Exploring Ketamine as a Treatment Option for Psychiatric Disorders

Balraj Sharma[1], Mrs. Vasudha[2], Yoshita Sood[3], Phanindrareddy Badduri[4], Rachna Chavda[5]
[1]*Assistant Professor, Liberty College of Nursing, Jaipur, Rajasthan, India*
[2,3,4]*Nursing Tutor Akal College of Nursing, Eternal University, Baru Sahib, India*
[4]*Professor cum Principal School of Nursing (Centurion University of Technology and Management) Paikasta, Gopalpur, Balasore*

***Abstract* — Pain Ketamine has emerged as a significant new alternative in the treatment of inappropriate mental health disorders like depression, anxiety, and post-traumatic stress disorder. Due to the ongoing rise in mental illnesses across the globe and inability to ameliorate some mental illnesses by means of standard drug medications, ketamine represents a potential option due to its special mode of action. Ketamine, firstly, was approved by the U.S. Food and Drug Administration in 1970 as an anesthetic drug, but in the past two decades has found more and more applications as an off-label treatment of psychiatric conditions. Moreover, esketamine, the S-ketamine derivative that is sold as Spravato, was approved in 2019 to treat resistant depression.**

The application of ketamine in mental health care nowadays takes various forms, such as intranasal ketamine, intravenous infusion, ketamine-aided psychotherapy, and home-based therapy, featuring greater or lesser levels of monitoring and supervision. The current situation with the ketamine treatment is complicated due to the lack of regulation, persisting development of research evidence, and drug need by numerous patients with treatment-resistant mental health symptoms. To discuss these problems, this article will provide the necessary clinical knowledge that nurses are expected to possess in conversations with patients when guiding them on ketamine usage or as an option of treatment. It additionally points out regulatory, ethical, and nursing-related elements of using ketamine in treating the mental illnesses.

***Index Terms* — anxiety, depression, ketamine, mental health, posttraumatic stress disorder.**

I. INTRODUCTION

We are experiencing a severe mental health crisis in the world. Depression, anxiety and post-traumatic stress disorder (PTSD) and other mental illnesses have been on an upward trend and the world has remained in an increasing burden of the mental illnesses. Moreover, results of the popular Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study revealed that close to one-third of people who received some medications to treat depression did not respond, which indicates the issue of treatment-resistant depression. It is not the only problem as individuals suffering depression, PTSD, and other psychiatric effects might not receive the relief they require under the dosage of first-line drugs.

The past two decades have been characterized by the establishment of ketamine as a potentially effective intervention against adults with challenging to manage mental disorders, including major depression, anxiety, and post-traumatic stress disorder. Logically, as many as eleven years prior to ketamine research on depression commenced, no new medications had been launched which targeted new synaptic pathways of signaling since 1957. Researchers are of the view that the unique mechanism of action of ketamine could be of advantage in treating diseases that have failed conventional treatments. Ketamine has been shown as an antidepressant, unlike oral antidepressants, which can take weeks before one starts to feel better, and some patients experience an improvement in their condition within four to twenty-four hours of ketamine use.

The use of ketamine in mental health care has a strange regulatory position. S-ketamine and R-ketamine are the mirror-image forms of ketamine, which is also known unofficially as racemic ketamine; the two components were officially permitted by the U.S. Food and Drug Administration (FDA) in 1970 as an anesthetic. Since the patent of ketamine has died a long

time ago, pharmaceutical companies have lacked financial incentive to conduct the massive clinical trials required to receive FDA approval by using mental health indications. Consequently, the atmosphere means that unless ketamine is used as an anesthetic agent but instead as the treatment of a mental disorder, it is treated as an off-label medication. One exception is esketamine, which is a brand sold under the name Spravato, by Johnson and Johnson. Esketamine is the racemic ketamine isolated form of S-ketamine administered as a nasal spray with the FDA approving it in 2019 in the treatment of treatment-resistant depression. Currently, the product is the only officially approved ketamine-based product that is used in this manner.

