

# Sustained Opioid Cessation Following Rapid Opioid Detoxification with Ketamine Infusion Therapy in Veterans a Preliminary Study

Randall J Malchow<sup>1\*</sup>, Jennifer W Baker<sup>2</sup> and Ashley P Yost<sup>2</sup>

<sup>1</sup>Department of Anesthesiology, School of Medicine, Vanderbilt University, Nashville, USA

<sup>2</sup>VA Tennessee Valley Health Care System Murfreesboro, TN, USA

\*Corresponding author: Dr Randall J Malchow, Department of Anesthesiology, School of Medicine, Vanderbilt University, 1301 Medical Center Drive, 4648 The Vanderbilt Clinic, Nashville, USA, Tel: 615-936-3198; Fax: 615-936-6493; E-mail: [malchowrj@comcast.net](mailto:malchowrj@comcast.net)

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## Abstract

**Objective:** The primary outcome of this study utilizing ketamine assisted opioid detoxification is long-term opioid cessation, while secondary outcomes are assessments of opioid withdrawal, pain reduction, and ketamine side effects.

**Design:** Preliminary observational study involving a comprehensive review of a prospectively collected database.

**Setting:** Veterans Affairs Medical Center in Nashville, Tennessee.

**Subjects:** 41 veterans with chronic non-cancer pain and on chronic opioids who received ketamine assisted opioid detoxification.

**Methods:** The authors conducted a review of a real time data collection of forty-one patients who met inclusion criteria. The authors reviewed data collected over a 28-month period (April 2016-July 2018). Following detoxification and the initial ketamine infusion series, the patients were monitored at regular intervals for up to 12 months post-infusion; this monitoring period extended through October 2018 to ensure all patients had at least 3 months of monitoring data.

**Results:** Most veterans remained opioid free long after treatment: 83%, 75%, and 58% at one, three, and six months respectively ( $p=0.0001$ ). Seventy-six percent of patients reported opioid withdrawal as either none or mild severity. Median pain reductions at one and three months were 50% and 40%, respectively. The incidence of troubling ketamine side effects was low.

**Conclusion:** Ketamine assisted opioid detoxification appears to be a safe and effective tool to target opioid misuse and has the potential to decrease opioid consumption, overdose related deaths, and chronic pain.

**Keywords:** Ketamine; Opioid epidemic; Opioid misuse; Detoxification; Chronic pain

## Introduction

The United States is currently battling an ongoing opioid crisis [1]. Opioid use for non-cancer chronic pain, opioid diversion, opioid abuse, and unintentional deaths due to opioid overdose have all increased exponentially over the past 20 years [2-4]. Most recent opioid statistics are staggering with an estimated 11.4 million people misusing opioids and an estimated 130 people dying daily (over 48,000 annually) from opioid overdoses [5]. Opioid misuse and opioid use disorders (OUD) continue to challenge America's veteran population with estimates of chronic opioid use for noncancer pain at over 28% [6,7]. To combat the opioid crisis, the U.S. Department of Veterans Affairs (VA) established the Opioid Stewardship Initiative in 2012, and the Department of Health and Human Services declared opioid abuse as a public health emergency in 2017. In spite of a high prevalence of OUD in veterans, long-term opioid treatment has been shown to be ineffective for many chronic pain patients and may in fact increase

dysfunction and opioid related adverse effects including death [8-10]. In addition, chronic pain patients frequently struggle with a triad of intertwined co-existing disorders including both anxiety and depression [6,11]. Ketamine, with its profound anti-hyperalgesic properties [12], may uniquely benefit all of these codependent conditions. Since most substance abuse treatment centers treat OUD with medication assisted treatment [13], long term opioid cessation is infrequent [14-16]. There is a need to assist with national metrics related to opioid misuse/abuse and to provide an effective, alternative treatment for chronic pain. Given ketamine's anti-hyperalgesic properties, this study sought to establish a novel ketamine assisted opioid detoxification program aimed at safely decreasing opioid use while simultaneously addressing chronic pain.

