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REVIEW

Spravato for Treatment-Resistant Depression: Efficacy and Sexual Side Effect Profile

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Background: Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) are debilitating psychiatric conditions associated with significant psychosocial and economic burdens. Conventional antidepressants, particularly SSRIs and SNRIs, often produce inadequate responses and cause sexual dysfunction, contributing to poor adherence and diminished quality of life.

Aim: This review aims to evaluate the clinical efficacy, safety, and sexual side effect profile of intranasal esketamine (Spravato) in the treatment of MDD and TRD, highlighting its potential advantages over traditional antidepressants.

Methods: A narrative literature review was conducted using PubMed, ScienceDirect, Cochrane Library, and Google Scholar. Clinical trials, meta-analyses, and systematic reviews published between 2000 and 2025 were included. Keywords used included "Spravato", "esketamine", "treatment-resistant depression", and "sexual dysfunction.".

Results: Clinical trials such as TRANSFORM-2, SUSTAIN-1, and ASPIRE I/II demonstrate that esketamine provides rapid antidepressant effects—often within hours—and improves remission and response rates in TRD. Its NMDA receptor antagonism promotes synaptogenesis and neuroplasticity, distinguishing it mechanistically from monoaminergic antidepressants. Compared to SSRIs/SNRIs, Spravato exhibits a significantly lower incidence of treatment-emergent sexual dysfunction (TESD), with less than 1% of patients reporting such side effects. However, the drug's use is constrained by dissociative symptoms, blood pressure changes, and its mandatory in-clinic administration due to REMS (Risk Evaluation and Mitigation Strategy) requirements.

Conclusion: Spravato (esketamine) is an innovative and effective treatment option for TRD and severe MDD, offering rapid symptom relief and a favorable sexual side effect profile. Despite logistical and financial limitations, it represents a critical advancement in personalized psychiatry, especially for patients unresponsive to conventional therapy.

Keywords: spravato, esketamine, major depressive disorder, treatment-resistant depression, sexual dysfunction

Introduction

Major Depressive Disorder (MDD), is expected to be the leading cause of disability worldwide, affecting an estimated 300 million individuals worldwide, ranked third by World Health Organization (WHO) report in 2018 and extrapolated to be the top in 2030s, substantially contributing to personal, societal and economic burden.[1] MDD prevalence varies globally with lifetime prevalence estimated between 2% and 21% and 12-month prevalence ranging from 1% to 10%. Europe has the highest rates, while Asia has the lowest. These variations reflect genetic, environmental, and sociocultural factors.[2]

Beyond these determinants, lifestyle factors also play a significant role in the onset and course of MDD and TRD. Higher adherence to cardiovascular health metrics, such as those outlined in the American Heart Association's Life's Essential 8 (LE8), has been associated with a reduced risk of depression.[3] Furthermore, large-scale population studies have shown that regular physical activity and balanced nutrition are linked to lower incidence and improved outcomes in depressive disorders.[4]

Despite treatment availability, up to almost ⅓ of the patients experience treatment resistant depression (TRD), defined as inadequate response to at least two different antidepressants given at an appropriate dose and duration.[5] This disorder

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most prevalent among geriatric population can be emphasized by the clinical trials that showed more notable percentages of people resistant to the antidepressant therapy ranging from a third to three quarters.[6] Individuals with MDD often face profound impairments in the quality of life, including difficulty maintaining employment, strained relationships, and an overall diminished ability to experience pleasure, which can be attributed not only to the disorder itself but also to associated medical comorbidities, social factors, and impaired functional outcomes.[7] Notably MDD is also associated with suicidal ideation, affecting 18–58% of patients, and serves as a significant predictor of suicide attempts and fatalities.[8] What even more concerning is the fact that suicidal attempts in TRD are sevenfold than in patients that respond to antidepressants, underscoring the need for more effective treatment options.[9]

The conventional diagnostic approach to MDD faces multifaceted challenges due its broad synonym parameters, leading to significant clinical heterogeneity and unpredictable treatment response. Precision medicine, which tailors treatment based on an individual's unique clinical and biological profile, holds promise for improving outcomes while minimizing side effects.[10] Spravato (esketamine) has emerged as a novel pharmacological modality for TRD and MDD, offering a distant mechanism of action compared to the traditional monoaminergic antidepressants with being approved by Food and Drug Administration (FDA) in 2019.[11] It is administered as a nasal spray and is a more potent derivative of ketamine as a S-isomer.[12] It modulates the glutamatergic transmission by antagonizing the N-methyl-D-aspartate (NMDA) receptor producing rapid antidepressant effects furthermore signalling and synaptogenesis is improved in areas of brain regulating mood and emotions.[13] Given its unique mode of action and emerging clinical data, esketamine presents a promising alternative for individuals unresponsive to conventional therapies.[14]

Spravato may offer a promising solution for treatment-emergent sexual dysfunction (TESD), a common and distressing adverse effect of many antidepressants that can significantly reduce sexual activity and quality of life.[5,15] TESD affects up to 70% of patients on conventional antidepressants,[16] contributing to poor adherence and higher dropout rates in long-term treatment.[17] Traditional agents, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are strongly linked to sexual side effects, with incidence rates ranging from 30% to 70%.[16] For example, fluoxetine has been associated with anorgasmia, reduced libido, and erectile dysfunction.[18]

Sexual dysfunction in major depressive disorder (MDD) may stem from both the illness itself and its treatments. Even without prior antidepressant exposure, approximately 46.2% of treatment-naïve MDD patients report sexual dysfunction, with higher rates in females than males.[19] In a condition where motivation, self-esteem, and interpersonal connectedness are already compromised, side effects that impair emotional intimacy can further undermine recovery. Thus, Spravato may offer a promising alternative for patients at risk of, or already experiencing, TESD.

The objective of this review is to examine the efficacy and safety of Spravato in the treatment of MDD and TRD, with a particular focus on its potential to minimize and avoid sexual dysfunction, a common and often treatment limiting side effect of many traditional antidepressant medications such as SSRIs and SNRIs, tricyclic antidepressants (except clomipramine) and mirtazapine.[20] Additionally, the review examines the clinical evidence supporting its use, practical considerations for its administration, and the broader implications for psychiatric practice in managing patients who are unresponsive to conventional therapies. A central emphasis of this review is Spravato's advantage in preserving sexual function, a key factor influencing treatment adherence, patient satisfaction, and overall quality of life. By focusing on this often overlooked dimension, we aim to highlight Spravato's potential not only for symptom relief but also for minimizing treatment-related adverse effects.

Methodology

This study was designed as a narrative literature review aimed at synthesizing current evidence on the efficacy, safety, mechanism of action, and sexual side-effect profile of intranasal esketamine (Spravato) in the management of Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD). To identify relevant literature, a comprehensive search was conducted across PubMed, Google Scholar, ScienceDirect, and the Cochrane Library databases, covering publications from January 2000 to May 2025. The search strategy employed the following combination of keywords and Boolean operators: ("esketamine" OR "Spravato") AND ("treatment-resistant depression" OR "TRD" OR "major depressive disorder" OR "MDD") AND ("sexual dysfunction" OR "sexual side effects" OR "sexual adverse events")

AND ("rapid-acting antidepressants" OR "NMDA receptor antagonists"). Filters were applied to restrict results to English-language, peer-reviewed articles involving human subjects. No ethical approval or patient consent was required.

Articles were screened in two stages. In the initial phase, titles and abstracts were reviewed to eliminate duplicates and studies unrelated to the research objective. The second phase involved a full-text review of potentially relevant articles. Studies were included if they met the following criteria: (1) investigated the clinical use of intranasal esketamine for MDD or TRD; (2) reported on efficacy outcomes such as changes in depression severity scores or remission rates; and (3) provided data on safety, with an emphasis on sexual dysfunction or treatment-emergent sexual dysfunction (TESD). Exclusion criteria comprised non-English publications, non-clinical studies, conference abstracts, case reports, and articles lacking sufficient clinical data on sexual function or adverse events.

Data from the included studies were extracted and organized using a standardized approach. For each study, information was recorded on authorship, year of publication, country, study design, sample size, participant characteristics, intervention details (dose, route, and duration), and reported outcomes. Particular attention was given to documenting measures of efficacy, onset of antidepressant effect, and the incidence of sexual side effects. When available, details of assessment tools used to evaluate sexual adverse events, such as the Arizona Sexual Experience Scale (ASEX) and the Changes in Sexual Functioning Questionnaire (CSFQ), were also captured. Extracted data were compiled into a structured table to facilitate comparison of key study characteristics, and the narrative synthesis was developed to highlight patterns, clinical implications, and gaps in the literature.

Major Depressive Disorder and Treatment-Resistant Depression

Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD) is a psychiatric ailment that is evaluated by checking whether the patient has at least one episode of depressive symptoms for a minimum two weeks. Among those depressive symptoms comes a vast array of manifestations such as pervasive feelings of sadness, loss of interest or pleasure in activities, and a range of cognitive and physical symptoms that impair daily functioning.[21] It is properly classified under mood disorders in the DSM-5 also shown in Figure 1 and is diagnosed when an individual experiences at least five of the following symptoms with at least one being either depressed mood or anhedonia (loss of interest or pleasure). These symptoms include a depressed mood most of the day, nearly every day; loss of interest or pleasure in most activities (anhedonia); significant weight change (loss or gain) or appetite disturbances; insomnia or hypersomnia (sleep disturbances); psychomotor agitation or retardation, observable by others; fatigue or loss of energy; feelings of worthlessness or excessive guilt; difficulty concentrating or making decisions; and recurrent thoughts of death, suicidal ideation, or suicide attempts.[22] Genetically, it has been linked with 178 genetic risk loci and 200 candidate genes identified by Genome-wide association studies (GWAS); however most of these findings are from minimal phenotyping data. Apart from these neurobiological factors and environmental stressors also play a part.[23] MDD is also linked with many comorbids including central nervous system disorders like dementia, Alzheimer's, and Parkinson's disease. It is also linked to various cardiovascular diseases, such as general cardiovascular disease, ischemic heart disease, coronary artery disease, myocardial infarction, and heart failure. In addition, metabolic and endocrine disorders, particularly diabetes in men and obesity in women, are often seen in MDD patients. The condition is also tied to certain autoimmune disorders, including Crohn's disease, psoriasis, and multiple sclerosis, as well as substance use disorders.[24] MDD is most common in females as some study reported that it is 1.7 times more prevalent in women than in men.[25]

Treatment-Resistant Depression (TRD)

Treatment-Resistant Depression (TRD) is a severe subtype of MDD for which the patient is unresponsive to the adequately administered treatment of antidepressants at least two times taken at the appropriate dose and duration. Moreover the clinicians come to the point of diagnosis when there is less than a half of reduction of depressive symptoms after a month however there is a conflict among themselves as some consider 6–8 weeks timeframe for pharmacotherapies and 10–12 weeks for psychotherapy.[26] TRD poses a significant challenge in psychiatric care, as individuals with this condition often experience more severe and prolonged depressive episodes, greater functional impairment, and a higher risk of suicide.[5]

