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Moving Forward with Ketamine Therapy: Ensuring Safety, Efficacy, and Accessibility in Depression Treatment

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FACULTY APPROVAL

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Moving Forward with Ketamine Therapy:

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A Thesis

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Abstract

Ketamine, a medication long used in anesthesia, has emerged as a promising treatment for depression and other mental health disorders. Its rapid onset of action and mechanism, which differs from traditional antidepressants by targeting NMDA receptors, offers a novel approach to managing depressive symptoms. Despite its potential, ketamine's use outside anesthesia, particularly in off-label ketamine clinics, is fraught with regulatory, safety, and accessibility challenges. This paper explores the historical medical use of ketamine and its emerging role in mental health treatment. It compares the efficacies and administration routes of different forms of ketamine, including intravenous (IV) and intranasal (nasal spray) forms. It highlights the distinctions between ketamine and its S-isomer, esketamine (Spravato), which was FDA-approved in 2019 for treatment-resistant depression. Given the substantial evidence supporting ketamine's promise as a treatment for depression and other mental health conditions, the paper concludes by emphasizing the importance of developing strategies that prioritize safety, efficacy, and widespread accessibility, ensuring ketamine can fulfill its potential as a transformative mental health therapy for many.

Keywords: depression, treatment-resistant depression, ketamine, intravenous (IV), intranasal (IN), esketamine, Spravato, safety and efficacy, accessibility

Moving Forward with Ketamine Therapy: Ensuring Safety, Efficacy, and Accessibility in Depression Treatment

Depression constitutes a significant public health concern in the United States, affecting an estimated 21 million adults, or approximately 8.3% of the adult population each year (NIH, 2023). Traditional treatments, which primarily include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), fail to adequately relieve symptoms in about 30% of patients, termed as having treatment-resistant depression (TRD) (Zhdanava et al., 2021). Even when medications are effective, they can take several weeks to improve symptoms, a significant delay that can be perilous for those at immediate risk of suicide. Ketamine, a medication historically recognized for its use as an anesthetic, has emerged as a novel treatment option due to its rapid antidepressant effects. Ketamine's role in treatment-resistant depression (TRD) has been repurposed due to its unique action on the N-methyl-D-aspartate (NMDA) receptors, offering potential relief within hours rather than the weeks typically required for conventional antidepressants.

The excitement surrounding ketamine's potential led to the rapid proliferation of ketamine clinics across the country, operating in a regulatory gray area and often without the comprehensive oversight typical of more conventional treatments. The FDA's recent approval of esketamine (Spravato), a nasal spray formulation of ketamine's S-enantiomer, has introduced new dynamics into the treatment landscape by potentially increasing accessibility yet also raising questions about comparative effectiveness and safety relative to racemic (IV) ketamine, which is often used off-label in clinical settings.

This thesis aims to explore the future of ketamine therapy, specifically comparing the efficacy, safety, and accessibility of intravenous ketamine and intranasal esketamine (Spravato)

in the treatment of depression. The objective is to supply current and accurate information to patients, healthcare professionals, and the wider community, aiding in the assessment of these two treatments for managing depression.

To provide a comprehensive understanding, this thesis will begin with a background on the historical use of ketamine and its emerging role in mental health treatment. The thesis will include a discussion of ketamine's mechanism of action as an NMDA receptor antagonist and its rapid antidepressant effects. Next, the development and FDA approval of Spravato will be discussed and its application in treating depression.

Building on this foundation, the thesis will compare the efficacy, safety, and accessibility of intravenous ketamine and intranasal esketamine. This comparative analysis will draw on direct observation studies, post-hoc analyses, and several meta-analyses to thoroughly assess outcomes associated with each treatment option. By examining patient outcomes, safety considerations, and practical considerations such as cost and insurance coverage, this thesis seeks to offer a clearer understanding of how these treatments compare in real-world settings, ultimately contributing to the growing field of alternative therapies for depression treatment.

