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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?: Scientific Publication

Conflict of Interest

<https://yoda.yale.edu/wp-content/uploads/2025/08/COI-FORM-DT.pdf>

<https://yoda.yale.edu/wp-content/uploads/2025/08/COI-FORM-NR.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. [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

Uncovering latent dissociative classes in response to Esketamine in TRANSFORM-1/2

Narrative Summary:

Esketamine can rapidly reduce symptoms in treatment-resistant depression, but it can also trigger dissociative experiences (e.g., feeling detached from one's body or surroundings). People vary widely in both the strength and duration of these responses. Using de-identified participant data from the TRANSFORM-1 and TRANSFORM-2 trials, we will track dissociative experiences across dosing sessions and use statistical modelling to identify subgroups with distinct dissociation trajectories (e.g., minimal, brief spike, or sustained dissociation). We will then examine whether these subgroups differ in antidepressant outcomes and whether dose and baseline severity help explain these patterns. The findings may improve understanding of esketamine's benefit--risk profile, support safer monitoring, and inform more personalized treatment.

Scientific Abstract:

Background: Esketamine reduces depression symptoms in treatment-resistant depression (TRD) but often causes dissociative experiences. Evidence for a link between dissociative and antidepressant responses is mixed. Prior research using total Clinician-Administered Dissociative States Scale (CADSS) scores and group averages may have overlooked heterogeneity in dissociative responses.

Objective: Identify latent subgroups with distinct magnitudes and trajectories of dissociation after esketamine dosing, and assess whether subgroups differ in antidepressant outcomes. **Study Design:** Post hoc re-analysis of data from TRANSFORM-1 and TRANSFORM-2 trials comparing esketamine+oral antidepressant vs placebo+oral antidepressant over a 4-week induction phase. **Participants:** ~576 adults 18--64 with TRD (nonresponse to ≥ 2 adequate antidepressant trials) who were randomized. **Outcomes:** Primary: CADSS item-level scores collected at multiple timepoints within dosing sessions and across visits. Secondary: Montgomery--Åsberg Depression Rating Scale (MADRS) change.

Statistical Analysis: Growth mixture modelling (GMM) will be used to identify an optimal model of latent classes with different acute trajectories of latent factors of state dissociation (e.g., depersonalization, derealization) in response to esketamine over multiple assessments. Factor mixture modelling will be used if data are not suitable for GMM. When possible, the analyses will adjust for baseline severity, treatment arm, and covariates. Latent classes will be compared on CADSS and antidepressant responses using mixed-effects modelling

Brief Project Background and Statement of Project Significance:

TRD is a major unmet need in psychiatric care, affecting ~33% of people with major depressive disorder and contributing to persistent symptoms, disability, and elevated relapse risk despite adequate treatment trials (1). The N-methyl-D-aspartate (NMDA) receptor antagonist esketamine, used adjunctively with an oral antidepressant, has demonstrated clinically meaningful antidepressant benefits in phase 3 trials and maintenance designs (2--4). However, esketamine also commonly produces acute dissociative experiences, including depersonalisation (feeling detached from one's body), derealisation (feeling detached from one's surroundings), and amnesic or perceptual disturbances, typically peaking shortly after dosing and resolving within hours (2,5,6). Understanding variability in dissociative responses to esketamine has significant implications for whether dissociation is meaningfully related to antidepressant outcomes, is important both clinically (tolerability, monitoring, adherence) and scientifically (mechanistic models of ketamine-class drugs and altered states of consciousness).

Evidence linking ketamine/esketamine-induced dissociation to antidepressant benefit remains mixed

(8,14,15). Some studies suggest that aspects of dissociation, particularly depersonalisation, may track early antidepressant response after ketamine-class interventions (7--9). In contrast, post hoc analyses of esketamine trials have generally reported weak or non-clinically meaningful associations between aggregate dissociation scores and antidepressant response (5,6). For example, in pooled analyses of TRANSFORM-1 and TRANSFORM-2, Mathai et al. found no clinically significant relationship between total CADSS scores and MADRS improvement across the induction phase (5). These discrepancies may be explained by reliance on total scores that treat dissociation as a single monolithic construct, potentially obscuring meaningful symptom dimensions (e.g., depersonalisation vs memory disruption), and heterogeneity in dissociative response patterns (magnitude and time-course), where subgroup effects could cancel out in group-average analyses.

