EFFICACY OF INTRANASAL ESKETAMINE AS A NOVEL RAPID ANTIDEPRESSANT IN ADULTS WITH TREATMENT-RESISTANT DEPRESSION

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ABSTRAK

Gangguan depresi mayor (MDD), penyebab utama kecacatan di seluruh dunia adalah gangguan kesehatan mental umum dan melumpuhkan yang terkait dengan tingkat morbiditas dan mortalitas terkait bunuh diri yang tinggi. Meskipun ketersediaan terapi antidepresan, sepertiga pasien dengan MDD gagal mencapai remisi dan dianggap memiliki Depresi Tahan Pengobatan (TRD). Penelitian telah menemukan esketamine intranasal, enansiomer obat anestesi yang disebut ketamine, sebagai terobosan potensial dalam memerangi resistensi pengobatan dan menurunkan jumlah bunuh diri terkait depresi. Namun, ulasan yang mencakup potensi penggunaan esketamine masih terbatas. Ulasan ini bertujuan untuk meringkas studi esketamin dan memberikan wawasan yang lebih baik tentang kemanjuran dan keamanannya pada pasien TRD sebagai titik akhir yang menjanjikan untuk remisi TRD. Sumber literatur diambil dari artikel jurnal yang diterbitkan dalam lima tahun terakhir. Database yang digunakan adalah PMC, SAGE Journals, ScienceDirect, Wiley, dan ResearchGate. TRD dikaitkan dengan gangguan fungsi sosial dan risiko ide bunuh diri yang akan segera terjadi. Efek antidepresan dari esketamin intranasal menunjukkan hasil yang patut diperhatikan bervariasi dari peningkatan tingkat respons hingga penurunan gejala depresi dan pikiran untuk bunuh diri. Temuan dari uji klinis menunjukkan bahwa esketamine intranasal efektif dan aman pada pasien dengan TRD. Ini menyiratkan bahwa esketamin memiliki efek antidepresan yang cepat pada pasien dengan MDD, termasuk TRD dan MDSI. Penelitian lebih lanjut mengenai khasiat esketamin pada beberapa populasi seperti pediatrik dan orang dengan riwayat psikosis, masih diperlukan untuk meningkatkan kemampuan kita dalam mengobati TRD.

Kata kunci *: esketamin, intranasal, depresi yang resistan terhadap pengobatan, antidepresan*

ABSTRACT

Major depressive disorder (MDD), the leading cause of disability worldwide is a common and disabling mental health disorder associated with high suicide-related morbidity and mortality rates. Despite the availability of antidepressant therapies, one-third of patients with MDD fail to achieve remission and are considered to have Treatment-Resistant Depression (TRD). Research have found intranasal esketamine, an enantiomer of anesthetic drug called ketamine, as a potential breakthrough in combating treatment resistance and lowering the number of depression-related suicides. However, reviews that cover the potential use of esketamine are still limited. This review aims to summarize the study of esketamine and provide a better insight into its efficacy and safety in TRD patients as a promising end point for TRD remission. Literature sources were taken from journal articles published in the last five years. The databases used were PMC, SAGE Journals, ScienceDirect, Wiley, and ResearchGate. TRD is associated with impaired social functioning and imminent risk of suicidal ideation. The antidepressant effect of intranasal esketamine showed a noteworthy result varying from increased response rate to decreased depression symptoms and suicidal thoughts. Findings from

clinical trials indicate that intranasal esketamine is effective and safe in patients with TRD. It implies that esketamine has rapid antidepressant effects in patients with MDD, including TRD and MDSI. Further research regarding esketamine efficacy in some populations such as pediatrics and people with a history of psychosis, is still needed to improve our ability to treat TRD.

Keywords *: esketamine, intranasal, treatment-resistant depression, antidepressant*

INTRODUCTION

Major depressive disorder (MDD), the leading cause of disability worldwide is a common and disabling mental health disorder associated with high suicide-related morbidity and mortality rates (Ardalan et al., 2017; Fedgchin et al., 2019). This complex psychiatric disease is characterized by debilitating features including persistently low mood or anhedonia; altered appetite, sleep, and activity; feeling of worthlessness; guilt; and eventually ideation of suicide (Salahudeen et al., 2020). According to WHO, as in April 2021, the number of MDD worldwide exceeded 264 million people (Sapkota et al., 2021). While in the United States alone, MDD affects more than 16 million adults each year and has significant impact concerning low productivity and impaired quality of life (Bahr et al., 2019).

MDD as a highly recurrent condition oftentimes requires long-term treatment. However, antidepressants that are currently available have several major drawbacks. The effects of drugs can be delayed ranging from four to six weeks as well as the low rates of response and remission to treatment, 50% and 30% respectively (Carreno et al., 2020).

Along with lengthy periods of therapy, the evolution of treatment resistance can develop in a proportion of patients. Approximately one-third of patients with MDD fail to achieve remission and are considered to have treatment-resistant depression (TRD). This condition is typically considered present in individuals who have not responded to at least two antidepressants from the same or different pharmacologic classes, with adequate dose, duration, and compliance (Doty et al., 2021). During this condition, patients remain symptomatic and this burden exponentially increases the longer TRD persists, with increasing possibility of impaired social functioning, morbidity, and mortality. This condition places patients at imminent risk of adverse outcomes, including suicide or Major Depressive Disorder with Suicidal Ideation (MDSI). Consequently, the treatment of TRD poses a major challenge in dealing with depression (S.Y. et al., 2019). Hence, there is a pressing need to develop effective new treatment strategies for MDD generally, and for treatment-resistant depression (TRD) specifically (Smith-Apeldoorn et al., 2022).

Recent research have found intranasal esketamine, a derivate of anesthetic drug called ketamine, as a novel breakthrough in improving remission rates, combating treatment resistance, and lowering the number of depression-related suicides. Taken together, evidence supports esketamine as a therapeutic option for this difficult-to-treat, potentially life-threatening condition of TRD (Katz et al., 2021). However, information and reviews that cover the potential use of estekamine are still very limited. This review aims to summarize the study of esketamine as a promising end point to treat TRD, the illness that contributes disproportionately to the disease burden of psychiatric disorder.

METHOD

The review was conducted using several databases, such as PMC, SAGE Journals, ScienceDirect, Wiley Online Library, and ResearchGate to identify literatures associated with esketamine and treatment-resistant depression (TRD) with 2 keywords; the first keyword was ((esketamine) AND antidepressant) AND "treatment-resistant depression"; the second keyword was ((esketamine) AND

intranasal) AND "treatment-resistant depression". Articles were entered if they met the following criteria (Figure 1.1). Afterwards, the articles will be evaluated for the correlation of the keywords with our topic to support the analysis in this literature review.

RESULTS

Researchers have found 5 journal articles from several databases that meet the inclusion criteria for this literature study contained. All journal articles used in this literature study use original research. Most journal articles have a sample of < 100 respondents. The results of analysis and synthesis from 5 journals are presented in Table 1.

Table 1. Results of Journal Analysis and Synthesis

No	Author (Year)	Research Title	Journal Title	Research Results
1	Eva G. Katz, Pauline McNulty, Bennett Levitan, Patricia Treichler, Jadwiga Martynowicz, Carol Jamieson (2022)	U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative: Experience with Integration of Patient-Experience Data in a New Drug Application for Esketamine Nasal Spray Plus a Newly Initiated Oral Antidepressant for Treatment-Resistant Depression	National Library Of Medicine	The FDA acknowledged reviewing the patient-experience data and determined that they supported esketamine + AD for treatment-resistant depression. This report highlights the importance of integrating patient-experience methods early in drug development, their impact on assessing patient-relevant benefits and risks, and how they can help improve clinical program design.
2	Steve Chaplin	Esketamine nasal spray for treatment-resistant depression (2020)	Prescriber	This article discusses the properties, clinical trial efficacy and adverse effects of this new treatment option.
3	Rebecca Bahr, Alicia Lopez, Jose A. Rey	Intranasal Esketamine (Spravato™) for Use in Treatment-Resistant Depression In Conjunction With an Oral Antidepressant (2019)	National Library Of Medicine	Many patients with MDD are at risk for poor outcomes because of the limitations of currently approved treatments
4	Benjamin Sanders, Abdul Q. Brula	intranasal esketamine: From origins to future implications in treatment-resistant depression (2021)	Journal Of Psychiatric Research	The eventual approval of intranasal esketamine for treatment-resistant depression by the U.S. Food and Drug Administration (FDA) in March 2019. By identifying and utilizing predictors of response, we can continue to refine our approach to treating treatment-resistant depression and optimize patient response to intranasal esketamine.
5	Mischel, Nicholas A. MD, PhD*; Balon, Richard MD	Esketamine (2021)	Journal Of Clinical Psychopharmacology	It is not clear whether the requirements of REMS and personnel are enough to assure not only safety, but also proper selection of patients, correct indications (which are quite vague) and long-term use. Whose responsibility it is, whether of the esketamine maker, FDA, or the field, is not clear. Maybe of all.

