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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/yoda_coi_george_i_papakostas.pdf  
https://yoda.yale.edu/system/files/yoda_coi_anna_feeney_2.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. NCT02918318 - 54135419TRD2005 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study
What type of data are you looking for?: Full CSR

Project Title

Rapidity of Symptom Improvement with Intranasal Esketamine for Major Depressive Disorder: A Systematic Review and Meta-analysis

Narrative Summary:

Rapid-acting treatment options are needed for depression. The objective of this systematic review and meta-analysis was to assess the treatment effect of intranasal esketamine compared to placebo at 24 hours after the first dose and at study endpoint. To complete the meta-analysis, we compiled data from a number of clinical trials which examined intranasal esketamine and synthesized the results. This research was submitted for publication and it has been suggested that some additional data be added to the paper to enhance it. This research will help clinicians to consider the role of intranasal esketamine in treating patients with depression.

Scientific Abstract:

Background: Rapid-acting treatment options are needed for MDD (Major Depressive Disorder). Significant progress has been made in understanding the potential of ketamine and its s-enantiomer, esketamine, as rapid-acting antidepressants.

Objective: The objective of this study was to estimate the magnitude of the treatment effect for intranasal (IN) esketamine over placebo at 24 hours post first dose and at study endpoint.

Study design: This was a systematic review and meta-analysis of randomized double-blind controlled trials comparing adjunctive treatment of standard antidepressants with IN esketamine versus placebo in subjects with MDD.

Participants: This analysis included participants from randomized, double-blind clinical trials comparing adjunctive treatment of standard antidepressants with IN esketamine for MDD. Studies of the following were excluded: patients with bipolar disorder, dysthymic disorder, psychotic MDD, minor depressive disorder, seasonal affective disorder, depressed patients with a specific medical condition, or active alcohol or substance abuse disorders.

Main outcome measures: Standardized mean difference (SMD) in change in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to study endpoint.

Statistical analysis: Estimates of the SMD in MADRS score changes were pooled after examining for homogeneity. A random effects model was used for this meta-analysis.

Data Sources: PubMed, abstracts of major psychiatric meetings, and ClinicalTrials.gov were searched up to November 2020 with no language constraints, cross-referencing “intranasal” with: “esketamine” and “randomized”. Study Selection: Of 27 studies reviewed, eight articles, with a total of 1437 patients with MDD, met study criteria and were included in the meta-analysis.

Results: Augmentation of standard antidepressants with IN esketamine resulted in greater Montgomery-Asberg Depression Rating Scale (MADRS) score reduction than adjunctive intranasal placebo at 24 hours. Across the trials, the SMD was 0.34 (95% CI (0.11, 0.46), p<0.0001) with a 2.9-point greater mean MADRS score reduction following IN esketamine versus active control plus intranasal saline. A similar finding was evident at endpoint.

Conclusions: Augmentation of antidepressants with IN esketamine was statistically and clinically more effective in reducing depression severity than augmentation with placebo, at both 24 hours and study endpoint.

Brief Project Background and Statement of Project Significance:

This is a meta-analysis that has been submitted and provisionally accepted by the Journal of Clinical Psychiatry, pending revision. The peer reviewers requested some additional analyses be completed to enhance the paper. These analyses will require collection of some additional data points; we are requesting these specific data points here. This study will enhance our understanding of the benefit of intranasal esketamine over placebo at 24 hours.
post first dose and at study endpoint.

**Specific Aims of the Project:**

The primary aim of this meta-analysis is to estimate the magnitude of the treatment effect for intranasal esketamine over placebo at 24 hours post first dose. A secondary aim of this analysis is to estimate the magnitude of effect for IN esketamine versus control at study endpoint. This study will update a previous meta-analysis of this topic completed by our research group (1), by including additional studies published since our first meta-analysis.

**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 Methods**

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

**Data Sources:** PubMed, abstracts of major psychiatric meetings, clinicaltrials.gov.

**Inclusion/exclusion criteria:**

We selected randomized, double-blind clinical trials comparing adjunctive treatment of standard antidepressants with IN esketamine for MDD. Further, we selected studies that used IN placebo augmentation as a comparator. We then selected studies that also met the following inclusion criteria:

1) Studies that used either the HDRS (Hamilton Depression Rating Scale)(14), or the MADRS (Montgomery Asberg Depression Rating Scale)(15) as their primary outcome measure;
2) Studies that exclusively focused on patients with MDD.

Reports were excluded if they exclusively focused on the treatment of patients with bipolar disorder, dysthymic disorder, psychotic MDD, minor depressive disorder, seasonal affective disorder, depressed patients with a specific medical condition, or active alcohol or substance abuse disorders. Reports not describing original data (i.e. containing data published elsewhere) and those that were not focused on the acute phase of treatment (i.e. continuation, maintenance, relapse prevention) were excluded.

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

All in included studies used the MADRS as the main outcome measure.

Main outcome measure for this meta-analysis: standardized mean difference for intranasal esketamine versus control at 24 hours post first dose.

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

Mean baseline severity (baseline MADRS score)

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

One reviewer suggesting reporting Hazard Ratios for remission versus non-remission at 24 hours and endpoint. This reviewer also suggested a meta-regression analysis for baseline severity. In order to run these additional analyses, we are seeking the following specific data points:

- NCT02417064: remission at 24 hours (N, %) for placebo, 56mg esketamine and 84mg esketamine groups.
- NCT02418585: remission at 24 hours (N, %) for placebo and flexibly dose esketamine.
- NCT02918318: baseline MADRS (mean and standard deviation), remission at 24 hours (N, %), remission at study endpoint (N, %) for all groups- placebo, 28mg esketamine, 56mg esketamine, 84mg esketamine.

**Statistical Analysis Plan:**

The primary outcome of the meta-analysis was to compare the standardized mean difference in change in primary
outcome scores between adjunctive esketamine and placebo. To accomplish this, we pooled the estimates of standardized mean difference (SMD) in change scores after examining for homogeneity using the test statistic proposed by DerSimonian and Laird. We presented our final estimate the findings of the random effects model; this model is more conservative than the fixed-effects model and incorporates both within-study and between-study variance. Exploratory analyses included evaluating TRD and SI studies separately and evaluating studies by dose separately. All exploratory analyses were conducted in an identical fashion as the primary and secondary analyses. All analyses utilized the meta package of meta-analytic tools as implemented in Stata 15.

Software Used:
STATA

Project Timeline:

A manuscript describing this meta-analysis has already been reviewed by the Journal of Clinical Psychiatry and accepted pending revisions. The peer reviewers have suggested some additional analyses. We hope to re-submit to the JCP within a month once we have gathered the additional data suggested.

Dissemination Plan:

Readership of the Journal of Clinical Psychiatry.

Bibliography: