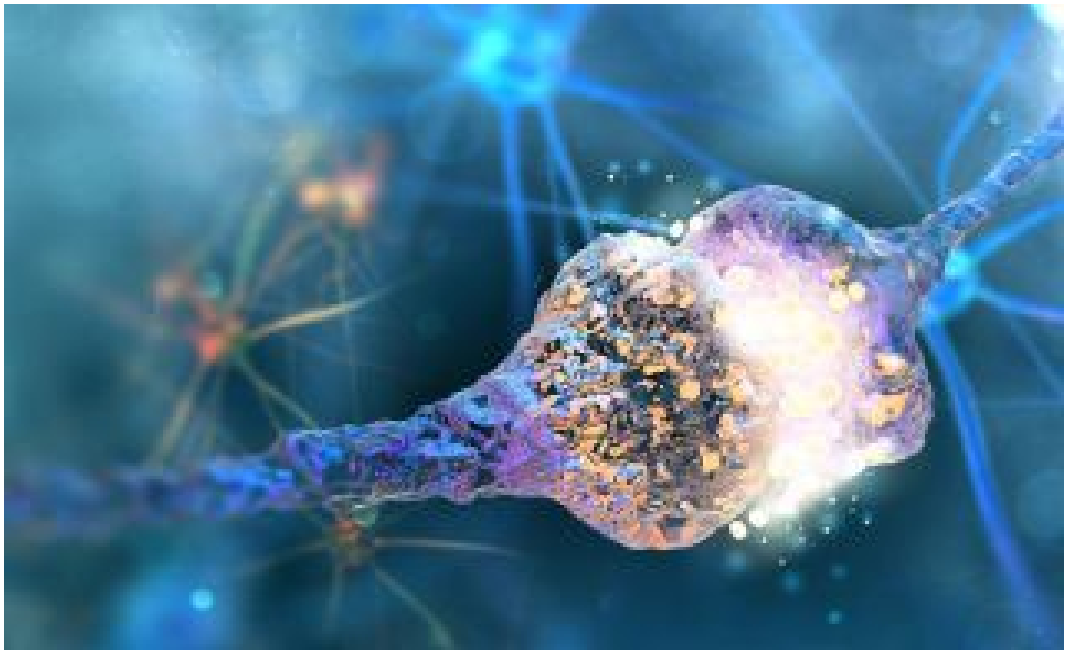
Association Between Body Mass Index and Treatment Response to Intranasal Esketamine in an Outpatient Clinical Setting



Dilan S Shah
TCU Burnett School of Medicine
January 31st, 2023

KEY:
Major Depressive Disorder (**MDD**); Treatment Resistant Depression (**TRD**); Quick Inventory of Depressive Symptomatology- Self Reported (**QIDS-SR**); Patient Health Quesstionnaire-9 (**PHQ-9**); Clinical Global Impression Scale (**CGI-S);** Generalized Anxiety Disorder 7-Item (**GAD-7**); Frontoparietal Network (**FPN**); Default Mode Network (**DMN**); Major Depression Episode (**MDE**).

TABLE OF CONTENTS:

1. Abstract

1.1 Research Question

1.2 Background, significance, and rationale

1.3 Materials and methods

1.4 Results

1.5 Conclusion

2. Research Questions & Aims

3. Introduction, Significance, and Rationale

3.1 Depression prevalence and impact

3.2 Pathophysiology and molecular mechanism of major depressive disorder (MDD)

3.2.1 Neurotransmitters

3.2.2 Neural circuitry

3.2.3 Social factors

3.2.4 Inflammatory markers

3.3 Treatment-resistant depression (TRD)

3.3.1 Impact of TRD

3.3.2 Pathophysiology of TRD

3.3.3 Proposed molecular mechanisms of TRD

3.4 Therapeutic interventions

3.4.1 Traditional pharmacotherapy for MDD

3.4.2 Traditional pharmacotherapy for TRD

3.4.3 Future treatments options for depression

3.5 Nontraditional therapies

3.5.1 Lifestyle modification

3.5.2 Psilocybin

3.5.3 Esketamine: a promising future

3.6 Ketamine

3.6.1 History of ketamine

3.6.2 Mechanism of action

3.6.3 Esketamine effect on neural circuits involved in depression

3.6.4 Safety concerns and adverse effects

3.7 Rational and purpose

4. Materials and Methods Approach

4.1 Patient population

4.2 Treatment protocol

4.3 Indexes of depression and suicidality

4.4 Demographic data and clinical items

4.5 Patient stratification

4.6 Data analysis

4.6.1 Efficacy of esketamine therapy after 8 treatments

4.6.2 BMI stratification and comparison

5. Results

5.1 PHQ-9

5.2 QIDS-SR

5.3 CGI-S

5.4 GAD-7

6. Discussion and Innovation

7. Future Directions

8. Conclusion

9. Compliance

10. References

1. Abstract

1.1 Research Questions

This study aims to determine if body mass index influences response rates of patients treated with intranasal esketamine after 8 treatments in the non-trial outpatient clinical setting.

1.2 Background, significance, and rationale

Major depressive disorder (MDD) is the most common psychiatric illness in the United States and presents with a significant economic, emotional, and healthcare burden. Treatment-resistant depression (TRD), a subset of MDD, is especially challenging to manage, with most current interventions proving largely unsuccessful at reaching long-term remission. Given that up to one-third of patients with MDD meet the criteria for TRD, there is a need for innovative approaches to helping this suffering patient population. Recently, intranasal esketamine was approved as the first mechanistically distinct medication for depression in over 50 years. Multiple proposed mechanisms of esketamine's anti-depressive functions exist, as do functional imaging studies that demonstrate the neurobehavioral changes of ketamine. The data and anecdotal evidence thus far are promising that esketamine can provide a real solution for patients with treatment-resistant depression. Work with intravenous ketamine has demonstrated a potential weight-based dosing effect with treatment. To the knowledge of the author, no similar work has been performed for intranasal esketamine to determine if BMI impacts treatment response. Further investigation will allow for the optimization of treatment regimens in the outpatient setting.

1.3 Materials and methods

This study is conducted as a retrospective chart review of more than 40 patients who received treatment with intranasal esketamine at the BL6 clinic at UT Southwestern medical center in Dallas, Texas. Inclusion criteria consist of patients aged 18 and older, with a primary diagnosis of major depressive disorder with failure of two or more oral antidepressants in the current depressive episode, and who have received intranasal esketamine for at least 8 treatments. All patients were treated with a 56mg starting dose of intranasal esketamine, unless otherwise specified, and received treatment at an escalated 86mg dose on a standardized 8-week schedule. The efficacy of treatment was determined by collecting survey data of indexes of depression and suicidality that are integrated into each patient's EPIC Flowsheet. These include the Patient Health Questionnaire

(PHQ-9), Quik Inventory of Depression Symptomology Clinical Rating/Self Reporting (QIDS-SR/C), the Clinical Global Impressions Scale (CGI), and the Generalized Anxiety Disorder 7-Item (GAD-7).

1.4 Results

After 8 treatments of intranasal esketamine, patients experienced a statistically significant reduction in the PHQ-9, QIDS-SR, and CGI depression questionnaires. The GAD-7 questionnaire likewise revealed a statistically significant reduction in anxiety symptoms after 8 treatments.

1.5 Conclusion

Prior to the stratification of BMI, analysis of efficacy on the full cohort of 40 patients deemed esketamine effective at reducing the severity of depression and anxiety. After stratification, observational results demonstrate some moderate changes in efficacy by BMI. No statistical analysis can support these observations due to the limited cohort size. Overall, the data provide no clear link that weight or BMI are linked to esketamine efficacy, echoing the results of the intravenous ketamine study.

2. Research Questions & Aims

Aim 1:

Determine if an 8-course treatment of esketamine effectively decreases the severity of depression and anxiety survey scores.

Hypothesis 1:

Patients will have a mean lower score after Treatment #8 of esketamine therapy than initially calculated on their pre-treatment surveys of PHQ-9, QIDS-SR, CGI-S, and GAD-7 questionnaires.

Aim 2:

How does body mass index affect the reduction of depression rating scales after 8 treatments of intranasal esketamine in a treatment-resistant depression population?

Hypothesis 2:

Patients with a higher body mass index will have a decreased response to esketamine treatment possibly due to the increased volume of distribution, altered metabolic profile, or another weight-based factor. Therefore, obese patients will have a lower *change from baseline* in the PHQ-9, QIDS-SR, and CGI-S.

Aim 3:

How does body mass index affect the reduction of anxiety rating scales after 8 weeks of intranasal esketamine in a treatment-resistant depression population?

Hypothesis 3:

Patients with a higher body mass index will have a decreased response to esketamine treatment possibly due to the increased volume of distribution, altered metabolic profile, or another weight-based factor. Therefore, obese patients will have a lower *change from baseline* in the GAD-7 questionnaires

Aim 4:

Observe the demographic and clinical characteristics of patients receiving intranasal esketamine treatment in the real-world clinical setting at UT Southwestern.

