

Ketamine: What's Old is New Again

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Conflict of Interest Disclosure Statement

Cornerstone Anesthesia Conference 2019

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- I have the following financial relationships to disclose:
 - I am a Partner in Neuromend Infusion Center, LLC.
- I will discuss the following off-label use during my presentation:
 - Ketamine infusion for non-anesthetic use

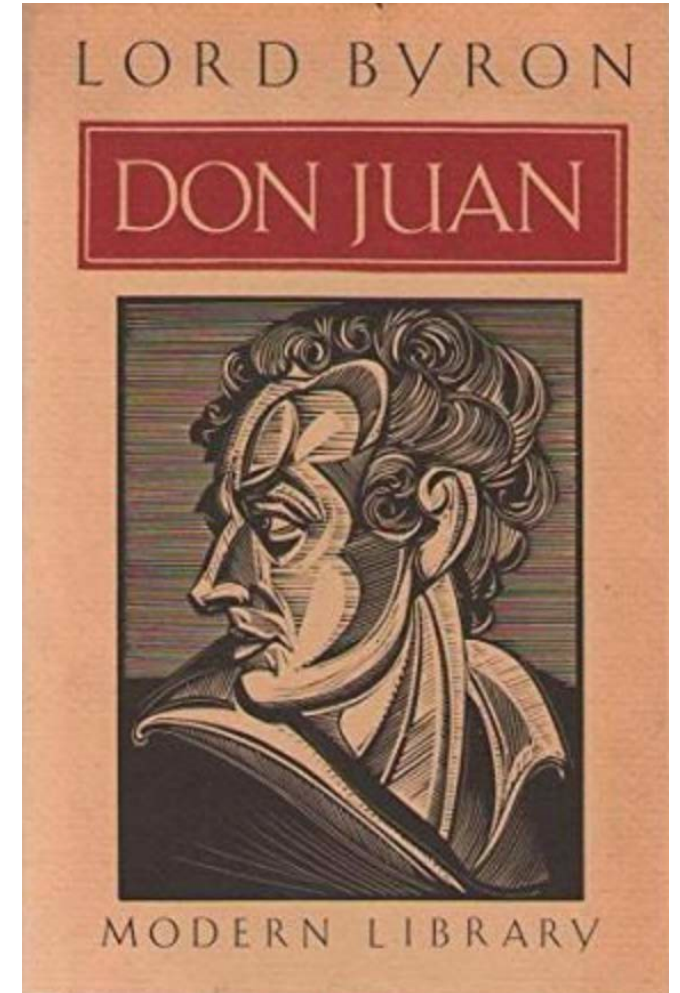
Objectives

- Identify the history of Ketamine
- Discuss the abuse potential for Ketamine
- Describe the mechanism of action of Ketamine
- Discuss common and alternative uses of Ketamine
- Identify studies looking at alternative Ketamine use
- Discuss protocols for Ketamine infusion therapy

What is Ketamine?

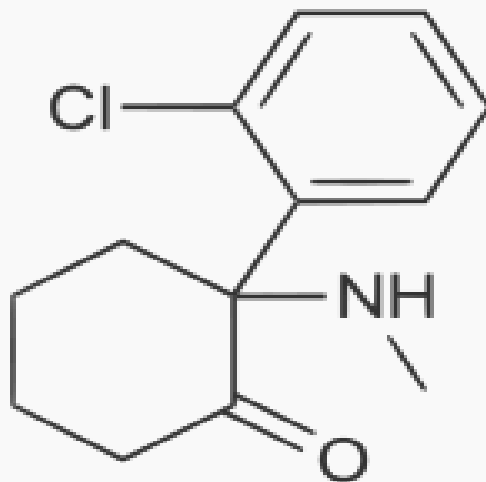
In 1823, Lord Byron wrote in canto 14 of his poem Don Juan “'Tis strange—but true; for truth is always strange; stranger than fiction.”

- Ketamine is a phencyclidine (PCP) derivative
- Classified as an anesthetic and is a schedule III drug in the US
- Depending on dosage, produces a Trance-Like state, pain relief, sedation and memory loss
- Also widely used in veterinary medicine



Chemical Compound of Ketamine

Ketamine



Systematic (IUPAC) name

(RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone

The History of Ketamine

- First synthesized in 1962 by American Scientist Calvin Stevens.
- Originally named CI-581 and was intended as an anesthesia drug
- Derived as a derivative of PCP which was first synthesized in 1926.
- Ketamine was intended to replace PCP because PCP caused prolonged and severe hallucinations and psychotic symptoms

The History of Ketamine

- First clinical use was in Belgium in 1963 as a veterinary anesthetic.
- First Human testing was in 1964 where it was found to have a shorter duration and less hallucinogenic side effects than PCP
- First known recreational use of Ketamine was in 1965 by noted Professor Edward Domino who noted potent psychedelic effects and coined the term “Dissociative Anesthetic”.