## Patients and Methods

Study data was prospectively collected and managed using Research Electronic Data Capture, a secure, web-based application designed to support data capture for research studies [17]. After obtaining approval from the VA Tennessee Valley Healthcare System Institutional Review

Board, the authors reviewed data collected from 41 patients over a 28-month period (April 2016-July 2018) who had met inclusion criteria and had undergone rapid opioid detoxification coupled with ketamine infusion therapy. Following detoxification and the initial ketamine infusion series, the patients were monitored at regular intervals for up to 12 months post-infusion; this monitoring period extended through October 2018 to ensure all patients had at least 3 months of monitoring data. The primary outcome was opioid cessation, while secondary outcomes were assessments of opioid withdrawal, pain reduction, and ketamine side effects.

### Patient selection

During the 28-month enrollment period, 169 patients with chronic pain lasting at least 6 months were referred to us for consideration for ketamine infusion therapy for reduction in chronic pain and possible opioid detoxification. Patients were referred primarily from the VA Pain Clinic, but also from a variety of other specialties including neurology, psychiatry/addiction medicine, rheumatology, and primary care. Chronic noncancer pain syndromes could include chronic regional pain syndrome (CRPS), amputation pain, low back pain, neuropathy, head and neck pain, central pain syndrome, radiculopathy, post-surgical pain, and fibromyalgia. From this referral population, 102 patients were excluded from participation in the program either due to specific exclusion criteria or patient declination following a comprehensive medical evaluation including review of radiographic, laboratory, and psychological evaluations, as well as a discussion of the risks, benefits, and alternatives. Exclusion criteria for the program included significant mental illness involving psychosis, symptomatic coronary artery disease, severe heart failure or valvular disease, severe hepatic or renal disease, elevated intracranial pressure, Body Mass Index (BMI)>40, and poorly controlled diabetes mellitus (A1c>9%). Of the remaining 67 patients who qualified and received ketamine infusion therapy, 22 patients who were not on chronic opioids were also excluded from this study. Finally, the analysis defined “intent to treat” as patients who received at least 3 out of the 4 initial ketamine infusions and who were using pure opioid agonists or buprenorphine. In total, 41 opioid-tolerant patients were included for analysis that had undergone rapid opioid detoxification coupled with ketamine infusion therapy.

### Protocol

Initially, to ensure patient safety, all patients were hospitalized for four consecutive days with daily ketamine infusions. In an effort to adhere to Centers for Medicare and Medicaid Services InterQual (Copyright © 2014 McKesson Corporation and/or one of its subsidiaries) criteria for inpatient admission, the need for hospitalization was later based on their level of opioid tolerance and medical co-morbidities. Patients taking greater than 35 Morphine Milligram Equivalents Daily (MMED) were admitted for the four day rapid opioid detoxification daily infusion program; those patients on low dose opioids (<35 MMED) underwent rapid opioid detoxification with a series of four infusions over a ten week period with possible hospitalization for the first 2-3 days depending on patient co-morbidities and social support at home. Patients could return quarterly for “booster” infusions if needed during the monitoring phase. Ketamine infusions were administered over four hours with progressive dosing each day as tolerated. Based on a literature review and Borsook's concept that treatment for chronic pain requires higher dosing than that for depression [18], ketamine infusions were started

at 50-90 mg/hour and progressed daily as tolerated to 50-125 mg/hour on subsequent days depending on patient age and comorbidities. In addition, patients were pretreated with oral diazepam, as well as anti-emetics including ondansetron, dexamethasone, and/or scopolamine. If necessary, additional parenteral sedation including intermittent midazolam or propofol infusion was titrated for agitation or self-reported troubling dreams to a goal of 0 to -2 on the Richmond Agitation Sedation Scale [19]. All potential ketamine induced side effects experienced during each of the infusions were recorded.

### Management of opioids and withdrawal

Extended release opioids were discontinued 72 hours prior to admission and all immediate release opioids were discontinued on the first infusion day; patients who discontinued extended release opioids were allowed to increase their immediate release opioids by 50% during the 72 hours prior to the first infusion if necessary for analgesia. No opioid antagonists were given to precipitate withdrawal. Opioid withdrawal was assessed using the Clinical Opioid Withdrawal Scale (COWS) [20] and was aggressively managed using anti-emetics, anti-diarrheals, anxiolytics (usually oral diazepam as needed for up to one week), oral clonidine for up to two weeks as tolerated, and oral muscle relaxants as needed. After each ketamine infusion, chronic pain was treated with only non-opioid medications including acetaminophen, anti-inflammatories, muscle relaxants, anticonvulsants (gabapentin or pregabalin), antidepressants, and topical analgesics.