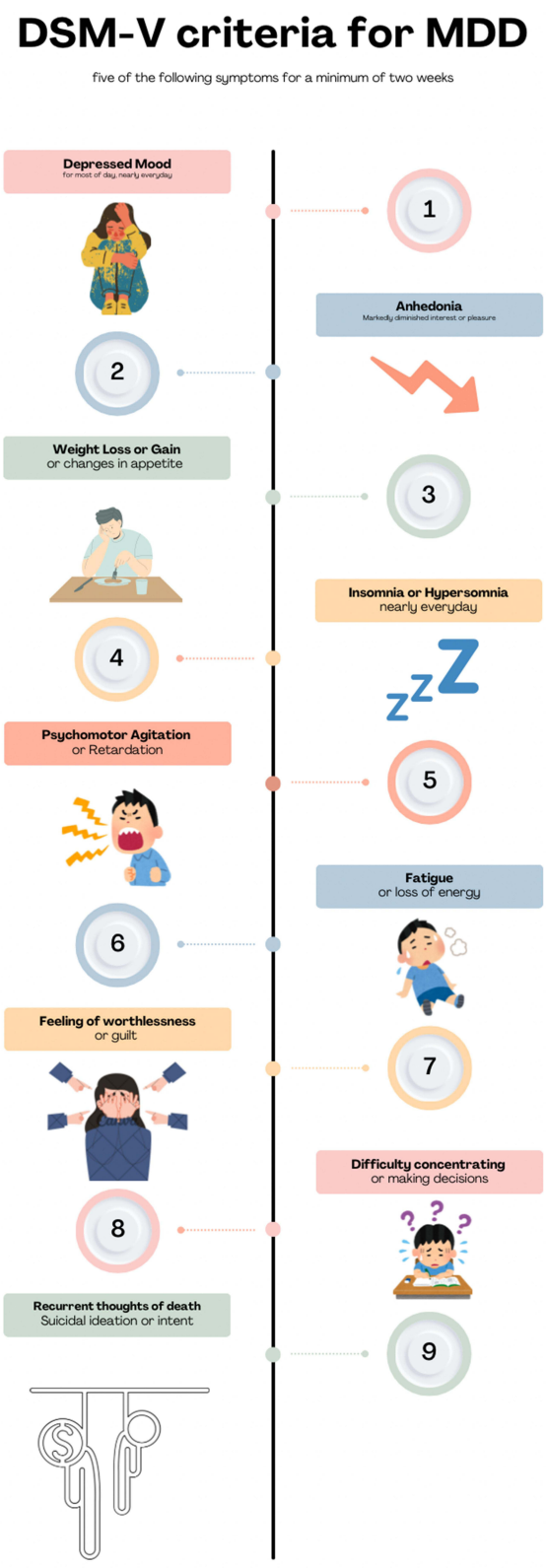

Figure 1 DSM-V Criteria for Major Depressive Disorder (MDD), illustrating the nine key symptoms used for diagnosis. To meet the criteria, an individual must experience at least five of these symptoms for a minimum duration of two weeks, with at least one being either depressed mood or anhedonia.

Burden of MDD and TRD

MDD and TRD have a profound impact on the quality of life as well as increases in morbidity and mortality, impairment of occupational, social and offspring development and overburdening of the health care structures cost.[27] It has also been found that patients with anhedonia are more likely to have a worse prognosis and worse quality of life with functioning deficits such as daily functioning, personal relationships, and overall well-being.[28] Not only does it impact life individually, it is also costing billions annually in lost productivity as it has been linked with absenteeism and presenteeism (reduced work efficiency while present at work).[29] TRD is also linked with higher hospitalization rates, more outpatient departments, psychiatrist and GPs visits with an excruciating cost of treatments with one study highlighting the average two-year cost for TRD patients was around 20,000 Canadian dollars.[30] The economic burden of MDD and TRD is staggering. In the US alone, MDD costs exceed $326 billion annually,[31] with TRD patients contributing disproportionately to these costs due to higher medical expenses, disability claims, and lost income.[30] MDD also remains the major risk factor for suicide taking 87% of the 800,000 lives annually which needs a urgent call to have appropriate treatment plans for the individuals affected with MDD.[32]

Current Treatment Landscape

Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) are commonly treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

For TRD, augmentation strategies include atypical antipsychotics (eg, aripiprazole), lithium, or combination antidepressants. However, these carry risks like metabolic side effects and extrapyramidal symptoms.[33]

Non-pharmacologic options such as cognitive behavioral therapy (CBT), electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS) are also effective, particularly when combined with medication.[34]

Esketamine, a novel NMDA receptor antagonist delivered intranasally, has shown rapid efficacy in TRD with a lower incidence of sexual side effects, offering a promising alternative to traditional treatments.[5]

A summary of current treatment modalities for Major Depressive Disorder and Treatment-Resistant Depression, comparing their efficacy, impact on sexual function, and key clinical considerations is provided in Table 1.

Spravato: Mechanism of Action and Clinical Efficacy

Mechanism of Action

Spravato (esketamine), the S-enantiomer of ketamine, acts as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor on glutamatergic neurons. This mechanism sets it apart from traditional antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which primarily act by increasing monoamine levels in the synaptic cleft. NMDA receptor antagonism by esketamine promotes increased extracellular glutamate levels, which subsequently activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Table 1 Comparative Overview of Treatments for MDD and TRD by Efficacy and Sexual Side Effects

Treatment Modality	Efficacy in TRD	Sexual Side Effects	Notes
SSRIs/SNRIs	Moderate	High	First-line; high TESD rates[16,17]
Atypical Antipsychotics	Moderate	Moderate	Effective as augmentation; metabolic risks[6,33]
Esketamine	High	Low	Rapid-acting; requires monitoring[35–37]
Psychotherapy + Medication	High	Low	Combined approach yields best outcomes[34]
rTMS	Moderate	Low	Non-invasive; suitable for outpatient care[38]
ECT	High	Low	Most effective; cognitive side effects[6,7]
tDCS	Low to Moderate	Low	Emerging modality; more research needed[39,40]

(AMPA) receptors. This triggers downstream signaling pathways including the release of brain-derived neurotrophic factor (BDNF), enhanced synaptogenesis, and increased synaptic plasticity—mechanisms associated with rapid antidepressant effects.[41,42] These neurobiological changes address core pathophysiological features of major depressive disorder (MDD), particularly in treatment-resistant cases where impaired glutamatergic transmission and synaptic connectivity have been implicated.

Although the primary antidepressant effect of ketamine and esketamine is mediated via NMDA receptor antagonism and downstream glutamatergic modulation, preclinical and clinical evidence indicates that these agents also influence monoaminergic systems. Studies have shown that ketamine can increase synaptic levels of serotonin, norepinephrine, and dopamine likely through enhanced presynaptic release and reduced reuptake thereby indirectly augmenting monoaminergic neurotransmission. These changes, while not the main mechanism, may contribute to mood improvement and could explain partial overlap in therapeutic effects with conventional antidepressants.[43]

Across Phase 3 trials, esketamine produced rapid and clinically meaningful improvements in depressive symptoms, with benefits emerging within hours of the first dose and maintained throughout treatment. Moreover, intranasal delivery is quick and provides a more convenient route by avoiding issues like gastrointestinal absorption, first-pass metabolism, and crossing the blood-brain barrier, making it less invasive than parenteral administration.[35] Notably, intranasal ketamine has an absolute bioavailability of 50%, reaching maximum plasma levels in about 20 minutes.[44]

Figure 2 illustrates the proposed mechanism of action of intranasal esketamine.

Clinical Trial Data

Several randomized controlled trials (RCTs) have assessed the clinical efficacy of Spravato in major depressive disorder (MDD) and treatment-resistant depression (TRD). [Table 2] In the TRANSFORM-2 trial (N = 223), patients with TRD received either intranasal esketamine plus a newly initiated oral antidepressant or placebo plus antidepressant. The study reported a statistically significant reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) scores from baseline to day 28 in the esketamine group (mean difference = −4.0; $p = 0.020$).[14] Another RCT, SUSTAIN-1 (N = 297), focused on relapse prevention in patients who achieved remission or response during the acute phase. Continued esketamine treatment significantly delayed relapse compared to placebo (hazard ratio = 0.49; $p = 0.003$).[36] The ASPIRE I and II trials assessed esketamine's rapid reduction of depressive symptoms in patients with MDD and active suicidal ideation. Both trials demonstrated a statistically significant improvement in MADRS scores within 24 hours of the first dose, though they did not show superiority over placebo for preventing suicide.[45,46] Additionally, pooled analyses from multiple phase 3 trials have reported remission rates ranging from 27% to 50%, with notable onset of action as early as 24 hours after the first dose.[47] Collectively, these trials demonstrate esketamine's capacity to produce rapid, clinically meaningful reductions in depressive symptoms, with effects often observed within the first 24 hours and sustained during maintenance phases.

Administration and Dosage

Spravato (esketamine) is administered as a nasal spray under strict medical supervision due to its dissociative and sedative side effects. Each device delivers 28 mg of esketamine, and dosing is based on both the indication and the treatment phase. For adults with treatment-resistant depression (TRD), the induction phase involves 56 mg on day 1, followed by 56 mg or 84 mg twice weekly for four weeks. During the maintenance phase, dosing is adjusted based on response, with once-weekly or once every two weeks administration of 56 mg or 84 mg.[49]

Spravato must be administered in a certified healthcare setting due to the risk of sedation, dissociation, and potential abuse. Patients are monitored for at least two hours post-administration, during which blood pressure, mental status, and vital signs are assessed.[36,47] It is not approved for home use, and the REMS (Risk Evaluation and Mitigation Strategy) program ensures controlled dispensing and mandatory observation. Oral antidepressants are continued alongside Spravato, as monotherapy has not been established. The intranasal route offers a rapid onset of action, contributing to its early antidepressant effects, often observed within 24 hours of the first dose.[14]

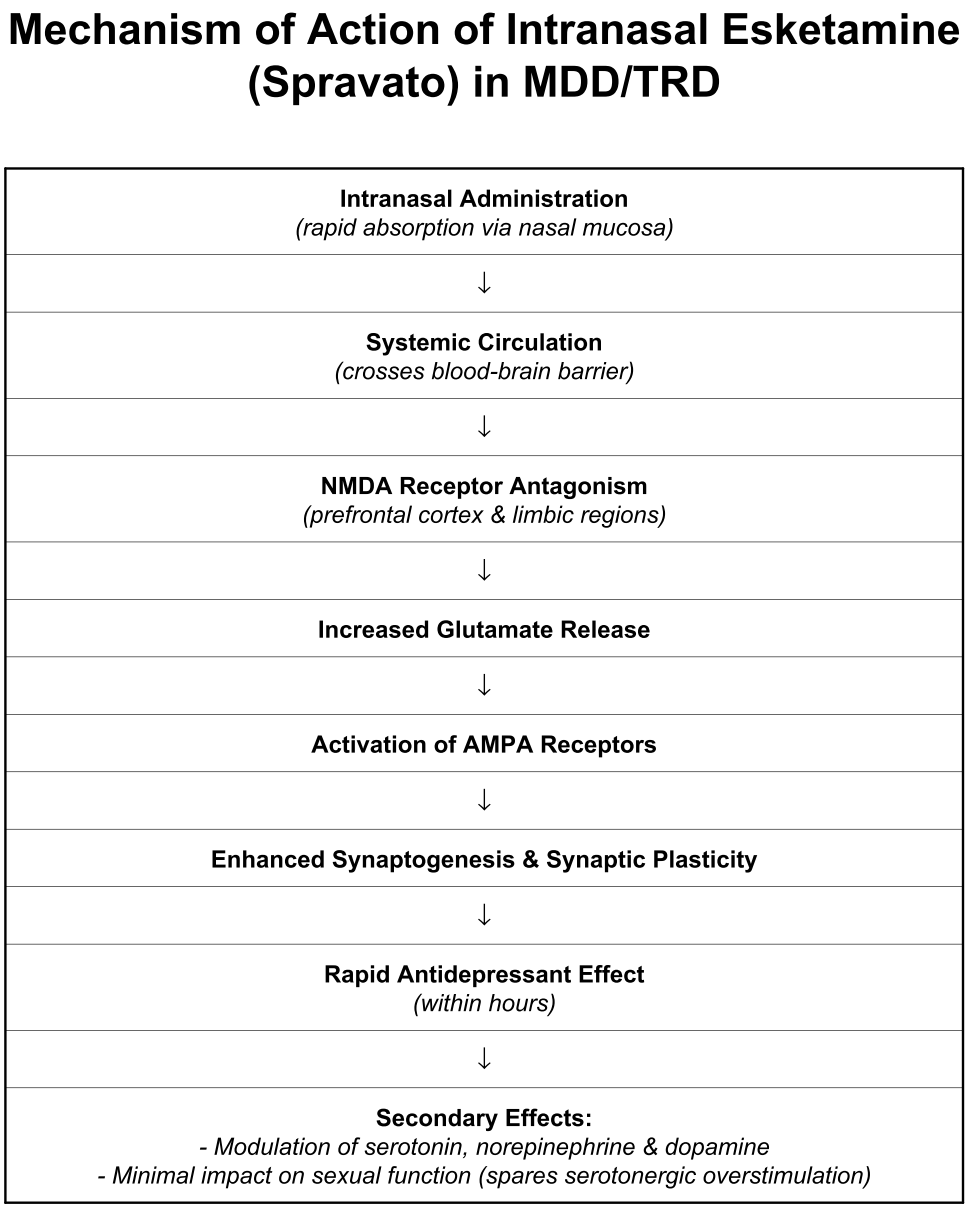

Figure 2 Mechanism of intranasal esketamine (Spravato) in depression, showing intranasal administration, systemic circulation, NMDA receptor antagonism, increased glutamate release, AMPA receptor activation, enhanced synaptogenesis, and rapid antidepressant effect. Italicized text within the figure denotes explanatory notes. Bold-italicized text indicates the mechanistic steps and final effect.

Spravato and Sexual Function

Impact on Sexual Function

Clinical trials assessing Spravato (esketamine) have reported a low incidence of sexual dysfunction. In three short-term, double-blind, phase 3 studies, treatment-emergent adverse events (TEAEs) related to sexual function were infrequent. Specifically, delayed ejaculation was reported in 0.2% of patients receiving Spravato plus an oral antidepressant, compared to 0% in the placebo group. Erectile dysfunction was observed in 0% of the Spravato group versus 0.6% in the placebo group. Overall sexual dysfunction was reported in 0.2% of the Spravato group and 0% of the placebo group. These findings suggest that Spravato has a minimal impact on sexual function.[14,36,45,46]

Table 2 Summary of Key Clinical Trials Investigating Spravato in MDD/TRD

Trial Name	Sample Size	Population	Primary Outcome	Key Findings	Reference
TRANSFORM-2	N = 223	Adults with TRD	Change in MADRS at Day 28	Significant reduction in MADRS (mean diff = −4.0; p = 0.020)	Popova et al., 2019[14]
SUSTAIN-1	N = 297	TRD patients in remission	Time to relapse	Esketamine significantly delayed relapse (HR = 0.49; p = 0.003)	Daly et al., 2019[36]
ASPIRE I	N = 226	MDD with suicidal ideation	MADRS score reduction at 24 hrs	Significant reduction in MADRS (difference = −3.8; $p < 0.05$)	Fu et al., 2020[45]
ASPIRE II	N = 240	MDD with suicidal ideation	MADRS score reduction at 24 hrs	Significant MADRS improvement (difference = −3.9; $p < 0.05$)	Ionescu et al., 2021[46]
Pooled Data	-	Pooled phase 3 trials	Remission, time to response	Remission rates 27–50%, onset within 24 hours	Wajs et al, 2020[48]

Abbreviations: MDD, Major Depressive Disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; TRD, Treatment-Resistant Depression.