Story of Early Ketamine Abuse

Dr. Domino published an intriguing tale about the early days of Ketamine in “Anesthesiology: The Journal of the American Society of Anesthesiologist” in 2010 named “*Taming the Ketamine Tiger*”.

One such story involved Marcia Moore, a yoga instructor, and Dr. Howard Alltounian, a respected clinical Anesthesiologist, and how they met through self administration of Ketamine in 1978.

Anesthesiology 9 2010, Vol.113, 678-684. doi:10.1097/ALN.0b013e3181ed09a2

The Ketamine Tiger



Ketamine Addiction

- **Ketamine**—also referred to as Special K, Kit Kat, cat valium, Dorothy or Vitamin K—is an anesthetic for humans and animals that is abused as a recreational drug. It is especially popular in the club scene among young adults.
- **Ketamine** is a Schedule III Controlled Substance, the same category as codeine and anabolic steroids. Schedule III substances can lead to physical dependence, but are very likely to lead to psychological dependence.
- **Ketamine** has a short-lived high and tolerance to the drug builds up quickly, requiring user to keep increasing quantities as they chase the initial high.
- **Ketamine** is produced as a liquid, which can be injected; as a white or off-white powder, which is snorted by abusers; or as a pill. It has been used as a date rape drug because it is odorless and colorless and is not detected by the victim in a beverage, often rendering its victim completely helpless.

Current Ketamine Abuse

74
percent

According to the Department of Justice's National Drug Intelligence Center, individuals aged 12 to 25 accounted for 74 percent of the ketamine emergency department visits in the United States in the year 2000.

2.3
million

According to the 2013 National Survey on Drug Use and Health in the United States, an estimated 2.3 million people aged 12 or older used ketamine in their lifetimes, with 203,000 users in 2013.

3
percent

In 2006, the University of Michigan's Monitoring the Future survey showed three percent of high school seniors had used the drug at least once that year.

Mechanism of Action of Ketamine

- The focus of all modern drug development has been on specificity and affinity. Scientist strive to isolate compounds that interact specifically with targeted receptors and have a high degree of binding to the target receptors.
- This produces “Clean” drugs that produce consistent actions and limited adverse reactions or side effects that could occur from multiple receptor stimulation.

Mechanism of Action of Ketamine

Known actions of ketamine include:

- [Non-competitive antagonist](#) of the [NMDA receptor](#) (NMDAR)
- [Negative allosteric modulator](#) of the [nACh receptor](#)
- Weak [agonist](#) of the [μ-opioid](#) and [κ-opioid receptors](#) (10- and 20-fold less affinity relative to NMDAR, respectively), and very weak agonist of the [δ-opioid receptor](#)
- Agonist of the [D₂ receptor](#)
- Weak [mACh receptor](#) antagonist (10- to 20-fold less affinity relative to NMDAR)
- [Inhibitor](#) of the [reuptake](#) of [serotonin](#), [dopamine](#), and [norepinephrine](#)
- [Voltage-gated sodium channel](#) and [L-type calcium channel blocker](#), and [HCN1 channel](#) blocker
- [Inhibitor](#) of [nitric oxide synthase](#)
- [σ receptor 1 and 2](#) agonist (μM affinities).
- Activation of AMPA receptors (producing Glutamate surge)