3. Introduction, Significance, and Rationale

3.1 Depression prevalence and impact:

Major Depressive Disorder (MDD) is the most common psychiatric disorder in the United States. In 2017, 17.3 million American adults, equaling 7.1% of the total population, experienced at least one major depressive episode. Of those individuals, 64% experienced severe functional impairment during their episode [1]. Patients suffering from depression experience sleep changes, anhedonia, feelings of low self-esteem, fatigue, difficulty concentrating, changes in appetite, impaired executive function, and are at higher risk for suicidal ideations [2].

Depression has made its way to the global stage and is now the leading cause of disability worldwide, sparking the World Health Organization to begin coordinated countermeasures to tackle this mental health pandemic. Domestically, depression acts as a significant economic burden on both the US healthcare system and the individual patient. In 2010, the economic impact of MDD was 210.5 billion dollars. Nearly half of that was attributed to direct medical costs and pharmaceutical usage, ~45% to workplace and larger economic impact of a depressed workforce, and 5% to suicide-related costs. While the distribution of cost impact varies, one study found that for each dollar spent on direct depression care, $4.70 is spent on the medical and social sequela of the disease [3, 4].

3.2 Pathophysiology and molecular mechanism of major depressive disorder (MDD)

3.2.1 Neurotransmitters

Depression has a heterogenous pathophysiology that goes far beyond early theories like the monoamine hypothesis. The early monoamine hypothesis was correct in that neurotransmitter levels in patients with depression do vary significantly from healthy controls. Recent work has shown that dopamine neurons are involved in signal reward prediction error, which impacts executive function and decision-making in depressed patients [5]. Similar paramount studies have elucidated the roles of other monoamines like serotonin and norepinephrine in depression symptomology [6]. Advances in the past two decades have catapulted the understanding of depression pathophysiology to new heights.

3.2.2 Neural circuitry

Variations in neurotransmitter levels have guided further studies of brain circuitry using functional imaging (fMRI). Patients with depression have consistently demonstrated specific abnormal resting state network connections. The brain of an MDD patient has hypoconnectivity within the frontoparietal network (FPN), a key player in executive function and control on emotion, hyperconnectivity within the default mode network (DMN), which is implicated in the agonizing cycles of rumination, and hyperconnectivity between these two networks (FPN and DMN)[7]. Nuanced variability in these circuits between healthy controls and patients with MDD demonstrates, for example, that depressed patients have maladaptive, depressive ruminations in the default mode network, while healthy controls utilizing the same network have adaptive, reflective ruminations [8].

3.2.3 Social factors

Socioeconomic risk factors of depression include education status, income, gender, race, and sexuality, to list a few. The interaction of these social factors can have a paradoxical relationship with the risk of major depression episode (MDE). For instance, higher income is found to be protective against MDE in white women but may predispose black men to a greater risk of MDE [9]. Certain abnormalities in brain connectivity are associated with these social factors and past life experiences. In fact, there is a strong association between childhood trauma and disruption of the architecture involved in various task-positive networks (DAN, FPN, CON) and sensory systems (AUD, VIS, and SMN) [10].

3.2.4 Inflammatory markers

Recent work into the mechanism of major depressive disorder has focused on identifying serum biomarkers of depression. Of note, are inflammatory factors like TNF-α, IL-6, BDNF, and IL-1β. All of which are consistently elevated in MDD and can be used to predict treatment response[11]. Levels of the sensitive but non-specific acute phase reactant CRP have been used to determine treatment response to SSRI monotherapy versus bupropion + SSRI combination therapy [12]. Therefore, a robust understanding of the pathophysiology of depression is derived from the complex interplay between brain activity, genetic predispositions, inflammatory markers, and other systemic bio-signatures, lifestyle choices, and environmental stressors.

3.3 Treatment-resistant depression (TRD)

3.3.1 Impact of TRD

Treatment-resistant depression is defined as the failure of a patient to respond to two or more depression therapies of adequate dose and duration. The suffering of patients with treatment-resistant depression is exacerbated due to increased healthcare utilization and subsequent higher overall medical costs. On average, patients with treatment-resistant depression spend between $4,000 and $8,000 more annually on medical therapy than their treatment-responsive counterparts [13]. This does not begin to account for the nonmedical economic and social burden of unremitting depression.

3.3.2 Pathophysiology of TRD

The pathophysiology of treatment resistant depression is highlighted again by functional imaging studies which identify variations between patients with refractory depression (treatment-responsive) and non-refractory patients (treatment-resistant). While refractory depression is associated with altered functional connectivity in the thalamo-cortical circuits, non-refractory depression shows greater decreased connectivity in the limbic-striatal-pallidal-thalamic circuit [7, 14]. All to say, the neural circuity undermining MDD and TRD may be vastly different, further challenging remission in TRD.

3.3.3 Proposed molecular mechanisms of TRD

Proposed mechanisms of treatment-resistant depression involve alternations to the extrasynaptic glutamatergic receptor pathways, dysfunction in glial cells, excessive early-life trauma, and glucocorticoid receptor dysfunction [9]. It has been proposed that single nucleotide polymorphisms of key molecules involved in the ideology of major depressive disorder, such as Catechol-O-methyltransferase (COMT), brain drive neurotrophic factor (BDNF), and norepinephrine transporters, to name a few, are involved in the pathogenesis of treatment-resistant depression [15, 16]. While the specific mechanism of TRD stills needs discovery, novel treatments, like esketamine, have been shown to modulate the interplay between these various factors [17].

3.4 Therapeutic interventions

3.4.1 Traditional pharmacotherapy for MDD

Though the understanding of depression has evolved in recent years, many of the therapeutic interventions have been steadfast for decades. The current gold standard for depression treatment involves a continuous trial and error process that can take months to perfect and often leaves patients frustrated and living with worsening depression and medication side effects. Common drugs include selective serotonin reuptake inhibitors (SSRIs) which require 4 to 8 weeks for appreciable effects. Tricyclic antidepressants (TCAs) inhibit 5-HT and norepinephrine reuptake but are associated with more overall side effects as well as severe side effects including coma and cardiotoxicity. Monoamine oxidase inhibitor's (MOIs) selectively increased levels of amine neurotransmitters like norepinephrine, serotonin, and dopamine. A myriad of atypical antidepressants can also be used with varying degrees of success [18].

3.4.2 Traditional pharmacotherapy for TRD

While all current antidepressant medications demonstrate favorable responses relative to placebo, none consistently cure patients with treatment-resistant depression. Before 2019, the only treatment approved by the FDA for treatment-resistant depression was a combination therapy of olanzapine and fluoxetine, branded Symbyax. This combination of an atypical antipsychotic and SSRI is moderately effective in managing TRD but presents with greater adverse effects than monotherapy, including increased body weight, increased prolactin concentration, and increased total cholesterol levels[19].

3.4.3 Future treatments options for depression

Recent advancements in depression research include identifying biosignatures or depression, using functional brain imaging to match patients with the correct medication, and even predicting depression before patients are symptomatic [11, 12, 20-22]. These innovations may one day bring a new wave of precision medicine depression therapies that far exceed today's standard approach. Nevertheless, the need for an effective, noninvasive, and widely available option for treatment-resistant depression is needed now.

3.5 Nontraditional therapies

3.5.1 Lifestyle modification

In addition to pharmacotherapy, prescribed aerobic exercise consistently reduces the Hamilton Rating Scale for Depression (HRDS) score for patients with mild to moderate depression. Similar work has also demonstrated the effective use of aerobic exercise for treating addiction disorders [23, 24]. The use of non-pharmacotherapy in treating mental illness, specifically depression, leaves room for promising new non-traditional therapies in the management of MDD. Though, there still exists a subset of patients with depression that is unresponsive to traditional pharmacotherapy and lifestyle modification.

3.5.2 Psilocybin

Due to the urgent need to address this growing public health crisis, alternative medical interventions have been receiving fast support from the Food and Drug Administration for the last 3 years. Most recently, intermittent psilocybin therapy for treatment-resistant depression has been granted "breakthrough status" by the FDA. Psilocybin is a 1A/2A serotonin receptor agonist that is administered orally and induces a psychedelic effect lasting several hours. The positive therapeutic effects for depression, as well as addiction, anxiety, and PTSD, last for several months after a single dose. Functional imaging of patients on psilocybin shows normalization of hyperactivity in the medial prefrontal cortex, and disruption of the default mode network (DMN) [25]. Converging evidence supports that the efficacy of "psilocybin-assisted psychotherapy" for depression is heavily influenced by environmental setting, mindset, and pre-session expectations [26]. Though psilocybin shows promise, and future investigations have been supported by the FDA, phase 2 trials are not expected to be complete until 2021. Other treatments for TRD are still needed.