Background

Historical Use of Ketamine

Ketamine was first synthesized in 1962 by chemist Calvin Stevens at Parke-Davis Laboratories as part of an effort to find a safer alternative to phencyclidine (PCP), an anesthetic known for its severe psychological side effects. PCP was noted to be reliable as an anesthetic but caused severe symptoms of delirium and hallucinations, making it unequipped for human use in medicine. Researchers, including Calvin Stevens, worked towards synthesizing a similar compound to phencyclidine, minimizing the potent adverse effects while maintaining its

profound analgesic and anesthetic properties. Subsequently, ketamine, a structurally similar molecule but only one-tenth as potent as phencyclidine, was created and selected for human trials (Hashimoto, 2019). The first human trials took place in 1964, and the researchers found that ketamine could quickly relieve pain and induce a unique state of altered consciousness, which could be safely maintained with repeated doses. By 1970, ketamine had gained FDA approval for use as an anesthetic in both human and veterinary medicine. Its approval was based on its safety profile and effectiveness in inducing anesthesia without the severe side effects associated with other anesthetics.

Ketamine saw extensive use during the Vietnam War, where it was employed as a battlefield anesthetic. Its rapid onset, short duration of action, and minimal impact on respiratory function made it ideal for emergency surgeries and pain management in combat conditions. Soldiers injured in the field received ketamine to manage pain and facilitate emergency medical procedures, highlighting its effectiveness and versatility in medicine.

Emergence in Mental Health Treatment

The potential psychiatric applications of ketamine were first hinted at in the 1970s when clinicians observed mood elevation in patients receiving ketamine anesthesia. However, it was not until the late 1990s and early 2000s that scientific investigations began to explore its antidepressant effects specifically. One of the seminal studies in this area was conducted by Berman et al. (2000), who found that a single sub-anesthetic dose of ketamine, administered intravenously, produced rapid and significant effects in patients with treatment-resistant depression (TRD). These findings were groundbreaking, as traditional antidepressants like SSRIs and SNRIs typically require weeks to achieve full therapeutic effects and are often ineffective in TRD.

Ketamine's Antidepressant Mechanism of Action

Preclinical models and human studies demonstrate that depressed individuals exhibit fewer synapses and atypical glutamatergic neurotransmission. The prefrontal cortex (PFC) and hippocampus, key brain regions involved in mood regulation, often show decreased synaptic density and dendritic spine loss in depression. This reduction in synaptic connectivity is believed to contribute to the cognitive and emotional symptoms of depression (Ren, 2024).

NMDA Receptor Antagonism

Glutamate, the primary excitatory neurotransmitter, plays a crucial role in synaptic plasticity, learning, and memory. In depression, there is evidence of dysregulated glutamate signaling, which can result in both excessive and insufficient activation of glutamate receptors (Krystal et al., 2013). Ketamine's antidepressant effects, while not entirely understood, are closely linked to its ability to modulate synaptic growth and plasticity. Ketamine acts on the glutaminergic system as a non-competitive NMDA receptor antagonist. Ketamine blocks NMDA receptors on inhibitory GABAergic interneurons in the brain. This blockade releases the inhibition on excitatory glutamatergic neurons, causing a surge in synaptic glutamate levels (Zarate & Niciu, 2015). With the NMDA receptors blocked, this excess glutamate preferentially activates AMPA receptors, leading to increased neural activity and synaptic plasticity.

Activation of AMPA receptors leads to membrane depolarization and the initiation of intracellular signaling cascades. These cascades include several key processes, including the activation of the mTOR pathway and increased production and release of brain-derived neurotrophic factor (BDNF). Enhanced levels of BDNF stimulate TrkB receptors on neurons, promoting long-term potentiation (LTP) which is the strengthening of synapses based on recent patterns of activity. These neuroplastic changes are thought to be the reason why a single

infusion of ketamine can produce effects that last up to two weeks (Autry et al., 2011). However, there is ongoing debate about whether ketamine's antidepressant effects are primarily due to its direct action on NMDA receptors or the downstream activation of AMPA receptors, as research remains ongoing. (Gao et al., 2016).

Comparison with Traditional Antidepressants

Traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), primarily target monoaminergic systems by increasing the availability of serotonin and norepinephrine. These drugs work by inhibiting the reuptake of these neurotransmitters, enhancing their levels in the synaptic cleft. However, monoamines are only involved in about 15-20% of the brain's synapses, and the mechanism can take several weeks to achieve significant therapeutic effects.

In contrast, ketamine rapidly produces antidepressant effects by impacting the glutamate neurotransmitter, which is involved at the majority of neuronal synapses (~50%) (Zarate & Niciu, 2015). By blocking NMDA receptors and promoting glutamate release, ketamine activates AMPA receptors and initiates intracellular signaling pathways that foster synaptic growth and connectivity. This difference allows ketamine to be effective in patients who do not respond to monoaminergic antidepressants.

Development of Spravato®

Formulation and Approval

The discovery of ketamine's efficacy in psychiatric treatments, particularly for depression, led to two major developments: the widespread establishment of private clinics offering off-label intravenous ketamine treatments and significant commercial interest in creating patentable new forms of the molecule. This interest was driven by the expiration of the original

racemic ketamine's patent in 2002 and apparent success of off-label use of ketamine by clinicians.

Ketamine is a racemic mixture containing equal parts of two enantiomers: S-ketamine (esketamine) and R-ketamine (arketamine). Both enantiomers share a similar mechanism involving NMDA receptor antagonism but differ in potency and effects. Research suggests that the S-enantiomer of ketamine, or esketamine, has a 3-4 times higher affinity for the NMDA receptor than R-ketamine (White et al., 1985). This higher affinity means esketamine can be more potent, leading to more effective NMDA receptor antagonism at lower doses.

The lack of patent protection for generic ketamine reduced pharmaceutical incentives to invest in its development and commercialization. This prompted companies to focus on developing and patenting the more potent enantiomer, esketamine. Preliminary studies suggested that esketamine could offer stronger therapeutic effects and fewer side effects compared to its R-counterpart, making it an ideal candidate for commercial development as a “novel antidepressant”. Recognizing this potential, Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson, developed esketamine into an intranasal formulation called Spravato. The intranasal route was chosen to provide a non-invasive and potentially more accessible form of administration compared to intravenous infusions.

Clinical Trials for FDA Approval

Janssen Pharmaceuticals conducted several clinical trials to evaluate the safety and efficacy of Spravato in treating treatment-resistant depression (TRD). One key trial, TRANSFORM-2, was a Phase 3 randomized, double-blind trial that compared the efficacy and safety of intranasal esketamine plus a newly initiated oral antidepressant to a placebo nasal spray plus a newly initiated oral antidepressant. The results showed that esketamine significantly

reduced depressive symptoms compared to placebo (Popava, 2019). Another important study, SUSTAIN-1, was a long-term trial that assessed the efficacy and safety of esketamine for relapse prevention in patients with TRD who achieved stable remission or stable response after initial treatment with esketamine. This study demonstrated that esketamine significantly delayed the time to relapse compared to placebo (Daly et al., 2018).

These trials demonstrated significant reductions in depressive symptoms in patients who had not responded to traditional antidepressants. In 2019, Spravato received FDA approval for the treatment of TRD with fast-track and breakthrough therapy designations based on the positive results from the clinical trials mentioned above.

However, the development of Spravato raises questions about whether pharmaceutical strategies are always in the best interest of patients or primarily profit-driven. The choice to focus on esketamine, which could be patented and marketed at a higher price, rather than the already known and unpatented racemic ketamine, suggests a strong commercial incentive. While these clinical studies comparing Spravato to placebo proved Spravato to have positive effects on relieving depressive symptoms, they did not clarify how it may compare to IV ketamine. Therefore, it was left unclear to doctors and patients how results achieved from Spravato administration compared to results of intravenous ketamine infusion, the method that is popularly used off-label in clinics. Additionally, there remains uncertainty regarding which option is safer and more accessible for patients seeking treatment for TRD, highlighting the need for comprehensive comparative analysis to address these critical questions.