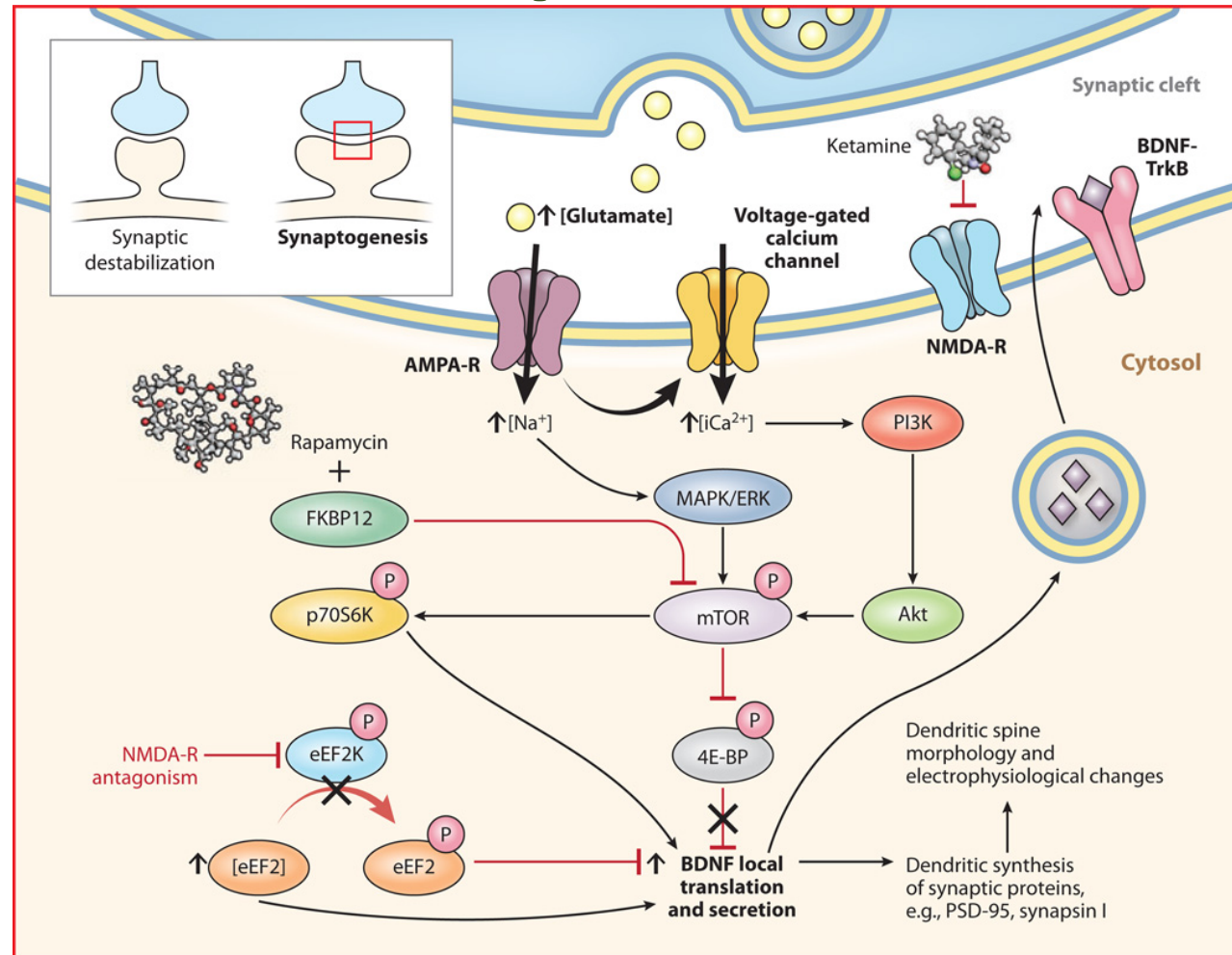
Mechanism of Action of Ketamine

Depression Mechanism of Action:

Scientists think they have isolated the series of reactions that produces ketamine's rapid relief of refractory depression in a large number of test subjects.

The activation of AMPA receptors which is part of the glutamate receptor complex is now thought by some scientists to be the mechanism of action that rapidly relieves patients of severe refractory depression.

Ketamine Mechanism of Action on Depression



Ketamine Mechanism of Action for Depression

- Synaptic and intracellular processes activated by the rapid-acting antidepressant ketamine. Preliminary preclinical and unpublished clinical data suggest that postsynaptic NMDA receptor antagonism increases presynaptic glutamate release (i.e., glutamate “surge”). Glutamate is then hypothesized to increase AMPA/NMDA receptor flux. AMPA channel opening in the CNS increases sodium and, indirectly, calcium, stimulating the PI3K cascade
- In sum, the translational activation induced by acute NMDA receptor blockade increases the expression of several neuromodulatory proteins involved in, among other effects, postsynaptic scaffolding, neurotransmitter dynamics, and dendritic spine morphogenesis from synaptically unstable filopodia to synaptically dynamic mushroom-shaped spines (see previous image), which form the morphological substrate for antidepressant-like behavioral effects.

Ketamine Mechanism of Action for Depression

While glutamate surge is still considered the primary mechanism of action in relieving depression, new studies have looked at how or why glutamate and ketamine is effective.

Scientists in China are looking at a region of the brain called the lateral habenula (LHb) which acts as the dark twin of the pleasure centers of the brain.

In depressed rats, the LHb was hyperactive and often sent burst signals to the rest of the brain. After an injection of ketamine into the LHb reduced the amount of burst signals being sent.

Ketamine blocks bursting in the lateral habenula to rapidly relieve depression: [Yan Yang](#), [Yihui Cui](#), [Kangning Sang](#), [Yiyan Dong](#), [Zheyi Ni](#), [Shuangshuang Ma](#) & [Hailan Hu](#)

Nature **volume554**, pages317–322 (15 February 2018)

Ketamine Effect on CNS

- The NMDAR antagonism is responsible for the anesthetic, amnestic, dissociative, and hallucinogenic effects of Ketamine.
- NMDAR antagonism is also responsible for some of the analgesic properties of Ketamine by preventing central sensitization in the dorsal horn neurons, thus preventing the transmission of pain signals through the spinal cord.
- Ketamine also inhibits the synthesis of nitric oxide synthase which lowers the production of nitric oxide which is a neurotransmitter involved in pain perception.
- The action of Ketamine at sigma and mu opioid receptors is relatively weak but also aids in the analgesic properties

Ketamine Effects on the PNS

Ketamine also has catecholaminergic effects by inhibiting the reuptake of serotonin, dopamine and nor-epinephrine.

- Cardiovascular effects are often an increase in BP, increase in HR and increased Cardiac Output.
- Gastrointestinal effects of serotonin reuptake inhibition is thought to cause the N&V seen in higher doses
- Respiratory effects are lack of respiratory depression, increased salivation and potential bronchodilator effects secondary to catecholamine elevation.

Pharmacokinetics of Ketamine

- Ketamine is absorbable IV, IM, Oral and Topically due to its water and lipid solubility.
- It is commercially prepared for IV, IM and intranasal use. Rarely used orally due to bioavailability of only around 20% due to first pass effect
- Peak plasma concentrations are reached in 1 minute IV, 5-15 Minutes IM, 30 minutes PO
- Intranasal administration associated with rapid onset and increased bioavailability over PO.

Pharmacokinetics of Ketamine

Biological Half-Life

- 2.5-3 Hours

Duration of Action IV/IM

- Typically less than 1 Hour IV
- Up to 2 Hours for IM Administration

Metabolized

- Primarily by the Liver
- Has Several Active Less Potent Metabolites

Excreted

- 90% by the Kidneys

Pharmacokinetics of Ketamine

- Despite the “Dirty” non-specific nature of Ketamine, it has a wide margin of safety; several instances of unintentional administration of overdoses of ketamine (up to ten times that usually required) have been followed by prolonged but complete recovery.
- Ketamine has been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies. During the course of these studies ketamine hydrochloride was administered as the sole agent, as induction for other general agents, or to supplement low-potency agents.

Results

In these studies, the anesthesia was rated either "excellent" or "good" by the anesthesia provider and the surgeon at 90% and 93%, respectively; rated "fair" at 6% and 4%, respectively; and rated "poor" at 4% and 3%, respectively. In a second method of evaluation, the anesthesia was rated "adequate" in at least 90% and "inadequate" in 10% or less of the procedures

Future of Ketamine

- Currently ketamine is seeing a bit of a renaissance in anesthesia as more providers are exploring it's usefulness in low doses and in combination with other anesthetics and anxiolytics.
- Also, Ketamine is seeing wide use in non-anesthesia treatments. While I think it would be a mistake to consider ketamine a panacea in mental health, promising Studies are being done examining the effects of ketamine on depression, suicidal ideations, drug dependence and abuse, PTSD and chronic regional pain syndrome.

Ketamine for Depression

- Multiple small studies have shown immediate and profound alleviation of depression symptoms in up to 75% of patients that have been refractory to conventional anti-depressants.
- The NIMH is conducting large scale studies with an estimation completion date of mid-late 2018.
- Most studies used a low and slow method of infusion (0.5-1mg/kg infusion over an hour) with 6 infusions over an initial 2 week period.
- Length of anti-depressant results varied but majority of patients went 2 months or greater before booster infusion needed.

Ketamine for Depression

Findings from one meta analysis by Han et al in Neuropsychiatric Treatment and Disease Journal in 2016 that looked at 9 high quality studies with 368 patients found:

Conclusion

- “These results indicated that ketamine could yield a good efficacy in the rapid treatment of MDD. Future large-scale clinical studies are needed to confirm our results and investigate the mid- and long-term efficacy of ketamine in treating MDD.”

Ketamine for PTSD

The first evidence from a randomized clinical trial that the anesthetic agent ketamine may provide rapid symptom reduction in patients with chronic posttraumatic stress disorder (PTSD) when delivered intravenously was been published in 2014.

- In it, researchers led by Adriana Feder, MD, found that intravenous (IV) infusion of ketamine hydrochloride (0.5 mg/kg) was associated with significant and rapid reduction of PTSD symptom severity compared with an active control agent.
- Study was small and is considered a proof of concept study only at this point.
- Ketamine clinic in San Antonio area treating large amount of military PTSD patients with reportedly great results.

Ketamine for Suicidal Patients in the ED

Suicidal ideation is an emergent problem in the Emergency Department (ED) that often complicates patient disposition and discharge. It has been shown that ketamine possesses fast acting antidepressant and anti-suicidal effects.

- The NIMH reviewed 4 studies and found that a decrease in suicidal ideation was independent of improvements in mood.
- Low dose IV Ketamine often can be an effective immediate short term treatment for Emergency Room patients with suicidal ideations. (as an aid to help patients to enter into long term conventional treatment regimens)

Ketamine for Migraines

Studies:

- Dr. Carlos Zarate, a Chief researcher at the National Institute of Mental Health, says that “we can take care of a migraine in hours” using ketamine.
- Dr. Zarate is mainly focused on using Ketamine for treating major depressive disorders, however there have been several studies geared toward treating Migraines.
- One study tested the effects of intranasal Ketamine on 11 patients with familial hemiplegic migraines. Under supervision, each participant was given a 25 mg dose via a nasal spray at the onset of a Migraine attack. They were asked to record their symptoms 15 minutes after each use and were then allowed to administer Ketamine at home. During the study, over half of the participants reported an improvement of all of their symptoms after using Ketamine.

Ketamine for Migraines

- In a separate study, researchers examined the effects of IV Ketamine infusions of participants who were actively having a Migraine attack. Over 159 minutes, participants were given 64 mg of Ketamine through an IV.
- On a 1-10 pain scale, participants had an average pain score of 6 before treatment. After the Ketamine infusion, the average pain score reduced to 2.5.

Ketamine for Migraines

The most promising study was performed by the late Dr. Andrew Sewell on a Ketamine web forum.

247 patients participated in an open outpatient study that used IV infusions of Ketamine. The participants represented five different types of Migraine sufferers. Every group reported at least a 50% reduction in their headaches.

- In 162 patients with **Refractory Migraines**, 150 reported greater than 50% reduction in their pain.
- In 39 patients with **Chronic Migraine**, 26 reported greater than 50% reduction in their pain.
- In 4 patients with **Paroxysmal Hemicrania**, all 4 reported complete resolution of their pain for an average of 7 days.
- In 11 patients with **Cluster Headaches**, all 11 reported complete resolution of their pain for an average of 6 days.
- In 31 patients with **non-specific headache** type and facial pain, 25 patients reported greater than 50% reduction in their pain.

Ketamine for Chronic Regional Pain Syndrome

Besides anesthesia implications, Ketamine for CRPS is probably the most studied use of Ketamine:

- Dose, length and frequency of infusions varied greatly from study to study
- Some studies used much higher doses and inpatient setting and some were outpatient with much lower doses
- Majority of the studies have shown a significant reduction in pain scores for up to ten days post infusion

Ketamine for CRPS

Complex Regional Pain Syndrome:

- Six studies focused exclusively on the use of ketamine infusions for the treatment of CRPS.
- The majority of these articles report pain relief of several weeks after an infusion in an inpatient setting over 4 to 5 days.
- However, outpatient infusion protocols requiring multiple serial infusions also reported pain relief lasting several months in some cases.
- Although the general trend when all studies are considered is that longer durations provide increased duration of pain relief, there may be an optimal infusion duration of several hours beyond which no benefit is derived but the potential for side effects increases.

Ketamine for Fibromyalgia

Fibromyalgia:

- Three studies focused on the use of ketamine infusions for the treatment of fibromyalgia.
- All 3 studies utilized a relatively low dose of ketamine between 0.3 and 0.5 mg/kg administered over 10 to 30 minutes.
- No study reported benefits beyond the first few hours after the infusion. It is not certain whether this is because of a lack of responsiveness of fibromyalgia pain to ketamine infusions or whether a higher dose is required to produce longer lasting analgesia.
- The changes in pain scores after the infusion in 2 studies are encouraging and suggest that further optimization of dose and duration may provide some degree of relief.

Table 2. Summary of Reported Ketamine Infusion Protocols

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Sigtermans et al ³	CRPS-1	60	PRCT parallel	100 h continuously	IP	22.2 mg/h normalized to a 70-kg patient. 0.43 mg/kg/h maximum. S(+)-ketamine used.	None	Decreased NRS-11 compared with placebo until 11 wk.	No difference in: 1. RASQ and WAQ. 2. AROM. 3. Threshold for touch. 4. Skin temperature. 5. Volumetric measurement of limb.	1. Ketamine increased the incidence of nausea, vomiting, psychomimetic effects. 2. No difference in headaches.
Schwartzman et al ⁴	CRPS	19	PRCT parallel	4 h for 10 nonconsecutive days	OP	100 mg over 4 h. 0.35 mg/kg/h maximum.	0.1 mg PO clonidine and 4 mg IV midazolam at the start of each daily infusion	1. Decrease in sensory and affective components of the MPQ at 12 wk. 2. Reduction in hyperesthesia at 8 wk. 3. Reduction in burning pain and pain in the most affect limb at 4 wk.	No difference in 2 quality of life questionnaires.	1. Four ketamine patients and 2 placebo patients experienced side effects, including nausea, headache, and tiredness. 2. No patient reported hallucinations or dysphoria.
Koffler et al ⁵	CRPS-1	9	PONRT	4.5 d continuously in an inpatient ICU setting	IP	3–7 mg/kg/h target serum level of 250–300 µg/dL resulting in medically induced coma.	Supportive ICU care	1. Decrease in acute pain measured by MPQ at 6 wk. 2. Decrease in overall pain measured by PRI at 6 wk.	1. All patients successfully weaned from opioid therapy at 6 wk. 2. No change in attention measured by CCPT. 3. No change in learning or memory measured by HVLT.	Weakness, dizziness, fatigue, hyperhidrosis, sensation of warmth, and slight anxiety reported at 2 wk. No side effects reported at 6 wk.

(Continued)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Kiefer et al ⁶	CRPS-1	20	PONRT	5 d continuously in an inpatient ICU setting.	IP	Bolus of 1–1.5 mg/kg, then 3 mg/kg/h and increased to 7 mg/kg/h.	1. Bolus of 2.5–7.5 mg midazolam, followed by infusion at 0.15–0.4 mg/kg/h. 2. Clonidine 0.2–0.85 µg/kg/h. 3. Supportive ICU care.	1. Pain relief at 1 wk, 1 mo, 3 mo, and 6 mo. 2. Recrudescence of CRPS symptoms in 6/20 patients at 6 mo and at lower intensities.	3. No change in depression or anxiety measured by BDI. Improved quality of life measured by WHYMPI.	None.
Goldberg et al ⁷	CRPS-1	16	PONRT	5 d continuously in an inpatient setting.	IP	10 mg/h increased to a maximum rate of 40 mg/h.	1. Midazolam 2–4 mg Q4h PRN. 2. Clonidine 0.1 mg/d transdermal. 3. Inpatient supportive care.	1. Pain relief starting at 3 d. 2. Sixty percent of patients reported pain relief lasting for 4 mo. 3. Forty percent of patients reported pain relief lasting for 6 mo. 4. Inpatient supportive care.	None.	None.
Correll et al ²⁶	CRPS-1 and 2	31 CRPS-1 RS and 2 CPRS-2		Continued for as long as patient-tolerated infusion. Ten patients received a second infusion and 2 received a third infusion.	IP	10 mg/h. Increased as tolerated. Average maximum tolerated infusion rate 23.4 mg/h.	None.	1. After first infusion, average duration of relief 9.44 mo. 2. After second infusion, average duration of pain relief 25 mo.	None.	1. Sensation of inebriation was used as the end point for titration and universally noted. 2. No patient experienced sedation. 3. Six patients experienced hallucinations.

(Continued)

