KETAMINE

ON DEPRESSION TREATMENT

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FOREWORD

Ketamine has been used as an anesthetic for many years. After the 1950s, it was found to have an antidepressant-like effect when used in low doses. Although it is not widely prescribed due to its potential for abuse, studies to unravel its mechanisms of action are quite abundant. In addition to being an antagonist of NMDA and AMPA receptors, it is also effective on monoaminergic and opioid systems. The prominent features of ketamine are that it acts on metabolism in different ways, has a much faster and longer-lasting effect than traditional antidepressants, and especially its performance in patients who are resistant to treatment. R- or S-ketamine enantiomers, or their racemic mixture, have been studied in both preclinical and clinical studies. The conclusion drawn from these studies is that all the properties of ketamine will be elucidated in the coming years and that it will be used as a safe antidepressant for patients suffering from depression.

Emre YILMAZOĞLU & İbrahim Metin HASDEMİR

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LIST OF ABBREVIATIONS

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AMPAR: AMPA Receptor

BD: Bipolar Disorder

BDNF: Brain-Derived Neurotrophic Factor

BMI: Body Mass Index

BPRS: Brief Psychiatric Rating Scale

BSS: Beck Scale for Suicide Ideation

BZDRs: Benzodiazepines and Related Drugs

CADSS: Clinician-Administered Dissociative States Scale

cAMP: Cyclic Adenosine Monophosphate

CREB: cAMP Response Element Binding Protein

CSDS: Chronic Social Defeat Stress

DEA: Drug Enforcement Administration

DRD1: Dopamine Receptor 1

eEF2: Eukaryotic Elongation Factor 2

ERK: Extracellular Signal Regulatory Kinase

FDA: Food and Drug Administration of United States

GABA: Gamma-Aminobutyric Acid

GAD/SAD: Generalized Anxiety Disorder/Social Anxiety Disorder

GAD65/GAD67: Glutamic Acid Decarboxylase Enzymes

GBCr: Global Brain Connectivity with Global Signal Regression

GFAP: Glial Fibrillary Acidic Protein

HADS(-D): Hospital Anxiety and Depression Scale (its subscale for depression)

HAM-D (HDRS): Hamilton Rating Scale for Depression

HSP-70: Heat Shock Protein 70

IDS-C30: Inventory of Depressive Symptoms-Clinician rated (30 item)

IL: Interleukin

IPSCs: Inhibitory Postsynaptic Currents

LPS: Lipopolysaccharide

MADRS: Montgomery–Åsberg Depression Rating Scale

MAO: Monoamine Oxidase

MDD: Major Depressive Disorder

mTOR: Mechanical Target of Rapamycin

NBQX: 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo (f) quinoxaline-2,3-dione

NLRP3: NLR Family Pyrin Domain Containing 3 Protein

NMDA: N-Methyl-D-Aspartate

NMDAR: N-Methyl-D-Aspartate Receptor

NRBP1: Nuclear Receptor Binding Protein 1

PFC: Prefrontal Cortex

PPIs: Proton Pump Inhibitors

SIDAS: Suicidal Ideation Attributes Scale

SOFAS: Social and Occupational Functioning Assessment Scale

SSRIs: Selective Serotonin Reuptake Inhibitors

TCAs: Tricyclic Antidepressants

TNF: Tumor Necrosis Factor

TRD: Treatment-Resistant Depression

TrkB: Tropomyosin Receptor Kinase B

VAS: Visual Analogue Scale

WCST: Wisconsin Card Sorting Test

WHO: World Health Organization

1. INTRODUCTION

Depression is a mental disorder that almost everyone experiences during a certain period or chronically. According to the World Health Organization (WHO), 280 million people were recorded suffering from depression in 2021. But only one-third of depressed patients receive adequate treatment. Treatment of depression is very important in terms of public health as well as the health of individuals. Because the behaviors triggered by depression can even lead to events such as suicide and murder, which can threaten the social structure. The causes of depression are as varied as its consequences. These include genetic, environmental, and biological factors.

Biogenic amine-based antidepressants have disadvantages such as delayed action up to weeks, low response rate of metabolism, low rate of relief in depression symptoms, and moderate effect size between groups in studies on these drugs (Rush, 2007). The two most important disadvantages of traditional antidepressants are the long time (up to 2 months) for adequate effect to occur and the high rate of those who do not respond to treatment (Martinotti et al., 2022). In addition, 20-30% of depressed patients show resistance to treatment. Up to one-third of major depressive disorder (MDD) patients are resistant to treatment modalities using conventional antidepressants (O'Brien et al., 2021). Methods such as transcranial magnetic stimulation or vagal nerve stimulation approved by the FDA can be used to increase the effectiveness of traditional antidepressants used in the healing of treatment-resistant depression (TRD) patients. However, the process takes quite a long time, and it is not clear whether definitive results can be obtained (Carreno et al., 2020).

Classical antidepressants, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), are drugs that require long-term use, have a low response rate, and may encounter high metabolic resistance (Gartlehner et al., 2011). Ketamine, taken below the required dose for anesthesia, stands out as a functional antidepressant in patients with rapid action and resistance to treatment (Abbasi, 2017). The antidepressant effect begins within

one hour and lasts up to two weeks, reaching a peak at 24 hours (Hashimoto, 2019). It has had an antidepressant effect lasting 24 hours in animal trials (Fukumoto et al., 2018). In a study examining applications over a 10-year period, it was shown that the symptoms of depression were reduced by 36.5% within 24 hours and by 47.6% within 2-7 days. In the same study, 18% of symptoms resolved within 24 hours and 28.2% within 2-7 days (Marcantoni et al., 2020).

Predictions of response in the use of ketamine, which starts within a few hours and has an effect for up to a week, even in a single dose in TRD patients, are very effective in drug selection (Rong et al., 2018; Vande Voort et al., 2016). Ketamine has been found to be effective against TRD patients, lasting up to 1-2 weeks, and starting within a few hours (Lally et al., 2015; Murrough et al., 2015; Price et al., 2014). It has been observed that intravenous ketamine supplementation reduces the effects of trauma-induced neurobiological resistance to traditional antidepressants, especially in patients with a trauma history (O'Brien et al., 2019). The effects of ketamine on sensitization are rapid (Gaytan et al., 2002). It is effective in relieving symptoms during and after trauma (Albott et al., 2018; Feder et al., 2014).

Psychotic MDD is a more difficult disease to treat, with a higher risk of recurring health problems, up to death, compared to non-psychotic MDD. It is tried to be treated by using antipsychotics together with antidepressants or by applying electroconvulsive therapy. Although the benefits of cognitive behavioral therapy are seen, the mechanism of action has not been clarified. In a study, it was concluded that ketamine can be used against psychotic behaviors and mood disorders, and that it weakens the metabolic systems it affects, suicidality and other psychotic symptoms (Le et al., 2021). Major beneficial and side effects of ketamine are seen in **Figure 1**.

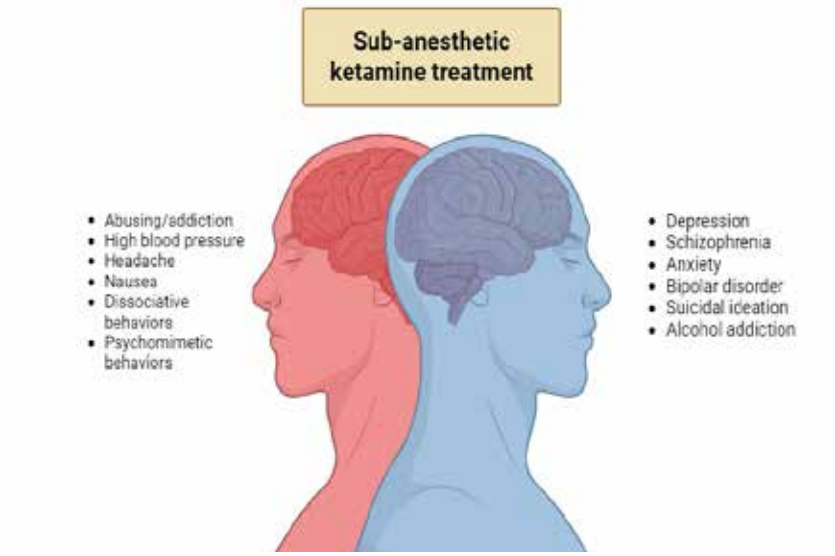


Figure 1. Featured advantages and disadvantages of sub-anesthetic use of ketamine

The subject that forms the backbone of this review is the anti-depressive effects of ketamine and the proposed mechanisms for the formation of these effects. The sections explaining these mechanisms have been tried to be kept as short as possible and yet comprehensive enough to be understandable. Clinical studies on ketamine, especially on humans, are focused on, and the effects seen in preclinical studies on animals are also given in some cases, depending on the context. Additionally, in the section, ketamine-drug interactions in the literature are summarized. Ketamine, which has a risk of abuse, is also used to treat addiction to alcohol and some drugs. This dilemma has been examined under a separate heading. While trying to objectively present the advantages and disadvantages of ketamine use, the author hopes to contribute to the knowledge of those concerned about ketamine so that this substance, whose medical use is generally accepted, can be used safely.

