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General Information

Key Personnel (in addition to PI):
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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/anthony_rodgers_-_yoda_project_coi_form_for_data_requestors_2019.pdf
https://yoda.yale.edu/system/files/colleen_loo_-_yoda_project_coi_form_for_data_requestors_2019.pdf
https://yoda.yale.edu/system/files/stevan_nikolin_-_yoda_project_coi_form_for_data_requestors_2019.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

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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 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. NCT02133001 - ESKETINSUI2001 - A Double-blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Subjects Who Are Assessed to be at Imminent Risk for Suicide
6. NCT03039192 - 54135419SUI3001 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide
7. NCT03097133 - 54135419SUI3002 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide
8. 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

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

Research Proposal

Project Title

Ketamine for the treatment of major depression: a systematic review and meta-analysis

Narrative Summary:

Ketamine has been shown to rapidly alleviate depressive symptoms within hours or days of administration of a single therapeutic dose. However, while the effects are large, they are transient and tend to dissipate over the course of a week. More recent trials have investigated the utility of repeated treatments to increase response rates and response duration.
The aim of this systematic review and meta-analysis is to 1) evaluate and provide an update of the antidepressant efficacy, suicidality, safety, and tolerability of ketamine; and 2) to assess whether repeated administrations of ketamine as part of a therapeutic course of treatment improve these outcomes over single-dose treatments.

Scientific Abstract:

Background: Ketamine rapidly alleviates depressive symptoms within hours or days of administration of a single therapeutic dose. However, several knowledge gaps remain, including whether repeated treatments show benefits over single doses, whether dose titration improves and prolongs response, and which route of administration optimises efficacy whilst concurrently minimising the risk of adverse events.
Objective: To address the remaining gaps in knowledge through a comprehensive systematic review and meta-analysis of studies investigating the use of ketamine as an antidepressant.

Study Design: Systematic review and meta-analysis of studies utilising either a parallel or crossover study design, investigating the use of ketamine primarily as a treatment for depression compared with an appropriate placebo control.
Participants: Individuals with a clinical diagnosis of major depressive disorder.
Main Outcome Measures: Depression severity using standardised scales of depression (e.g. MADRS/HDRS), response and remission rates, changes in suicidality measured using standardised scales, all-cause dropout rates, and a qualitative review of adverse events reported in included studies.
Statistical Analysis: Random effects meta-analyses, performed using open source statistical software, will estimate the antidepressant efficacy and acceptability of ketamine relative to the control condition. Follow-up subgroup and sensitivity analyses will additionally investigate potential moderators of effects and will confirm robustness of results.

Brief Project Background and Statement of Project Significance:

Ketamine, an n-methyl-d-aspartate antagonist commonly used as an anaesthetic agent, has been shown to improve specific depressive symptoms such as sadness, suicidality, and helplessness, rather than induce a nonspecific mood-elevating effect. Early trials have demonstrated its usefulness in patients with treatment resistant depression, and in those with acute suicidal ideation, producing rapid alleviation of depressive symptoms within hours or days of administration of a single therapeutic dose. However, several gaps in knowledge remain. These include whether the use of individualised titration protocols to enhance efficacy and accommodate individual intolerances to ketamine improves outcomes relative to fixed-dose protocols, which route of administration optimises efficacy whilst concurrently minimising the risk of adverse events, and whether repeated administrations of ketamine have the potential to prolong and improve the durability of antidepressant effects relative to single-dose infusions.

This systematic review and meta-analysis seeks to address these remaining gaps in knowledge, and thereby facilitate the translation of ketamine into the clinic as a potent novel treatment for depression.

Specific Aims of the Project:

The aims of this systematic review and meta-analysis are to provide an update of ketamine antidepressant efficacy, suicidality, and acceptability, whilst addressing several outstanding questions within the field, including whether personalised titration approaches have improved efficacy, whether repeated administrations of ketamine as part of a therapeutic course of treatment improve outcomes over single-dose administrations, and lastly whether there are efficacy differences between routes of administration.

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

Our systematic review was conducted by searching bibliographic databases Embase, Medline Pubmed, and PSYCinfo. Database search terms included “controlled trial” AND “ketamine” AND “depression”, in addition to several permutations and variations of these terms. Studies were included in the systematic review if: (1) they reported efficacy results in a sample of participants with a clinical diagnosis of major depressive disorder; (2) they reported the use of ketamine primarily for the treatment of a depressive episode. Identified trials could deliver ketamine as a single dose, or repeatedly as part of a treatment course; and (3) they used a control condition, either saline or an active control such as midazolam, to which participants were randomly assigned.

Main Outcome Measure and how it will be categorized/defined for your study:

The primary outcome measure will be depression severity, obtained using a standardised and validated observer-rated scale of depression, such as the Hamilton Depression Rating (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS).
Secondary outcomes will include:

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response rates, operationalised as a reduction in symptoms of depression by >=50% from baseline;
remission according to thresholds as defined by the previously mentioned observer-rated scales of depression;
all-cause dropout rates; and
where available, suicidality scores using a standardised scale (e.g. Beck scale for suicide ideation)

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

We will examine the time-course of antidepressant efficacy of ketamine from the time of the initial treatment. Additionally, to compare the longevity of response between repeated- and single-administration protocols, we will compare effects from the time of the final treatment.

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

Subgroup analyses will additionally investigate the effect of dose titration (i.e. adjusting individualised dosage to optimise treatment outcomes), the route of ketamine administration (e.g. intranasal, subcutaneous, intravenous, or intramuscular) using dose conversion to allow comparison between different routes, differences in onset and durability of ketamine effects between repeated- and single-administrations, differences between the two enantiomers of ketamine (racemic ‘arketamine’ or r-ketamine, and s-ketamine or ‘esketamine’), differences in trials using a saline placebo control with those that used active medication (e.g. midazolam), and lastly whether the participant cohort consisted of participants with treatment resistant depression (operationalised as failure of ? 2 adequate treatment trials).

Statistical Analysis Plan:

All statistical analyses will be performed using open source R statistical software version 4.0.2 (R Core Team, 2020), using the metafor package. Aggregate effects will be estimated using random-effects models with significance set at $p < 0.05$. We will calculate standardised mean differences for continuous outcomes (e.g. depression severity and suicidality scores), and odds ratios for categorical outcomes (e.g. response, remission, and all-cause dropout rates), for participants randomised to receive ketamine relative to those receiving a placebo control.
Publication bias and small study effects will be assessed using the Egger test (Egger et al., 1997), and visual inspection of contoured funnel plots (Sterne & Egger, 2001). In the event of a statistically significant Egger statistic, we will use the Trim & Fill procedure to minimise potential publication bias and provide a revised estimate of effect sizes (Duval & Tweedie, 2000).
Heterogeneity will be reported using the I^2 and Tau^2 statistics. An I^2 value greater than 50% was considered as indicative of substantial heterogeneity.
Software Used:
RStudio
Project Timeline:

The systematic review has been completed, as has data extraction from the included studies.
Preliminary analyses have been conducted and a manuscript draft has been generated.
Several corresponding authors have communicated their willingness to contribute additional aggregate data missing from the respective study manuscripts to the meta-analysis. These are currently being awaited. Manuscript submission is therefore expected to occur soon after this remaining data has been acquired, within 3 months, i.e. estimated submission date of July-August 2021.

Dissemination Plan:

The meta-analysis will be submitted to a reputable and leading medical journal in the field for peer-review and publication.

Target journals include: JAMA Psychiatry and Lancet Psychiatry.

Bibliography:

Our registered meta-analysis protocol can be found at PROSPERO 2021 CRD42021221157
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021221157