3.5.3 Esketamine: a promising future

In March 2019, the FDA approved a nasal spray depression treatment for treatment resistant depression based on the analgesic ketamine: Esketamine, branded as Spravato by Janssen Pharmaceuticals. The drug has been approved for use under a "restricted distribution system" due to the lack of studies performed outside of the recently concluded phase 3 clinical trials and

uncertainty about the drug's mechanism of action. Nevertheless, esketamine therapy is the first mechanistically new fully FDA-approved medication for depression in fifty years.

3.6 Ketamine

3.6.1 History of ketamine

Ketamine has been used as an analgesic since the 1960s and is appreciated for its lack of respiratory depression. In the early 2000s, a single randomized control trial found that a subanesthetic dose of intravenous ketamine produced an antidepressant response in patients with MDD. Remission lasted for one week, but relapse was noticed within two weeks of a single dose [27]. Treatment with multiple doses of ketamine two or three times a week was more favorable for long-term remission. This response period was observed in patients with TRD as well [28].

While intravenous ketamine has a greater bioavailability, which is useful in the drug's first-pass metabolism, IV administration is not convenient or realistic for recurrent long-term care. Oral administration of ketamine has a low bioavailability of 24% while intranasal administration reaches a more acceptable bioavailability of greater than 45% [29]. Therefore, due to its greater bioavailability and clinical convenience, current use of therapeutic ketamine is administered intranasally.

3.6.2 Mechanism of action

The mechanism of action of ketamine differs from that of other monoaminergic antidepressant medications in that it affects glutamate receptor modulation. Standard ketamine is a racemic mixture of the S (Esketamine) and R (Arketamine) enantiomers. Esketamine acts as a strong non-competitive glutamatergic N-methyl- D-aspartate (NMDA) receptor antagonist by binding to the phencyclidine binding site [30].

While NMDA receptor antagonism is the best-understood mechanism by which esketamine provided depression relief, it is not the only hypothesized mechanism of the drug. Esketamine is thought to have a "dirty" mechanism of action by affecting multiple cell-signaling pathways and neurotransmitter-receptor interactions, again differentiating it from standard monoamine-modulating therapy. Other targets of ketamine and ketamine metabolites include receptors for γ-

aminobutyric acid (GABA), dopamine, serotonin, and opioid, as well as voltage-gated sodium channels [30].

Regardless of its molecular mechanism, treatment with esketamine enhances synaptogenesis and plasticity of neurons that are lost to the synaptic retraction observed in depression and chronic stress [31]. Ketamine administration incites a rapid regeneration of functional spine synapses in the prefrontal cortex in animal models. The molecular mechanism of this rapid synaptogenesis is due to ketamine's activation of the mammalian target of rapamycin (mTOR) pathway, which causes an increase in synaptic signaling protein expression. Directly blocking the mTOR signaling cascade completely blocks ketamine's effect on synaptogenesis and plasticity, further supporting the significance of this mechanism of action [32].

3.6.3 Esketamine effect on neural circuits involved in depression

Ketamine demonstrates a profound effect on neural circuitry at the molecular level by increasing plasticity and synaptogenesis, this can be observed by alterations to circuit connectivity on functional imaging. The distinction between the two enantiomers of ketamine becomes increasingly important when looking at the functional connectivity of the brain. Pharmacologic magnetic resonance imaging (phMRI) findings show that esketamine, but not Arketamine, elicits NMDAR antagonist-like brain activation. Furthermore, differential responses in the medial prefrontal, motor, cingulate, and somatosensory cortex regions as well as subcortical regions are noted between the two enantiomers [33].

3.6.4 Safety concerns and adverse effects

Adverse effects of esketamine treatment tend to last no more than 6 hours, occur on the day of the treatment itself and are typically mild to moderate in severity. These side effects include dissociation and a feeling of being drunk, dizziness, nausea, vomiting, anxiety, lethargy, sedation, and a transient increase in blood pressure and heart rate. The primary concern for intranasal esketamine treatment is its potential for abuse, given ketamine's history as a street drug used to induce an "out-of-body" dissociative state. Clinical use of esketamine though requires administration under the direct supervision of a clinician and monitoring for a minimum of 2 hours after the drug has been given. In addition to the risk of addiction and abuse, the long-term effects

of chronic ketamine usage include ulcerative cystitis and liver injury, though neither of these sequelae have been noted in patients treated with repeated doses of the esketamine enantiomer [34].

3.7 Rationale & purpose

The current study aims to determine if the UT Southwestern esketamine clinical service provides effective care for patients with treatment-resistant depression, accounting for the "real world" setting which may include patients who would not have qualified for the phase 2 and 3 clinical trials, and thus represent confounding variables that have yet to be identified in esketamine treatment. Answering this question and identifying "real world" variables that may affect esketamine efficacy, will refine which patient populations this time-consuming and resource-intensive procedure is indicated for. Results may also inform any modifications to the UT Southwestern esketamine treatment protocol.

Part of a "real-world" patient population includes a spread of patients with different body habitus. While most antidepressants are not dosed in a weight-based format for adults, research with intravenous ketamine, which is dosed by weight, has encouraged the researchers to examine this variable more closely. In a 2020 study by Lipsitz et al., investigators hypothesized that increased BMI would portend a better response to IV ketamine therapy as determined by similar depression and anxiety rating scales. Intravenous ketamine is delivered at weight-based dosing with the standard of practice being 0.5mg/kg for anti-depressive effects. The researchers ultimately found no statistically significant evidence that greater BMI, and therefore a higher ketamine dose, correlated with a greater reduction of symptom severity (Figure 1). The study followed patients in four BMI groups after four intravenous ketamine treatments. Given that intranasal esketamine (Spravato) is standardized regardless of body habitus, the authors determined that the present investigation was necessary to compare against the Lipsitz et al. intravenous findings. To the knowledge of the authors, no similar work has been done in the real work clinical setting to determine treatment response for intranasal esketamine by BMI.

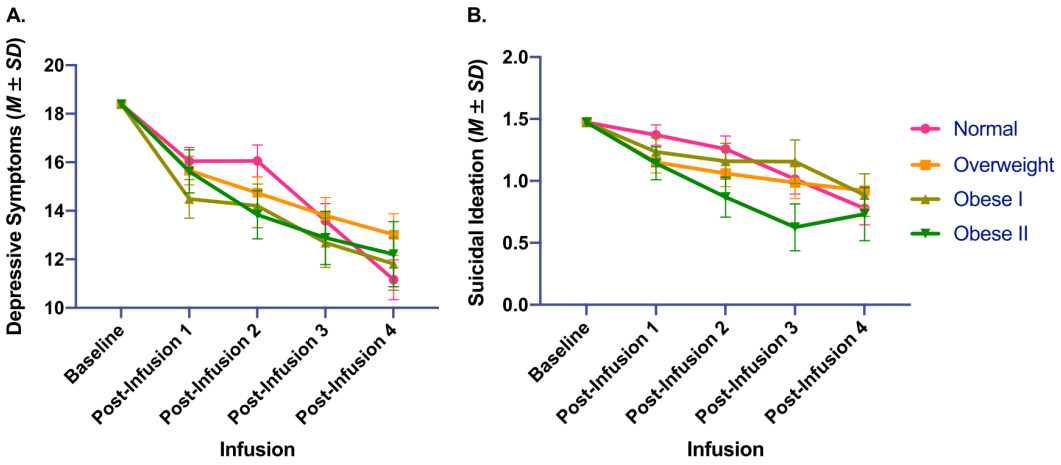


Figure 1. Changes in depressive symptoms (A) and suicidal ideation (B) (ie, measured by the Quick Inventory for Depressive Symptomatology-Self-Report 16 total score and suicidal ideation score) with repeated IV ketamine infusions, adjusted for baseline symptom severity, age, sex, and level of treatment resistance.

