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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/wp-content/uploads/2014/10/coi_form_moffa_new.pdf
https://yoda.yale.edu/wp-content/uploads/2018/12/nikolin_stevan_-_yoda_coi.pdf
https://yoda.yale.edu/wp-content/uploads/2021/09/martin_coi.pdf
https://yoda.yale.edu/wp-content/uploads/2020/02/yoda_project_coi_form_cao.pdf
https://yoda.yale.edu/wp-content/uploads/2023/06/COI-form-SP.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. 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)
5. 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
6. NCT03039192 - 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
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

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

Research Proposal

Project Title

Cognitive effects of repeated-dose Ketamine in the treatment of major depression: a systematic review and individual patient data meta-analysis.

Narrative Summary:

Depression affects millions of people worldwide, with up to one-third of patients presenting a chronic course of the disease even after adequate use of psychotropic drugs and behavioural interventions. Ketamine has attracted attention as it has been shown to rapidly alleviate depressive symptoms

after the administration of a single dose. However, how significant or persistent Ketamine?s cognitive effects are in this clinical population remains unclear. Therefore, we propose to conduct an individual participant data meta-analysis of randomised clinical trials with the aim of evaluating the cognitive effects of Ketamine in depressed patients and the factors that may impact cognitive outcomes.

Scientific Abstract:

Background: Ketamine rapidly alleviates depressive symptoms after a single therapeutic dose. However, it remains unclear which cognitive domains are most affected by Ketamine and to which extent and which factors may influence the effects of multiple Ketamine administrations on cognition.

Objective: In the proposed systematic review and meta-analysis, we will examine placebo-controlled randomised clinical trials (RCTs) in depression, exploring the acute effects of multiple Ketamine administrations on cognitive functions. Additionally, we will perform meta-regression analyses to investigate how factors such as route of administration, dose, sex, and age modulate the cognitive effects of Ketamine.

Study Design: Systematic review and meta-analysis of placebo-controlled RCTs utilizing either a parallel or crossover design, reporting the effects of multiple Ketamine administrations on cognition in the treatment of depression.

Participants: adults with a clinical diagnosis of a major depressive episode

Main Outcome Measure: Cognitive performance using standardized cognitive scales/tests (e.g., RAVLT and CVLT-II) pre/post ketamine administration.

Secondary Outcome Measure: clinical, demographic and treatment variables predictors of cognitive outcomes.

Statistical Analysis: Random effects meta-analyses, performed using open-source statistical software, will estimate the cognitive effects of Ketamine relative to the control condition. Follow-up subgroup and sensitivity analyses will additionally investigate potential moderators of effects and confirm the robustness of the results.

Brief Project Background and Statement of Project Significance:

Ketamine is an n-methyl-d-aspartate antagonist commonly used as an anaesthetic agent that has been shown to rapidly improve specific depressive symptoms such as sadness, suicidality, and helplessness. Early trials have demonstrated its usefulness in patients with treatment-resistant depression and those with acute suicidal ideation, producing rapid alleviation of depressive symptoms within hours or days of administration of a single therapeutic dose. Although the antidepressant effects of ketamine have been studied in clinical research, important gaps in knowledge regarding its cognitive effects in depressed populations remain. In healthy volunteers, it was noted that ketamine impaired cognition in domains such as free recall, recognition memory, attention (Malhotra et al., 1996), and executive and sensorimotor functions (Giorgetti et al., 2015). The ketamine-induced cognitive effects were shown to be highly dependent on dose, and resultant plasma levels, with sex and age also considered factors that may account for the variability observed in ketamine's effects on cognition. Because depression is associated with significant cognitive impairments, it is critical to better understand the cognitive effects associated with multiple ketamine administrations for the treatment of this clinical population before its widespread therapeutic application.

Since a limited number of studies explored as the primary outcome of interest the effects of ketamine on the cognition of depressed patients, we propose to conduct an individual participant data (IPD) meta-analysis of randomised clinical trials (RCTs) to assess the cognitive effects of repeated-dose ketamine for the treatment of depression. The main advantage of an IPD meta-analysis compared to the aggregated data approach is that the first is more accurate in estimating the effects of an intervention and also superior for obtaining predictors of treatment outcomes since it uses the raw data collected from each participant of each study instead of the summarised estimates from the original published results.

This systematic review and meta-analysis seek to address these remaining gaps in knowledge and

thereby facilitate the translation of ketamine into the clinic as a potent and safe novel treatment for depression. The present meta-analysis is clinically relevant because it will inform on the types of cognitive deficits that may be observed, in the immediate term, during the acute effects of multiple ketamine treatments for depression.

Specific Aims of the Project:

The proposed systematic review and meta-analysis aims to provide an update on the acute effects of repeated-dose ketamine administrations on the cognitive functions of adult depressed patients whilst addressing several outstanding questions within the field, including whether factors such as personalised titration approaches, repeated administrations of ketamine as part of a therapeutic course of treatment, routes of administration and clinical and demographic characteristics have a differential impact on the cognition of patients. In summary, this project's objectives are to evaluate the cognitive effects of repeated-dose ketamine in depressed patients and to investigate the impact of relevant predictor variables on cognitive outcomes.