Comparative Analysis

Efficacy

IV ketamine continues to be administered in clinics for its rapid antidepressant properties, even though it is not patented or FDA-approved specifically for depression treatment. In recent years, however, some clinics have opted to administer Spravato instead. The next section of this paper will compare the efficacy of this traditional intravenous administration of racemic ketamine in clinical settings against the FDA-approved intranasal administration of esketamine. This comparison will be based on data from direct observation studies, post-hoc analyses, and several meta-analyses.

Direct Comparison: Observational Study

To date, only one published study has directly compared the relative efficacies of intranasal esketamine and intravenous racemic ketamine. In this real-world observational study by Singh et al. (2022) 63 adults with TRD received either IV ketamine (n=48) or IN ketamine (n=15), following standard treatment protocols over a six-week period. Depression symptoms were self-reported using the Quick Inventory of Depressive Symptomatology (QIDS-SR) scale before treatment and 24 hours after treatment. The results revealed that both IV ketamine and IN esketamine showed similar improvements in QIDS-SR scores, response rates, and remission in TRD patients. The mean change in QIDS-SR score for both IV and IN was -8.7 ± 0.7 ($P < .001$), which shows depressive symptoms were significantly reduced following treatment. The response rates for IV ketamine and IN esketamine (56.3% vs 53.3%) and the remission rates (39.6% vs 26.8%) were similar. Interestingly, the findings indicated that patients receiving IV ketamine needed significantly fewer treatments to achieve a response or remission (2.5 and 2.4 treatments, respectively) compared to those treated with IN esketamine (4.6 and 6.3 treatments). These

differences were statistically significant, with a p-value less than 0.005. Because there is only one published direct comparison study between IV ketamine and intranasal ketamine, these findings must be further investigated with a larger sample size and within a randomized control environment.

Indirect comparison: Post-hoc

Given the absence of direct head-to-head trials between intravenous ketamine and intranasal esketamine, the research field has adapted by conducting both post-hoc analyses and meta-analyses in recent years. This approach proves effective when the trials share key similarities in terms of study design, conditions being compared, the populations studied, and the outcomes measured. These studies help fill the knowledge gap by leveraging existing data to compare the effectiveness of these two treatments in real-world settings.

A study published in the Journal of Affective Disorders utilized a retrospective analysis to compare the antidepressant effects of IV ketamine and intranasal esketamine in real-world settings (d'Andrea et al., 2024). In this research, data was combined from two separate cohorts of treatment-resistant depression patients: those treated with intravenous ketamine (n = 171) at the Canadian Rapid Treatment Center of Excellence in Toronto, Canada, and those receiving intranasal esketamine (n = 140) at various TRD clinics in Italy. Results found that IV ketamine demonstrated a more significant and rapid reduction in depressive symptoms compared to intranasal esketamine in treatment-resistant depression (TRD). Initial assessments, conducted one month post-treatment, found a greater effect size for IV Ketamine (Cohen’s d=1.666) than for intranasal esketamine (Cohen’s d=1.244). Furthermore, IV ketamine had greater response rates with 36% of patients reporting a significant response (n= 61/171) compared to 25% for intranasal esketamine (n=35/140).

Indirect Comparison: Meta-analyses

Researchers Bahji et al. (2021) were the first to conduct a systematic review and meta-analysis comparing the respective efficacies of intravenous ketamine and intranasal esketamine for depression. These researchers carefully selected 24 randomized controlled trials, representing data from 1877 participants, and measured improvement in depression score, overall response to treatment, remission from depression, and participant dropout rates. Compared to intranasal esketamine, intravenous racemic ketamine showed higher overall response and remission rates, along with fewer patients discontinuing treatment due to adverse effects. Specifically, racemic ketamine had response and remission rate ratios of 3.01 and 3.70 respectively, while esketamine had rate ratios of 1.38 and 1.47 for response and remission.