We will model item-level CADSS scores across repeated within-visit (pre-dose, ~40 min, ~1.5 h) and across-visit assessments to characterise latent patterns of esketamine-induced dissociation. Using bifactor latent-variable finite-mixture methods, we will evaluate whether the latent structure of the CADSS reflects the presence of a general dissociation factor plus domain-specific factors (depersonalisation, derealisation, amnesia/memory distortion) and apply latent growth mixture modelling (LGMM/GMM) to identify trajectory classes (e.g., low, high-transient spike, high-sustained). If item variance limits factor estimation, we will run a LGMM on CADSS subscales. We will evaluate whether latent classes differ in antidepressant outcomes using MADRS change trajectories during induction and responder/remitter endpoints. The results will refine esketamine's side-effect profile, support monitoring/patient counselling, and inform mechanistic research on the links between the dissociative and antidepressant effects of esketamine.

Specific Aims of the Project:

To characterize heterogeneity in acute dissociative responses to intranasal esketamine in TRD using item-level CADSS scores and test whether latent dissociative classes relate to antidepressant outcomes.

Aim 1: Identify latent dissociation factors (general + domain-specific factors) from CADSS items at repeated assessments (pre-dose, ~40 min, ~1.5 h; across visits) and use latent growth mixture modelling (LGMM) to identify latent subgroups with distinct dissociation trajectories.

H1: ≥ 2 trajectory classes will emerge that differ in magnitude and time-course (e.g., low, high-transient "spike", high-sustained) and/or dimensional composition (e.g., depersonalisation).

Aim 2: Compare latent classes on antidepressant response to esketamine using MADRS change trajectories and responder/remitter endpoints, adjusting for dose, treatment arm, baseline severity, and key covariates.

H2: Latent classes will differ in MADRS outcomes; we hypothesise that a moderate/high-transient dissociation class will show greater early MADRS improvement than a low-dissociation class, while sustained/high dissociation will not confer additional benefits (directional but tested alongside the possibility of null effects).

Ketamine studies have reported that greater acute dissociation (CADSS; especially depersonalisation) can predict greater subsequent symptom improvement (7,12), whereas esketamine post hoc analyses in TRANSFORM datasets have generally found weak/absent correlations at the total-score level (5,6).

Study Design:

Other

Study Design Explanation:

Post hoc secondary re-analysis of de-identified individual participant data from the TRANSFORM-1 and TRANSFORM-2 phase 3 randomized, double-blind, placebo-controlled parallel-group trials of

intranasal esketamine plus a newly initiated oral antidepressant versus placebo nasal spray plus oral antidepressant. No new data will be collected; analyses will model repeated within-visit (pre-dose, ~40 min, ~1.5 h) and across-visit assessments of CADSS and MADRS during the 4-week induction phase. CADSS item-level data will be analysed using bifactor methods and latent growth mixture modelling to identify dissociation trajectory classes, followed by mixed-effects models to compare classes on CADSS and MADRS outcomes.

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

Other: Participant-level data re-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:

None - No exclusion criteria

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

Primary outcomes: Acute dissociative response following study dosing, measured using CADSS scores at all available within-visit assessments (extending from pre-dose through to ~1.5 h post-dose) and across dosing visits during the induction phase. Primary dissociation metrics will be CADSS latent factor scores (general dissociation and domain-specific factors) if latent factors can be estimated reliably; if they cannot, predefined CADSS subscale scores (amnesia, depersonalization, derealisation) will be used.

Depressive symptom severity, measured by MADRS total score (0--60) at all available visits. The primary depression endpoint will be the change in MADRS total score from baseline (Day 1, pre-dose) to Day 28 (end of double-blind induction).

Secondary outcomes:

1) MADRS response at Day 28 (binary): $\geq 50\%$ reduction from baseline MADRS.

2) MADRS remission at Day 28 (binary): MADRS ≤ 12 .

3) Latent dissociation class membership (categorical), estimated from modelling of CADSS latent factor (or subscale) trajectories across within-visit and across-visit assessments (e.g., low, high-transient, high-sustained).

Planned changes, if required, in the final analyses:

If near-zero variance in CADSS at some assessments prevents stable latent factor estimation, primary dissociation analyses will be repeated using CADSS subscales. The primary MADRS endpoint (baseline→Day 28 change) will not change.

