

# USES OF KETAMINE

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## Uses of Ketamine

Ketamine is a Schedule III controlled substance sedative hypnotic. It is commonly used for anesthesia. It works by direct action on the cortex and limbic system, producing trance-like cataleptic state by non-competitively blocking N-methyl-D-aspartate (NMDA) receptors and both sympathomimetic and bronchodilator effects with minimum respiratory depression. There are many different uses for ketamine, such as for refractory depression, pain and sedation. The primary role of ketamine in low doses is as an ‘anti-hyperalgesic’, ‘anti-allodynic’ or ‘tolerance-protective’ agent. It therefore has a role in the treatment of opioid resistant or ‘pathological’ pain (central sensitization with hyperalgesia or allodynia, opioid induced hyperalgesia, neuropathic pain) rather than as an ‘analgesic’ in its own right. Low dose ketamine also has ‘preventive analgesia’ properties. Furthermore, in higher doses it provides effective and safe sedation and analgesia for painful procedures.

### ❖ Ketamine dose chart

Ketamine			
Route	Indication	Dose	Comments
<b>Oral</b>	Depression <sup>(3, 5)</sup>	0.5 mg/ kg PO for 28 days	Can titrate up to 3 mg/kg/day
	Post-Traumatic Stress Disorder <sup>(48)</sup>	Doses ranged from 0.5 to 7.0 mg/kg *titration is needed	All different routes for this indication used the same dose range
	Pain <sup>(12)</sup>	Adults: 220 mg PO every day	Starting with 100 mg in divided doses. Titration done every 2 days in increments of 40 mg, final dose: 140-500 mg/day, median dose: 220 mg
		Children <sup>(45)</sup> :10 mg/kg	
Fibromyalgia <sup>(6,7,22)</sup>	30-1,000 mg/day		
<b>Sublingual</b>	Depression <sup>(b)</sup>	10 mg SL every once  Dosing based on: 0.5 mg/kg	Swish for 5 min and then  100 mg/ml solution (Very low dose) Buccal administration: deliver the solution in a syringe to the space between the teeth and cheek
	Pain <sup>(45)</sup>	12.5 mg to 25 mg SL	0.25-0.5 ml solution** this was combined with 20 units of SL oxytocin

<b>Intranasal</b>	Juvenile Bipolar Disorder <sup>(49)</sup>	as 0.1 ml sprays of <b>50–200 mg/ml</b> ketamine in 0.01% benzalkonium chloride to alternating nostrils	repeat this administration every 3–4 days
	Breakthrough pain <sup>(14,13,40,41)</sup>	Adults: 50 mg IN	PCCA formula available for 100 mg/ ml nasal spray (#7836)
		Children: 3 - 5 mg/kg	
	Migraines <sup>(44)</sup>	25 mg IN	Effective in reducing severity but not duration of aura
	Fibromyalgia* <sup>(6,7,22)</sup>	6 mg/kg/day	
Depression <sup>(7,9)</sup>	50 mg IN		
<b>Topical</b>	Pain <sup>(16,17)</sup>	0.5-1% ketamine cream	* 1% ketamine with combined 2% amitriptyline showed no significant difference in lowering pain
		5 mg/ml ketamine gel	*dose used for post-herpetic neuralgia
	Chemo-induced peripheral neuropathy (CIPN) <sup>(18)</sup>	20 mg ketamine in placebo organogel	
	Complex regional pain syndrome (CRPS) <sup>(30)</sup>	0.25%-1.5% ointment	
<b>Intravenous</b>	Depression <sup>(1,2,4,9)</sup>	0.5 mg/kg IV infused over 40-50 mins	Two treatments separated by one week, patients will need infusions every few weeks. Peak effects were seen 1-2 days later and lasted up to one week
	Post Traumatic Stress Disorder <sup>(4b)</sup>	Single IV infusion of ketamine hydrochloride (0.5 mg/kg)	Administered over 40 minutes. Second infusion was administered based on patient reaction.
	Breakthrough pain <sup>(24)</sup>	0.1 mg/kg/hr. increased by the same amount every 3-4 hours as tolerated titrated to a pain score.	

Intramuscular	Complex regional pain syndrome (CRPS) <sup>(19)</sup>	3–7 mg/ kg/ hr	
	Fibromyalgia <sup>(6,7,22)</sup>	0.125-3 mg/kg/hr IV or SC	
	Surgical anesthesia* <sup>(45)</sup>	1-4.5 mg/kg IV slowly over 60 seconds, on average, 2 mg/kg will produce 5-10 mins of anesthesia	If a longer effect is desired, additional increments can be administered IV to maintain anesthesia without producing significant cumulative effects
	Reactive airway disease <sup>(45)</sup>	loading dose of 0.1–0.2 mg/kg followed by an infusion of 0.15–2.5 mg/kg/h	
	Fibromyalgia <sup>(6,7,22)</sup>	0.4 mg/kg	
	Pediatric premedication* <sup>(45)</sup>	2–4 mg/kg	
Rectal	Surgical anesthesia <sup>(45)</sup>	3.25—13 mg/kg	As needed for maintenance
	Fibromyalgia* <sup>(6,7,22)</sup>	6-10 mg/kg/day	
	Children anesthetic dose * (3-9 y/o) <sup>(45)</sup>	9 mg/kg	
	Infant anesthetic dose* (16-48 mnths) <sup>(45)</sup>	5 mg/kg	

\*anesthetic doses

**Doses on this chart are based on the studies and are NOT guideline based! Please refer back to studies for further details on dosing and patient specific characteristics. This table is also not all inclusive of all the doses different disease states but merely a reference to clinical data up to this point.**

## 1. Refractory Depression:

### ❖ Oral ketamine for depression

Oral ketamine appears to have the lowest bioavailability, about 20%, among the dosage forms. A systematic oral ketamine study for depression took place in a hospice care setting. Hospice patients with depression received 0.5 mg/kg of oral ketamine daily for 28 days. Eight of the participants completed the study and the conclusion was that “oral ketamine had significant antidepressant and anxiolytic efficacy”<sup>3</sup>. Side effects were reported and included diarrhea, insomnia, and akathisia.

Recently, a case series was published about two patients that were treated with an escalated dosing regimen. (0.5 mg/kg/day to 3 mg/kg/day). They experienced sustained antidepressant and anti-suicidal effects.

One hospice patient received 27.5 mg ketamine (0.5 mg/kg) orally. She experienced mood improvement as seen by her Hamilton Rating Scale for Depression (HDRS) drop by 45% one hour after her dose. By day 15, there was a 66% improvement. Her anxiety based on Hospital Anxiety and Depression Scale (HADS) decreased by 83% two hours after her dose, and 50% reduction was observed by day 15. She tolerated oral ketamine well, and its effects lasted several months before significant depressive symptoms returned (although not as severe as before). She did not respond to a ketamine repeat dose at that time. The second hospice patient also received oral ketamine (0.5 mg/kg) of 32.5 mg. He also experienced improvement in anxiety symptoms within an hour of his dose. No adverse effects were noted. His depressive symptoms, appetite, and mood slowly improved within days of oral ketamine. Due to worsening physical health of his prostate cancer, he was unable to continue with assessments past day 13<sup>5</sup>.

#### ❖ Sublingual ketamine for depression

Sublingual administration of ketamine renders better bioavailability (~30%) and less conversion to norketamine than oral administration. The authors evaluated the therapeutic effects and tolerability of very low dose sublingual (VLDS) racemic ketamine 10 mg from a 100 mg/ml solution. The small amount of ketamine was administered by mouth with directions to rinse for 5 min and then swallow, repeatedly every 2-3 days or weekly, in 26 outpatients with refractory unipolar or bipolar depression. According to patients' reports, VLDS ketamine produced rapid, clear and sustained effects, improving mood level and stability, cognition and sleep in 20 patients (77%), with only mild and transient light-headedness as a common side-effect (no euphoria, psychotic or dissociative symptoms). Remission remained in some patients after stopping ketamine. Thus, VLDS ketamine may have broad-spectrum effects beyond its antidepressant properties, with rapid onset of action, high efficacy, good tolerability and low cost, allowing extended treatment as needed<sup>6</sup>.

#### ❖ Intranasal ketamine for depression

Bioavailability of intranasal ketamine has been reported to be between 25% and 50%. A randomized, double-blind, crossover placebo- controlled trial enrolled 20 patients with major depression. The treatment group received 50 mg of intranasal ketamine. This study concluded that intranasal ketamine is safe and effective for rapid recovery from depression in patients that have failed at least one antidepressant trial. The antidepressant effect from ketamine was detectable 40 minutes after the dose was given. Although intranasal ketamine does appear to be effective, it has reduced efficacy when compared to previous studies done on intravenous ketamine. This is because intravenous administration of ketamine achieves higher levels in the blood than intranasal ketamine. Intranasal ketamine was associated with minor dissociative side effects while IV ketamine is associated with more prominent dissociative side effects<sup>7</sup>. Inhaled ketamine is a growing topic for healthcare professionals, physicians, and pharmacists all over<sup>9</sup>. It is still in its initial stages of development and not a lot of data is available specific to inhaled ketamine. The next major step in terms of research is to perform clinical trials on a larger scale to assess the safety and efficacy of inhaled ketamine in a wide range of patient populations and numbers.

## ❖ IV ketamine for depression

In a clinical study performed by Berman et al, a single dose of ketamine was used in patients with depression. Seven subjects with major depression completed two test days that involved IV treatment of ketamine hydrochloride at a dose of 0.5 mg/kg infused over 40 minutes and placebo saline. The treatments were separated by at least 1 week. Subjects who were treated with ketamine showed significant improvement in depressive symptoms within 72 hours. HDRS (Hamilton Depression Rating Scale) scores were found to be significantly reduced. Studies have shown that 60-70% of people with treatment resistant depression respond to ketamine. One common side effect of other antidepressants is the risk of suicide, not so with ketamine. Ketamine trips are known to make people feel like there is a disconnect from their bodies and their thoughts and this has been reported on several occasions. There is the issue of dependence, and long-term use has been linked to bladder toxicity and cognitive problems in individuals who abuse ketamine recreationally. Another drawback is the effects of ketamine are temporary; depressions eventually will resurface, and patients will need infusions every few weeks (typically 6).<sup>1</sup>

There are studies and case reports on intravenous ketamine in the treatment of refractory depression with related results on safety and efficacy of ketamine. Low-dose ketamine infusion of 0.5 mg/kg in normal saline (over 40 minutes) has been shown to significantly improve depressive symptoms within 1-2 hours in refractory depression<sup>1-2</sup>. Relief of symptoms occurred within hours post-infusion. Adverse effects of IV ketamine include confusion, dizziness, euphoria, perceptual disturbances, and increased blood pressure- all lasting between 1-2 hours<sup>2</sup>. Peak effects were seen 1-2 days later and lasted up to one week. Repeated infusion-maintained effects almost up to two weeks<sup>3</sup>. Intravenous ketamine (0.5 mg/kg) produces robust, rapid and long-lasting antidepressant effects. There are no studies available on the use of transdermal ketamine for refractory depression.

A case report of a 55-year old male with treatment-resistant major depression and co-morbid alcohol and benzodiazepine dependence was treated with 0.5 mg/kg IV infusion of ketamine over 50 minutes. His Hamilton Depression Rate Scale (HDRS) dropped more than 50% from severely depressed to mildly depressed within two days of therapy. Immediately post-infusion, the patient reported feeling less depressed and his mood continued to improve over the next few hours. Symptoms of dizziness and dissociation were reported 25 minutes into the infusion and lasted two hours post-infusion. No other adverse events were reported<sup>4</sup>.