2. THE CHEMICAL STRUCTURE AND SYNTHESIS OF KETAMINE

Ketamine is an arylcyclohexylamine derivative first synthesized from phencyclidine by Calvin L. Stevens in search of a safer anesthetic with less hallucinogenic effects (Stevens et al., 1965). Ketamine, a chiral compound, exists as R and S enantiomers (**Figure 2**). The more active enantiomer, S-ketamine, is available for medical use under the brand name Ketanest S. In contrast, the less active enantiomer, R-ketamine, has never been marketed as an enantiopure drug for clinical use. S-ketamine is more effective as an analgesic and anesthetic through N-methyl-D-aspartate (NMDA) receptor antagonism, while R-ketamine produces more long-lasting effects as an antidepressant (Sachdeva et al., 2023). A given ketamine enantiomer's optical rotation can differ between the compound's salt and free base forms. Since (S)-ketamine displays dextrorotation, it is called (S)-(+)-ketamine in its free base form. On the other hand, its hydrochloride salt exhibits levorotation and is designated as (S)-(−)-ketamine hydrochloride.

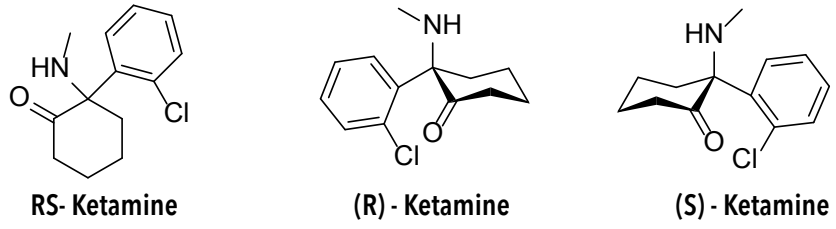
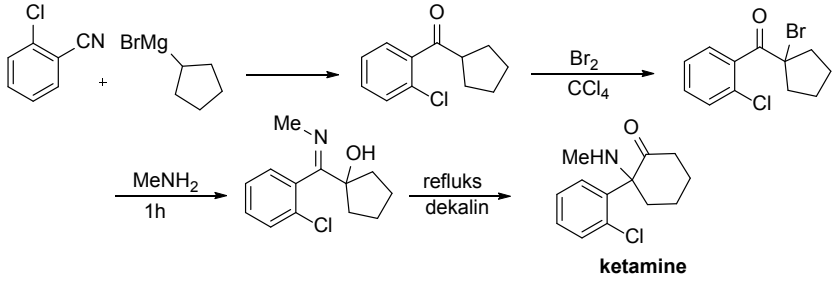


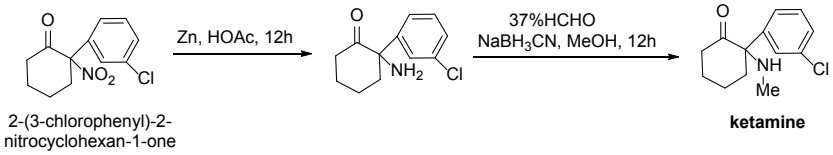
Figure 2. Chemical structure of ketamine

Many synthesis procedures have been developed since the first discovery of ketamine. The synthesis procedure realized by Stevens in 1965 is shown in **Scheme 1** (Stevens et al., 1965).



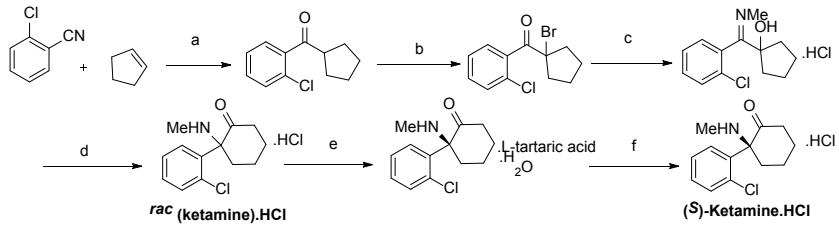
Scheme 1. The synthesis procedure of ketamine by Stevens et al. 1965

In 2017, Zhang et al. developed a new method for the preparation of ketamine that is easier and more efficient than the existing procedure. Thus, they successfully synthesized ketamine with a 56% yield starting from 2-(3-chlorophenyl)-2-nitrocyclohexan-1-one (**Scheme 2**) (Z. Q. Zhang et al., 2017)



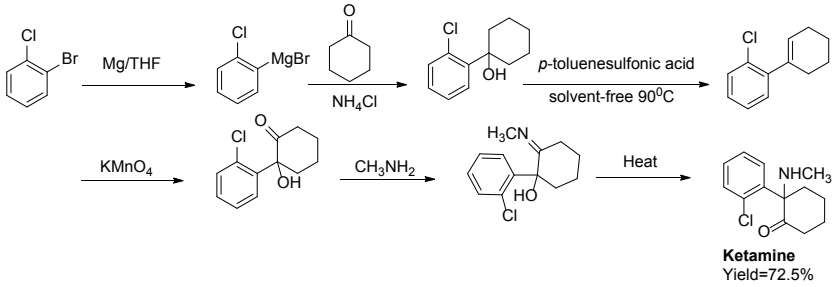
Scheme 2. Synthesis of ketamine

In another study, Gao et al. developed a cost-effective, recoverable, and industrially scalable synthesis method for (S)-ketamine (esketamine), obtaining (S)-ketamine with 99% purity (**Scheme 3**). Additionally, the other isomer (R-ketamine) formed during the reaction was recycled three times, increasing the overall process yield from 14.0% without racemization to 51.1% (Gao et al., 2020).



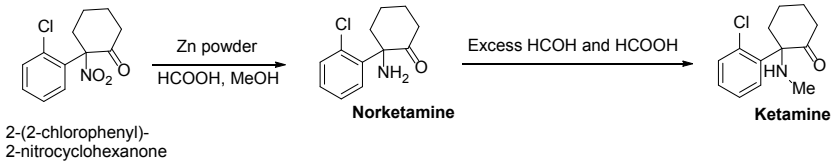
Scheme 3. Synthesis route to S-ketamine suggested by Gao et al. 2020. Reagents and conditions: (a) (1) $AlCl_3$, CH_2Cl_2, and −10 °C and (2) $AlCl_3$, cyclopentane, 40 °C, 3 h, vacuum distillation, and 70.3%; (b) 48% HBr, 30% H_2O_2, 70−80 °C, 3 h, and 96.8%; (c) (1) 15−20% CH_3NH_2 aqueous solution, 15−20 °C, 48 h, and 90% and (2) 2 N EA/HCl; (d) PhCOOEt, $AlCl_3$, 125 °C, 5 h, and 93.6%; (e) L-(+)-tartaric acid, acetone/H_2O, and 41%; (f) (1) NaOH and 2 N EA/HCl and (2) crystallized with acetone/H_2O and 80%.

In a study performed in 2020, a new and effective protocol was developed for ketamine synthesis using the hydroxy ketone intermediate and ketamine was obtained with a 72.5% yield (**Scheme 4**) (Zekri et al., 2020).



Scheme 4. Synthetic route of ketamine from 1-bromo-2-chlorobenzene

In 2023, Yen et al. achieved the synthesis of ketamine starting from 2-(2-chlorophenyl)-2-nitrocyclohexanone (**Scheme 5**) (Yen et al., 2023).



Scheme 5. Proposed process of ketamine synthesis.

3. ANTIDEPRESSANT EFFECTS OF KETAMINE

3.1. Effects of Ketamine's Enantiomers

The antidepressant effects of ketamine have been studied for more than 60 years. Despite its common side effects, its off-label intravenous and intranasal use is increasing in the USA (Wilkinson et al., 2017; Zhu et al., 2016). The mechanisms that provide the antidepressant effect of R,S-ketamine, which is frequently used in the treatment of severe depression, have not yet been fully resolved (Abdallah et al., 2018; Duman, 2018; Gould et al., 2019; Krystal et al., 2019). R,S-ketamine is a racemic mixture containing equal proportions of R- and S-ketamine (arketamine and esketamine) (Ebert et al., 1997). Studies examining the antidepressant and side effects of the two isomers of ketamine are contradictory. In some of these, it is stated that esketamine has less antidepressant effect but more side effects. On the other hand, there are also studies showing the opposite. The reasons for this contradiction are the use of animals or humans in studies, inconsistencies between preclinical and clinical effects,

triggering different mechanisms by ketamine, and examining different stress factors.

Animal studies have shown that arketamine has a stronger and longer-lasting antidepressant effect compared to the other enantiomer (Yang et al., 2018; J. C. Zhang et al., 2014). In addition, it was observed that this enantiomer did not cause psychomimetic side effects and abuse tendency in experiments on rodents (Yang et al., 2016). Contrary to its isomer and mixture, the use of arketamine does not cause the formation of the heat shock protein HSP-70, which is an indicator of neuronal injury (Tian et al., 2018). With intranasal use in mice, the anti-chronic social defeat stress (CSDS) effect was R-ketamine>R,S-ketamine>S-ketamine, while the rate of occurrence of side effects was the opposite. Therefore, arketamine has emerged as a more effective and safer antidepressant compared to esketamine and the racemic mixture (Chang et al., 2019). When used in rats against corticosterone-induced depressive behaviors, R- and R,S-ketamine were severely effective, while S-ketamine did not (Fukumoto et al., 2018). A more sustained antidepressant effect was observed when arketamine was used on dexamethasone-treated mice. This effect enhanced the response in forced swimming and tail suspension tests (J. C. Zhang et al., 2014). It has been found that arketamine is much more effective than esketamine in reversing the decline in sucrose consumption caused by the stress of social defeat and the inevitable shock-induced deficits in learned helplessness. In contrast to esketamine, it was observed that arketamine did not impair the prepulse inhibition of the acoustic startle response, thus not having a psychomimetic effect. Similarly, in conditioned place preference, esketamine, not arketamine, caused the subject to be conditioned and revealed its addictive effect. Since the anesthetic effect of esketamine is 3-4 times greater than that of arketamine, it has a high potential to produce psychomimetic effects (Yang et al., 2015). Although there are studies observing the antidepressant effects of arketamine, the use of arketamine in patients suffering from depression has not yet been studied clinically (Zanos & Gould, 2018a; K. Zhang & Hashimoto, 2019a).

In some studies, however, esketamine was found to be safer. It is also convenient to use as a nasal spray instead of intravenous administration (Martinotti et al., 2022). In 2019, after the FDA approved the esketamine spray, Spravato, suitable for intranasal use in the treatment of TRD, it started to be used as an effective method for eliminating depression symptoms such as suicide (Daly et al., 2018; Popova et al., 2019). Recurrence of depressive symptoms 3-4 months

after drug discontinuation, especially an increased risk of suicide, has been reported (Perez-Esparza et al., 2019; Schatzberg, 2019). Intranasal bioavailability of R,S-ketamine (17-29%) is much lower than intravenous (100%) and intramuscular (93%) use (K. Zhang & Hashimoto, 2019a). Intranasal use was less effective than intraperitoneal use. On the other hand, it has been understood that the antidepressant effects of these isomers and their mixtures are not proportional to their effects on the N-methyl-D-aspartate (NMDA) receptor molecule. Contrary to S- and R,S-ketamine use, proton pump inhibitors (PPIs), which increase with depression, deficiency does not occur with the use of intranasal and intraperitoneal R-ketamine, and there was no increase in conditioned place preference scores with the use of intranasal arketamine, while the use of others caused an increase (Chang et al., 2019; Yang et al., 2015). However, there is also a publication showing that esketamine interrupts PPI concentration 2.5 times that of arketamine (Halberstadt et al., 2016). In **Figure 3**, it is seen that different administration techniques of ketamine.

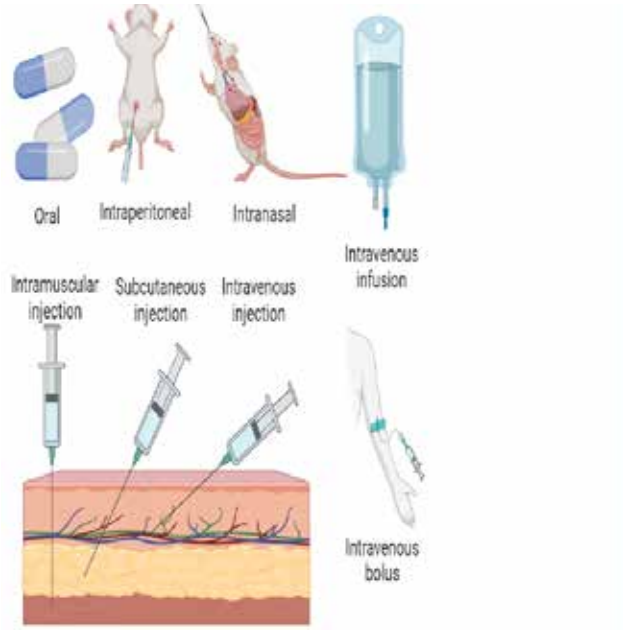


Figure 3. Ketamine administration techniques

3.2. **Preclinical Studies**

Before the clinical application of ketamine in the treatment of depression, many preclinical studies were conducted, especially on rodents. An up-to-date

and comprehensive review was conducted by Le et al in 2022 (Le et al., 2022). Ketamine showed a positive effect against the forced swim test in rodents (N. Li et al., 2011). The antidepressant effect of ketamine is impressive as it has a shorter half-life in rodents (Veilleux-Lemieux et al., 2013). Even the use of a single dose of the drug provides a longer lasting effect than the effect of standard antidepressants only when the drug is in metabolism. There are studies showing that its effect is realized by acutely inducing AMPA-mediated currents to provide a rapid increase in activity-related brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB), which is also associated with this factor, and in this way, it creates neuroplastic changes (Autry et al., 2011; Carreno et al., 2016; Duman et al., 2012). Studies on astrocyte cells, which contribute to the maintenance of the stability of the blood-brain barrier, the elongation of the axons of the nerve cells and the continuity of intercellular communication, have shown the relationship of these cells with depression. During depression, astrocytes-specific markers such as glial fibrillary acidic protein (GFAP) and calcium-binding s100beta protein were decreased in the prefrontal cortex, hippocampus, and amygdala (Gittins & Harrison, 2011). Elimination of astrocyte cells by pharmacological ablation in mice resulted in depression-like behavior. The antidepressant effect can be enhanced by overexpression of the brain-derived neurotrophic factor protein in astrocyte cells. There are antidepressants such as imipramine that affect such properties of astrocytes (Stenovec et al., 2020; Wang et al., 2018). Conditions such as shortening/reducing the number of dendrites in brain nerve cells have been associated with chronic stress, which causes behavioral deficits. It has been understood that ketamine eliminates the problem of dendrite spines caused by stress, re-coordinates the activity of microcircuits in the medical prefrontal cortex region and creates a positive situation in the forced swimming test (Moda-Sava et al., 2019).

The positive results of ketamine in the forced swimming test of female mice were ahead of the results of male mice. It is the hormones estrogen and progesterone that create this sensitivity (Carrier & Kabbaj, 2013). On the other hand, the duration of antidepressant effect in male mice was longer than in female mice, and repeated administration of ketamine caused antidepressant effect in males while causing depression and anxiety in females (Franceschelli et al., 2015; Thelen et al., 2016). While preclinical studies have shown that these differences may be similar in humans due to hormones, results from clinical studies have determined that men and women suffering from TRD have metabolically

similar responses. In the same study, no difference was observed in the pre- and post-menopausal status of women. However, it has been noted that female metabolism may respond differently to ketamine administration at different periods of the menstrual cycle (Freeman et al., 2019).

3.3. **Clinical Studies and Ketamine-Drug Interactions**

The increase in the number of clinical studies examining the antidepressant effects of ketamine has been continuing for years. The main outcomes of reliable clinical studies added to the literature on this subject in recent years are summarized in **Table 1**.

Table 1. Clinical applications of ketamine for depression

Study design	Subjects (who completed the study)	Ketamine administration	Outcomes
Randomized, placebo-controlled, double-blinded study (Berman et al., 2000)	9 (7) with MDD	0.5 mg/kg iv for 40 min	Ketamine showed greater change in HDRS score than placebo. The dissociative effects of the application on the subjects disappeared in 3 days.
Double-blind, cross-over, placebo-	27 with MADRS≥20	0.27 mg/kg iv for 10 min followed by	Ketamine produced a significant decrease in the mean MADRS score, starting from day one and lasting for a week. An inverse

controlled (Sos et al., 2013)		0.27 mg/kg iv for 20 min	correlation was detected between HDRS scores and BPRS positive symptoms on the first day.
Hospital-based, open-label, prospective study (Mandal et al., 2019)	25 (20) with moderate depression	6 0.5 mg/kg bolus doses over 2 weeks	The highest effect was seen within the first hour, and temporary side effects disappeared. HAM-D scale measurements showed a significant decrease in depression and anxiety scores after 2 weeks, and this effect was maintained for one month after the last dose.
Randomized, double-blind, crossover study (Lapidus et al., 2014)	20 (18) with MDD	50 mg intranasal (5 nasal application of 10 mg ketamine in 20 min)	Ketamine showed an effect that peaked at 24 hours and lasted for a week compared to placebo. The largest decrease in MADRS score and the highest response rate were seen 24 hours after application. Intranasal administration had a very low effect on psychomimetic and dissociative behaviors and blood pressure.

Randomized, double-blind, active placebo-controlled study (Shiroma et al., 2020)	54 (54) with MDD	6 0.5 mg/kg ketamine doses or 5 0.045 mg/kg midazolam+1 0.5 mg/kg ketamine doses iv for 40 min over 12 days	Continuous ketamine administration maximized the difference in MADRS scores compared to midazolam, especially after 5 doses. Although continuous use of ketamine showed superiority in the treatment of depression, a single dose of ketamine after midazolam treatment closed the gap. The relapse rate of depression at 6 months after treatment was lower after continuous ketamine administration. Side effects of ketamine have been observed to be particularly high blood pressure, headache, and anxiety. Dissociative behaviors and CADSS score increased with continuous ketamine administration.
Double-blind, placebo-controlled, dose-ranging	99 (86) with TRD	0.1, 0.2, 0.5 or 1.0 mg/kg ketamine or 0.045 mg/kg	The effect of ketamine on HAM-D scores was seen from the first day. MADRS score was also measured after 3 days and the positive effect of ketamine was observed. It has been suggested that below the standard dose of 0.5 mg/kg, the antidepressant effect is ineffective compared to placebo. On the other hand,