### Monitoring phase

Following detoxification and the initial ketamine infusion series, the patients were monitored at regular intervals including one week, one month, three months, six months, and twelve months post-infusion. Patients were monitored at follow up visits either as face to face clinic appointments or via completed telephone encounters. Data collection included current analgesics, pain level assessment, opioid withdrawal side effects, and ketamine side effects. All analgesics and their doses were recorded; this included documentation of opioid utilization. Regular chart reviews and occasional random urine drug screens (UDS) were performed during the monitoring phase to reaffirm a patient's report. Pain level assessment utilized a percent pain reduction compared to baseline.

### Statistical analysis

Sample size was based on our primary outcome of long-term opioid cessation. With a desired effect of at least 50% sustained opioid cessation at 6 months, as well as an alpha of 0.05 and a beta of 0.20, a sample size of 19 patients was required. Continuous variables that were parametric were represented by the mean+SD (Standard Deviation), while non-parametric results were represented by median (IQR-Interquartile range) values. T-test was used for all continuous data. Fisher's exact analysis was used to evaluate categorical data. All analyses were performed using Excel (Microsoft Office 2013) or GraphPad 2018 Software systems.

### Results

#### Demographics

The demographics of the 41 patients are summarized in Table 1. Mean patient age was 53.8 years. Males comprised 85% of the study population. Most patients, 54%, were ASA (American Society of

Anesthesiologists) III status. The mean BMI was 29.6 kg/m<sup>2</sup>. The three most common pain conditions were low back pain (68%), nonspecific (non-CRPS) extremity pain (39%), and head and neck pain (39%). Mean pain intensity score was 6.5/10 with a mean duration of 15 years. Mean MMED was 117.9 mg. Veterans also had a high incidence of comorbid mental health conditions including depression (80%), anxiety (73%), insomnia (66%), and post-traumatic stress disorder (PTSD) (54%). Poly-pharmacy was common with 85% of patients prescribed antidepressants and 68% prescribed anticonvulsants (most commonly gabapentin or pregabalin); while all study patients were taking chronic opioids prior to treatment, types of opioids varied as follows: 85% prescribed short-acting opioids, 59% long-acting opioids, and 5% buprenorphine as well as various combinations.

Demographics, n=41	
Age in years, mean (SD)	53.8 (11.9)
Male, N (%)	35 (85)
ASA II/III, N (%)	19 (46)/22 (54)
BMI mean (SD)	29.6 (4.8)
Baseline MMED, mean (SD)	117.9 (96.6)
Tobacco Use, N (%)	15 (37)
Average pain score, mean (SD)	6.5 (1.5)
Duration of pain in years, mean [SD]	15 (10.2)
Pain Diagnoses, N (%)	
Low back pain	28 (68)
Extremity pain (non-CRPS)	16 (39)
Head and neck	16 (39)
Global body pain/Fibromyalgia	7 (17)
CRPS	4 (10)
Chronic post-surgical pain	4 (10)
Neuropathy	4 (10)
Spinal cord injury	3 (7)
Amputation pain	2 (5)
Mental health comorbidities, N (%)	
Depression	33 (80)
Anxiety	30 (73)
PTSD	22 (54)
Medications, N (%)	
Antidepressants	35 (85)
Opioid-short acting	35 (85)
Gabapentin/Pregabalin	28 (68)
Opioid-long acting	24 (59)
NSAIDs	21 (51)

Muscle relaxant	19 (46)
Topical medications	17 (41)
Other analgesics	14 (34)
Buprenorphine	2 (5)
SD: Standard Deviation; n: total number of subjects; N (%): number (percentage) of subjects in the specific category; ASA: American Society of Anesthesiologists classification; BMI: Body Mass Index; MMED: Morphine Milligram Equivalents Daily; PTSD: Post-traumatic stress disorder; CRPS: Chronic Regional Pain Syndrome; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs	

**Table 1:** Baseline Characteristics.

### Ketamine dosing and protocols

The majority of patients (93%) undergoing rapid opioid detoxification were treated as inpatients with most receiving four consecutive days of ketamine infusions (Table 2); the remaining patients were treated primarily as outpatients with four infusions over a ten-week period.