Comparison to Other Antidepressants and Neuromodulation Approach

Unlike traditional antidepressants such as SSRIs and SNRIs, which are often associated with sexual dysfunction through their effects on serotonergic pathways, Spravato acts as an NMDA receptor antagonist and does not directly target serotonin systems. Thus, a low incidence of sexual side effects has been observed in Spravato clinical trials suggesting a more favorable sexual side effect profile compared to traditional antidepressants.[14,36,47] Clinical trial data in treatment-resistant depression (TRD) consistently show a very low incidence of treatment-emergent sexual dysfunction (TESD) with Spravato typically under 1%, across both short- and long-term phases.[50] However, no head-to-head comparisons between MDD and TRD populations have been conducted to determine whether TESD manifests differently between them, nor whether Spravato's sexual side-effect profile differs by diagnostic subtype.

Meanwhile, non-invasive neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are increasingly used in TRD, are well tolerated, and exhibit minimal side effects such as transient scalp discomfort or headache with no evidence of associated sexual dysfunction likely due to their mechanism involving cortical modulation rather than serotonergic pathways. Thus, Spravato and neuromodulation share a critical advantage: they preserve sexual function, a dimension of treatment tolerability that is often overlooked but central to adherence and quality of life. While Spravato offers rapid onset of action and a pharmacological option for patients who cannot access or do not respond to neuromodulation, rTMS and tDCS provide non-drug strategies that may be particularly appealing for patients wishing to avoid systemic side effects. Together, they broaden the therapeutic landscape for TRD, offering complementary, mechanistically distinct approaches that address efficacy while minimizing the burden of TESD.[51–53]

Significance of Preserving Sexual Function

Preserving sexual function is essential for patient quality of life and treatment adherence. Sexual side effects can reduce medication adherence and increase dropout rates, particularly in depression, where self-esteem, motivation, and relationships are already strained.[17] If Spravato can relieve depressive symptoms without significantly affecting sexual function, it may boost treatment success and patient satisfaction.

Advantages of Spravato Over Conventional Antidepressants

Rapid Onset of Action

Across multiple phase 3 trials, esketamine produced rapid and clinically meaningful improvements in depressive symptoms, with benefits emerging within hours of the first dose and maintained throughout treatment. This rapid

onset contrasts with the delayed therapeutic effect of conventional antidepressants, which often require weeks to achieve comparable symptom relief. In addition, intranasal esketamine also showed rapid anti-suicidal effect. This suggests the drug may help overcome the typical treatment delay seen with traditional antidepressants, offering timely relief which could particularly be beneficial for patients with major depressive disorder with suicidal ideation or behavior (MDSI).[54]

Treatment with SSRIs is associated with symptomatic improvement in depression by the end of the first week of use, and the improvement continues at a decreasing rate for at least 6 weeks.[55] Moreover, a meta-analysis of 76 controlled trials on antidepressants found that approximately 60% of the total symptom improvement occurred within the first two weeks. This shows that symptomatic relief unfolds over days to weeks.[56]

Esketamine has the fastest onset of action among available antidepressants, with effects seen within hours to one day versus weeks required for SSRIs, SNRIs, and TCAs. This makes it particularly valuable for treatment-resistant depression and acute suicidal risk.[54]

Efficacy

While intravenous ketamine is known for its rapid antidepressant effects, it is limited by the need for trained personnel and specialized administration equipment.[57] In contrast, intranasal delivery is quick and provides a more convenient route making it less invasive than parenteral administration.[35] Intranasal doses around 50–175 mg administered every 3 to 7 days can markedly improve mood symptoms with comparatively few side effects.[58]

A landmark RCT that contributed to esketamine's approval as an anti-suicidal treatment investigated its clinical efficacy versus placebo in high-risk MDD patients. It was discovered that intranasal esketamine significantly improved MADRS (Montgomery-Åsberg Depression Rating Scale) scores as early as 4 hours after the initial dose. Furthermore, within the esketamine group, 21.1% of participants experienced a resolution of suicide risk within four hours of the first dose and this increased to 40% by the subsequent day. Although no changes in CGI-SS-R (Clinical Global Impression of Severity of Suicidality Scale) were reported, post-hoc analyses of two phase 3 trials found that esketamine had a greater MADRS improvement one day after the initial treatment in those who attempted suicide in the last month and those with baseline scores above the median.[59,60]

In addition, adolescents with TRD given a single administration of esketamine also exhibited improved total MADRS and MADRS-SI (MADRS suicide item), indication its significant antidepressant and antisuicidal effects.[61]

Comparison of racemic ketamine and esketamine found that both greatly reduced MADRS-SI within a day and effects lasted up to a week. No difference was observed between the forms.[62] Further,

Bahji et al reported same-day antisuicidal efficacy of both forms.[63] However, Xiong et al cautioned that the limited number of comparative esketamine studies makes direct comparison premature.[64]

It can be concluded that esketamine has notable antidepressant and antisuicidal efficacy although it is undetermined whether this effect is a consequence of overall depressive symptom alleviation.

Sexual Dysfunction

Clinical studies have consistently demonstrated that intranasal esketamine nasal spray has minimal adverse effect on sexual function in treating TRD. In a comprehensive analysis of three phase 3 studies, the incidence of TESD was low. In particular, delayed ejaculation and sexual dysfunction was reported in 0.2% of patients receiving esketamine + oral antidepressant versus 0% in the placebo + oral antidepressant group. However, erectile dysfunction was observed in none of esketamine patients compared to 0.6% of the placebo patients.[14,36,45]

Additionally, a long-term, open-label, phase 3 study found a low incidence of TESD wherein 0.4% of patients experienced sexual dysfunction, 0.3% had erectile dysfunction and 0.1% had priapism. These effects were uncommon and did not lead to treatment cessation.[48] These results were supported by the long-term SUSTAIN-3 study,[65] with no sex differences noted.[66]

The emergence of sexual dysfunction during antidepressant therapy can significantly impact treatment compliance and quality of life. Therefore, it is vital for clinicians to consider TESD profiles of antidepressants when devising treatment plans for MDD patients, ensuring therapeutic efficacy with the preservation of sexual function.

