

# Ketamine as a Mental Health Treatment

## A primer for nurses

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The world is in the midst of a mental health crisis. Rates of depression, anxiety, posttraumatic stress disorder (PTSD), and other mental health disorders continue to climb, and the global burden of mental health disorders has increased over the past 30 years.<sup>1</sup> Additionally, the seminal Sequenced Treatment Alternatives to Relieve Depression study (better known as STAR\*D) found that approximately one-third of patients treated for depression did not respond to treatment with currently available agents—even when multiple different agents were trialed—indicating treatment resistance.<sup>2</sup> Treatment resistance is not unique to depression; individuals struggling with PTSD, anxiety, and other mental health conditions may also not get adequate relief from currently available first-line pharmacological treatments.<sup>3</sup>

Over the past two decades, ketamine has emerged as a potential treatment for adults struggling with mental health conditions such as intractable depression, anxiety, and PTSD.<sup>4-6</sup> Until research on the use of ketamine in the treatment of depression was begun, no agents that “engage novel synaptic signaling mechanisms” had been introduced since 1957.<sup>4</sup> It is hypothesized that ketamine’s unique mechanism of action may be able to confer benefit when other interventions have been unsuccessful.<sup>7</sup> Unlike oral antidepressants, which may take several weeks to confer benefits, ketamine has been shown to have rapid-acting antidepressant effects, with patients reporting symptom reduction in four to 24 hours after administration.<sup>8,9</sup>

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The approval status for ketamine’s use as a mental health treatment is unusual. Racemic ketamine (hereinafter, simply ketamine) is an equal mixture of two nonsuperimposable mirror-image molecules (referred to as enantiomers), S-ketamine and R-ketamine, and was approved by the U.S. Food and Drug Administration (FDA) as an anesthetic in 1970.<sup>10</sup> Ketamine’s patent is long expired, reducing the financial incentive for pharmaceutical companies to sponsor large and expensive trials that could be submitted to the FDA for approval of new indications. This means that ketamine is being used off-label when the use is for any indication other than anesthesia. The exception is esketamine, marketed as Spravato by Johnson & Johnson. Esketamine is the isolated S-ketamine enantiomer of racemic ketamine. It is administered as a nasal spray and received FDA approval for treatment-resistant depression (TRD) in 2019. It is the only form of ketamine approved for this indication.<sup>11</sup>

Both the potential for benefit and a lack of standardized regulation shape the current ketamine landscape. As the evidence base grows and formal oversight remains limited, people with treatment-resistant mental health conditions are often left on their own to navigate treatment options that vary widely in standards and supervision. This uneven landscape poses challenges for nurses, who may be called on to educate patients, assess medication and patient safety, and support informed decision-making. Because nurses play a central role in direct care and system-level advocacy, they must approach ketamine therapy with sound clinical judgment and a clear ethical grounding. This article offers a practical overview of ketamine’s use in mental health care, including routes of administration, therapeutic models, regulatory gaps, and ethical considerations. It is intended as a foundational primer for nurses in all settings—bedside, community-based, and advanced practice—who may support patients considering, or receiving, ketamine therapy. By drawing on current research and evolving standards, we aim to equip nurses with the basic knowledge they need to engage safely and thoughtfully in this emerging area of care.

### FROM ANESTHETIC TO MENTAL HEALTH TREATMENT

Ketamine is a dissociative anesthetic related to the anesthetic phencyclidine.<sup>12</sup> It was viewed as an improvement over phencyclidine because it maintained phencyclidine’s lack of respiratory depression and favorable safety profile while decreasing the risks of delirium and psychosis, so-called emergence phenomena commonly seen with phencyclidine.<sup>13</sup> Ketamine is still widely used in emergency settings<sup>14</sup> and remains on the World Health Organization’s List of Essential Medicines as an anesthetic because of its effectiveness and safety profile.<sup>15</sup> In addition to its anesthetic properties, ketamine also has analgesic,<sup>16</sup> antidepressant,<sup>17</sup>