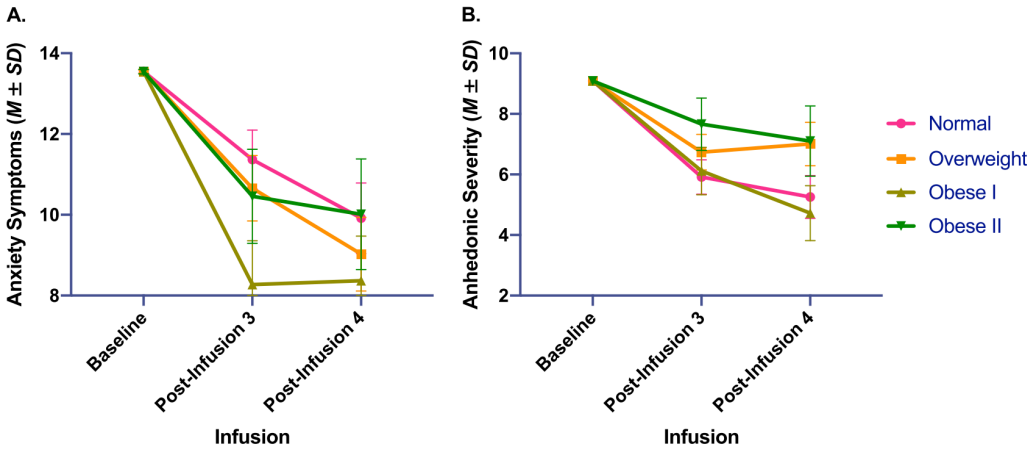


Figure 2. Changes in symptoms of anxiety (A; measured by Generalized Anxiety Disorder-7 scale) and anhedonic severity (B; measured by the Snaith–Hamilton Pleasure Scale) with repeated intravenous ketamine infusions, by BMI category, adjusted for baseline depression severity, baseline symptom severity, age, sex, and level of treatment resistance.

Figure 1. Adapted from Lipsitz et al (2020) demonstrating no statistically significant difference in treatment response to intravenous ketamine by body mass index across multiple depression and anxiety surveys.

4. Materials and Methods Approach

4.1 Patient population

Patients are 18 years and older with a primary diagnosis of Major Depressive Disorder with failure of 2 oral antidepressants in the current depressive episode who received esketamine through the UT Southwestern depression clinic. Certain restrictions have been placed on concomitant continuous medication use. Any history of aneurysmal vascular disorder or intracranial hemorrhage is exclusionary for esketamine treatment due to transient hypertension being a common side effect of Spravato. Pregnancy or active breastfeeding are exclusionary criteria, and heterosexual sexually active females are required to agree to use contraception during treatment. All patients received outpatient esketamine treatment at the BL-6 clinic at UT Southwestern Medical Center in Dallas, Texas.

4.2 Treatment protocol

New patients began with a 56mg dose of intranasal esketamine, unless otherwise specified by the treating clinician. Patients greater than 65 years of age warranted a 28mg starting dose. If the initial dose was well tolerated, patients were stepped-up to 84mg for the remainder of the acute phase of treatment. The acute phase of treatment consisted of patients receiving treatment twice a week, or at least every four days, for four weeks. After four weeks patient received treatment weekly for an additional four weeks. At the end of eight weeks, the patient and provider made a treatment plan that included weekly, biweekly, or monthly treatment, or discontinuation from the treatment plan altogether.

4.3 Indexes of depression and suicidality

Depression-related outcome measures–include the Patient Health Questionnaire (PHQ-9), Quick Inventory of Depression Symptomology Clinical Rating/Self Reporting (QIDS-SR/C), and the Clinical Global Impressions Scale (CGI). These surveys were administered before and after esketamine therapy was initiated. Anxiety symptoms, which can be associated with depression, were tracked via the Generalized Anxiety Disorder 7-Item (GAD-7) questionnaire. All assessment scale data is available to access through the EPIC flowsheet. Clinical outcomes and efficacy of treatment were determined by improvement on these surveys.

The PHQ-9 survey measures depression severity on a scale of 1-27. A score of 1-4 indicates minimal depression, while a score of 20-27 indicates severe depression. Full remission on the PHQ-9 scale is defined as a score of less than 5 [35]. The Quick Inventory of Depression Symptomology Clinical Rating/Self Reporting (QIDS-SR/C) is a 16-item self-administered scale that measures depression severity over the last 7 days regarding 9 symptom domains. The overall score ranges from 0 to 27, with a higher score indicating more severe depression symptoms[36]. The Clinical Global Impressions Scale has two components, a severity measure (CGI-S) and a measure of improvement (CGI-I). The severity measure asks the clinician, "*considering your total clinical experience with this particular population how mentally ill is the patient at this time?*" The clinician can then rate the patient on a scale of 1 (normal) to 7 (amongst the most ill). The improvement scale is formatted similarly and ranges from 1 (very much improved since last treatment) to 7 (very much worse since initiation of treatment) [37]. The Generalized Anxiety Disorder 7-Item scale is rated out of 21 points.

4.4 Demographic data and clinical items

As the purpose of this study is to assess the impact of esketamine therapy in a real-world setting with a diverse patient population, additional data on patient demographics and clinical items were collected. Demographic data will include criteria like body mass index (BMI), race, gender, age, SES, and education status. Clinical items may include any comorbid conditions (hypertension, diabetes, cancer, etc.) or concomitant medications (antihypertensives, insulin, other psychiatric medications, etc.), as well as any unintended adverse effects like sedation, dissociation, or changes in blood pressure during treatment. No restrictions, aside from those made by the treating physician which deem any potential patient as not fit for therapy or which suspend care, were applied in this retrospective chart review study. These broader inclusion criteria may reveal patients in this study who would not have qualified for phase 3 clinical trials and thus represent confounding variables that have yet to be identified in esketamine treatment. Materials used to perform this study are de-identified electronic health records (EHRs), accessed through EPIC, Excel Spreadsheets of REDCap database, and personal computers. No Protected Health Information (PHI) will be collected.

4.5 Patient Stratification

To assess the effects of BMI on esketamine's efficacy, patients were divided into one of three BMI groups: BMI <25, BMI 25 to 30, and BMI >30. The study began with 56 qualifying patients with disqualification and stratification demonstrated below (Figure 2).

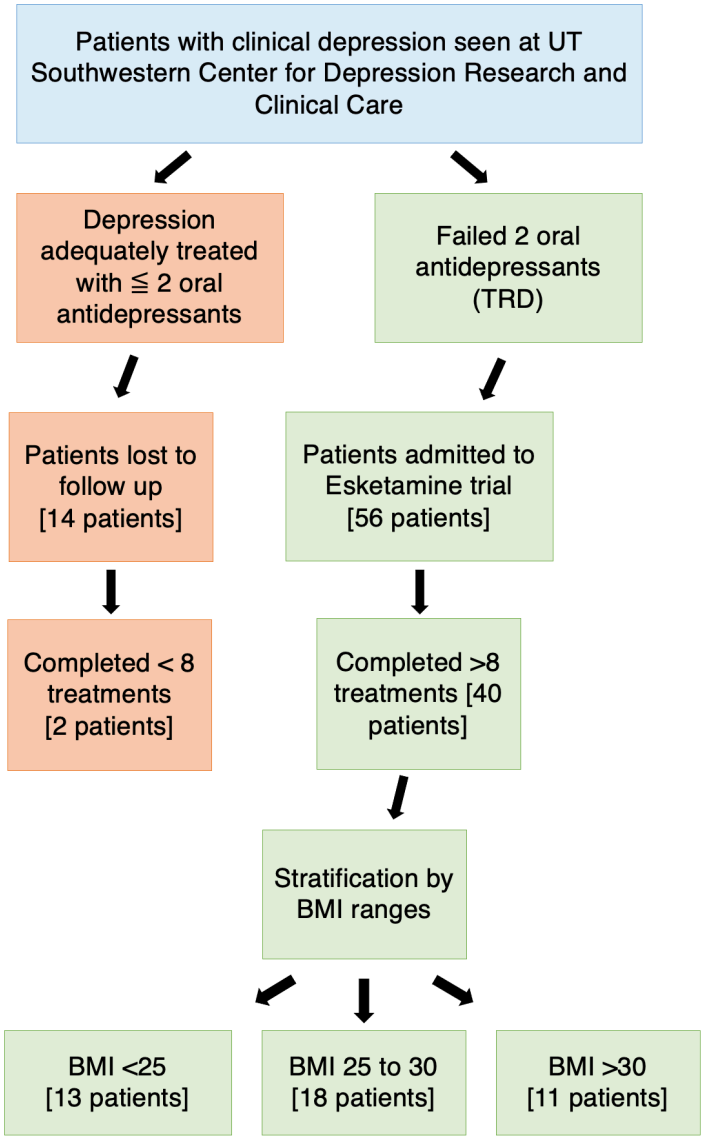


Figure 2: Of the 56 patients enrolled in the study, 40 completed more than 8 treatments. Of those, thirteen had a BMI of less than 25; eighteen had a BMI of 25 to 30; eleven patients had a BMI of greater than 30. Green represents included patients; red is excluded patients.

Moving forward, patients will be categorized by the following labels and in the following order to better contrast the two terminal ends of the BMI spectrum, *normal weight* vs *obese*, with *overweight* as an intermediate category.

BMI < 25: Normal Weight

BMI >30: Obese

BMI 25 to 30: Overweight

4.6 Data analysis

4.6.1 Efficacy of esketamine therapy after 8 treatments

To validate the results of other studies performed, which strongly support that esketamine is an effective therapy for treatment-resistant depression, this study began with a comparison of survey scores pre-treatment vs after treatment # 8. Mean scores across all participants were calculated. Statistical analysis consisted of a Student's T-Test for each data set. P-value was set at 0.05. Data were depicted in bar graphs with standard deviation bars provided.

