Principal Investigator

First Name: Benjamin
Last Name: Anderson
Degree: MD
Primary Affiliation: University of Connecticut School of Medicine
E-mail: benjamesanderson@gmail.com
State or Province: CT
Country: USA

General Information

Key Personnel (other than PI):
First Name: Grace
Last name: Chan
Degree: N/A
Primary Affiliation: UCONN Health
SCOPUS ID:
Requires Data Access? Yes

First Name: Andrew
Last name: Winokur
Degree: MD
Primary Affiliation: UCONN Health
SCOPUS ID:
Requires Data Access? Yes

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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/09/SV_57KskaKADT3U9Aq-R_T0ZgxtplTW3QO8V.pdf
https://yoda.yale.edu/wp-content/uploads/2023/09/YODA-COI-Winokur.pdf
https://yoda.yale.edu/wp-content/uploads/2023/09/YODA-COI-Chan.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. NCT02493868 - A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in 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

Effectiveness of Intranasal Esketamine in the Treatment of Patients with Treatment Resistant Depression: An Observational Study Based on Data Collected in a Spravato Treatment Program at the Institute of Living

Narrative Summary:

In 2019, Spravato (Intranasal Esketamine) was approved by the FDA for treatment resistant Major Depressive Disorder. The preceding clinical trials consistently demonstrated a clinically meaningful and statistically significant superiority compared with antidepressant and placebo, both in short term improvement (after 4 weeks), but also in delaying relapse in patients in stable remission or stable response after 16 weeks of treatment with esketamine and an oral antidepressant. Efficacy can be defined as performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance in real world conditions. Years of clinical research have demonstrated the efficacy of ketamine and esketamine in the treatment of depression, but it is important to evaluate the effectiveness of this intervention in the "real world" clinical practice. I have been involved in a clinical program at the Institute of Living/Hartford Hospital with intranasal esketamine for treatment resistant depression. I would like to compare the results of my patient outcomes/data to the data in the attached clinical trial. We are working with the sponsor (Janssen) on this project, and they directed us to you.

Scientific Abstract:

Background: Intranasal Esketamine has been approved in 2019 as adjunct for treatment resistant depression after years of clinical trials demonstrated it's clinically significant and statistically significant superiority when compared to an antidepressant and placebo. While its efficacy has been demonstrated through these clinical trials, it is important to consider it's effectiveness, specifically how it performs in the real world clinical setting.
Objective: To compare results from 50 patients in a Spravato clinic treated from 2021 to 2023 with results from the clinical trials
Study Design: Retrospective chart review
Participants: The first 50 patients with treatment-resistant depression who were treated with intranasal esketamine in the Spravato Treatment Program at the Institute for Living (IOL).
Primary Outcome Measures: Montgomery Asberg Depression Rating Scale (MADRS) scores pre-treatment, after induction phase (4 weeks), and at 16 weeks. No secondary outcome measures.
Statistical Analysis: Descriptive statistics (mean, standard deviation, median, range) and confidence intervals will be computed.
One sample tests used to determine whether real-world data is consistent with historical clinical trial results, using one sample t-tests.

Brief Project Background and Statement of Project Significance:

Major depressive disorder (MDD) is one of the most common mental health disorders in the US, with a lifetime prevalence of about 16% (Kessler et al., 2003) and is the leading cause of disability from a mental health disorder in the US and ranks second as a cause of disability overall after lower back pain (US Burden of Disease Collaborators, 2013), with lost workplace productivity costing billions of dollars (Greenberg et al., 2015).
For more than three decades, the term treatment-resistant depression (TRD) has been employed to describe a subset of depressed patients who manifest a more severe, impactful and, by definition, more difficult to treat form of depressive disorder. For example, studies have reported that, as

compared to typical MDD patients, hospitalized patients with TRD have 36% longer hospital stays (Amos et al., 2018) and a 7-fold higher suicide rate (Feldman et al., 2012). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, patients who had failed two previous adequate trials with standard antidepressant drug demonstrated a disappointing 13.7% remission rate after receiving a third antidepressant drug treatment trial. (Rush et al., 2006). These findings underscore the importance of identifying new and more effective treatment options for patients suffering with TRD.
Following on early promising pilot studies reporting the efficacy of intravenous ketamine administration to produce transient improvement in symptoms of depression in TRD patients, Janssen Pharmaceuticals undertook a full drug development initiative to explore the efficacy and safety/tolerability of esketamine in patients with TRD. On the basis of two pivotal Phase III clinical trials in TRD patients, esketamine (S-enantiomer of ketamine) nasal spray was approved by the FDA in March, 2019 for the management of TRD in adults, in conjunction with newly initiated or continuing treatment with a standard antidepressant drug. Published results from a Phase II clinical trial sponsored by Janssen Research and Development LLC reported that 36%-50% of TRD patients demonstrated a response to the administration of intranasal esketamine plus an oral antidepressant drug after two weeks of treatment, with response to treatment, defined as a 50% reduction from baseline in depression severity scores based on assessments with the Montgomery-Åsberg Depression Rating Scale (MADRS) (Daly et al., 2018). The MADRS is a validated depression symptom severity scale that has been used extensively in clinical trials for over three decades and was the primary outcome measure employed in these esketamine pivotal trials.
Clinical trials also showed that continued treatment with esketamine and an antidepressant drug demonstrated clinically meaningful and statistically significant superiority compared with antidepressant and placebo in delaying relapse in patients who had achieved stable remission or stable response after 16 weeks of treatment with esketamine and an antidepressant (Daly et al., 2019). Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under “real world” conditions (Revicki et al., 1999). Years of clinical research have demonstrated the efficacy of ketamine and esketamine in the treatment of depression, but it is important to evaluate the effectiveness of this treatment intervention in TRD patients being treated in “real world” clinical practice.