Protocol (n=41) N (%)	
4 consecutive days	35 (85)
4 days over 10 weeks	4 (10)
Status (n=41)	N (%)
Inpatient	38 (93)
Outpatient	3 (7)
Dosage <sup>a</sup> Mean (SD)	
1 <sup>st</sup> Infusion	311 (50)
2 <sup>nd</sup> Infusion	368 (52)
3 <sup>rd</sup> Infusion	430 (54)
4 <sup>th</sup> Infusion	472 (75)
Overall [mg/kg/hr]	1.08 (0.26)
Booster Administered <sup>b</sup> (n=41) N (%)	
3-4 months	10 (24)
5-8 months	7 (17)
9-12 months	2 (4)
Number of Boosters <sup>c</sup> (n=19) N (%)	
1	12 (63)
2	4 (21)
3 or more	3 (16)
<sup>a</sup> Total dosage of 4 hr infusion in milligrams	
<sup>b</sup> Time in months to first booster infusion after initial series	
<sup>c</sup> Number of booster infusions within Note: 1 <sup>st</sup> year after initial series	
n, total number of subjects; N (%), number [percentage] of subjects in the specific category; SD: Standard Deviation	

**Table 2:** Ketamine Protocol/Dosing.

All patients completed four-hour infusions for each session with progressive mean dosages of 77.5 mg/hr on day one, 92.0 mg/hr on day two, 107.5 mg/hr on day three, and 118.0 mg/hr on day four. Overall mean ketamine dosing was 1.08 mg/kg/hr. Nineteen patients (46%) elected to return for booster infusions within the first year, most frequently presenting three to four months after their first ketamine infusion. Twelve (63%) received only one booster, while three (16%) received four booster infusions during the first year.

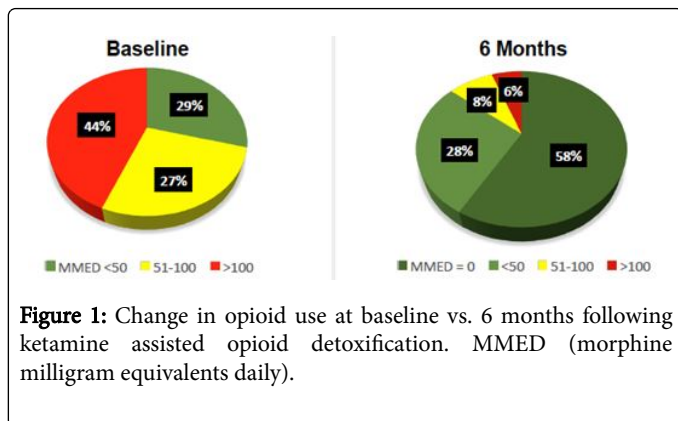
### Opioid cessation-primary outcome

Most patients remained opioid free long-term after their rapid opioid detoxification: 83%, 75%, 58%, and 50% at one, three, six, and

twelve months respectively (p=0.0002) (Table 3). Of the patients who reinitiated opioids following their opioid detoxification, their mean opioid consumption was reduced from 117.9 at baseline to 55.5 and 74.3 at six and twelve months (p=0.0001) representing a 53% and 37% reduction in opioid consumption respectively. In addition, the distribution of MMED doses shifted dramatically from baseline to 6 months: patients consuming less than 50 MMED increased from 29% to 86%, while patients consuming over 100 MMED decreased from 44% to 6% (Figure 1). Comparing opioid types from baseline to twelve months, more patients consumed tramadol/tapentadol (5% vs. 36% respectively) and fewer patients consumed long-acting opioids (59% vs. 36% respectively).

