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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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/10/conflictofinterest_malestroit.pdf
https://yoda.yale.edu/wp-content/uploads/2023/10/conflictofinterestform_OLIE.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. NCT03097133 - 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
2. NCT03039192 - 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

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

Research Proposal

Project Title

Association between the reduction of Suicidal ideation, Anhedonia and Psychological pain in patients treated by intranasal esketamine

Narrative Summary:

Suicidal depression, i.e. depression with active suicidal ideation (SI), carries an increased high risk of suicide, worsened depressive symptoms, and poorer efficiency to standard antidepressants. Beyond its rapid antidepressant effect, intranasal (IN) esketamine rapidly reduces the intensity of SI effect up to 25 days. We aim to 1) assess its effects on hopelessness, psychological pain and anhedonia, which are predictive of future suicidal act and 2) determining their role in the anti-SI effect. Understanding its effect on these dimensions could provide valuable insights into improving treatments for suicidal depression and help in identifying patients who will benefit most from treatment.

Scientific Abstract:

Background: Suicidal depression, marked by active suicidal ideation (SI), carries a high suicide risk and often resists conventional antidepressants. The ASPIRE studies examined the anti-SI effects of IN esketamine (84 mg) versus placebo, administered biweekly for four weeks, in suicidal, depressed patients. IN esketamine yielded higher resolution of suicidality, with 34.5% vs. 32.9% at 24 hours and 61.9% vs. 54.7% at day 25.
Objectives: 1) Analyze hopelessness, anhedonia, and psychological pain trajectories post-IN esketamine administration. 2) Evaluate baseline hopelessness, anhedonia, and psychological pain as predictors of SI reduction at 24h, 7 days, and 25 days. 3) Explore relationships between these dimensions and concurrent SI reduction. 4) Identify treatment responder profiles.
Study design: Case control study
Participants: 456 patients from both ASPIRE studies, aged 18-64, with severe unipolar depression (meeting DSM-5 criteria and MADRS >28), active SI, and intent.
Outcomes: Primary measures include anhedonia (MADRS items), psychological pain (SIBAT items), and hopelessness (Beck Hopelessness Scale). Secondary measures involve suicidal ideation (MADRS suicidal item) and alternative assessments (FoST).
Statistical analysis: Esketamine’s effects on anhedonia, psychological pain, and hopelessness will be estimated via mixed-effect models. Linear/logistic regression models will assess the predictive value of initial dimension levels on SI improvement at critical time points. Mediation analysis will explore these dimensions as mediators between treatment and SI reduction.

Brief Project Background and Statement of Project Significance:

Suicidal depression (depression with active suicidal ideation (SI)) appears to be a specific phenotype with poorer response to conventional antidepressants (Nobile et al., 2022). Evolution of SI often follows the same pattern as depression, but is not overlapping (Batterham et al., 2019). Up to 10% of patients with suicidal depression report persistent SI after 6 weeks of antidepressant treatment, despite improvement in depressive symptomatology (Nobile et al., 2020). The development of molecules specifically targeting SI, a suicide risk factor (Franklin et al., 2017) is therefore necessary. Administration of intravenous (IV) ketamine has demonstrated a rapid (within 24h) anti-SI effect lasting up to 7 days (Wilkinson et al., 2018), partially depending on its antidepressant effect (Grunebaum et al., 2018). The anti-SI effect of a 4 week treatment of Intranasal (IN) esketamine has been reported up to 25 days (Canuso et al., 2021) but results were not controlled for level of depressive symptoms. The anti-SI effect may be related to antidepressant effect but also to its

action on dimensions of interest such as anhedonia and psychological pain.
Indeed, IV ketamine has also been shown to reduce intensity of anhedonia which is associated to SI and future suicidal behaviors. Indeed IV ketamine reduces anhedonia independently of depression (Ballard et al., 2017; Delfino et al., 2021; Vieira et al., 2021), amplifying the rapid anti-SI effect (Ballard et al., 2017). Moreover, a mediation effect of psychological pain on anti-SI effect of IV ketamine has been suggested (Abbar et al., 2022). Similarly, a better understanding of anti-SI of esketamine is critical by identifying its impact on clinical psychological pain, anhedonia and hopelessness and their mediation effect on anti-SI effect. Regarding the high cost of IN esketamine and its strict monitoring, it would be important to determine predictive factors of anti-SI effect, i.e. sub-groups of patients who could benefit from IN esketamine.
The originality of this project relies on the re-analysis of data on Aspire studies in order to identify the impact of IN esketamine on dimensions of interest in suicidal risk. We hypothesize that our results may have an impact on management of SI by identifying dimensions involved in anti-SI effect of IN esketamine and to identify clinical profile of treatment responders to better guide prescribing IN esketamine.

Specific Aims of the Project:

This project aims to investigate the treatment effect and predictive factors for SI improvement during Aspire studies' double-blind phase. The primary objective is to analyze hopelessness, anhedonia, and psychological pain trajectories post-IN esketamine..
Secondary aims:
1. Evaluate if baseline hopelessness, anhedonia, and psychological pain predict SI improvement at key time points (24h, 7days, and 25 days after the first dose).
2. Explore the relationships between the reduction in the aforementioned and concurrent SI reduction at the same intervals..
3. Identify unique treatment responder profiles through a comprehensive analysis of clinical and socio-demographic data.
Main hypotheses:
• Hypothesis 1: IN esketamine administration reduces anhedonia and psychological pain levels but will not significantly impact hopelessness.
• Hypothesis 2: Baseline psychological pain and anhedonia predict IN esketamine's anti-SI effect independently of baseline depression levels..
In sum, these specific aims and hypotheses aim to shed light on the treatment dynamics and predictors of therapeutic response in the context of suicidal depression, ultimately contributing to our understanding of effective intervention strategies for individuals experiencing SI.

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

Research Methods

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

Inclusion criteria:
Patients included in the ASPIRE I (Fu et al., 2020) and II (Ionescu et al., 2021) projects:
- Men or Women aged between 18 and 64
- Current diagnosis of major depressive disorder
- Active suicide ideation and suicidal intent within the last 24 hours
- Clinical need for psychiatric hospitalization due to imminent suicidal risk
- MADRS score strictly greater than 28
Exclusion criteria:
- Presence of bipolar disorder, obsessive-compulsive disorder, antisocial or borderline personality traits

- Presence of a moderate to severe substance or alcohol use or abuse disorder in the past 6 months, or a positive test for Phencyclidine, Cocaine or Amphetamines.

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

To fulfill our primary objective, specific outcome are:
(1) anhedonia assessed by items 5, 7, 8, and 10 from the Montgomery-Åsberg Depression Rating Scale (MADRS)(Borentain et al., 2022).
(2) psychological pain assessed by items from the Suicide Ideation and Behavior Assessment Tool (SIBAT). A preliminary study has substantiated that SIBAT includes items describing the main dimensions of psychological pain (Lengvenyte et al., 2020). We identified items 1, 8, 5, 18, 6, 9, 13, 15, 17, 32, 4, 11, 12, 22 from module 2, and items 38, 4, 24, 19, 26, 29, 44, 13, 10, 17, 18, 30, 35, 45, 3, 11, 14, 15, 38, 28, 47, 7, 20, 39, 2, 34 from module 3.
(3) hopelessness assessed by the Beck Hopelessness Scale (BHS).
For our secondary objectives, suicidal ideation (SI) will be assessed using the MADRS suicidal item (continuous or categorical (<2 and >= 2)). Additionally, we will explore the possibility of obtaining congruent results through alternative measures, including the Clinical Global Impression-Severity Scale-Revised (CGI-SS-r), the clinician-reported Frequency of Suicidal Thinking (FoST), and patient-reported FoST from SIBAT.

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

For the main objective, our primary dependent variable will be the allocation group, which comprises two categories (placebo and esketamine). This categorization enables us to explore the differential effects of these two treatment conditions.
For our second hypothesis, we will focus on baseline levels of anhedonia, hopelessness, and psychological pain (defined as described above). These predictors have been selected based on their theoretical relevance to our research questions and their potential influence on the outcomes of interest. By carefully categorizing and defining these dimensions, we aim to gain a deeper understanding of how they may shape and interact with the treatment.