trial (Fava et al., 2020)		midazolam iv for 40 min	0.1 mg/kg ketamine administration gave better results than placebo without observed side effects. While there were significant decreases in responses after 5 days, the effect of high doses of ketamine was detected for up to a month.
Open-label study (Can et al., 2021)	32 (30) with MDD or other diagnoses with MDD, BSS score≥6	Oral dosage starting from 0.5 mg/kg per week and increasing up to 3 mg/kg in the 6th week	While the average BSS score was 20 before treatment, it decreased to 5.6 in the first week after treatment, reaching a level that did not require clinical treatment. The average of BSS measurements 1 month after treatment was 9.1. Ketamine treatment reduced the frequency of suicidal ideation according to the SIDAS scale and reduced depression from severe to mild according to the MADRS scale. Additionally, according to SOFAS, there was an improvement in social and functional behaviors. No serious side effects were observed.
Ambi-directional	22 (21) with unipolar and	6 0.5 mg/kg iv doses twice for	Of the 21 patients who completed the treatment, 20 discontinued BZDRs and 14 of them did not use the drug for an

cohort study (Garel et al., 2023)	bipolar TRD depression using BZDRs for more than 6 months	two weeks and once for two weeks	average of 1 year. It has been evaluated that ketamine enabled participants to take long breaks from benzodiazepine use. According to participants, ketamine was effective in eliminating depression, anxiety, and sleep disturbance caused by BZDRs withdrawal.
Randomized, double-blind, crossover study (Phillips et al., 2020)	37 (37) MDD with MADRS≥25	0.5 mg/kg ketamine or 30 µg/kg midazolam iv for 40 min	The study showed that the antidepressant effect was not directly related to the effect of preventing suicidal thoughts. Following ketamine in the treatment of depression, once a week application was sufficient to prevent suicidal tendencies.
Open-label study (Murrough,	24 with MDD	6 0.5 mg/kg iv doses over 12 days	The mean MADRS score decreased from 31.8 to 12.9 within 2 hours after the first dose. While the score of patients who responded to the drug continued to decrease throughout the process, there was an increase in those who did not respond. In the 83-day follow-up of 17 patients who responded to the

Perez, et al., 2013)			medication, the median time to relapse of depression was 18 days. Depression was not observed in 4 patients for 83 days. It was observed that the psychomimetic effect of ketamine in increasing the BPRS score disappeared after 4 hours. The dissociative effect also ended in the same period.
Two-site, parallel-arm, randomized, controlled study (Murrough, Iosifescu, et al., 2013)	73 (72) with TRD	0.5 mg/kg ketamine or 0.045 mg/kg midazolam iv for 40 min	Ketamine showed a greater effect on MADRS score and response rate within 24 hours compared to midazolam. After 7 days, there was no significant difference between ketamine and midazolam.

Open-label study (Irwin et al., 2013)	14 (8) with HADS≥15 or HADS-D≥8	0.5 mg/kg for 28 days orally	According to HADS, the highest response for anxiety was achieved in 3 days and for depression in 14 days. Side effects have been seen rarely. It has been suggested that oral administration produces the effects obtained in classical applications in a longer period of time and with fewer side effects.
Uncontrolled, open-label study (Glue et al., 2017)	12 with treatment-resistant GAD/SAD	0.25, 0.5, or 1.0 mg/kg subcutaneously	Anxiety decreased within 1 hour and the effect lasted up to 1 week. Dissociative behaviors began to appear 5 minutes after the injection, peaked after 30 minutes, and disappeared after 1 hour. The effect of the low dose on anxiety was weak and transient.
Randomized, open-label, parallel-group study	27 (2) with MDD	0.5 mg/kg iv for 40 min, 0.25	HAM-D measurement was made. All three groups experienced antidepressant effects within 2 hours and lasting up to 4 days.

(Chilukuri et al., 2014)		mg/kg im, or 0.5 mg/kg im	No change in blood pressure was measured. Regardless of the dose, iv administration was as effective as iv administration.
Resting-state functional connectivity magnetic resonance imaging (Abdallah, Averill, Collins, et al., 2017)	18 with MDD and 25 healthy	0.5 mg/kg iv for 40 min	The effect of ketamine on the brain in MDD patients and healthy individuals was measured by GBCr. GBCr in the PFC, which was lower in patients, improved within 24 hours with ketamine. Apart from PFC, an increase is also seen in the caudate and insula. On the contrary, GBCr values, which are high in the posterior cingulate, precuneus and occipital cortices in MDD, decrease with treatment. Partial improvement is seen in the cerebellum.

TRD: Treatment Resistant Depression, **MDD:** Major Depressive Disorder, **GAD/SAD:** Generalized Anxiety Disorder/Social Anxiety Disorder, **MADRS:** Montgomery–Åsberg Depression Rating Scale, **HADS(-D):** Hospital Anxiety and Depression Scale (its subscale for depression), **HAM-D:** Hamilton Rating Scale for Depression, **BPRS:** Brief Psychiatric Rating Scale, **CADSS:** Clinician-Administered Dissociative States Scale, BSS: Beck Scale for Suicide Ideation, **SIDAS:** Suicidal Ideation Attributes Scale, **SOFAS:** Social and Occupational Functioning Assessment Scale, **BZDRs:** Benzodiazepines and related drugs, **GBCr:** Global Brain Connectivity with Global Signal Regression, **PFC:** prefrontal cortex

Some of the situations suggested and proven in these studies can be summarized as follows:

- The standard dose of ketamine used in depressant treatment is 0.5 mg/kg.
- Its effect occurs within a few hours and is successful in acute treatment.
- Repeated application is not effective in reducing the symptoms of depression, but in prolonging the duration of relapse.
- Intravenous use is common. Bolus application, intramuscular application and subcutaneous application give similar results in terms of effects and side effects, depending on the dose.
- The most common side effects of subanesthetic dose are high blood pressure, headache, nausea, dissociative behaviors, anxiety, and psychomimetic behaviors. These effects may be severe or mild depending on the drug dose, peak within an hour and disappear within a few hours.
- In clinical studies, factors such as age, gender, race, and time of use did not create statistically significant differences.

Ketamine is effective not only in the treatment of TRD but also in improving the mood of suicidal patients and in the treatment of anxiety. It was observed that the use of standard doses of ketamine in 10 MDD patients and 15 healthy individuals produced a response regardless of age and gender (Vasavada et al., 2016).

108 TRD and bipolar I/II patients receiving 0.5 mg/kg for 40 minutes were examined. Data for MDD are taken from Zarate et al. 2006 and Ibrahim et al. 2012 and for BD from Diazgranados et al. 2010 and Zarate et al. 2022 studies.

Those with a high body mass index (BMI) and those with a family history of alcohol addiction showed the best HDRS (HAM-D) improvement within 230 minutes after treatment. In the measurements the next day, the improvement was greater in these two groups, as well as in those who showed more BPRS positive symptoms and those who received psychiatric clinical treatment. However, all these factors were not effective one week after treatment. The highest response was seen in people who had never attempted suicide before. The effect of ketamine was higher in patients with MDD than in those with bipolar disorder. Because people with higher BMI took more ketamine, their scores may have been affected more quickly. Alcohol is a weak NMDAR antagonist, and it has been suggested that a genetic polymorphism in the NR2A subunit of this receptor caused by alcohol consumption makes individuals with a family history of alcohol dependence more sensitive to the antidepressant effects of ketamine. This suggests that ketamine may be more functional in the treatment of alcoholics suffering from depression (Niciu et al., 2014).

It has been stated that giving midazolam to the control group would be more appropriate than giving saline to protect blindness in clinical applications of ketamine. In the 9 studies reviewed, it was understood that the use of midazolam in MDD and BD patients was closer to the average antidepressant effect of ketamine than the effect of saline. On the other hand, the dissociative effects of ketamine are seen neither with midazolam nor with saline (Wilkinson et al., 2019).

Although ketamine is frequently used in the treatment of depression, studies are continuing to eliminate its side effects. In clinical studies conducted for this purpose, it is especially important not to weaken the effect of ketamine in relieving depression symptoms. Therefore, the effects of different psychiatric drugs along with ketamine should be carefully examined. The review made by Veraart et al. in 2021 remains up-to-date on this subject (Veraart et al., 2021).

Midazolam and pentazocine were useful in weakening the dissociative behaviors caused by the use of ketamine in anesthesia. Diazepam alone did not show this effect. Promethazine has been very effective in eliminating these behaviors (Kothari et al., 2003).

Lamotrigine, an anticonvulsant, eliminated the effects of ketamine in many studies. Benzodiazepines may increase the rate of relapse by weakening the antidepressant effect of ketamine. Tranylcypromine is an MAO inhibitor and there is no indication that it interacts with ketamine. While it interacts with ketamine,

haloperidol, risperidone and clozapine, it does not interact with olanzapine, which is used for the same purpose. A summary of ketamine-drug interactions is given in the **Table 2**.

Table 2. Major outcomes of ketamine administration using with other drugs (adapted from (Veraart et al., 2021)

Drug name and administration	**Ketamine administration**	**Subjects**	**Major outcomes**
Lithium, 600-1200 mg oral (Costi et al., 2019)	0.5 mg/kg iv for 40 min	34 with MDD (average MADRS score=32)	Lithium had no effect compared to placebo.
Lithium, 0.6-1.2 mEq/L to blood or valproate (Xu et al., 2015)	0.5 mg/kg iv for 40 min	36 with bipolar TRD and MADRS score≥20	It did not contribute to the antidepressant effect of ketamine.

