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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi._yoda.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT02417064 - ESKETINTRD3001 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression
2. NCT02418585 - ESKETINTRD3002 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression
3. NCT02422186 - ESKETINTRD3005 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in

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Elderly Subjects With Treatment-resistant Depression
4. NCT01998958 - ESKETINTRD2003 - A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in an Adaptive Treatment Protocol to Assess Safety and Efficacy in Treatment-Resistant Depression (SYNAPSE)
5. NCT02918318 - 54135419TRD2005 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Doses of Intranasal Esketamine in Japanese Subjects With Treatment Resistant Depression
6. NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression
7. NCT03434041 - ESKETINTRD3006 - A Randomized, Double-blind, Multicenter Active-controlled Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Esketamine for treatment-resistant depression in adults: Cochrane systematic review and meta-analysis on efficacy and tolerability of esketamine

Narrative Summary:

An international team and I are conducting a Cochrane systematic review and meta-analysis on esketamine for treatment resistant depression at the WHO collaborating and Cochrane centre of Verona led by Prof. Barbui. Here you can find the published protocol: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015071/full (also attached).
Esketamine is a new medication available for treatment resistant depression and cumulative evidence is needed to define its profile in terms of efficacy and tolerability. Thus, we are collecting all available RCTs to perform a meta-analysis of efficacy, tolerability and side effects.

Scientific Abstract:

BACKGROUND: esketamine is a new medication for TRD, a comprehensive analysis of the literature on efficacy and tolerability is needed.
OBJ:The main aim of this Cochrane review is to assess the efficacy and tolerability of esketamine for treatment-resistant depression. Secondary aims are to assess the risk of specific adverse events during esketamine treatment, and its acceptability.
DESIGN: cochrane systematic review and meta-analysis of RCTs
PARTICIPANTS: Participants will be adults, aged 18 years or older. We will include studies that include both participants under 18 years and 18 years or older only if fewer than 20% of participants are younger than 18 years. We will define TRD as a primary diagnosis of a depressive episode with inadequate response to at least two trials of antidepressants (AD) of adequate dose and duration. We will include studies that applied any standardised diagnostic criteria for unipolar depression, including the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases criteria.
PRIMARY AND SECONDARY OUTCOMES:
1. Efficacy (continuous outcome): change in depressive symptoms from baseline to study end point, measured with any rating scale for depression
2. Tolerability: number of participants who dropped out due to side eHectsduring the trial, as a proportion of the total number ofrandomised participants
3. Efficacy (dichotomous outcome): number of participants who responded to treatment, where treatment response is defined as (1) a reduction of at least 50% compared to baseline on any depression scale.
4. a. Total number of participants experiencing at least one side effect, b. Total number of participants experiencing at least one serious adverse event,
5. Total number of participants experiencing the following specific side effects: dissociative symptoms or

dissociative disorder, sedation, nausea, vomiting, abuse or misuse ,completed suicide or attempted suicide, suicidal ideation or thoughts, agitation or anxiety, increased blood pressure or hypertension, dizziness, feeling abnormal or feeling drunk, headache, vertigo, dysgeusia.
STATISTICAL ANALYSIS: We will analyse continuous outcomes by calculating the mean difference (MD) and 95% confidence intervals (CI) between groups,
if studies use the same outcome measure for comparison. When available. we will use the mean change from baseline to end point. If the mean change is not available, we will use the mean end point score. If different scales are used to assess the same outcome, we will calculate the standardised mean difference (SMD) and 95% CI. For dichotomous data, we will calculate the relative risk (RR) with corresponding 95% CI for dichotomous or event-like outcomes for each comparison. We will calculate response rates out of the total number of randomised participants.
If meta-analysis is not possible (e.g. due to insufficient data or substantial heterogeneity), we will provide a narrative assessment of the evidence. If heterogeneity is low (<40%), we will examine the robustness of the results by comparing the fixed-effect model and the random-effects model.
where possible we will perform subgroup analyses by dose, level of resistance and diagnosis. And sensitivity analysis excluding RCTs with unclear allocation concealment or double blinding and with imputations of missing data. Analyses will be performed with review manager and RSTUDIO