The present-day ketamine treatment paradigm is not only informed by its potential on therapeutic use, but it also lacks a consistent overall control. Despite the growing research to support its application, there is a lack of formal regulation on its application; thus, individuals experiencing treatment-resistant mental health disorders have few options to make when it comes to treatment options, choices of supervision, and care standards, which vary dramatically across several factors. This discrepancy poses significant problems to nurses as they can be tasked with patient education, monitoring of medication safety, as well as assist patients in making informed choices. Considering that nurses are critical in the immediate care of the patient, along with the overall healthcare delivery as advocates, ketamine therapy has to be taken with keen clinical judgment and ethically conscious minds. The article is a practical introduction of the use of ketamine in mental health treatment, including its routes of administration, care models, regulatory issues, and ethical issues. It is created to be a general guide of nurses in bedside and community and advanced practice who might deal with patients who consider ketamine therapy or receive it. Through the analysis of the existing evidence and the best practices, the article aims to provide the necessary knowledge required by nurses to approach this emerging care field safely and conscientiously.

II. FROM ANESTHETIC TO MENTAL HEALTH TREATMENT

Ketamine is a dissociative anesthetic drug that is a chemical relative of phencyclidine. It was originally seen as an improvement on phencyclidine, due to maintenance of the benefits of minimal respiratory depression and good safety, without the risk of delirium and psychotic reaction or "emergent phenomena." Ketamine continues to be widely used in emergency care, and its beneficial activity as an anesthetic places it in the World Health Organization's List of Essential Medicines due to its safety and effectiveness. Beyond anesthesia, ketamine shows other effects such as analgesic, antidepressant, anti-suicidal and psychedelic effects when administered in subanesthetic doses.

Pharmacologically, the main action of ketamine is as a noncompetitive antagonist of the N-methyl-D-aspartate receptor in the glutamate system in the brain. However, it is often described as a "dirty drug" in that it interacts with multiple receptors instead of acting on a single receptor. Although blockade of the NMDA receptor is thought to be involved in the fast-acting antidepressant effect of ketamine, studies have indicated that downstream activation of a-amino 3-hydroxy 5-methyl 4-isoxazolepropionic acid receptors may be especially relevant. This receptor activation causes a variety of effects that include a rapid increase in brain-derived neurotrophic factor, which aids in synaptic growth, plasticity and the improved neuroplasticity that is associated with ketamine use.

The antidepressant effects of ketamine were first discovered using studies performed in the early 2000s. At first, its psychotomimetic properties had been being studied in an attempt to gain a better understanding of psychosis. Unsurprisingly, participants who received ketamine via intravenous infusion noted measurable improvements in mood, so more research was conducted. Subsequent studies revealed that ketamine rapidly works as an antidepressant and possesses good anti-suicidal properties. These findings eventually led to the development of esketamine, and the growth of ketamine infusion clinics, as well as to more general research into the use of ketamine for other psychiatric disorders.

Over the past 20 years, there has been a fair amount of research into the use of ketamine in mental health treatment, especially in patients suffering from depression. Many studies have proven its efficacy as a rapid-acting antidepressant. Esketamine was later approved by the FDA for adults with treatment-resistant depression based on clinical trials that found

greater improvement and remission rates of symptoms compared with those of placebo. Ketamine also has proven to rapidly decrease the symptoms of post-traumatic stress disorder and anxiety. In addition, exploratory studies have been done on the use in substance use disorders, eating disorders, and obsessive compulsive disorder, with encouraging beginnings, though more studies are needed to confirm its usage in line with this direction.

The patient's experience with ketamine treatment may vary, according to the dose and route of administration. This can be administered by intravenous infusion, intramuscular injection, sublingual lozenges or intranasal spray. Lower doses often give anxiolytic and analgesic effects, and higher, yet subanesthetic doses, can induce dissociation and perceptual changes in sensory experience of the patient.

Ketamine is listed as a Schedule III controlled substance, which means that it has a moderate to low risk of physical and psychological dependence according to the U.S. Drug Enforcement Administration. Although illicit use of ketamine is still a relatively rare circumstance, misuse of ketamine has been on the rise for the last two decades. Cases of ketamine poisoning associated with deliberate abuse, attempted suicide or unintentional exposure have also increased in recent years. Prolonged misuse may lead to cognitive and urinary problems such as cognitive decline, declining executive function, ketamine-induced cystitis and other lower urinary tract disorders.