Lamotrigine, 200 mg oral (Abdallah, Averill, Salas, et al., 2017)	0.23 mg/kg iv for 2 min followed by 0.58 mg/kg for 70 min	18 healthy	Lamotrigine pretreatment did not contribute to the positive effect of ketamine on BPRS and CADSS scores. It negatively affected the ketamine-induced GBCr increase and glutamate level in bilateral dorsomedial and left frontolateral cortex.
Lamotrigine, 300 mg oral (Anand et al., 2000)	0.26 mg/kg iv for 1 min followed by 0.65 mg/kg for 90 min	16 healthy	The mood-boosting effect of ketamine has been strengthened. The positive and negative symptoms caused by ketamine decreased.
Lamotrigine, 300 mg oral (Deakin et al., 2008)	0.26 mg/kg iv for 1 min followed by 0.25 mg/kgh	19 healthy	With Lamotrigine pre-treatment, there were decreases in the BPRS score created by ketamine, as well as in thinking disorders and hallucinations. According to blood signal

			measurements, ketamine levels were higher in ketamine treatment after placebo than in lamotrigine treatment.
Lamotrigine, 300 mg oral (Mathew et al., 2010)	0.5 mg/kg iv for 40 min	26 with MDD (IDS-C30 score>32)	There was no change in MADRS and CADSS scores, and there was no improvement in the side effects caused by ketamine.
Lamotrigine, 300 mg oral (Doyle et al., 2013)	0.12 mg/kg iv for 1 min followed by 0.31 mg/kgh	16 healthy	The response in the frontal and thalamic regions of the brain was higher than that in the subgenual cingulate and ventral medial prefrontal cortex.
Lamotrigine, 300 mg oral (Joules et al., 2015)	0.12 mh/kg iv for 1 min followed by 0.31 mg/kgh	16 healthy	Lamotrigine did not produce any significant difference compared to placebo.

Lamotrigine, 300 mg oral (Shcherbinin et al., 2015)	0.12 mh/kg iv for 1 min followed by 0.31 mg/kgh	16 healthy	Lamotrigine did not produce any significant difference compared to placebo.
Lorazepam, 3.5 mg/d and lithium, fluoxetine and quetiapine (Ford et al., 2015)	0.5 mg/kg iv for 10 infusions	1 with BD	While the effect of the first two doses of ketamine lasted 2-3 days, subsequent doses showed an effect of at most 1 day. Following discontinuation of lorazepam, the effects of ketamine were prolonged from several days to two weeks. Benzodiazepines blocked ketamine-induced dopamine release.
Lorazepam, 2 mg oral (Krystal et al., 1998)	0.26 mg/kg bolus followed by 0.65 mg/kgh	23 healthy	It was observed that it did not eliminate the effects of ketamine in BPRS, VAS, CADSS and WCST measurements. Lorazepam reduced emotional distress and

			sensory disturbance and increased sedative and memory impairing effects.
Lorazepam, 2.75 mg per day (Albott et al., 2017)	0.5 mg/kg iv for 40 min, 6 infusions in 12 days	13 with TRD	Patients using lorazepam took longer to respond to the antidepressant and took less time for depression to recur. Since benzodiazepines such as lorazepam are GABA-A receptor agonists, they attenuated the effects of ketamine by reducing glutamatergic stimulation.
Diazepam, 10 mg (Andrashko et al., 2019)	0.54 mg/kg iv	47 with MDD (MADRS≥20)	Regression analysis showed that ketamine effects would disappear within one week after ketamine treatment in case of concurrent use.
GABAergic (Carbamazepine, lamotrigine, divalproex sodium) and	0.5 mg/kg iv for 100 min, 4	10 with TRD or BD II	There was no significant difference between those who used GABAergic or glutamatergic drugs and those who did not.

glutamatergic (benzodiazepines, gabapentin) drugs (Frye et al., 2015)	infusions in 2 weeks		
Tranylcypromine, 10 mg/d up to 80 mg/d oral (Bartova et al., 2015)	S-ketamine, 12.5 mg up to 75 mg iv repeatedly	2 with TRD (severe suicidal thoughts)	The lack of a change in blood pressure and pulse raised suspicion about ketamine's inhibition of monoamine reuptake.
Tranylcypromine, 20 mg/d oral (Bartova et al., 2015)	S-ketamine, 25 mg up to 50 mg iv twice a week	2 with TRD (severe suicidal thoughts)	The lack of a change in blood pressure and pulse raised suspicion about ketamine's inhibition of monoamine reuptake.

Tranylcypromine, 60 mg (Dunner et al., 2020)	S-ketamine, 28 mg for 2, 56 mg for 1, and 42 mg 4 doses nasal	1 with MDD (severe anxiety and melancholia)	An improvement in mood was observed at the end of treatment. The blood pressure that increased during treatment also returned to normal. No monoamine enhancing effect of ketamine was observed.
Haloperidol, 5 mg oral (Krystal et al., 1999)	2.26 mg/kg bolus followed by 0.65 mg/kgh iv	20 healthy	Ketamine-induced memory impairment and anxiety were reduced. There was no change in euphoria, attention deficit, and BPRS positive and negative symptoms. The sedative effect and prolactin response are increased.
Haloperidol, 0.3 mg/kgd for 4 weeks (Lahti et al., 1995)	0.1, 0.3, and 0.5 mg/kg in 1 min iv	9 with schizophrenia	The use of 0.3 and 0.5 mg/kg ketamine increased BPRS scores in patients using haloperidol. The antagonistic effect of ketamine on glutamatergic transmission potentiated schizophrenia symptoms.

Haloperidol, 2 mg oral (Oranje et al., 2009)	0.3 mg/kg for 40 min, 0.0495 mg/kg for 10 min, and 0.213 mg/kg for 85 min iv continuously	18 healthy	Ketamine had as negative an effect on focus and decision-making as placebo. Pretreatment with haloperidol improved distractibility but not rapid decision making.
Risperidone, 2 mg oral (Doyle et al., 2013)	0.12 mg/kg for 1 min followed by 0.31 mg/kgh iv	16 healthy	Risperidone attenuated the effect of ketamine in the entire brain except the striatum. This showed that risperidone weakens the effect of ketamine through 5-HT2A receptor antagonism.
Risperidone, 2 mg oral (Joules et al., 2015)	0.12 mg/kg for 1 min followed	16 healthy	Ketamine increased synaptic connections. Risperidone corrected the decentralization caused by ketamine. However, since the effect of risperidone is not directly proportional to the effect of ketamine, it has been claimed

	by 0.31 mg/kgh iv		that risperidone has the opposite effect to ketamine on NMDAR. Additionally, the opposing effects in the striatum are due to the agonist behavior of ketamine versus the antagonist behavior of risperidone for the D2 receptor.
Risperidone, 2 mg oral (Shcherbinin et al., 2015)	0.12 mg/kg for 1 min followed by 0.31 mg/kgh iv	16 healthy	No significant difference was observed between the effects of ketamine on brain regions. Risperidone increased ketamine-induced hypertension.
Risperidone, 2 mg oral (Schmechtig et al., 2013)	100 ng/ml iv	72 healthy	Ketamine decreased the eye's tracking speed and increased the saccadic frequency. Risperidone did not correct the impairment caused by ketamine on oculomotor performance.

Clozapine, 50 mg oral(Lipschitz et al., 1997)	0.5 mg/kg for 60 min iv	7 healthy	Clozapine did not reduce BPRS scores. It reduced perceptual distortion measured by CADSS.
Clozapine 430 mg/d for 51.8 days followed by ketamine infusion after 20.5 days drug-free duration (Malhotra et al., 1997)	0.12 mg/kg bolus followed by 0.65 mg/kg	10 with schizophrenia or schizoaffective disorder	Ketamine-induced conceptual disorganization and BPRS eliminated positive symptoms but not negative symptoms.
Clozapine, 30 mg oral (Vollenweider et al., 2012)	S-ketamine, 0.006 mg/kgmin	20 healthy	Ketamine acts throughout the brain and causes cognitive impairment. Pretreatment with clozapine improved the effect of ketamine, especially in the anterior cingulate, insula, temporomedial cortex, and cerebellum.

Olanzapine, 5 mg for healthy individuals and 10 mg for patients with schizophrenia (Lahti et al., 1999)	0.3 mg/kg iv	5 healthy and 9 with schizophrenia	Olanzapine was no more effective than placebo in ketamine-induced psychosis.

TRD: Treatment Resistant Depression, **MDD:** Major Depressive Disorder, **BD:** Bipolar Disorder, **MADRS:** Montgomery–Åsberg Depression Rating Scale, **IDS-C30:** Inventory of Depressive Symptoms-Clinician rated (30 item), **BPRS:** Brief Psychiatric Rating Scale, **CADSS:** Clinician-Administered Dissociative States Scale, **GBCr:** Global Brain Connectivity with Global Signal Regression, **VAS:** Visual Analogue Scale, **WCST:** Wisconsin Card Sorting Test

4. DISINHIBITION AND DIRECT INHIBITION HYPOTHESES

Ketamine is one of the NMDAR antagonists of glutamate, which acts as an excitatory neuron. Although this antagonism theoretically means decreased excitatory conduction, neuroimaging studies have shown a significant increase in cortical activity under the influence of antagonism (Jackson et al., 2004; Suzuki et al., 2002; Vollenweider, Leenders, Scharfetter, et al., 1997). It has been suggested since the earliest times that NMDAR antagonism lies in the antidepressant effect of ketamine. The contribution of this antagonism to the antidepressant effect is tried to be explained by the disinhibition and direct inhibition hypotheses (Miller et al., 2016).

