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Project Funding Source: Programme Hospitalier de Recherche Clinique, French Ministry of Health [Esketamine for "treatment resistant depression": an Individual Patient Data Meta-analysis: ESK-T-Dep]
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_fn.pdf
https://yoda.yale.edu/system/files/coi_cp.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

Efficacy of esketamine for "treatment resistant depression" assessed by MADRS score after at least 4 weeks, an IPD meta-analysis

Narrative Summary:

In 2019, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved a nasal spray formulation of esketamine for “treatment resistant depression” (TRD). However, the evidence base for its use proved to be controversial.

This study aims to independently reappraise the efficacy and safety of esketamine in TRD and to explore the effect of resistance stage and age as treatment effect modifiers with a meta-analysis of individual patient data.

The results will be of direct interest to national, European and American health authorities to help them assess whether the efficacy of esketamine adequately balances its safety concerns.
Scientific Abstract:

Background:
In 2019, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved a nasal spray formulation of esketamine for “treatment resistant depression” (TRD). However, the evidence base for its use proved to be controversial.

Objective:
This registered report aims to independently reappraise the efficacy of esketamine in TRD, by i) exploring the possibility of data integrity issues, ii) re-analyzing and iii) pooling the trial data. Main secondary objectives are to reappraise the safety of esketamine in the treatment of TRD and to explore whether esketamine’s efficacy and safety vary with level of treatment resistance and patient age.

Study Design:
Systematic review and meta-analysis of individual patient data derived from double-blind, randomised, placebo-controlled [placebo or active placebo] trials for the indication of TRD.

Participants:
All doubleblind, randomised, placebo-controlled trials of intranasal esketamine (with the following approved doses: 56 mg or 84 mg or “flexible” doses) for the indication of TRD.

Main Outcome Measure(s):
The primary outcome will be the MADRS score (continuous outcome) assessed after at least 4 weeks (the end of treatment in the pivotal initiation trials / it is expected to be 4 weeks but may be longer depending on the studies selected for the meta-analysis). To take into account the possible rapid effect of esketamine, we will also study the MADRS score at week 1 as a secondary outcome.

Statistical Analysis:
For efficacy and safety outcomes a two-step approach will be adopted. First, we will perform a reanalysis of each study. Then, a fixed effect meta-analysis, or a random effect meta-analysis (in case of heterogeneity), will be used to employed the different efficacy indexes derived from these re-analyses. Initiation and continuation design will be analysed separately. In order to explore the impact of resistance stage and age, a one stage IPD meta-analysis using a mixed model will be performed. If applicable (> 10 studies), we will use a funnel plot to look at small study effects. We will use GRADE to rate the overall certainty of evidence.

Brief Project Background and Statement of Project Significance:

In 2019, the Food and Drug Administration (FDA) approved a nasal spray formulation of esketamine for “treatment resistant depression” (TRD). Esketamine’s licensing application was granted “breakthrough designation”, an expedited review process for drugs “intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)” [1]. The European Medicines Agency EMA promptly followed and approved esketamine [2]. However, the evidence base for its use proved to be controversial, as outlined by Schatzberg [3], Gastaldon and colleagues [4] and in various comments by our group in the Lancet Psychiatry [5-8].

The randomised controlled trials (RCTs) barely demonstrate short-term benefits and did not investigate long-term efficacy of esketamine. Two [9, 10] out of the 3 pivotal initiation RCTs [9-11] failed to demonstrate that esketamine was superior to placebo [5]. For the first time for the FDA’s Division of Psychiatry Products, a continuation RCT was counted as a second positive pivotal trial. The FDA described in its assessment some possible data integrity issues for two trials [5]. For the continuation study, the FDA reported that “one site in Poland drives the overall study result due to a 100% rate of placebo arm relapses” [12]. After our pieces drew attention to this issue, the sponsor reported a sensitivity analysis [13]: the P-value changed from highly significant to “barely significant”. However, the sponsor did not explain why the FDA used the word “drives”, implying that its result was nonsignificant when this center was removed, nor why the FDA reported slightly different numbers of relapsed patients [8].
In August 2020, the FDA approved a supplemental New Drug Application for esketamine nasal spray (SPRAVATO). However, even the sponsor’s press release admits that “effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated” [14]. In contrast, a pharmacovigilance analysis showed that suicide ideation might be increased in people taking esketamine [15].

