Sublingual Ketamine for Chronic Pain and/or Depression
Information for Prescribers, *12/28/2017*

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I. Abstract

Low dose ketamine has been used clinically for decades as a treatment for acute and chronic pain, and in recent years for rapid relief of treatment-resistant depression. However, ketamine remains off-label for treatment of pain and depression; the FDA has approved it only for use as an anesthetic. For this reason, there is no formal guidance available to prescribers who wish to offer this treatment to their patients.

In published studies of its use for treating pain or depression, ketamine has most often been administered as an intravenous infusion. However, the high cost and expertise required to administer the infusions limit patient access. Sublingual ketamine, when self-administered by the patient at home in repeated low doses, may provide the same benefits without these limitations.

This document provides insights gained from the clinical experience of one prescriber of low dose sublingual ketamine for both pain and depression in approximately four hundred patients over five years. A short list of references is provided; detailed references will be included in a future version. A suggested protocol for initiation and maintenance is available separately.

II. Introduction

Current treatment options for chronic pain and depression are often unsatisfactory. For patients with chronic pain, opioid medications are often used but carry a high risk of adverse effects including opioid use disorder, increased pain sensitivity, decreased function, and overdose death. For patients with depression, currently available antidepressants can take weeks to improve symptoms, and many patients have an incomplete response.

In my outpatient family practice, ketamine has provided profound relief for many patients with garden-variety chronic pain syndromes such as low back pain, fibromyalgia, sciatica and osteoarthritis, as well as more unusual chronic pain conditions such as complex regional pain syndrome and phantom pain. It has also provided rapid relief of depression and suicidal thoughts. I have not prescribed ketamine for patients with suicidal intent, and would not recommend its use for that outside of hospitalization.

Most patients with chronic pain also have some degree of depression, and ketamine can improve both conditions in these patients. Acute pain, anxiety and post-traumatic stress disorder may also benefit.

This article is intended as practical guidance for licensed prescribers considering offering sublingual ketamine to their patients. The article is not intended as a replacement for the FDA package insert, and of course I can't guarantee either effectiveness or safety for your patients.

There have been many randomized controlled trials of ketamine infusions showing benefit in acute perioperative pain, and more recently for treatment-resistant depression, anxiety, PTSD, and end-of-life care. Evidence of ketamine's effectiveness in chronic pain and via the oral or sublingual routes is limited to case reports and case series. A large-scale randomized controlled trial has not yet been performed. It would require non-commercial funding, since ketamine is off-patent. My own randomized controlled trial - a 32 subject pilot study of oral ketamine for opioid-tolerant patients with chronic pain - showed trends toward improvement of both pain and depression, although the results were not statistically significant. Pharmaceutical companies are at work developing patentable ketamine variants that, once FDA-approved, may ultimately increase clinical acceptance of existing less expensive formulations.

In my recent retrospective analysis of 390 patients prescribed ketamine, obtaining of repeated refills was used as an indicator of perceived value to patients. There was a high likelihood of perceived value among those with chronic pain (61%, n=240, $p<0.002$) or depression (67%, n=33, $p<0.17$). Among patients with chronic pain, significant predictors of perceived value were depression (74%) and chronic opioid use (69%), with trends toward perceived value among those with bipolar disorder, PTSD, opioid use disorder, anxiety and insomnia (unpublished data). Average daily dose among those with and without chronic opioid use was approximately 120 mg/day and 60 mg/day, respectively.

Several categories of patients who seem to benefit particularly are 1) patients with cancer-related pain - both during treatment and at end-of-life - who can reduce reliance on opioids and maintain a higher level of cognition and function, 2) elderly home-bound patients with both chronic pain and depression, and 3) patients using buprenorphine for either opioid use disorder or chronic pain.

III. Starting New Patients

Addressing pre-conceived notions. When you mention the name "ketamine," many people will ask you, "Isn't that a rave drug?" or "Isn't that a horse tranquilizer?" Ketamine is a Schedule III drug because of its potential for abuse. However, among patients with chronic pain or depression, I have seen little evidence of problematic use. This is partly due to careful patient selection and preparation, and also due to dissociation, which is a cognitive effect that occurs at higher doses that many people find uncomfortable. A dosing strategy of upward titration allows patients to achieve symptom relief while avoiding this effect. Dissociation is described in more detail in the section below on Risks and Side Effects. And yes, it is also a horse tranquilizer. Ketamine is commonly used as an anesthetic in veterinary medicine, and also in human medicine including in young children. It is often used for brief procedures because it has quick onset and recovery. It is unique among anesthetics in not causing respiratory depression at clinically relevant doses, so it is useful for painful procedures when a breathing tube is undesirable. I provide a two-page patient-oriented introduction to those considering this treatment. It addresses patients' concerns, and they are often willing to give it a try after reading it.

