“Exploring the Role of Esketamine Nasal Spray in Treatment-Resistant Depression”

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

School of Pharmacy
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Declaration

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled “Exploring the Role of Esketamine Nasal Spray in Treatment-Resistant Depression” submitted by Hasbun Nahar Anika (21346098) of Spring, 2025 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on September.

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Ethics Statement

This study does not involve any human or animal trials.

Abstract

Esketamine nasal spray is now a revolutionary drug in treating patients with treatment-resistant depression (TRD), exhibiting a rapid and strong response to depressive symptoms. In contrast to traditional antidepressants, which mainly affect the monoaminergic pathway, esketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and causes fast adjustment of glutamatergic neurotransmission. The main aim of the current review was to discover the evidence that can potentially prove the utility of esketamine in patients with a diagnosis of TRD and the information concerning its potential side effects in the short-term and in the long-term. This review also provides a summary of the available evidence on the pharmacology, clinical effectiveness, safety profile, and therapeutic usefulness of intranasal esketamine in TRD. The results point to esketamine nasal spray as an effective, but closely monitored, approach to the treatment of resistant depression.

Keywords: Depression, Esketamine**,** Treatment-resistant depression, NMDA Receptor, Antidepressant.

Dedication

This work is lovingly dedicated to my parents, whose unwavering support and blessings have been my strength, and to my husband, whose encouragement and understanding have been a constant source of inspiration.

Acknowledgement

I would like to express my sincere gratitude to Dr. Sabrina Sharmin, PhD, Associate Professor, School of Pharmacy, BRAC University, for her valuable guidance, continuous support, and encouragement throughout the course of this work.

Table of Contents

List of Tables

List of Figures

List of Acronyms

MDD	Major Depressive Disorder
TRD	Treatment-Resistant Depression
NMDA	N-methyl-D-aspartate
ECT	Electroconvulsive Therapy
PK	Pharmacokinetics
HPA	Hypothalamic Pituitary Adrenal
BDNF	Brain-Derived Neurotrophic Factor
ACTH	Adrenocorticotropic hormone
CRH	Corticotropin-Releasing Hormone

Chapter 1

Introduction

1.1 Background

Depression is a common, but serious mental health disorder that's characterized by persistent feelings of sadness, hopelessness, loss of interest or pleasure in daily activities, and a decrease in energy or motivation. Unlike typical mood ups and downs or short-lived emotional reactions to stress, depression is persistent and seriously disrupts a person's thinking, behavior, and ability to function in everyday life (Psychiatry.Org - What Is Depression?, 2025)

Major Depressive Disorder (MDD) under the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is defined as an episode of at least five specific symptoms within the identical 2-week timeframe, one of which is either a depressed mood, or a lack of enthusiasm/pleasure (Curley et al., 2023). The symptoms are feelings of sadness and emptiness, feelings of hopelessness and despair, weight gain and weight loss, sleep problems, psychomotor agitation and retardation, feelings of fatigue, feelings of worthlessness, loss of the ability to think or concentrate, and thoughts of death (Curley et al., 2023). The symptoms indicated are making a person suffer clinically, and they impair social, occupational, and several other essential sectors of functioning, but cannot be attributed to substances or other medical conditions. Psychotic disorders cannot be the best explanation of the episode; there should be no history of manic or hypomanic episodes to diagnose MDD (DSM-5). On the other hand, the features of the ICD-11 definition of the recurrent depressive disorder are that the current depressive disorder has occurred in the last few months, without significant mood disturbance, at least two depressive episodes. Each depressive episode includes a depressed

mood or a marked diminishing interest in activities, more or less all day, nearly every day for at least two weeks (Francia et al., 2025).

Major depressive disorder (MDD) is one of the most common mental health disorders in the world. According to the World Health Organization, estimates show that around 5 percent of adults experience depression in the world, with an estimated 280-310 million individuals having depression. The estimated lifetime prevalence of MDD is approximately 5-17% with the average rate of 12% (Curley et al., 2023). The prevalence rate is nearly twice as much in women than in men, where adult women register 10.3% prevalence as compared to the 6.2% prevalence in males (Curley et al., 2023). The highest prevalence is in the group between the ages of 18-25 (18.6%). In 2019, there were 290 million cases, and this is an increase of 59.3% compared with 1990 (Wu et al., 2024). Here, age-standardized rates show minimal declines. Moreover, the financial cost of depression is high, and the condition is among the most widespread causes of disability in different countries around the world (Wu et al., 2024).

Treatment-resistant depression (TRD), more specifically, is defined as major depression that fails to respond sufficiently after at least two unsuccessful antidepressant medication trials (McIntyre et al., 2023). All the unsuccessful attempts at the treatment have to be conducted with the use of an adequate number of doses and during a considerable (usually 6 to 8 weeks) time period. The definition includes a focus on no substantial clinical attainments, usually less than 25 percent in the diminished depressive symptoms on standardized assessment scales (McIntyre et al., 2023). Research has shown that around 30.9 percent of patients who undergo medication treatment of MDD develop treatment resistance, and the estimates vary between 12 and 20 percent in all patients with MDD (J. Liu et al., 2024). Treatment resistance is frequent

in up to 30 percent of patients who receive treatment, and one-third of major depression patients suffer from treatment-resistant depression. The remission rates after the first or second treatment round are 37% and 31%, indicating that therapeutic response is challenging to achieve (Depressive Disorders Prevalence, 2021). Among the patients who are diagnosed with TRD, another 37% will be unresponsive to the other TRD-specific strategies in treatment. According to the WHO, the economic cost of one TRD in the USA is significant and is estimated to be $43.8 billion (47.2%) of the total economic cost of medication-treated MDD in the USA in one year (Depressive Disorders Prevalence, 2021).

