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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/system/files/sandeepnayak.pdf>
<https://yoda.yale.edu/system/files/albertgarcia-romeu.pdf>
<https://yoda.yale.edu/system/files/davidmathai.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

Examining the relationship between esketamine-induced dissociation and antidepressant effects

Narrative Summary:

Two recently published short-term drug efficacy studies (TRANSFORM-1 and TRANSFORM-2) that were used toward FDA approval of esketamine suggest that drug-induced dissociation is an adverse clinical event and does not meaningfully predict antidepressant outcome. However, this conclusion requires additional group- and item-level analysis for validity and is of high scientific importance, given the ongoing use of esketamine along with emerging data on therapeutic hallucinogens. We plan to conduct a pooled analysis with the TRANSFORM-1 and TRANSFORM-2 datasets to clarify the relevance of dissociative effects in the psychiatric use of esketamine.

Scientific Abstract:

Background: Further work is needed to characterize the dissociative-type effects of ketamine and to clarify the relationship between esketamine-induced dissociation and antidepressant response.

Objective: We plan to achieve the following aims: 1) examine the relationship between esketamine-induced dissociation and antidepressant efficacy, 2) examine the impact of subgroup variables on dissociation and esketamine response and 3) clarify possible distinctions between placebo- and esketamine- induced dissociation.

Study Design: This study will involve a pooled post-hoc analysis of full datasets from the TRANSFORM-1 and TRANSFORM-2 esketamine trials, representing an expected sample of >500 patients.

Participants: All randomized patients from the TRANSFORM-1 and TRANSFORM-2 esketamine trials who received ? 1 dose of study medication and 1 dose of oral antidepressant during the double-blind induction phase will be included in this study.

Main Outcome Measure(s): We will primarily analyze antidepressant effect as measured by changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) and dissociation as measured by the Clinician Administered Dissociative States Scale (CADSS).

Statistical Analysis: We will use a combination of linear and logistic regression methods with defined covariates to achieve the aims as above. All analyses will be conducted in R.

Brief Project Background and Statement of Project Significance:

Ketamine is an NMDA receptor antagonist that originated as a dissociative anesthetic agent (Curran & Morgan, 2000). The mental state produced by the drug was first classified as “dissociative” to capture its hallucinogenic profile – one which left subjects feeling “disconnected” from their environments (Domino, 2010). Interest in

psychiatric applications of ketamine had long-existed but accelerated with positive findings from the first randomized controlled trial using ketamine for the treatment of depression (Berman et al., 2000). Subsequent trials of ketamine and esketamine – one isomeric form of ketamine – confirmed these findings, culminating in FDA approval and legitimization of esketamine as an antidepressive and antisuicidal agent. However, questions surrounding the nature and relevance of the drug’s psychoactive effects remain (Mathai et al., 2020).

Notably, there has been growing interest in the therapeutic properties of “hallucinogens” – agents that function by various mechanisms of action but exhibit similarities in their ability to occasion temporary but profound alterations of consciousness, involving acute changes in somatic, perceptual, cognitive, and affective processes (Garcia-Romeu et al., 2016; Wolff & Winstock, 2006). There is considerable evidence that the effects of classic hallucinogens are mediated in part by activity at 5HT-2A receptors, though also to some extent by a glutamatergic pathway, which may be shared with ketamine (Kadriu et al., 2021). Though formal investigation into the subjective ketamine experience has been limited, there is evidence to suggest that ketamine induces alterations in consciousness and personal frameworks similar to those achieved by the serotonergic hallucinogens (Dakwar et al., 2014; Dore et al., 2019; Krupitsky & Grinenko, 1997). Moreover, strategies to develop mechanistically similar drugs as ketamine with fewer dissociative effects have generally failed to replicate its therapeutic benefits (Wei et al., 2020; Yang et al., 2019).

Scales such as the Clinician Administered Dissociative States Scale (CADSS) are widely administered to measure ketamine’s dissociative-type effects, which have generally been classified as an adverse drug effect; however, these measurements may also allow for better understanding of the relationship between ketamine’s hallucinogenic and antidepressant properties (Mathai et al., 2020). A strong relationship could indicate that psychiatric uses of ketamine are optimized within drug administration protocols and environments that safely facilitate, rather than mitigate, these hallucinogenic and dissociative effects, as has been demonstrated with agents such as MDMA and psilocybin. Such evidence would also have substantial investigative significance, with support for dissociation and related processes as key pharmacological targets in the study of depression.

To address these questions, we plan to conduct a comprehensive analysis of CADSS and antidepressant data from two recently published short-term efficacy studies used toward FDA approval of esketamine. To our knowledge, this would represent the largest and most robust investigation of this topic to date.

Specific Aims of the Project:

Aim 1: Examine the relationship between esketamine-induced dissociation and antidepressant efficacy.

Ai. Initial dissociation predicts early- and late- MADRS change.

Aii. Initial dissociation predicts responder status.

Aiii. Early antidepressive effect of esketamine predicts late- MADRS change and responder status.

Bi. Peak dissociation predicts late- MADRS change.

Bii. Peak dissociation predicts responder status.

Biii. Timepoint of peak dissociation is delayed in 84mg vs 56mg dose group.

Ci. Cumulative dissociation predicts late- MADRS change.

Cii. Cumulative dissociation predicts responder status.

Aim 2: Examine the impact of subgroup variables on dissociation and esketamine response.

A. Subgroup variables may predict esketamine-induced dissociation.

B. Subgroup variables may predict MADRS changes for esketamine.

C. Subgroup variables may predict esketamine responder status.

Aim 3: Clarify possible distinctions between placebo- and esketamine- induced dissociation.

A. For “dissociators,” subscale- and item-level dissociative data for esketamine and placebo suggest diverging phenomenological profiles.