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

Within our analytical framework, we will incorporate several other variables of interest to ensure a comprehensive exploration of our research objectives. 1) we will consider the level of depression (MADRS) as a continuous measure; 2) we will consider standard-of-care antidepressant as randomized as a categorical variable. The "standard-of-care antidepressant" category will encompass participants undergoing either antidepressant monotherapy or an antidepressant combined with augmentation therapy. 3) given that studies are conducted across multiple research centers, we will include the variable "center of analysis" as a categorical factor.
4) Demographic characteristics (items 1,3,6,7,8,9 from SIBAT Module 1) and baseline clinical ratings (depression severity with MADRS total score, suicidal ideation with the MADRS item), group of allocation (esketamine or placebo), history of suicidal attempt (according to SIBAT module 1 : item 18l-x; SIBAT Module 4 : item 3-10, 13a; SIBAT module 3 : item 26, 21; SIBAT module 5 : items 1-5) and psychiatric history (SIBAT module 1 items 15, 15a) will be used to characterize the study sample.

Statistical Analysis Plan:

The first step involves data recovery and standardization between the two studies, including variable selection, calculation, qualitative variable grouping, and quantitative variable transformation if necessary. Missing data will be addressed if required.
The statistical analysis comprises several components:
1) Focus on constructing psychological dimensions, primarily centered on anhedonia and psychological pain scores using MADRS and SIBAT questionnaires. Confirmatory Factor Analysis will

identify components based on MADRS and SIBAT items. This model will calculate anhedonia and psychological pain scores at inclusion and during follow-up.
2) Estimate the effect of Esketamine treatment on anhedonia, psychological pain, and hopelessness using mixed-effect models for repeated measures (MMRM) on observed case data. Factors include baseline scores, time point, treatment, analysis center, SOC antidepressant treatment as randomized, and day-by-treatment interaction.
3) Assess predictive value using linear or logistic regression models, depending on the outcome variable chosen, for improvement in SI at critical time points (24 hours, 7 days, and 25 days). Incorporate covariates from previous analyses as adjustment factors.
4) Building upon the findings from our initial objectives and drawing insights from the existing literature (Abbar et al., 2022), our statistical analysis plan will investigate the mediating effects of anhedonia and/or psychological pain on the anti-SI effect of esketamine. Mediation analysis will determine whether anhedonia and/or psychological pain are intermediate variables between esketamine and the SI reduction. This effect will be determined by an intra-individual multiple mediation analysis including anhedonia and psychological pain as mediators of the treatment effect on the SI reduction at 24h, 7 days and 25 days after the first administration of treatment. Indirect effects will be estimated by the product method and confidence intervals will be estimated by parametric Bootstrap (Montoya & Hayes, 2017).
Additional analyses may be considered to clarify and confirm the links assessed by the mediation analysis: The hypothesis that the effect of treatment on the evolution of SI would be enhanced by a strong reduction in the level of anhedonia (or psychological pain), will be tested by evaluating an interaction effect between treatment and variation in anhedonia (or psychological pain) during follow-up. This analysis will be carried out using linear mixed models (or generalized models, depending on the type of variable to be explained) including an individual random effect and an F-test (or likelihood ratio test). Beta intra-individual effects will be estimated, as well as marginal means, evaluated for treatment groups and for different levels of anhedonia and psychological pain. The estimators will be accompanied by their 95% confidence intervals. Where the effect of the interaction is significant, post-hoc tests comparing the levels of suicidal ideation for each treatment x anhedonia level (or treatment x psychological pain) combinations will be calculated. The p values will be corrected for multiple testing.
More exploratory, unsupervised analysis of joint trajectories (Anhedonia, psychological pain and suicidal ideation or depression) during follow-up (Genolini et al., 2013) will make it possible to identify and test the association between Esketamine treatment and particular trajectories for which mediators and judgment critera show a joint improvement over the 25 days. The different trajectory groups can be characterized according to clinical and socio-demographic variables. A multinomial model describing the probability of belonging to a particular trajectory group depending of treatment can be used to estimate adjusted Odds ratios and their confidence intervals. A likelihood ratio test will be used to establish the significance of association between treatment group and trajectory group.

Software Used:

RStudio

Project Timeline:

We plan to begin the project November 15th, 2023 with data management for one month. We plan to run analyses on January 2nd, 2024 and to draft the manuscript at the beginning of May 2024 with a report of results to YODA Project in June 2024

Dissemination Plan:

We plan to submit the related manuscript to a journal of psychiatry : Journal of Clinical Psychiatry, European Psychiatry or Psychiatric Research.

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