1.2 Objectives

The objectives of this review are to critically evaluate the role of esketamine nasal spray in the management of treatment-resistant depression (TRD). This involves reviewing evidence from clinical trials about its effectiveness in reducing symptoms, inducing remission and preventing relapse. The review also seeks to analyze safety and tolerability profiles, emphasizing both the short- and long-term considerations. Furthermore, it aims to investigate the clinical relevance of esketamine's new mechanism of action relative to traditional antidepressants. Finally, the work aims to identify current research gaps and future directions to optimize therapeutic use of esketamine in TRD patients.

1.3 Rationale of this Work

Treatment-resistant depression (TRD) is one of the greatest challenges in psychiatric practice because a large proportion of patients do not respond adequately to standard antidepressant therapies. This unmet clinical need not only increases patient suffering time but also increases

the risk of chronic disability, co-morbidities and suicide. In recent years, esketamine nasal spray has become a novel choice of therapy. Because it provides a novel, rapid-acting mechanism of action via the antagonism of the N-methyl-D-aspartate receptor (also known as the NMDA receptor). This special mechanism distinguishes it from traditional monoaminergic antidepressants (Vasiliu, 2023). Exploring its role is of vital importance to better understand its efficacy, safety, and its potential to overcome the weaknesses of current treatments for TRD.

Chapter 2

Methodology

This review was carried out in a detailed literature review through database search in PubMed, Google Scholar, and Scopus websites, with related keywords searching on treatment-resistant depression and esketamine antidepressant treatments. Studies published between 2015-2025 which focused on the novel approach of esketamine nasal spray in the management of treatment-resistant depression. Articles were screened for relevance and key data relating to esketamine nasal spray in terms of their mechanism of action, chemical structure, clinical efficacy and limitations were extracted and analyzed. The findings were synthesized thematically to provide an overview of current treatments and emerging therapies of esketamine nasal spray.

Chapter 3

TRD Pathophysiology

The pathophysiology of treatment-resistant depression (TRD) is complex and multifactorial. The pathophysiology of TRD involves a number of interconnected mechanisms. For example, one major aspect is the dysregulation of neurotransmitters, especially abnormalities of serotonin, norepinephrine, and dopamine systems. This makes patients less responsive to conventional antidepressants (Kajumba et al., 2024). Another important mechanism is hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Due to chronic stress and increased cortisol, mood regulation and feedback control HPA axis is impaired (Georgiou et al., 2024). Additionally, TRD is also highly correlated with the development of impaired neuroplasticity, such as decreased brain-derived neurotrophic factor (BDNF) and connectivity in areas like the hippocampus and prefrontal cortex (Richardson et al., 2022). Furthermore, the neuroinflammation contributes through elevated cytokines, which interfere with neurotransmission and synaptic adaptation with worsening treatment resistance (Richardson et al., 2022).

3.1 TRD and Neurotransmitter Dysregulation

Treatment-resistant depression (TRD) is associated with a complex dysregulation of neurotransmitters that contributes to its pathogenesis and the difficulty in treatment. Recent research has focused on the intricate interactions between the monoaminergic systems like serotonin, (5-HT); dopamine, (DA); norepinephrine (NE) as central in TRD (Kajumba et al., 2024). Here, selective serotonin reuptake inhibitors (SSRIs) elevate serotonin but may simultaneously inhibit dopamine and norepinephrine release through inhibitory 5-HT2C

receptors and excitatory 5-HT2A receptors found on the gamma-amino acid (GABA) interneurons. This can perpetuate depressive symptoms and contribute to depressive resistance. This monoamine interplay suggests that residual symptoms in TRD are due in part to insufficient dopaminergic and noradrenergic neurotransmission (Kajumba et al., 2024). Moreover, dopamine dysregulation is especially associated with key TRD symptoms such as anhedonia and motivational deficits (Kajumba et al., 2024). Stimulating dopamine pathways, such as dopamine receptor agonists such as pramipexole, has shown promise of quick antidepressant effects in TRD. Similarly, serotonin-norepinephrine reuptake inhibitors (SNRIs) tend to indirectly increase dopamine at higher doses, and provide better efficacy than SSRIs (Kajumba et al., 2024).