Analysis studies showed an increase in glutamate level in the prefrontal cortex extending to 100 minutes after ketamine use (Moghaddam et al., 1997). Low doses of ketamine cause an acute increase in extracellular glutamate, although it inhibits the action of NMDA receptors in gamma-aminobutyric acid producing (GABAergic) interneurons associated with glutamate release. According to the disinhibition hypothesis, when ketamine is administered at subanesthetic doses, it preferentially creates an antagonistic effect on NMDARs in GABAergic interneurons. This phenomenon has been found in the literature under the name of the disinhibition hypothesis (Duman, 2014; Homayoun & Moghaddam, 2007). According to the defense of this hypothesis, blocking these inhibitory interneurons increases the firing of excitatory pyramidal neurons. Due to the rapid firing of these neurons, ketamine can enter the channel where the Mg^{2+} block in the NMDA receptor exits and the receptor is blocked. As a result, glutamate release and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor transmission are accelerated. Thus, the antidepressant effect of ketamine occurs (Gerhard et al., 2020). This hypothesis has been supported by studies that concluded that AMPAR antagonists cause an increase in glutamate release, thereby creating an antidepressant effect (Widman & Mcmahon, 2018; Zanos et al., 2016).

With respect to the direct inhibition hypothesis, the antagonist effect on NMDARs in excitatory pyramidal neurons weakens NMDAR activation via circulating glutamates in metabolism, thus increasing protein synthesis as the pressure on eukaryotic elongation factor 2 (eEF2) is relieved (Autry et al., 2011). With a mechanism involving AMPAR activation independent of NMDAR, ket-

amine enabled the downstream BDNF-TrkB cascade to operate in the cortex and hippocampus (Zanos et al., 2018). Likewise, it potentiated GluA1 expression and phosphorylation-independent of NMDAR and associated with AMPAR (Zanos et al., 2016). In another study to understand the contribution of NMDAR to the mechanism of action of ketamine, it strengthened the downstream BDNF-TrkB cascade by increasing cAMP-induced phosphorylation of the cyclic adenosine monophosphate (cAMP) response element binding protein after NMDAR was destroyed. The potentiation of this mechanism increases the excitatory signal (Wray et al., 2019).

Weakening/interruption of GABA signals in the medial prefrontal cortex causes stress-induced depression. The reason for the problem in this signal flow is the decrease in the functional capacities of GABA transporters, glutamic acid decarboxylase (GAD65 and GAD67) enzymes and GABA interneurons, which is manifested by the decrease in the frequency of IPSCs. With ketamine administration, both GABA and glutamate transition are increased. GABA firing is also mediated by both glutamate and NMDA receptors. Blocking the action of ketamine by GABA stimulation indicated that an AMPA-induced depolarization occurred due to glutamate burst as a result of disinhibition of GABA interneurons. Activation of the potential difference-dependent Ca^{2+} channels ensures the release of BDNF and the operation of the TrkB-Akt system. This increases the synthesis of proteins responsible for mTOR1 signaling and synapse formation and maturation as seen in **Figure 4** (Ghosal et al., 2020).

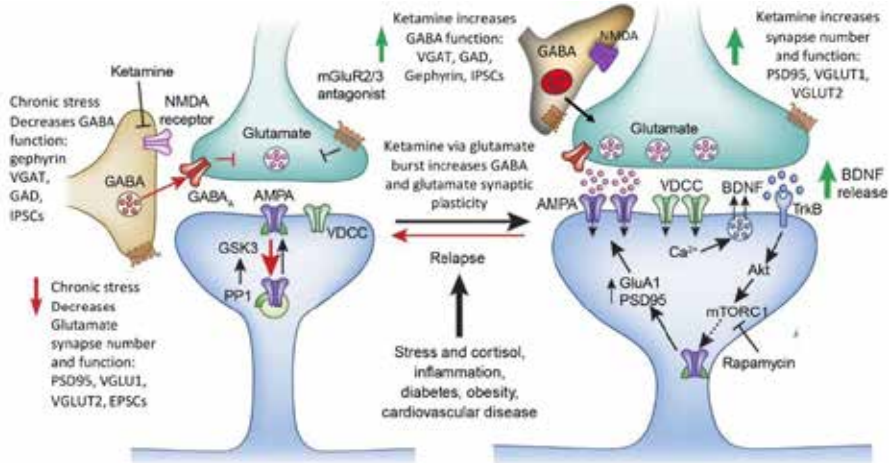


Figure 4. Effects of ketamine on stimulations and neurotransmissions in the mPFC (Ghosal et al., 2020)

5. MECHANISMS OF KETAMIN'S ANTIDEPRESSANT EFFECT

Although Miller et al. (2014) claimed that the NMDA receptor caused the antidepressant effect of ketamine, Yang et al. (2015) determined that only NMDA receptor blockade did not show a strong and rapid antidepressant effect similar to ketamine (Miller et al., 2014; Yang et al., 2015). There are also studies showing that the glutamatergic AMPA receptor mediates this effect (Zanos et al., 2016). Apart from its glutamatergic effect, ketamine acts as a monoamine reuptake inhibitor by acting as a regulator of dopamine receptor. Ketamine is also effective as an agonist of the opioid receptors such as mu, delta or kappa and antagonist of the muscarinic receptor (Matveychuk et al., 2020).

5.1. Monoaminergic Mechanism

The treatment of major depression has been shaped by the theory of dysfunction of monoamines such as noradrenaline and/or serotonin since the 1980s. But the most important disadvantage of them is that their effects occur over time and their usage period is prolonged.

Since one of the symptoms of depression is a decrease in the level of monoamine neurotransmitters such as serotonin, norepinephrine or dopamine, most traditional antidepressants are produced and used with the monoaminergic hypothesis to increase these levels. It has been understood that ketamine increases these levels in the prefrontal cortex, thus having a monoaminergic effect among other mechanisms (Ago et al., 2019). For example, when serotonin was inhibited using tryptophan hydroxylase, the antidepressant effect of esketamine was also not observed (Du Jardin et al., 2018). Ketamine has increased serotonin receptors and transporters in many studies (Spies et al., 2018; Yamanaka et al., 2014). The antidepressant effect of arketamine, on the other hand, was not abolished by inhibition of serotonin (K. Zhang et al., 2018). It also corrected anhedonia, which traditional antidepressants often could not treat, with its corrective effect on behavioral disorder caused by dopamine levels (Abdallah, Jackowski, et al., 2017; Ballard et al., 2017; Mkrtchian et al., 2021). Ketamine has treated disorders caused by blocking dopaminergic signals. The increase in this receptor with the administration of ketamine also increased cortical spinogenesis (Wu et al., 2021). Dopamine receptor D1 (DRD1) gene expression in the prefrontal

cortex and hippocampus also increased with increasing ketamine dose (X. jin Li et al., 2022). Although repeated use of ketamine increased the firing activity of dopaminergic and norepinephrine neurons, no such effect was observed in serotoninergic neurons. The fact that arketamine was not blocked by the DRD1 antagonist indicated that this isomer did not have dopaminergic effects. Thus, it has been proven that the dopaminergic effect of ketamine is due to esketamine (Chang et al., 2020). The possibility that the dopamine-increasing effect may encourage abuse is also a point that should not be overlooked. It has been determined that esketamine, unlike arketamine, reduces D2/3 dopamine receptors binding. Accordingly, it has been claimed that dopamine release triggered by esketamine may be associated with the occurrence of acute psychomimetic and dissociative side effects (Hashimoto et al., 2017).

5.2. Glutamatergic Mechanism

5.2.1. Ketamine actions on NMDAR

In the middle of the 20th century, it was accepted that N-methyl-D-aspartate receptor antagonists could be used for antidepressant purposes, years after it was seen that the NMDA receptor modulator D-cyclosporine had antidepressant effects in studies on tuberculosis. A receptor antagonist occupies the receptor, displacing substances that stimulate the corresponding receptor. The occupied receptor cannot be stimulated against the relevant substance and the activities that will emerge as a result of stimulation are prevented. It was understood in 2000 that the use of one of NMDAR antagonists, R,S-ketamine in subanesthetic doses, was beneficial in the treatment of major depression (Carreno et al., 2020). In TRD patients, intravenous use of an NMDAR blocker under anesthetic dose of ketamine has been found to be effective (Murrough, Perez, et al., 2013; Singh et al., 2016; Zarate et al., 2006). Thus, it is highly functional, especially in patients with a treatment-resistant metabolism and in patients whose depression does not last for long periods of time (Fond et al., 2014; McGirr et al., 2015).

Hypotheses about ketamine are related to the glutamatergic system. For example, the disinhibition hypothesis suggests that it preferentially binds to NMDARs containing the GluN1/GluN2C system appearing on GABAergic interneurons, thus preventing inhibition on excitatory pyramidal neurons. The enhancing effect of preferential binding to GABAergic interneurons, an effect blocked by Gad1-producing NMDAR-GluN2B degradation, on the formation

of the antidepressant effect has also been expressed in recent studies (Pothula et al., 2021).

The direct inhibition hypothesis includes the reorganization of signaling pathways that affect protein synthesis by inhibiting NMDARs at post-synaptic terminals. It is stated that this process is also related to the dissociative effects of ketamine. In antidepressant administration of ketamine, even at the highest possible concentration, the effect on NMDARs is less than half inhibited. At sub-anesthetic doses, the NMDAR mechanism cannot be completely blocked. Interestingly, however, other substances such as MK-801, memantine, and lanicemine used as NMDAR antagonists could not stably show the antidepressant-like effect of ketamine on rodents. This showed that the effect of ketamine on mechanisms other than NMDAR was effective in the formation of the anti-depression feature as a whole. However, these and other antagonists other than ketamine are antidepressants used in TRD conditions (Johnston et al., 2023). In **Figure 5** it is shown that when ketamine blocks neuron channels, the passage of ions is prevented and the signal transmission of neurons that cannot be depolarized is restricted.

