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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/wp-content/uploads/2026/01/COI_OL.pdf
https://yoda.yale.edu/wp-content/uploads/2026/01/COI_MC.pdf
https://yoda.yale.edu/wp-content/uploads/2026/01/COI_ACR.pdf
https://yoda.yale.edu/wp-content/uploads/2026/01/COI_JR.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. NCT02497287 - ESKETINTRD3004 - An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression
2. NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression
3. 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)
4. 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
5. 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
6. 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
7. 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
8. NCT02493868 - ESKETINTRD3003 - A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression
9. 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
10. 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
11. 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
12. 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
13. NCT04338321 - 54135419TRD3013 - A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended Release, Both in Combination With a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment Resistant Major Depressive Disorder (ESCAPE-TRD)
14. NCT04599855 - 54135419TRD4005 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Esketamine Nasal Spray, Administered as Monotherapy, in Adult Participants 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

Depression, functioning, and quality of life as a multi-domain clinical trial outcome for major depressive disorde

Narrative Summary:

Response to esketamine clinical trials is traditionally measured based on whether or not the drug reduces symptoms of depression. However, people living with depression have also identified improvements in quality of life and everyday functioning as meaningful outcomes, which are often not adequately captured in traditional measures of depression symptoms. In fact, depression symptoms, quality of life, and functioning sometimes change at different rates. This study will aggregate data across multiple trials of esketamine for depression to evaluate whether people are differentially characterized as treatment responders depending on whether response is defined as improvements in symptoms, functioning, or quality of life. This study will also identify whether there are subgroups of people with different response patterns across domains.

Scientific Abstract:

Background: Most clinical trials of depression interventions use reduction in depressive symptoms as the primary metric of treatment efficacy. However, daily functioning and quality of are treatment priorities for those living with depression, which can follow divergent response trajectories. Therefore, a multi-domain metric to characterize treatment outcomes may be more informative compared to current primary emphasis on symptom changes.
Objectives: The objectives of this study are to (1) identify the number of participants who response to esketamine as defined by clinically meaningful improvements in depression symptoms, functioning, and quality of life, (2) identify concordance and discordance of symptom response when defined across these three different domains, (3) identify subgroups of participants with different trajectories of change across these three domains, and (4) identify whether there are difference between these clusters on cognition.
Design: We will aggregate data across multiple clinical trials of esketamine for the treatment of depression.
Participants: Adults with major depressive disorder who participated in esketamine clinical trials.
Outcome Measures: The primary outcome measures include the clinician-administered Montgomery-Asberg Depression Rating Scale (MADRS), Sheehan Disability Scale, and the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L). CogState/HVLT-R and Patient Health Questionnaire-9 will be used as secondary outcome measures.
Statistical Analyses: Joint longitudinal clustering will be used to identify subgroups.

Brief Project Background and Statement of Project Significance:

Most depression clinical trials evaluating treatment efficacy focus on reduction of symptoms as the primary outcome to determine whether or not a treatment is beneficial. However, individuals living with depression have identified other outcomes, such as improvement in daily functioning and quality of life, as treatment priorities (Baune & Christensen, 2019). Despite these domains being identified as meaningful outcomes for individuals with lived experience of depression, they often follow divergent response trajectories and are often only considered as secondary outcomes in treatment efficacy trials. Failing to consider all three of these important metrics when evaluating treatment efficacy can result in under-detection of meaningful improvements, or over-emphasis on symptom improvements that do not translate to real-world meaningful improvements in daily life (Rabin et al., 2022).
In response to this, recent frameworks have proposed considering a tripartite, or conjoint, outcome measure for evaluating depression treatments that brings together measures of symptomatic change, functional recovery, and improvements in quality of life. When applying a tripartite metric to characterize treatment response following vagus nerve stimulation for depression, it was found that this tripartite metric more strongly correlated with clinician global improvement ratings compared to

any of the three domains independently (Conway et al., 2025). As well, operationalizing response as solely reduction in depression symptoms did not capture 25-51% of participants who had a clinically meaningful improvement in symptoms of depression, quality of life, or functioning.
Despite initial evidence suggesting utility of the tripartite metric for capturing more holistic patient-centred treatment outcomes, this framework has yet to be applied to other interventions. This framework may be particularly useful for applying to clinical trials of esketamine in order to identify how changes in quality of life and functioning may change in concordant or discordant patterns to symptomatic changes. This has the potential to inform treatment selection, appropriately match patients with interventions that meet their treatment goals, and manage treatment expectations. Therefore, this study aims to identify the proportion of participants in esketamine clinical trials who had a clinically meaningful improvement in one, two, or all three domains (functioning, quality of life, depression symptoms). We then aim to characterize treatment response trajectories as defined according to all three metrics, in which response trajectories are estimated simultaneously across all domains. Finally, given the close association between functioning, quality of life, and cognitive performance, we will evaluate whether tripartite response trajectories differ based on cognitive functioning.