DISCUSSIONS

Diagnostic criteria for MDD are stated from DSM-5 (Diagnostic Criteria for Major Depressive Disorder). For diagnosing MDD, ≥ 5 of the following symptoms must be present every day for ≥ 2 weeks: depressed mood and/or anhedonia; and significant change in weight; decreased appetite; insomnia or hyperinsomnia; psychomotor agitation or retardation; fatigue; feeling of worthlessness; decreased concentration or indecisiveness; recurrent thoughts of death or suicidal ideation with or without plan (Bahr et al., 2019). However, there are 681 combinations of symptoms that could meet the DSM criteria, portraying the heterogeneity and complexity of symptoms related to MDD (Akil et al., 2018).

During the course of therapy, some MDD patients will show decreasing sensitivity to medication. This emergence of resistance can develop gradually or as a progressive, deteriorating illness course over time. Approximately 30% patients who meet this criteria will show no therapeutic response after two or more antidepressants medications. While usually MDD episodes resolve within 6–15 months, the duration of depressive symptoms in patients with TRD is typically three times longer (Rathod et al., 2022). Untreated depression is a major risk factor for disability and suicide. Each year, approximately 800,000 people— one person every 40 seconds—successfully complete suicide (Bahr et al., 2019).

TRD represents a heterogenous state with possibly multiple causal mechanisms. Patients who show indications of TRD can exhibit the same diversity of symptoms, history, course and conditions as treatment-responsive MDD. Several studies report that history of early life stress increases the risk of treatment-resistance, however differences between the two groups and the underlying mechanism remain mostly obscure. Multiple modalities of treatment are effective for depression, including antidepressant medications and psychotherapies, however, these efforts are not sufficient to achieve depression remission. Further, matching patients to their optimal treatment requires multiple trials of different treatments, with the sobering realization that the more treatments tried without success, the less likely a successful outcome. In addition, as resistance encompasses a broad spectrum of drugs, including combination and augmenting medications, toxicity can appear as the next problem. Thus, discovering a new treatment is likely the best way to reduce the high number of morbidity and mortality by lessening the burden of MDD and TRD (Akil et al., 2018).

The successful role of ketamine in the early 2000s led to numerous studies and trials regarding its potential. Seeing the promising impact this anesthetic drug has for psychiatry, and depression in particular, the advancement of ketamine usage continues until esketamine – an enantiomer of ketamine – which holds an even greater therapeutic potential towards TRD was finally discovered (Kaur & Sanches, 2021).

Esketamine

The beginning of esketamine was when Parke Davis pharmaceutical company found phencyclidine (PCP) in 1956. PCP was utilized as a preoperative anesthetic and was found to produce delirium in post-surgical patients. Therefore, PCP analog with less delirium effect were begun to be searched for. In 1962, ketamine was first developed by Parke Davis consultant Calvin Stevens and was proved to produce shorter duration of psychic alterations in 1964 (Sanders & Brula, 2021). Later in the early 1970s, it was introduced to the U.S. market as a replacement anesthetic and analgesic agent for phencyclidine (PCP) (Bahr et al., 2019). The escalating number of depression cases and consequently TRD, led to continuous development of ketamine in the following years.

Ketamine (or RS-ketamine) acts as a nonselective, noncompetitive antagonist on the N-methyl-D-aspartate (NMDA) receptor that exists in two enantiomers of R-ketamine and S-ketamine (or esketamine). The effective utility of both enantiomers in psychiatry have been proven by numerous studies. However, most of the studies showed that esketamine compared with ketamine and arketamine had better analgesic, intraoperative amnesia and anaesthetic properties, with less drowsiness, lethargy, cognitive impairment and psychotic emergent reactions. In addition, Esketamine has fourfold higher affinity for the NMDA receptor binding site compared to (R)-ketamine (Sanders & Brula, 2021). Hence, interest in the potential efficacy of ketamine in MDD focused on esketamine (Salahudeen et al., 2020).

There are several methods of esketamine administration, such as IV, oral, subcutaneous,

and intranasal. However, the difficulties regarding the invasive and painful procedure of IV and subcutaneous esketamine administration make intranasal as a more favored method of delivery (Salahudeen et al., 2020 ; (Lucchese et al., 2021). In 2018, a double-blind, multicenter, proof-of-concept study published their significant results on the efficacy and safety of intranasal esketamine on rapid reduction of symptoms of depression and suicidality in patients with MDD considered to be at high risk for suicide (Bozymski et al., 2020). Later in 2019, the intranasal use of esketamine was approved by the US Food and Drug Administration (Smith-Apeldoorn et al., 2022).