Brief Project Background and Statement of Project Significance:

The term treatment resistant depression refers to a depressive episode that failed to respond or remit to one or more treatments (pharmacological, non-pharmacological, or both(Cosgrove2021). Among clinical studies, the most commonly used definition of treatment-resistant or treatment refractory depression is the absence of clinical improvement to at least two antidepressants, prescribed at adequate dose and duration (Brown 2019; Cosgrove 2021; Malhi 2016). Currently, switching to another antidepressant, adjunctive treatment (i.e. added treatment to assist the primary treatment), psychotherapy, or neuro stimulation, are treatments that have been suggested for people with TRD (Kennedy 2016; NICE 2016). Considering the large body of evidence of involvement of
the glutamate system in the pathophysiology of depression, pre-clinical studies were conducted to assess the potential antidepressant efficacy of glutamateinhibition with NMDA receptor antagonists, such as ketamine and esketamine, with positive results (Altamura 1995; Zarate 2006). However, clinical studies have not confirmed the eHicacy of ketamine for depression. in March 2019, the US Food and Drug Administration approved a nasal spray formulation of esketamine for people with TRD, and more recently, for people with MDD and acute suicidal ideation (FDA 2019; FDA Committee 2019). At the
end of 2019, esketamine was also granted marketing authorisation by the European Medicine Agency (EMA) for the same clinical indication (EMA 2019). According to the FDA and EMA label, esketamine is indicated in TRD in association with antidepressant treatment. In Europe, this is the only licensed treatment for TRD, while in the USA, there is another treatment for TRD, which is a combination of fluoxetine and olanzapine.
Why it is important to do this review
There is a particular concern about esketamine safety and acceptability. A safety signal, based on reports of esketamine-associated suicidal ideation, was detected and requires clarification and careful reanalyses of existing data (Gastaldon 2021). In addition to safety and acceptability, concerns have been raised about the clinical relevance of the esketamine-placebo difference (Cristea 2019; Gastaldon 2020; Turner 2019). Therefore, a thorough risk-benefit assessment of the esketamine profile in people with TRD is urgently needed to assist people with TRD, healthcare professionals, policy makers, and other interested stakeholders in making informed choices. Therefore, a comprehensive and indipendent analysis of all available evidence is needed.

Specific Aims of the Project:

The main aim of this Cochrane review is to assess the efficacy and tolerability of esketamine for treatment-resistant depression.
Secondary aims are to assess the risk of specific adverse events during esketamine treatment, and its acceptability.

What is your Study Design?:

Meta-analysis (analysis of multiple trials together)

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What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

New research question to examine treatment safety

Summary-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

We searched databases and trial registers using relevant keywords.
Participants will be adults, aged 18 years or older. We will include studies that include both participants under 18 yearsand 18 years or older only if fewer than 20% of participants are younger than 18 years. Definition of treatment-resistant depression (TRD) We will define TRD as a primary diagnosis of a depressive episode with inadequate response to at least two trials of antidepressants (AD) of adequate dose and duration. We will exclude studies enrolling participants based on other explicit criteria defining different levels of treatment resistance. We will include studies that applied any standardised diagnostic criteria for unipolar depression, including the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases criteria (ICD-10 (WHO 1992)). Comorbidity: We will exclude studies with participants with comorbid schizophrenia or bipolar disorder. We will only include studies in which fewer than 20% of participants may be suffering from bipolar depression, and thus, at least 80% of participants will have unipolar disorder.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Main outcomes
1. Efficacy (continuous outcome): change in depressive symptoms from baseline to study end point, measured with any rating scale for depression
2. Tolerability: number of participants who dropped out due to side eHectsduring the trial, as a proportion of the total number ofrandomised participants
Secondary outcomes
3. Efficacy (dichotomous outcome): number of participants who responded to treatment, where treatment response is defined as (1) a reduction of at least 50% compared to baseline on any depression scale.
4. a. Total number of participants experiencing at least one side effect, b. Total number of participants experiencing at least one serious adverse event,
5. Total number of participants experiencing the following specific side effects: dissociative symptoms or dissociative disorder, sedation, nausea, vomiting, abuse or misuse ,completed suicide or attempted suicide, suicidal ideation or thoughts, agitation or anxiety, increased blood pressure or hypertension, dizziness, feeling abnormal or feeling drunk, headache, vertigo, dysgeusia.
6. Acceptability (dichotomous outcome):a. Overall dropouts, b.due to lack of efficacy