Initiation. I provide patients with an information handout, a prescription for ketamine syrup, and a customized dosing plan. The reader can refer to my dosing protocol for details. The patient is to start

with a low dose and increase stepwise to a specified maximum dose - until they experience either a benefit or an uncomfortable adverse effect. We arrange a followup call or visit within a week. At that point, some patients want to continue increasing the dose; others want to split the total daily dosage according to their own formula.

I ask patients to call at any time with problems or concerns. The first return visit to clinic occurs within a few weeks. When the patient is ready for a prescription refill, I will increase the syrup concentration for those using a higher dose. After a stable dose has been achieved, a transition to lozenge or "troche" form may be possible for patient convenience. Cost of lozenges has been prohibitive for most of my patients.

Choice of starting dose and frequency. Dosing is highly individual. The effective daily dose range varies widely, from 8 mg to 200 mg daily, and even higher in a few exceptional cases. As stated above, average dose is 60-120 mg/day.

The optimum dosing plan for each individual can only be determined by trial and error. For reference, 16 mg taken orally is equivalent to about 4% of a typical anesthetic dose given intravenously, based on bioavailability estimates. Doses above 32 mg are usually taken in divided doses. The dose at which dissociative cognitive effects begin to occur is different for each person; these effects may be well tolerated, but can be avoided completely by slow upward titration and use of divided doses.

In the dosing protocol, factors that influence choice of starting dose and frequency include age, severity of depression or pain, history of high dose opioid use, medical frailty, anxiety, and history of drug sensitivities. For example, an anxious patient who frequently has an adverse reaction to new medicines should be started at an exquisitely low dose of 2 mg taken once or twice daily. In contrast, for a patient plagued by continuous suicidal thoughts, I would start with 16 mg every 2 hours (maximum 4 doses in one day) – a strategy aimed at rapid onset. The ultimate goal is to find the lowest total daily dose that provides a therapeutic benefit.

More on dosing frequency: The chronicity of ketamine's benefit does not seem to be strictly related to its elimination half-life, which is 2 ½ hours. The time course of action may be related to adaptive changes of the nervous system (intracellular molecular changes and synaptic growth which can occur quickly and have prolonged duration of effect). For both depression and pain, a noticeable benefit often occurs within 2-3 hours of a suitable dose, and then reaches a steady state after a few days. To achieve a steady state, a daily dose at bedtime is adequate for many patients. However, some patients seem to find a short-term benefit after each dose. For them, dosing two or more times daily provides the best symptom relief. Others, particularly those with depression but not pain, prefer a strategy of higher bolus dosing at longer intervals. These patients can still avoid dissociative symptoms if they split a large total dose into several smaller doses taken 1-2 hours apart. In rare cases, the effective dose is so high that dissociative symptoms are unavoidable. Patients who find this experience uncomfortable can precede each dose with a low dose short-acting benzodiazepine.

IV. Additional Background Information

Sublingual vs. oral: Swallowing oral capsules is convenient but absorption is variable. The variability results in unpredictable time of onset and increased risk of uncomfortable cognitive effects. Onset can vary from 15 minutes to several hours after consuming the capsule. Absorption can be so poor that neither benefit nor side effect occurs at doses of 64 mg or more. In contrast, sublingual administration

allows transmucosal absorption directly into the bloodstream. The rapid absorption results in a faster and more predictable onset of effect, typically within 10-15 minutes. The predictability allows the patient to fine-tune dosing to avoid dissociative effects. Transmucosal absorption of the liquid syrup may also be more potent because it avoids first-pass metabolism. For these reasons I now prescribe ketamine exclusively as syrup for sublingual use, except to long-term patients who prefer continuing with capsules. For greater patient convenience, the ketamine can be compounded into a lozenge (also known as a troche) for sublingual use. Lozenges are expensive, but a high-dose lozenge can be split into smaller individual doses.

Compounding Pharmacies. Ketamine in capsule, syrup or lozenge form can only be obtained at a compounding pharmacy, since it is only FDA-approved in the injectable liquid form. Compounding pharmacies use their own proprietary formulas to prepare the prescribed form. The cost for a month's supply of syrup is typically $40-$50. A patient using a higher daily dose will pay more.