3.2 TRD and Neuroendocrine Dysfunction

Treatment-resistant Depression (TRD) in particular is associated with neuroendocrine dysfunction, specifically the hypothalamic-pituitary-adrenal (HPA) axis (Georgiou et al., 2024). In the case of TRD, a dysregulated neuroendocrine stress system causes impaired feedback of stress hormones and contributes to the persistence of depressive symptoms (Georgiou et al., 2024). The HPA axis normally controls the stress response by the sequential release of corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary, and cortisol from the adrenal glands (Georgiou et al., 2024)In TRD, this axis tends to be hyperactive or dysregulated, leading to higher levels of the stress hormone cortisol being maintained in the brain, and causing the parts of the brain responsible for regulating mood, like the hippocampus and prefrontal cortex of the brain to be muted. Chronic cortisol exposure can cause neuroinflammation, decreased neurogenesis, and atrophy of synapses that can perpetuate depression and make it harder for people to get relief

with treatment (Georgiou et al., 2024). Recent research has also shown that higher HPA axis activity is associated with increased duration of illness and poor clinical outcome. Modulation of HPA axis hormones such as ACTH and CRH with therapeutics in resistant cases may enhance treatment efficacy (Georgiou et al., 2024).

3.3 TRD: Neuroplasticity and Neuroinflammation

Treatment-resistant depression (TRD) is highly related to deficits in neuroplasticity and increased neuroinflammation. These are significant components of its pathophysiology. Neuroplasticity describes the brain's ability to structurally and functionally adapt in response to environmental stimuli and stress. In TRD, neuroplasticity deficits are characterized by lower synaptic density, dendritic atrophy and loss of neural connectivity (especially in important mood regulating areas such as the hippocampus and prefrontal cortex) (Richardson et al., 2022). Neuroinflammation worsens these neuroplasticity deficits. Pro-inflammatory cytokines such as IL-1b, IL-6, and TNF-a are increased in TRD patients, activating microglia and astrocytes, resulting in synaptic dysfunction and dysfunction of neurotransmitter systems (Richardson et al., 2022). Excessive glutamate release triggered by neuroinflammation can lead to excitotoxicity which can lead to further damage to neurons, as well as decreased levels of brain-derived neurotrophic factor (BDNF). Since the growth and plasticity of synapses is dependent on the presence of BDNF, its reduction leads to the perpetuation of these synaptic losses, which limit the brain's ability to recover from depressive episodes (Richardson et al., 2022).

Chapter 4

TRD Treatment

The treatment of treatment-resistant depression (TRD) includes strategies for those patients who don't respond to common antidepressant treatments. Management usually initially involves optimisation of current antidepressant treatment, including dose adjustment or a change in class. Augmentation strategies are usually used with the addition of agents such as atypical antipsychotics, lithium, or thyroid hormones to boost efficacy. Non-pharmacological interventions such as electroconvulsive therapy (ECT) play a vital role for patients with prolonged symptoms. Recently, novel treatments such as esketamine nasal spray have shown promise in quickly reducing symptoms of depression. Individualized treatment plans and careful monitoring are important for better outcomes for TRD.

4.1 Conventional Treatment

The traditional management of Treatment-Resistant Depression (TRD) involves the adoption of several strategies, which are primarily pharmacological and somatic treatment, and psychotherapy. Initial pharmacological intervention usually consists of selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs), which are preferred due to their comparatively well-tolerated side effects (Al-Harbi, 2012). In case of failure, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are frequently turned to, as they are effective even in some resistant cases, despite the increased potential to induce adverse effects (Al-Harbi, 2012). First-line treatment may be augmented or combined, whereby it is possible to combine antidepressants of different classes (e.g., SSRI with TCA) or to augment with non-antidepressants such as lithium, thyroid hormones, atypical

antipsychotics, or psychostimulants. A supportive role is provided by psychotherapy, especially the cognitive behavioral method (CBT), which achieves better results when employed alongside pharmacotherapy (Al-Harbi, 2012). Furthermore, somatic treatment (such as the use of electroconvulsive therapy) has stood as one of the best interventions for TRD, especially in cases of severe or refractory cases, and its response rates are 50% to 70% (Voineskos et al., 2020). Other new techniques of brain stimulation include repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and magnetic seizure therapy (MST), which provide treatment options to patients who are not responding to medication or electroconvulsive therapy (Voineskos et al., 2020). The combined strategies will enable a treatment plan that is structured and specific to each patient to meet the goal of achieving remission or significant improvement of symptoms.

Antidepressant Class	**Primary Receptors/Transporters Targeted**	**Mechanism of Action**
Selective Serotonin Reuptake Inhibitors (SSRIs)	Serotonin transporter (SERT)	Block reuptake of serotonin (5-HT) into presynaptic neurons, enhancing serotonergic neurotransmission.
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	SERT, Norepinephrine transporter (NET)	Inhibit reuptake of serotonin and norepinephrine, increasing their synaptic availability.
Tricyclic Antidepressants (TCAs)	SERT, NET, plus block muscarinic, histaminic (H1), alpha-1 adrenergic receptors	Block reuptake of serotonin and norepinephrine; also antagonize muscarinic, histamine H1, and alpha-1 receptors causing side effects.
Monoamine Oxidase Inhibitors (MAOIs)	Monoamine oxidase enzyme (MAO-A and MAO-B)	Inhibit breakdown of monoamines (serotonin, norepinephrine, dopamine) leading to increased neurotransmitter levels.
Atypical Antidepressants (e.g., Bupropion)	Dopamine transporter (DAT), NET	Inhibit reuptake of dopamine and norepinephrine, enhancing neurotransmission.
Serotonin Receptor Modulators (e.g., Trazodone, Vilazodone)	5-HT2A receptor antagonist, SERT	Block specific serotonin receptors and inhibit serotonin reuptake to modulate serotonergic signaling.

Table 1: Conventional antidepressant classes based on receptor(Sheffler et al., 2023)

4.2 Limitations of Conventional Treatment

Even when using a wide range of possible interventions, conventional TRD treatments have many shortcomings that undermine their clinical efficacy and patient outcomes. Drug therapies have high variability in response rates, and many patients fail to have an adequate response after multiple trials of medication. The typical side effects of MAOIs are weight gain, fatigue, and hypotension, and they cannot be combined with SSRIs because the combination can cause fatal serotonin syndrome, so treatment options are minimal (Y. Wang et al., 2025). The sequential characteristic of medication interventions results in an extensive timeframe of insufficient treatment, where patients remain with impaired functions and reduced quality of life. Although very helpful in treatment, Psychotherapy demands much time. It is not accessible to every patient due to economic reasons, as well as the severity of symptoms limiting interactivity. Despite high efficacy rates, ECT (Electroconvulsive therapy) has significant limitations in that it presents cognitive side effects, especially memory impairment, that may be distressing to patients and caregivers (Hsieh, 2023). ECT is not effective in the prevention of the relapse of the illness in the future, and most of those subjected to ECT require some form of maintenance treatment, which needs constant medication or psychotherapeutic treatment (Hsieh, 2023). Patients who showed treatment resistance before ECT showed a greater rate of relapse compared to those who were treatment-resistant but before ECT, which indicates that a treatment-resistant phenotype may have been the most significant predictor of unfavorable long-term outcomes, independent of treatment modality (Zhdanava et al., 2021). ECT also needs the use of special facilities, anesthesia, and a series of sessions, which adds logistical issues to the process as well as additional healthcare expenses (Zhdanava et al., 2021). The ECT stigma can also inhibit patient acceptance, which further restricts treatment options to severely affected individuals who would otherwise benefit from this treatment modality (Hsieh, 2023).

4.3 Novel Approaches to TRD Treatment

New and innovative treatment methods for TRD have been developed as new options to traditional treatments and these provide optimism for the efficiency of new approaches in the future. The treatment of depression with both esketamine and psilocybin shows both short-term and long-term improvement in depressive symptoms, which is a paradigm shift towards psychedelics-assisted therapies (Curley et al., 2023). Ketamine and its derivative, esketamine, act on the NMDA receptor system to offer quick antidepressant effects in a few hours as compared to weeks (McIntyre et al., 2023). Moreover, transcranial magnetic stimulation (TMS) is proving to be promising, as 60% of individuals who had not responded to other forms of depression treatments responded to the typical TMS procedures, and over two-thirds of these patients had their remission maintained at their 6-month follow-ups (McIntyre et al., 2023). Deep brain stimulation is another invasive procedure that implants electrodes in discrete regions of the brain to provide continuous electrical stimulation and is being studied in the treatment of severe and intractable depression (Wang et al., 2025). Psilocybin is under active investigation as a treatment option in treatment-resistant depression, with an opportunity to receive a breakthrough therapy designation (Al-Harbi, 2012). The novel treatments affect neurobiological pathways that differ from some of the traditional antidepressants, exposing new treatment options to treatment-resistant individuals (Wang et al., 2025).

Chapter 5

Esketamine: A Novel Antidepressant

MDD is one of the major causes of disability globally, and a substantial percentage of patients do not respond to the standard antidepressants and develop treatment-resistant depression. Conventional monoaminergic-based treatments have a long time lag before clinical improvement is seen and are ineffective in many individuals. In recent years, esketamine, the S-enantiomer of ketamine, has become a promising new antidepressant (Sial et al., 2020). Esketamine is a rapidly acting nasal spray that works as an NMDA antagonist. Its approval is like a paradigm change in the treatment of depression, in particular patients with TRD and acute suicidal thought (Brietzke et al., 2020).

5.1 Chemical Structure of Esketamine

Esketamine, chemically known as (S)-2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one, has the molecular formula C13H16ClNOC13H16ClN (*Esketamine | C13H16ClNO | CID 182137 - PubChem*, n.d.). It is the S-enantiomer of ketamine, which is differentiated by its three-dimensional structure. The structure of esketamine includes a cyclohexanone ring connected to a methylamino group and a 2-chlorophenyl group, which confers it pharmacological activity (*Esketamine | C13H16ClNO | CID 182137 - PubChem*, n.d.). Its molecular weight is approximately 274.19 g/mol and its IUPAC name is (S)-2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one hydrochloride. Its stereochemistry is essential to cause antidepressant action due to its interaction with NMDA receptors (Brietzke et al., 2020). The 3D structure has such important functional groups as a chlorophenyl moiety and the ketone group that provide binding in the central nervous system. This molecular

structure distinguishes esketamine as opposed to its R-enantiomer (arketamine) and racemic ketamine (Brietzke et al., 2020).

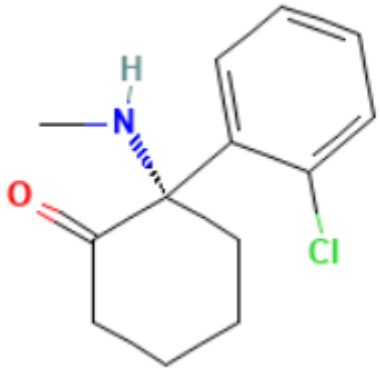

Figure 1: 2D Chemical structure of esketamine (*Esketamine | C13H16ClNO | CID 182137 - PubChem*, n.d.)