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

The principal independent variable will be latent class. Latent class will be estimated in each individual patient using either LGMM or FMM, depending on data suitability. The predictor will be

treated as a categorical variable (e.g., low dissociation, high-transient "spike," high-sustained). It is anticipated that there will be 2-5 latent classes.

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

Participant characteristics (baseline and descriptive + adjustment/exploratory)

Age (years, continuous), sex (categorical), race/ethnicity (trial categories), region/country (region grouped as North America/Europe/Other), education and employment status (categorical).

Treatment/exposure variables (adjustment and effect modification)

Randomised arm (esketamine+oral AD vs placebo+oral AD). Dose per session (56 vs 84 mg, categorical) and cumulative exposure (number of doses received, continuous). Multiple dosing visit/day indicators (e.g., session index/ Day 1, 4, 8, 11, 15, 18, 22, and 25) and "within-session" assessment timepoints (pre-dose, ~40 min post-dose, ~1.5 h post-dose for CADSS).

Study timing variables

Visit/day (study day) and assessment window (within-visit timepoint).

Baseline clinical covariates (risk adjustment)

Baseline MADRS total score (continuous) and baseline CADSS (pre-dose)

Concomitant treatments (confounding control and exploratory)

Newly initiated oral antidepressant class (SSRI vs SNRI, categorical) and specific drug (categorical).

Statistical Analysis Plan:

Descriptive analyses

We will summarise baseline characteristics by randomised arm and overall (e.g., age, sex, region/site, baseline MADRS and baseline CADSS). For CADSS and MADRS, we will report means/SDs (or medians/IQRs if skewed) at each scheduled assessment and visualise mean trajectories (+/- SEs) over time.

Estimation of latent subgroups

We will use a bifactor latent growth mixture model in which individual CADSS items (23 items; 0--4 scale) are used to estimate a general dissociation factor and one or more specific factors at each assessment, and then identify latent subgroups distinguished by their response trajectories on these CADSS latent factors. CADSS in TRANSFORM-1 and TRANSFORM-2 includes repeated assessments within dosing visits (pre-dose, ~40 minutes post-dose, ~1.5 hours post-dose) and across multiple dosing days/visits throughout the induction.

This analysis might not be possible due to near-zero variance in CADSS at some timepoints. If the factor model cannot be fit, bifactor models will be applied to timepoints of greatest variance to identify CADSS latent factors. These will be assessed for replicability across multiple assessments (e.g., factor structure and loading patterns). If replicable, these latent factor scores across timepoints will be included in a latent growth mixture model as above.

As a complementary analysis, we will fit a latent growth mixture model to pre-defined CADSS subscale scores (amnesia, depersonalisation, derealisation). Although this does not represent as robust a measure as item-derived latent factors, it aligns with common use of CADSS subscales in the literature and is more amenable to reproducibility.

Comparison of latent subgroups

Latent classes will first be compared on CADSS latent factor (or subscale) scores for descriptive purposes and to illustrate differential dissociative response patterns (e.g., low dissociation vs high

transient dissociation vs high sustained dissociation). This will be done using mixed-effects models with latent class, dose, within-session timepoint (pre-dose, ~40 min, ~1.5 h), dosing visit/session (day), and baseline severity (baseline CADSS for CADSS models; baseline MADRS for MADRS models) as fixed effects and CADSS latent class (or subscale) scores as outcome variables. Models will account for the nested/repeated structure of the data (timepoints within dosing sessions within participants). Random intercepts and random slopes for participant ID and time will be included if model fit improves (lower AIC/BIC), and random effects variables will be sequentially entered and retained if model fit improves (lower AIC/BIC) (13).

Same analysis as above on MADRS

We will repeat the mixed-effects model with MADRS total score as the outcome (including baseline MADRS as a covariate), comparing MADRS trajectories across latent dissociation classes. Binary endpoints (response/remission) will be analysed with generalized mixed-effects models using the fixed effects variables described above.

Software Used:

R

Project Timeline:

Start date -- April 2026

Analysis completion -- July 2026

Manuscript drafted -- September 2026

Submitted for publication -- November 2026

Results reported to YODA -- December 2026

Dissemination Plan:

The results of this study will be disseminated to relevant stakeholders through at least presentation at an academic conference and one academic article in a peer-reviewed journal. Potential target conferences include the European College of Neuropsychopharmacology (ECNP) Congress and the Society of Biological Psychiatry (SOBP) Annual Meeting, whereas potential target journals include the British Journal of Psychiatry and Translational Psychiatry.

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