## ABSTRACT

Ketamine has emerged as a promising intervention for treatment-resistant mental health disorders, such as depression, anxiety, and posttraumatic stress disorder. With rising global mental health burdens and the limitations of existing pharmacological treatments, ketamine's novel mechanism of action provides a potential alternative for individuals who have not responded to traditional therapies. Ketamine was initially approved by the U.S. Food and Drug Administration in 1970 for use as an anesthetic, and over the past two decades, has increasingly been investigated and used as an off-label treatment for mental health disorders. Additionally, the S-ketamine enantiomer of ketamine, esketamine (marketed as Spravato), received approval for treatment-resistant depression in 2019. Clinical applications of ketamine in the treatment of mental health disorders include intranasal administration (esketamine), IV infusions, ketamine-assisted psychotherapy, and at-home therapy, with varying levels of oversight. The current ketamine landscape has created a perfect storm in which the regulation of ketamine's use in mental health treatment remains fragmented, the evidence is constantly evolving, and a vulnerable population of individuals who are struggling with treatment-resistant mental health symptoms are desperate for relief. This article addresses these considerations by providing a foundation of clinical information that nurses should understand as they advise patients who are receiving, or curious about ketamine, as well as by discussing the regulatory, ethical, and nursing implications of using ketamine in the treatment of mental health disorders.

**Keywords:** anxiety, depression, ketamine, mental health, posttraumatic stress disorder

antisuicidal,<sup>18</sup> and psychedelic<sup>19</sup> properties when used at subanesthetic doses.

Ketamine is primarily a noncompetitive *N*-methyl-d-aspartate receptor (NMDAR) antagonist in the brain's glutamate system; however, it is considered a "dirty drug" because of its affinity for multiple receptors in the brain, not just NMDARs.<sup>20</sup> Although NMDAR antagonism is thought to be responsible for ketamine's rapid antidepressant effects, research suggests that it is the downstream activation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) in the glutamate system that may play a crucial role in ketamine's antidepressant properties.<sup>20,21</sup> Activation of AMPARs has many consequences, one being the rapid increase of brain-derived neurotrophic factor (BDNF) levels.<sup>20</sup> BDNF regulates synaptic growth and plasticity and plays a vital role in the increased neuroplasticity that ketamine induces.<sup>22</sup>

Ketamine's antidepressant properties were first discovered through research conducted in the early 2000s. Initially, these studies were conducted to investigate the psychomimetic properties of ketamine; it was hypothesized that ketamine could be used to better understand the phenomenon of psychosis.<sup>23</sup> Instead, these early research participants reported that their mood had improved after receiving ketamine via IV infusion, which sparked further investigation. This research demonstrated that ketamine is a rapid-acting antidepressant with potent anti-suicidal ideation effects.<sup>17,24</sup> Ultimately, these studies led to the development of esketamine, proliferation of ketamine-infusion clinics, and investigation into ketamine's potential use in other mental health disorders.

Research has been conducted over the past two decades on the use of ketamine in the treatment of mental health disorders, especially depression. Ketamine's effectiveness and efficacy as a rapid-acting antidepressant have been demonstrated across numerous studies.<sup>8,25,26</sup> Esketamine received FDA approval for adults with TRD after clinical trials showed that study participants receiving esketamine were more likely to achieve depressive symptom response and remission than participants receiving placebo.<sup>27</sup> Ketamine has also been found to rapidly reduce PTSD<sup>28-30</sup> and anxiety<sup>31,32</sup> symptoms. Research has also been conducted on the use of ketamine in the treatment of substance use disorders, eating disorders, and obsessive-compulsive disorder; initial results have been promising, but more research is needed to clarify whether ketamine is an effective treatment for these disorders.<sup>5,33,34</sup>

The patient experience during ketamine treatment will depend on many factors, including the route of administration and dose administered. Routes of administration include IV infusion,<sup>35</sup> intramuscular injection,<sup>36</sup> sublingual lozenge,<sup>37</sup> or intranasal spray.<sup>38</sup> Lower doses of ketamine will have an anxiolytic and analgesic effect.<sup>31,39</sup> Higher—although still subanesthetic—doses will induce a dissociative experience, generating subjective changes in the patient's sensorium.<sup>19</sup>

Ketamine is a Schedule III controlled substance, meaning that, according to the U.S. Drug Enforcement Administration (DEA), it is viewed as having "moderate to low potential of physical and psychological dependence."<sup>40</sup> Data indicate that illicit use of ketamine has increased over the past two decades, although it remains uncommon.<sup>41</sup> However, rates of ketamine poisoning through intentional misuse, suicide attempt, or unintentional exposure have increased in recent years.<sup>41</sup> Long-term misuse of ketamine can have both cognitive and urological consequences; ketamine misuse has been implicated in the development of memory impairment and decreased executive functioning,<sup>42</sup> as well as the development of ketamine-induced cystitis and other lower urinary tract complications.<sup>43</sup>