	Baseline	1 week	1 month	3 month	6 month	12 month
<b>Opioid Cessation N (%)</b>						
	(n=41)	(n=41)	(n=41)	(n=40)	(n=36)	(n=22)
On opioids	41 (100)	6 (15)	7 (17)	10 (25)	15 (42)	11 (50)
Off opioids	0 (0)	35 (85)*	34 (83)*	30 (75)*	21 (58)*	11 (50)*
<b>Opioid Reduction <sup>a</sup></b>						
	n=41	n=6	n=7	n=10	n=15	n=11
Mean MMED	117.9	38.8*	48.2*	56.45*	55.5*	74.3*
<50 MMED, N (%)	12 (29)	4 (67)	3 (43)	5 (50)	10 (67)	6 (55)
50-100 MMED, N (%)	11 (27)	2 (33)	4 (57)	4 (40)	3 (20)	4 (36)
>100 MMED, N (%)	18 (44)	0 (0)	0 (0)	1 (10)	2 (13)	1 (9)
<b>Correlations with Opioid Cessation at 6 months</b>						
	Off Opioids (n=21)		On Opioids (n=15)		P value	
Age, average (SD)	55.6 (10.9)		52.6 (12)		0.44	
Male Gender, N (%)	20 (95)		11(73)		0.14	
ASA III, N (%)	13 (62)		5 (33)		0.18	
BMI, average (SD)	30 (5)		27.7 (3.6)		0.12	
Depression, N (%)	16 (76)		14 (93)		0.37	
Anxiety, N (%)	16 (76)		11 (73)		1	
PTSD, N (%)	13 (62)		7 (47)		0.5	
Baseline Pain level, mean (SD)	6.2 (1.6)		6.9 (1.4)		0.16	
Baseline MMED, mean (SD)	87 (71.5)		162.5 (116.9)		0.04	
Ketamine, mg/kg/hr, mean (SD)	1.01 (0.2)		1.23 (0.3)		0.02	
% Pain Reduction, mean (SD)	45.8 (34)		19.4 (32)		0.03	
a. patients reinitiated on opioid therapy *p value<0.0001 †p value=0.0002 n: Total number of subjects; N(%): Number (percentage) of subjects in the specific category; MMED: Morphine milligram equivalents daily; SD: Standard deviation; PTSD: Post-traumatic stress disorder; ASA: American Society of Anesthesiologists classification; BMI: Body mass index						

**Table 3:** Opioid Cessation/Reduction.



**Figure 1:** Change in opioid use at baseline vs. 6 months following ketamine assisted opioid detoxification. MMED (morphine milligram equivalents daily).

We also examined specific variables at six months following detoxification, which could correlate with long term opioid cessation. There was no difference in age, gender, ASA, or BMI. In addition, greater ketamine dosing did not correlate to a higher degree of success.

However, patients taking lower baseline opioids (87 MMED) enjoyed greater abstinence than those patients taking higher doses (162.5 MMED) ( $p=0.04$ ); in addition, those patients who reported a greater reduction in pain had a higher likelihood of remaining off opioids ( $p=0.03$ ).

### Opioid withdrawal

The severity of opioid withdrawal was low during the initial series of ketamine infusions using this rapid opioid detoxification protocol; 76% of veterans described none to mild symptoms based on the COWS (Table 4). One week after detoxification, diarrhea was the most common symptom with 30% of patients reporting this complaint, followed by agitation in 24% of patients, and insomnia in 22% of patients. Diarrhea lingered in some patients with 19% still reporting this symptom at one month, 13% at three months, and 7% at six months. One month following the initiation of ketamine infusions, 97% of veterans reported none to mild symptoms. Other withdrawal symptoms were very infrequent (<3%) at three months.