Specific Aims of the Project:

To evaluate the effectiveness and safety/tolerability of intranasal esketamine in the real world clinical setting, and compare these results to the results reported in the efficacy trials.
Specific Aims
Aim 1: To estimate intranasal esketamine’s effectiveness at the conclusion of a four-week induction phase [primary endpoint] and at the conclusion of a four-month induction (four-week) plus maintenance (three-month) phase [secondary endpoint] based on MADRS measured at baseline (pre-treatment), primary and secondary endpoints among 50 IOL participants in the Spravato Treatment Program.
Aim 2: To describe type and prevalence of emerging adverse events during the four-month treatment program.
Aim 3: To evaluate how well the estimated effectiveness and tolerance and safety profiles in this real-world data match the efficacy data in previous clinical trials in order to assess the efficacy-effectiveness gap. All data from the previous clinical trials will be de-identified. They will be obtained from YODA (Yale Open Data Access), which can be accessed through https://yoda.yale.edu. YODA on the NCT02493868 study will include the number of patients with TRD started on treatment with esketamine, as well as the numer of patients at week 4 and at week 16 who were categorized as "responders" and "remitters" following treatment with esketamine. This will be a limited data set and a de-identified data set.

We are asking the question about whether the observed efficacy of intranasal esketamine in the clinical trial setting can be generalized to the “real world” setting treating the general population with treatment resistant depression. We will compare the outcome measures (MADRS scale) in the clinical setting with the same scale used in the clinical trials. We will look specifically at MADRS scores pre-treatment, after 4 weeks of treatment, and after 4 months of treatment in our clinic, and compare to the clinical trial assessments at the same timepoints. This will answer the question about

whether the observed efficacy in the clinical trial setting can be generalized to the clinical setting.

Study Design:

Methodological research

Study Design Explanation:

MADRS total scores at each of the two endpoints will be used to determine if patients achieve remission [MADRS≤10] and changes in MADRS from baseline to each of the two endpoints will be computed, which will be used to determine if patients responded [50% or greater reduction from baseline].

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

Confirm or validate previously conducted research on treatment effectiveness

Research Methods

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

Human Subjects
Record inclusion criteria
Records of patients meeting all of the following criteria will be included:
• any gender
• any race/ethnicity
• ≥18 years old, with no upper limit
• in psychiatric treatment (medication management) for Treatment-Resistant Depression at the IOL Spravato Treatment program
• seen from March 1, 2021 and followed through July 15, 2023
Record exclusion criteria
Records of patients meeting any of the following criteria will be excluded:
• <18 years old
• Uncontrolled hypertension
• Active substance use disorder
• Pregnant/breastfeeding
• History of intracerebral hemorrhage, aneurysm, arteriovascular malformation

Date Use, Collection
All data will be extracted through Epic. The primary outcome measure will be the Montgomery-Åsberg Depression Rating Scale (MADRS) scores prior to and throughout treatment with intranasal esketamine. All patients whose records are eligible for this study received the MADRS at the time of intake and at all visits for treatment with Spravato.
Additional elements to be collected include medical record number (MRN), demographic characteristics such as age, gender, race and ethnicity, co-morbid psychiatric diagnoses, treatment duration, treatment response, oral antidepressant medication and remission.
Data analysis also will include review and analysis of the types of adverse events recorded at the intake visit and at all visits involving treatment with Spravato. Please refer to the data collection form for complete list of data points to be collected.
The study team will extract data from patient charts using a paper data collection form. Data then will be entered directly into an Excel database.

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

All data will be extracted through Epic. The primary outcome measure will be the Montgomery-

Åsberg Depression Rating Scale (MADRS) scores prior to and throughout treatment with intranasal esketamine. All patients whose records are eligible for this study received the MADRS at the time of intake and at all visits for treatment with Spravato. MADRS total scores at each of the two endpoints will be used to determine if patients achieve remission [MADRS≤10] and changes in MADRS from baseline to each of the two endpoints will be computed, which will be used to determine if patients responded [50% or greater reduction from baseline].
Additional elements to be collected include medical record number (MRN), demographic characteristics such as age, gender, race and ethnicity, co-morbid psychiatric diagnoses, treatment duration, treatment response, oral antidepressant medication and remission. No secondary outcomes measures.
Data analysis also will include review and analysis of the types of adverse events recorded at the intake visit and at all visits involving treatment with Spravato. Please refer to the data collection form for complete list of data points to be collected.
The study team will extract data from patient charts using a paper data collection form. Data then will be entered directly into an Excel database.