## USE IN MENTAL HEALTH CLINIC SETTINGS

Ketamine may be a reasonable treatment option for patients struggling with mental health symptoms who have not benefited from medications or psychotherapy and who are feeling stuck. Ketamine offers an alternative to neuromodulation interventions such as transcranial magnetic stimulation (approved for TRD and obsessive-compulsive disorder) and electroconvulsive therapy (approved for depression, bipolar disorder, and psychosis).<sup>44,45</sup> Patients interested in seeking treatment for mental health symptoms via ketamine can access ketamine through a variety of clinical approaches.

**Esketamine** is administered only under the supervision of a health care practitioner in a clinic setting; esketamine cannot be obtained through a pharmacy. Esketamine comes in prefilled single-dose devices containing 28 mg of the drug. Patients self-administer one, two, or three doses, depending on the prescription; most patients are prescribed 56- or 84-mg doses.<sup>46</sup> Because of the risk of adverse reactions, such as dissociation, sedation, a feeling of intoxication, nausea, dizziness, and increased blood

pressure, patients must be monitored for at least two hours after esketamine administration and cannot drive themselves home.<sup>46</sup> While under observation, patients are typically not provided with structured therapeutic interventions; instead, they may engage in activities such as listening to music, reading, or using electronic devices. Clinics vary in approach, but the environment is generally designed to be calm and supportive, with periodic monitoring by trained staff.

Per the manufacturer's prescribing instructions, esketamine is administered twice per week for four weeks, then once per week for four weeks, and then once every one or two weeks as maintenance treatment.<sup>46</sup> Although esketamine's structured dosing and in-clinic monitoring help ensure patient safety, they can also present significant logistical challenges, particularly for individuals working full-time or with childcare responsibilities. The requirement to remain on-site for at least two hours following administration may necessitate time off work, flexible scheduling, or the use of leave benefits. These demands may pose a barrier to initiating or sustaining treatment for patients in jobs without such flexibility or who do not have alternative childcare support.

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## Nurses interested in administering ketamine therapy should consult their state's nurse practice act to determine whether ketamine administration falls within their scope of practice.

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Clinics or hospitals offering esketamine must be enrolled in the esketamine Risk Evaluation and Mitigation Strategy (REMS) program.<sup>47</sup> Esketamine may be prescribed by a psychiatric practitioner (such as a psychiatrist or psychiatric-mental health NP) or a practitioner trained in another discipline, such as anesthesia, who has received additional training. Initially, esketamine's FDA labeling required it to be prescribed in conjunction with daily oral antidepressants. Following an FDA priority review, esketamine was recently approved as monotherapy for adults with TRD.<sup>48</sup> Health insurance coverage of esketamine varies.<sup>49</sup> Out-of-pocket costs range from \$1,000 to \$1,500 per esketamine treatment session<sup>50</sup>; patients may be eligible for assistance through the esketamine withMe program offered by Janssen Pharmaceuticals.<sup>51</sup>

**IV infusion.** In the early studies of ketamine use for mental health disorders, the drug was administered intravenously,<sup>17,24</sup> and the protocols developed through these early studies continue to shape clinical practice today. Clinics typically begin with an induction phase of two or three infusions per week for three to five weeks, followed by individualized maintenance sessions as needed. Dosing starts at 0.5 mg/kg infused over 40 minutes and may be titrated based on patient response and tolerability.<sup>35</sup>

Unlike esketamine, which is subject to the FDA's REMS program, there is no equivalent federal protocol for IV ketamine. This lack of standardized regulatory oversight results in greater variability at clinics regarding monitoring practices, patient selection, and practitioner training.<sup>52</sup> However, professional organizations such as the American Psychiatric Nurses Association have developed ketamine-infusion guidelines.<sup>53</sup> Ketamine infusions may be

provided by psychiatric practitioners, anesthesiologists, certified registered nurse anesthetists, or physicians trained in other disciplines. Infusion clinics often employ RNs to start IV lines and monitor patients. Because of ketamine's off-label status, insurance does not typically cover ketamine infusions, requiring patients to pay out of pocket for services.<sup>54</sup>

