

Ketamine Infusion for the Treatment of Intractable Neuropathic Pain National Protocol Guidance April 2018

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives,
and the VHA National Emergency Medicine Office**

Purpose: To provide general guidance on ensuring access to intravenous ketamine for the treatment of complex neuropathic pain disorders under a National VA protocol that will facilitate collection of safety and effectiveness outcomes via a prospective medication use evaluation (MUE).

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications to the protocol as necessary to operationalize the use of ketamine for treating treatment resistant pain disorders.

Background

Ketamine is a noncompetitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor. Ketamine reduces hyperalgesia and opioid tolerance and provides analgesia by blocking N-methyl-D-aspartate (NMDA) receptors to reduce glutamate release and by binding to sigma-opioid receptors.¹ Ketamine has been employed as a substitute or adjunct for opioid therapy in selected patients.² Ketamine is occasionally used to help manage opioid tolerance, withdrawal, hyperalgesia, or neuropathic pain.³⁻⁶

Peri- and Postoperative Pain

In the perioperative setting, ketamine reduces hyperalgesia and opioid tolerance, thereby decreasing postoperative opioid requirements and, possibly, chronic postsurgical pain.¹ It may be used in subanesthetic doses in the perioperative period, generally for patients whose pain may be difficult to manage with opioids alone. However, the results from systematic reviews on the use of ketamine in the peri- and post-operative setting have been mixed and fraught by significant heterogeneity among studies.^{3,7,8}

In a 2011 systematic review of trials of perioperative IV ketamine, there was a reduction in total opioid consumption and an increase in the time to first analgesic.³ Patients having the most painful surgical procedures, including thoracic, upper abdominal, and major orthopedic operations, had improvement in pain scores despite a decrease in opioid consumption. Ketamine was not effective for patients having surgery associated with mild pain, such as tonsillectomy, dental, or head and neck surgery. Hallucinations and nightmares were more common with ketamine, but sedation was not. Postoperative nausea and vomiting were less frequent in the ketamine group when ketamine was efficacious for pain.

A 2016 meta-analysis of randomized trials comparing ketamine plus morphine or hydromorphone PCA versus morphine or hydromorphone PCA in postoperative pain included 36 trials with 2502 patients who underwent a variety of surgical procedures.⁷ Addition of ketamine to PCA resulted in a small decrease in postoperative pain at rest at 6 to 72 hours (<1 cm pain reduction on a 10-cm visual analog scale), lower cumulative postoperative morphine consumption (5 mg at 24 hours, 20 mg at 72 hours), and less postoperative nausea and

vomiting (RR 0.71). There were no differences in adverse events, including hallucinations, dysphoria, or vivid dreams, though adverse events may have been underreported.

A systematic review and meta-analysis of ketamine for the prevention of persistent post-operative surgical pain (PPSP) included 17 studies with 1015 patients randomized to receive ketamine and 785 randomized to receive placebo.⁸ Heterogeneity among studies was significant with highly variable timing and dosing of intravenously administered ketamine suggesting that no unifying effective regimen has emerged. The overall risk of developing PPSP was not significantly reduced at any time-point in the ketamine vs placebo groups nor did comparisons of pain severity scores reach statistical significance. Subgroup analysis of only intravenously administered ketamine demonstrated statistically significant reductions in the risk of developing PPSP at 3 and 6 months ($P = 0.01$ and $P = 0.04$, respectively) with an NNT of 12 and 14 patients, respectively, to be treated with ketamine for one less patient to develop PPSP. Adverse events were similar between the ketamine and placebo groups.

Cancer Pain⁹⁻¹⁵

Ketamine, in subanesthetic doses, has been given as an adjuvant to opioids for the treatment of cancer pain that is poorly responsive to opioids. It has been administered as a brief infusion (“Burst” therapy) for treatment of severe refractory pain, or as a more prolonged infusion or oral therapy in the context of refractory pain associated with advanced illness.¹³⁻¹⁵ Despite some favorable anecdotal experience, the evidence to support the benefit of ketamine as an adjuvant to opioid therapy is quite limited. A 2017 Cochrane Review evaluated randomized controlled trials (RCTs) of adult cancer patients with pain that were treated with an opioid, and receiving either ketamine (any dose and any route of administration) or placebo or an active control.¹² The review concluded that given the small total number of participants (30) and presence of clinical heterogeneity, the evidence was insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain.

