Ketamine Therapy for Psychiatric Disorders and Chronic Pain Management

Practice Considerations

Introduction

Ketamine hydrochloride is approved by the U.S. Food and Drug Administration (FDA) for the induction and maintenance of anesthesia.[1] Esketamine nasal spray, the s-enantiomer of ketamine, is FDA-approved for the treatment of treatment-resistant depression (TRD) in adults and depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.[2-6] Because several decades of research have shown that ketamine has antidepressive properties it has been incorporated into the treatment and management of psychiatric disorders (e.g., TRD, MDD, bipolar disorder, and post-traumatic stress disorder [PTSD], schizophrenia, anxiety, obsessive-compulsive disorder) and through ketamine's analgesic properties it has been incorporated into the treatment and management of chronic pain management (e.g., postsurgical pain, complex regional pain syndrome [CRPS], neuropathic pain, cancer pain).[5-30] Ketamine is not a singular treatment agent or a first-line therapy for psychiatric disorders or chronic pain management; therefore, it may be considered by the patient's interdisciplinary team after treatment resistance or as an adjunct treatment in the plan of care.[16]

Purpose

These practice considerations discuss ketamine infusion clinics and the role of Certified Registered Nurse Anesthetists (CRNAs), also known as nurse anesthesiologists or nurse anesthetists, in the delivery of ketamine infusion therapy for patients with psychiatric disorders or chronic pain or esketamine for patients with TRD and MDD.

Audience

These practice considerations are written for all members of the interdisciplinary team who treat patients with psychiatric disorders or chronic pain.

Interdisciplinary Patient-Centered Care

A patient-centered, interdisciplinary team approach with consistent, clear communication to coordinate the care management plan is necessary to address the patient's complex clinical conditions and optimize the patient's outcome. CRNAs have the knowledge, skills, and abilities to treat and manage acute and chronic pain, administer all forms of ketamine, and manage any associated side effects or complications.[31] Throughout their careers, CRNAs may incorporate new techniques and technologies into their practice in accordance with their personal experience and competencies, professional and individual scope of practice, federal, state, and local law, and facility policy.[31,32]

Collaboration between psychiatric clinicians, including psychiatric-mental health nurses, and ketamine infusion providers is recommended for diagnosis of psychiatric disorders, referral for evaluation and treatment, and management of patient issues.[6,26,33] These professionals complement each other's skills and knowledge in the assessment, management, and delivery of ketamine infusion therapy for appropriate psychiatric disorders with a focus on improved patient safety, outcomes, and general well-being.[33] The CRNA's role in ketamine infusion therapy may include, but is not limited to, reviewing healthcare records; obtaining a health history; conducting a pre-infusion assessment and evaluation; ordering and evaluating diagnostic tests; ordering or prescribing medications; initiating, maintaining, titrating, and discontinuing the infusion;

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monitoring the patient; conducting post-infusion assessment and evaluation; and managing infusion-related adverse events or complications.[31,33,34]

Similarly, CRNAs collaborate with other clinical providers, including primary care providers, orthopedists, neurologists, psychiatrists, social workers, radiologists, physical therapists, or other pain specialists to provide chronic pain management services.[35] CRNAs may receive referrals from other clinicians or serve as the sole provider of chronic pain management services. CRNAs provide patient-centered chronic pain management and treatment, working toward the common goal of decreasing the patient's pain and improving the patient's quality of life and functionality.[35] When working in collaboration with a patient's primary care provider or other referring clinician, CRNAs may share certain responsibilities of chronic pain management.[35] The CRNA reviews and may add relevant findings (e.g., history and physical, diagnostic results) to information provided by a referring clinician to administer chronic pain management services safely.[35] More detail on CRNA chronic pain management delivery is found in the American Association of Nurse Anesthesiology (AANA) *Chronic Pain Management Guidelines*.