This original article was published in JAMA Psychiatry in 2007 to determine whether rapid antidepressant effects can be seen using a NMDA antagonist in patients with major depressive disorder. Eighteen patients with Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-IV) treatment resistant major depressive disorder were given an IV infusion of either ketamine (0.5 mg/kg) or placebo on two test days a week apart. Subjects were rated at baseline, 40, 80, 110, and 230 minutes and on days 1, 2, 3, and 7 post-infusion. Changes in scores on the 21-item HAM-D rating scales were measured. The results indicated that patients showed significant improvement in depressive symptoms within 110 minutes after injection compared to those who were given placebo. The results show that 71% met response and 29% met remission criteria the day following ketamine infusions, 35% maintained response for at least a week<sup>9</sup>.

## 2. Juvenile Bipolar Disorder

### ❖ Intranasal ketamine for juvenile bipolar disorder

Fear of Harm (FOH) is a pediatric onset phenotype of bipolar disorder (BD) characterized by BD plus treatment resistance, separation anxiety, aggressive obsessions, parasomnias, and thermal dysregulation. Intranasal ketamine (InK) in 12 youths with BD-FOH produced marked improvement during a two-week trial. Here we report on the open effectiveness and safety of InK in maintenance treatment of BD-FOH from the private practice of one author.

Sixty patients who met DSM-IV criteria for bipolar disorder as well as the Fear of Harm (FOH) phenotype and demonstrated treatment resistance to traditional mood-stabilizing agents and atypical neuroleptics, were ascertained through the private practice of one of the authors (DFP). Written consent of patients was obtained after informed consent was provided about the risks of short-term and long-term ketamine. As part of a thorough clinical appraisal, information on side-effects and effectiveness was obtained from patients (if aged 18 or older) or parents through regular clinical contact and a retrospective survey. All patients were treated with InK and closely followed for 3 months to 6.5 years.

Patients were administered InK, as 0.1 ml sprays of 50–200 mg/ml ketamine in 0.01% benzalkonium chloride to alternating nostrils. Patients were instructed to administer sprays until a minimum intolerable dose (MID) was found and to repeat this administration every 3–4 days. If a satisfactory clinical response was not sustained for at least 3 days (as determined by twice weekly clinical evaluation), doses were raised incrementally by increasing the number of intranasal sprays until a new MID was achieved, or there was an 80% or greater reduction in symptom severity. InK every 3–4 days at sub-anesthetic doses appeared to be a beneficial and well-tolerated treatment. Use of InK may be considered as a tertiary alternative in treatment refractory cases.<sup>49</sup>

## 3. Post-Traumatic Stress Disorder (PTSD)

### ❖ IV ketamine for PTSD

Patients with chronic PTSD were enrolled between May 2009 and December 2012. Eligible participants were between 18 and 55 years of age, had a primary diagnosis of PTSD assessed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Patient Version 2.0 and a score of at least 50 on the Clinician-Administered PTSD Scale (CAPS). Exclusion criteria included a lifetime history of psychotic or bipolar disorder, current bulimia or anorexia nervosa, alcohol abuse or dependence in the previous 3 months, serious unstable medical illness or sleep apnea, active suicidal or homicidal ideation on presentation, or current use of any psychotropic medications. All patients underwent a physical examination and laboratory screening, including routine hematologic, biochemical, and urine toxicology testing, as well as undergoing electrocardiography to rule out unstable medical illness and active substance use. To receive the second IV infusion, a CAPS score of at least 50 was required prior to the second infusion.

Study participants were free of concomitant psychotropic medications for 2 weeks prior to randomization and for the duration of the study. For each procedure day, patients were assigned to receive a single IV infusion of ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg), administered over 40 minutes. The order of infusions (ketamine then midazolam or midazolam then ketamine) was randomly assigned, and administrations were 2 weeks apart. Midazolam was chosen as the active placebo control because its pharmacokinetic parameters and nonspecific behavioral effects are similar to those of ketamine. Only the research pharmacy was aware of drug identity, and all study personnel, including investigators, anesthesiologists, raters, patients, and data analysts, were blinded to randomization order.<sup>46</sup>

Monitoring of pulse and blood pressure, pulse oximetry, and electrocardiographic monitoring were instituted (see Murrough et al<sup>47</sup> for details). Ratings were administered by a trained rater during infusions and 40, 120, and 240 minutes after infusion. A different trained rater, blinded to the ratings conducted during and after infusion on infusion days, administered ratings at pre-infusion baseline and 24 hours (day 1) after infusion (before patients were discharged from the hospital), 48 hours (day 2) after infusion, 72 hours (day 3) after infusion, and 7 days (day 7) after infusion. Ratings were also administered 10 and 13 days after infusion, although data analyses focused on the first week after infusion owing to the expected duration of ketamine action. Patients were instructed to abstain from taking psychotropic medications and from using alcohol or substances of abuse for the duration of the trial. As already described, patients who scored 50 or higher on the CAPS 2 weeks after the first infusion received an infusion of the second study drug. Patients whose symptoms remained significantly improved 2 weeks after infusion (indicated by a CAPS score of <50 at 2 weeks) were considered to have completed the study after 1 infusion.<sup>46</sup>

Of 57 potential participants who completed informed consent procedures, 41 met eligibility criteria and were randomly assigned to receive ketamine or midazolam during the first infusion. All 41 patients received study medication and completed 24-hour ratings; 29 of them completed both infusions and ratings following each infusion. Of the remaining 12 participants, 6 (all of whom had been randomly assigned to receive ketamine first) completed the study at 2 weeks, following only their first infusion and ratings, because their CAPS scores were less than 50 at 2 weeks, precluding the second infusion. Two additional participants also had a CAPS score of less than 50 at 2 weeks, one who received ketamine first and the other who received midazolam first, but they both received their second infusion a week later.