**Ketamine-assisted psychotherapy (KAP)** is precisely what the name implies: ketamine is administered in conjunction with psychotherapy.<sup>55</sup> Although specific practices differ among clinics, KAP practitioners generally follow a four-phase model: assessment; preparation; administration, in what is known as a medicine session; and integration.<sup>37</sup> The preparation and integration phases are individual therapy sessions without the administration of ketamine. KAP aims to make use of the psychedelic properties of ketamine—patients may experience alterations in their sensory perceptions (such as to sight or hearing) and sense of self (ego dissolution) while under the influence of ketamine—and prolong the psychological benefits of ketamine treatments.<sup>5,56</sup> The frequency of medicine sessions and duration of treatment vary. However, most patients participating in KAP will have at least two medicine sessions over the course of several weeks. The ketamine in KAP is most commonly delivered via intramuscular injection or sublingual lozenge, although some clinics use IV infusion or an intranasal spray composed of compounded racemic ketamine. The dose of ketamine administered during a medicine session will vary based on the route of administration and targeted experience, and medicine sessions last from two to three hours. KAP practitioners may be psychiatric practitioners, psychotherapists, or physicians trained in other disciplines. As with ketamine infusions, KAP is generally not covered by insurance and must be paid for out of pocket.

**At-home therapy.** At-home self-administration of ketamine may occur via sublingual tablets or subcutaneous injections. During the initial emergent phase of the COVID-19 pandemic, the DEA suspended the requirement that prescribers see a patient in person before prescribing a controlled substance.<sup>57</sup> This reduction in regulation led to a proliferation of online ketamine clinics offering virtual assessment services and at-home ketamine therapy. Several safety concerns have been raised about these virtual ketamine clinics: the thoroughness of the assessment process of some online clinics has been called into question; high doses of ketamine have reportedly been prescribed, potentially leading to misuse or abuse of ketamine; and there may be no monitoring during the ketamine sessions.<sup>58</sup> A survey of at-home ketamine recipients revealed that 55% took more ketamine than prescribed,<sup>59</sup> suggesting that misuse is common. Unintentional overdose due to inappropriate prescribing practices has been reported.<sup>60</sup> In October 2023, the FDA issued a warning about the use of compounded ketamine products such as those prescribed through these online ketamine clinics.<sup>61</sup> In 2024, at least one online clinic was known to have offered injectable ketamine for at-home use without any requirement for the patient to be monitored by a health care practitioner.<sup>62</sup> Prescribers employed by virtual ketamine clinics may or may not have a background in psychiatric care. Insurance does not cover at-home ketamine treatments.

## CONTRAINDICATIONS TO KETAMINE THERAPY

Ketamine treatment is not appropriate for all individuals, and in some cases, the potential benefits of ketamine treatment do not

outweigh the risks. Psychiatric contraindications for ketamine treatment include a history of psychosis or mania.<sup>63</sup> Ketamine increases cardiovascular tone, so a recent history of myocardial infarction or cerebrovascular accident and currently uncontrolled hypertension are contraindications; ketamine is also contraindicated in individuals with severe hepatic disease.<sup>64</sup> Patients with a remote history of myocardial infarction, cerebrovascular accident, or currently controlled hypertension should consult with their primary care practitioners or specialists before proceeding with ketamine treatment. Additional contraindications to ketamine treatment include active ketamine or other substance abuse, pregnancy, and previous adverse reactions to ketamine.<sup>63,64</sup> Prolonged use of high doses of ketamine, particularly with illicit use of ketamine, has been shown to cause genitourinary complications such as interstitial cystitis.<sup>65</sup> In light of these safety concerns, regulatory oversight is crucial in guiding appropriate use.

### REGULATORY IMPLICATIONS

Because ketamine is a legally available Schedule III controlled substance, its use is regulated by the DEA, and prescribers must hold an active DEA license to prescribe it.<sup>60</sup> However, when it comes to the use of ketamine in treating mental health conditions, regulation is fragmented and inconsistent. There are no federal guidelines that specify which health care practitioners are permitted to administer ketamine for psychiatric use, what training is required prior to doing so, or how to determine appropriate patient eligibility. The murky regulatory landscape surrounding ketamine can lead to legal consequences, such as lawsuits or the revocation of DEA licenses, as has been reported in the media, if ketamine is administered outside established safety and regulatory standards.<sup>66,67</sup> This lack of standardized oversight has contributed to significant variability in practice and raised concerns about patient safety and practitioner qualifications.<sup>68</sup> Esketamine, the only form of ketamine approved by the FDA for a psychiatric indication, is the one exception and is subject to the FDA's REMS program, which outlines specific requirements for practitioner training, patient eligibility, in-clinic administration, and postdose monitoring.<sup>69</sup>

Nurses interested in administering ketamine therapy should consult their state's nurse practice act to determine whether ketamine administration falls within their scope of practice. In addition, they should confirm that their malpractice insurance explicitly covers ketamine-related services. Psychiatric-mental health NPs who plan to administer esketamine must register with the esketamine REMS program and follow all associated protocols to comply with federal regulations.

### ETHICAL IMPLICATIONS

The current landscape of ketamine therapy raises multiple ethical concerns for nurses, especially as off-label use grows and formal oversight remains limited.<sup>70</sup> As nurses strive to uphold the ethical principles of autonomy, beneficence, nonmaleficence, and justice, they must navigate a treatment modality characterized by therapeutic promise, evolving evidence, and a lack of standardization in practice. The most prominent of these ethical questions are those surrounding informed consent, the potential vulnerability of patients seeking ketamine therapy, and equitable access to treatment.

A fundamental way to respect a patient's autonomy is to obtain informed consent for a proposed intervention.<sup>71</sup> Patients should

be thoroughly educated on the potential risks and benefits of ketamine therapy, the various means through which ketamine therapy is available, and alternatives to ketamine therapy.<sup>72</sup> Patients interested in ketamine therapy should be advised that only esketamine is approved for a mental health indication and that all prescriptions of racemic ketamine are therefore off-label and likely not covered by insurance. Patients should be encouraged to inquire about a practitioner's credentials, including formal psychiatric training, completion of advanced ketamine therapy certification, and a demonstrated record of safe and effective clinical care. Nurses interested in administering ketamine therapy must be prepared to provide a thorough informed consent process so that patient autonomy is respected.

The ethical principles of beneficence and nonmaleficence require that nurses promote the well-being of their patients and prevent harm when possible.<sup>73</sup> These two ethical principles are fundamental in ketamine therapy because of the vulnerability of patients seeking out this form of treatment. Ketamine is not yet a first-line treatment for mental health disorders, meaning that individuals seeking ketamine treatment have often spent years seeking to treat their mental health symptoms with medication or psychotherapy. Understandably, these patients may be desperate for relief from their symptoms and, out of that desperation, seek out care without thoroughly vetting their options or practitioners. Experts have advocated for the development of a ketamine registry to track ketamine prescribers and adverse outcomes,<sup>74</sup> but no such registry yet exists. Without the oversight that a national registry would provide, patients seeking relief from their mental health symptoms are left susceptible to potentially unscrupulous practitioners who may lack the training to safely care for this vulnerable population, leading to patient harm and adverse outcomes. Furthermore, the advent of at-home ketamine treatments may lead patients to seek out forms of care that lack any supervision during ketamine treatments, which is a safety concern and may increase the risk of ketamine misuse. Although ketamine does have a favorable safety profile with minimal risk of respiratory depression, it is still a dissociative anesthetic. Even at the sub-anesthetic doses used to treat mental health disorders, ketamine should not be used without supervision. Nurses administering ketamine should be sensitive to how the ethical principles of beneficence and nonmaleficence can be upheld while caring for vulnerable patients.

The ethical principle of justice stipulates that individuals should be treated equitably<sup>75</sup>; nurses should be aware of the challenges in creating equitable access to ketamine therapy. Ketamine therapy can be prohibitively expensive, reducing access to a potentially beneficial treatment. Although esketamine is an FDA-approved treatment for TRD, not all insurance plans will cover it, and the out-of-pocket cost (\$1,000 to \$1,500 for a single treatment) can be a substantial barrier to care.<sup>50</sup> Insurance plans generally do not cover other forms of ketamine therapy, such as IV infusions, KAP, or at-home treatments, because of its off-label status, and each ketamine treatment can cost several hundred dollars. This leaves patients in a bind: those who most need treatment for intractable mental health symptoms might be least able to access it. Geographic access—physical proximity to care—to ketamine treatment is another equity issue. Perhaps the most compelling argument in favor of virtual ketamine clinics is that they give individuals living in

rural areas without nearby in-person options a means to access treatment.

Based on current research, there is justified optimism about ketamine's potential to alleviate symptoms in individuals with otherwise intractable mental health disorders. However, optimism must be tempered by ethical awareness. The off-label status of racemic ketamine, variability in practitioner training, and lack of consistent regulation may expose patients to harm. Nurses must maintain an understanding of these evolving dynamics to effectively advise patients seeking ketamine therapy.