5.2 Esketamine Mechanism of Action

5.2.1 NMDA Receptor Antagonism

The mechanism of action of esketamine in the treatment of depression is mainly the activity of an antagonist of the N-methyl-D-aspartate receptor (NMDA receptor). NMDA is a subtype of ionotropic receptors of glutamate and it plays an important role in the brain's excitatory neurotransmission and synaptic plasticity system (Kawczak et al., 2024). Unlike other traditional antidepressants, that target primarily monoamine systems and can take weeks to take effect, esketamine works to target glutamate transmission and may work in a few hours to days. This time advantage is crucial to patients whose depression is resistant to traditional

therapy and those who are at high risk of committing suicide (Vasiliu, 2023). By selectively blocking those NMDA receptors on a high proportion of the gamma interneurons, which are more usually associated with the inhibitory system of neurons called "gamma interneurons", esketamine temporarily disinhibits the glutamatergic neurons. This disinhibition results in a greater release of the transmitter substance glutamate from presynaptic terminals into the synaptic space which in turn translates into enhancement of the activation of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic neurons (Kawczak et al., 2024).This greater signaling at AMPA receptors activates downstream intracellular signaling pathways, including brain-derived neurotrophic factor (BDNF) and the mammalian target of rapamycin complex 1 (mTORC1). Stimulation of these pathways enhances synaptic protein synthesis and development of synapses, specifically in those areas of the brain that are involved in mood, such as the prefrontal cortex, hippocampus, and limbic system. This biological remodeling can repair impaired synaptic connectivity present in major depressive disorder and treatment-resistant depression, playing a role in the rapid antidepressant effect of esketamine (Kawczak et al., 2024).

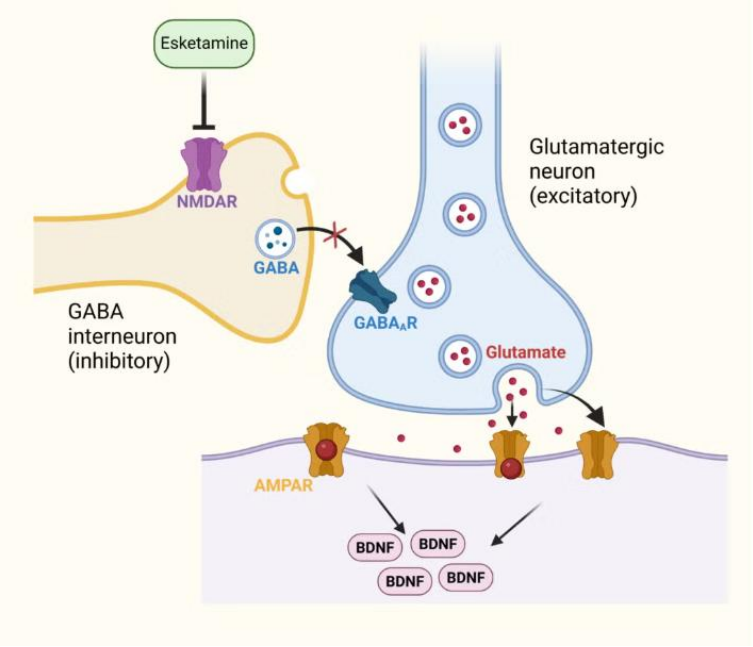

Figure 2: Esketamine mechanism of action(Vasiliu, 2023)

5.2.2 Esketamine Effects on the Dopaminergic System

Esketamine affects the dopaminergic system in brain regions associated with reward. There is a possibility of dopamine release in the striatum to promote improvements in anhedonia (loss of pleasure), one of the core symptoms of depression, and it partially explains some of the short-term psychotomimetic effects noted in the course of treatment (Vasiliu, 2023a). This dopamine tone elevation is not primarily achieved through an elevation in dopamine release, but rather via a failure to undergo various dopamine-clearing mechanisms, resulting in higher extracellular dopamine concentrations (Rizzo et al., 2025). Moreover, esketamine alters the firing pattern of the dopaminergic neurons and enhances the activity of the neurotransmitter-producing neurons of the ventral tegmental area (VTA), which is one of the important nodes in the mesolimbic dopamine system. The improvement leads to an increase in motivation, reward processing, and mood. Nevertheless, the changes in dopamine signaling may also be underlying some of the transient psychotomimetic or dissociative side effects that occur during esketamine administration (Kokkinou et al., 2018).

