Research proposal—Team 3

Project title

Negative Effect and Clinical Trajectories of Esketamine in Major Depression: an Individual Participant Data Meta-Analysis

Narrative Summary:

Major depression is a leading cause of disability worldwide. Many people do not get better with standard antidepressants, and this is known as treatment-resistant depression (TRD). Esketamine is a newly approved nasal spray for TRD, but we still do not fully understand patients' day-to-day response to the drug over time. Studies investigating the drug efficacy also rarely study the negative impact on depression from the drug. This study will combine raw data from multiple previous clinical trials to explore the response to esketamine over time and its negative impact. By understanding these specific paths—such as when esketamine starts to take effect, how long the effect lasts, and whether esketamine can introduce temporary negative impact—doctors can better tailor treatments, set realistic expectations, and improve care for those suffering from severe depression.

Scientific Abstract:

Background: Esketamine nasal spray is a rapid acting antidepressant and efficacious to treat adult treatment-resistant depression (TRD) patients. Current evidence mainly relied on treatment response at one time point without investigating the dynamic trajectories occurring throughout the treatment course. Meanwhile, some patients may experience divergent outcomes despite the overall beneficial treatment effect.

Objective: To explore the negative effect and clinical trajectories responded to esketamine in adults with TRD.

Study Design: An individual participant data meta-analysis (IPD-MA) of randomized controlled trials (RCT).

Participants: Adults (≥18 years) with a confirmed diagnosis of TRD, randomized to receive intranasal esketamine or placebo, both combined with a newly initiated oral antidepressant. Trials targeting imminent suicidal ideation or utilizing intravenous administration are excluded.

Primary and Secondary Outcome Measure(s): The primary outcome is time-varying clinical response based on the percentage change in Montgomery–Åsberg Depression Rating Scale (MADRS) score from baseline, categorized ordinally into response (≥50% decrease), partial response (25% to 50% decrease), non-response (0% to <25% decrease), and deterioration (≥0% increase). There is no secondary outcome.

Statistical Analysis: A one-stage IPD-MA will be conducted using a mixed-effects ordinal logistic regression with random intercepts for participants nested in studies. A treatment-time spline interaction will be modeled. The model will be adjusted for baseline MADRS, geographic region, and concurrent oral antidepressant class/oral antidepressant monotherapy. Proportional

odds assumption will be assessed graphically. A sensitivity analysis will be performed using a continuous-time semi-Markov multistate model if the data is sufficient. Analyses will be conducted in R.

Brief Project background and Statement of Project Significance:

Major depressive disorder (MDD) affects over 332 million individuals globally (World Health Organization, 2025) and is a leading cause of disability worldwide. (GBD 2019) A substantial subgroup of patients, approximately 30-40%, failed to respond adequately to at least two antidepressants, develop the treatment-resistant depression (TRD). (McIntyre et al., 2023) TRD is associated with prolonged suffering, elevated suicide risk, and disproportionate healthcare costs, representing one of the most pressing unmet needs in psychiatry.

Esketamine nasal spray (Spravato®), received regulatory approval from the FDA and EMA to treat adults with TRD. It works through N-methyl-D-aspartate (NMDA) receptor antagonism, that demonstrating fast-acting efficacy in reducing depressive symptoms, which is a temporally distinct mechanism from conventional monoaminergic therapies. ASPIRE I and II showed significant MADRS reductions at 24 hours post-dose, and SUSTAIN-1 showed esketamine delayed relapse versus placebo in treatment responders. This adjunctive therapy represents paradigm shift and has recently gained traction for its benefits.

However, existing evidence has limitations. Current clinical evidence heavily relies on static efficacy measurements evaluated at single, isolated time points. This approach masks the highly dynamic, non-linear trajectories that patients undergo during the acute treatment course. It failed to capture patients who experience divergent or negative outcomes, such as symptomatic stagnation or acute deterioration. Furthermore, the durability of esketamine's effect post-induction and how the transient adverse events (AEs) including disassociation, dizziness, nausea modulate these trajectories remains poorly characterized at the individual participant level.

This study addresses this gap through a one-stage Individual Participant Data Meta-Analysis (IPD-MA). This study will generate scientific and medical knowledge by providing the comprehensive map of time-varying clinical trajectories in TRD patients treated with esketamine.

Specific Aims of the Project:

The primary objective of this study is to evaluate the time-varying clinical trajectories and investigate potential negative effects in adults with TRD receiving intranasal esketamine compared to placebo. We aim to model the longitudinal probabilities of patients in ordinal categories based on their percentage change in MADRS scores from baseline.

The therapeutic effect of intranasal esketamine on the clinical trajectory of TRD varies significantly over time and is non-linear. Esketamine significantly accelerates the initial transition to partial and full response compared to placebo. However, there is a distinct and identifiable subgroup of patients who experience divergent, unfavorable outcomes characterized by

symptom stagnation or acute worsening (an increase in MADRS score of ≥0%) despite the overall beneficial therapeutic effect.

Study Design:

Meta-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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research methods

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

Data Source

The study will utilize participant-level data exclusively from the Yale University Open Data Access (YODA) Project to conduct a one-stage IPD meta-analysis. We will not pool data from any studies outside the YODA Project. All data harmonization and modeling will be conducted within the given computing environment with R.

Inclusion Criteria

The following criteria will define the study sample:

- **Study design**: Randomized Controlled Trials (RCTs)
- **Demographics**: Adults (≥18 years of age).
- **Clinical Characteristics**: A confirmed diagnosis of Treatment-Resistant Depression (TRD) which is defined as non-response to the full treatment regimen of two anti-depressants
- **Intervention/Comparator**: Participants randomized to receive intranasal esketamine combined with a newly initiated/optimized oral antidepressant, or intranasal placebo combined with a newly initiated/optimized oral antidepressant.