Acute Pain Management^{16,17}

Low dose ketamine infusions have been used successfully in the ED and pre-hospital setting for the treatment of acute and acute over chronic pain when given with or without opioids as a single agent. Ketamine dosed in the range of 0.2-0.5 mg/kg IV or IM bolus followed by infusion have been shown to produce good analgesia and reduce overall opioid use compared to control groups. In one randomized, double-blinded trial, patients received either an initial dose of ketamine at 0.3 mg/kg of total body weight (maximum dose 25mg) IV for 5 minutes, or morphine at 0.1 mg/kg of total body weight (maximum dose 8 mg) infused IV for 5 minutes.¹⁷ The dose could be repeated after 20 minutes per patient request. Low-dose ketamine was not superior to morphine in the maximum change of Numeric Rating Scale (NRS) pain scores from baseline. However, the maximum change in NRS pain score took place at 5 minutes in the low-dose ketamine group and at 100 minutes in the morphine group. There was also greater than 50% reduction in pain scores for 2 hours following low dose ketamine at all intervals. As with the use of ketamine in other pain conditions, the optimal dose and timing of ketamine infusions for acute pain management remain to be determined.

Neuropathic Pain/CRPS

Ketamine has been studied in a number of neuropathic pain conditions including peripheral and central neuropathic pain, postherpetic neuralgia, orofacial pain, phantom limb pain, and Complex Regional Pain Syndrome (CRPS) as well as in fibromyalgia.^{18,19} Of the various routes of administration studied including subcutaneous, intravenous, intranasal, oral and topical, the

intravenous route provided the greatest efficacy with better outcomes observed in the CRPS subgroup of patients. Despite the extensive utilization of ketamine in various clinical settings, there is no consensus on an optimal intravenous (IV) ketamine infusion protocol for the treatment of neuropathic pain. Both the dose and duration of ketamine treatment varied widely among studies with doses ranging from 0.35 mg/kg/h to a high of 7mg/kg/h and durations of infusion ranging from minutes to hours to 10 days. The optimum dose, route and timing of administration remain to be determined. When examining the common components of ketamine infusion protocols for neuropathic pain that are associated with increased pain relief, prolonged duration of pain relief, and minimal side effects, certain trends and relationships emerge that may provide guidance for initiation of ketamine infusions and for future optimization research:¹⁹

1. **Apply the longest possible infusion duration that is logistically feasible using multiple outpatient clinic visits if necessary.** Longer duration of infusions may provide longer pain relief for patients with neuropathic pain. Multihour outpatient treatments over the course of several days may provide longer-lasting benefit than single- or short-duration infusions and provide a more feasible alternative to 5 to 10 day continuous infusions in the ICU.
2. **Use a dose of ketamine between 0.1 and 0.5 mg/kg/h to avoid excessive sedation in the majority of patients.** The total dose of ketamine administered, rather than the rate of infusion, appears to be related to a higher degree, and possibly a greater duration, of pain relief. This observation however is limited due to the lack of comparative efficacy studies and different efficacy endpoints of the different ketamine protocols.
3. **Use adjunct medications such as midazolam, ondansetron and clonidine to decrease the incidence of psychotomimetic and other adverse effects and possibly improve the degree of pain relief.** Patients administered ketamine may experience side effects regardless of the infusion protocol, infusion rate, infusion duration, or total ketamine dose infused. Serious side effects may occur and should be monitored. A benzodiazepine such as lorazepam or midazolam may reduce the incidence of emergence reactions and provide sedation. Ondansetron may prevent the common adverse effect of nausea and vomiting associated with ketamine use while clonidine may help control increased blood pressures and minimize dissociative effects.^{18,19}

Departments Affected: Pharmacy, Nursing, Pain Management (Anesthesia on call)

Procedure:

- Patients can either be treated as outpatients or inpatients

Patient Selection

Inclusion Criteria

- Current diagnosis of Complex Regional Pain Syndrome, or centralized pain disorder.
- In patients who have failed adequate trials, unless otherwise contraindicated, of each of the following therapeutic classes for neuropathic pain
 - TCAs (amitriptyline, desipramine or nortriptyline)

- Serotonin/Norepinephrine reuptake inhibitors (venlafaxine, duloxetine)
- alpha-2-delta calcium channel blockers (gabapentin, pregabalin)
- A pain management or interventional pain specialist with experience in use of Ketamine has evaluated the patient and determined that the patient qualifies for ketamine treatment in patient's medical record. The reasoning for trial of Ketamine should be documented in the medical record.
- A Mental Health Pain Provider has evaluated the patient and determined and documented that the patient has no mental health contraindications for ketamine treatment in patient's medical record.
- The patient or their legal representative is able to provide verbal informed consent.
- The patient has an adult who can accompany him/her and assist with transportation, or another method of safe transport has been arranged and documented.

Exclusion Criteria

- Current or past history of schizophrenia, schizoaffective disorder, bipolar disorder, or decompensated psychiatric disorder
- Dementia
- Current or recent (within the 7 days) delirium
- Current uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg)
- Conditions in which an increase in blood pressure would be hazardous
- Severe cardiac decompensation
- Myocardial ischemia/angina, recent MI (within 3 mos)
- Pregnant (via positive pregnancy test) or lack of birth control method in women of childbearing potential
- Positive urine drug screen or current or previous abuse of ketamine. Patients prescribed an opioid, benzodiazepine, or barbiturate by a VHA provider (including CHOICE) are eligible for ketamine; however, it is advised that concurrent use while receiving ketamine may prolong recovery time. Patients in acute intoxication or in need of detoxification should be excluded until those issues are addressed.
- Allergy or previous serious adverse effects to ketamine
- Recent infection or illness.
- Psychosis or decompensated psychiatric condition.
- Ketamine related cystitis.
- Illicit drug use, e.g. cocaine, methamphetamine, marijuana
- Morbid obesity with BMI > 40
- End-stage renal or hepatic disease
- DM2 with HbA1c > 9.0 (Patients who have demonstrated improvement in their diabetic control as evidenced by their most recent 2 week glucose diary recordings may be candidates for ketamine)
- Pulmonary HTN (mod-severe)

Screening and Referral

- Each facility will be responsible for developing and operationalizing a procedure to screen and refer potential candidates for treatment with ketamine.

- Screening should be completed no more than 30 days prior to acceptance and administration of the first dose of ketamine.
- Screening will include the following: verbal informed consent, inclusion/exclusion criteria, physical examination including vitals (blood pressure, heart rate, respiratory rate, oxygen saturation, and weight), relevant laboratory measures, and urine toxicology and pregnancy screens.
 - Patients with a SBP >150 mm Hg or a DBP >95 mm Hg at screening should be considered at higher risk and treatment for hypertension should be considered prior to initiating treatment with ketamine. Patients with a diagnosis of hypertension are to be adequately treated prior to receiving an infusion of ketamine.
 - Patients with a history of cardiopulmonary or cerebrovascular disease, recent myocardial infarction, symptomatic ischemic heart disease, dyspnea marked by shortness of breath or wheezing, poor exercise capacity (<6 metabolic equivalent of tasks (METs); bicycling – light effort (10-12 mph) =6.0), or any disease that could be associated with increased risk of acute cardiac demand or blood pressure or respiratory depression should be considered on an individual case basis, considering risk/benefit ratios.
 - Patients with a baseline heart rate of <60 beat per minute (bradycardia) or >100 beats per minute (tachycardia) should be considered on a case-by-case basis for the relative risks of ketamine.
 - SpO₂ at screening should be >94 after mild exertion.
- Other physical and laboratory screening procedures should be determined according to the patient's individual risk factors based on his/her demographics, medical history and review of systems and is the responsibility of the prescribing psychiatrist.
- Whether to obtain medical clearance from the patient's primary care provider or consults from a cardiologist, anesthesiologist, or other medical specialist should be based on the patient's risk factors and is the responsibility of the prescribing provider.
- Concurrent use or abuse of CNS depressants
 - In light of ketamine's abuse as a recreational drug, other factors to consider when screening for appropriate patients is a history of substance abuse including ketamine, extent of past and current alcohol use, smoking history, a history of medication misuse or inappropriate medical care, and a positive urine drug screen. There is no clear evidence of recent substance abuse associated with the risk of relapse with ketamine. Length of sobriety should be considered when making a decision.
 - Concurrent use of barbiturates, opioids and other Scheduled medication may delay recovery following ketamine infusion. It is important to wean off opioids as much as possible prior to ketamine infusion because of the higher risk of developing respiratory depression in combination with benzodiazepine coadministration.

Location of Administration, Monitoring and Recovery

- The facility is responsible for identifying a physical location for the infusion of ketamine and monitoring the patient during and after the infusion. The place for administration and recovery should be private or semi-private and large enough to accommodate the patient and required personnel.
- The treatment setting should be able to provide immediate care if necessary. A crash cart should be readily accessible. The facility must have the means to monitor basic

cardiovascular functions (including electrocardiogram and blood pressure) and respiratory function (oxygen saturation and end-tidal CO₂).

- The facility must also be capable of administering oxygen, medication and restraints to manage potentially dangerous behavioral symptoms.
- The facility must have a plan to rapidly address any sustained alterations in cardiovascular function including advanced cardiac life support or transfer to a hospital capable of caring for acute cardiovascular events.
- Patients determined to be at high risk for complications based on pretreatment evaluation should be treated at a facility equipped and staffed to manage any cardiovascular or respiratory events that may occur.

Ketamine Procurement and Infusion

- There is no consensus on an optimal intravenous (IV) ketamine infusion protocol for the treatment of pain. The optimum dose, route and timing of administration for efficacy and safety remain to be determined.
- The facility is responsible for determining the procedure that ketamine is ordered, prepared and transported to the place of administration.
- A pain management or interventional pain specialist will order the ketamine intravenous infusion and pre-medication and/or concurrent medication to prevent or manage adverse effects (e.g., intravenous lorazepam for agitation).
- An ACLS certified pain physician or anesthesiologist should be present at initiation, intermittently during, and at the end of the infusion. An ACLS certified nurse will be present during the infusion. The ordering provider can leave once the infusion is completed and the patient considered stable based on vital signs and cognitive status. The ordering provider must return at the end of the infusion to evaluate the patient, and clear the patient for discharge. An ACLS certified provider is to remain with the patient until discharge.
- Ketamine infusion timeline
 - **T-2 days** or sooner: Urine drug screen and pregnancy tests are collected. Review all medications and obtain Informed Consent.
 - **T-60 min**: Intravenous line started by a nurse or other qualified provider. Perform vital signs (sitting/standing blood pressure, sitting/standing pulse, respiratory rate, and oxygen saturation) test. Administer the Brief Pain Inventory (BPI) as baseline measures.
 - **T-0 min**: Provided vitals are acceptable and urine drug screen and pregnancy tests are negative (See Exclusion Criteria). Administer ketamine 0.5 mg/kg by intravenous infusion using an infusion pump over 4 hours. For patients with a body mass index ≥ 30 kg/m² it is suggested that the dose be calculated using the patient's ideal body weight (Men = 50 kg + (2.3 kg x each inch >5 feet); Women = 45.5 kg + (2.3 kg x each inch >5 feet)) rather than their actual body weight.
 - **T+10, 20, and 30 min**: Vital signs and check patient's cognitive status if indicated
 - **T+40 min**: Vital signs; check patient's cognitive status if indicated
 - **T+80 min**: Vital signs; check patient's cognitive status if indicated
 - **T+110 min**: Vital signs; check patient's cognitive status if indicated
 - **T+240 min**: Vital signs, Pain NRS (or other pain scale)
- Parameters for stopping infusion

- Blood pressure should remain <180 mm Hg systolic and < 110 mm Hg diastolic at all times during the infusion. Stopping the infusion often results in a rapid decline in blood pressure.
 - Systolic blood pressure can also drop by >10 mm Hg during the infusion. Should such a drop occur and be accompanied by an increased heart rate or any evidence of distress, then the infusion should be stopped.
- Heart rate should remain below the age adjusted maximum heart rates of 20 yrs <140 bpm, 30 yrs <133, 40 yrs <126, 50 yrs <119, and 60 yrs <112. For patients 65 years and older the maximum heart rate should be individualized based on exercise capacity and other risk factors.
- The appearance of any of the following necessitates stopping the infusion: 1) pallor, cyanosis, or any symptoms of poor perfusion, 2) respiratory symptoms such as shortness of breath, wheezing, 3) the appearance of chest, jaw or arm pain suggesting cardiac involvement, or 4) the patient's desire to stop.

Repeat Infusion Schedules and Alternate Regimens.

- IV Ketamine infusion may be administered and repeated daily at the discretion of the pain physician for up to 4 hr and up to 5 days (excluding weekends), depending on response to treatment.
- If necessary "Booster" session(s) may be administered but no more frequently than every 3 months; this will need to be individualized based on the patient's response, tolerability, and preference/availability.
- Alternatively, ketamine may be trialed every other day x 3 days (M-W-F) for 1-2 weeks, failure to respond to this initial trial would result in discontinuation of ketamine therapy.
- In the interest of patient safety, ketamine should be tapered and discontinued. At present this time frame is undefined and will need to be individualized.

Ketamine Treatment Failure/Discontinuation

- Discontinue if patient wishes to for any reason.
- Discontinue if the patient needs to have the infusion stopped more than once due to exceeding the blood pressure or heart rate thresholds.
- After 4 to 6 infusions without an adequate response
 - An adequate response is defined as a 50% or greater decline in NRS pain score from baseline
- Discontinue when dosing cannot be spaced out to a minimum of 1 dose per week by the second month of treatment.

Ketamine Adverse Effects

- **Cardiovascular:** hypertension, tachycardia, increase cardiac output, paradoxical direct myocardial depression, hypotension, and bradycardia.
- **Central nervous system (CNS):** tremors, tonic-clonic movements, fasciculation, increased intracranial pressure, dysphoria, amnesia, confusion, vivid dreams, delirium, sedation, dizziness.
- **Gastrointestinal (GI):** hypersalivation, vomiting, nausea.
- **Neuromuscular/skeletal:** increased skeletal tone, muscular rigidity.
- **Ocular:** diplopia, nystagmus, increase intraocular pressure.

- **Respiratory:** increase airway resistance, depression of cough reflex, respiratory depression or apnea with large doses or rapid infusions, laryngospasm.
- **Endocrine/Metabolic:** increased metabolic rate, Diabetes Insipidus
- **Genitourinary:** ulcerative or hemorrhagic cystitis (severity of symptoms are associated with the chronicity of use and doses > 700mg/day, resolves with cessation)
- **Hepatic:** possible risk for increased LFTs

Ketamine Outcomes Monitoring:

Baseline, 1-2 weeks post-infusion, and monthly

- Brief Pain Inventory (BPI)
- Number of and dosing regimens of opioid (MEDD) and non-opioid pain medications as applicable

Consent Statement for Ketamine Infusion for Treatment Resistant Neuropathic Pain

The following is to be read to and/or given to the patient or person authorized to approve treatments to read. A verbal acknowledgment of consent is required and is to be documented in the patient's medical record.

Your VA pain physician has recommended that you be treated with a drug called KETAMINE because your pain has not responded to other treatments commonly used for pain. Ketamine is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of neuropathic pain and complex regional pain syndrome and its use to treat these conditions is considered "off-label." This is why you are being asked to give verbal and written consent for treatment with ketamine.

Ketamine is approved by FDA as a general anesthetic, a drug that induces deep sleep or an unconscious state during which the patient does not feel pain. General anesthesia is used during surgery. The dose of ketamine used in surgery is much higher than the dose you will receive.

To treat your pain, you may receive a dose of ketamine daily for up to 5 days or two to three times a week for 1 to 2 weeks, at that point your physician will begin to increase the time between treatments as felt to be medically necessary. This will be done based on your response and how well you tolerate ketamine. If after 3 treatments your pain physician determines that you have not responded to ketamine, the treatments will stop and he/she will discuss other treatment options with you.

What can you expect during the treatment?

Prior to your receiving ketamine, you will be examined to determine if ketamine is safe for you. This will include physical and mental status exams as well as labs and other tests decided on by the examining healthcare provider.

- Patients with certain heart conditions, uncontrolled high blood pressure or breathing conditions may not be eligible for treatment with ketamine.
- Women who are pregnant or may become pregnant are not eligible for ketamine.
- Many patients who are abusing drugs or have a history of drug abuse may not be eligible for ketamine.

Each ketamine treatment will take approximately 5 hours; this includes your arrival an hour before you receive ketamine so your vital signs (heart rate, blood pressure, and breathing) can be assessed and an intravenous (IV) line started. These will be repeated periodically during your treatment. The remaining 4 hours include the time to infuse ketamine and to make sure that you have recovered and are safe to leave. During this time you will not be alone, a physician, nurse or other qualified health professional will be with you.

You are advised not to drive for 24-hours after receiving ketamine. Therefore, you will need a driver or another pre-arranged form of transportation to return home.

What are the potential risks or discomforts of ketamine infusion?

When used in general anesthesia ketamine has been reported to increase the risk for certain side effects such as anxiety, panic, fear reactions, hallucinations (such as seeing or hearing things that are not really present), paranoid thinking, agitation, dissociation (to feel disconnected from thoughts, memories, or surroundings), derealization (a sense that things around you are not real), depersonalization (out of body experiences), dream-like states, or agitation upon awakening from general anesthesia. Because ketamine is being used at much lower amounts and delivered over a longer period of time than is typically done in anesthesia practice, it is anticipated that these side-effects, while still possible, are less likely.

Ketamine is a known drug of abuse; in most cases it is swallowed or snorted, at substantially higher dosages and often with other illicit drugs or alcohol. While the dose of ketamine you will receive is generally well-tolerated, repeated doses may increase the side effects described by at risk individuals.

Importantly, there are no known permanent psychological effects reported in patients experiencing the side effects described above. Tolerance (a decreased in effect) to ketamine may develop with repeated use or in susceptible individuals with pre-existing illnesses. Other side-effects, such as high blood pressure and a change in heart rate or rhythm, can occur. You will be frequently monitored for these effects during and after the ketamine infusion.

It is your right to have ketamine discontinued at any time during your treatment –even while receiving the medication.

If you have any additional questions about ketamine or your treatment, please ask your pain physician or pain pharmacist.

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