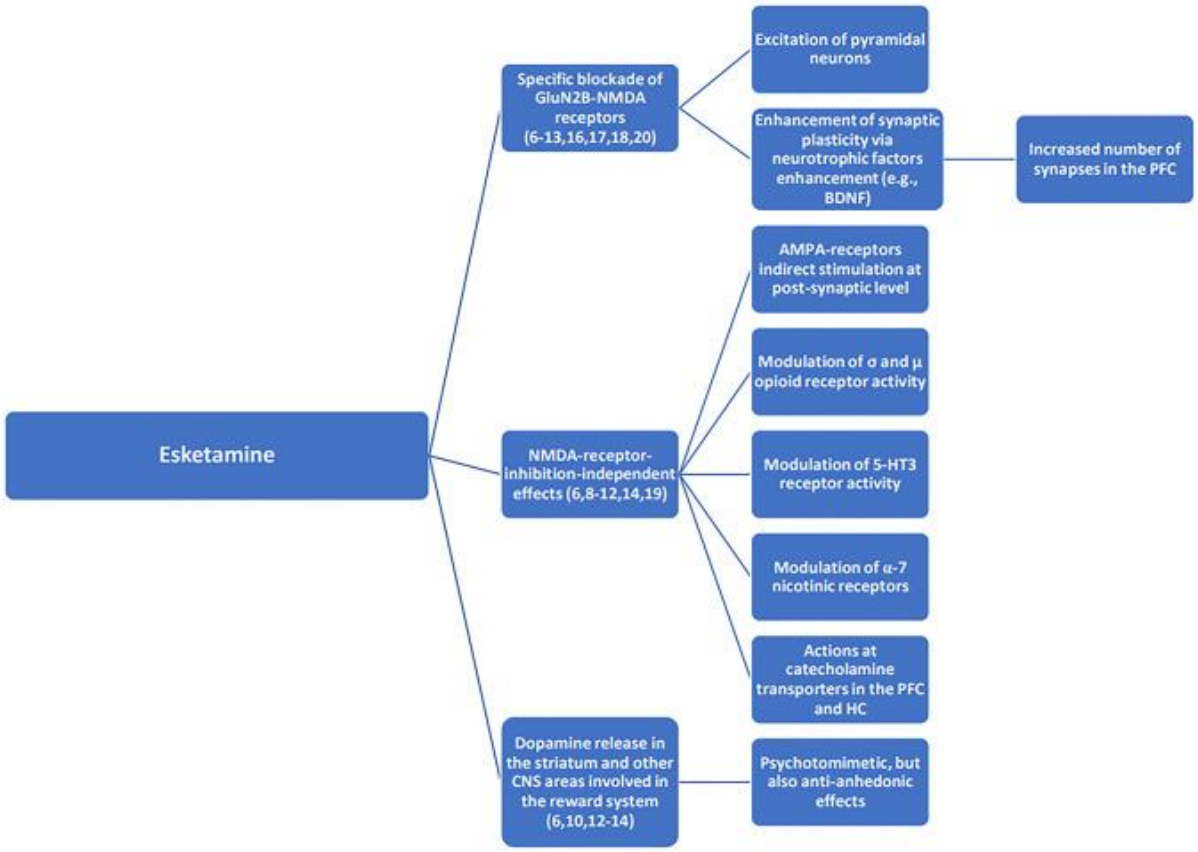

Figure 3: Flow chart of the Esketamine mechanism of action(Vasiliu, 2023)

5.3 Pharmacokinetics of Esketamine

Esketamine, the S-enantiomer of ketamine, has unique pharmacokinetic characteristics that add to its clinical profile for the treatment-resistant depression. When given intranasally, the percentage of dose absorbed via the nasal mucosa is about 48-54% with peak plasma concentrations (Cmax) achieved between 20-40 minutes (Tmax). Esketamine has a rather large volume of distribution (approximately 709 liters at steady state) and intermediate plasma protein binding (43-45%) permitting extensive diffusion into tissues, including through the blood-brain barrier, necessary to its central nervous system action (Vasiliu, 2023). Moreover, Esketamine is metabolized through the liver via cytochrome P450 enzymes, most significantly

CYP2B6 and CYP3A4 (with some minor roles played by CYP2C19 and CYP2C9). When this metabolism occurs, the product is the major active metabolite S-norketamine, which has a longer half-life (~8 hours) than the parent compound (7-12 hours) and possibly leads to prolonged pharmacodynamic effects. A small fraction of the dose ingested is excreted intact in the urine; most of the drug is excreted in urine (renal: ≥ 78%) and a smaller amount in feces (renal: ≤ 2%). This means esketamine clearance is approximately 89 L/h following intravenous dosage (J. Wang et al., 2019). Furthermore, CNS depressant drug-drug interactions may raise the risk of sedation and may require close observation. Close attention should be paid to the co-administration of stimulants and monoamine oxidase inhibitors (MAOIs) because of potential hypertension. Pharmacodynamically, esketamine is a non-competitive, non-selective antagonist of NMDA receptors with a relative affinity that is about two or three times higher than that of R-ketamine, leading to rapid antidepressant and synaptogenic effects via activation of AMPA receptors and downstream signaling through mTOR pathways and brain-derived neurotrophic factor (BDNF) release (Vasiliu, 2023).