III. USE IN MENTAL HEALTH CLINICAL SETTINGS

Ketamine can be considered as a good treatment option, for those who have mental health symptoms and have not responded to medications or psychotherapy and feel as though their recovery is stagnant. It may be an alternative to neuromodulation therapies like transcranial magnetic stimulation, which has the FDA approval for treatment-resistant depression and obsessive-compulsive disorder, and electroconvulsive therapy, which is used to treat depression, bipolar disorder and psychosis. Patients seeking ketamine treatment for mental health issues may be prescribed the drug in a few different ways within the clinical models.

Esketamine is only available in a clinical setting with direct supervision from a healthcare professional and is not available from a pharmacy for self-injection back home. It is provided in pre-filled single-dose devices with 28 mg/contents Depending upon prescribed dose, patients self-administer one, two or three devices 56 mg and 84 mg are most common doses. Because of side effects associated with use of esketamine, such as dissociation, sedation, feeling drunk, nausea, dizziness, and high blood pressure, patients must be monitored for at least two hours after treatment and not drive themselves home.

During this monitoring period, usual care is for patients to not participate in formal psychotherapy or other structured therapy activities. And, instead, they may spend the time listening to music, reading or playing electronic devices. Although specific practices vary from clinic to clinic, the environment is usually designed to be relaxing, comfortable and supportive, with trained personnel checking in and on patients on a regular basis.

Based on manufacturer's guidelines, administration of esketamine is twice weekly for the first four weeks followed by once weekly for the next four weeks and once every one or 2 weeks for maintenance. While such scheduled dosing and supervised administration makes for safer patients, this can also create problems of practicality. Patients may have to take time off work, change their schedules and arrange for child care in order to be able to come in for appointments and to be able to stay in the clinic for the amount of observation required. For some who lack the ability to work flexibly or have sufficient support from family or friends to help with childcare, these demands will make it harder to start or maintain treatment.

IV. NURSES WHO WANT TO ADMINISTER KETAMINE THERAPY SHOULD LOOK AT THEIR STATE NURSE PRACTICE ACT TO SEE IF ADMINISTERING KETAMINE IS PERMISSIVE IN THEIR PROFESSIONAL ROLE OR SCOPE OF PRACTICE

Clinics and hospitals that administer esketamine need to be registered under the esketamine Risk Evaluation and Mitigation Strategy (REMS) program. Esketamine may be prescribed by psychiatric professionals including psychiatrists or psychiatric and mental health nurse practitioners, as well as those

from other disciplines including anesthesia provided that they have received appropriate additional training. At first, the FDA demanded that esketamine be paired with a daily oral antidepressant; however, it has been approved as a standalone treatment for adults with treatment-resistant depression. As for insurance coverage requirements, the coverage for esketamine varies with the insurance plan and the amount of individual payoff of the treatment for each procedure session may vary around $1,000 and $1,500. Some patients may be able to receive financial support through this Janssen Pharmaceuticals assistance program.

In the case of ketamine's early studies in mental health disorder, the drug was most frequently administered via intravenous infusion injections, and those early-ketamine protocols continue to have an impact on today's ketamine practice. Many clinics start with an induction period of two or three infusions a week for three to five weeks followed by maintenance courses that are adjusted in accordance with patient's needs. Treatment typically begins at 0.5 mg/kg over 40 minutes, the dosage adjusted according to tolerance and response. Unlike esketamine, IV ketamine does not fall under a federal REMS protocol, resulting in significant variation between clinics with respect to the level of patient monitoring, patient selection and practitioner qualifications. Even so, there have been infusion guidelines released by professional bodies such as the American Psychiatric Nurses Association. IV ketamine can be given by psychiatric doctors, anesthesiologists, certified registered nurse anesthetists, or other trained doctors and registered nurses can help the doctor by starting and maintaining the intravenous access, and by monitoring patients. Because ketamine is administered intravenously through an IV, for off-label use, insurance typically does not cover the treatment, and patients typically pay for ketamine treatment themselves.