Table 2. Continued										
Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Eide et al ⁸	Traumatic spinal cord injury	9	PRCT crossover	17–21 min	IP	60 µg/kg bolus infusion of 6 µg/kg.	None.	Decreased continuous VAS pain intensity and allodynia. compared with placebo immediately after infusion.	1. No change in heat pain threshold.	4. Four patients experienced elevated transaminases. Five patients reported side effects with modest dizziness being most common.
Kvarnström et al ⁹	Traumatic spinal cord injury	10	PRCT crossover	40 min	Not reported	0.4 mg/kg of ketamine.	None.	Five of 10 had a 50% reduction in VAS immediately.	2. No change in wind up-like pain. Quantitative sensory testing, vibratory testing, thermal threshold testing were equivalent between the placebo and the ketamine group.	Nine of 10 patients reported adverse side effects after ketamine infusions with somnolence, dizziness, and changes in vision being the most common.
Amr ¹⁰	Traumatic spinal cord injury	40	PRCT crossover active placebo	5 h	IP	80 mg ketamine.	1. 2–5 mg IV midazolam. 2. 300 mg gabapentin.	1. Reduction of pain immediately after and 2 wk after infusion. 2. No difference in pain at 3 and 4 wk after infusion.	None.	None.
Eichenberger et al ¹¹	Phantom limb pain	10	PRCT Crossover	1 h	OP	0.4 mg/kg ketamine.	One arm of study combined ketamine infusion with a 200 IU calcitonin infusion over 1 h.	1. Six of 10 patients reported a 50% reduction in VAS. 2. Only combination of calcitonin and ketamine produced 50% reduction in VAS at 48 h.	Study not powered to detect changes in pain threshold or pain tolerance.	1. Five patients experienced visual hallucinations, hearing impairments. 2. Three patients experienced sedation during the ketamine infusion.
Kim et al ¹²	PHN	30	PRNCT 15 ketamine 15 MgSO ₄	1 h every other day for 3 d	IP	0.1 mg/kg ketamine or 30 mg/kg of MgSO ₄ .	0.1 mg/kg midazolam to render patients unconscious.	1. Decreased mean VAS at 2 wk for both ketamine and MgSO ₄ from baseline but no group difference.	1. Ketamine group had improved allodynia and electrical pain.	The most common complications reported in both infusion groups included somnolence and dizziness.

(Continued)

Table 2. Continued										
Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Eide et al ¹³	PHN	8	PRCT crossover	10 min	IP	0.15 mg/kg ketamine.	None.	2. Inpatient supportive care. 2. No difference in DN4 scale at 2 wk.	2. Painful cold and tingling sense improved in MgSO ₄ group.	All patients experienced some degree of nonspecified unpleasant side effects.
								1. Reduced pain immediately after infusion.	1. No changes in thresholds for cold, warm, heat pain, or tactile sensations.	
								2. Reduced experimentally induced allodynia and wind up-like pain. 3. Normalization of abnormal thermal pain sensations.		
Graven-Nielsen et al (Part 1) ¹⁴	Fibromyalgia	29	PRCT crossover	30 min	OP	0.3 mg/kg ketamine.	None.	1. Seventeen patients reported at least a 50% reduction in VAS. 2. Seven patients did not report a 50% reduction in VAS. 3. Five patients reported at least a 50% reduction in VAS in response to saline placebo.	None.	None.
Graven-Nielsen et al (Part 2) ¹⁴	Fibromyalgia	15	PRCT crossover	30 min	OP	0.3 mg/kg ketamine.	None.	1. No change in VAS duration.	1. Reduced IM saline induced VAS pain area and peak. 2. Reduced local pain area and referred pain area. 3. Attenuation of temporal summation after cutaneous and muscular electrical stimulation. 4. No change in electrical pain threshold.	None.
Sørensen et al ¹⁵	Fibromyalgia	11	PRCT crossover	10 min	Not reported	0.3 mg/kg ketamine.	None.	1. Reduced VAS at 20 and 80 min after infusion.	1. Increased pressure pain threshold at 20 and 80 min.	None.

(Continued)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Noppers et al ¹⁶	Fibromyalgia	24	PRCT parallel active placebo	30 min	OP	0.5 mg/kg of S(+)-ketamine or 5 mg IV midazolam.	None.	1. Both groups reduced NRS-11 pain at 90 and 180 min. 2. No reduction in pain was observed at 8 wk in either group measured by FIQ.	2. Increased pain tolerance at tender points, control points, and muscle endurance at 20 and 80 min. None.	No difference in psychedelic effects measured by Bowdle questionnaire.
Mercadante et al ¹⁷	Cancer-induced neuropathy	8	PRCT parallel	30 min	OP	0.25 mg/kg of ketamine or 0.5 mg/kg ketamine.	None.	1. All patients reported decreased pain after both doses at 3 h. 2. Larger dose was associated with larger decrease in pain at 3 h. 3. One patient continued to report decreased pain at 12 h.	None.	1. Four patients reported visual hallucinations after the 0.5-mg/kg infusion and 1 after the 0.25-mg/kg infusion. 2. No changes in MMSE.
Jackson et al ¹⁸	Cancer pain	29	PONRT	3–5 d	IP	100 mg/24 h for day 1, 300 mg/24 h for day 2, and 500 mg/24 h thereafter.	All patients were taking concurrent opioids.	1. Five of 29 initial responders had pain within 24 h of cessation of infusion. 2. Maximum duration of relief was 8 wk.	None.	12 patients reported psychomimetic effects with increased incidence at higher doses.
Salas et al ¹⁹	Cancer pain refractory to opioids	20	PRCT	48 h	IP	0.5 mg/kg for 24 h, increased to 1 mg/kg if NPIS >1.	All patients received 1 mg/kg MSO ₄ if opioid naive. Equivalent opioid dose if not naive.	1. NPIS equivalent between the 2 groups at 2 h, 24 h, and 48 h postinfusion.	1. No differences in MSO ₄ utilization were noted. 2. No differences in patient satisfaction were noted. 3. No difference in ESAS.	No difference in ESS.