#### ❖ Oral and SL ketamine for PTSD

This study represents the largest retrospective review of patients receiving long-term oral ketamine for treatment-resistant depression and post-traumatic stress disorder (PTSD). Our purpose was to examine the safety and efficacy of oral ketamine therapy in an outpatient setting as measured by changes in hospitalisation for psychiatric episodes. Methods Hospital records of 37 patients who received oral ketamine treatment were reviewed to compare the number and duration of psychiatric hospital admissions before and after treatment. Records were also screened for adverse medical events and changes in ketamine dosage over time. Results Following treatment, inpatient hospital days were reduced by 70%, and hospital admissions were reduced by 65%. The dose of ketamine

patients required was stable over time with no evidence of tolerance building. There were no serious adverse events and no long-term negative effects associated with ketamine.

Treatment of: Dosage began at 0.5 mg/kg and was titrated up by 20–50% at each subsequent treatment. During the titration period, participants were given ketamine twice daily, 3 h apart. This was conducted at most twice per week. After titration was complete, they received treatment between twice weekly and fortnightly. Titration was deemed complete when the patient exhibited transient signs of psychotropic effects—often described as a ‘glass of wine’ feeling. Additionally, any other systemic effects, such as a change in blood pressure, would mark titration as complete. Final doses ranged from 0.5 to 7.0 mg/kg. Doses were adjusted throughout the course of therapy to target minimum threshold psychoactive effects. All participants continued to use their usual medication initially, but many required adjustments to their regime depending on their response to ketamine augmentation. During the maintenance phase of treatment, participants attended the clinic between weekly and fortnightly.

Conclusion: Oral ketamine offers a promising pharmacologic adjunct to depression treatment. It may offer a more approachable alternative to IV or IM ketamine. The results warrant further investigation into the safety and efficacy of oral ketamine for psychiatric treatment.<sup>48</sup>

## 4. Pain

Ketamine can be used for several types of pain, such as migraines, neuropathic pain, and general analgesia. Ketamine is a non-competitive NMDA receptor antagonist that has a different mechanism of action than conventional nociceptive drugs. The following are other ways ketamine control pain:

- Progressive changes in neuronal excitability in central sensitization
- Development of allodynia, hyperalgesia, or other neuropathic pain symptoms
- Reduction in opioid analgesia
- Development of tolerance

### ❖ Oral ketamine for pain

**Neuropathic pain:** Enarson and colleagues evaluated the analgesic benefits of oral ketamine as an adjunct therapy in 21 patients with chronic neuropathic pain who have been unresponsive or poorly responsive to standard analgesic therapies<sup>11</sup>. The starting dose was 100 mg/day in divided doses. Titration was done every 2 days in increments of 40 mg/day until clinical efficacy was obtained, or side effects became limiting. After the titration, the final doses were between 140-500 mg/day, with a median dose of 220 mg/day. Discontinuation of ketamine in nine patients were due to psychomimetic symptoms (“elevator” effect, dissociative feeling), alertness disturbances (somnia or insomnia), and sensory changes (taste changes, numbness, tingling, hot, cold). Nevertheless, the analgesic benefits of ketamine were demonstrated in some patients as improvements in pain, mood, energy, activity, and sleep<sup>11</sup>.

**Pain in children:** The analgesic efficacy was examined in children requiring laceration repair. Qureshi found that oral ketamine at a dose of 10 mg/kg was effective in sedation and analgesia for young children between the ages of one and seven years old. The ketamine-treated group demonstrated a significantly greater tolerance to suturing in comparison to the placebo group<sup>4</sup>. Additionally, according to Lexi.com, the oral pediatric dosing for the unlabeled use of sedation is 6-10 mg/kg for one dose. There is a minor drug interaction between ketamine and Suboxone (buprenorphine and naloxone). The concomitant use of ketamine and other CNS depressants may potentiate CNS depression and/or increase the risk for respiratory depression. If combined with another NMDA antagonist such as memantine, additive effects may be observed<sup>12</sup>.

#### ❖ **Sublingual ketamine for pain**

##### **Combination of oxytocin and ketamine for pain:**

Innovative approach to treat intractable pain in patients who are taking a high number of opiates: SL Oxytocin 40 units/ ml using 0.5ml then 15 minutes later using Ketamine 12.5 to 25mg SL. Oxytocin is a natural pain reliever that is produced in the hypothalamus. It is naturally released in pregnant women during labor and in any stressful events. Oxytocin usually binds to their receptors in the brain and stimulates endogenous opioid release. Furthermore, oxytocin lowers serum cortisol, which is often called “stress hormone”, therefore, it can improve your mood. Ketamine has psychomimetic and euphoric properties which may have a high potential for abuse. Therefore, only low-dose ketamine should be added to oxytocin for treating intractable pain. A study has shown that sublingual oxytocin and ketamine may be effective for treating the pain. First, five patients received 20 units of SL oxytocin and they reported some pain relief within 10 minutes. 15 minutes later, the patients received 0.25 to 0.50 ml (12.5 to 25mg) of SL Ketamine. As a result, two patients became completely pain free. The pain relief lasted about 4 hours with no side effects for the rest of the patients. One of the patients also stopped taking opioids when she started this combination therapy. As a result, this new combination therapy can be useful for the patients who are addicted to opioids. It can also possibly overcome the issue of drug addiction. However, the study was very small and further researches are highly required to find significant therapeutic effect on intractable pain<sup>43</sup>.