Study Design:

Meta-analysis (analysis of multiple trials together)

Research Methods

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

Our systematic review will be conducted by searching bibliographic databases Embase, Medline Pubmed, PSYCinfo and CENTRAL between database inception to June 25, 2023. Database search terms include ?controlled trial? AND ?ketamine? AND ?depression?, in addition to several permutations and variations of these terms. Studies will be included in the systematic review if: (1) they report cognitive outcomes in a sample of participants with a clinical diagnosis of major depressive disorder; (2) they report the use of repeated Ketamine administrations primarily as part of a treatment course for a depressive episode; (3) they use a control condition, either saline or an active control such as midazolam, to which participants were randomly assigned; and (4) individual patient data is available.

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

The primary outcome measure will be the cognitive performance using standardized cognitive scales/tests, such as RAVLT and CVLT-II, pre/post ketamine administration.
Secondary outcomes will include predictor clinical, demographic and treatment variables of cognitive outcomes.

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

We will examine performance in cognitive tasks pre and post-ketamine administration (difference from baseline) compared to the control group.

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

Subgroup analyses will additionally investigate the effect of dose titration (i.e., adjusting individualised dosage to optimise treatment outcomes), the route of ketamine administration (e.g., intranasal, subcutaneous, intravenous, or intramuscular) using dose conversion to allow comparison between different routes, differences in onset and durability of ketamine effects after repeated administrations, differences between ketamine preparation types (racemic, esketamine/s-ketamine,

arketamine/r-ketamine), differences in trials using a saline placebo control with those that used active medication (e.g., midazolam), and lastly whether the participant cohort consisted of participants with treatment-resistant depression (operationalised as the failure of 2 or more adequate antidepressant drug trials).

Statistical Analysis Plan:

All statistical analyses will be performed in open-source R statistical software version 4.0.2 (R Core Team, 2020). A one-stage IPD meta-analyses approach was selected, as this allows for the inclusion of covariates at an individual level. The dependent variables for each analysis will be the cognitive measure z-score or age/education-adjusted scores (where available) for individual change from baseline to post-ketamine time points calculated for each study. Z-scores will be used to enable the collation of data from analogous cognitive measures between studies (e.g., RAVLT and CVLT-II). For timed cognitive measures, z-scores will be calculated using baseline minus post-intervention scores to reflect performance improvement. Individual mood change z-scores will be similarly calculated for each study. Primary analyses will be conducted using one-stage mixed effects models with a fixed effect of Ketamine condition (i.e., ketamine vs control), random effects for subject and study, and individual mood change added as a covariate to examine the effect of ketamine on cognitive dependent variables. Secondary subgroup analyses will examine whether the cognitive effects of ketamine are modulated by individual-specific factors: gender (male or female), diagnosis (bipolar disorder or major depressive disorder), mood improvement, baseline global cognitive functioning level (Impaired: pre-treatment MMSE less than or equal to 26 or MoCA less than or equal to 26 or baseline cognitive functioning z-score for a given measure is less than -1; Not impaired: MMSE greater than 26 or MoCA greater than 26), and study site. This will be conducted using the same statistical models of the primary analyses but with the specific characteristics of the individuals considered separately. Treatment group differences will be examined using independent t-tests for continuous and Chi tests for categorical variables. All tests will be two-tailed, and the significance level will be set at p less than 0.05. Publication bias and small study effects will be examined using a standard ?aggregate? meta-analysis approach and assessed using the Egger test and visual inspection of contoured funnel plots at the study's primary endpoint. In the event of a statistically significant Egger statistic, we will use the Trim & Fill procedure to minimise potential publication bias and provide a revised estimate of effect sizes. Heterogeneity will be reported using the I and Tau statistics. An I value greater than 50% will be considered indicative of substantial heterogeneity.

Project Timeline:

project start date: 8/5/2023
analysis completion date: 1/9/2023
date manuscript drafted: 10/10/2023
first submitted for publication: 1/11/2023
date results reported back to the YODA Project: 15/12/2023

Dissemination Plan:

The meta-analysis will be submitted to a reputable and leading medical journal in the field for peer review and publication.

Bibliography:

Giorgetti, R., Marcotulli, D., Tagliabracci, A., & Schifano, F. (2015). Effects of ketamine on psychomotor, sensory and cognitive functions relevant for driving ability. Forensic Science International, 252, 127-142. https://doi.org/https://doi.org/10.1016/j.forsciint.2015.04.024
Malhotra, A. K., Pinals, D. A., Weingartner, H., Sirocco, K., Missar, C. D., Pickar, D., & Breier, A. (1996). NMDA Receptor Function and Human Cognition: The Effects of Ketamine in Healthy Volunteers. Neuropsychopharmacology, 14(5), 301-307. https://doi.org/10.1016/0893-133X(95)00137-3