Collectively, these studies suggest that intranasal esketamine nasal has a negligible impact on sexual function. This profile is particularly advantageous for patients concerned about sexual side effects.

Challenges and Limitations

Side Effects

In terms of safety and tolerability, intranasal esketamine showed greater number of adverse effects than the placebo group. In particular, there was a greater risk of somnolence, dizziness, vertigo, nausea and dysgeusia.[45] Moreover, intranasal esketamine is linked to causing dissociation[67] and rise in blood pressures.[68] The dissociative symptoms peak soon after administration and resolve by 2 hours.[69,70] Rate and intensity of dissociation lessened with frequent administrations. Rise in blood pressures were short-term, asymptomatic, and not associated with adverse cardiovascular events.[68]

Psychiatric symptoms consist of fatigue, anxiety, altered mood and behavior, panic attacks and visual and auditory disturbances. Other medical symptoms include frequent urination, chest pain and anaphylaxis.[38]

The most intense side effects are usually experienced during the first two treatments, typically peaking around 40 minutes after administration and subsiding within 2 hours.[71]

In Addition, There's a Rare Possibility of Developing Dependence

Esketamine is the S-enantiomer of ketamine which is classified as a Schedule I controlled substance. Ketamine has a potential for recreational misuse and addiction as it can induce vivid dreams and dissociative experiences. Subsequently, regular use leads to the development of tolerance, requiring higher doses to achieve the same effects.[39] The warning label for intranasal esketamine highlights risks of sedation, abuse, misuse, and increased suicidal thoughts and behaviors, particularly in children and young adults.[40]

Consequently, esketamine administration requires rigorous monitoring. The dissociative effects emphasize the importance of carefully monitoring patients to minimize distress and maintain safety.[72] Its risk of abuse and misuse has led to strict prescribing control under the Risk Evaluation and Mitigation Strategy (REMS). This program limits the administration of this drug in certified healthcare facilities under strict supervision.[37] However, such regulatory limitations may pose barriers to treatment access. Striking a balance between safety and accessibility remains a major challenge in the broader implementation of esketamine. Across both acute-phase RCTs (eg, TRANSFORM-2, SUSTAIN-1) and long-term open-label studies (eg, SUSTAIN-3), the most frequent adverse events included dissociation, transient blood pressure elevation, and urinary symptoms.[33–35] Dissociation was reported in ~25–31% of patients during early treatment phases, typically resolving within 2 hours;[33–35,69,70] long-term studies show reduced incidence (~10–-15%) with repeated dosing.[65] Blood pressure elevations occurred in ~8–17% of acute-phase participants and ~7–12% in maintenance phases, generally mild and transient.[65,68] Urinary adverse events (eg, dysuria, increased frequency) were rare in short-term studies (<2%) but reached ~13% in SUSTAIN-3, without cases of severe bladder pathology.[65,73] Table 3 summarizes these findings, highlighting consistency in safety profiles across treatment durations. Presently, more research is needed to better characterize the long-term risks, side effects, safety profile and administration strategies of this medication to improve patient outcomes and minimize dependence and abuse.

Cost Disadvantage

Despite promising results, intranasal ketamine remains out of reach for most people with depression due to high costs and limited availability. Financially, studies show that the cost of the treatment often exceeds thousands of dollars per month. This creates a substantial burden for both patients and healthcare facilities.[74]

Moreover, access is further impacted by insurance constraints due to inconsistent coverage of this treatment and stringent prior authorization requirements imposed by some providers.[75]

Esketamine accessibility is also limited by REMS requirements. This program mandates that patients undergo treatment only in certified healthcare systems under direct supervision thereby limiting the number of providers available

Table 3 Summary of Key Adverse Events with Intranasal Esketamine Across Acute and Long-Term Studies

Adverse Event	Acute-Phase Trials[a] (eg, Transform-2, Sustain-1)	Long-Term Studies[b] (eg, Sustain-3)	Notes / Clinical Context
Dissociation	~25–31%	~10–15%	Peaks within first 40 min post-dose, resolves by 2 h; incidence decreases with repeated dosing
Blood Pressure Elevation	~8–17%	~7–12%	Mild, transient increases; not linked to adverse CV events; monitor per REMS requirements
Urinary Adverse Events (eg, dysuria, increased frequency)	<2%	~13%	No severe bladder pathology reported; rare cases of LUTS; recommend monitoring symptoms
Sedation / Somnolence	7–11%	5–8%	Often overlaps with dissociation timeframe; transient
Nausea	8–10%	6–9%	Mild to moderate; manageable with supportive care
Anxiety / Mood Changes	2–5%	1–4%	Typically self-limited; may require reassurance or brief observation

Notes: [a] Acute-phase = short-term randomized controlled trials, typically 4–6 weeks. [b] Long-term = open-label maintenance or extension trials, up to ~4.5 years.

to patients.[37,76] Furthermore, healthcare facilities may encounter administrative burdens and finances related to REMS certification, which might discourage them from offering the treatment.[77]

These barriers exacerbate healthcare inequalities, disproportionately affecting patients from rural areas and lower socioeconomic backgrounds.[78] Moreover, they present significant challenges to the broader adoption of this potentially life-saving medication for individuals who need it. Thus, tackling these barriers through policy reform, financial aid, and the expansion of REMS-certified clinics is imperative.

