Principal Investigator

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General Information

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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/01/YODA-COI.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. 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
2. 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
3. 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
4. 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
5. NCT02497287 - ESKETINTRD3004 - An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression
6. NCT02493868 - ESKETINTRD3003 - A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression
7. 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

8. NCT01627782 - KETIVTRD2002 - A Double-blind, Randomized, Placebo-controlled, Parallel Group, Dose Frequency Study of Ketamine in Subjects With Treatment-resistant Depression
9. NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression
10. 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
11. 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)
12. 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
13. 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

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

Research Proposal

Project Title

Differential Effects of Esketamine on Individual Symptoms of Major Depression

Narrative Summary:

Esketamine is a dissociative hallucinogen frequently used to rapidly treat major depression. The drug has a unique mechanism of action relative to other antidepressants and thus may possess unique effects on the individual symptoms of major depression. For example, esketamine may be particularly effective in rapidly reducing suicidal behaviors and ideation but have equivocal effects on other symptoms such as anhedonia (lack of interest in activities). We propose to compare the effects of esketamine monotherapy and augmentation on the individual symptoms of major depression, rather than on conglomerate scores such as total depression severity or remission status used in past studies.

Scientific Abstract:

Background: Esketamine is a dissociative hallucinogen commonly used to treat major depression. The drug has a unique mechanism of action and thus may affect the individual symptoms of major depression differently than other existing antidepressants.

Objective: We will investigate the unique effects of esketamine on individual symptoms of major depression using the Supervised Varimax algorithm [1, 2]. Supervised Varimax combines the individual items of a clinical rating scale into a few optimal outcome measures that maximally differentiate between treatments.

Study Design: We will combine multiple clinical trials investigating esketamine monotherapy and augmentation in the treatment of major depression.

Participants: We will include all participants from Phase 2 and Phase 3 clinical trials of either esketamine monotherapy or esketamine augmentation in major depression or treatment-resistant major depression.

Primary and Secondary Outcome Measure(s): The primary outcome measure includes all of the individual items of the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcome measures include the individual items of the Sheehan Disability Scale, the Cognitive Test Battery, the Hopkins Verbal Learning Test, and the Suicide Ideation and Behavior Assessment.

Statistical Analysis: We will run Supervised Varimax with post-model selection permutation testing at the omnibus, factor and treatment-pair levels. We will control for multiple comparisons using the family-wise error rate when investigating treatment pair differences.

Brief Project Background and Statement of Project Significance:

Brief Project Background: Esketamine is an NMDA receptor antagonist and dissociative hallucinogen commonly used to rapidly treat major depression. The drug has shown efficacy in mildly reducing the symptoms of major depression in one of three short-term 4 week efficacy trials. However, the change in the total score of the MADRS only differed by 4 points in the trial [3]. Esketamine has also been shown to be mildly effective in treating major depression with co-occuring suicidal ideation and behaviors at 24 hours, although the drug was not shown to be effective in reducing suicidality [4].

Statement of Project Significance: Esketamine has only shown marginal benefit in reducing the total MADRS score, but it may be effective at reducing specific constellations of depression symptoms both in the short and long term. If we find specific symptom constellations targeted by esketamine, then this would enable precision psychiatry because clinicians could identify patient subpopulations that benefit more from esketamine than other antidepressants.

Specific Aims of the Project:

Aim 1: Determine the unique effects of esketamine monotherapy and augmentation on individual symptoms of major depression using the Supervised Varimax algorithm.

Rationale: Esketamine has a unique mechanism of action compared to other antidepressants, such as serotonin-reuptake inhibitors. As a result, esketamine may affect the symptoms of major depression differently than other antidepressants.

Hypothesis: Esketamine is a dissociative hallucinogen and therefore will rapidly reduce emotional-cognitive symptoms of major depression but not the neurovegetative symptoms involving sleep, appetite, energy and psychomotor function.

Aim 2: Identify the effects of esketamine on functional outcomes, cognition and suicidal ideation also using the Supervised Varimax algorithm.

Rationale: Esketamine is an NMDA receptor antagonist that may have other beneficial effects on states or behaviors not directly related to major depression. We will therefore investigate the effects of esketamine on functional outcomes, cognition and suicidal ideation in secondary analyses.

Hypothesis: Esketamine will improve functional outcomes and cognition with long (>4 weeks) but not short-term treatment. Esketamine will have no detectable effect on suicidal ideation or behaviors.

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Develop or refine statistical methods

Research Methods

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

Inclusion criteria: We will include all participants from the requested YODA trials. We will not include any additional patients.

Exclusion criteria: None

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

Primary: The Supervised Varimax algorithm takes the individual items of a clinical rating scale as input. All requested datasets use the Montgomery-Asberg Depression Rating Scale (MADRS) scale to measure depression severity. We will therefore use the individual items of the MADRS rating scale as the primary outcome measures.

Secondary:
(1) Functional outcomes as assessed by the individual items of the Sheehan Disability Scale.
(2) Cognition as assessed by the individual items of the Cognitive Test Battery, and the Hopkins Verbal Learning Test.
(3) Suicidality as assessed by the individual items of the Suicide Ideation and Behavior Assessment.

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

Independent variables: Treatment assignment to esketamine monotherapy, placebo monotherapy, esketamine augmentation, and placebo augmentation.

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

Nuisance variables: Age and sex as a biological variable. Both will be partialed out before downstream analyses.

Statistical Analysis Plan:

We will perform permutation testing with the Supervised Varimax algorithm. Supervised Varimax outputs a small number of factors that maximally differentiate between treatments. The permutation testing is therefore performed at three levels: omnibus, by factor and by treatment pairs [1,2]. Omnibus testing determines if there is any differential treatment effect between any pair of treatments in any factor. Post hoc by factor testing determines the factor(s) harboring any differential treatment effect. Post hoc treatment pair testing identifies specific pairs of treatments with differential effects. All permutation testing will involve selective inference, in order to account for the selection of the number of factors, and multiple comparisons by the family-wise error rate, in order to account for multiple treatment pairs. Each test will involve at least 10,000 permutations.

Software Used:

R

Project Timeline:

Start date: February 2025
Analysis completion date: August 2025
Date manuscript drafted: September 2025
First submitted for publication: November 2025
Results reported back: December 2025

Dissemination Plan:

Anticipated products: all R code necessary to replicate results will be provided in a publicly accessible Github repository.

Target audience: Clinicians and researchers in psychiatry

Expectation for study manuscript and journals: We will submit the manuscript to major psychiatry journals, such as The Journal of Affective Disorders, Psychotherapy and Psychosomatics, and Psychological Medicine

Bibliography:

[1] Strobl EV, Kim S. Learning Outcomes that Maximally Differentiate Psychiatric Treatments. medRxiv. 2024 Dec 5:2024-12.

[2] Strobl EV. Consistent Differential Effects of Bupropion and Mirtazapine in Major Depression. medRxiv. 2024:2024-12.

[3] Horowitz MA, Moncrieff J. Are we repeating mistakes of the past? A review of the evidence for esketamine. The British Journal of Psychiatry. 2021 Nov;219(5):614-7.

[4] Canuso CM, Ionescu DF, Li X, Qiu X, Lane R, Turkoz I, Nash AI, Lopena TJ, Fu DJ. Esketamine nasal spray for the rapid reduction of depressive symptoms in major depressive disorder with acute suicidal ideation or behavior. Journal of clinical psychopharmacology. 2021 Sep 1;41(5):516-24.