Possible Explanations for Different Efficacies

Studies have shown differences in the efficacy of IV ketamine and intranasal esketamine in treating depression, particularly in the speed and number of treatments required to achieve remission. IV ketamine often leads to quicker remission with fewer treatments compared to intranasal esketamine (Bahji et al., 2021; d'Andrea et al., 2024; Singh et al., 2022). One possible explanation is that racemic ketamine, most commonly administered intravenously, is composed of both the S-enantiomer and the R-enantiomer. As previously mentioned, FDA-approved intranasal esketamine, Spravato, only consists of the S-enantiomer which was initially believed to be the more affinitive enantiomer to the NMDA receptor. However, recent research has also highlighted the potential of arketamine as a rapid-acting antidepressant, with several preclinical and initial clinical studies underscoring its effectiveness (Chang et al., 2019; Zhang et al., 2024). These findings suggest that arketamine might be responsible for the rapid antidepressant effects of ketamine, which could explain the disparities in the speed of response between the two

formulations. Still, further exploration and validation through extensive comparative studies are needed to confirm the specific roles of each enantiomer in the treatment of depression.

One study published in 2020 found that when both formulations were administered intravenously, esketamine was as equally effective as ketamine in achieving remission in patients with treatment-resistant depression (Correia-Melo et al.). In a double-blind clinical trial, 63 patients were randomly assigned to a 40-minute single IV administration of 0.5mg/kg of ketamine (n=29) or a 0.25 mg/kg dose of esketamine (n=34). Results showed that remission rates at 24 hours post-treatment were similar between the two groups, with 24.1% in the ketamine group and 29.4% in the esketamine group. Both formulations caused a reduction in depressive symptoms, with similar mild treatment adverse effects. Therefore, it may be logical to assume that differences in efficacy may not be due to the formulations themselves, whether racemic ketamine or esketamine, but may be linked to the route of administration.

It is known that there are differences in the bioavailability of a drug depending on the mode of administration. Bioavailability describes the proportion of the drug that enters the systemic circulation and exerts an active effect. Intravenous administration of ketamine provides nearly optimal bioavailability, reaching close to 100%, which facilitates immediate systemic absorption and rapid pharmacological action (McIntyre et al., 2021). In contrast, the bioavailability of intranasal esketamine is significantly lower, typically ranging around 30-50%. This marked difference in bioavailability likely contributes to the more rapid antidepressant effects observed with intravenous ketamine compared to intranasal esketamine.

Safety

In comparing the safety profiles of intravenous (IV) ketamine and intranasal esketamine (Spravato) for treating treatment-resistant depression, several key factors need to be considered, including acute side effects, long-term effects, potential for misuse, and regulatory guidelines.

Acute Side Effects

IV ketamine, used off-label for many years due to its rapid antidepressant effects, presents several safety concerns. At therapeutic doses, ketamine can induce mild to moderate dissociative symptoms, such as feelings of detachment from reality or euphoria. Dissociation usually peaks at around 40 minutes after administration begins, and resolves within a few hours after (McIntyre et al., 2021). It remains unclear whether or not the experience of dissociation is correlated with acute or longer-lasting antidepressant effects with ketamine. Additionally, ketamine can cause transient increases in heart rate and blood pressure, which may pose risks for patients with pre-existing cardiovascular conditions. Other common side effects, which may be distressing for some patients, include dizziness, drowsiness, and light-headedness.

Existing research that compares IV ketamine to intranasal esketamine generally finds there to be no significant difference in terms of side effects experienced by patients. Yet, one post-hoc analysis found that patients treated with IV ketamine reported higher levels of symptoms, specifically hypertension, dizziness, sedation, and dissociation, compared to IN esketamine patients (d'Andrea et al., 2024). However, these side effects dissipated shortly after drug administration and did not significantly impact whether the patient completed the treatment process.

Long-Term Risks and Concerns

Research involving animal models has raised concerns that neurodegeneration could be a potential long-term risk associated with ketamine, particularly at high doses or with prolonged use that exceeds typical clinical conditions (Gao et al., 2016). Although these adverse neurological outcomes have primarily been observed under extensive exposure conditions, the lack of long-term data in humans necessitates comprehensive studies to better understand and mitigate these risks. Additionally, ketamine's psychoactive properties may contribute to its potential for abuse. Often known by its street name, "Special K," ketamine can be appealing in the recreational drug scene, posing significant challenges in clinical settings. This potential for misuse requires stringent regulatory measures, careful patient selection, and close monitoring to prevent abuse (Krystal et al., 2013).

