**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**

**Introduction/Background**

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.

**Purpose/Aim**

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](https://urldefense.com/v3/__https:/yoda.yale.edu__;!!KCs9X-8!cwgslipfuMa5I8E_Z592SSClo3iO-QBwCEO5QLNXkmX_BQw93nB-F5eRjWl8etKbdHZeJ-ZnM_jMHzQjZvz0wrNTym2JoA$)**.  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.

Exploratory Aim: To examine whether patient characteristics affect their responses and occurrence of adverse events in this real-world study.

**Research Question**

While esketamine’s efficacy has been consistently demonstrated in clinical trial efficacy studies, what is the effectiveness of esketamine the treatment of TRD patients in a real world clinical setting?

**Study Design**

This study will be conducted as a retrospective chart review of 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).

**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.

**Data Storage and Security**

Only the specific protected health information (PHI) necessary to conduct the study [MRN, age ≤90 (if applicable)] will be collected; no patient names or dates of birth will be collected. All data will be coded with a unique study ID number. The research team at HHC/IOL will maintain a master list with the MRN and subject ID. The study database will be accessed by HHC and UCH study personnel, and will use only the subject ID number. The master list will be linked only by the subject ID and will be maintained on a secure HHC network server apart from the coded database.

The data will be stored with encryption and only the study investigators will have access to the data. Data will not be stored in any form on portable media without encryption. All electronic data collected will be stored on secure, encrypted, password-protected computers. All hardcopy (paper) data collected will be securely stored in double-locked research offices/filing cabinets. All data will be maintained for six years.

**Power Analysis and Sample Size Estimate**

Although the design of this observational study is every similar to the early, pre-randomization phases of one of Janssen’s Phase 3 clinical trial - NCT02493868, results needed for this observational study were not included in Daly et al. (2019) as the trial’s focus was relapse prevention. Historical clinical trial results reported in Daly et al. (2018), NCT01998958, a safety and efficacy phase 2 study, were used to guide this power and sample size analysis. However, a collaborative arrangement with Janssen is being discussed and actual historical results from NCT02493868 will be used to compare with real-world data. At that time, a modification will be submitted to the IRB and a copy of the collaborative agreement will be provided.

Table 1 in Daly et al. (2018) reported that the standard error of change in MADRS total score at various post treatment time points and at various esketamine doses to be approximately equal to 3 for n = 11 or 12. Assuming the standard deviation of mean change in MADRS total score approximately equal to 10 (3 x ), 50 patients will allow the estimation of mean change in MADRS total score with a margin of error at 95% confidence level as small as 3.5 points and has approximately 80% power to detect the differences in mean change of 4 points or more. This sample size will also allow the estimation of the proportion of various interested events (such as response, remission, adverse event) with a 15% margin of error at 95% confidence level and has over 80% power to detect the differences in proportion of 20% or more.

**Data and Statistical Analysis**

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 to achieve Aims 1 – 3.

To achieve Aims 1 and 2: 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.

To achieve Aim 3 when it is approved by the IRB: 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.

To achieve Exploratory Aim: Analyses of variance or covariance and logistic regressions will be used to assess the associations between patient’s response to the intranasal esketamine treatment and patient characteristics.

SAS 9.4 or later version will be used at the nominal 5% level of significance.

**Clinical Significance**

Findings from this study will increase general knowledge about the role of esketamine in clinical practice for patients with treatment-resistant depression.

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