Long Term Usage

Data suggests that esketamine's long-term side-effect profile is similar to its short-term profile. In long-duration trials (up to ~4.5 years), the most commonly reported adverse effects included nausea, dissociation, blood-pressure and heart-rate increments. These effects were clinically negligible, mild-to-moderately intense and transient.

Furthermore, sedative and dissociative symptoms were resolved on the day of administration.[65,73]

Among healthy volunteers, a single dose of this drug caused cognitive deterioration after 40 minutes of administration.[79] However, its prolonged use was not linked to cognitive decline. Neurocognitive testing in SUSTAIN-3 showed that mean performance remained mostly stable or even slightly improved over time.[65]

There was an increased incidence of lower urinary tract symptoms. For instance, SUSTAIN-3 reported UTIs in ~13% of patients. However, esketamine-induced interstitial cystitis or severe bladder pathology was not documented.[65,73] Thus, the current label highlights evaluating bladder symptoms during treatment.[79] Moreover, there was no report of drug-related adverse hepatic events.

Recreational ketamine misuse is associated with tolerance and withdrawal. Regarding esketamine, no instances of drug-seeking behavior or misuse were reported in clinical studies, and there were no withdrawal symptoms after therapy cessation.[80,81] However, vigilance is warranted as esketamine is classified as a Schedule III controlled substance with potential abuse risk.[79] Consequently, risk-benefit analysis is vital for prescription and it is necessary to look out for signs of misuse and addiction.

Esketamine's antidepressant effect also appears significant. In the long-term SUSTAIN-3 extension, MADRS improved notably during the 4-week induction phase and remained this way throughout maintenance. 35.6% of patients were in remission at the end of induction and this number rose to over 50% at 1 year and 46.1% at the final end-point. Patient-reported measures (PHQ-9) showed similar improvements.[65] This is consistent with earlier studies wherein Wajs et al reported ~47.2% remission at one year.[48]

Contraindications

Esketamine has several well-defined contraindications and precautions. The FDA label specifies absolute contraindications in patients with aneurysmal vascular disease (eg aortic or cerebral aneurysms), arteriovenous malformation, history of hemorrhagic stroke and hypersensitivity to esketamine, ketamine, or any formulation excipient.

Beyond these, the label and clinical reviews emphasize relative contraindications/precautions. Patients with significant cardiovascular or cerebrovascular disease (e.g severe hypertension) should be carefully evaluated and if pre-dose blood pressure rises above 140/90 mmHg, treatment should be delayed or avoided. As trials have not included patients with active psychotic symptoms, caution is warranted in cases of psychiatric instability as esketamine's dissociative effects and dysgeusia may exacerbate these conditions.

Similarly, esketamine is a Schedule III controlled substance with known abuse potential, so patients with a history of substance use disorder, especially involving ketamine, should be carefully monitored.

Finally, esketamine is not approved for the pediatric, pregnant and breastfeeding population. Antidepressants can increase suicidal thoughts and behaviors in pediatric and young adult patients. In pregnancy, the label states that esketamine may cause embryo-fetal toxicity. Furthermore, as esketamine is excreted in breast milk and animal data reports neurotoxicity, women are advised not to breastfeed during therapy.[79,82]

Theoretical Basis for Low Impact on Sexual Function

Esketamine appears to have a relatively small effect on sexual function, which may be explained by its selective action on NMDA receptors. Normal sexual response depends on nitric oxide pathways that regulate blood flow and arousal in genital tissues. Glutamatergic activity, particularly through NMDA receptors, influences nitric oxide synthase in brain regions connected to sexual behaviour. Experimental studies have shown that ketamine can disrupt neurogenic relaxation of penile tissue by interfering with NMDA-mediated nitric oxide release.[83] In contrast, clinical research among ketamine abusers has reported higher rates of sexual dysfunction, suggesting that broad and repeated NMDA inhibition may negatively affect sexual performance.[84] Esketamine, however, has a more targeted mechanism and does not appear to suppress the nitric oxide circuits that are essential for arousal and orgasm. Reviews of nitric oxide's central role in sexual motivation and performance further support this explanation, highlighting its importance in hypothalamic and extrahypothalamic pathways that regulate sexual behaviour.[85] This theoretical framework helps explain why esketamine is associated with a lower incidence of sexual side effects compared to many traditional antidepressants.

Conclusion

Spravato (esketamine) marks a pivotal advancement in the management of Major Depressive Disorder and Treatment-Resistant Depression, offering rapid relief and a lower risk of sexual side effects compared to traditional antidepressants. Its unique mechanism of action provides new hope for patients who have not responded to standard treatments, improving both clinical outcomes and quality of life. Preservation of sexual function is particularly important, as treatment-emergent sexual dysfunction is a common reason for non-adherence, reduced patient satisfaction, and diminished relationship well-being. By minimizing this burden, Spravato may enhance long-term adherence and therapeutic success. However, further research is essential to address key gaps in knowledge particularly regarding long-term safety, durability of response, and individualized predictors of treatment success. Future studies should also investigate optimized dosing strategies, combination therapies, and next-generation alternatives with enhanced tolerability and accessibility. As the field evolves, integrating Spravato into a comprehensive, patient-centered treatment model will be vital to advancing care for those with difficult-to-treat depression.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author, A.S., upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no conflicts of interest related to this work.

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