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SCOPUS ID:
Requires Data Access? Yes

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Young leaders overseas program
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/12/COI-1.pdf
https://yoda.yale.edu/wp-content/uploads/2025/12/COI-FORM-KR.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. 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
2. 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)
3. 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
4. NCT02497287 - ESKETINTRD3004 - An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression

5. NCT02493868 - ESKETINTRD3003 - A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in 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. 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. 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
11. 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
12. 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
13. 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
14. 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
15. 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

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

Research Proposal

Project Title

Personalized Ketamine Dosing: A Population PK/Pharmacogenomic Model Using Participant-Level Esketamine Trial Data

Narrative Summary:

Major depressive disorder and treatment-resistant depression remain leading causes of disability. Ketamine and esketamine offer rapid antidepressant effects but show wide variability in clinical response and acute adverse events, largely driven by pharmacokinetic and pharmacogenomic differences. This project will use participant-level data from esketamine clinical trials to build a predictive model linking dose, CYP2B6/CYP3A4 activity, patient characteristics, and exposure--response outcomes. The goal is to develop a transparent, evidence-based framework for

individualized ketamine dosing that enhances safety and effectiveness. This work may ultimately inform precision-medicine approaches and improve outcomes for patients receiving ketamine-based treatments.

Scientific Abstract:

Background: Esketamine is an FDA-approved treatment for TRD, yet patients exhibit substantial heterogeneity in exposure, dissociation, BP elevations, and antidepressant response. Pharmacokinetic variation--including contributions from CYP2B6, CYP3A4, and patient covariates--plays a major role.
Objective: To evaluate exposure--response relationships and develop a personalized ketamine/esketamine dosing model based on participant-level data.
Study Design: Retrospective individual-participant analysis of esketamine clinical trials requested from the YODA Project.
Participants: Adult subjects enrolled in the selected esketamine randomized or open-label trials.
Primary Outcome Measures: (1) Exposure metrics (Cmax, AUC) generated from population PK modeling; (2) antidepressant response at 24h and 7 days; (3) acute safety outcomes (BP, dissociation, adverse events).
Secondary Outcome Measures: Associations between CYP2B6/CYP3A4 genotypes, covariates, and PK parameters.
Statistical Analysis: Develop a population PK model incorporating demographic, clinical, and genotypic covariates. Fit multivariable models (logistic, linear, or hierarchical) to relate exposure to efficacy/safety outcomes. Validate using cross-validation within the secure YODA computing environment.

Brief Project Background and Statement of Project Significance:

Ketamine and esketamine represent major advances for treatment-resistant depression, yet clinical outcomes vary markedly across individuals. Key drivers of variability include differences in hepatic metabolism--particularly via CYP2B6 and CYP3A4--body weight, age, sex, co-medications, and comorbidities. Understanding how these factors alter ketamine exposure and downstream pharmacodynamic effects is essential for designing safer and more effective dosing strategies.
While several population pharmacokinetic (PopPK) models have been published for esketamine, these models were developed either in healthy volunteers or within limited clinical contexts. Few studies integrate patient-level PK/PD outcomes, genetic variation, and safety signals simultaneously. As ketamine and esketamine usage expands clinically, clinicians lack a validated framework to tailor dosing to individual risk and expected benefit.
The proposed study directly addresses this gap. Using participant-level data from esketamine trials made available through the YODA Project, we will (1) quantify covariate effects on exposure, (2) map exposure to antidepressant response, and (3) characterize the risk of dissociation and BP elevations. This information will be used to construct a precision-dosing model to improve individualized ketamine/esketamine treatment strategies. Findings will materially advance scientific understanding of ketamine pharmacology and support safer real-world implementation.

Specific Aims of the Project:

Aim 1: Develop a population PK model for esketamine using participant-level data, estimating typical clearance, volume, and covariate effects (CYP2B6, CYP3A4, weight, age, sex, co-medications).
Aim 2: Quantify exposure--response relationships by relating predicted exposure metrics (Cmax, AUC) to antidepressant response at 24h and 7 days.
Aim 3: Quantify exposure--safety relationships linking exposure to dissociation, BP changes, and adverse events.
Aim 4: Integrate PK, pharmacogenomic, and clinical covariates into an individualized dosing framework to estimate safe and effective dose ranges.

Hypotheses:

1.CYP2B6/CYP3A4 activity significantly alters esketamine exposure.
2.Higher exposure is associated with increased dissociation but also greater likelihood of antidepressant response. (Hypertension)
3.A combined PK-PGx model can meaningfully stratify patients by predicted benefit and risk.

Study Design:

Individual trial analysis

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

Develop or refine statistical methods

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:

Data Source: Participant-level data from selected esketamine trials requested via the YODA Project.
Inclusion Criteria:
All adult participants enrolled in the selected YODA-provided esketamine clinical trials.
Participants with available dosing, clinical outcomes, and covariate data.
Exclusion Criteria:
Participants missing key PK-relevant variables (e.g., dose or outcome).
Participants withdrawn prior to receiving any esketamine dose.
No external datasets will be uploaded unless allowed under the YODA Data Use Agreement and accompanied by documented rights to use that data.

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

Primary Outcomes:
1.Exposure metrics: model-predicted Cmax and AUC for esketamine.
2.Antidepressant response: change in MADRS or similar scale at 24 hours.
3.Acute safety reactions: dissociation scores, maximum systolic/diastolic BP, adverse events.
Secondary Outcomes:
Response at 7 days.
Exposure--covariate interactions.
PK parameter variability attributable to CYP2B6/CYP3A4 genotype, weight, and co-medications.

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

Esketamine dose (mg and mg/kg)
CYP2B6 genotype/activity score
CYP3A4 genotype/activity score
PopPK-derived exposure metrics (Cmax, AUC)
Definitions will align with trial variable formats in the YODA dataset.

Other Variables of Interest that will be used in your analysis and how they will be

categorized/defined for your study:

Age, sex, weight, BMI
Baseline depression severity
Co-medications (SSRIs/SNRIs, benzodiazepines, CYP inducers/inhibitors)
Comorbidities (hypertension, anxiety disorders)
Ethnicity
Prior treatment history
Baseline vital signs
All variables will be coded using standardized categories.

Statistical Analysis Plan:

Descriptive statistics will summarize baseline characteristics.
PopPK modeling will use nonlinear mixed-effects methods (FOCEI, SAEM, or equivalent). Models will assess covariate effects using forward-addition/backward-elimination guided by AIC/BIC and clinical plausibility.
Exposure--response analyses will use:
Linear or logistic regression (ΔMADRS at 24h/7d).
Mixed-effects models accounting for repeated measurements when applicable.
Nonlinear Emax models for exposure--dissociation relationships.
Interaction terms for genotype x dose and genotype x exposure.
Exposure--safety analyses will use logistic regression for acute risks (e.g., BP > threshold, dissociation above prespecified scale cutoffs). Model performance will be assessed using AUROC, calibration curves, and sensitivity analyses. All modeling will be conducted within the YODA secure environment using R.

Software Used:

Python, R, RStudio

Project Timeline:

Project Start: Within 4 weeks of data access approval
Data Exploration & Cleaning: Months 1--2
PK Modeling: Months 2--4
Exposure--Response Modeling: Months 4--6
Manuscript Drafting: Months 7--9
Submission to Journal: Month 10
Reporting Results to YODA Project: Month 11--12
All work completed within the 12-month data access window (extensions if needed).

Dissemination Plan:

Findings will be disseminated via a peer-reviewed manuscript and presented at relevant psychiatry, pharmacology, and clinical pharmacometrics conferences. Target journals include: American Journal of Psychiatry, Clinical Pharmacology & Therapeutics, and Journal of Clinical Psychopharmacology. Results will also be shared with the YODA Project according to the Data Use Agreement and made available to the research community to support safe, evidence-based esketamine use.

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