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How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/05/CI-Jens.pdf
https://yoda.yale.edu/wp-content/uploads/2025/05/CI-Juliana.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

Brain-derived neurotrophic factor as a blood-based biomarker of the antidepressant response to ketamine and esketamine: A meta-analysis

Narrative Summary:

Ketamine and esketamine represent efficacious pharmacological treatments for around 20-50% of the individuals with depression who have not responded to conventional antidepressant treatment. This meta-analysis integrates the results of previous studies investigating whether baseline or longitudinal changes in the blood levels of brain-derived neurotrophic factor are associated with the antidepressant response to (es)ketamine. The results could facilitate the identification of individuals with depression who are most likely to benefit from (es)ketamine treatment and enhances the neurobiological understanding of the antidepressant efficacy.

Scientific Abstract:

Background: Ketamine and esketamine represent efficacious pharmacological treatments for around 20-50% of the individuals with depression who have not responded to conventional antidepressant treatment. Brain-derived neurotrophic factor (BDNF) plays a central role in the mechanism of action, including the reversal of neuronal atrophy in brain regions involved in mood regulation. In relation, an increase in the serum and plasma levels of BDNF has been proposed as a potential biomarker of the antidepressant response.
Objective: Investigate whether baseline and longitudinal changes in BDNF levels are associated with the antidepressant response to ketamine and esketamine in individuals with depression.
Study Design: Systematic review and meta-analysis.
Participants: Adults with a primary diagnosis of unipolar or bipolar depression.
Primary and Secondary Outcome Measure(s): The primary outcome are baseline and longitudinal changes in BDNF levels and antidepressant response. Secondary outcomes include the following potential effect modifiers: administration route, blood fraction, primary diagnosis, overall risk of bias, and BDNF assessment time.
Statistical Analysis: Random-effects models will be utilized to investigate baseline and longitudinal changes on BDNF levels in responders and non-responders using standardized mean differences (SMD) and 95% confidence intervals (CI). Heterogeneity (I^2), publication bias (funnel plots, Egger's tests) will be additionally examined. Meta-regressions will be performed to identify potential effect modifiers.

Brief Project Background and Statement of Project Significance:

Depression is one of the most common psychiatric disorders worldwide (1). Importantly, around 20 to 30% of the individuals treated for depression do not achieve a clinically relevant treatment response following sequential treatment with at least two antidepressant agents provided at an adequate dose and treatment duration, commonly classified as treatment-resistant depression (TRD) (2). For these patients, intranasal (IN) esketamine represents a promising treatment approach, with studies showing rapid and substantial improvement in depressive symptoms compared to placebo (3,4).
Reduced neuroplasticity plays a crucial role in the pathophysiology and treatment of depression. In this context, brain-derived neurotrophic factor (BDNF), a protein that supports the survival of existing neurons and stimulates the growth of new neurons and synapses, is one of the most widely studied neurotrophins A recent meta-analysis of 97 studies demonstrated that the serum or plasma levels of BDNF in individual depression are significantly lower relative to healthy controls (5). In

relation, research suggests that an elevation in the serum and plasma BDNF levels represents a potential biomarker for antidepressant response to pharmacological antidepressant agents (6). Elaborating on research on monoaminergic antidepressant agents (6), recent studies have investigated BDNF as a potential biomarker of antidepressant response to (es)ketamine. A meta-analysis summarizing the effects of ketamine and esketamine on peripheral BDNF reported no significant associations between baseline levels of BDNF and antidepressant response (7). In contrast, the assessment of longitudinal changes demonstrated that peripheral BDNF levels following ketamine treatment significantly increased in responders but not in non-responders (7). While illustrating the potential relevance of BDNF as a biomarker of the antidepressant efficacy ketamine, the meta-analytic calculations were limited to studies administering intravenous (IV) ketamine, limiting the generalizability to other routes of administration.
Following the initial meta-analysis, a considerable number of studies investigating the influence of intranasal (IN), oral (PO), and IV (es)ketamine blood BDNF levels in the treatment for TRD have been published. The proposed meta-analysis therefore aims to provide an updated summary of the results of all available studies investigating whether (a) baseline serum or plasma levels of BDNF are associated with antidepressant response to ketamine and/or esketamine in individuals with depression; and (b) longitudinal changes in serum or plasma levels of BDNF are associated with antidepressant response to ketamine and/or esketamine in individuals with depression
The results of this meta-analysis will help to elucidate the relevance of BDNF as a biomarker for antidepressant response to ketamine and esketamine in the treatment of TRD. The findings will further contribute to the growing body of knowledge on the neurobiological mechanisms underlying the rapid antidepressant effects of ketamine and esketamine, potentially leading to more personalized and effective treatment approaches for TRD patients.

Specific Aims of the Project:

For the purpose of the proposed meta-analysis, we would like to obtain the results concerning the relationship between baseline and longitudinal changes in BDNF levels with antidepressant response, as reported in a published conference abstract (8).
The aim of the broader meta-analysis is to investigate whether (a) baseline serum or plasma levels of BDNF are associated with antidepressant response to ketamine and/or esketamine in individuals with depression; and (b) longitudinal changes in serum or plasma levels of BDNF are associated with antidepressant response to ketamine and/or esketamine in individuals with depression.
Based on the previous literature, we hypothesize that (a) baseline serum or plasma levels of BDNF are not associated with antidepressant response to ketamine and/or esketamine in individuals with depression; and (b) longitudinal changes in serum or plasma levels of BDNF are associated with antidepressant response to ketamine and/or esketamine in individuals with depression as demonstrated by a significant increase in responders but not in non-responders.

Study Design:

Meta-analysis (analysis of multiple trials together)

What is the purpose of the analysis being proposed? Please select all that apply.

Summary-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

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

Data Source
Based on the systematic literature search performed for studies to be included in the meta-analysis, the total sample size includes 741 participants from 14 different trials (8, 10-22). Data has been

obtained from the original publications or by contacting the authors.
Data from the YODA Project includes participants that received IN esketamine treatment in the double-blinded randomized controlled trials ESKETINTRD3001 (N = 233) and ESKETINTRD3002 (N = 114) with available data on BDNF levels.

Inclusion Criteria
Inclusion criteria for inclusion in the meta-analysis compromises (a) adult human subjects (i.e. individuals aged 18 years or older), (b) with a depression diagnosis, (c) assessment of BDNF levels pre- and post-treatment with ketamine or esketamine.
Exclusion Criteria
Exclusion criteria for inclusion in the meta-analysis include (1) individuals with depressive symptoms due to other disorders besides major depressive disorder or bipolar disorder, (2) concurrent neuromodulatory treatments including repetitive transcranial magnetic stimulation, electroconvulsive therapy, and vagal nerve stimulation (concurrent medications and psychotherapy are allowed), (3) individuals with serious comorbid medical or neurological diseases (e.g., cancer).

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

The primary outcomes for the meta-analysis are (a) BDNF baseline levels in responders and non-responders following (es)ketamine treatment, (b) longitudinal changes in BDNF levels in responders and non-responders following (es)ketamine treatment.
Deriving from the data from the trials ESKETINTRD3001 and ESKETINTRD3002, the primary outcomes will be (a) baseline BDNF levels in responders and non-responders, (b) changes in BDNF levels from baseline to day 25 in responders and non-responders. A previous conference abstract applied general linear modelling to the data from these trials to identify the relationship between BDNF levels and change in MADRS (8). However, SMD and CI cannot be derived from the published data. Therefore, the authors from the current meta-analysis aim to obtain this data through the YODA Project.