#### ❖ **Intranasal ketamine for pain**

**Postoperative pain:** Christensen et al. Evaluated intranasal ketamine at 10 mg, 30 mg, and 50 mg doses in acute postoperative pain. Statistically significant analgesia was achieved with 50 mg and was superior to placebo. Rapid onset was reported as less than 10 minutes and pain relief was achieved within 15 minutes of the 50 mg dose. Safety – adverse events were considered mild and transient and resolved within 60 minutes following administration of the medication; most frequently reported adverse events included transient hypertension, difficulty concentrating, burning sensation in the throat or nose, tachycardia, nausea and vomiting; no auditory or visual hallucinations but 5 patients had feelings of unreality; 1 patient experienced “kinetic hallucinations”<sup>14</sup>. Total dose used in the studies was 50 mg of ketamine used intranasally. It is tolerable with mild and transient adverse events that resolve within 60 minutes of administration. A formula is available through PCCA for a 100 mg/mL nasal spray with benzalkonium chloride as the preserved water (#7836).

**Break-through pain:** The efficacy and safety of intranasal ketamine for break-through pain (BTP) was studied in a randomized, double-blind, placebo-controlled, crossover trial. Twenty patients with

chronic pain and at least two spontaneous BTP episodes daily self-administered up to five doses of intranasal ketamine or placebo at the onset of a spontaneous BTP episode (pain intensity >5 on a 0-10 scale). Each dose was 10 mg. Two BTP episodes at least 48 hr. apart were treated with either ketamine or placebo. Patients reported significantly lower BTP intensity following intranasal ketamine than after placebo  $P < 0.0001$ ; with pain relief within 10 min of dosing and lasting for up to 60 min. No patient in the ketamine group required his/her usual rescue medication to treat the BTP episode, while seven out of 20 (35%) patients in placebo group did ( $P = 0.0135$ ). Intranasal ketamine was well tolerated with no serious adverse events. However, four patients reported a transient change in taste, one patient reported rhinorrhea, one patient reported nasal passage irritation, and two patients experienced transient elevation in blood pressure.

Carr et al. Evaluated safety and efficacy of ketamine administered by intranasal route for breakthrough pain. Study drug was formulated with 10% aqueous solution of ketamine hydrochloride, with 0.002% benzalkonium chloride as the preservative vehicle in the nasal 0.1 mL metered pump. This pump delivered a total of 10 mg of ketamine hydrochloride. Patient would administer one spray into the nostril up to a maximum of five separate sprays in alternating nostrils, or until pain relief was achieved; 90 second-intervals between sprays. Maximum total dose was 50 mg of ketamine hydrochloride. Significant analgesic superiority seen in ketamine group over placebo as early as 10 minutes and persisted for 60 minutes after administration. Safety tolerable; the only reported adverse events were transient change in taste, rhinorrhea, nasal passage irritation, and transient elevation in blood pressure; no auditory or visual hallucinations but 1 patient had feelings of “unreality”<sup>13</sup>.

**Intranasal administration for children:** Currently, Ketamine intranasally has been studied as a premedication option in children for tonsillectomy or other dental procedures. Natan Weksler first reported using ketamine nose drops (5 mg/kg) when oral ketamine was refused by children<sup>40</sup>. Another study by Abrams and colleagues, reviews the safety and effectiveness of intranasal administration of ketamine, midazolam, and sufentanil for urgent brief pediatric dental procedures. This study used intranasal ketamine at 3 mg/kg in which ketamine had a mean sedation score of 4 (on a scale of 5) and a short recovery period (7 +/- 7 min). Two children experienced brief measure in low blood oxygen concentration<sup>41</sup>. Aldrete and colleagues are studying possible applications of intranasal ketamine administration with various dosage forms. Currently, a study regarding three different doses of intranasal ketamine is underway. Results of Phase I show intranasal ketamine is fast-acting, with onset of pain relief occurring within 2 to 10 minutes following administration. In addition, analgesic effectiveness and duration of effect depend on the dose and intranasal ketamine appears safe and well tolerated.

**Intranasal for migraines:** Performed a double-blinded, randomized parallel-group controlled study investigating the effect of 25 mg intranasal ketamine on migraine with prolonged aura in 30 migraines using 2 mg intranasal midazolam as an active control. Each subject recorded data from 3 episodes of migraine. Eighteen subjects completed the study. Ketamine reduced the severity ( $p = 0.032$ ) but not duration of aura in this group, whereas midazolam had no effect. The aim of the study was to test the hypothesis that ketamine would affect aura in a randomized controlled double-blind trial, and thus to provide direct evidence for the role of glutamatergic transmission in human aura<sup>44</sup>. Another study looked at intranasal ketamine in 18 patients with migraines with prolonged auras. They were treated

with 25mg of intranasal ketamine and the ketamine reduced the severity but not the duration of the aura in the migraines<sup>10</sup>.

#### ❖ Topical ketamine for pain

Ketamine topical is in the literature for multiple treatments of various kinds of pain (neuropathic, local, surgical, spinal, etc.). There is a plethora of information about how ketamine is a viable option for all types of pain. There are also increasing evidences that support the efficacy of topical preparations in blocking nociceptive and neuropathic pain. Topical administration reduces the pill burden and increases patient compliance and adherence to medications. Ketamine is a noncompetitive NMDA receptor antagonist with opioid activity. Its analgesic effects rely on glutamate receptor activity, voltage-sensitive calcium channel blockage, interference with opioid receptors, and cholinergic and monoaminergic functions. Ketamine hydrochloride is Food and Drug Administration (FDA) approved for intravenous and intramuscular use and comes in three forms of liquid, powder, and tablet. Small trials indicate that 0.5 - 1 % ketamine cream may benefit postoperative, sympathetically maintained and cancer pain when applied topically<sup>16</sup>. One case report used 0.5% ketamine cream and it showed efficacy for pain relief and improve of quality of life.

Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndrome. A double-blind, randomized placebo-controlled 3-week study was done to evaluate the efficacy of topical 2% amitriptyline, 1% ketamine, and a combination of both in treating patients with neuropathic pain. 92 patients with diabetic neuropathy, postherpetic neuralgia, or postsurgical/posttraumatic neuropathic pain with allodynia, hyperalgesia, or pinprick hypesthesia were randomly assigned to receive 1 of 4 creams (placebo, 2% amitriptyline, 1% ketamine, or a 2% amitriptyline-1% ketamine combination). The primary outcome measured was the change in average daily pain from baseline to final week using an 11 -point numerical pain rating scale. The results indicated a decrease in pain scores of 1.1-1.5 units in all groups and there was no significant difference between the groups. The conclusion was that since there was no difference among the groups, they are viable options for pain relief<sup>17</sup>.

**Topical ketamine for chemotherapy induced peripheral neuropathy:** A double blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: The purpose of this study was to evaluate a novel compounded topical gel for the treatment of chemotherapy induced peripheral neuropathy (CIPN). Patients with CIPN were randomized into three groups: baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in a placebo (PLO) organogel versus a placebo to determine its effect on numbness, tingling, pain, and function. The primary outcome measured was the baseline-adjusted sensory subscale of the EORTC QLQ-CIPN20 at 4 weeks. The results of the 208 patients in this study revealed a trend that showed greater improvement in the placebo organogel versus placebo in both the sensory and the motor subscale. There were no undesirable toxicities associated with the organogel PLO and no evidence of systemic toxicity. The conclusion of this study is that treatment with the organogel PLO appears to improve symptoms of CIPN, it is well tolerated, and has no evidence of systemic toxicity<sup>18</sup>.

**Painful diabetic neuropathy** remains a difficult pathologic condition to manage effectively despite numerous pharmacologic interventions. A randomized, placebo-controlled, double-blind study was undertaken to determine whether topical 5% ketamine cream is effective in reducing the pain of diabetic neuropathy. Seventeen diabetic patients completed the study. The Michigan Neuropathy Screening Instrument was used to determine whether the neuropathy was likely caused by the

diabetic condition. Patients applied 1 mL of either ketamine cream or placebo cream for 1 month. The intensity of seven different pain characteristics was evaluated before and after treatment. A two-way repeated analysis of variance design was used to test for differences between treatments and within patients (time). The authors found no significant treatment effect, but pain improved significantly over time in both groups. There was no statistical interaction effect (treatment × time) in any of the pain characteristics, indicating that pain improved in the two treatment groups similarly with time<sup>20</sup>.

#### ❖ Intravenous ketamine for pain

Cluster headaches happen in cyclical patterns or clusters and are an extremely painful type of headache. Ketamine could be used to control the pain of the headaches but has not been studied in treating the condition of cluster headaches, specifically. Intravenous and intranasal ketamine have been studied in migraines. In chronic migraine sufferers, a retrospective review was performed of 77 patients who had IV administration of ketamine with a mean length of time of 4.8 days. Most patients tolerated it well with some adverse events reported but limited serious side effects<sup>23</sup>. Another retrospective report looked at six patients who received IV ketamine with refractory migraines with infusions that started at 0.1 mg/kg/hr. and increased by the same amount every 3-4 hours as tolerated titrated to a pain score. All patients tolerated the ketamine well<sup>24</sup>. Although there is no data for ketamine in cluster headaches, it has been studied for breakthrough pain in patients with chronic pain.

## 5. Complex regional pain syndrome (CRPS):

#### ❖ Intravenous ketamine for CRPS

Complex regional pain syndrome is a chronic, longer than 6 months pain, which mostly affects one, limb. Typically, this is seen after an injury. It is believed to be caused by damage to or malfunctioning of the PNS and CNS. A prolonged or excessive pain and changes in skin color, temperature and/or swelling in the affected area (NIH, 2017) categorize CRPS. Reflex Sympathetic Dystrophy (RSD) (also known as complex regional pain syndrome (CRPS), causalgia, and Sudeck's atrophy) has two types associated with this disease. Type I does not demonstrate nerve lesions, whereas Type II has obvious nerve damage. Topical therapy with ketamine hydrochloride, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist appears to be beneficial in providing analgesic effects in patients with reflex sympathetic dystrophy. In a case study by Gammaitoni et. al., topical ketamine gel was applied to 5 patients (3 of which were RSD patients). Patients reported significant pain relief, alterations in temperature sensation, and feelings of relaxation and decreased tension in application<sup>29</sup>. Reflex Sympathetic Dystrophy (RSD) (also known as complex regional pain syndrome (CRPS), causalgia, and Sudeck's atrophy) is a chronic progressive disease characterized by severe pain, swelling, and over-reaction of pain sensation. Type I does not demonstrate nerve lesions; whereas, Type II has obvious nerve damage. Topical therapy with ketamine hydrochloride, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist appears to be beneficial in providing analgesic effects in patients with reflex sympathetic dystrophy.

A study published in the Archives of clinical Neuropsychology was done to investigate the effectiveness of deep ketamine anesthesia (3–7 mg/ kg/ hr.) for the treatment of pain in patients with refractory CRPS and to evaluate its neurocognitive consequences for immediate and prolonged use.

The study also included measures of mood and personality at baseline and following treatment to assess the degree of change, if any, in emotional symptomatology. The study found that deep ketamine infusion therapy is effective for relief of CRPS. There was a marked reduction in the report of both acute and overall pain after treatment. There were no adverse cognitive effects of extended treatment with ketamine. Brief attention and processing speed improved significantly post-treatment, other cognitive functions tested remained the same<sup>19</sup>.

#### ❖ Topical ketamine for CRPS

In a case study by Gammaitoni et. al., topical ketamine gel was applied to 5 patients (3 of which were RSD patients). Patients reported significant pain relief, alterations in temperature sensation, and feelings of relaxation and decreased tension in application<sup>29</sup>.

In addition, case reports by Ushida et. al., ketamine 0.25%-1.5% ointment was applied to the affected area of 7 patients. Improvement was observed in 4 patients with acute CRPS Type I; however, no apparent changes were noticed in 1 patient with chronic CRPS Type I and in both patients with CRPS Type II. Therefore, topical ketamine seems to be beneficial for patients with acute early stage of CRPS. Whereas, patients with chronic atrophic stage of CRPS and CRPS II patients do not seem to respond to this treatment. Other possible topical alternatives include capsaicin, dimethyl sulfoxide (DMSO), and antidepressants such as doxepin<sup>30</sup>.

## 6. Fibromyalgia:

Fibromyalgia: In simple term, fibromyalgia is a disorder in which skeletal muscle or its adjacent fibrous tissue is painful or becomes so in response to use or physical pressure<sup>20</sup>. There are multiple studies which suggest ketamine does indeed relieve pain caused by fibromyalgia, which include a double blinded, placebo-controlled study by Graven-Nielsen et al., which involved included 17/29 ketamine responders to fibromyalgia on two separate occasions. The study concludes that ketamine can attenuate muscle pain and hyperalgesia and suppress temporal pain summation<sup>22</sup>. Ketamine may be useful for the treatment of fibromyalgia pain due to the regulation of glutamate and glycine at the NMDA receptor. It has been proven to reduce muscle pain as well as referred pain in patients with fibromyalgia.<sup>5</sup> Ketamine can be given intravenously, epidural, intramuscularly, orally, rectally, and intranasal. Reported doses vary greatly depending on the route of administration, from 0.125-3 mg/kg/hr. IV or SC to 20-30 mg/day epidural to 30-1000 mg/day orally or 0.4 mg/kg IM.<sup>6,7</sup> There are no clear dosing guidelines for the use of ketamine in fibromyalgia so clinical trials should be conducted to find the optimum dose and route of administration. The doses are reported in the Ketamine dose chart on pages 3-5.

## 7. Ketamine use for reactive airway disease:

For patients with reactive airways disease: Ketamine by virtue of its bronchodilating property and profound analgesia allowing use of high oxygen concentration is considered to be the IV induction agent of choice in patients with active bronchospasm. Some researchers have found that ketamine not only protected against precipitation of asthma in asymptomatic surgical patients, but it also alleviated bronchospasm in patients with respiratory distress prior to induction of anesthesia

Ketamine is considered the bronchodilator of choice in rescue therapy for refractory bronchospasm in emergency and refractory status asthmaticus in the intensive care unit (ICU). A loading dose of 0.1–0.2 mg/kg followed by an infusion of 0.15–2.5 mg/kg/h can be used in these cases<sup>45</sup>.

## 8. Anesthesia

### ❖ Rectal ketamine for anesthesia

Rectal 9 mg/kg for anesthesia in eight 3-9-year-old patients.

Rectal 5 mg/kg as anesthetic premedication in sixteen 16-48-month patients<sup>45</sup>.

### ❖ Intravenous and Intramuscular ketamine for general anesthesia for induction and maintenance

IV: ≥16 years: increments of one-half to the full induction dose (i.e. 0.5–4.5 mg/kg) IV over 60 seconds and repeated as needed;

IM: ≥16 years: increments of one-half to the full induction dose (i.e. 3.25–13 mg/kg) IM as needed may be used for maintenance.

IM: In children, a dose of 2–4 mg/kg of ketamine has been used as an induction drug in children difficult to manage mentally retarded and patients regardless of age<sup>45</sup>.

For general anesthesia induction:

IV: ≥16 years: 1-4.5 mg/kg IV slowly over 60 seconds, on average, 2 mg/kg will produce 5-10 minutes of surgical anesthesia (if a longer effect is desired, additional increments can be administered IV to maintain anesthesia without producing significant cumulative effects)

IM: ≥16 years: 6.5-13 mg/kg IM, approximately 10 mg/kg will usually produce 12-25 minutes of surgical anesthesia (if a longer effect is desired, additional increments can be administered intramuscularly to maintain anesthesia without producing significant cumulative effects) Transition to anesthesia is sudden and abrupt – “all or nothing”. Implies that if the patient is awake, the drug would be exhibiting its analgesic effects without any anesthesia<sup>45</sup>.

### ❖ Intranasal ketamine for anesthesia

Ketamine use to pre-medicate children for anesthesia: Ketamine in a dose of 6 mg/kg was nasally administered in 86 healthy children, aged from two to five years undergoing elective general, urological or plastic surgery, 20 to 40 min before the scheduled surgery time. These children were compared with 62 others, also aged from two to five years, in whom promethazine and meperidine, 1 mg/kg of each, were injected IM. Sedation was started in 48 and as adequate in 19 children in the ketamine group, compared with nine and 12 respectively in Group 2 (P < 0.05), while salivation was similar in both groups<sup>13</sup>. It was concluded that nasal ketamine is an alternative to IM pre-anesthetic sedation administration.

## 9. Ketamine's effects on seizure activity

The cellular basis of epilepsy is thought to be the paroxysmal depolarizing shift (PDS) that occurs in the seizure foci. This is a change in the threshold of the neurons in the focus of the seizure activity, which makes the neuron more likely to depolarize. This shift has been thought to be mediated by excitatory amino acids (EAA) since increasing the concentration of EAA in the vicinity increases the frequency of PDS, and NMDA receptor antagonists reduce the frequency<sup>38</sup>. Glutamate is an excitatory amino acid, which is thought to be responsible for some seizure-related brain injury. Gamma-

aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. Seizure foci are deficient in this inhibitory neurotransmitter.

Ketamine is typically known as an anesthetic that also provides analgesia. It is a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor, which means it binds to a site on the receptor that is distinctive from the active site and changes the receptors ability to interact with its normal substrate, glutamate. The co-administration of drugs that act as an agonist at the GABA receptor (GABA, muscimol, diazepam, and baclofen) and NMDA receptor antagonists (dizocilpine) with ketamine provide a synergistic anticonvulsant action<sup>39</sup>.

## **10. Long-term effects of ketamine**

As an injectable, the long-term effects have been extensively studied, mostly due to the drugs association with recreational use. In an article by the International Association for the Study of Pain, the authors researched the long-term effects of ketamine on cognition, memory and mood. They found that when ketamine was used in long-term recreational abusers, it produced severe impairment of working, episodic and semantic memory. It also increased schizophrenic and dissociative symptoms for up to three days after use. Dependence and tolerance (without withdraw) with prolonged abuse is also likely to develop<sup>31</sup>. In another study, Doctor Petr Cvrcek studied the side effects of ketamine in the long-term treatment of neuropathic pain. In this study, 32 patients with diabetic polyneuropathy and post-herpetic neuralgia were treated with an initial infusion of ketamine (10 mg in 100 ml of NS infused over 30 min.), followed by three months of oral ketamine therapy (30 mg in 6 ml of NS 5 times per day). Prior to completion of the study, 5 patients withdrew to non-effectiveness and 4 patients withdrew because of intolerable side effects. The most common side effects noted were drowsiness, dizziness, sedation and dry mouth<sup>32</sup>.

As a topical treatment, the long-term effects of ketamine are less studied. It is proposed that ketamine exerts its effects peripherally by action at both the opioid and sodium/potassium channels. In a recent study, Quan et al. studied the effects of long-term (average of 31.8 months) topical ketamine as a treatment option for post-herpetic neuralgia (PHN). In the study, 23 patients with PHN applied topical ketamine gel (5 mg/ml) 2-3 times a day to the affected area. Of the 23 patients, 15 reported significant reduction in pain associated with PHN. During this study, the only reported side effects were 2 cases of transient skin irritation that improved once the drug was discontinued<sup>33</sup>. In an open clinical case trial performed by Gammaitoni and colleagues, the authors evaluated the use of ketamine gel 1% (10 mg /ml) as a possible treatment of neuropathic pain. In 5 cases, using a dose of ketamine determined by site and surface area (range of 0.093mg/kg - 9.33 mg/kg), they found that reduction in pain decreased by 53-100%. During this study, the only adverse effect reported was one case of slight sedation; it should be noted that this patient was also receiving high-dose opioid analgesics, so the origin of the side effect could not be accurately determined<sup>34</sup>.

### **❖ Long-term data for the use of ketamine in severe, treatment-resistant depression**

Depression is a condition that affects millions of people across the world and has severe health and socioeconomic consequences. Current therapies focus on alterations in the pathways of serotonin, norepinephrine, and dopamine. In recent years, the administration of low dose ketamine has shown to be a possible therapeutic alternative in patients suffering from severe, treatment-resistant depression. Ketamine is a potent antagonist of the N-methyl-D-aspartate receptor. This mechanism

allows for an increase in glutamate transmission. The effects of this medication produce an antidepressant effect within hours compared to current therapy, which typically takes 6 to 8 weeks<sup>35</sup>. Evidence supporting the use of low dose ketamine in patients with depression is available; however, there are currently no randomized controlled studies supporting the long-term use of this medication. A few case reports have shown the utility of ketamine in patients with depression.

Messer and colleagues reported a case of a 46-year old female with major depressive disorder (MDD) who had received successive interventions over 15 years, which included the use of 24 psychotropic medications and 273 electroconvulsive therapies (ECT). All interventions during this time failed to produce remission in the patient. After multiple failures of ECT and pharmacological therapy, patient was counseled on the use of single dose ketamine and consented to treatment. Ketamine was administered at 0.5 mg/kg of ideal body weight (IBW) over 40 minutes. After administration, there was a significant reduction in the Beck Depression Inventory (BDI) with a decrease in score from 22 to 6. Patient was initially provided with a customized ketamine administration schedule which had periods of remissions lasting anywhere from 16-28 days. Ultimately, the patient ended up on a 0.5 mg/kg IBW dose given at 3-week inter-dose intervals. At this maintenance dose, the patient remained in remission for >15 months with no significant adverse events<sup>36</sup>.

Kwon and colleagues reported a case of a 49-year old female with a 6-year history of treatment-resistant major depression. During this time, the patient received quetiapine, desvenlafaxine, trazodone, lorazepam, aripiprazole, and 10 ECTs with no improvement. Patient's original Korean Montgomery-Asberg Depression Rating Scale (K-MADRS) was 45/60 (severe depression). Once consent was received, patient was given midazolam 2-5 mg and thiopental sodium 150-200 mg for sedation and reduction of hallucinations associated with ketamine. Ketamine was administered at a dose of 0.5 mg/kg over 40 minutes. Patient had a significant improvement in K-MADRS score (25/60-moderate depression) after the first week of therapy and treatment was scheduled once every 1 to 2 weeks for a total of 10 months. During the treatment duration, the patient did not experience any significant adverse effects except for mild visual and auditory hallucinations, which were short lived<sup>37</sup>.

In conclusion, while data supporting long-term use of ketamine is lacking, these case reports provide evidence that the use of long-term ketamine given at 0.5 mg/kg over 40 minutes is effective in patients who present with treatment-resistant major depression. Further studies are required within this patient population to assess the safety and efficacy of this long-term ketamine administration.

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