Opioid Withdrawal Symptoms N (%)								
	Diarrhea	Agitation	Insomnia	Body Aches	Nausea	Leg Jerking	Diaphoresis	Yawning
Days 2-4 (n=41)	6 (15)	10 (24)	6 (15)	7 (17)	4 (10)	6 (15)	3 (7)	4 (10)
1 Week (n=37)	11 (30)	9 (24)	8 (22)	7 (19)	4 (11)	3 (8)	1 (3)	0 (0)
1 Month (n=36)	7 (19)	3 (8)	4 (11)	1 (3)	2 (6)	1 (3)	1 (3)	1 (3)
Opioid Withdrawal Severity N (%) <sup>a</sup>								
	None		Mild		Moderate		Severe	
Days 2-4 (n=41)	11 (27)		20 (49)		9 (22)		1 (2)	
1 Week (n=37)	17 (46)		14 (38)		6 (16)		0 (0)	
1 Month (n=36)	25 (69)		10 (28)		1 (3)		0 (0)	
3 Month (n=32)	27 (84)		4 (13)		1 (3)		0 (0)	
Ketamine Side Effects N (%)								
	Hallucinations (None/Mild)	Polyuria <sup>b</sup>	Urinary Retention	Hallucinations (Disturbing)	Hypoventilation <sup>c</sup>	Nausea and/or Vomiting	Hypotension <sup>d</sup>	Headache
Days 1-4 (n=41)	33 (80)	15 (37)	14 (34)	8 (20)	7 (17)	3 (7)	2 (5)	2 (5)
Based on COWS (Clinical Opioid Withdrawal Scale)								
Polyuria defined as urine output=2 × intravenous fluids								
Hypoventilation defined as needed CPAP								
Hypotension defined as systolic blood pressure<90 mmHg								
Note: n: Total number of subjects; N(%): Number (percentage) of subjects in the specific category								

**Table 4:** Side effects.

### Pain reduction

Following the rapid opioid detoxification utilizing ketamine infusions, most patients reported substantial long-term pain reduction. Median pain reduction at both one week and one month was 50% (IQR=25-65) and at three months was 40% (IQR=10-60). However, at

six months, the mean reduction in pain diminished to 30%, representing a gradual decrease in effect with time.

### Ketamine side effects

Mild hallucinations were common; occurring in up to 80% of patients, while troubling hallucinations that were reported at least once

during their 4-day series, occurred in 20% (Table 4). Urinary complaints were frequent during the infusions with 37% of patients having polyuria (defined as urine output greater than twice the intravenous fluids), and 34% experienced urinary retention. Hypoventilation occurred in 17% of patients, all of whom had obstructive sleep apnea and was effectively treated with application of continuous positive airway pressure, usually at their home settings. Other uncommon side effects included hypotension, hypertension, headache, and nausea, all of which were easily managed. In the monitoring phase, ketamine related side effects were uncommon and fully resolved within three months post-infusion.

## Discussion

This comprehensive retrospective observational study using prospectively collected and audited data provides new evidence that moderate dose ketamine infusions may contribute towards successful opioid detoxification, while simultaneously decreasing chronic pain and opioid withdrawal. These beneficial effects from ketamine-assisted opioid detoxification may be preferable compared to existing techniques including opioid maintenance therapy (OMT) and opioid tapering techniques. While opioid maintenance therapy using methadone or buprenorphine may control opioid administration in patients with opioid use disorders, such treatment does not adequately address the incumbent risks including cardiac arrhythmias, respiratory depression, constipation, opioid diversion, opioid induced hyperalgesia (OIH), tolerance, addiction, physical dependence, death, as well as risks to the fetus in case of parturients on chronic opioids (i.e. intrauterine fetal demise and neonatal abstinence syndrome) [12,21-24]. Interestingly, Uebelacher reported that a majority of patients actually prefer to be "opioid free", rather than choosing OMT, for a variety of reasons, including the goals of minimizing clinic visits, side effects, and complications.

