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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/coi_gustavo_c_medeiros.pdf  
https://yoda.yale.edu/system/files/coi_fernando_s_goes_0.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
3. 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
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
7. 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
8. 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
9. 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
10. 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
11. NCT01627782 - KETIVTRD2002 - A Double-blind, Randomized, Placebo-controlled, Parallel Group, Dose Frequency Study of Ketamine in Subjects With Treatment-resistant Depression
12. NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine 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
Clinical predictors of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis

Narrative Summary:
Ketamine and esketamine are effective in treating depression but individual patients respond differently to these medications. Unfortunately, it is still unclear who are the individuals that are more likely to benefit from ketamine/esketamine. We will conduct a comprehensive summary of the available evidence including data from the YODA project and from other studies to investigate if clinical predictors (such as demographics, depression characteristics, comorbidities) can indicate the patients who are more likely to respond to ketamine/esketamine. Our ultimate goal is to identify patients who are more likely to respond to ketamine/esketamine, and increase treatment success.

Scientific Abstract:
Background: (R,S)-ketamine (ketamine) and its enantiomer (S)-ketamine (esketamine) can produce rapid and substantial antidepressant effects. However, individual response to ketamine/esketamine is variable, and there are no well-accepted methods to differentiate persons who are more likely to benefit. Objective: To conduct a pre-registered systematic review and meta-analysis (PROSPERO protocol CRD42020206937) of clinical predictors of response to ketamine/esketamine in individuals in a major depressive episode (MDE) in major depressive disorder (MDD) and bipolar disorder (BD). Study Design: This systematic review and meta-analysis will combine the data on esketamine from the YODA project with other clinical trials conducted with ketamine and/or esketamine identified by systematic searches.
analytical calculations will be conducted if there are at least three comparable studies on the same clinical predictor. Participants: Adult human subjects with a MDE in MDD or BD who participated in clinical trials (randomized controlled and/or open label) and received at least one dose of ketamine or esketamine. Main Outcome Measure(s): In the quantitative summary, results across studies will be compared using response status as primary outcome (i.e., responder versus non-responder where response is defined as at least 50% improvement in standardized depression measures). Statistical Analysis: The meta-analyses will utilize a random-effects models with inverse-variance weighting. Effect sizes will be reported as standardized mean differences (continuous variables) or odds-ratio (categorical variables).

Brief Project Background and Statement of Project Significance:

There is a substantial body of research showing that (R,S)-ketamine (ketamine) and its (S)-ketamine enantiomer (esketamine) are effective in treating a major depressive episode (MDE) in major depressive disorder (MDD) and bipolar disorder (BD), including difficult-to-treat cases. However, individual patients respond differently to ketamine/esketamine, and about 30 to 60% of the persons with treatment-resistant depression show limited response to ketamine/esketamine (1-9). There is also the risk of side effects such cardiovascular symptoms and short term psychotomimetic and dissociative symptoms, which in severe cases can lead to the interruption of treatment. Therefore, there is a need to identify persons that are more likely to respond to ketamine/esketamine, which will increase treatment success and maximize the use of available resources. Despite continued efforts to identify biomarkers of response to ketamine/esketamine, the results have been inconsistent, and unable to reliability inform treatment selection (10-15). In addition, costs associated with obtaining neuroimaging or more comprehensive blood-based biomarkers may be prohibitive given their current limited clinical utility (16). In contrast, potential clinical predictors can be easily and freely obtained from naturalistic clinical care practice. Previous studies have indicated potential clinical predictors of response to ketamine/esketamine such as a personal and/or family history of alcohol use disorder (17-19), higher body mass index (BMI) (18), and the presence of co-occurring anxiety disorder (20). Clinical features suggestive of a more severe depressive course, such as history of psychiatric hospitalization (21, 22) or suicide attempts (18), have also been shown to correlate with worse outcomes. However, these studies have been conducted in generally with small samples, and is still unclear if findings replicate across different studies (23). Consequently, there are still no well-established clinical approaches to guide selection of ketamine/esketamine, highlighting the need to perform a systematic and rigorous summary of current evidence to comprehensively assess the utility of clinical predictors of response to ketamine/esketamine.