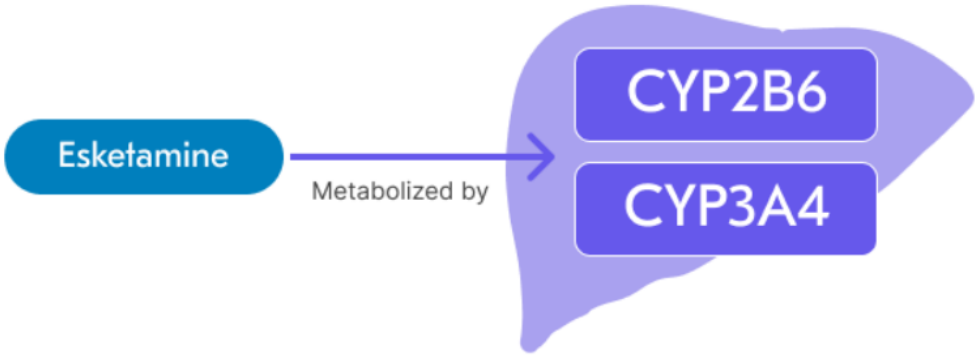

Figure 4: Metabolism process of esketamine(Vasiliu, 2023)

5.3.1 Effect of Age on Esketamine PK

Older patients are more likely to experience increased plasma levels of esketamine than the young adults. Elderly patients have been reported to show an increase of 18-67% in the maximum plasma concentration (Cmax) following intranasal administration, perhaps due to age-related alterations of hepatic metabolism and changes in the nasal mucosa absorption. Regardless of this increment, there is no significant difference in the elimination half-life (7-12 hours) between older and younger adults, indicating that the rate of drug clearance is not highly affected by age. Tolerability in older individuals can be supported using clinical safety data without the need to change the dose (Vasiliu, 2023).

5.3.2 Effect of Renal Impairment on Esketamine PK

Esketamine is hepatically metabolized and excreted through the kidneys as the major metabolites. Plasma levels of esketamine and its metabolites are slightly increased in patients with moderate to mild renal impairment (30 to 89 mL/min creatinine clearance) but not so much as to necessitate a dose increase. There is little data on severe cases of renal impairment (creatinine clearance below 30 mL/min), although existing evidence indicates that there is no significant accumulation of the parent drug since less than 1 percent is excreted unchanged through the urine. However, the close observation of such patients is recommended to identify the possible negative outcomes(Vasiliu, 2023).

5.4 Clinical Trials of Esketamine

A strong sequence of Phase II, Phase III, and Phase IV studies has demonstrated the esketamine nasal spray effectiveness, safety, and commercial usefulness in the treatment of TRD. After

initial Phase I trials that assessed the pharmacokinetics and tolerability of esketamine, as well as establishing the most appropriate dose plans in healthy volunteers, Phase II trials presented the strongest evidence of the rapid-acting and antidepressant effects of the drug. Interestingly, a recent double-blind randomized placebo-controlled Phase II study revealed that intranasal esketamine can produce significant improvements in depressive symptoms, as assessed using the Montgomery-Asberg depression rating scale (MADRS), within 24 hours of administration in comparison to placebo (Daly et al., 2019). These results were highly significant considering the limitations associated with conventional antidepressants, which often take weeks before their potential clinical effect is achieved. Initial studies also demonstrated the potential of esketamine to reduce acute suicidal thoughts, which is a highly unmet need in mental health treatment. Based on this, pivotal Phase III trials, with the TRANSFORM and SUSTAIN programs being the highlight, confirmed the therapeutic profile of esketamine. The TRANSFORM trials were multiple short-term randomized controlled trials to determine whether esketamine nasal spray is safe and effective in treating adults with TRD. In another example, the TRANSFORM-2 trial randomized 223 adults with TRD into intranasal esketamine and a newly initiated oral antidepressant or placebo and an oral antidepressant. The outcomes indicate a significantly higher decrease in the MADRS scores in the group of patients who received esketamine than in patients treated with placebo, and the noticeable improvement is observed already on day two of treatment. Such a quick-acting profile was also a significant improvement in depression treatment, compared to traditional drugs. Pooled analyses revealed statistically significant results, although not all individual TRANSFORM studies achieved statistical significance across primary endpoints, indicating clinically substantial improvements that support overall esketamine efficacy in TRD(Vasiliu, 2023).

5.5 Efficacy of Esketamine

Esketamine has shown strong efficacy in multiple clinical studies as adjunctive therapy to oral antidepressants and as first-line therapy in treatment-resistant depression (TRD).

5.5.1 Efficacy of Esketamine in Lowering Suicide Risk

Esketamine has been demonstrated to be largely effective in lowering suicidal ideation in a short period in patients with major depressive disorder (MDD) who are at high risk of suicide. In ASPIRE I and II phase III trials of over 450 patients with active suicidal ideation and intent, intranasal esketamine 84 mg twice a week showed a significant reduction in depressive symptoms within an hour after the initial dose, with continued reduction at 24 hours and throughout the 4 weeks of treatment, as compared to placebo plus standard care (hospitalization and oral antidepressants) (Canuso et al., 2021). Although general indicators of suicidality (Clinical Global Impression-Severity of Suicidality-Revised scale) showed positive changes in both groups, the benefits of the treatment in depressive symptoms and suicidal belief were noticed early and significantly in the esketamine group, particularly in patients with a history of attempted suicide (Canuso et al., 2021). The influence of esketamine on treatment-resistant depression is also supported by further data from real-world observational studies and meta-analyses, and the reductions in suicidal thoughts occur within hours to days of treatment administration (Canuso et al., 2021). With these advantages, it was observed in the trials that the magnitude of suicide risk at follow-up was not significantly different between esketamine and placebo in addition to the fact that continuous and comprehensive standard care with pharmacotherapy was significant. Notably, the fast antidepressant effect of esketamine can be the basis of its ability to reduce suicide risk in that the underlying depressive symptoms that cause most suicidal behavior are relieved by the use of esketamine (Canuso et al., 2021).