Continued screening, monitoring, and follow-up of patients with psychiatric disorders or chronic pain are important throughout treatment and management. The interdisciplinary team should engage in ongoing staff education and review outcomes and metrics for continuous quality improvement and research to improve processes and patient outcomes.

Ketamine Infusion Clinics

Ketamine infusion clinics are becoming more available. These clinics should establish clear standard operating procedures, protocols, and policies supporting positive treatment outcomes and patient safety.[6,9,36] Even when using a sub-anesthetic ketamine dose, considerations include minimizing the potential for adverse events through premedication, individualized patient therapy, and monitoring of vital signs and general condition during the peri-infusion period. The involvement of psychiatric mental health providers in the treatment and monitoring of patients receiving IV ketamine for psychiatric disorders is important because of the potential for psychiatric side effects, including but not limited to dissociation, agitation, and out-of-body experiences.[33,37] When developing or joining a ketamine infusion service, CRNAs should participate in the creation, review, and periodic updating of evidence-based policies and procedures and evaluation of the availability of necessary routine and emergency monitors, supplies, and equipment.[6] Within the facility, clinicians should be able to monitor cardiovascular, hemodynamic, and respiratory function; electrocardiography and measurement of oxygen saturation are essential.[26,28]

The AANA *Ketamine Infusion Therapy Considerations Checklist* was developed for CRNAs and other clinicians who are interested in integrating ketamine infusion therapy into their practice. This document provides an overview of practice and policy considerations for the use of ketamine infusions as an adjunct treatment for the treatment and management of psychiatric disorders or chronic pain. Additional information on office-based and ambulatory surgical center practice is located at *www.aana.com/FacilityConsiderations*.

Plan of Care

The selection of appropriate candidates for ketamine treatment requires careful consideration of the risks and benefits of the treatment in the context of the severity of the patient's condition, duration of current episode, previous treatment history, and urgency for treatment.[28,37] Appropriate patient selection requires an assessment of other medical, psychological, or social factors that may alter the risk-to-benefit ratio of the treatment and affect the patient's capacity to

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provide informed consent.[28] Exclusion criteria for treatment may include current or past history of psychosis, dementia, current or recent delirium, history of intracranial pressure, uncontrolled hypertension, severe cardiac decompensation, pregnancy, positive urine drug screen or current or previous abuse of ketamine, allergy to ketamine, and/or previous serious adverse effects from ketamine.[37,38]

Ketamine is associated with few drug-drug interactions, and no contraindications are currently known to exist when combined with antidepressants, benzodiazepines, or other psychotropic medications.[39] Depression and obesity are often co-occurring conditions.[40] Additionally, many psychiatric medications have weight gain and metabolic dysregulation as common side effects.[40,41] Several studies have shown that a higher BMI and weight categorization as obese were associated with a greater acute improvement from a single dose administration of IV ketamine.[40]

For patients who are predisposed to psychosis or schizophrenia, ketamine use has a markedly increased risk of provoking psychotic and schizophrenic symptoms.[27,42] In patients with TRD, a higher number of therapeutic failures and severity of the disease may predict reduced response and remission at 24 hours and 7 days, respectively, after a single ketamine infusion or esketamine nasal spray infusion.[43]

Clinicians should engage the patient in shared decision-making to plan and manage patient and caregiver expectations. These discussions should include realistic expectations of when symptoms may improve, the series of infusions that may be necessary for improvement, and the potential for nonresponse and treatment-emergent adverse events.[44] Through the informed consent process, the patient is made aware of the risks and benefits of proposed treatment and provided information that ketamine infusions for his or her condition are considered an off-label use of the product.[45] Alternative therapies and their benefits and risks should also be explained to the patient.[45]

The dose, frequency, and length of ketamine infusion treatment are individualized to each patient's condition, needs, and responsiveness to therapy with input from the psychiatric clinician in the case of psychiatric disorders and other members of the interdisciplinary team. A clear monitoring plan should be in place to avoid or manage adverse events.[6,28,46] Serial infusions appear to be more effective than a single infusion for psychiatric or chronic pain conditions.[7,47-50] Ongoing patient evaluation and communication between the patient and clinicians, both psychiatric-mental health providers in the case of psychiatric disorders and ketamine infusion providers, will help direct the continued course of treatment.