Specific Aims of the Project:

Aim 1: To investigate whether demographic characteristics are associated with response to ketamine/esketamine. Hypothesis: Responders, when compared to non-responders, will have a higher socioeconomic status (e.g., better education and occupational level).
Aim 2: To investigate whether psychiatric and medical characteristics are associated with response to ketamine/esketamine. Hypothesis: Responders, when compared to non-responders, will have lower rates of psychiatric/medical comorbidities, lower duration of current episode, lower number of previous psychiatric hospitalizations, and greater BMI.
Aim 3: To investigate whether treatment-related side effects are associated with response to ketamine/esketamine. Hypothesis: Responders, when compared to non-responders, will have higher scores in the derealization and depersonalization subscales of the Clinician-Administered Dissociative States Scale (CADSS).
Aim 4: To investigate whether concurrent medications are associated with response to ketamine/esketamine. Hypothesis: Responders, when compared to non-responders, will have lower rates of use of medications that reduce glutamatergic neurotransmission (e.g., lamotrigine) or medications that enhance GABAergic neurotransmission (e.g., benzodiazepines).

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
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:

The data provided by the YODA project will be combined with other clinical trials, which will identified by electronic searches in five databases and manual searches - see attachment 1 for current list of clinical trials that were identified.

We will include manuscripts that 1) examined adult human subjects, 2) studied individuals with a MDE in MDD or BD, 3) were published in English, 4) reported on clinical trials (randomized controlled and/or open label) that administered at least one dose of ketamine or its S-enantiomer esketamine, 5) measured improvement of depressive symptoms with a standardized depression tool, and 6) assessed the association between clinical variables and improvement of depressive symptoms after ketamine/esketamine treatment.

This study will exclude articles that 1) investigated individuals with current psychotic symptoms, 2) examined persons with depressive symptoms due to other disorders besides MDD and BD, 3) allowed concurrent neuromodulatory treatments (concurrent medications and psychotherapy will be allowed), 4) studied individuals with serious comorbid medical or neurological diseases, and 5) assessed individuals in surgical/perioperative settings.

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

The main goal of this study is to investigate associations between clinical variables and improvement of depressive symptoms in individuals who were treated with ketamine or esketamine. In the qualitative summary (systematic review), we will report on the association between levels of blood-based biomarkers and any measure of improvement, including continuous improvement in depression scores (such as absolute and percentage changes in depression scores) and categorical improvement (such as response and remission). In the quantitative summary (meta-analysis), results across studies will be compared using response status as primary outcome (i.e., responder versus non-responder where response is defined as at least 50% improvement in standardized depression measures).

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

We will assess four categories of clinical predictors:
- Demographic characteristics such as age (in years), sex (male versus female), education (in years of education), and occupational status (employed versus non-employed).
- Psychiatric and medical characteristics such as duration of depressive episode (in months), age at illness onset (in years), psychiatric and medical comorbidities (yes versus no), BMI (in kg/m2), previous suicide attempts (yes versus no), and previous hospitalizations (yes versus no).
- Treatment-related side effects such as dissociation (change in Clinician Administered Dissociative States Scale - CADSS), psychotomimetic symptoms (change in Brief Psychiatric Rating Scale – BPRS), cardiovascular changes (changes in blood pressure and heart rate) and onset of other physical side effects (e.g., vertigo, dissociation, somnolence and dizziness).
- Concurrent medications including lamotrigine and benzodiazepines (yes versus no).

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

Meta-regressions will be performed to identify potential effect modifiers, and will examine the impact of variables such as number of treatments (single versus multiple), primary diagnosis (MDD versus bipolar depression), and treatment-resistance status. As recommended by Cochrane, meta-regressions will be conducted only if the number of studies is ten or more in the meta-analytical calculation (24).

Statistical Analysis Plan:

Meta-analytical calculations will be conducted if there are at least three comparable studies on the same clinical predictor. If there are studies with overlapping samples, only the study with the largest sample will be included in the quantitative summary. Clinical predictors compared between responders and non-responders using standardized mean differences for continuous variables, and odds-ratio for categorical variables. A significant degree of heterogeneity between studies is anticipated, therefore, random-effects models will be used (inverse-variance weighting).

Heterogeneity between studies was examined using I2 where values between 0 and 40% are considered trivial heterogeneity, values between 30 and 60% are considered moderate heterogeneity, values between 50 and 90%...
are considered substantial heterogeneity, and between 75 and 100% are seen as considerable heterogeneity (24). Publication bias will be assessed by funnel plots.

Software Used:
RStudio

Project Timeline:

- Systematic searches: finished in October, 2021
- Screening process: ongoing (estimated to be finished by February, 2022)
- Data extraction: March and April, 2022
- Data analysis: May and June, 2022
- Manuscript elaboration: July, 2022
- Manuscript submission: August, 2022

Dissemination Plan:

This systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal, and for presentation in scientific meetings.

Bibliography:

23. Fanelli D. Negative results are disappearing from most disciplines and countries. Scientometrics. 2012;90(3):891-904.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/attachment_1_-_list_of_studies.pdf