Secondary outcomes from the meta-analysis include meta-regressions with the following variables: administration route (single IV ketamine, multiple IV ketamine, oral esketamine, IN esketamine), blood fraction (serum versus plasma), primary diagnosis (unipolar versus bipolar depression), overall risk of bias, and BDNF assessment time (< 24 hours versus >= 24 hours).

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

The main independent variable is antidepressant response at treatment completion, defined as a >=50% reduction from baseline in depressive symptom scores on standardized rating scales such as the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D).

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

Other variables that will be used to characterize the study sample include demographic characteristics, namely, age (in years), sex (male versus female), and education (low, middle, or high); and clinical characteristics, namely depression severity (based on the Clinical Global Impression Severity scale and the 30-item Inventory of Depressive Symptoms scale) and level of treatment resistance (based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire).

Statistical Analysis Plan:

Pre-registration
The proposed meta-analysis is registered in PROSPERO under registration number CRD42025599356.

Systematic literature search
A systematic literature search was performed on MEDLINE (PubMed), the Cochrane Library, Embase, and Web of Science on 01 October 2024, with no restriction to language or publication date. Snowballing search through searches of references of review papers and grey literature were also conducted. The search strategy included 'BDNF', 'ketamine', 'depression', and related terms.
Titles and/or abstracts of studies retrieved using the search strategy and the snowballing search were screened independently by two review authors to identify studies that potentially met the inclusion criteria. The software Rayyan (https://new.rayyan.ai/) was used to facilitate the screening process. The full text of these potentially eligible studies were retrieved and independently assessed for eligibility by two reviewers. Any disagreement was resolved through discussion with a third reviewer. A standardized form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Two review authors extracted the data independently, and discrepancies were resolved through discussion with a third author when necessary.
Quality assessment
Risk of bias was determined by the Quality in Prognostic Studies (QUIPS) tool, which is a standardized assessment of six domains of bias (participants, attrition, prognostic factor measurement, outcome measurement, confounders, and analysis/report) as well as the overall risk of bias. Two reviewers independently assessed the risk of bias of the included studies, and disagreements were resolved through discussion with a third author when necessary.
Meta-analysis
If there are studies with overlapping samples, only the study with the largest sample will be included in the quantitative summary. Baseline levels and longitudinal changes of BDNF will be evaluated in responders and non-responders using standardized mean differences (SMD) and 95% confidence intervals (CI). SMD values of 0.2, 0.5, and 0.8 are considered thresholds for small, medium, and large effect size, respectively (9).
Random-effects models will be used as a significant degree of heterogeneity between studies is anticipated. Heterogeneity between studies will be examined using I^2, where values between 0 and 40% will be 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.
Publication bias will be visually assessed by inspection of funnel plots and objectively measured by Egger's tests. Meta-regressions will be performed to identify potential effect modifiers and individually examine the impact of (a) administration route (single IV ketamine, multiple IV ketamine, multiple oral esketamine, multiple IN esketamine), (b) blood fraction (serum versus plasma), (c) primary diagnosis (unipolar versus bipolar depression), (d) overall risk of bias based on QIPS, and (e) BDNF assessment time (< 24 hours versus >= 24 hours). Statistical analyses will be performed using the software R studio version 4.0.3.

Software Used:

R, RStudio

Project Timeline:

- Data extraction of studies include in the meta-analysis: from 01 November 2024 to 01 September 2025
- Data analysis: from 01 September 2025 to 01 October 2025
- Manuscript writing: from 01 July 2025 to 01 November 2025
- Results reported back to the YODA Project: 01 December 2025
- Manuscript submission: 01 Janury 2026

Dissemination Plan:

The project is expected to result in the publication of a scientific article in a high-quality peer-reviewed journal in the field of psychiatry or psychopharmacology. Potential suitable journals for submission include Molecular Psychiatry, Biological Psychiatry, Lancet Psychiatry, Psychiatry Research, the Journal of Psychopharmacology, and the Journal of Clinical Psychiatry

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