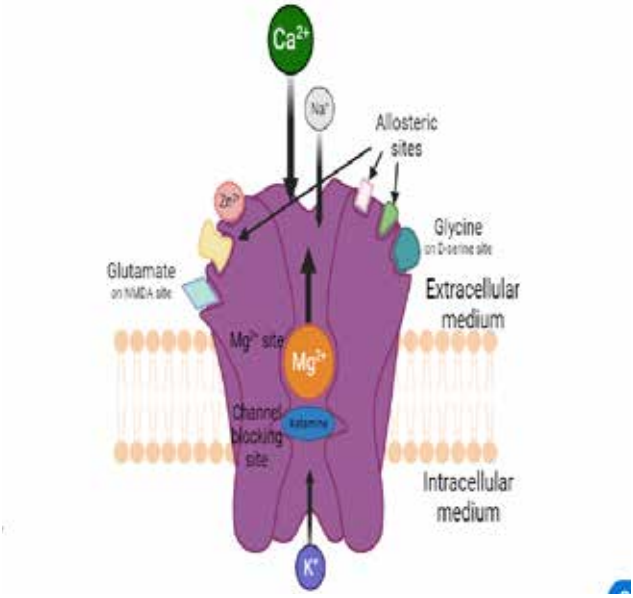


Figure 5. Blockage of neuronal depolarization with ketamine acting as NMDAR antagonist (adapted from Kokane et al., 2020)

Reliable clinical studies have shown that R,S-ketamine is functional as an

antagonist of the NMDAR in relief from major depression MDD in patients who are resistant to treatment. Another effect of the compound during these studies is the prevention of important symptoms of depression such as anhedonia and suicidal ideation. With its strong antidepressant effect, it has been beneficial not only in MDD patients but also in patients with bipolar disorder (Grunebaum et al., 2018; Su et al., 2017). For R- and S-ketamine isomers and their mixtures, it has been understood that the antidepressant potencies of antidepressant for CSDS in intranasal use are not proportional to the effects of these isomers and their mixtures on the NMDAR molecule (Chang et al., 2019; Yang et al., 2015).

5.2.2. Ketamine actions on AMPAR

Recent studies have shown that the effects of ketamine on NMDAR are flexible. Studies on this subject have started to attract attention after it was determined that antidepressants effective on AMPAR accelerate the treatment process. The source of the glutamatergic effect of ketamine is the increase in AMPAR activation, glutamate release and the mechanical target of rapamycin (mTOR) signals, especially in the prefrontal cortex. This process increases neuroplasticity through neurite growth, synapse formation, and strengthening of inter-synaptic interaction. These events are important for the longevity of the antidepressant effect. Protein synthesis and excitatory behavior are prominent, while NMDAR and 5-HTR antagonisms activate mTOR downstream. Another mechanism contributing to protein synthesis is eukaryotic elongation factor 2 (eEF2) dephosphorylation (Johnston et al., 2023).

Under conditions where GABA signals are inhibited, glutamate is released from excitatory pyramidal neurons. Glutamates with increased concentration in the medium bind to AMPARs at the synapse end, which increases BDNF release by Ca^{2+} influx. BDNF binding with tropomyosin-related kinase B activates mTOR complex 1 through downstream signaling molecules. This activation is temporary and as a result, the environment is enriched in terms of the concentration of proteins that increase the excitatory transition (Zanos et al., 2016; Y. Zhang et al., 2014). In particular, it has been observed that arketamine provides a long and stable antidepressant effect in the chronic stress model through AMPA and TrkB activation. Esketamine, on the other hand, affects mTOR without activating TrkB. Inactivation of eukaryotic initiation factor 4E-binding proteins via mTOR is one of the most important factors underlying antidepressant proper-

ties. Rapamycin, which inhibits mTOR, prolonged the antidepressant effect of ketamine in TRD patients. While rapamycin contributed to the anti-depression treatment due to its anti-inflammatory effect, it could not be helpful in preventing symptoms such as suicidality. It has been argued that the higher potency of arketamine relative to esketamine is related to increased phosphorylation of the extracellular signal regulatory kinase (ERK) cascade. It has been observed that the affected system follows the ERK-NRBP1-CREB-BDNF pathway in microglia (Johnston et al., 2023).

Blocking the AMPA receptor with an inhibitor prior to ketamine administration abolished the antidepressant effect of ketamine. This demonstrated the importance of the AMPA receptor in the antidepressant effect of ketamine (Zanos et al., 2016). 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo (f) quinoxaline-2,3-dione (NBQX), an antagonist of the AMPA receptor, has been shown to counteract the antidepressant effects of ketamine in rodents (Koike et al., 2011). Ketamine inhibits the production and release of proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor(TNF)-α, IL-6 and IL-10, and the decrease in the levels of these cytokines is effective in the formation of the antidepressant effect, both in chronic depression in mice and in rodents. It has been shown to be effective in the treatment of depression induced by lipopolysaccharide (LPS) (Simma et al., 2014; Tan et al., 2017; Yang et al., 2013; Yuhas et al., 2015). The NLRP3 receptor, an adaptor protein named ASC, and the NLRP3 inflammasome containing the caspase-1 protein regulate the release of IL-1β proinflammation, which causes depression-like behaviors triggered by LPS (Y. Zhang et al., 2014). The ketamine metabolite, hydroxynorketamine, produces an antidepressant effect by increasing AMPA receptor levels at synapses (Zanos et al., 2016). Inhibition of caspase-1, which is located in the NLRP3 multiprotein, also increases AMPA receptors, preventing the depressive state induced by chronic stress (M. X. Li et al., 2018). NLRP3 inflammasome inhibition attenuates both acute LPS-induced and chronic depression induced by CUMS (J. C. Zhang et al., 2014; Y. Zhang et al., 2015). A sub-anesthetic dose of ketamine significantly reduced the depression induced by LPS. It was concluded that ketamine is an antidepressant by suppressing the presence of NLRP3 inflammasome and IL-1β, and increasing the presence of the hippocampal AMPA GluA1 receptor (J. M. Li et al., 2019).

5.3. GABAergic Mechanism

The relationship between depression and GABAergic signals has been identified in many studies. In addition, the relationship of ketamine with the GABAergic system is also included in the disinhibition hypothesis. Many fast-acting antidepressants in use also act to increase these signals (Zanos & Gould, 2018b). Examples of depressive behavior such as anhedonia and neophobia have been seen in animals with mutated GABA receptors. Mice in a GABAergic inhibition state responded more strongly to ketamine administration than non-stressed mice, indicating the effect of ketamine on this mechanism (Ghosal et al., 2020). Depression processes resulting from GABAergic deficiency may be associated with a metabolic decrease in glutamatergic release or preferentially regional strengthening of GABAergic synapses. GABAergic and glutamatergic deficiencies are seen together in MDD. Extrinsic stress factors and genetic defects that cause GABAergic inhibition are due to the increase in glutamatergic concentration and homeostasis-like down-regulation of NMDA and AMPA receptors on cell surfaces, due to disorders in glutamatergic synapses or weakened/disconnected connections between neurons (Ren et al., 2016).

Chronic stress-based defects that cause GABAergic inhibition may be deficiencies in glutamic acid decarboxylase enzyme involved in GABA synthesis, vesicular GABA transporter protein worked for GABA release in synapses, postsynaptic structure protein gephyrin, which is effective in clustering and working of GABA receptors, or proteins that mark stress-sensitive GABAergic interneurons (Luscher et al., 2020).

Ketamine strengthens the work of $GABA_A$ receptors in the cortex and hippocampus. The increase in the concentration of $GABA_A$ receptors causes a decrease in the antidepressant effect of ketamine. The administration of muscimol and high doses of benzodiazepines increased $GABA_A$ receptor transmission and weakened the relieving effect of ketamine symptoms of depression (Pham et al., 2020; Silberbauer et al., 2020).

The negative allosteric modulators of $GABA_A$ receptors rapidly abolished anhedonia when directed specifically to receptors containing alpha-5 subunits. It also treated stress symptoms by strengthening the stress sensitive hippocampal synapses of rats used in the chronic stress model. Since the distribution of the receptors containing these subunits in the brain is much less common

than the distribution of NMDAR, the occurrence of side effects is less common. Therefore, there is a trend towards ketamine acting on alpha-5 $GABA_A$ receptors rather than other receptors (Zanos et al., 2017).

In the process following ketamine administration, first GABA and glutamate are converted to glutamine, and then reverse conversion is observed. Glutamine concentration, which decreased for 14 hours in prefrontal cortex cells, then started to increase (Weckmann et al., 2019).