Pharmacological Overview

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. Ketamine's interaction with the NMDA receptor is important in analgesia because these receptors play a key role in central sensitization.[7,26] Ketamine has different binding sites such as opioid, monoaminergic, cholinergic, nicotinic and muscarinic receptors. The NMDA receptor, as a glutamate-dependent mechanism, is responsible for principle pharmacologic properties of ketamine.[8] Subanesthetic doses disrupt the NMDA receptor functions. At low doses, these alterations may include increased glutamate transmission and secondarily increased brain-derived neurotrophic factor.[51] This ultimately may activate a complex signaling pathway for improved neural synaptic activity, notably in the pre-frontal cortex, which can improve psychiatric functions.[51] Ketamine undergoes hepatic metabolism and renal excretion and has an elimination half-life of 2-4 hours.[7,26] Although subanesthetic doses administered once or in a

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series of infusions have been shown to be safe, the safety profile of prolonged ketamine use has not been established.[6,28,52]

Table 1 summarizes the pharmacologic properties and administration considerations for IV ketamine and esketamine.

Table 1. IV Ketamine and Esketamine Comparison Chart

	IV Ketamine	Esketamine
FDA Approved Indications	• Sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation.[1] • Induction of anesthesia prior to the administration of other general anesthetic agents.[1] • Supplement to other anesthetic agents.[1]	• Treatment-resistant depression (TRD) in adults.[2] • Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.[2]
Route of Administration	• IV	• Nasal spray
Route of Administration	• Non-selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor.[1]	• Non-selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. • The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with less affinity.[2]
Dosage for Psychiatric Disorders	• 0.5 mg/kg for 40 min.[6,12-14,16,17,19,20,22,26,28,29,43]	• Dosage for Treatment Resistant Depression[2] Induction Phase: Weeks 1 to 4: Administer twice per week: Day 1 starting dose: 56 mg; Subsequent doses: 56 mg or 84 mg Maintenance Phase: Weeks 5 to 8: Administer once weekly: 56 mg or 84 mg

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		<table><tr><td></td><td>Week 9 and after: Administer every 2 weeks or once weekly*</td><td>56 mg or 84 mg</td></tr></table> ** Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.*
Absorption	• 100% bioavailable. • Rapidly attains maximum plasma concentrations.[53]	• The mean absolute bioavailability is approximately 48% following nasal spray administration. [2] • The time to reach maximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session. [2]
Distribution	• Quick distribution to the central nervous system. • Following IV administration, the ketamine concentration has an initial slope (alpha phase) lasting about 45 minutes with a half-life of 10 to 15 minutes. This first phase corresponds clinically to the anesthetic effect of the drug.[1] • Ketamine undergoes hepatic metabolism and renal excretion and has an elimination half-life of 2-4 hours.[7,26] • Steady-state volume of distribution is 3-5 L/kg.[54] • Central compartment volume of ketamine is 70 L, and the distribution volume at steady state is 200 L or 2.3 L/kg.[55] • Plasma protein binding is approximately 10-50%.[54,55]	• The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.[2] • Plasma protein binding of esketamine is approximately 43% to 45%.[2]
Metabolism	• Metabolized via N-dealkylation to the active metabolite norketamine primarily by CYP2B6 and CYP3A4 and to a lesser extent by other CYP enzymes. Norketamine	• Esketamine is primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19.