5.5.2 Efficacy of Esketamine on Cognitive Functioning

The impact of Esketamine on cognitive functioning has been examined both in the short run and in the long run, and the results are rather positive with some temporary limitations only in the post-administration period. In healthy subjects, intranasal esketamine produced a short-term, mild, and reversible deterioration of cognitive function approximately 40 minutes after administration that returned to baseline within 2 hours, which suggested that esketamine has acute, reversible effects on cognition (Barbosa & Guedes, 2022). The adjunctive treatment with esketamine nasal spray over a period of six months, in the treatment-resistant depression (TRD), improved several cognitive functions, such as attention, memory, working memory, set-shifting, and inhibitory control. Interestingly, these cognitive gains were associated with decreases in the severity of depression, and no cognitive deficits, were detected throughout the therapy (Barbosa & Guedes, 2022). On the other hand, comparative esketamine versus racemic ketamine revealed no significant differences in terms of cognitive functioning, with both medications enhancing short-term visuospatial memory, executive functioning, processing speed, and episodic verbal memory in the near future after drug delivery (Vasiliu, 2023c). Furthermore, esketamine did not have any significant effect on the driving performance of patients with major depressive disorder 6 to 18 hours post-dose, which confirms its low effect on operational cognition at therapeutic doses. Esketamine also enhanced cognitive recovery following propofol sedation in the surgical unit, at postoperative day 3, which further supports the possibility of cognitive benefits beyond mood enhancement (D. Liu et al., 2025).

5.6 Esketamine Tolerability

Esketamine is usually well tolerated however it has some common side effects most of which are transient. In a big clinical trial of 1,148 participants under treatment with esketamine nasal

spray to treat treatment-resistant depression, headache (37%), dizziness (34%), nausea (34%), dissociation (26%), nasopharyngitis (24%), somnolence (23%), dysgeusia (20%), and back pain (20%), were the most commonly reported adverse events (≥ 20%). One-quarter of patients reported dissociation (perceptual disturbances or a feeling of detachment), which usually cleared up the same day without permanent effects. Sedation occurred in 8.2 percent of the participants and was also easily resolved (Zaki et al., 2025a). Moreover, approximately 19 percent of participants experienced serious adverse effects, and few of them were considered associated with esketamine. The frequency of serious adverse effect involving depression and suicidality was approximately 2% each, and 6.4% had to discontinue treatment because of adverse effects, such as increased blood pressure, aggravation of depression, or dissociation. A significant side effect was an increase in blood pressure, especially in patients who had a history of hypertension, although these complications were avoidable and reversible (Ammendolia et al., 2025). Dissociation, sedation, and hypertension are the most frequent adverse reactions that have been confirmed by post-marketing surveillance with no new safety signals. Close attention to monitoring of blood pressure and mental condition during the dosing is advisable (Ammendolia et al., 2025).

Chapter 6

Future Direction

The future development of esketamine as a therapeutic agent is focused on expanding its indications, improving delivery methods, and optimizing dosing regimens to enhance efficacy and safety. Recent clinical data and regulatory approvals support the use of esketamine as a standalone monotherapy for adults with treatment-resistant depression (TRD). It's marking a significant advancement from its initial approval as an adjunctive therapy with oral antidepressants. Johnson & Johnson's SPRAVATO nasal spray received FDA approval for monotherapy based on phase 3 trial data demonstrating rapid and sustained depressive symptom improvement as early as 24 hours post-dose and at 28 days, with favorable tolerability (*Janssen Announces Results of Esketamine Nasal Spray Phase 3 Study in Patients with Treatment-Resistant Depression*, n.d.). Furthermore, there is ongoing research to investigate the potential of esketamine in other psychiatric conditions including post-traumatic stress disorder (PTSD), bipolar depression, and suicidality in various subgroups of individuals, including adolescents and older adults (Zaki et al., 2025). In addition, combinations of esketamine with cognitive behavioral therapy or precision medicine in genetic or biomarker-based subgroups are in trials to ensure the highest response and sustainability to treatment. Researchers are also looking into other formulations and administration routes such as oral and intravenous routes to make it more convenient and adhered to by patients (Zaki et al., 2025).

Chapter 7

Conclusion

Esketamine is a breakthrough in the management of major depressive disorder, especially patients resistant to treatment and those who are at risk of committing suicide. Since being defined as a breakthrough therapy by the FDA, esketamine has been in a fast clinical development, demonstrating rapid-acting antidepressant properties and long-term efficacy as an adjunctive and monotherapy. This is because it has a new mechanism of action that works on the NDM receptors and enhances synaptic plasticity, unlike current antidepressants, and it meets the urgent need to achieve a quick symptom response. Current studies are expanding their therapeutic potential to other neuropsychiatric disorders and to a wider range of patients and optimization of delivery, dosage and combination therapies is a focus of ongoing research. Safety data is encouraging in the long term and lends itself to inclusion into clinical practice with close observational care. The accumulation of research on esketamine throughout the world indicates a long-term interest among scientists and clinicians. The future will most likely be devoted to maximization of efficacy, minimization of side effects and expansion of accessibility to realize the potential of esketamine as a disruptive agent in psychiatry.

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