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Efficacy (continuous outcome): change in depressive symptoms from baseline to study end point, measured with any
rating scale for depression.
Tolerability: number of participants who dropped out due to side effects during the trial, as a proportion of the total number
of randomised participants

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

level of resistance: ie. number of previous treatments, doses, quality of studies (according to the ROB2 of cochrane)
We will assess the risk of bias according to the following domains:
(1) bias arising from the randomisation process;
(2) bias due to deviations from intended interventions;
(3) bias due to missing outcome data;
(4) bias in measurement of the outcome;
(5) bias in selection of the reported result.

Timing of outcome assessment
We will assess primary and secondary outcomes at the study end point. We will also consider the following time points for the primary outcomes:
1. At 24 hours, ranging between 12 and 36 hours after randomisation
2. At four weeks, ranging between three and six weeks afer randomizations
3. At three months, ranging between seven weeks and six months after randomizations

Statistical Analysis Plan:

Main planned comparisons
1. Esketamine versus placebo
2. Esketamine versus other active pharmacological treatments
3. Esketamine versus physical therapies
Analyses
we plan a pooled analysis of means of studies. We do not plan to use individual patient level data.
We will analyse continuous outcomes by calculating the mean diHerence (MD) and 95% confidence intervals (CI) between groups,
if studies use the same outcome measure for comparison. When available. we will use the mean change from baseline to end point. If the mean change is not available, we will use the mean end point score. If different scales are used to assess the same outcome, we will calculate the standardised mean difference (SMD) and 95% CI. For dichotomous data, we will calculate the relative risk (RR) with corresponding 95% CI for dichotomous or event-like outcomes for each comparison. We will calculate response rates out of the total number of randomised participants.
If meta-analysis is not possible (e.g. due to insufficient data or substantial heterogeneity), we will provide a narrative assessment of the evidence. If heterogeneity is low (<40%), we will examine the robustness of the results by comparing the fixed-effect model and the random-effects model.
where possible we will perform subgroup analyses by dose, level of resistance and diagnosis. And sensitivity analysis excluding RCTs with unclear allocation concealment or double blinding and with imputations of missing data.
We will first investigate heterogeneity between studies by visual inspection of the forest plots. If the 95% CIs of the MD, SMDs, or RRs
for each study in the pooled analysis do not include means of other studies, we will investigate potential sources of heterogeneity. We will also calculate the IP statistic (Higgins 2021). We will use the Cochrane Handbook for Systematic Reviews of Interventions' rough guide to its interpretation as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.
We will include all eligible studies in the primary analysis. We will combine treatment groups as clinically appropriate, based on the
clinical similarity of treatments, e.g. different dosages of the same drug will be combined only if the different doses are clinically comparable. Given the potential for heterogeneity in the included studies, we will use a random-effects model for all analyses. This approach will incorporate the assumption that the different studies are estimating diHerent, yet related, intervention effects, and takes into account diHerences between studies, even if there is no statistically significant heterogeneity.
subgroup analyses
1. Dosage: as diHerent doses could have diHerent eHects on both efficacy and tolerability, we plan to perform a subgroup analysis,
keeping the twolicensed dosages separate, i.e. 56 mg and 84 mg. 2. Level of resistance: studies defining TRD as an inadequate response to at least two trials of antidepressant at adequate doses and duration, versus studies enrolling participants based on other criteria used to define treatment resistance
3. Diagnosis: studies with participants exclusively diagnosed with unipolar treatment-resistant depression versus