Controlled Use in Clinical Settings

Given these risks, the administration of both IV ketamine and intranasal esketamine must be carefully managed. The FDA-approved intranasal esketamine, Spravato, has a drug safety program that patients and providers are required to follow to mitigate any concerns associated with the drug. Under the Risk Evaluation and Mitigation Strategy (REMS) program, patients who self-administer the intranasal formulation of esketamine are required to remain under the supervision of a healthcare provider for at least two hours within a healthcare setting certified for Spravato administration.

On the other hand, IV ketamine lacks a formal FDA-approved indication for this use, which has implications for its regulatory oversight and standardization in clinical settings. The lack of clear guidelines contributes to the reputation of ketamine clinics being referred to as "the Wild West" of mental health treatment (Megli, 2024). Many ketamine clinics operate without

consistent guidelines, which can vary significantly in terms of dosing and monitoring, increasing the risk of variable patient outcomes and safety concerns. In these clinics, providers often base their protocols on novel research studies to determine dosages and treatment plans. The issue with this approach is that these studies about IV ketamine for TRD are often difficult to generalize, small in size, and not intended to inform standardized guidelines or use in private practice.

Furthermore, Spravato is available in one dosage strength of 28 milligrams, which limits the ability to finely adjust doses to the specific needs of individual patients. The starting dose is 56 milligrams, or one spray in each nostril, and can later be increased to 84 milligrams if necessary. However, due to the mode of administration, it is less certain how much of the medication takes effect, which can be a significant drawback in cases where a more customized dosing strategy might be beneficial. On the other hand, IV ketamine, while used off-label for depression, offers a distinct advantage in terms of dosage flexibility. In clinical settings, the dosage of IV ketamine can be carefully adjusted and tailored to the immediate responses and needs of the patient. This allows clinicians to optimize the dose for efficacy while minimizing potential side effects, providing an approach to treatment that is not feasible with the fixed doses of Spravato.

Accessibility

When considering the accessibility of intravenous (IV) ketamine and intranasal esketamine (Spravato) for treating treatment-resistant depression (TRD), cost and insurance coverage are significant factors that impact patient access to these therapies.

Cost and Insurance Coverage

The cost of ketamine and esketamine treatments can be a major barrier to accessibility. IV ketamine, while frequently used off-label for TRD, faces considerable financial barriers due to its lack of FDA approval. As a result, it is rarely covered by insurance plans, necessitating out-of-pocket payments that make it less accessible for many patients. The cost per visit for IV ketamine, which includes the medication and necessary monitoring, typically ranges between $400 and $1000, with the total treatment cost for a typical course of 4-6 treatments over 2-3 weeks amounting to $2000 to $4000 (*Ketamine Clinics Directory*, n.d.).

In contrast, IN esketamine, known commercially as Spravato, is FDA-approved specifically for TRD, which significantly enhances its financial accessibility. This approval means it is more likely to be covered by insurance, reducing the financial burden on patients. For those with insurance coverage, the cost per visit for IN esketamine, including the medication and monitoring, is relatively modest at $40 to $60, with a total treatment cost of $480 to $720 over 12 sessions across 8 weeks. However, for patients without insurance coverage, the costs escalate dramatically, with per-visit costs ranging from $900 to $1300 and a total treatment cost of $10,800 to $15,600 (Tan, n.d.).

Regardless of the comparative accessibility due to insurance coverage, the total cost of brand-name esketamine treatment remains significantly higher than that of IV ketamine treatment, despite both having comparable therapeutic outcomes. A 2022 study found that while esketamine nasal spray is not cost-effective compared to intravenous ketamine from a healthcare perspective, it offers similar effectiveness and lower costs from a patient perspective due to insurance coverage (Brendle et al.). IV ketamine's high out-of-pocket costs due to its off-label status can be prohibitive for many patients, limiting its accessibility. In conclusion, the

accessibility of ketamine and esketamine treatments largely depends on the patient's insurance coverage, making IN esketamine more viable for those with coverage, despite its higher overall marketed drug cost.