Ketamine-assisted psychotherapy is a combination of ketamine administration and psychotherapy. Although techniques vary from one clinic to another, this approach usually includes four phases: Assess, prepare, medicine session, integrate. The preparation and integration stages include therapy sessions without the use of ketamine while the medicine session includes ketamine administration along with therapeutic support. This model attempts to capitalize on the psychedelic properties of ketamine such as altered perception and altered feelings of self, while also extending the psychological benefits of treatment. The number of medicine sessions and total time vary but for most patients at least two sessions are completed over a number of weeks. In this setting, ketamine is most frequently administered in intramuscular injection and sublingual lozenges however some clinics are also using IV infusion and intranasal compounded racemic ketamine. The dose depends upon the route administration and the intended therapeutic effect and sessions usually last two to three hours. Providers can be psychiatric practitioners, psychotherapists or physicians in other specialties. Like Ketamine infusions, this form of therapy is usually not reimbursed by insurance and is usually self-funded.

At-home ketamine therapy could be by self-administration via sublingual tablets or subcutaneous injections. During the early phase of the pandemic that began with the diagnosis of the spread of the Coronavirus, DEA removed the requirement for the personal delivery of the prescription for controlled substances for a few months. This regulatory change was a contributing factor to why virtual assessment and virtual home-based treatment for ketamine clinics grew at a rapid rate. However, there have been a number of concerns about the safety of such services. These include failure to assess patients adequately, prescribing of high doses which may lead to an increased risk of misuse, and failure to monitor them during treatment sessions. One survey has found over half of users of ketamine at home were taking more of the medication than they were prescribed, indicating that misuse might be relatively common. Cases of accidental overdoses related to poor prescribing practices have been reported too. In October 2023, the FDA issued a warning about the compounded products of ketamine, including ketamine supplied via online ketamine clinics. However, as of 2024, there is at least one online service that was seen using no supervision from a healthcare professional to provide injectable ketamine for home use. Prescribers in these virtual clinics may or may not be formally trained in psychiatry, and insurance does not usually cover ketamine treatment done at home.

V. CONTRAINDICATIONS TO KETAMINE THERAPY

Ketamine therapy is not for every patient, however, and in some cases, the harm it can cause may outweigh the hopefully beneficial effects it can have. Examples of psychiatric contraindications include past history of psychosis or mania. Because ketamine has been associated with an increase in CV activity, ketamine is not recommended for those with recent myocardial infarction, cerebrovascular accident, uncontrolled hypertension, or who have severe liver disease. Patients with haematologic history of myocardial infarction or stroke and well-controlled hypertension should seek clearance of their primary care provider or relevant specialist to start the treatment. Other contraindications being current ketamine or substance abuse, pregnancy and any prior negative reaction to ketamine. Long-term use of high doses, particularly because of illicit abuse, has been linked to genitourinary entities such as interstitial cystitis. Given all of these safety issues, there must be strong regulatory oversight to ensure use of ketamine treatment is actually used appropriately.

VI. REGULATORY IMPLICATIONS

Since ketamine is considered a Schedule III controlled substance, the prescription of the drug is regulated by the Drug Enforcement Administration (DEA) and only practitioners with a valid DEA license are allowed to prescribe it. However, the regulatory status of the use of ketamine for mental health treatment remains unclear and erratic. At the federal level there are no specific guidelines that outline the types of healthcare professionals that can provide ketamine for psychiatric purposes, the type of training they must complete and how appropriate patients might be identified. This unsure regulatory may lead to the legal impacts of suits or loss of DEA license if ketamine is dispensed outside the accepted practices of safety and regulation.

The lack of consistent oversight has resulted in widespread variations in clinical practice and more general worry about both patient safety and the quality of practitioners. Esketamine, the sole ketamine-based drug approved by the FDA for a psychiatric use indication, is an exception. It is regulated under the FDA's Risk Evaluation and Mitigation Strategy (REMS) program, which offers clear requirements with regard to practitioner training, patient selection, administration in a clinical setting, and monitoring after administration. Nurse who would like to provide ketamine therapy should check their state nurse practice act to make sure their responsibility is listed within their professional scope of practice. They should also check to make sure that their malpractice insurance covers ketamine-related services. Psychiatric-mental health nurse practitioners who plan to use esketamine need to join an esketamine REMS program and strictly follow all necessary protocols in order to stay in line with federal regulations.

VII. ETHICAL IMPLICATIONS

The existing use of ketamine therapy raises a number of ethical issues for nurses, especially since the use of ketamine is rapidly becoming recognised off-label, but not formally regulated. As nurses work to uphold the principles of ethics of autonomy, beneficence, nonmaleficence and justice, ethics they must deal with treatment that shows promise, but is still developing in terms of evidence and standardisation. Among the important ethical issues are informed consent, safe care of vulnerable patients seeking ketamine treatment, and fair access for treatment.

Respect for patient autonomy starts with gaining proper informed consent before treatment starts. Patients should be treated with clear and ample information about the potential risks and benefits of ketamine therapy, as well as the various ways of administering it and the possible alternatives. They should also be made aware that the only one approved for psychiatric treatment is esketamine, while racemic ketamine is a psychiatric off-label drug that is frequently not covered by insurance. In addition, victims ought to be encouraged to enquire about qualifications, like psychiatric training, standard criteria in ketamine medicine, and proof of secure and effective clinical practice, of the practitioner. Nurses engaged in the administration of ketamine therefore need to be prepared to conduct a detailed informed consent process that adequately supports patient decision-making.

The principles of beneficence and nonmaleficence call for nurses to advance patient wellbeing and reduce harm. These principles are particularly

relevant in ketamine therapy as many of the patients seeking ketamine treatment are in a particularly vulnerable state. Since ketamine is not a first-line approach to treating mental health disorders, the people who seek it have often been unsuccessful for years when they attempted medications or psychotherapy to have the desired outcomes. Their desperation to find relief may make them more likely to accept treatment without carefully evaluating providers or treatment options. Though a ketamine registry has been recommended among the experts to track prescribers and adverse events no current system is in place. As a result, patients can be exposed to poorly qualified or unethical practitioners, with a higher risk of unsafe care and harmful outcomes to patients.

The popularity of home-based treatments for ketamine has raised additional ethical and safety issues. Without the direct supervision of every treatment session, there are chances that patients could fall into higher risks, including misuse. Although ketamine has a relatively good safety profile and it does not cause much respiratory depression, ketamine is also a dissociative anesthetic and should not be used without adequate monitoring even at subanesthetic doses. Nurses working with ketamine therapy must therefore be vigilant about how they can ensure the safety of vulnerable patients, while also maintaining the care needs.

The ethical principle of justice is concerned with fairness and equality of treatment and nurses need to be aware of barriers related to equitable access to ketamine therapy. The high price of treatment makes it out of reach for many patients. Even though esketamine is approved for treatment-resistant depression, coverage from insurance companies is spotty and the personal cost of a single treatment session is very high. Other forms of ketamine therapy are ketamine intravenous infusions, ketamine-assisted psychotherapy, and at-home treatment that are usually not covered by insurances because they are 'off-label' and each treatment session may cost in the hundreds of dollars. This creates a situation in which the patients who may have the most to gain, are also the least able to afford care. Geographic access is also an accessibility issue because many people who live in rural areas don't have treatment centers in the vicinity. In such cases, virtual ketamine clinics may be an improvement in access for those who otherwise would have no option for care.

Current evidence offers cause for cautious optimism with the use of ketamine for the relief of symptoms in patients with severe and treatment-resistant mental health conditions. However, this optimism should be tempered with ethical responsibility. The off-label use of racemic ketamine, variations in the training of providers and lack of consistent regulation may put patients at risk. Therefore, nurses need to be aware of such evolving issues so as to provide guidance and support to the patients safely and responsibly.

VIII. NURSING IMPLICATIONS

As ketamine therapy gains increased usage in mental health conditions, nurses in a variety of practice roles, from bedside clinicians to advanced practice providers, are likely to see patients that may be interested in, undergoing, or recovering from this type of treatment. Such encounters may occur within the general public, in diverse healthcare and community environments which may include outpatient departments, inpatient wards, emergency rooms, schools, and community programs. For this reason, nurses must be well prepared in providing education to patients and families, accessing safety and suitability, and supporting evidence-based as well as ethically right care.

IX. CONCLUSIONS

Ketamine is a promising drug to consider as an effective treatment option for depression and other mental health disorders. Although it has been found to result in a rapid improvement in symptoms such as depression and also has a favorable safety profile, its use still carries certain risks. For this reason, patients should be encouraged to receive ketamine only in the properly supervised clinical environment. Nurses should be prepared to explain ketamine to patients, their potential benefits and dangers, and various methods of administration.