Insurance. Some insurance companies will reimburse patients for off-label use of ketamine for chronic pain or depression but most do not, because it is not FDA-approved for these indications.

Central Sensitization. The pain relief benefit of ketamine in patients with chronic pain, regardless of the etiology of the pain, is thought to be primarily due to its antagonist effect at the NMDA-type glutamate receptor. The NMDA receptor plays a crucial role in central sensitization, the process by which neural pain pathways of the brain and spinal cord become hypersensitive after a prolonged or severe nociceptive stimulus. By blocking this receptor, ketamine seems to reverse central sensitization, or at least temporarily interfere with the facilitation of pain signal processing that has developed along these sensitized pathways. Central sensitization tends to result in pain that has an amplified intensity, a functional rather than anatomical distribution, and an agonizing quality with a suffering component. These specific pain features seem to be selectively reduced or eliminated by ketamine. New or ongoing nociceptive stimuli continue to be perceived as painful, but patients find their continuing pain much more tolerable. Pain interferes less with their desired activities.

Interaction with opioids. Opioid pain medications cause central sensitization. Regular use of opioids, particularly at high doses, can induce those same features of pain that ketamine blocks – amplified intensity (sometimes known as "opioid-induced hyperalgesia"), non-anatomical distribution and emotional suffering. Ketamine remarkably seems to block these adverse effects while reinforcing the favorable pain relieving effect of opioid pain medications – and of endogenous opioids (endorphins). Many patients report that taking the ketamine and the opioid at the same time provides optimal pain relief. Ketamine sometimes reinforces the sedating effect of opioids. Sedation can be reduced more safely by lowering the dose of the opioid rather than the ketamine. In theory, ketamine could also reinforce opioid-induced respiratory depression, although this is rarely clinically relevant. Some patients are able to decrease their opioid dose after starting ketamine; this could happen immediately, but it sometimes takes weeks or months before they are ready.

Depression. Ketamine has been shown in multiple well-designed clinical trials to produce a profound and rapid reversal of severe treatment-resistant depression. Laboratory studies suggest that this effect occurs in part due to reversal of an intracellular process in the frontal lobe as a response to stress. Prolonged or severe stress interrupts a chemical cascade known as the mTOR pathway which, in healthy brains, results in rapid sprouting of dendrites during learning. Stressed brains consequently have stunted dendrites, a condition which corresponds with the experience of depression (or at least with depressed

behavior in rats, where this process has been studied in detail). Ketamine allows the return of healthy dendrite sprouting, and rapid resolution of depression. In clinical trials, profound resolution of depression occurs within hours in the majority of study subjects receiving a ketamine infusion.

No withdrawal symptoms: Patients have not reported withdrawal symptoms, even after abrupt discontinuation from a high dose. Patients who forget to take their ketamine for a few days or run out will notice their original symptoms returning.

Pharmacodynamics and pharmacokinetics: Metabolized by the liver. Excreted in the urine. Elimination half life: 2 ½ hours. Oral bioavailability: 16%. This means that an 8 mg oral dose is less than 2% of a typical 100 mg intravenous dose used in anesthesia, and 64 mg is 10% of that intravenous dose.

Pregnancy category B. This means that ketamine as an anesthetic has been deemed safer during pregnancy than acetaminophen. However, there is no information available about the safety of chronic daily use of ketamine during pregnancy.

V. Risks and side effects

Ketamine is an extremely low risk drug, particularly in comparison with opioid pain medications, which were responsible for 20,000 deaths in the U.S. in 2015. Below is a review of the adverse effects I have observed. Patients occasionally discontinue the drug due to adverse effects.

Dizzy/tipsy feeling: Many patients don't experience any side effects using an upward titration strategy. The most common side effect is a dizziness or "tipsy" sensation. When it occurs, it tends to last 15-30 minutes. At low doses it is usually experienced as a pleasant sensation.

Dissociative symptoms: As the dose increases, the patient may report that objects appear farther away or the patient feels disconnected from his/her surroundings. This sensation is pleasant for some but uncomfortable or frightening for others. It may be tolerated it if it is followed by a profound relief of pain or depression. While this cognitive effect is not necessary for relief of pain or depression for most people, it is considered useful by psychiatrists performing monitored ketamine-assisted psychotherapy. However, patients self-administering low-dose ketamine for chronic pain or depression can find it disturbing enough to discontinue treatment. A low dose benzodiazepine can help these patients tolerate a higher dose.

Denial phenomenon: Some patients don't recognize symptom improvement despite increased activity, improved sleep, new cheerfulness and even laughter while under treatment. They don't interpret the changes to be from the ketamine because they have no side effects. Patients with this denial phenomenon may say, "I just decided it was time to get out and do something, rather than sit around." Unfortunately, these patients may discontinue ketamine because they feel it is not working. They later will complain of a return of their symptoms. A patient may agree to another try, and then recognize that ketamine is helping when symptom relief occurs again.

Tolerance can occur, more commonly at higher doses. It ultimately will result in the loss of any significant benefit from the treatment. Advising patients of this risk will build an alliance to keep the dose low rather than to seek perfect symptom relief at a higher dose.

Headache, paresthesia, visual changes, nasal congestion and tremor have been reported. These symptoms usually resolve quickly after the dose is reduced.

Elevated blood glucose has resulted in discontinuation or dose reduction for several patients with diabetes.

Bladder pain: Three patients with pre-existing interstitial cystitis had to discontinue use of ketamine after a few weeks due to worsening of bladder pain. This is noteworthy because a study of long-term ketamine recreational users found that bladder ulceration had occurred in some.

Confusion: One elderly lady with mild cognitive impairment discontinued use due to worsening confusion.

Hypomania: Ketamine may trigger hypomania or mania in a patient with bipolar disorder. This effect can be prevented or mitigated with use of a mood stabilizer.

Personality change: One very pleasant woman developed a narcissistic personality disorder over several months of using ketamine. Her normal personality returned after discontinuing treatment.

Hypersensitivity reaction: One man described facial flushing and later skin peeling.

Overuse: Rarely, a patient will find the use of a high dose to be pleasurable and will repeatedly ask to escalate the dose. The prescriber must consider whether the therapeutic effect has become secondary to the pleasurable experience. True addiction – continued use despite harm - is exceedingly rare; prescribing should be discontinued if this is encountered.

Psychosis: Two young men, both with a history of substance use disorder, used poor judgment and escalated their dose much more rapidly than prescribed, resulting in psychosis and hospitalization.

Vivid dreams. These are not unusual, but are well-tolerated by most patients.

U-shaped pain curve. In this phenomenon, as ketamine dose is increased, pain decreases up to a point. When the ketamine dose is increased further, pain can then begin to increase, or strange new pains can appear. The optimum dose for each patient is unique. In one patient this value was precisely 12 mg. 8 mg didn't relieve pain, and 16 mg caused strange new pains. Ketamine has a much wider therapeutic window for most patients. The dose-limiting factor for a given patient may therefore be either the dissociative symptoms, the cost, development of tolerance, or increased pain.

Cardiac issues. At the high doses used for anesthesia, ketamine is a cardiovascular stimulant that can cause hypertension and tachycardia. In contrast, at low doses in patients with chronic pain, it seems to reduce blood pressure. This may result from reduced vasoconstriction due to reduced noradrenergic autonomic stimulation due to reduced pain. One patient incidentally noted that his chronic palpitations resolved after starting low dose ketamine for chronic pain. However, the stimulant effect could theoretically induce a cardiac arrhythmia in susceptible individuals.

Overexertion. Ketamine increases activity level in most patients. While this effect has mental health benefits and is usually appreciated by patients, it does have risks. For example, it can exacerbate arthritis pain. Patients will push themselves harder than usual after starting ketamine, and often feel sore the next day. As an extreme, there were two men in their 70's who discovered critical coronary artery stenosis when they developed angina during a new vigorous walking program after starting ketamine.

Drug interactions. As discussed above, ketamine can facilitate the side effects of opioids and other sedating medications. In one extreme case, a man with advanced cirrhosis on high dose methadone fell into a prolonged sleep after starting low-dose ketamine for post-surgical pain. He eventually emerged from his stupor, cheerful and nearly pain-free. I suspect the deep sedation was a facilitated side effect of methadone, which was metabolized slowly by his dysfunctional liver.

Elevated intraocular pressure. This is a theoretical concern for patients with narrow-angle glaucoma. It is listed on the FDA package insert. Ketamine should be avoided in these patients.

Seizure threshold. The published literature is ambiguous, with examples of the seizure threshold being either raised or lowered by ketamine in humans and non-human animals. For a patient with a history of seizures, consultation with the patient's neurologist may be helpful. In one tragic case, a patient without a history of seizures developed ketamine-induced seizures after two years of use. Although the ketamine had relieved her chronic suicidal depression, she ultimately chose to discontinue it, and shortly afterwards committed suicide.

VI. References (Limited Selection)

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