Discussion

In comparing efficacy, both IV ketamine and Spravato have demonstrated significant antidepressant effects in patients with TRD. Findings from various studies suggest that IV ketamine may offer more rapid and robust antidepressant effects compared to Spravato. However, these conclusions are primarily based on indirect comparisons and smaller-scale studies, which makes it difficult to draw definitive conclusions without direct, head-to-head randomized controlled trials (RCTs).

In comparing safety, both formulations appeared to have similar side effects, with a possibility of a higher incidence of side effects for the IV ketamine group, as suggested by a recent post-hoc analysis (d'Andrea et al., 2024). Spravato benefits from a structured safety program under the Risk Evaluation and Mitigation Strategy (REMS), which mandates that patients be monitored by a healthcare provider for at least two hours post-administration to manage acute side effects. This regulatory oversight ensures a consistent safety protocol. In contrast, IV ketamine, while offering the advantage of flexible dosing that can be tailored to individual patient responses, lacks formal FDA approval for depression treatment. This results in variability in practice standards and potential safety concerns due to the absence of standardized guidelines. Organizations such as the American Psychiatric Association have attempted come up with a set of best practices for off-label use, to potentially mitigate additional safety risks, but updates have not been made since the release of Spravato (Sanacora et al., 2017).

Lastly in comparing accessibility, IV ketamine, used off-label, often incurs high out-of-pocket costs and is typically not covered by insurance, posing significant financial barriers for patients. Spravato, although FDA-approved and more likely to be covered by insurance, is expensive and requires administration in certified healthcare settings, which can limit access.

Although findings from direct and indirect comparisons seem to suggest that intravenous ketamine is more effective, a significant limitation is the lack of direct, randomized control trials (RCTs) comparing IV ketamine and intranasal esketamine. Most existing studies evaluate these treatments independently or through indirect comparisons, which can introduce bias and limit the reliability of the conclusions. The lack of head-to-head RCTs means that we cannot definitively ascertain which treatment is superior in terms of efficacy, safety, and patient outcomes. IV ketamine has been shown to provide rapid and robust antidepressant effects, but the evidence is often derived from smaller, less rigorous studies that are not directly comparable to those conducted on Spravato. Additionally, these studies vary widely in their methodologies, dosing regimens, and patient populations, making it challenging to draw generalizable conclusions.

Therefore, future research should prioritize conducting direct, head-to-head RCTs comparing the long-term efficacy, safety, and overall patient outcomes of IV ketamine and intranasal esketamine. These studies should include diverse patient populations and standardized protocols to ensure more generalizable findings. Additionally, research should explore the long-term safety data for both treatments, as current studies primarily focus on short-term outcomes. Exploring other forms of ketamine administration, such as intramuscular, oral, and subcutaneous routes, could also provide valuable insights to the field.

As IV ketamine continues to gain popularity in off-label administration at ketamine clinics, it is crucial to establish standardized protocols to ensure consistent patient care and outcomes. This involves defining optimal dosing regimens, monitoring protocols, and follow-up procedures. Furthermore, integrating patient feedback and experiences into the refinement of ketamine therapy protocols can improve patient satisfaction throughout the treatment process. This research also found that accessibility remains a challenge, with IV ketamine's high out-of-pocket costs and intranasal esketamine's significant drug cost without insurance coverage. Expanding access to ketamine treatment, possibly through state policy changes and wider insurance coverage, may help ensure that more patients can benefit from these therapies.

Conclusion

As treatment-resistant depression continues to have debilitating impacts on millions of individuals worldwide, optimizing potential alternative treatment options is urgent. Ketamine's emergence as a promising treatment for treatment-resistant depression (TRD) marks a significant advancement in mental health care. Given its rapid onset of action and novel mechanism targeting NMDA receptors, ketamine offers hope for patients who have not found relief with traditional antidepressants. As this thesis has demonstrated, both intravenous ketamine and intranasal esketamine (Spravato) show considerable promise, yet they come with distinct challenges in terms of efficacy, safety, and accessibility. To move forward, it is crucial to prioritize comprehensive research, develop standardized clinical practices, and expand accessibility so that ketamine can fulfill its potential as a transformative treatment for those suffering from TRD.

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