4.6.2 BMI stratification and comparison

Due to the small sample size and nature of the clinical outcome measures, a decision was made to exclude any quantitative statistical analysis from the study results. Data were interpreted in an observational fashion. Mean changes from baseline were calculated for the various patient surveys (i.e., PHQ-9, QIDS-C, CGI, CHRT-SR). Change from baseline (CFB) data is presented as boxplots. Standard of deviation is presented on the box plot but due to the study being qualitative and observation in nature, it is not accounted for in the results description.

5. Results

5.1 PHQ-9

The Patient Health Questionnaire-9 measures depression severity on a scale of 0 to 27, with 27 representing the worst symptoms. When analyzed as one cohort of all 40 patients, PHQ-9 scores averaged at 19.2 pre-treatment and 13.2 after the treatment #8 (Figure 3). The reduction of depression severity by 6 points was deemed statistically significant after a Student's T-Test revealed a p-value of 0.00019, well below the p=0.05 threshold for significance.

After stratifying into the three BMI cohorts, observational conclusions were drawn for the box-plot diagrams (Figure 4). Patients in the normal weight category had a reduction of 3 points in this depression rating scale after 8 weeks of esketamine treatment under the existing protocol. Obese patients (BMI >30) experienced no reduction. Overweight patients (BMI 25 to 30) had a 4-point reduction in this depression severity scale.

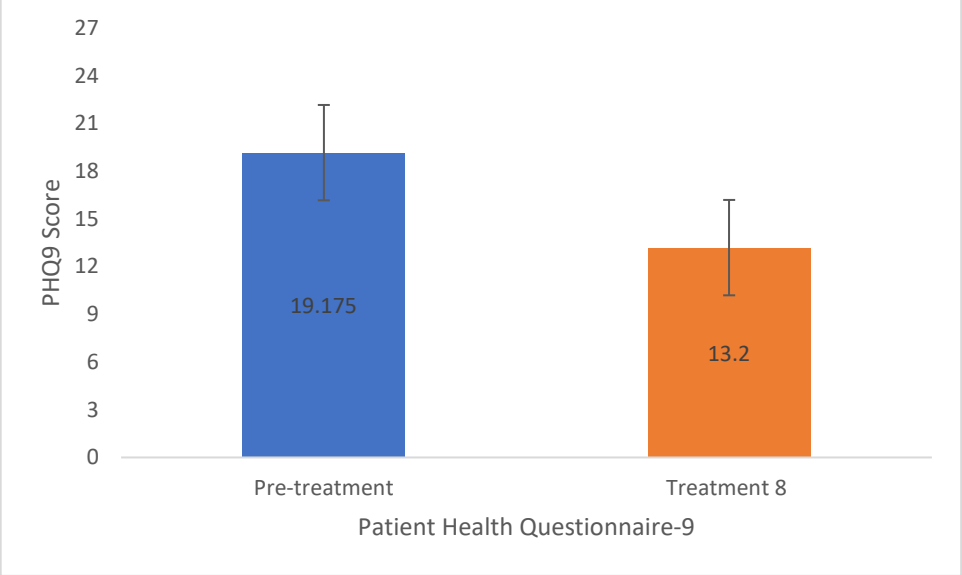


Figure 3. Mean scoring on PHQ-9 questionnaire of patients before treatment initiation (blue) and after treatment #8 of intranasal esketamine (orange). Error bars depict standard deviation. Student's T-Test yields significance with a p-value of less than 0.05.

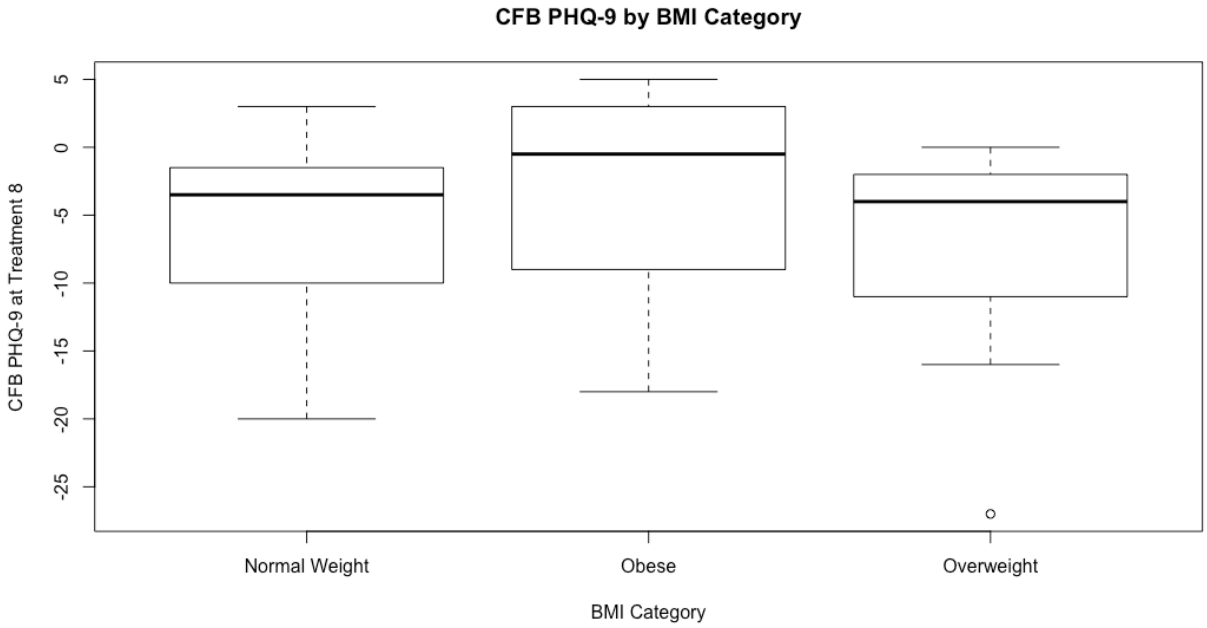


Figure 4. Change from baseline of PHQ-9 after >8 weeks of intranasal esketamine treatment by BMI classification.

5.2 QIDS-SR

The Quick Inventory of Depression Symptomology- Self Reported is a patient completed scale that measures depression severity over the past 7 days with a scale ranging from 0 to 27 (most severe). When analyzed as one cohort of all 40 patients, QIDS-SR scores averaged at 18.4 pre-treatment and 13.3 after treatment #8 (Figure 5). The reduction of depression severity by 5 points was deemed statistically significant after a Student's T-test revealed a p-value of 0.00015, well below the p=0.05 threshold for significance.

After stratifying patients into the three BMI cohorts, observational conclusions were drawn for the box-plot diagram (Figure 6). Patients in the normal and obese cohorts had a 5-point reduction in symptoms after the study period. Patients in the overweight cohort experienced a 6-point reduction in the same period.

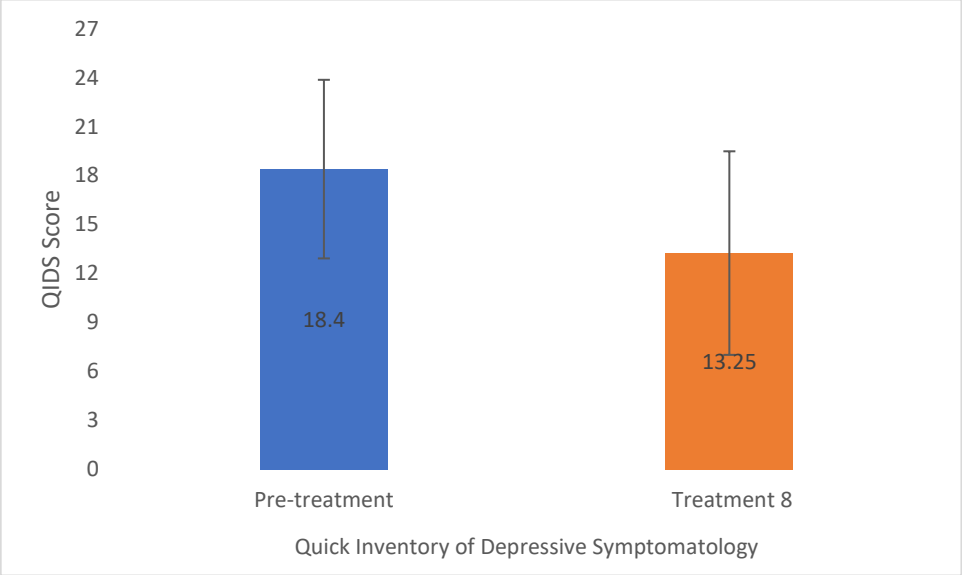


Figure 5. Mean scoring on QIDS-SR questionnaire of patients before treatment initiation (blue) and after treatment #8 of intranasal esketamine (orange). Error bars depict standard deviation. Student's T-Test yields significance with a p-value of less than 0.05.