In addition, nurses should be familiar with the regulations and ethics regarding the use of ketamine for mental health treatment. When the administration of ketamine treatment occurs in a safe and ethical manner by well-trained nurses who abide by current evidence, ketamine therapy can provide meaningful

support to patients with severe mental health conditions that have not responded to conventional treatment.

REFERENCES

[1] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137-150. doi:10.1016/S2215- 0366(21)00395-3

[2] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-1917. doi:10.1176/ ajp.2006.163.11.1905

[3] Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry. 2022;27(1):58-72. doi:10.1038/s41380-021-01200-3

[4] Krystal JH, Kavalali ET, Monteggia LM. Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms Neuropsychopharmacology. 2024;49(1):41-50. doi:10.1038/s41386-023-01629-w

[5] 5. Martinotti G, Chiappini S, Pettorruso M, et al. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. Brain Sci. 2021;11(7):856. doi:10.3390/brainsci11070856

[6] Philipp-Muller AE, Stephenson CJ, Moghimi E, et al. Combining ketamine and psychotherapy for the treatment of posttraumatic stress disorder: a systematic review and meta-analysis. J Clin Psychiatry. 2023;84(2):22br14564. doi:10.4088/JCP.22br14564

[7] Johnston JN, Kadriu B, Kraus C, Henter ID, Zarate CA Jr. Ketamine in neuropsychiatric disorders: an update. Neuropsychopharmacology. 2024;49(1):23-40. doi:10.1038/s41386-023-01632-1

[8] McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am J Psychiatry. 2021;178(5):383-399. doi:10.1176/appi.ajp.2020.20081251

[9] Seshadri A, Prokop LJ, Singh B. Efficacy of intravenous ketamine and intranasal esketamine with dose escalation for major depression: a systematic review and meta-analysis. J Affect Disord. 2024;356:379-384. doi:10.1016/ j.jad.2024.03.137

[10] Jelen LA, Young AH, Stone JM. Ketamine: a tale of two enantiomers. J Psychopharmacol. 2021;35(2):109-123. doi:10.1177/0269881120959644

[11] Nikayin S, Murphy E, Krystal JH, Wilkinson ST. Long-term safety of ketamine and esketamine in treatment of depression. Expert Opin Drug Saf. 2022;21(6):777-787. doi:10.1080/14740338.2022.2066651

[12] Moore TJ, Alami A, Alexander GC, Mattison DR. Safety and effectiveness of NMDA receptor antagonists for depression: a multidisciplinary review. Pharmacotherapy. 2022;42(7):567-579. doi:10.1002/phar.2707

[13] Lodge D, Mercier MS. Ketamine and phencyclidine: the good, the bad and the unexpected. Br J Pharmacol. 2015;172(17):4254-4276. doi:10.1111/ bph.13222 14. Natoli S. The multiple faces of ketamine in anaesthesia and analgesia. Drugs Context. 2021;10:2020-12-8. doi:10.7573/dic.2020-12-8

[15] World Health Organization. WHO model list of essential medicines—23rd list, 2023. Updated 2023/07/26. https://www.who.int/publications/i/item/ WHO-MHP-HPS-EML-2023.02

[16] Kreutzwiser D, Tawfic QA. Expanding role of NMDA receptor antagonists in the management of pain. CNS Drugs. 2019;33(4):347-374. doi:10.1007/ s40263-019-00618-2

[17] Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351-354. doi:10.1016/ s0006-3223(99)00230-9

[18] Murrough JW, Soleimani L, DeWilde KE, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med. 2015;45(16):3571-3580. doi:10.1017/s0033291715001506 \

[19] Marguilho M, Figueiredo I, Castro-Rodrigues P. A unified model of ketamine's dissociative and psychedelic properties. J Psychopharmacol. 2023;37(1):14-32. doi:10.1177/02698811221140011

[20] Colla M, Scheerer H, Weidt S, Seifritz E, Kronenberg G. Novel insights into the neurobiology of the antidepressant response from ketamine research: a mini review. Front Behav Neurosci. 2021;15:759466. doi:10.3389/fnbeh.2021.759466

[21] Zanos P, Moaddel R, Morris PJ, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev. 2018;70(3):621-660. doi:10.1124/pr.117.015198