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	undergoes hydroxylation of the cyclohexone ring to form hydroxynorketamine compounds via CYP-dependent pathways, which are conjugated with glucuronic acid and subsequently undergo dehydration of the hydroxylated metabolites to form the cyclohexene derivative dehydroxynorketamine.[1]	Noresketamine is metabolized via CYP-dependent pathways and certain subsequent metabolites undergo glucuronidation.[2]
Excretion/Elimination	• Following intravenous administration, the ketamine concentration decreases due to a combination of redistribution from the CNS to slower equilibrating peripheral tissues and hepatic biotransformation to norketamine. The redistribution half-life of ketamine from the CNS to slower equilibrating peripheral tissues (beta phase) is 2.5 hours.[1] • Ketamine undergoes hepatic metabolism and renal excretion and has an elimination half-life of 2-4 hours.[7,26] • Metabolites are excreted in the urine and detectable for up to 5 days.	• After C_{max} is reached following intranasal administration, the decline in plasma esketamine concentrations is biphasic, with rapid decline for the initial 2 to 4 hours and a mean terminal half-life ($t_{1/2}$) that ranges from 7 to 12 hours.[2] • The mean clearance of esketamine is approximately 89 L/hour following intravenous administration.[2]
Post-Administration Monitoring	• Although the minimum adequate duration is unknown for monitoring adults with TRD receiving intravenous ketamine, a period of up to 2 hours should be considered.[6,26,56]	• 2 hours before discharge.[6,26,56]
Side Effects	• Common side effects of IV ketamine include nausea, agitation/anxiety, psychotomimetic symptoms, dissociative psychiatric symptoms, headache, confusion, inebriation, blurred vision, dizziness, euphoria, elevated blood pressure, elevated	• The most common adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant):[2,4,16] ○ TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.

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	heart rate, and increased libido.[6,7,14,16,17,20,27,29,47,52,57,58]	○ Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, increased blood pressure, hypoesthesia, vomiting, euphoric mood, and vertigo.
Contraindications	• Patients for whom a significant elevation of blood pressure would constitute a serious hazard.[1] • Patients with known hypersensitivity to ketamine or to any excipient.[1]	• Patients with unstable or poorly controlled hypertension or pre-existing aneurysmal vascular disorders may be at increased risk for adverse cardiovascular or cerebrovascular effects.[4]
Other Considerations	• Ketamine has minimal effect on the central respiratory drive if given slowly, although rapid IV injection may cause transient apnea.[59] • Ketamine can have deleterious effects on liver and urinary tract function.[6,27,48] • There may be a greater risk of ketamine-induced liver injury when infusions are prolonged or repeated over a short timeframe.[6,27,48] • Patients with a history of psychosis may be more vulnerable to the effects of ketamine, and may require slower infusions (e.g., 40-60 minutes).[13,60] • Those with a history of dissociation may expect stronger intra-infusion dissociative experience but can also expect the ketamine-induced dissociation to resolve after infusion.[20] • Ketamine rapidly passes through the placental barrier.[61,62]	• Esketamine rapidly passes through the placental barrier.[63]

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Abuse/Addiction Properties

Ketamine abuse and misuse are widely recognized problems throughout the world, and while low, rates are continuing to increase.[64-71] Prolonged patient use in the outpatient setting could produce physiological and psychological dependence on ketamine.[64] The number and frequency of treatments should be limited to the minimum necessary to achieve clinical response.[28] Appropriate patient screening, such as a urine toxicology screen, may be warranted before the initiation of ketamine treatment, and caution should be taken when administering ketamine infusions due to the risk of abuse, addiction, and complications of long-term use.[11,28,37,38,52,72] Proper drug storage and disposal measures are recommended to prevent drug diversion and misuse.[7,37,73]