In UK, the National Institute for Health and Care Excellence (NICE), did not recommend its use [16]. In France, the “Commission de la transparence” expressed a favorable opinion for reimbursement for a subgroup of patients; an unfavorable opinion regarding reimbursement in the other indications and stressed that there was no clinical added value in the therapeutic strategy [17].

Based on these divergent viewpoints, concerns surrounding data integrity, and doubts about esketamine’s efficacy in TRD patients, an independent re-appraisal of the evidence is urgently warranted. An independent reanalysis and IPD meta-analysis will help resolve these uncertainties. These data will be of direct interest to national, European and American health authorities such as EMA and FDA. The exploration of efficacy/safety modifiers may help to better delineate the clinical indications of esketamine.

Specific Aims of the Project:

The main objective is to independently reappraise the efficacy of esketamine in TRD using an individual participant data meta-analysis methodology. The secondary objectives are to reappraise the safety of esketamine in the treatment of TRD and to explore moderating factors of esketamine efficacy and safety, including level of treatment resistance, patient age, site-specific effects, among others.

For the primary outcome, mean differences in MADRS scores observed will be calculated. Point estimates and confidence intervals will be compared with 0 (absence of difference) and 6.5 points (the threshold defined a priori in initiation studies).

Please find attached the protocol for more details. It is also registered on the Open Science Framework (https://osf.io/xetvn); and on Prospero (ID CRD42021290721, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=290721).

The protocol has been reviewed and accepted for publication (in-principal acceptance) at BMC Medicine as a registered report.

What is the purpose of the analysis being proposed? Please select all that apply.
- Confirm or validate previously conducted research on treatment effectiveness
- Confirm or validate previously conducted research on treatment safety
- Participant-level data meta-analysis
- Participant-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 source:
Systematic searches will be conducted by two independent researchers using PubMed, the Cochrane library, Embase, ClinicalTrials.gov, Clinicaltrialsregister.eu, FDA, EMA and the manufacturer website. Selection, coding and risk of bias assessment of the different study characteristics will be performed by two independent researchers in a blinded manner.

Inclusion/Exclusion Criteria:
We will consider studies that include all patients with TRD meeting the inclusion criteria of esketamine’s development program for this indication: depressive episode with inadequate response to at least two antidepressant trials of adequate doses and duration. There will be no age limit. In terms of strategy the systematic review search criteria will include all studies of esketamine for the primary treatment of depression. The IPD analysis will then be restricted to patients with TRD within the included studies. Included studies will be studies that compare the use of intranasal esketamine (56 mg or 84 mg or “flexible” doses) to a placebo. All randomised controlled trials (initiation and continuation trials) will be considered.
Main Outcome Measure and how it will be categorized/defined for your study:

The primary outcome will be the MADRS score (continuous outcome) assessed after at least 4 weeks (end of treatment in pivotal initiation trials). The possible rapid effect of esketamine will be assessed by the MADRS score at week 1 as a secondary outcome.

All of the following secondary outcomes will be assessed at end of treatment and at the last follow-up visit post-treatment in initiation trials; at the end of the study in continuation trials. Efficacy: suicide/suicide attempt (binary outcome); suicidal ideations, e.g. Beck Scale for Suicidal Ideation (BSS, continuous outcome); MADRS (continuous outcome, similar to the primary outcome but, here using the last follow-up visit post-treatment); remission (binary outcome); Sheehan Disability Scale (continuous outcome); PHQ-9 (continuous outcome); relapse (censored outcome) for continuation trials. Safety: serious adverse events (count outcome, events per patient); dropout for any cause (binary outcome); dropout due to adverse events (binary outcome); Adverse events (count outcome events per patient); Blood pressure (continuous repeatedly measured outcome); Dissociation (binary outcome); Sedation (binary outcome).

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

Reanalysis:
Same predictors as in the initial studies, at least the group (esketamine versus placebo).

Moderators of response to esketamine:
In order to study the impact of resistance stage and age, a one-step meta-analysis approach will be used: each participant will be classified according to Thase and Rush resistance stages in accordance with their baseline characteristics. This classification, as well as age of the patient will be explored as treatment effect modifiers in a one stage IPD meta-analysis using a mixed model.

