline, mean (SD)	No. of prior failed ADs at baseline, n (%)	≥ 3 failed ADs, n (%)	MADRS, mean (SD)	HAM-D, mean (SD)	PHQ-9, mean (SD)	CGI-S, mean (SD)

Table B3: Quality Rating

Trial	Comparable Groups	Non-differential Follow-up	Patient/Investigator Blinding (Double-Blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Measurements Equal and Valid	Approach to Missing Data	USPSTF Rating

Table B4: Efficacy Outcomes

Trial	Week	Arm	N	Change in MADRS		Change in HDRS		Response		Remission		CGI-S		PGI-S		Other outcomes
				Mean	SD	Mean	SD	n	%	n	%	Mean	SD	Mean	SD	

Table B5: Safety Outcomes

Trial	Week	Arm	N	Serious Adverse Events		Discontinuation due to AE		Commonly occurring AEs in ≥5% of patients*				
				n	%	n	%	Dissociation, %	Nausea, %	Dizziness	Vertigo	Somnolence

*Commonly occurring AEs to be populated based on data from the trial