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

intranasal esketamine will be the independent variable. Dose will either be either 56mg or 84mg, schedule either twice weekly, weekly, every other week, or monthly.

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

None

Statistical Analysis Plan:

First, the distribution of patient characteristics (demographics, pre-treatment and during treatment clinical) will be examined. This will help the detection of outliers or unusual cases and the evaluate whether assumptions of parametric methods are met and when nonparametric methods should be used instead. Second, patients' MADRS total scores at each of the two endpoints will be used to determine if patients achieve remission [MADRS≤10] and changes in MADRS from baseline to each of the two endpoints will be computed, which will be used to determine if patients responded [50% or greater reduction from baseline].
Since this is a single-arm observational study and its objective is to compare real-world data against historical clinical trial data, one-sample statistical methods will be used.
For continuous outcomes of interest (mean change of MADRS total score from baseline to each of the two endpoints), descriptive statistics (such as mean, standard deviation, median, and range) as well as confidence intervals for the location of center (mean and median) will be computed. For dichotomous outcomes of interest (response and remission at each of the two endpoints, and specific adverse events throughout the four-month treatment period), descriptive statistics (such as frequency and percentage) as well as confidence intervals for the proportion will be computed.
One-sample tests will be used to determine whether the real-world data is consistent with the historical clinical trial results. For continuous outcomes, either one-sample t-tests or Wilcoxon signed rank tests will be used. For dichotomous outcomes, binomial proportion tests will be used

Software Used:

Open Office

Project Timeline:

12 months

Dissemination Plan:

To be determined, most likely plan to publish in reputable psychiatric journal(s), probably ones that focus on mood disorders and psychopharmacology.

Bibliography:

References

Amos, TB, Tandon, N, Lefebvre, P, Pilon, D, Kamstra, RL, Pivneva, I, Greenberg, PE. Direct and indirect cost burden and change of employment status in treatment-resistant depression: A matched-cohort study using a US commercial claims base. J Clin Psychiatry 79(2):24-33, 2018.

Daly, E, Singh, J, Fedgehin, M, Cooper, M, Lim, P, Shelton, R, Thase, M, Winokur, A, Van Nueten, L, Manji, H, Drevets, W. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression. Results of a double-blind, doubly-randomized, placebo-controlled study. JAM A Psychiatry, 75(2):139-148, 2018.

Daly, E., Triveldi, M., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A., Hough, D., Thase, M., Zajecka, J., Winokur, A., Divacka, I., Fagiolini A., Cubala, W., Bitter, I., Blier, P., Shelton, R., Molero, P., Manji, H., Drevets, W., Singh, J., Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment in Relapse Prevention in Patients with Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry, 76(9):893-903, 2019.

Feldman, RL, Dunner, DL, Muller, JS, Stone, DA, Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. J Med Econ 16(1):62-74, 2013.

Greenberg, P.E. Fourmier, A.A., Sisitsky, T., Pike, C.T, Kessler, R.C., 2015. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J. Clin. Psychiatry 70, 1128-1137.

Kessler, R.C., Berglund, P., Demler O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., National Comorbidity Survey Replication, 2003. The epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R). JAMA 289, 3095-3105.

Janssen Pharmaceuticals, Inc. SPRAVATO (Esketamine) Nasal Spray, CIII, 2019. Prescribing Information, revised 05/2019. Available at https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf

Popova, V., Daly E., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M., Shelton, R., Molero, P., Vieta, E, Bajbouj, M., Manji, H., Drevets, W., Singh, J., Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined with a Newly Initiated Oral Antidepressant in Treatment Resistant Depression: A Randomized Double Blind Active Control Study. Am. J. Psychiatry 176:6, June 2019.

Revicki, D.A., Frank, L., Pharmacoeconomic evaluation in the real world. Effectiveness vs efficacy studies. Pharmacoeconomics 1999; 15: 423-434.

Rush, AJ, Trivedi, MH, Wisniewski, SR, Nirenberg, AA, Stewart, JW, Warden, D, Nierderhe, G, Thase, M E, Lavori, PW, Lebowitz, BD, McGrath, PJ, Rosenbaum, JE, Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry 163(11):1905-1917, 2006.

U.S. Burden of Disease Collaborators, 2013. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 310, 591-608.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2023/09/Anderson-et-al-esketamine-protocol-final-8-14-23.docx

https://yoda.yale.edu/wp-content/uploads/2024/02/Protocol-Amendment-2-13-24.docx