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

Reanalysis:
For each RCT, we will explore a center effect by performing sensitivity analyses removing a center at a time.

Moderators of response to esketamine:
Sensitivity analysis will be performed to explore if efficacy varies according to the World Bank categorization into low, middle, and high income (https://data.worldbank.org/country) as initial evidence on antidepressants suggests that per capita gross national income is associated with trial results.

Statistical Analysis Plan:

Analysis strategy:
For efficacy and safety outcomes a two-step approach will be adopted, the a one-stage approach will be used to explore moderators of esketamine efficacy. All the analyses will be performed with R (R core Team, 2021).

Reanalysis:
First, we will perform a reanalysis of each study following the initial protocol of each study and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This first approach will allow for indepth description of any deviations from the protocol and for documentation of the data integrity issues mentioned in the FDA appraisal. For each RCT, we will explore a center effect by performing sensitivity analyses removing a center at a time.

Meta-analysis:
Then, a fixed effect meta-analysis, or a random effect meta-analysis (in case of heterogeneity defined as an I2 index > 25 % and/or detection of significant heterogeneity (p<0.10) detected using Cochran's Q test statistic), will be used to pool the different efficacy indexes (mean differences or relative risks or odds ratio or hazard ratios) that will be derived from these reanalyses. Initiation and continuation designs will be analyzed separately. For the primary outcome, mean differences in MADRS scores observed (point estimates and confidence intervals will be compared with 0 (absence of difference) and 6.5 points (the threshold defined a priori in initiation studies).
sensitivity analysis including the studies from which IPD are not available will be performed to explore the robustness of findings observed in the IPD meta-analysis. If applicable (> 10 studies), we will use a funnel plot to look at small study effects. We will use GRADE to rate the overall certainty of evidence.

Moderators of response to esketamine:
In order to study the impact of resistance stage and age, a one-step approach will be used: each participant will be classified according to Thase and Rush resistance stages in accordance with their baseline characteristics. This classification, as well as age of the patient will be explored as treatment effect modifiers in a one stage IPD meta-analysis using a mixed model. Another sensitivity analysis will be performed to explore if efficacy varies according to the World Bank categorization into low, middle, and high income (https://data.worldbank.org/country) as initial evidence on antidepressants suggests that per capita gross national income is associated with trial results.

Software Used:
RStudio

Project Timeline:

January 2022: Systematic review and request of the data
March 2022: Access to the individual patient data
April to November 2022: Analysis of the data
December 2022: Writing of the article
January to March 2023: Submission of the article and responses to reviewers
June 2023: End of data sharing (15 months after the beginning of the data sharing of all required trials)

Dissemination Plan:

We will make sure that our protocol is peer reviewed. For this reason, we have chosen to publish the study as a registered report. This approach eliminates many questionable research practices, including low statistical power, selective reporting of results, and publication bias, while still allowing flexibility to report serendipitous findings. In addition, the protocol will be registered on PROSPERO prior starting our research. All prespecified analysis plans and the code to reproduce our analyses will be shared on the Open Science Framework. We will indicate how to retrieve and access all the datasets as we did in a previous project [26]. Before submission of the final manuscript, results will be shared using a pre-print server (e.g. medRxiv) and will encourage peer review at this step. We will detail each step of the project in dedicated blogpost, on the ReiTheR website (https://www.reither.org/blog) and will invite comments.

Bibliography:

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8. Turner EH: Approval of esketamine for treatment-resistant depression - Author’s reply. The lancet Psychiatry 2020, 7(3):236.
12. Briefing Information for the February 12, 2019 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). [https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM630970.pdf]
14. Janssen Announces U.S. FDA Approval of SPRAVATO® (esketamine) CIll Nasal Spray to Treat Depressive Symptoms in Adults with Major Depressive Disorder with Acute Suicidal Ideation or Behavior [https://www.janssen.com/janssen-announces-us-fdaapproval-
spravator-esketamine-ciii-nasal-spray-treat-depressive-symptoms]
16. Mahase E: Esketamine for treatment resistant depression is not recommended by NICE. BMJ (Clinical research ed) 2020, 368:m329.
17. Avis de la commission de la transparence [https://www.hassante.fr/jcms/p_3192924/en/spravato]

Supplementary Material:

https://yoda.yale.edu/sites/default/files/registered_report_stage_1_acceptance.pdf