Exclusion Criteria

To ensure clinical and methodological homogeneity, the following trial types will be excluded:

- **Non-TRD Populations**: Trials targeting MDD patients primarily for imminent/active suicidal ideation where TRD is not a required inclusion criterion (e.g. ASPIRE I and II).
- **Different administration route**: Trials evaluating intravenous ketamine or intravenous esketamine rather than intranasal esketamine.

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

Primary Outcome Measure

The primary outcome is the time-varying **clinical response** of participants assessed longitudinally throughout the trial. This framework captures dynamic clinical trajectories over time.

Outcome Categorization and Definitions

At each post-baseline assessment, a participant's clinical status will be classified into four ordinal categories based on the percentage change in the total depression severity score (e.g., MADRS) from baseline:

- **Response**: ≥50% decrease from baseline in the total severity score. (Samalin et al., 2026)
- **Partial response**: 25% to <50% decrease from baseline in the total severity score.
- **Non-response**: >0% to <25% decrease from baseline in the total severity score.
- **Deterioration**: ≥0% increase from baseline in the total severity score (representing no clinical improvement or a worsening of symptoms).

Secondary Outcome Measure(s)

None. The analysis is strictly focused on time-varying transitions between the primary clinical states.

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

Main Predictor/Independent Variable

The primary independent variable is the randomized treatment group assignment, operationalized as a binary categorical variable:

- **Intervention**: Esketamine nasal spray combined with a newly initiated or optimized oral antidepressant.
- **Comparator**: Placebo nasal spray combined with a newly initiated or optimized oral antidepressant.

Within our primary mixed-effects ordinal logistic model, we will evaluate the independent effect of this treatment variable on the odds of participants transitioning between the distinct clinical response states over time.

Covariates and Model Adjustments

To appropriately isolate the independent treatment effect within the IPD meta-analysis, the models will systematically adjust for the following prespecified covariates:

- **Baseline Disease Severity**: Modeled as a continuous variable utilizing the baseline MADRS total score.

- **Geographic Region:** Categorized by country or continent to account for regional clinical variations.
- **Concurrent Antidepressant Medication**: The class of oral antidepressant or antidepressant monotherapy status.

All statistical analyses will be performed using R.

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

No other variable will be used in the analysis.

Statistical Analysis Plan:

The primary outcome is the longitudinal response in MADRS from baseline to week 4. The primary estimand will be the response trajectory of the use of esketamine in conjunction with an anti-depressant on depression from baseline to week 4 post randomization, compared with placebo, among adults with TRD. Negative change in depression is measured by the change in MADRS score, classified into one of the four ordinal categories: deterioration, non-response, partial response, or response. Participants with observed outcome data will be included according to their assigned treatment, irrespective of treatment discontinuation, rescue medication use, or other post-randomization events. Esketamine was considered as a class effect across all doses, frequencies, and treatment durations used in the included trials. The individual MADRS scores will be visualized using spaghetti plots for each trial. The proportion of participant responses at each time point will be summarized by treatment groups.

We will use the 1-stage IPDMA approach with the mixed-effects ordinal logistic model with random intercepts on participants nested within studies. (Christensen 2018) To better model the time-varying treatment effect, we will add an interaction between treatment and time spline function in the model. Time will be modelled in natural cubic spline with 3 or 4 knots depending on the model fit and convergence. (Harrell 2001) Analyses will be adjusted for baseline MADRS scores and country/continent. Additionally, depending on data availability in each study, adjustments will be made for either the class of oral antidepressant or antidepressant monotherapy. For studies conducted in one country, the country will be entered based on trial protocol. The proportional odds assumption will be assessed graphically. When the proportional odds assumption is not met, we will use the mixed-effects multinomial logistic model. Prediction intervals will be calculated when more than 10 trials are included in the analysis. We will use the complete case analysis and report the percentage of missing data. The small study effect will be assessed using funnel plots when more than 10 trials are included.

When there are more than 5 trials eligible for inclusion, we would consider a sensitivity analysis using multistate model to compare the transition rates between each outcome categories during the intervention period between esketamine and placebo groups. In order to check whether enough transitions are observed in the data for a reliable model estimation, we will summarize the number of transitions between each outcome categories for the whole data. When the transitions between states are larger than 40 each, we will fit a continuous-time semi-Markov multistate model to investigate the transition rates between each outcome categories. (Meira-

Machado et al., 2009) All possible transitions are allowed except for the direct transitions between response and deterioration. Since MADRS were measured only at scheduled visits, the exact transition times are unknown and will be assumed to occur between observation times. (Jackson 2011) Similar to the primary analysis, baseline MADRS scores, country/continent, the class of oral antidepressant/antidepressant monotherapy will be adjusted for in the model. Given the rapid reaction of esketamine, we expect a lower transition rate when participants stay in one category for a long time. Thus, duration in the state will be modelled as a fixed effect. Since the current package for interval-censored data doesn't not account for clustering within studies, study will be included as a fixed effect in the model. Treatment effects will be estimated separately for each transition and reported as transition-specific hazard ratios with 95% confidence intervals. All the available data will be used, and no imputation will be performed.

Software to be used:

R

Project Timeline:

- Before the Datathon (June - September 7): Determine research question, draft research proposal, and harmonize data
- During the Datathon (September 7-11): analyzed data and present results
- During and after the Datathon (September 7 and onward): Finalize the analysis

Dissemination Plan:

Results of the datathon will be published in a research journal.

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Supplementary Material: