Principal Investigator

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General Information

Key Personnel (other than PI):
First Name: Martin
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SCOPUS ID:
Requires Data Access? Yes

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/wp-content/uploads/2024/07/yoda-coi-ploederl.pdf
https://yoda.yale.edu/wp-content/uploads/2024/07/yoda-coi-moncrieff.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. 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
3. 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
4. NCT01627782 - KETIVTRD2002 - A Double-blind, Randomized, Placebo-controlled, Parallel Group, Dose Frequency Study of Ketamine in Subjects With Treatment-resistant Depression
5. NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-

Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression
6. 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)
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. 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
9. 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
10. 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
11. 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

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Effects of ketamine and esketamine on death, suicidal behavior and suicidal ideation in psychiatric disorders: A systematic review and meta-analysis

Narrative Summary:

Ketamine and esketamine have been considered as innovative and powerful means to reduce depression and suicide risk in many studies. An updated review of the literature is lacking, however. In this research project we want to study the suicide preventive effect of ketamine and esketamine. Therefore, we systemtically search and review the results of randomized controlled clinical trials where ketamine or esketamine were compared to placebo or another control condition. We will analyze if patients who are treated with ketamine/esketamine have lower levels of suicide ideation, suicide attempts, suicides, and all-cause mortality compared to patients in the control group.

Scientific Abstract:

Background: Esketamine and ketamine are considered to have rapid and clinically meaningful effects on depression and suicidality and are considered as novel strategies to mitigate suicide risk. Whereas some systematic reviews have been done already, several important new studies were published in the meantime, requiring an updated review. Moreover, reviews often lack a closer look at the timing of the effects and also on important moderators of the effects (dosing, application, drug-type, self-report vs. clinician assessment).
Objective: to provide and updated systematic review of the effects of esketamine and ketamine on

suicidality and moderators of these effects.
Study design: Systematic review and meta-analysis of randomized clinical trials.
Participants: Patients from randomized clinical esketamine/ketamine trials with any psychiatric disorders.
Primary and secondary outcome measures: primary outcome is suicidal behavior (suicides and suicide attempts) and all cause mortality. Secondary outcome will be suicide ideation based on clinician ratings or patient self-reports.
Statistical Analysis: random effects meta-analyses and subgroup analysis.

Brief Project Background and Statement of Project Significance:

Esketamine and ketamine are considered to have rapid and clinically meaningful effects on depression and also suicidality and are considered as novel strategies to mitigate suicide risk [1]. Whereas some systematic reviews have been done already [2,3], several important new studies were published in the meantime, requiring an updated review is lacking. Moreover, reviews often lack a closer look at the timing of the effects, which is important as the efficacy varies with time, at least for single administration of ketamine/esketamine. Moreover, there is a lack of meta-analytic research on potential moderators, such as dosing (single vs. repeated), application (intravenous vs. intranasal), drug-type (esketamine vs. ketamine) etc. Finally, we are not aware of a systematic review which also investigated at suicidal behavior. Thus, a updated systematic review is necessary that also accounts for the characteristics for the interventions and also to provide evidence if esketamine and ketamine have an impact on suicidal ideation/behavior and mortality.

Specific Aims of the Project:

The aim is to provide an updated systematic review an meta-analysis of the suicide-preventive efficacy (suicide ideation, suicidal behavior, all-cause-mortality) of ketamine and esketamine based on randomized controlled clinical trials. The analysis will account for temporal effects (immediate, short-term, longer-term effects) and also will explore potential moderators of efficacy, such as dosing (single vs. repeated), application (intravenous vs. intranasal), drug-type (esketamine vs. ketamine) etc.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Preliminary research to be used as part of a grant proposal

Summary-level data meta-analysis

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

Research on clinical trial methods

Research Methods

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

Inclusion criteria
- RCTs (either double-blind, single-blind) comparing the effect of ketamine or esketamine with placebo or active placebo for the treatment of any primary psychiatric disorder

- Cross over trial data from the period prior to the cross-over will be included (data from the second period is excluded to protect against the carry -over effect)
- Trials comparing ketamine or esketamine in combination with an antidepressant, psychotherapy or other intervention will be included as long as other interventions are equally available to those in

Exclusion criteria
Trials where Ketamine was used as an analgesic agent eg. within an ECT or surgical protocol.

Pooling with other studies
We will not pool IPD but instead use aggregated data (means, standard deviations, percentages etc) from the YODA data and from other studies. Thus, we will only use the YODA platform to get the aggregated results for suicide ideation and suicidal behavior for the Esketamine trials. We then use these aggregated data in meta-analysis, together with aggregated non-YODA data

We will base our meta-analysis on summary results (effect size) of each study and not on individual participant data.

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

Primary Outcome: suicide attempts, suicides, all-cause-mortality
Secondary Outcome: suicide ideation (based on self-reports and clinician interviews).

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

Main Predictor: treatment (esketamine/ketamine vs. placebo or active control).

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

Moderators: time (rapid/short-longer), mode of application (intravenous/nasal etc), drug-type (esketamine/ketamine), dosing (single vs. multiple dosing), primary diagnosis, suicidality as inclusion/exclusion criterion, active vs. non-active placebo, assessment (clinician vs. self-report)

Statistical Analysis Plan:

Random effects meta-analysis, with subgroup analysis to investigate the moderators.

Software Used:

R

Project Timeline:

Data extraction and analysis: End of 2024. Manuscript draft: Spring 2025

Dissemination Plan:

Publication in psychiatric/medical journal and perhaps also in suicide prevention conferences.

Bibliography:

McIntyre RS, Rosenblat JD, Nemeroff CB, *et al.* Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *Am J Psychiatry*. 2021;appiajp202020081251. doi: 10.1176/appi.ajp.2020.20081251

Witt K, Potts J, Hubers A, *et al.* Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry*. 2020;54:29–45. doi: 10.1177/0004867419883341

Dean RL, Hurducas C, Hawton K, *et al.* Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. *Cochrane Database Syst Rev*. 2021;2021. doi: 10.1002/14651858.CD011612.pub3