studies with mixed diagnosis (unipolar and bipolar)
Sensitivity analysis
We plan the following sensitivity analyses for the primary outcomes.
• Excluding trials with unclear allocation concealment or unclear double blinding of participants and outcome assessors.
• Excluding trials for which missing data have been imputed in the review process.
Software Used:
I am not analyzing participant-level data / plan to use another secure data sharing platform

Project Timeline:

june-september:analyses
September-november: write up of results
November-december 2023: submission to Cochrane

Dissemination Plan:

publication on the cochrane library as a cochrane review.

Bibliography:

Altamura 1995
AltamuraC, MaesM, DaiJ, MeltzerHY.Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine
in major depression. European Neuropsychopharmacology 1995;5(Suppl):71-5.
APA 1980
American Psychiatric Association.Diagnostic and Statistical Manual of Mental Disorders (DSM-III). 3rd edition. Washington,
DC: American Psychiatric Association, 1980.
APA 1987
American Psychiatric Association.Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3rd edition. Washington, DC: American Psychiatric Association, 1987.
APA 1994
American Psychiatric Association.Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th edition. Washington,
DC: American Psychiatric Association, 1994.
APA 2000
American Psychiatric Association.Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IVTR). 4th
edition. Washington, DC: American Psychiatric Association, 2000.
APA 2010
American Psychiatric Association.Practice guideline for the treatment of patients with major depressive disorder. 3rd
edition. Washington, DC: American Psychiatric Association, 2010.
APA 2013
American Psychiatric Association.Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th edition. Washington,
DC: American Psychiatric Association, 2013.
Bauer 2002
BauerM, WhybrowPC, AngstJ, VersianiM, MollerHJ, World Federation of Societies Biological Psychiatry (WFSBP) Task
Force on Treatment Guidelines for Unipolar Depressive Disorders.World Federation of Societies of Biological Psychiatry
(WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: acute and continuation treatment
of major depressive disorder. World Journal of Biological Psychiatry 2002;3(1):5-43.
Beck 1996
BeckAT, SteerRA, BrownGK.Beck Depression Inventory - Second Edition: Manual. San Antonio (USA): The Psychological
Corporation, 1996.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

Brown 2019
BrownS, RittenbachK, CheungS, McKeanG, MacMasterFP, ClementF.Current and common definitions of treatmentresistant depression: findings from a systematic review and qualitative interviews. Canadian Journal of Psychiatry 2019;64:380-7.
Canuso 2018
CanusoCM, SinghJB, FedgchinM, AlphsL, LaneR, LimP, et al.EHicacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality inpatients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. American Journal of Psychiatry 2018;175(7):620–30.
Cipriani 2018
CiprianiA, FurukawaTA, SalantiG, ChaimaniA, AtkinsonLZ, OgawaY, et al.Comparative eHicacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391(10128):1357-66.
Cohen 1988
CohenJ.Statistical Power Analysis in the Behavioural Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc, 1988.
Conway 2017
ConwayCR, GeorgeMS, SackeimHA.Toward an evidence-based, operational definition of treatment-resistant depression:when enough Is enough. JAMA Psychiatry 2017;74(1):9-10.
Cosgrove 2021
CosgroveL, NaudetF, HögbergG, ShaughnessyAF, CristeaIA.Reconceptualising treatment-resistant depression as diHicult-to-treat depression. Lancet Psychiatry 2021;8(1):11-3.
Cristea 2019
CristeaIA, NaudetF.US Food and Drug Administration approval of esketamine and brexanolone. Lancet Psychiatry 2019;6(12):975-7.
Daly 2018
DalyEJ, SinghJB, FedgchinM, CooperK, LimP, SheltonRC, et al.EHicacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2018;75(2):139-48.
Dean 2021
DeanRL, HurducasC, HawtonK, SpyridiS, CowenPJ, HollingsworthS, et al.Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. Cochrane Database of Systematic Reviews 2021, Issue 9. Art. No: CD011612. [DOI: 10.1002/14651858.CD011612.pub3]
Egger 1997
EggerM, SmithGD, SchneiderM, MinderC.Bias in metaanalysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34.
EMA 2019
European Medicine Agency.Esketamine approval. www.ema.europa.eu/en/medicines/human/EPAR/spravato 2019.
Fava 2005
FavaM.Diagnosis and definition of treatment-resistant depression. Biological Psychiatry 2005;53:649-59.
Fava 2020
FavaGA, CosciF, GuidiJ, RafanelliC.The deceptive manifestations of treatment resistance in depression: a new look at the problem. Psychotherapy and Psychosomatics 2020;89(5):265-73.
FDA 2019
US Food and Drug Administration (FDA).FDA approval of esketamine nasal spray. www.fda.gov/news-events/pressannouncements/ fda-approves-new-nasal-spray-medicationtreatment- resistant-depression-available-only-certified 2019.
FDA Committee 2019
FDA CommitteeMembers of the PsychopharmacologicDrugs Advisory Committee (PDAC) and Drug Safety and Risk