[22] Aleksandrova LR, Phillips AG. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends Pharmacol Sci. 2021;42(11):929-942. doi:10.1016/j.tips.2021.08.003

[23] Frohlich J, Van Horn JD. Reviewing the ketamine model for schizophrenia. J Psychopharmacol. 2014;28(4):287-302. doi:10.1177/0269881113512909

[24] Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methylD-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864. doi:10.1001/archpsyc.63.8.856

[25] Alnefeesi Y, Chen-Li D, Krane E, et al. Real-world effectiveness of ketamine in treatment-resistant depression: a systematic review and meta-analysis. J Psychiatr Res. 2022;151:693-709. doi:10.1016/j.jpsychires.2022.04.037

[26] McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med. 2015;45(4):693-704. doi:10.1017/s0033291714001603

[27] Agboola F, Atlas SJ, Touchette DR, Fazioli K, Pearson SD. The effectiveness and value of esketamine for the management of treatment-resistant depression. J Manag Care Spec Pharm. 2020;26(1):16-20. doi:10.18553/jmcp.2020.26.1.16

[28] Albott CS, Lim KO, Forbes MK, et al. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. J Clin Psychiatry. 2018;79(3):17m11634. doi:10.4088/JCP.17m11634

[29] Albuquerque TR, Macedo LFR, Delmondes GA, et al. Evidence for the beneficial effect of ketamine in the treatment of patients with post-traumatic stress disorder: a systematic review and meta-analysis. J Cereb Blood Flow Metab. 2022;42(12):2175-2187. doi:10.1177/0271678x221116477

[30] Feder A, Costi S, Rutter SB, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. Focus (Am Psychiatr Publ). 2023;21(3):296-305. doi:10.1176/appi.focus.23021014

[31] Hartland H, Mahdavi K, Jelen LA, Strawbridge R, Young AH, Alexander L. A transdiagnostic systematic review and meta-analysis of ketamine's anxiolytic effects. J Psychopharmacol. 2023;37(8):764-774. doi:10.1177/02698811231161627

[32] Tully JL, Dahlén AD, Haggarty CJ, Schiöth HB, Brooks S. Ketamine treatment for refractory anxiety: a systematic review. Br J Clin Pharmacol. 2022;88(10):4412-4426. doi:10.1111/bcp.15374

[33] Ragnhildstveit A, Slayton M, Jackson LK, et al. Ketamine as a novel psychopharmacotherapy for eating disorders: evidence and future directions. Brain Sci. 2022;12(3):382. doi:10.3390/brainsci12030382

[34] Rodriguez CI, Kegeles LS, Levinson A, et al. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology. 2013;38(12):2475-2483. doi:10.1038/npp.2013.150

[35] Marcantoni WS, Akoumba BS, Wassef M, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009–January 2019. J Affect Disord. 2020;277:831-841. doi:10.1016/j.jad.2020.09.007

[36] Ahuja S, Brendle M, Smart L, Moore C, Thielking P, Robison R. Real-world depression,

anxiety and safety outcomes of intramuscular ketamine treatment: a retrospective descriptive cohort study. BMC Psychiatry. 2022;22(1):634. doi:10.1186/s12888-022-04268-5

[37] Yermus R, Bottos J, Bryson N, et al. Ketamine-assisted psychotherapy provides lasting and effective results in the treatment of depression, anxiety, and post-traumatic stress disorder at 3 and 6 months: findings from a large retrospective effectiveness study. Psychedelic Med (New Rochelle). 2024;2(2):87-95. doi:10.1089/psymed.2023.0021

[38] Boudieu L, Mennetrier M, Llorca PM, Samalin L. The efficacy and safety of intranasal formulations of ketamine and esketamine for the treatment of major depressive disorder: a systematic review. Pharmaceutics. 2023;15(12):2773. doi:10.3390/pharmaceutics15122773

[39] Riccardi A, Guarino M, Serra S, et al. Narrative review: low-dose ketamine for pain management. J Clin Med. 2023;12(9):3256. doi:10.3390/ jcm12093256

[40] United States Drug Enforcement Administration. Drug scheduling. https:// www.dea.gov/drug-information/drug-scheduling