## NURSING IMPLICATIONS

As ketamine therapy for mental health indications becomes more common, nurses across a variety of roles—from bedside nurses to advanced practice clinicians—will increasingly encounter patients who are curious about, receiving, or recovering from ketamine treatment. These interactions can occur in diverse settings, including outpatient clinics, inpatient units, EDs, schools, and community-based programs. Nurses must therefore be prepared to educate patients and families, assess safety and appropriateness, and advocate for evidence-based, ethically sound care.

## Nurses should remain aware of systemic barriers to care, such as high costs, limited insurance coverage, and geographic hurdles.

Patient and family education is essential before and during ketamine treatment. Nurses should explain the treatment process, expected effects, safety precautions, and signs of adverse reactions. This includes discussing the differences between FDA-approved esketamine and off-label uses of racemic ketamine, as well as potential risks, adverse effects, and treatment alternatives. Education should also address the importance of adherence to follow-up care and participation in psychosocial supports—such as cognitive behavioral therapy, mindfulness-based approaches, sleep hygiene strategies, and movement-based practices<sup>75-77</sup>—and reinforce the importance of avoiding unsupervised or nonclinical ketamine use.

Nurses administering or supporting ketamine therapy must be familiar with common adverse effects, including dissociation, nausea, elevated blood pressure, and sedation, as well as potential adverse effects such as bladder dysfunction or cognitive changes with long-term use.<sup>78</sup> Patients should be advised to fast prior to ketamine administration to reduce the risk of nausea, and vital signs should be monitored throughout the session to support early detection of hypertension or excessive sedation. Clinically significant hypertension may be managed with medications such as metoprolol or clonidine; nausea may be managed with ondansetron or dimenhydrinate.<sup>78</sup> Nurses can further enhance patient comfort by creating a calm, supportive environment during treatment; simple interventions such as dimmed lighting and comfort items like blankets or pillows can be effective.

In addition to managing acute effects of ketamine, nurses should be vigilant for signs of ketamine misuse or diversion,

especially when patients receive ketamine at home or through online clinics.<sup>59</sup> As part of comprehensive safety monitoring, nurses must also consider pharmacological factors that can influence ketamine's therapeutic response or introduce new risks. Although no significant interactions have been documented between ketamine and most conventional antidepressants,<sup>79</sup> some medications may influence its efficacy. Benzodiazepines may dampen ketamine's antidepressant effects and increase sedative effects, and although evidence is mixed, lamotrigine may also attenuate ketamine's impact.<sup>80</sup> Furthermore, medications that induce the cytochrome P-450 (CYP) isozymes CYP2B6 and CYP3A4 may reduce ketamine's effectiveness, whereas CYP2B6 and CYP3A4 inhibitors may increase the risk of adverse effects.<sup>79</sup>

Significantly, nurses working in diverse settings such as outpatient mental health clinics, inpatient mental health units, primary care, and public health may encounter patients who are curious about or actively receiving ketamine therapy. In these roles, nurses are well positioned to offer education, promote safety, assess patient understanding, and help coordinate ongoing care, even if they are not directly administering or prescribing ketamine themselves. Nurses should remain aware of systemic barriers to care, such as high costs, limited insurance coverage, and geographic hurdles, that shape who receives ketamine therapy and under what conditions. Advocating for equitable access—particularly for those who qualify for treatment but cannot afford care—is a professional and ethical imperative.

## CONCLUSIONS

Ketamine is an emerging treatment for depression and other mental health conditions. Although ketamine has been shown to rapidly reduce mental health symptoms such as depression and has a favorable safety profile, the use of ketamine is not without risk, and patients should be advised only to use ketamine in clinically supervised settings. Nurses should be prepared to discuss ketamine with their patients, along with its relative potential risks and benefits and the ways in which ketamine can be administered. Furthermore, nurses should be aware of the regulatory and ethical implications associated with the use of ketamine in the treatment of mental health disorders. However, ketamine treatment that is administered safely and ethically by trained nurses who are guided by the available evidence can help mental health patients struggling with otherwise intractable mental health conditions. ▼

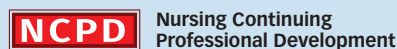
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## REFERENCES