Management (DSARM) Advisory.FDA Briefing Document – Psychopharmacologic Drugs Advisory Committee (PDAC)
and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting.
www.fda.gov/media/121376/download
2019.
Fedgchin2019
FedgchinM, TrivediM, DalyEJ, MelkoteR, LaneR, LimP, et al.EHicacy and safety of fixed-dose esketamine nasal spray
combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, activecontrolled
study (TRANSFORM-1). International Journal of Neuropsychopharmacology 2019;22(10):616-30.
Fekadu 2009
FekaduA, WoodersonS, DonaldsonC, MarkopoulouK, MastersonB, PoonL, et al.A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. Journal of Clinical Psychiatry 2009;70(2):177-84.
Furukawa 2006
FurukawaTA, BarbuiC, CiprianiA, BrambillaP, WatanabeN.Imputing missing standard deviations in metaanalyses can provide accurate results. Journal of Clinical Epidemiology 2006;59(1):7-10.
Gastaldon 2020
GastaldonC, PapolaD, OstuzziG, BarbuiC.Esketamine for treatment resistant depression: a trick of smoke and mirrors?
Epidemiology and Psychiatric Sciences 2020;29:e79. [DOI: 10.1017/S2045796010751900]
Gastaldon 2021
GastaldonC, RaschiE, KaneJM, BarbuiC, SchoretsanitisG.Postmarketing safety concerns with esketamine: a dsproportionality
analysis of spontaneous reports submitted to the FDA adverse event reporting system. Psychotherapy and Psychosomatics
2021;90:41-8.
GBD 2017
Disease and Injury Incidence and Prevalence Collaborators.Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases
and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study
2017. Lancet 2017;392(10159):1789–858.
Guy 1976
GuyW.ECDEU Assessment Manual for Psychopharmacology. Rockville (MD): U.S. Department of Health and Human Services, 1976.
Hamilton 1960
HamiltonM.A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 1960;23:56-62.
HAS 2020
Haute Autorité de Santé (HAS).Spravato technical information.www.has-sante.fr/jcms/p_3192924/en/spravato (accessed
Higgins 2021
HigginsJPT, ThomasJ, ChandlerJ, CumpstonM, LiT, PageMJ, et al, editor(s).Cochrane Handbook for Systematic Reviews of
InterventionsVersion 6.2(updated February2021).Cochrane, 2021. www.training.cochrane.org/handbook.
Kennedy 2016
KennedySH, LamRW, McIntyreRS, TourjmanSV, BhatV, BlierP, et al.Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3pharmacological treatments. Canadian Journal of Psychiatry 2016;61(9):540-60.
Malhi 2016
MalhiGS, ByrowY.Is treatment-resistant depression a useful concept? Evidence-based Mental Health 2016;19(1):1-3.
Montgomery 1979
MontgomerySA, AsbergM.A new depression scale designed to be sensitive to change. British Journal of Psychiatry 1979;134:382-9.
NICE 2016
National Institute for Health and Care Excellence
(NICE).Depression in adults: recognition and management. Clinical guideline CG90. Updated 2016.
www.nice.org.uk/ guidance/cg90 (accessed October 2021).