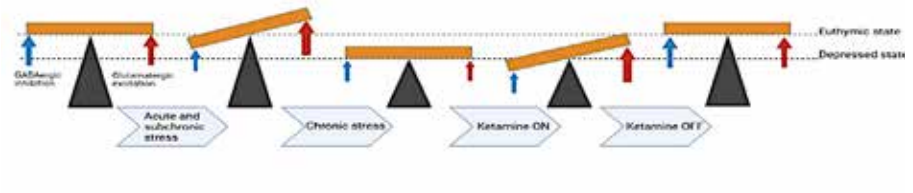


Figure 6. Homeostasis between GABAergic and glutamatergic systems

In the euthymic state, the GABAergic and glutamatergic systems are in homeostasis (**Figure 6**). The activities of the glutamatergic system become dominant in the nervous system due to the inability to synthesize various structures that take on tasks such as neuron development and signal transmission due to biological or external effects or other factors that will disrupt homeostasis. The source of this may be deactivation of GABAergic neurons, as well as over-firing of glutamatergic neurons. Due to the imbalance created by these two systems, NMDA and AMPA receptors are homeostatically downregulated. This low equilibrium state is responsible for the low neural interaction seen in MDD states. Although the systems are in balance, they are below the values required for the euthymic state. With the subanesthetic application of ketamine, glutamatergic release is increased due to the adjustment seen in the structure and interactions of neurons, and homeostasis is impaired in a way that increases signal transmission. Then, after the administration of ketamine, it is seen that the glutamatergic and GABAergic systems are strengthened and the depressive state is released by activating the structures responsible for release and transmission (Luscher et al., 2020).

5.4. Opioid Receptor Mechanism

Low-dose use of the opioid antagonist buprenorphine has worked in the treatment of depression. A relationship has also been observed between the misuse of opioid antagonists and the occurrence of depression. On the other hand, the binding of ketamine to opioid receptors is 5-20 times weaker than its binding to NMDA receptors (Johnston et al., 2023). Ketamine has a strong association with mu-opioid receptors, while its association with kappa-opioid receptors is weaker (Bonaventura et al., 2021; Nemeth et al., 2010). It has been determined that the antidepressant mechanism of action of ketamine also includes mu-opioid receptor agonism, but its relationship with this receptor is not well understood (Williams et al., 2018). In a study, which revealed the relationship between ketamine and the mu-opioid receptor, the use of the opioid disorder drug naltrexone before ketamine abolished the antidepressant effect (Yoon et al., 2019). The results in studies on mice are also interesting. In one study, naltrexone did not inhibit the antidepressant effect of ketamine in the treatment of CSDS and depression caused by the lipopolysaccharide-induced inflammation model (K. Zhang & Hashimoto, 2019b). In the face of innate learned helplessness, however, this drug affected the outcome of ketamine. While the antidepressant activities of ketamine can be mimicked by NMDAR antagonists, it is irreplaceable by mu-opioid receptor antagonists (Klein et al., 2020).

6. KETAMINE ADDICTION AND KETAMINE AGAINST ADDICTION

Ketamine is used for dissociative anesthesia in surgeries. In this case, the patient is unconsciously awake and cannot react to painful stimuli (Zanos et al., 2018). Depending on the dose of the drug used or the duration of use, it shows psychomimetic effects that cause hallucinations, delusions, and delirium-like states, increasing the pressure in the skull and in the vessels (Dillon et al., 2003). Side effects such as blurred vision, hearing impairment, dizziness and illusions were more severe with esketamine (0.45 mg/kg, intramuscular) than with arketamine (1.8 mg/kg, intramuscular), while the relaxing effects of arketamine were more pronounced (Mathisen et al., 1995; Vollenweider, Leenders, Øye, et al., 1997). It has been observed that low-dose continuous post-operative ketamine

application has a lower psychomimetic effect than bolus-based application in pain relief (Rasmussen, 2016). In other low dose applications, it has been stated that the rate of sub-anesthesia dose creating a psychomimetic effect in schizophrenic and normal individuals is very low (Perry et al., 2007).

The changes that ketamine creates in neurons can lead to addiction (Trujillo et al., 2011). Ketamine is one of the hallucinogens listed on the DEA's site. It is stated that it is known by names such as purple, special k, super acid, super k, jet k, vitamin k, kit kat, and cat tranquilizer in the street. It can be abused by injection, smoking, or mixing with drinks (Anonymous, 2021).

An average of 0.5 mg/kg antidepressant effective doses of ketamine do not have much psychoactive effects. While 80% of TRD patients "feel weird" and expressed the dissociative effect of ketamine, while 50% of them "feel like swimming" and expressed the psychoactive effect. These are transient effects, lasting much shorter than the antidepressant effect (Acevedo-diaz et al., 2020). The temporary psychoactive state created by ketamine reaches its highest level in about 40 minutes. During this situation, changes in perceptions, mentality and mood should be kept under medical supervision. Otherwise, the patient may not be able to manage these changes correctly and may be harmed by the process or abuse may be paved.

The hallucinatory effects of ketamine, which was first synthesized under the name CI-581 in 1962, began to be examined in 1965 (Domino et al., 1965). It is one of the substances that is frequently abused because it is more easily available and has medical use compared to other psychedelic and hallucinogenic substances. A comprehensive and detailed study on psychedelic effects was conducted by Ingram et al. In this study, it was suggested that ketamine triggered such behaviors in the brain, especially due to NMDAR antagonism (Ingram et al., 2018). Among its most reported psychological effects, apart from hallucinations and mystical experiences, are near-death and out-of-body experiences. Unreasonable happiness and increased awareness when taken intramuscularly at 25-50 mg are replaced by a feeling of separation from the body when taken at 75-125 mg. With an infusion of 150-200 mg, which is below the anesthetic dose, a state of consciousness disconnected from the real world and a near-death experience are experienced (Kolp et al., 2014). Although these effects are limiting in medical applications, there are users who want these experiences. Unfortunately, this use has been the cause of death for some of those who un-

consciously used ketamine (Morgan & Curran, 2012). Because these effects are similar to schizophrenia, they have been used as a model for the diagnosis and treatment of schizophrenia in mice and subsequently in humans (Keilhoff et al. 2004; Driesen et al. 2013).

There is evidence that ketamine causes addiction in individuals who do not have a family or personal history of addiction. It has been reported that the use of naltrexone is beneficial for the individual in getting rid of this addiction. A decrease in the symptoms of the ketamine withdrawal was observed with the use of 25 mg/day naltrexone for two weeks, and then with the use of naltrexone 50 mg/day for three weeks, ketamine addiction and the tendency to other substances when ketamine was not available were ended (Garg et al., 2014). It has been reported that the use of opioid antagonists naloxone and naltrexone, partial agonist buprenorphine, and agonist methadone are effective in eliminating the symptoms caused by ketamine withdrawal (Edinoff et al., 2022).

Interestingly, ketamine, which can be abused, is also used in the treatment of various addictions. In a study using rats, administration of 20 mg/kg ketamine disrupted memories of alcohol addiction and reduced alcohol consumption of the subjects without a decrease in motor activity (Sabino et al., 2013). Similarly, in the morphine-induced conditioned place preference test, after administering 60 mg/kg ketamine to rats, the subjects' morphine preference decreased while place preference was preserved (Zhai et al., 2008). These two studies have shown that ketamine can be used successfully in the treatment of addictions to disrupt drug-related memory. In a study on the use of ketamine in heroin addiction, 70 addicts were divided into two groups. Individuals who were administered a high dose of ketamine (2 mg/kg) in addition to psychotherapy had a significant decrease in their heroin tendencies over a 24-month period compared to individuals who were administered a low dose of ketamine (0.2 mg/kg) (Pertwee, 2008). Co-administration of psychotherapy and ketamine was effective against anxiety and other symptoms other than addiction and contributed to giving meaning to life (Krupitsky et al., 2007).

CONCLUSION

Ketamine has been used for a long time for anesthesia. After it was understood that it had antidepressant-like effects when used in subanesthetic doses, it was aimed to understand the mechanism of action of ketamine and to use it more reliably in various studies. Considering the different effects of S- and R-ketamine in these studies, it is seen that both can be used under different conditions in terms of efficacy and safety. These conditions have created effective processes on the activity of different mechanisms in preclinical and clinical studies. Clinical studies point to 0.5 mg/kg as the standard medical dose for the treatment of depression. This application, which generally takes 40 minutes intravenously, has been used in many studies. Side effects, which last on average a few hours, usually include headache, nausea, boredom, anxiety, restlessness, high blood pressure and pulse rate. Dissociative, psychomimetic and hallucinative effects are also likely to occur at sub-anesthetic doses. Although no side effects are observed below this dose, the antidepressant effect is short-lived. There are studies showing that the antidepressant effect seen in intravenous application also occurs in bolus, oral, intramuscular, subcutaneous, and nasal applications. There is no evidence that its use with some other psychiatric drugs poses a significant problem. Additionally, in many clinical studies, ketamine has been administered as an adjunct to ongoing treatments. In clinical studies, factors such as age, gender, race, and time of use did not create statistically significant differences. Factors that create significant differences are included in the relevant sections. While examining the antidepressant effect of ketamine, the most emphasized mechanism is its behavior as an antagonist of NMDA receptors. Trying to explain its effect with both disinhibition and direct inhibition hypotheses is related to the NMDAR mechanism. However, AMPAR antagonism was another prominent glutamatergic mechanism. Although these processes have now been proven in various ways, it is stated that ketamine has an antidepressant effect not only with these processes, but also with its relationship with opioid antagonism and the GABAergic system. As a result of these developments, it is possible to say that the use of ketamine as an alternative to traditional antidepressants

will increase, especially in the rapid and effective treatment of treatment-resistant depression patients. Although ketamine is widely used medically, attention should be paid to the dosage and frequency of use when using it outside anesthesia. Although side effects are temporary, the patient's medical history must be taken into account in medical use. Although it is possible to obtain this drug illegally, it should not be forgotten that the effects vary from person to person and the use of ketamine to enjoy its hallucinatory effects can be addictive and can even lead to death in overuse.

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