Specific Aims of the Project:

The specific aims of this project are to examine the following exploratory objectives:
(1) To identify the number of participants who meet the criteria for a minimum clinically important difference in depression symptoms, quality of life, and functioning
(2) To identify overlap in response between depression, quality of life, and functioning
(3) To identify different response clusters along these 3 features
(4) Whether cognitive functioning, sex/gender, and age predict group membership

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

Research on clinical prediction or risk prediction

Research Methods

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

Unique adult participants with data at baseline and at least one other timepoint will be included in the analyses. Trials in which timepoints are not conducive to pooling will be excluded from the pooled analysis (e.g., large variability in timing of assessments).

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

Participants will be clustered into groups based on response trajectories to the three primary outcome variables of: depression, quality of life, and functioning.

Depression symptoms will be measured using the MADRS total score. Overall quality of life will be

measured using the EQ-5D-5L, while each of the EQ-5D-5L subscales may be individually explored in secondary follow-up analyses. To measure functioning, the SDS total score will be used where possible. If a total score cannot be calculated, individual subscale scores (e.g., family, social, work functioning) may be used in follow-up analyses.

Therefore, in the clustering analyses, depression, functioning, and quality of life will be used as the dependent variables. Heterogeneity in the associations between time and each of the three dependent variables will be explored using clustering analysis (described below) to parse possible subgroups in the data that share trajectory patterns.

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

We aim to create clusters of different treatment response trajectories, defining response in different ways - depression, quality of life, and functioning across various timepoints. Given that the purpose of the primary analysis is to measure trajectories of change over time, all timepoints within the requested trials that can (1) be clustered across trials, and (2) have available data for the respective domains of interest will be used in the analyses. The independent variable in this analysis is time.

Secondary analyses will include cognition as a predictor/covariate (e.g., how do treatment clusters differ in cognition). To measure cognitive functioning for secondary analyses, standardized cognitive tests, such as CogState, RAVLT and CVLT will be used.

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

Sex/gender and age (where applicable) will be used as a covariate. Other baseline demographic variables will be used to characterize the sample. Treatment group assignment may be used to characterize whether there are differences in trajectories depending on group assignment.

Statistical Analysis Plan:

Number of participants with a minimum clinically important difference (MCID) will be calculated on each outcome. Then, the number of participants with improvements in one, two, and all three of these domains will be described. The MCID for the MADRS has been found to be a difference of 2 points (Hengartner & Ploderl et al., 2022), for the SDS in depression/anxiety 4 points (Abdin et al., 2025), and for the EQ-5D-5L, estimates range from 0.01 to 0.41 (Cheng et al., 2024).

Participants will be clustered based on their longitudinal data on the three main variables mentioned above (depression, QOL, functioning) and determine whether there are significant differences in cognition, sex/gender, and age between these clusters. Regression analyses will be conducted prior to clustering to describe trajectories on each outcome, accounting for individual trials.

Clustering methods will be used to subgroup participants based on similar trajectories on three different features: depression (MADRS), quality of life (EQ-5D-5L), and functioning (SDS) in R Statistical Software. Specifically, we will implement latent class mixed models (via the lcmm R package; Proust-Lima, Philipps, & Piquet, 2015), which allows for missing and unbalanced data (Lu et al., 2023). Unique to joint clustering of multiple longitudinal features is that it allows for the identification of co-occurring trajectories across multiple features of interest - depression, quality of life, and functioning (Lu et al., 2023). This results in participants being assigned to a cluster that is characterized by their trajectory across all 3 domains simultaneously (as well as illustrating each cluster's trajectory across each domain). Models will be estimated with a successive number of clusters, from 1 to 5, as done in previous papers implementing this method. If solutions are not interpretable or lack convergence, a higher number of clusters will be tested. Clusters will be compared and retained based on model fit, parsimony, and interpretability. Model fit criteria will include Bayesian Information criteria (BIC) and entropy, where BIC considers model fit and parsimony, and penalizes model complexity, and a lower BIC value indicates better model fit (Schwarz et al, 1978). Entropy indicates how distinct the different clusters are from one another,

with a value closer to 1.0 suggesting a clearer delineation of clusters - a threshold of 0.8 has been suggested as delineating between separate clusters (Nylund-Gibson et al., 2019).

Class Differences
Analysis of variance (ANOVA) will be used to examine subgroup differences across the different clusters that are identified in regards to cognitive functioning, sex/gender, and age. Post-hoc group differences will be tested. Exploratory analyses may be conducted to predict group membership based on demographic characteristics (multinomial logistic regression).
Exploratory analyses looking at subscales of each measure may be tested.

Software Used:

R, RStudio

Project Timeline:

Anticipated Project Start Date: April 2026
Estimated Analysis Completion Date: August 2026
Manuscript Draft Date: November 2026
Estimated Journal Submission: December 2026
Date Results Reported Back to YODA: April 2027

Dissemination Plan:

The target audience includes scientists and clinicians. Scientists may use the results of this research to inform research on treatment trajectories, develop enhanced treatment protocols, and optimize interventions. Clinicians may use findings from this research to guide clinical decision making, treatment selection and planning, and match treatments with patient goals and characteristics. Results will be disseminated in peer-reviewed journals with a clinical psychiatry interest (e.g., American Journal of Psychiatry, JAMA Psychiatry, Neuropsychopharmacology) and presented at relevant conferences (e.g., American College of Neuropsychopharmacology, American Society of Clinical Psychopharmacology, Biological Psychiatry).

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