Use for Psychiatric Disorders

Because major psychiatric disorders such as MDD are among the most disabling mental, neurologic, and substance use-related illnesses, new therapeutic approaches are being considered to treat or delay the onset of these disorders.[60] Ketamine infusions have been used as an adjunct to psychiatric treatment and can offer substantial short-term resolution of symptoms, although long-term resolution has not been demonstrated.[5,16,17,36,74,75] IV low-dose ketamine can induce rapid and robust, although temporary, antidepressive effects, even in treatment-resistant patients who do not respond to electroconvulsive therapy.[8,10,14,16,36,58,64,72,76] The dosage commonly found in literature for ketamine infusions for psychiatric disorders is 0.5 mg/kg over a 40 minute infusion titrated based on patient response.[6,12-14,16,17,19,20,22,26,28,29,43] Some research has noted a dose-response relationship, where a higher dosage leads to increased time to relapse for TRD, but more research is needed on this specific topic.[17,77]

Some studies have concluded that ketamine infusion may provide acute symptom improvement of suicidal ideation within 24 hours of treatment, although in a meta-analysis, Dean et al. found no difference in suicidal ideation scores between ketamine and placebo at any time point.[16,21,75,78,79] Dean et al. also note short-term effectiveness of esketamine for treatment of depression, but recommend further studies exploring long-term outcomes.[16] The authors indicate no differences in suicidality between esketamine over placebo at any time point.[16]

Ketamine can effectively ameliorate symptoms of patients suffering from PTSD.[7,18,39] In a randomized controlled trial in individuals with chronic PTSD, repeated IV ketamine infusions administered over 2 weeks were associated with a clinically significant improvement in PTSD symptoms compared with repeated psychoactive placebo control medication.[18]

Mental health disorders in the adolescent population continue to rise, with 16.39% of adolescents (12-17 years old) reporting suffering from at least one major depressive episode in the past year and 11.5% of adolescents experiencing severe major depression.[80] While ketamine infusion therapy has been reported to have utility in the adolescent population, further research regarding safety and efficacy is needed to make a conclusive recommendation.[81-89] Adolescence is a critical period for neurodevelopment, therefore additional considerations include the effects of ketamine on the developing brain as well as other medications the patient may be receiving, such as mood stabilizers or atypical psychotics.[87]

Use for Chronic Pain Treatment

Chronic pain is most effectively treated using a patient-centered, interdisciplinary, multimodal approach, recognizing the complexity of chronic pain, accounting for the diverse needs of the patient, and offering an individualized multimodal treatment strategy.[30,35] Ketamine may be

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used for short-term pain relief in patients with chronic pain, including ischemic limb pain, refractory chronic pain, phantom limb pain, fibromyalgia, and other neuropathic conditions.[7,18,24,25,27,30,39,48,57,74,90-97] A 2017 Cochrane review concluded that the evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain.[98] Through a systematic review and meta-analysis, Sun, et al. concluded that perioperative IV ketamine may reduce the incidence of chronic postsurgical pain in patients, especially 3-6 months post-surgery.[96]

Ketamine has also been shown to alleviate other unintended effects (e.g., depression) in the context of chronic pain and other chronic illnesses.[8,91] Preliminary evidence supports the efficacy of ketamine in treating comorbid depression and chronic pain and comorbid depression and acute pain.[99] As part of a multimodal approach, ketamine is not considered as the first or second choice in treatment for neuropathic pain, irrespective of the cause.[30] Ketamine is often reserved for cases where other treatments have failed due to its potential side effects and the need for careful monitoring.

Ketamine may have a role as an adjunct for cancer pain and may be a treatment option for patients who cannot tolerate opioids or those with problems with opioid responsiveness. [7,98,100] Ketamine can reduce the incidence and severity of opioid side effects, which is an important factor in patient compliance.[30] Ketamine treatment in chronic pain patients may counteract opioid-induce hyperalgesia and improves pain management while simultaneously reducing a patient's required total daily morphine equivalent.[90] In some instances, this may improve quality of life and improve respiratory and hemodynamic stability.[90]