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. 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. Murrrough 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-methyl-D-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 Cl, Kegeles LS, Levinson A, et al. Randomized controlled cross-over 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. *Psychodelic 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>
  41. Palamar JJ, Jewell JS, El-Shahawy O, Black JC. Trends in poisonings involving ketamine in the United States, 2019–2023. *Drug Alcohol Depend*. 2025;268:112549. doi:10.1016/j.drugalcdep.2025.112549
  42. Strous JFM, Weeland CJ, van der Draai FA, et al. Brain changes associated with long-term ketamine abuse, a systematic review. *Front Neuroanat*. 2022;16:795231. doi:10.3389/fnana.2022.795231
  43. Anderson DJ, Zhou J, Cao D, et al. Ketamine-induced cystitis: a comprehensive review of the urologic effects of this psychoactive drug. *Health Psychol Res*. 2022;10(3):38247. doi:10.52965/001c.38247
  44. Havlik JL, Wahid S, Teopiz KM, McIntyre RS, Krystal JH, Rhee TG. Recent advances in the treatment of treatment-resistant depression: a narrative review of literature published from 2018 to 2023. *Curr Psychiatry Rep*. 2024;26(4):176-213. doi:10.1007/s11920-024-01494-4
  45. Jha MK, Wilkinson ST, Krishnan K, et al. Ketamine vs electroconvulsive therapy for treatment-resistant depression: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2024;7(6):e2417786. doi:10.1001/jamanetworkopen.2024.17786
  46. Spravato: highlights of prescribing information. 2025. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/211243s019bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/211243s019bl.pdf)
  47. U.S. Food and Drug Administration. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. 2019. <https://www.prmnews.com/news-releases/fda-approves-new-nasal-spray-medication-for-treatment-resistant-depression-available-only-at-a-certified-doctors-office-or-clinic-300807354.html#>
  48. SPRAVATO (esketamine) approved in the U.S. as the first and only monotherapy for adults with treatment-resistant depression. 2025. <https://www.jnj.com/media-center/press-releases/spravato-esketamine-approved-in-the-u-s-as-the-first-and-only-monotherapy-for-adults-with-treatment-resistant-depression>
  49. Ochigbo EB, Beinfeld MT, Chambers JD. Balancing evidence and need: variation in US commercial payer coverage of esketamine. *Clin Ther*. 2024;46(10):808-811. doi:10.1016/j.clinthera.2024.06.017