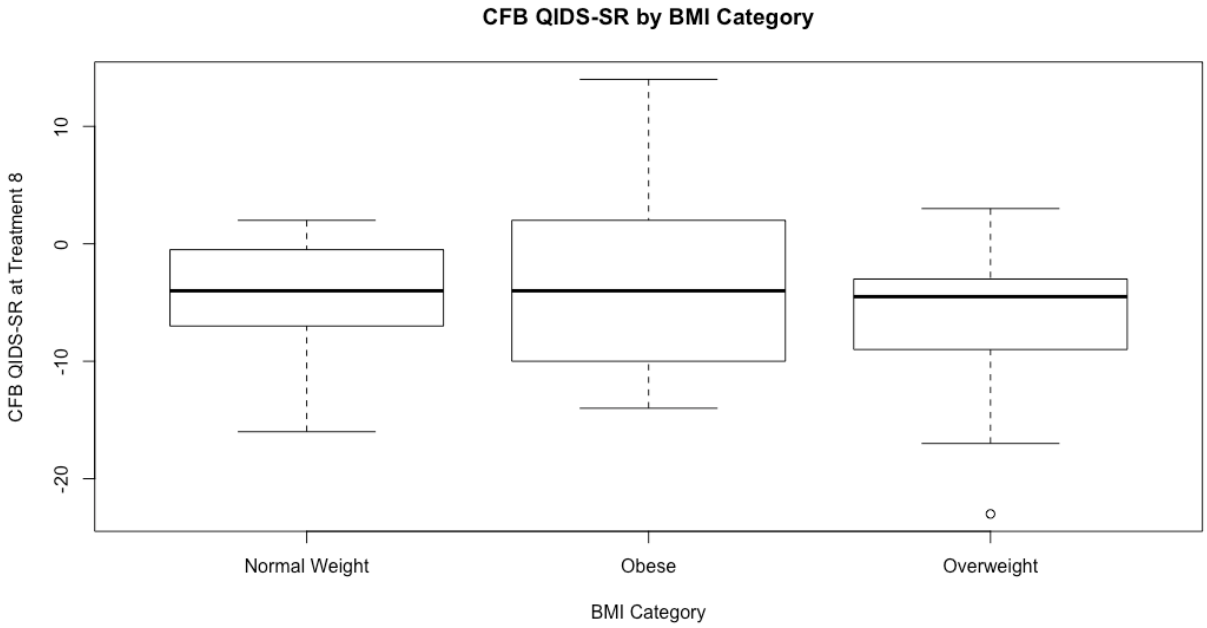


Figure 6. Change from baseline of QIDS-SR after >8 weeks of intranasal esketamine treatment by BMI classification.

5.3 CGI-S

The Clinical Global Impression Scale-S measures the severity of depression symptoms and is completed by the clinician treating the patient over an extended period, with a maximum severity score of 7. When analyzed as one cohort of all 40 patients, CGI-S scores averaged at 4.8 pre-treatment and 3.8 after treatment #8 (Figure 3). The reduction of depression severity by 1 point was deemed statistically significant after a Student's T-test revealed a p-value of 0.0000037, well below the p=0.05 threshold for significance.

After stratifying into the three BMI cohorts, observational conclusions were drawn for the box-plot diagrams (Figure 8). Patients in the normal weight cohort had no reduction from baseline after 8 weeks of treatment. Patients in the obese and overweight cohorts improved by 1 point after the treatment period.

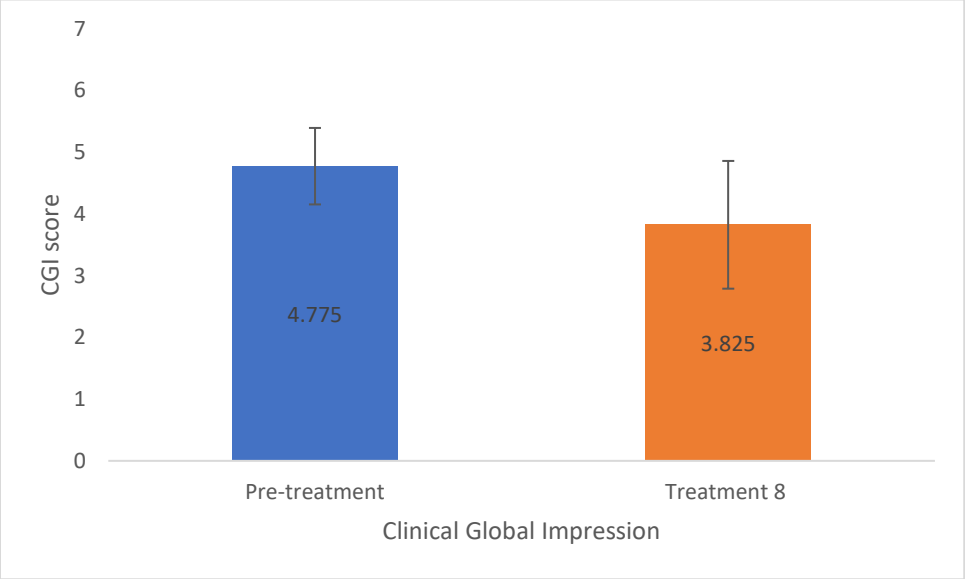


Figure 7. Mean scoring on CGI questionnaire of patients before treatment initiation (blue) and after treatment #8 of intranasal esketamine (orange). Error bars depict standard deviation. Student's T-Test yields significance with a p-value of less than 0.05.

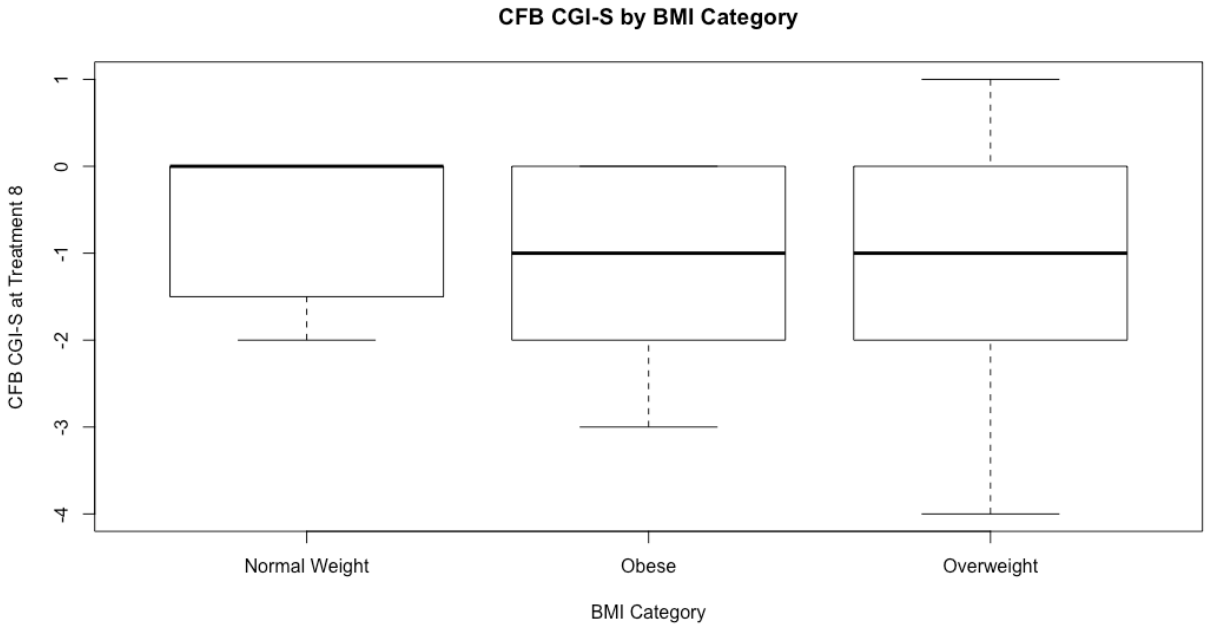


Figure 8. Change from baseline of CGI-S after >8 weeks of intranasal esketamine treatment by BMI classification.

5.4 GAD-7

The General Anxiety Disorder- 7 assessment is the only outcome measure collected that does not focus directly on depression severity, but rather anxiety which can contribute to or follow depression. When analyzed as one cohort of all 40 patients, GAD-7 scores averaged at 13.6 pre-treatment and 10.2 after treatment #8 (Figure 9). The reduction of depression severity by ~3 points was deemed statistically significant after a Student's T-Test revealed a p-value of 0.016, falling below the p=0.05 threshold for significance.