Our success rate of complete opioid cessation of 83%, 75% and 58% at one, three, and six months respectively, as well as a dramatic overall reduction in opioid consumption, compares favorably to current techniques at opioid cessation/detoxification. With opioid tapering techniques, high dropout rates (32%-100%) and high recidivism (45%-90%) are common, especially when depression, high MMED, and increased levels of pain coexist [25-27] such as in our patient population. During an opioid wean, difficulty managing pain, poor coping skills, unrealistic expectations, significant withdrawal symptoms, poor social support, ongoing stressors, pseudo-addiction or addiction, medicolegal issues including diversion and aggravating mental health conditions, and illicit opioid use may contribute to the challenge with opioid tapers. [27,28]. Diaper describes a "mountain of detoxification" with current approaches that is simply too high to climb for many patients, resulting in either disinterest in entering or completing a detoxification program [15]. In addition, our results exceed the latest Consensus Guidelines from the American Society of Regional Anesthesia and Chronic Pain, the American Academy of Pain Medicine, and the American Society of Anesthesiologists on what constitutes a "positive treatment response" involving ketamine infusions for chronic pain, namely a 20% reduction in opioid consumption for at least six weeks [29]. Our finding that a greater ketamine dose was not associated with a higher likelihood of long-term opioid cessation suggests that lower dosing protocols may be equally effective.

Our protocol using ketamine-assisted rapid opioid detoxification was initiated without prior knowledge of previous programs using

ketamine for detoxification, but rather on ketamine's unique ability to abolish OIH after both acute and chronic opioid administration [12,21]. However after protocol initiation, we did identify other studies which support ketamine assisted detoxification. Jovaisa employed ketamine 0.5 mg/kg/hr in a randomized controlled trial with 58 patients undergoing precipitated opioid withdrawal and noted "better control of withdrawal symptoms" in the ketamine infusion group [30]. Quinlan briefly describes a small cohort of chronic pain patients who were treated with chronic opioids using subanesthetic ketamine infusions for five days to assist with opioid withdrawal in patients with chronic pain, opioid tolerance, and OIH; 27% of patients were opioid free at six months and most patients felt "better" for at least the first month after the program [31]. Strickler successfully employed a low-dose ketamine infusion for seven days to assist in a rapid opioid taper in a patient on over 400 MMED [32].

While 25% and 42% of our study patients reinitiated opioids at three and six months respectively, their dose was substantially less than pre-infusion doses, reducing the risk of dose-related opioid side effects. Mean opioid dose of those patients who restarted by six months was 55.5 MMED, representing a 53% decrease in opioid consumption at six months. In addition, patients consuming greater than 100 MMED, a well-recognized dose associated with significant increased risk of respiratory depression, decreased from 44% at baseline to 9% at six months. Ketamine appears to "reset" opioid receptors via N-methyl-D-aspartate (NMDA) receptor antagonism allowing far less dosing needs in the chronic pain patient (i.e. decreased opioid tolerance).

Weiss reported that the major deterrent to opioid cessation in chronic users is the fear of opioid withdrawal; Mattick states that opioid withdrawal can be "immiserating, like a week of bad influenza" [16,33]. With our protocol, 76% of patients had minimal (none to mild) opioid withdrawal during their rapid opioid detoxification. Most symptoms including agitation, insomnia, irritability, nausea, and diarrhea were effectively treated with both symptom directed treatment and clonidine administration as tolerated. Interestingly, other reports demonstrate ketamine's ability to minimize opioid withdrawal partly by decreasing NMDA activation and central nervous system hyperactivity [32,34]. Most opioid detoxification programs employ an opioid taper over months to minimize opioid withdrawal yet may unnecessarily prolong the opioid cessation process contributing to patient dissatisfaction and may still be associated with some opioid withdrawal [15]. The Food and Drug Administration, however, has recently published a Safety Announcement having received reports of serious harm when opioid medicines are discontinued rapidly including serious withdrawal symptoms, uncontrolled pain, and suicide [35]. While we recognize this concern of rapid opioid detoxification without a proper treatment plan or monitoring, we believe ketamine assisted opioid detoxification addresses these concerns by minimizing withdrawal, decreasing chronic pain, and decreasing suicidality [36]. While ultra-rapid opioid detoxification programs using aggressive naloxone administration under general anesthesia to precipitate opioid withdrawal have been associated with significant risks [33], our antagonist-free protocol is well tolerated without serious side effects in our series. Unexpectedly, persistent diarrhea beyond six months was reported in 7% of patients, but was effectively treated with anti-diarrheals, generally diminished with time, and was still associated with high patient satisfaction for the program.

In addition, the fear of worsening pain is also a major deterrent to opioid cessation for patients with chronic pain syndromes [15,16]. Our

ketamine infusion protocol simultaneously assists in opioid withdrawal while treating the patient's chronic pain condition. Rather than increasing pain levels as opioids were discontinued, most patients reported a prolonged reduction in their pain, with a median pain reduction of 50% at one week and one month and 40% at 3 months. As noted, the large standard deviation in our pain reduction data indicates a large variance between individual patient responses, suggesting that some patients or pain conditions respond better than others to ketamine infusions; for example, patients who prefer to remain on opioids may respond differently to this infusion therapy compared to those who truly want to discontinue opioids. The primary mechanism in decreasing pain is ketamine's antagonism of NMDA pain receptors within the central nervous system [37] and reversal of the opioid induced hyperalgesia. [24]. Other studies demonstrate ketamine's effect on decreasing inflammation [38], excitatory amino acids [39], and depression [36,40] as well as modulation of the descending inhibitory pain pathway, all of which contribute to a reduction in chronic pain.

Finally, the above benefits of opioid cessation and decreased chronic pain outweighed the risks involved with ketamine administration. While the greatest fear with moderate dose ketamine infusion therapy is troubling hallucinations, only 20% reported this concern at any time during their four-day infusion. Troubling hallucinations were successfully treated with either increasing sedation or changing from intermittent benzodiazepine use to a low dose propofol infusion. Two (5%) patients reported post-infusion nightmares yet both patients remained highly satisfied and in fact returned for subsequent booster infusions. Besides mild psychomimetic effects, the most common side effects in our series were polyuria (37%) and urinary retention (34%); these symptoms dropped precipitously when low dose vasopressin administration and rigorous bladder monitoring were later added to the protocol. No patient had prolonged urinary symptoms suggestive of interstitial cystitis. In addition, elderly patients in particular reported transient post-infusion confusion (<5%), decreased memory (<5%), and/or falls (<5%) during the first three months, emphasizing the need for careful observation of older patients in the post-infusion period. We have since modified our protocol in patients over 55 years of age by diminishing ketamine dosing, administering only propofol or dexmedetomidine infusion for sedation, and adding cognitive/memory impairment testing to better monitor cognitive status following ketamine administration.

In spite of the significant results, there are certain limitations to this study. Most importantly, this preliminary study is an observational database study involving 41 consecutive patients with real time data collection at a single institution. Therefore, results may have been impacted by a number of variables, which have not been controlled, including patient and provider bias. In addition, ketamine dosing was not dosed by weight but rather by a pre-established protocol based on clinical judgment and a literature review, with flexibility for titration based on age and/or possible side effects. This study did not require scheduled UDS during the monitoring phase nor was the Controlled Substance Monitoring Database checked for opioid prescriptions. However, investigators did utilize random, unannounced UDS as well as regular chart reviews at each monitoring point with verification of no opioid prescription in the electronic medical record. Finally, we recognize the possible economic challenge in applying this government-based model in a private or academic practice. We agree with Bahji who recently discussed the high value of hospitalization in detoxification in order to adequately manage these complex patients with multiple co-morbidities, to minimize withdrawal symptoms with

the use of pharmacologic assistance (e.g. ketamine, clonidine, benzodiazepines), and to provide adequate multidisciplinary support including mental health and chronic pain specialists [41]. Compared to long-term opioids and the need for long-term care, regular close follow-up, costs of complications and side effects [22], and decreased productivity, we believe that this ketamine-assisted opioid detoxification with short-term hospitalization is cost-effective.

## Conclusion

Overall, this study provides new evidence that the utilization of a standardized ketamine infusion protocol coupled with a rapid opioid detoxification is very effective, results in a high rate of prolonged opioid cessation, decreases chronic pain, and minimizes opioid withdrawal, using strictly non-opioid analgesics. Future studies could consider a randomized, controlled trial, although patient and clinician blinding may be challenging. In addition, studies could focus on a dose response curve, identifying the lowest possible dose that is still effective in opioid cessation, as well as determining which patient populations most benefit from ketamine-assisted detoxification. Finally, additional research could focus on the feasibility of application in a strictly outpatient setting to increase external validity and facilitate widespread adoption.

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