Another reason for choosing intranasal over other routes of delivery comes from the pharmacokinetic profile of estekamine itself. Through intranasal administration, maximum plasma concentration happens 20 to 40 minutes following the second administration of nasal sprays. Nasal esketamine has an estimated mean bioavailability of 48%, with hepatic first-pass avoided through this route. This is in contrast to oral esketamine, with a reported bioavailability of only 8–11%, and its mean half-life is 7 to 12 hours (Salahudeen et al., 2020).

Intranasal esketamine is primarily metabolized to noresketamine via the CYP450 enzymes of CYP2B6 and CYP3A4, with a lesser contribution from CYP2C9 and CYP2C19. The half-life is biphasic, with an initial rapid decline in concentration within two to four hours and a terminal half-life of seven to twelve hours. Noresketamine is further metabolized via CYP-dependent pathways with hydroxylation to hydroxynoresketamine. Subsequent metabolites will then undergo glucuronidation. Elimination of metabolites primarily through the kidney (>78%) and feces (2%) (Bozymski et al., 2020).

Esketamine is metabolized by the CYP-enzyme system, suggesting a predisposition to potential drug–drug interactions of that system, however, no significant interactions have been reported so far. Patients with moderate hepatic impairment may require increased monitoring for adverse drug reactions for a longer period of time as a result of the increased plasma levels and half-life of esketamine in that population. However, there is also no clinical experience in patients receiving renal dialysis or in those with severe hepatic impairment (Salahudeen et al., 2020).

Although the mechanism of action of ketamine (MOA) as an anesthetic has been widely studied, the MOA for the antidepressant effect of esketamine is not well understood. Proposed mechanisms include stimulation of brain-derived neurotrophic factor (BDNF) production and mammalian target rapamycin (mTOR) activation. The action of ketamine on the NMDA receptor is believed to produce effects that activate the amino-hydroxy-methyl-isoxazolepropionic acid (AMPA) receptor, which appears to decrease phosphorylation of eukaryotic elongation factor 2 kinase, and result in increased BDNF production. Downstream regulation of mTOR is thought to stimulate additional BDNF production and increase brain plasticity through dendritic growth and enhanced synaptic transmission. Recent evidence suggests that ketamine features a more direct stimulatory effect on BDNF and mTOR than current oral antidepressants. This may explain the rapid onset of esketamine's effect and therefore the mechanism by which it remains effective even after the drug has been completely eliminated (Bahr et al., 2019).

Evidence of Intranasal Esketamine Efficacy in Treatment-Resistant Depression and Suicide IdeationTreatment

Esketamine has shown rapid antidepressant effects in Major Depressive Disorder (MDD) patients, including Treatment-Resistant Depression (TRD) and Major depressive disorder with suicidal Ideation (MDSI). The efficacy of esketamine as an adjunctive drug to antidepressants (AD) was assessed in international, TRANSFORM and SUSTAIN trials in adults with TRD. The TRANSFORM trials were randomized, double-blind, multicenter, active-controlled (patients received a newly initiated AD plus intranasal placebo), phase 3 studies that also assessed the safety and tolerability of esketamine plus AD (Katz et al., 2022).

The primary outcome measure was a ≥50% reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to end of day 28 and rates of remission (MADRS≤12) at Day 28. TRANSFORM trials are measured with Montgomery-Asberg Depression Rating Scale (MADRS). Response rate, the first primary outcome measure was a ≥50% reduction in the

total score MADRS from baseline until Day 28. The second primary outcome measure was remission rate (MADRS≤12) at day 28. Participants who were considered responders (defined as more than half reduction in MADRS total score from baseline) could then be entered into either the SUSTAIN-1 or SUSTAIN-2 trial (Chaplin, 2020).

Meanwhile, SUSTAIN-1 and SUSTAIN-2 is defined as a study of intranasal esketamine plus an oral antidepressant for relapse prevention in adult participants with treatment-resistant depression. SUSTAIN-1 and SUSTAIN-2 compared IN esketamine plus oral AD with IN placebo plus oral AD for long-term efficacy in TRD. SUSTAIN-2 also studied safety and tolerability. Patients in remission went through a 16-week dose adaptation phase and some of them who were still in remission or in response were randomized to obtain maintenance treatment with esketamine plus an oral AD or change to placebo plus oral AD. The primary outcome measured in this study is relapse rate (Chaplin, 2020).

