VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Ketamine for Chronic Pain

CDI Number: 00031

Original Effective Date: October 1, 2024

Last Review Date: October 1, 2024

I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Ketamine

Ketamine, administered by any route, (including but not limited to subcutaneous, oral, intravenous, intramuscular, transdermal, and intranasal) is considered investigational and experimental for the following indications:

- Chronic pain

There is insufficient evidence from peer-reviewed medical literature to support the safety and efficacy of this treatment. Therefore, ketamine for the treatment of chronic pain is considered **not medically necessary**.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determination for medical necessity and is in alignment with generally accepted standards of medical practice.

a. Background Information

Chronic pain is a long-standing pain that persists beyond the usual recovery period. This type of pain is typically associated with a chronic health condition such as arthritis, nerve pain, fibromyalgia, etc. Chronic pain may be sporadic or continuous and can affect one's quality of life. Treatment options may include over the counter and prescription medications, physical therapy, exercise, medical procedures (e.g., nerve blocks, surgery, behavioral psychotherapy, or complementary therapy (e.g., meditation, acupuncture, biofeedback, relaxation techniques)), and lifestyle changes.

b. Research, Clinical Trials, and Evidence Summaries

Currently, there are no FDA-approved indications for using ketamine as a treatment modality for chronic pain. Case reports, case series, and observational studies have reported a beneficial effect of ketamine for chronic pain conditions. However, to date, controlled studies have not proven ketamine to be effective for treating chronic pain. No definitive consensus or regulatory guidelines for the dosage or duration of therapy exists.

Fallon et al. (2018) conducted a double-blind randomized clinical trial to evaluate the effectiveness of oral ketamine in adults with cancer-related neuropathic pain. A total of 214 patients who were unsuccessfully treated with adjuvant analgesics for neuropathic pain were equally randomized into either a ketamine treatment group or a placebo group. Each group received either ketamine, with a starting dose of 40 mg/d and a maximum dose of 400 mg/d, or a placebo for 16 days and preexisting analgesia was continued throughout the trial. The primary end point was duration of analgesic benefit, defined as an improvement of 5 points or more in the index pain score (using the Sensory Component of the Short Form McGill Pain Questionnaire), compared with a baseline score. Secondary end points included mean and worst pain, mood, mean change in global distress in the last 24 hours, quality of life, and serious adverse events. The results showed there was no difference in the duration of analgesic benefit or the mean and worst pain assessment between the treatment or placebo group. The authors concluded that ketamine was equivalent to placebo for cancer-related neuropathic pain.

Kamp et al. (2019) performed a systematic review of randomized controlled trials on the pharmacokinetics and pharmacodynamics of ketamine for the treatment of chronic neuropathic pain (NP). Data on intranasal and inhaled ketamine was included. Seven systematic reviews and meta-analyses, published since 2012, on ketamine efficacy in chronic NP were reviewed. Because current treatment options lack adequate efficacy in most patients, ketamine is often administered to treat refractory NP. Systematic reviews on randomized controlled trials significantly contrast with the findings from observational studies and case series. Proof of sustained, large effects of ketamine in the treatment of chronic NP from randomized controlled clinical trials is lacking. Data from observational trials and case series do suggest the efficacy of ketamine in producing effective pain relief in chronic NP with positive patient-related outcome measures. Current findings on the efficacy of ketamine to treat chronic NP concluded that definitive proof of the efficacy of ketamine in management of neuropathic pain is limited, with just small analgesic effects lasting no longer than a few days to a few weeks.

Orhuruh et al. (2019) conducted a systematic review and meta-analysis of Medline, Embase,Google Scholar, and clinicaltrials.gov through December 16, 2017, for randomized control trials comparing intravenous (IV) ketamine to placebo infusions for moderate chronic pain that reported outcomes for ≥48 hours after the intervention. Human subjects ≥18 years of age who had chronic pain for ≥3 months and reported an intensity of pain of moderate or severe were included in this review. The search yielded 696 studies, seven of which met the inclusion criteria, for a total of 211 patients with neuropathic and non-neuropathic pain included in the review. The study excluded trials for patients <18 years of age, animal studies, case series, use of non-IV formulations of ketamine, uncontrolled trials, and review articles. A meta-analysis of the data from these trials revealed a significant reduction in pain scores, favoring ketamine over standard or control comparative treatments, although pooled difference in pain reduction at four weeks was insignificant. Evidence suggests that IV ketamine provides significant short-term analgesic benefit in patients with refractory chronic pain, with some evidence of a dose-response relationship. Although several reviews have been published on ketamine for chronic pain, they do not address pertinent questions or are limited, as outlined in consensus guidelines based on a collaborative effort of three pain societies (American Society of Regional Anesthesia & Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM) and the American Society of Anesthesiologists (ASA)). Larger, multicenter studies with longer follow-ups are needed to better select patients and determine the optimal treatment protocol.

Riccardi et al. (2023) completed a narrative review of articles published on PubMed and Medline, without any time constraints, to explore the expanding role of ketamine as a unique analgesic drug and to define the benefits and possible risks of a therapy. The purpose was to address the drug characteristics of ketamine specifically related to the antidepressant, postoperative and chronic pain effects, adverse events, patient monitoring, abuse risk, and contraindications. Based on its pharmacokinetics and pharmacodynamics, particularly antagonist of NMDA receptors and associated antidepressant effect, ketamine is of interest for its potential in treating the common co-occurrence of chronic pain and depression. However, there is a lack of studies on mechanisms, administration route, dosing and patient response.

Evidence for the efficacy of low-dose ketamine for chronic pain is conflicting in part due to large methodological differences in existing studies. Studies have yet to prove which patients or types of pain benefit most from an analgesic dose of ketamine. Currently, there is no clinical evidence to predict individual patient responses to ketamine treatment for chronic pain. Knowledge of ketamine specifics and appropriate management are critical to

improving the management of adverse events and reducing their prevalence. More extensive studies are needed to define the role of ketamine more precisely, including reviews of individual patient response and the psychomimetic side effects to ketamine.

c. Medicare Coverage Determinations

There are no available Medicare coverage determinations for ketamine for chronic pain. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

d. TRICARE Policy Manual

Available TRICARE coverage determinations are listed below as a resource. VA and TRICARE are governed by separate laws and regulations; thus, VA coverage determinations may be different.

TRICARE Policy Manual 6010.63-M, Chapter 07, Section 3.8

- Off-label use of Ketamine (subcutaneous, sublingual, IV, injectable, nasal spray, or orally) is excluded.

IV. Definitions

Term	Definition
Analgesic	Medications that relieve pain
Biofeedback	Type of mind-body technique used to control some functions of the body, such as heart rate, breathing patterns, and muscle responses
Fibromyalgia	A disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory, and mood issues
Neuropathic	Used to describe pain, weakness, numbness or tingling in one or more parts of the body, due to nerve damage
Pharmacodynamics	The study of a drug's molecular, biochemical, and physiologic effects or actions
Pharmacokinetics	The study of the time course of drug absorption, distribution, metabolism, and excretion
Psychomimetic	Substances or drugs that produce symptoms of psychosis or hallucinations

V. References

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VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	
	MM/DD/YYYY	