IV ketamine therapy for CRPS can provide clinically effective pain reduction for less than 3 months.[24,93,94] In a systematic review, Chitneni, et al. concluded that patients who received ketamine infusion for treatment-resistant CRPS reported adequate pain relief with treatment, therefore ketamine infusion may be a useful treatment for patients with no significant pain relief from other conservative measures.[101] Esketamine infusions can also provide clinically effective pain relief in CRPS patients with refractory pain.[25]

The effect of IV ketamine among chronic pain patients may vary widely.[95] IV ketamine may be associated with improvement in pain scores observed during the infusion, quantified as early as 48 hours after the infusion, and lasting for ≥2 weeks when high-dose regimens are used.[95] While IV ketamine has shown short-term pain relief benefits for chronic pain conditions, there is a lack of consensus on the optimal treatment protocols for prolonged ketamine infusion in chronic pain management.[30] Large-scale studies with standardized assessments, different infusion protocols, and long-term follow-up periods are needed to establish its long-term effectiveness, dose-response relationship, and safety profile.[95-97]

Barriers to Care

Access to ketamine infusion therapy for psychiatric disorders and chronic pain management is hindered by several barriers. One barrier is the limited availability of trained providers and specialized clinics offering this treatment, especially in rural or underserved areas. Another factor is that ketamine must be administered via IV infusion in a clinical setting, which may limit accessibility.[16] Because ketamine is a schedule III drug and requires specific monitoring, as described above, it should be administered by a trained professional in a clinical setting. Additionally, the cost of ketamine infusion therapy can be prohibitive for many patients, as it may not be covered by insurance, and out-of-pocket expenses can be substantial. Notably, the U.S. Department of Veterans Affairs and the U.S. Department of Defense provide coverage for patients with suicidal ideation and major depressive disorder. Their guidelines suggest offering

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ketamine infusion as an adjunctive treatment for short-term reduction in suicidal ideation.[79] Stigma and misinformation surrounding ketamine may also deter individuals from seeking this treatment, despite its potential benefits.

CRNAs, as highly skilled anesthesia professionals, play a crucial role in overcoming many of these challenges. CRNAs have the expertise to safely administer all forms of ketamine, making their involvement a valuable solution. Additionally, their ability to provide anesthesia services independently in various healthcare settings can increase the availability of this therapy, especially in underserved or remote areas. CRNAs' holistic approach to patient care, including their strong focus on patient education and emotional support, can help reduce the stigma surrounding ketamine treatment and improve patient acceptance.

Conclusion

Ketamine and esketamine are both effective and safe in short-term clinical trials in adults with psychiatric disorders.[29] More research on long-term effects is needed as the clinical use of ketamine infusion therapy for psychiatric disorders and chronic pain management continues to evolve.[29] While there is supportive evidence demonstrating positive results from ketamine therapy, there are still challenges for clinical application that require consideration, discussion, and further research.[16] Clinicians, including CRNAs, should continue to monitor and contribute to the development of the related science, as well as engage in publication of new clinical findings and research on this topic.

Disclaimer

These practice considerations are solely for general informational purposes. Certified registered nurse anesthetists (CRNAs) practice in accordance with professional ethics, scope and standards of practice, sound professional judgment, the best available evidence, the best interests of the patient, and applicable law. AANA recommends obtaining legal and expert assistance regarding requirements for ketamine infusion therapy, including review of all applicable federal, state, and local laws and regulations specific to your practice.

The dosages listed in this document are intended to serve as a guide to patient care, rather than a one-size-fits all approach. Every patient is unique. Each anesthesia professional is responsible for independently confirming the correct dosage of medication before administration, based on an assessment and evaluation of the patient, the plan of care, the patient's clinical needs, and any relevant facility policies and procedures. AANA and our content experts are not responsible for incorrect dosage administration, and each anesthesia professional assumes full responsibility for how the information in this document is used.

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10275 West Higgins Road, Suite 500 | Rosemont, IL 60018
Professional Practice Division l 847-655-8870 l practice@aana.com