The result of response rate as the first primary outcome from TRANSFORM-1 and TRANSFORM-3 indicates that esketamine plus oral AD was not significantly superior to placebo nasal spray plus oral AD. In contrast, two different trials of TRANSFORM-2 showed a significant reduction in depressive symptoms. One of their results states esketamine (either 56mg or 84mg) plus oral AD, significantly reduced the mean MADRS score than placebo plus oral AD (mean change from baseline -17.7 *vs* -14.3), which a difference of 2.0 is already taken as clinically meaningful. Therefore, the response to placebo plus oral AD in these studies were considered substantial (Chaplin, 2020).

On the other hand, response rate from TRANSFORM-1 and -2 indicates a noteworthy result. Response rates of esketamine plus oral AD at Day 2 were 15–17% compared with placebo plus oral AD which shows only 7–10% response rate. This rapid response is a valuable aspect that has always been searched for in treatments for patients with suicidal ideation. After 28 days, response rates had increased to 46–61% with esketamine plus oral AD *vs* 37–48% with placebo plus oral AD, meanwhile their remission rates reached 33–47% vs 28–29% respectively. In TRANSFORM-3 (in adults over 65 years), response rates after seven days were similar for esketamine plus oral AD *vs* placebo plus oral AD (5.6% *vs* 4.6% respectively), rising to 24% (Chaplin, 2020).

The certain proportion of respondents who went through SUSTAIN-1 and SUSTAIN-2 trials showed a significant effect of esketamine. For those in stable remission, the relapse rate after 12 and 24 weeks was 13% and 32% respectively for esketamine vs 37% and 46% for placebo. For those in stable response, the relapse rate after 12 and 24 weeks was 21% at both time points for esketamine *vs* 47% and 56% for placebo. About two-thirds of patients in remission used a fortnightly dose of esketamine and about half of those with a stable response used a weekly dose. In another study of SUSTAIN-1, the primary endpoint of stable remission after 16 weeks of intranasal esketamine plus oral AD showed a significant delay to relapse compared with placebo, with risk of relapse decreasing by 51% in intranasal esketamine (Bahr et al., 2019).

Aside from TRANSFORM and SUSTAIN, several other studies also proved the efficacy and safety of intranasal esketamine to rapidly reduce depressive symptoms and suicidal tendencies in patients MDD with suicidal tendencies (Sanders & Brula, 2021 ; Mischel & Balon, 2021). Research in 2018 observed a significant improvement in suicidal ideation measured from MARDS from the administration of esketamine group compared to placebo group. In August 2020, esketamine was FDA approved to treat depressive symptoms in MDD patients with acute suicidal ideation or behavior (Mischel & Balon, 2021).

Dosage and Administration

Esketamine can only be prescribed by a psychiatrist. It is delivered through a nasal spray device containing a single dose of 28mg delivered in two applications (one spray per nostril). Doses of 56mg and 84mg require multiple devices, the use of which should be separated by a five-minute interval. Other nasally administered medications such as corticosteroids or decongestants should be administered at least one hour before IN esketamine is given (Bahr et al., 2019).

The recommended dose for adults under 65 years is 56mg initially, then 56mg or 84mg twice weekly for 4 weeks. For week 5–8, the dosing frequency is reduced to 56mg or 84mg once weekly, and from week 9, the maintenance dose is 56 mg or 84mg once weekly or every two weeks. Treatment should continue only if

there is evidence of therapeutic benefit. Older people (≥65 years) and those with Japanese ancestry need a reduced starting dose of 28mg, and may need a 28 mg dose at each stage (Daly et al., 2018).

No dose adjustment is recommended for individuals with renal impairment or mild hepatic impairment; the maximum dose of 84 mg should be used with caution in people with moderate hepatic impairment. Esketamine has not been studied in people with severe hepatic impairment. It is contraindicated in patients with a history of hemorrhagic stroke, recent cardiovascular event (within six weeks), aneurysmal vascular disease, or for whom an increase in blood pressure or intracranial pressure poses a serious risk (Chaplin, 2020).

Safety Results

Findings from the analysis of olfactory function and nasal tolerability in patients with TRD indicate that there was no evidence of adverse effect on either olfactory or nasal health measures with repeated intermittent administration of esketamine nasal spray at any dose over the course of short-term (4 weeks) or long-term (16–100 weeks) studies. Esketamine nasal spray was well tolerated, as indicated by responses on the NSQ and negative nasal examination findings (Doty et al., 2021).