After stratifying into the three BMI cohorts, observational conclusions were drawn for the box-plot diagrams (Figure 10). Patients of normal weight experienced a 2-point reduction in anxiety symptoms after the treatment period. Patients in the obese cohort experienced a 1-point reduction. Patients in the overweight cohort experienced a 4-point reduction in anxiety symptoms after treatment with intranasal esketamine.

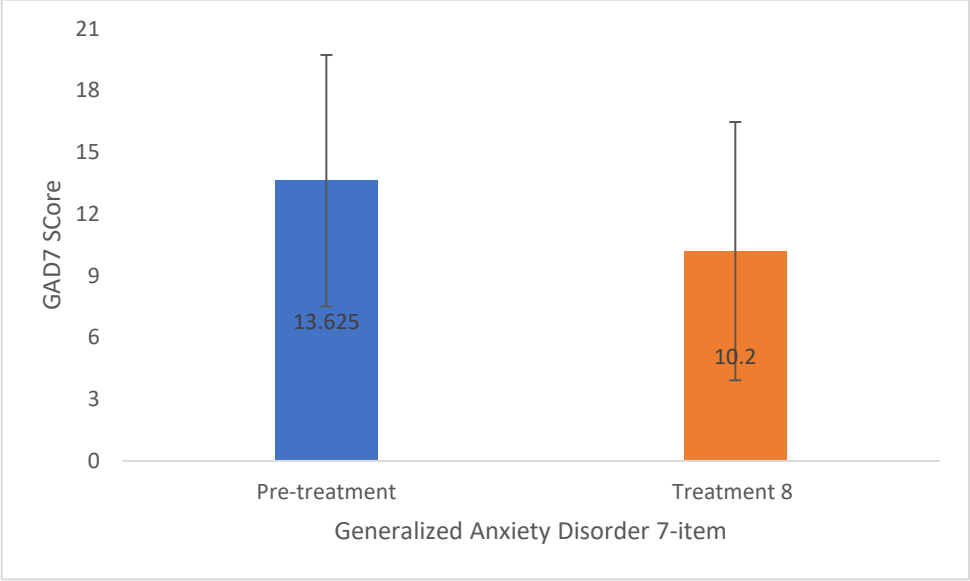


Figure 9. Mean scoring on GAD-7 questionnaire of patients before treatment initiation (blue) and after treatment #8 of intranasal esketamine (orange). Error bars depict standard deviation. Student's T-Test yields significance with a p-value of less than 0.05.

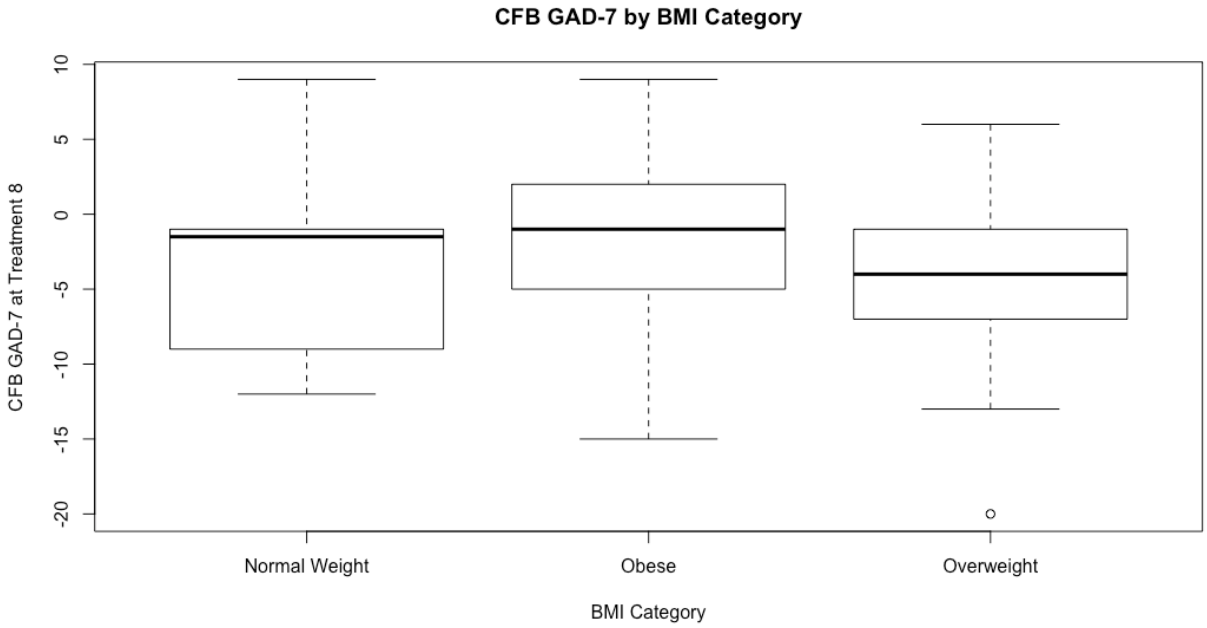


Figure 10. Change from baseline of GAD-7 after >8 weeks of intranasal esketamine treatment by BMI classification.

6. Discussion and Innovation

Intranasal esketamine therapy for major depressive disorder made waves in the field of psychiatry as the first mechanistically new FDA-approved antidepressant in 50 years. The need for such innovation is especially highlighted in the treatment-resistant population, which fails to respond to multiple conventional treatment options including monotherapy, combination therapy, and even electroconvulsive therapy. After abounding success in Phase 3 clinical trials, the present authors found it necessary to continue investigation into this new medication.

First (Aim 1), the authors aimed to determine how effective Spravato (brand name of intranasal esketamine) was in patients with treatment-resistant depression who received care at the BL6 UT Southwestern clinic in Dallas, TX. After 8 treatments, data from various mood and illness questionnaires revealed significant observational improvement with quantitative statistically supported reduction on questionnaires. Specifically, there was an improvement in depression severity as determined by the PHQ-9, QIDS-SR, and CGI scores reductions. Given that anxiety often co-presents with major depressive disorder, patients' anxiety severity was tracked with the GAD-7 questionnaire. This also demonstrated a statistically significant reduction in anxiety severity after treatment # 8, as compared to pre-treatment scores. As a measure of further support for the Phase 3 trials, the authors were able to conclude that intranasal esketamine reduces depression and anxiety severity in patients with treatment-resistant depression after 8 treatments. Therefore, the study confirms the hypothesis of Aim 1.

Aim 2 and Aim 3 of this study were to determine if body mass index affects treatment response to standard dose intranasal esketamine across three different depression questionnaires and one anxiety questionnaire, respectively. These aims were developed following the findings of a 2020 retrospective analysis by Lipsitz et al. The 2020 study did not find any relationship between pretreatment BMI and response to intravenous ketamine therapy [38]. The infusions in the Lipsitz et al. study used the patient’s body weight to dose the intravenous ketamine, meaning patients with larger BMIs would receive a larger infusion of ketamine. These patients were studied after 4 treatments over 1-2 weeks. In the current study, patients received a standard dose of intranasal esketamine and were treated for 8 sessions before final metrics were collected. While intravenous esketamine is dosed at 0.5mg/kg, intranasal esketamine is delivered in a standard dose, of 56mg

or 84mg as indicated. The present study also exploits the enantiomeric differences between intravenous racemic (S and R) ketamine and intranasal (S) esketamine. Aim 2 and Aim 3 hypothesized that patients with higher BMI would have a diminished treatment response, and therefore present with a dampened reduction on the depression and anxiety questionnaires after 8 treatments when compared to pre-treatment scores.

Observationally, patients in the obese cohort had no mean change from baseline on PHQ-9 when compared to the modest reduction observed in the normal weight and overweight cohorts. No difference in change from baseline was observed between cohorts according to the QIDS-SR questionnaire. As per the CGI questionnaire, there was a greater observed reduction in depression severity after 8 treatments in the obese and overweight cohorts. For anxiety, as per the GAD-7, the overweight cohort had the greatest reduction in symptomatology while the normal weight and obese cohorts had little to no reductions in severity.

Although the observations above begin to draw some pattern in treatment response, the present study failed to provide any conclusive statistically significant evidence to accept or reject the hypotheses of Aim 2 and Aim 3. The small sample size and inability to perform robust statistical analysis prevent a conclusive answer from being formed about whether intranasal esketamine demonstrates weight-dependent efficacy. While observations of the data are fruitful in guiding the next iteration of the study or in planning for future expansions of the study design, it is not possible to draw any meaningful conclusions until further supporting work is conducted.

Nevertheless, the present study does expand the body of knowledge regarding this new and innovative treatment option for major depressive disorder and its more severe counterpart, treatment-resistant depression. It is critical to remember that depression is a destructive disease process with negative ramifications to individuals, families, and communities. Esketamine provides new hope as even more effective therapeutic options present on the horizon.