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

NICE 2020
National Institute for Health and Clinical Excellence (NICE).Esketamine for treating treatment-resistant depression. www.nice.org.uk/guidance/gid-ta10371/documents/129
(accessed October 2021).

Ochs-Ross 2020
Ochs-RossR, DalyEJ, ZhangY, LaneR, LimP, MorrisonRL, et al.Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression – TRANSFORM-3. American Journal of Geriatric Psychiatry 2020;2:121-41.
Page 2021
PageMJ, McKenzieJE, BossuytPM, BoutronI, HoHmannTC, MulrowCD, et al.The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. [DOI: 10.1136/bmj.n71]
Papakostas 2020
PapakostasGI, JacksonWC, RafeyanR, TrivediMH.Inadequate response to antidepressant treatment in major depressive disorder. Journal of Clinical Psychiatry 2020;81(3):OT19037COM5.
Papakostas2020b
PapakostasGI, SalloumNC, HockRS, JhaMK, MurroughJW, MathewSJ, et al.EHicacy of esketamine augmentation in major depressive disorder: a meta-analysis. Journal of Clinical Psychiatry 2020;81(4):19r12889.
Popova 2019
PopovaV, DalyEJ, TrivediM, CooperK, LaneR, LimP, et al.EHicacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized doubleblind active-controlled study. American Journal of Psychiatry
2019;176(6):428-38.
Salanti 2016
SalantiG, ChaimaniA, FurukawaTA, HigginsJPT, OgawaY, CiprianiA, et al.Impact of placebo arms on outcomes in antidepressant trials: systematic review and metaregression analysis. International Journal of Epidemiology 2018;47(5):1454-64.
Singh 2016
SinghJB, FedgchinM, DalyE, XiL, MelmanC, De BrueckerG, et al.Intravenous esketamine in adulttreatment-resistant depression: a double-blind, double-randomization, placebocontrolled study. Biological Psychiatry 2016;80(6):424–31.
Trivedi 2006
TrivediMH, RushAJ, WisniewskiSR, NierenbergAA, WardenD, RitzL, et al.Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. American Journal of Psychiatry 2006;163(1):28-40.
Turner 2019
TurnerEH.Esketamine for treatment-resistant depression: seven concerns about eHicacy and FDA approval. Lancet Psychiatry 2019;6(12):977-9.
WHO 1992
World Health Organization (WHO).The ICD-10 Classification of Mental and Behavioural Disorders. Geneva: World Health Organization, 1992.
WHO 2013
WHO.Priority Medicines for Europe and the World 2013 Update. www.who.int/medicines/areas/priority_ medicines/Ch6_ 15Depression.pdf 2013.
Zarate 2006
ZarateC, SinghJB, CarlsonPJ, BrutscheNE, AmeliR, LuckenbaughDA, et al.A randomized trial of an N-methyl-Daspartate antagonist in treatment-resistant major depression. Archives of General Psychiatry 2006;63(8):856-64.
Zhu 2016
ZhuW, DingZ, ZhangY, ShiJ, HashimotoK, LuL.Risks associated with misuse of ketamine as a rapid-acting antidepressant. Neuroscience Bulletin 2016;32(6):557-64.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/gastaldon_et_al-2022-cochrane_database_of_systematic_reviews_protocol.pdf

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }