Tara J. Belsare, MD
Contemplative Medicine
38 Riverside Drive, 3rd FL
Binghamton, NY 13905

Meditation, Therapy, Medication
(607)215-1705 voice
(607)304-2374 fax
Tbelsare@psychiatry.life

Introductory Information on Ketamine

Low dose ketamine has proven to be effective in the treatment of chronic pain and treatment resistant depression. Patients using a very low dose of oral Ketamine for chronic pain experience relief that enables increased levels of functioning. Patients who use it for depression (with or without pain) can feel relief within a few hours. While some patients do not get symptom relief or have unacceptable side effects, most patients are very happy with it.

Background: Ketamine is a drug used most commonly as an intravenous anesthetic for human and veterinary surgery. It was developed in 1962 and was first used for American Soldiers injured in Viet Nam. At high doses it puts people into a dreamlike, semi-conscious state where they can undergo surgery without feeling any pain. The dose prescribed here is about 1/20th of that used for anesthesia.

Opioids: Ketamine seems to have a particular benefit for people who have had exposure to high dose opioid medications, either recently or a long time ago. It reverses the exaggerated experience of the pain that occurs in people who use opioid drugs frequently, especially at high doses. Nerve cells that have repeatedly been exposed to opioids become over-excitable, responding more quickly and powerfully to a pain stimulus. Ketamine quiets down these over-excited nerve cells.

Depression: There are now quite a few articles published in the psychiatric journals about high dose intravenous ketamine being used to rapidly reverse depression in patients that did not improve with other treatments. Mood is lifted often within hours. Low dose oral ketamine does not act as quickly, but is safe to use in an outpatient setting and it does work over time.

Reversal of Stress: Yale Scientists recently did some experiments that show that ketamine's remarkable effects on depression seems to be a result of its action inside nerve cells. It unleashes a cascade of chemicals which results in new connections to other nerve cells. The same cascade of chemicals is known to be clogged with stresses of all kinds. It seems that ketamine may be reversing some of the destructive effects of stressful events that have occurred over a lifetime throughout the brain and the spinal cord. I suspect that this same action inside nerve cells may be part of the reason ketamine is so helpful for chronic pain, which is often suffered by people who have had severe life stressors.

Oral, intranasal, or Sublingual Use: While intravenous ketamine can only be given in a hospital under the direction of an anesthesiologist, this drug can be used safely by patients out of the hospital when swallowed, placed under the tongue, or inhaled. It has to be specially prepared by a compounding pharmacy , as it is currently not made by drug companies in a form for oral or sublingual (under the tongue) use.

There is a form of ketamine that is DEA and FDA approved for use in treatment resistant depression. It is called Spravato (esketamine). It is reimbursable by insurance. It involves a nasal spray followed by in-office monitoring. This is available from Dr. Gary Dean at 607-251-2400. Sublingual ketamine, which is used here, can be sent home with you for at-home dosing - without having to spend more than one extended session in the clinic. That one session is used to insure tolerance and lack of allergy.

Dosing: For chronic pain and depression, the dose is equal to about 1/20th of the normal anesthetic dose. It is taken once or twice daily and increased to achieve maximum benefit. Those who benefit may start feeling results after a few hours and will feel continuing improvement over days to weeks.

Precautions: Ultra-low dose of ketamine is safe for people with any medical conditions except uncontrolled high blood pressure (HTN), heart rhythm problems (arrythmia), aneurysm, arteriovenous malformation, high intracranial pressure, severe glaucoma, history of unstable angina/heart attack/stroke/mini-stroke, or psychosis such as schizophrenia. The frequent side effects of ketamine are hallucinations or a feeling of unreality, but those normally don't occur at this extremely low dose. Lowering the dose or the number of doses each day takes care of these unpleasant symptoms. At the low dose we use, ketamine can increase blood pressure and cause a lightheaded feeling. It can also cause decreased concentration and increased reaction time. It is for this reason that you will need someone to drive you home after your first in-office dose.

Mechanism of action: The pain relief benefit of ketamine in patients with chronic pain, regardless of the cause 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 painful stimulus. By blocking this receptor, ketamine seems to reverse central sensitization and 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 painful stimuli continue to be perceived as painful, but continuing pain much more tolerable. Pain interferes less with desired activities.

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.

Tara J. Belsare, MD
Contemplative Medicine
38 Riverside Drive, 3rd FL
Binghamton, NY 13905

Meditation, Therapy, Medication
(607)215-1705 voice
(607)304-2374 fax
Tbelsare@psychiatry.life

Effects from long-term daily use of low-dose ketamine are unknown. Among long-term high-dose recreational users, some individuals developed bladder problems including ulcers. Individual people may have their own unique side effects, but there is no reason to expect anything really dangerous or life threatening, especially in comparison with opioid pain medicines, which slow or stop breathing and were responsible for the deaths of 20,000 people in the U.S. in 2016. If someone swallowed a week's supply of ketamine at once, as with many other prescription medications they would likely end up in the hospital or worse. Please don't try that.

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.

Risks and side effects - The following is taken from Sublingual Ketamine for Chronic Pain and/or Depression Information for Prescribers, 12/28/2017
by Lucinda Grande, MD Pioneer Family Practice, 5130 Corporate Ctr Ct SE, Lacey, Washington 98503

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.

Tara J. Belsare, MD
Contemplative Medicine
38 Riverside Drive, 3rd FL
Binghamton, NY 13905

Meditation, Therapy, Medication
(607)215-1705 voice
(607)304-2374 fax
Tbelsare@psychiatry.life

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.

And lastly,

Please do not drive a motor vehicle for the first hour after you take a dose, until you have experience at that dose level. If you are currently on a high dose opioid medication , it would be wise to reduce the opioid dose when starting ketamine. You may become more sedated than usual from the opioid when the high dose is no longer needed for the pain.

_____

client signature

_____

date