7. Future Directions

Future work should aim to increase the sample size allowing for statistical analysis to be performed between BMI cohorts. Extension of the study period beyond 8 treatments may provide more robust long-term efficacy data as metabolic profile differences may become more apparent weeks after treatment initiation. Extension beyond the 8-week study period may also allow for better assessment of depression remission as well as relapse, which was not examined in the present work. Future work may attempt to stratify BMI into more cohorts with tighter ranges per cohort or analyze the data in a continuum rather than in cohorts as done in the present study.

8. Conclusion

Esketamine is the first mechanistically new FDA-approved medication for depression in over 50 years. Promising clinical trials and community outcome measures have demonstrated their efficacy in providing relief for treatment-resistant depression. The dosing schedule is standard for all patients and does not follow any weight-based calculation, unlike intravenous ketamine. Studies with IV ketamine found no difference in treatment response by patient weight. Due to the lack of weight-based dosing, these results do not necessarily translate to intranasal ketamine. The present study compared depression symptom reduction by patient and clinician-reported surveys to three different BMI cohorts. In the cohort of all 40 patients, before BMI stratification, esketamine was deemed effective at reducing the severity of scores on mood and illness questionnaires after 8 treatments. Statistical analysis provides significance to these findings. After stratification, observational results demonstrate some moderate changes in efficacy by BMI, but no statistical analysis can support these observations due to the limited cohort size. Overall, the data provide no clear link that weight or BMI are linked to esketamine efficacy, echoing the results of the intravenous ketamine study.

9. Compliance

The Esketamine Treatment Service Evaluation at UT Southwestern aims to assess and improve the delivery of this novel therapeutic intervention in outpatient clinical care. This work intends to perform quality control rather than generate knowledge about a disease or condition. Therefore, in accordance with the UT Southwestern Human Resource Protection Program (HRPP), the outlined work does not meet the definition of research under the 45 CFR 46. 102 code and therefore does not require IRB approval or oversight. Under this classification, the results of this study can also inform up to three case reports, given that they are written by retrospective review of medical records and are HIPAA compliant. Please contact Maria Monastirsky (maria.monastirsky@utsouthwestern.edu) at the Human Resource Protection Program Office for any additional compliance queries.

This work was conducted under the supervision and guidance of Dr. Andrew Czysz M.D., Ph.D., a practicing psychiatrist and Assistant Professor in the Department of Psychiatry at UT Southwestern Medical Center in Dallas, Texas. The medical records being assessed in this study are all from patients of the BL6 outpatient psychiatry clinic at UTSW and will be accessed via EPIC. REDCap or Microsoft Excel was used for secure data collection, storage, and analysis.

10. REFERENCES

1. Health, T.N.I.o.M. *Major Depression*. 2019 February 2019 [cited 2020; Available from: https://www.nimh.nih.gov/health/statistics/major-depression.shtml.
2. American Psychiatric Association, *Depressive Disorders*. 5th ed. Diagnostic and Statistical Manual of Mental Disorders. 2013, Washington, DC.
3. Greenberg, P.E., et al., *The economic burden of adults with major depressive disorder in the United States (2005 and 2010).* J Clin Psychiatry, 2015. **76**(2): p. 155-62.
4. Scott, J. and B. Dickey, *Global burden of depression: the intersection of culture and medicine.* Br J Psychiatry, 2003. **183**: p. 92-4.
5. Eshel, N., et al., *Dopamine neurons share common response function for reward prediction error.* Nat Neurosci, 2016. **19**(3): p. 479-86.
6. Ruhe, H.G., N.S. Mason, and A.H. Schene, *Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies.* Mol Psychiatry, 2007. **12**(4): p. 331-59.
7. Greicius, M.D., et al., *Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus.* Biol Psychiatry, 2007. **62**(5): p. 429-37.
8. Hamilton, J.P., et al., *Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination.* Biol Psychiatry, 2011. **70**(4): p. 327-33.
9. Assari, S., *Social Determinants of Depression: The Intersections of Race, Gender, and Socioeconomic Status.* Brain Sci, 2017. **7**(12).
10. Yu, M., et al., *Childhood trauma history is linked to abnormal brain connectivity in major depression.* Proc Natl Acad Sci U S A, 2019. **116**(17): p. 8582-8590.
11. Trivedi, M.H., et al., *Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design.* J Psychiatr Res, 2016. **78**: p. 11-23.
12. Jha, M.K., et al., *Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial.* Psychoneuroendocrinology, 2017. **78**: p. 105-113.
13. Shrestha, A., et al., *Incremental Health Care Burden of Treatment-Resistant Depression Among Commercial, Medicaid, and Medicare Payers.* Psychiatr Serv, 2020: p. appips201900398.
14. Lui, S., et al., *Resting-state functional connectivity in treatment-resistant depression.* Am J Psychiatry, 2011. **168**(6): p. 642-8.
15. Li, Z., et al., *The role of BDNF, NTRK2 gene and their interaction in development of treatment-resistant depression: data from multicenter, prospective, longitudinal clinic practice.* J Psychiatr Res, 2013. **47**(1): p. 8-14.
16. Lin, Z., et al., *Influence of Val108/158Met COMT Gene Polymorphism on the Efficacy of Modified Electroconvulsive Therapy in Patients with Treatment Resistant Depression.* Cell Biochem Biophys, 2015. **71**(3): p. 1387-93.

17. Kim, Y.K. and K.S. Na, *Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression.* Prog Neuropsychopharmacol Biol Psychiatry, 2016. **70**: p. 117-26.
18. Cipriani, A., et al., *Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis.* Lancet, 2018. **391**(10128): p. 1357-1366.
19. Bobo, W.V. and R.C. Shelton, *Efficacy, safety and tolerability of Symbyax for acute-phase management of treatment-resistant depression.* Expert Rev Neurother, 2010. **10**(5): p. 651-70.
20. Jha, M.K., et al., *Dysfunctional adaptive immune response in adolescents and young adults with suicide behavior.* Psychoneuroendocrinology, 2020. **111**: p. 104487.
21. Gadad, B.S., et al., *Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks.* J Affect Disord, 2018. **233**: p. 3-14.
22. Nguyen, K.P., et al., *Predicting Response to the Antidepressant Bupropion using Pretreatment fMRI.* Predict Intell Med (2019), 2019. **11843**: p. 53-62.
23. Trivedi, M.H., et al., *Randomized Controlled Trial Comparing Exercise to Health Education for Stimulant Use Disorder: Results From the CTN-0037 STimulant Reduction Intervention Using Dosed Exercise (STRIDE) Study.* J Clin Psychiatry, 2017. **78**(8): p. 1075-1082.
24. Dunn, A.L., et al., *Exercise treatment for depression: efficacy and dose response.* Am J Prev Med, 2005. **28**(1): p. 1-8.
25. Smigielski, L., et al., *Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects.* Neuroimage, 2019. **196**: p. 207-215.
26. Studerus, E., et al., *Prediction of psilocybin response in healthy volunteers.* PLoS One, 2012. **7**(2): p. e30800.
27. Berman, R.M., et al., *Antidepressant effects of ketamine in depressed patients.* Biol Psychiatry, 2000. **47**(4): p. 351-4.
28. Zarate, C.A., Jr., et al., *A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression.* Arch Gen Psychiatry, 2006. **63**(8): p. 856-64.
29. Yanagihara, Y., et al., *Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers.* Biopharm Drug Dispos, 2003. **24**(1): p. 37-43.
30. Zanos, P., et al., *Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms.* Pharmacol Rev, 2018. **70**(3): p. 621-660.
31. McEwen, B.S., et al., *Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress.* Neuropharmacology, 2012. **62**(1): p. 3-12.
32. Li, N., et al., *mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists.* Science, 2010. **329**(5994): p. 959-64.
33. Masaki, Y., et al., *(R)- and (S)-ketamine induce differential fMRI responses in conscious rats.* Synapse, 2019. **73**(12): p. e22126.

34. Wajs, E., et al., *Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2).* J Clin Psychiatry, 2020. **81**(3).
35. Schueller, S.M., et al., *Cut points on the Patient Health Questionnaire (PHQ-9) that predict response to cognitive-behavioral treatments for depression.* Gen Hosp Psychiatry, 2015. **37**(5): p. 470-5.
36. Zhen, L., et al., *Evaluation of the Paper and Smartphone Versions of the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16) and the Patient Health Questionnaire-9 (PHQ-9) in Depressed Patients in China.* Neuropsychiatr Dis Treat, 2020. **16**: p. 993-1001.
37. Busner, J. and S.D. Targum, *The clinical global impressions scale: applying a research tool in clinical practice.* Psychiatry (Edgmont), 2007. **4**(7): p. 28-37.
38. Lipsitz, O., et al., *Does body mass index predict response to intravenous ketamine treatment in adults with major depressive and bipolar disorder? Results from the Canadian Rapid Treatment Center of Excellence.* CNS Spectr, 2020: p. 1-9.