Clinical trials for esketamine in TRD demonstrated an acceptable safety profile. Rates of common treatment-emergent adverse effects (TEAEs) reported in these studies, with the most commonly reported being nausea, dissociation, dizziness, vertigo, and headache. Important transient adverse effects to note include sedation, blood pressure increases, and cognitive impairment (Sapkota et al., 2021). There are also some other mild to moderate adverse events to esketamine administration such as dysgeusia, somnolence, blurred vision, and oral hypoesthesia. Dissociation, described as distortion of time and space, illusions, derealization, and depersonalization, was the second most commonly reported TEAE in the TRANSFORM trials. Median Clinician-Administered Dissociative States Scale (CADSS) scores were higher for esketamine versus placebo, indicating increased dissociation events, moreover, higher dose caused larger average increase in CADSS score. It does not appear that age contributes to increased sedation risk because all those experiencing severe sedation were less than 65 years old (Bozymski et al., 2020). Psychiatric effects (e.g. euphoria, panic attack, hallucination) and mental impairment were common. Most adverse events were resolved on the day of administration. Ketamine has abuse potential but no cases of abuse were reported with esketamine (Chaplin, 2020).

IN esketamine has not been studied in pediatric populations. Clinical trials demonstrate that the use of IN esketamine in the geriatric population is safe and effective. Studies in elderly patients ≥ 65 years old with TRD have found significant reduction of MADRS score with only mild-to-moderate side effects, similar to those found in the general population of adults aged 18–64 years. Most adverse events occurring on dosing days were transient and either mild or moderate in severity. No death was reported (Daly et al., 2018).

Contraindication

Esketamine is contraindicated in patients with a known hypersensitivity to esketamine, ketamine, or any component or excipient of the formulation, and in patients for whom an increase in blood pressure would be hazardous. IN esketamine increases BP, predominantly systolic, and increases cardiac output; therefore, medical conditions such as aneurysmal vascular diseases and arteriovenous malformation are contraindications to IN esketamine use. The dose of intranasal esketamine for TRD treatment is much lower than analgesic dose, therefore respiratory depression is less likely to occur (Bahr et al., 2019).

Due to the limited clinical trials, esketamine should still be avoided in MDD patients with psychotic features, a history of psychosis, personality disorders, or substance use disorders, which should be screened for prior to use secondary to the risk of dissociation, worsening psychosis, and abuse potential (as well as the fact that these populations were excluded in clinical trials) (Bozymski et al., 2020).

Cost Effectivity

IN esketamine will likely cost more in the initial phase of treatment and less during long-term management. From a cost-effectiveness point of view, esketamine could potentially be an option for TRD patients not able to undergo

other kinds of treatment (Degerlund Maldi et al., 2021).

CONCLUSION

Depression patients are at major risk of disability and mortality. Due to the fact that only few options exist for patients with TRD and the previously available treatments have a slow onset of action, a rapid-acting treatment holds a promising prospect to achieve depression remission. In clinical trials, intranasal esketamine appears to significantly improve the symptoms of TRD in the short term which can be potential in the utility for patients at high risk of suicide. Side effects of esketamine are also often reported to be transient, mild to moderate. It implies that esketamine has rapid antidepressant effects in patients with MDD, including TRD and MDSI. The study also suggested that esketamine might be associated with rapid anti-suicidal effects for patients with MDSI (Wang et al., 2021).

The intranasal esketamine (the S-enantiomer of ketamine) becomes the easier method of administration, with a rapid onset of action, reasonable bioavailability, and being more practical and less resource-demanding. The findings from limited clinical trials indicate that intranasal esketamine is effective and safe in patients with TRD. It was recently approved in the United States for treating treatment-resistant depression (TRD) (Salahudeen et al., 2020).

Some research indicates that esketamine produces abuse potential. However, there is still a contradiction whether esketamine has abuse potential or not due to the other research pointing to cases of abuse reported with ketamine, but not esketamine (Chaplin, 2020).

The requirement to be dosed in a clinic setting and observed for 2 hours post dose, as well as its high cost and abuse potential, may limit its clinical use. Further research related to efficacy of esketamine in some populations such as pediatrics and people with a history of psychosis, is still needed to improve our understanding and ability to treat treatment-resistant depression (Sanders & Brula, 2021).

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