B. Placebo-induced dissociation is not associated with late- MADRS change.

C. Placebo-induced dissociation is not associated with responder status.

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

Participant-level data meta-analysis

Participant-level data meta-analysis using only data from YODA Project

Research on comparison group
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:

We plan to analyze data from the TRANSFORM-1 (Fedgchin et al., 2019) and TRANSFORM-2 (Popova et al., 2019) studies and use identical inclusion/exclusion criteria. The full trial methods are described in those publications and the associated supplements. We aim to use the full analysis set, consisting of all randomized patients who received ? 1 dose of study medication and 1 dose of oral antidepressant during the double-blind induction phase.

Main Outcome Measure and how it will be categorized/defined for your study:

Antidepressant effect

- As measured by the Montgomery-Åsberg Depression Rating Scale (MADRS)
- Will examine MADRS score change as a continuous variable
- Will examine “responder” as a binary variable (for purposes of analysis, “responders” will be defined as those with ?50% reduction from baseline MADRS score)

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

Dissociation

- As measured by the Clinician Administered Dissociative States Scale (CADSS)
- Will include total, subscale (Niciu et al., 2018), CADSS-6 (Rodrigues et al., 2021), and individual- item CADSS scores as available and unless otherwise specified in analysis
- Will examine initial (Day 2 score), peak (highest single dose score across timepoints), and cumulative (summed score across all drug sessions) dissociation
- Will examine “dissociators” as binary variable (For purposes of analysis, “dissociators” will be defined as those with single dose peak CADSS ? 4 across timepoints)

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

Age, sex, baseline MADRS, diagnosis of PTSD, diagnosis of anxiety disorder, and number of previous treatment failures as characterized by original study authors

Statistical Analysis Plan:

Aim 1: Examine the relationship between esketamine-induced dissociation and antidepressant efficacy

A. Role of initial dissociation and early treatment effects

i. Hypothesis: Initial dissociation in esketamine group predicts early- and late- MADRS change

Analysis: Linear models with Day 2/15/28 MADRS change from baseline predicted by Day 2 dissociation with adjustment for the following covariates: age, sex, baseline MADRS, diagnosis of PTSD, diagnosis of anxiety disorder and number of previous treatment failures

ii. Hypothesis: Initial dissociation in esketamine group predicts responder status

Analysis: Logistic regression with Day 28 responder status predicted by initial dissociation with adjustment for previously defined covariates

iii. Hypothesis: Early antidepressive effect of esketamine predicts late- MADRS change and responder status

Analysis: Linear regression with Day 28 MADRS change and logistic regression with responder status predicted by Day 2 MADRS change from baseline with adjustment for previously defined covariates

B. Role and timepoint of peak dissociation

i. Hypothesis: Peak dissociation in esketamine group predicts late- MADRS change

Analysis: Linear models with Day 28 MADRS change from baseline predicted by peak single-dose dissociation with adjustment for previously defined covariates

ii. Hypothesis: Peak dissociation in esketamine group predicts responder vs non-responder status

Analysis: Logistic regression with Day 28 esketamine responder status predicted by peak dissociation with

adjustment for previously defined covariates

iii. Hypothesis: Timepoint of peak dissociation is delayed in 84mg vs 56mg dose group

Analysis: Compare mean timepoint of peak of both dosing groups with t-test for significance testing

C. Role of cumulative dissociation

i. Hypothesis: Cumulative dissociation in esketamine group predicts late- MADRS change

Analysis: Linear models with Day 28 MADRS change from baseline predicted by cumulative dissociation with adjustment for previously defined covariates

ii. Hypothesis: Cumulative dissociation in esketamine group predicts responder status

Analysis: Logistic regression with Day 28 responder status predicted by cumulative dissociation with adjustment for previously defined covariates

Aim 2: Examine the impact of subgroup variables on esketamine-induced dissociation and response

A. Hypothesis: Subgroup variables may predict esketamine-induced dissociation

Analysis: Linear regressions using dissociation as the outcome variable with the following predictor variables: age, sex, baseline MADRS, diagnosis of PTSD, diagnosis of anxiety disorder and number of previous treatment failures

B. Hypothesis: Subgroup variables may predict MADRS changes for esketamine

Analysis: Linear regressions within Day 2/15/28 MADRS change from baseline as the outcome variable with the previously defined predictor variables

C. Hypothesis: Subgroup variables may predict esketamine responder status

Analysis: Logistic regression using Day 28 responder status as the outcome variable with the previously defined predictor variables

Aim 3: Clarify possible distinctions between placebo- and esketamine- induced dissociation

A. Hypothesis: For “dissociaters,” subscale- and item-level dissociative data for esketamine and placebo suggest diverging phenomenological profiles

Analysis: T-tests between esketamine versus placebo “dissociaters” comparing cumulative CADSS subscale and individual items

B. Hypothesis: Placebo-induced dissociation is not associated with late- MADRS change

Analysis: Linear regression with Day 28 MADRS change from baseline predicted by cumulative dissociation with adjustment for previously defined covariates

C. Hypothesis: Placebo-induced dissociation is not associated with Day 28 responder status

Analysis: Logistic regression with Day 28 placebo responder status predicted by cumulative dissociation with adjustment for previously defined covariates

Software Used:

R

Project Timeline:

Anticipated project start date: Immediately upon availability of data

Analysis completion date: 3 months from start date

Date manuscript drafted and first submitted for publication: 6 months from start date

Date results reported back to the YODA project: 6 months from start date

Dissemination Plan:

Anticipate manuscript and poster for clinical psychiatry audience- candidate journals include JAMA Psychiatry, American Journal of Psychiatry, and Journal of Clinical Psychiatry

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