50. SingleCare Team. How much does Spravato cost without insurance? SingleCare. Updated 2025/06/24. <https://www.singlecare.com/blog/spravato-without-insurance>
51. Johnson and Johnson. Spravato with Me. Updated 2025/02. <https://www.spravatohcp.com/patient-support>
52. Megli D. The ketamine economy: new mental health clinics are a 'Wild West' with few rules. *NPR*. 2024. <https://www.npr.org/sections/healthshots/2024/01/30/1227630630/ketamine-infusion-clinic-mental-health-depression-anxiety-fda-off-label>
53. American Psychiatric Nurses Association. Ketamine infusion treatment considerations. <https://www.apna.org/ketamine-infusion-therapy>
54. Aslam AM, Shinozuka K, Muir O, Tabaac BJ. Mapping the use of ketamine in treatment-resistant depression and other psychiatric disorders: a scoping review of practice patterns, efficacy, and patient demographic trends. *Am J Ther*. 2025;32(3):e242-e246. doi:10.1097/mjt.0000000000001951
55. Dore J, Turnipseed B, Dwyer S, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs*. 2019;51(2):189-198. doi:10.1080/02791072.2019.1587556
56. Drozd SJ, Goel A, McGarr MW, et al. Ketamine assisted psychotherapy: a systematic narrative review of the literature. *J Pain Res*. 2022;15:1691-1706. doi:10.2147/jpr.S360733
57. DEA's response to COVID-19. March 20, 2020. <https://www.dea.gov/press-releases/2020/03/20/deas-response-covid-19>
58. Jacobs A. F.D.A. issues warning over misuse of ketamine. *The New York Times*. October 11, 2023. <https://www.nytimes.com/2023/10/11/health/fda-ketamine-warning.html>
59. Kuntz L. Self-medicating: more than half of at-home ketamine users misuse the treatment. *Psychiatric Times*. June 21, 2023. <https://www.psychiatrictimes.com/view/self-medicating-more-than-half-of-at-home-ketamine-users-misuse-the-treatment>
60. Johnson BE, Borges ES, Gaspari RJ, Galletta GM, Lai JT. Unintentional ketamine overdose via telehealth. *Am J Psychiatry*. 2024;181(1):81-82. doi:10.1176/appi.ajp.20230484
61. U.S. Food Drug Administration. FDA warns patients and health care providers about potential risks associated with compounded ketamine products, including oral formulations, for the treatment of psychiatric disorders. 2023. <https://www.fda.gov/drugs/human-drug-compounding/fda-warns-patients-and-health-care-providers-about-potential-risks-associated-compounded-ketamine>
62. Yup K. People are injecting ketamine at home. *Wall Street Journal*. August 16, 2024.
63. Sanacora G, Frye M, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74:399-405. doi:10.1001/jamapsychiatry.2017.0080
64. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43(5):456-466. doi:10.1097/aap.0000000000000806
65. Zhou J, Scott C, Miab ZR, Lehmann C. Current approaches for the treatment of ketamine-induced cystitis. *Neurourol Urodyn*. 2023;42(3):680-689. doi:10.1002/nau.25148
66. Hu J. Mindbloom sued for wrongful death of 27-year-old, and preliminary results for Delix's non-hallucinogenic 5-MeO-DMT analog. *The Microdose*; 2025. <https://themicrodose.substack.com/p/mindbloom-sued-for-wrongful-death>
67. Putka S. DEA shuts down telehealth ketamine prescriber. *Medpage Today*; 2023. <https://www.medpagetoday.com/special-reports/features/104467>
68. Harding L. Regulating ketamine use in psychiatry. *J Am Acad Psychiatry Law*. 2023;51(3):320-325. doi:10.29158/jaapl.230040-23
69. U.S. Food and Drug Administration. Risk evaluation and mitigation strategies: REMS. Updated 2025/05/20. <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems>
70. Haeusermann T, Chiong W. Ethical considerations in rapid and novel treatments in psychiatry. *Neuropsychopharmacology*. 2024;49(1):291-293. doi:10.1038/s41386-023-01635-y
71. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 8th ed. Oxford University Press; 2019.
72. Mathai DS, Lee SM, Mora V, O'Donnell KC, Garcia-Romeo A, Storch EA. Mapping consent practices for outpatient psychiatric use of ketamine. *J Affect Disord*. 2022;312:113-121. doi:10.1016/j.jad.2022.06.036
73. Varkey B. Principles of clinical ethics and their application to practice. *Med Princ Pract*. 2021;30(1):17-28. doi:10.1159/000509119
74. Burton KW. Time for a national ketamine registry, experts say. *Medscape*. February 15, 2023. [https://www.medscape.com/viewarticle/988310#wp\\_1?form=fpf](https://www.medscape.com/viewarticle/988310#wp_1?form=fpf)
75. Drüge M, Guthardt L, Haller E, Michalak J, Apolinário-Hagen J. Cognitive behavioral therapy and mindfulness-based cognitive therapy for depressive disorders: enhancing access and tailoring interventions in diverse settings. *Adv Exp Med Biol*. 2024;1456:199-226. doi:10.1007/978-981-97-4402-2\_11
76. Lopresti AL. It is time to investigate integrative approaches to enhance treatment outcomes for depression? *Med Hypotheses*. 2019;126:82-94. doi:10.1016/j.mehy.2019.03.008
77. Wilkinson ST, Rhee TG, Joormann J, et al. Cognitive behavioral therapy to sustain the antidepressant effects of ketamine in treatment-resistant depression: a randomized clinical trial. *Psychother Psychosom*. 2021;90(5):318-327. doi:10.1159/000517074
78. Ceban F, Rosenblat JD, Kratiuk K, et al. Prevention and management of common adverse effects of ketamine and esketamine in patients with mood disorders. *CNS Drugs*. 2021;35(9):925-934. doi:10.1007/s40263-021-00846-5
79. Andrade C. Ketamine for depression, 5: potential pharmacokinetic and pharmacodynamic drug interactions. *J Clin Psychiatry*. 2017;78(7):e858-e861. doi:10.4088/JCP.17f11802
80. Veraart JKE, Smith-Apeldoorn SY, Bakker IM, et al. Pharmacodynamic interactions between ketamine and psychiatric medications used in the treatment of depression: a systematic review. *Int J Neuropsychopharmacol*. 2021;24(10):808-831. doi:10.1093/ijnp/pyab039



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