(Continued)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Tawfic et al ²⁴	Sickle cell crisis	9	RS	2–5 d	IP	0.25 mg/kg ketamine bolus. 0.2–0.25 mg/kg/h.	1 mg midazolam bolus followed by 0.5–1 mg/h. 2. Supportive ICU care.	1. Improved pain scores compared with baseline on first day.	1. Lower MSO ₄ requirement compared with baseline. 2. Patients reported durable improved sleep.	1. One patient had psychomimetic effects. 2. Five patients had pre-existing nausea, which continued during the study period.
Kang et al ³⁸	Mixed neuropathic pain diagnoses	103	PONRT	2 h for 3 sessions every other day	IP	0.2 mg/kg bolus 0.5 mg/kg ketamine.	0.1 mg/kg midazolam loading dose followed by 0.025 mg/kg midazolam.	Decreased VAS compared with baseline 2 wk after treatment.	None.	50% of patients reported adverse events either during or after infusions, including snoring, muscle movement, decreased HR, decreased BP, and increased BP. No patient reported dysphoria.
Leung et al ²⁰	Mixed neuropathic pain diagnoses	12	PRCT parallel	20 min	OP	Target plasma level of 50, 100, and 150 ng/mL.	Compared with alfentanil with a target plasma concentration of 25, 50, 75 ng/mL or a diphenhydramine placebo control.	1. Concentration-dependent reduction in stroking pain immediately after the infusion.	1. Both ketamine and alfentanil decreased the stroking-evoked and cold allodynia areas. 2. Only ketamine decreased the Von Frey-evoked allodynia area.	1. A third of patients receiving ketamine developed lightheadedness. 2. Three subjects developed mild sedation.
Max et al ²¹	Mixed neuropathic pain diagnoses	8	PRCT parallel	2 h	OP	0.75 mg/kg/h, doubled at 60 and 90 min if no analgesic benefit.	One study arm combined with alfentanil at of 1.5 µg/kg/mL.	1. Equivalent decrease in pain after the infusion. 2. Equivalent decreased allodynia after infusion.	Side effects occurred before the onset of pain relief.	Three patients experienced dissociative reactions. Two patients each experienced muteness, nausea, and dizziness.
Felsby et al ²²	Mixed neuropathic pain diagnoses	10	PRCT, crossover	Up to 1 h	OP	0.84 µg/kg over 10 min; 1.3 µg/kg/h infusion.	None.	1. VAS and reduced area of allodynia were related after infusion.	1. Ketamine reduced VAS scores.	1. No significant hemodynamic changes.

(Continued)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Jørum et al ²³	Mixed neuropathic pain diagnoses	10	PRCT, crossover, active control	25 min	OP	60 µg/kg over 5 min, 6 µg/kg/h infusion.	None.	Decreased VAS for spontaneous pain immediately after infusion.	2. Ketamine reduced area of allodynia. 1. Reduced hyperalgesia to cold pain without alteration in cold pain threshold. 2. Decreased radiation from the site of cold pain. 3. Attenuation of mechanoallodynia.	2. Psychomimetic effects were common after ketamine infusions. 1. Dizziness was more common in patients who received ketamine. 2. Other side effects were similar in frequency when compared with alfentanil.
Patil and Anitescu ²⁷	18 CRPS, 8 chronic headache and 7 LBP, 16 mixed neuropathic pain diagnoses	49 patients 369 infusions	RS	CRPS average 43.5 min every 30.8 d. Non-CRPS average 34.7 min every 34 d	OP	Average CRPS dose 1.0 mg/kg. Average non-CRPS dose 0.9 mg/kg.	None.	27% report relief lasting several hours, 73% report relief lasting more than 1–2 d, 38% report relief lasting more than 3 wk.	1. CRPS average VAS change was 7.7. 2. Non-CRPS average VAS change was 6.	1. Minimal side effects reported in all patients. 2. Hypertension and sedation were the most common side effects. 3. Higher incidence of hallucination and confusion in patients without CRPS.
Polomano et al ²⁵	Neuropathic pain after combat limb injury	19	RS	3 d	IP	120 µg/kg/h ketamine.	None.	1. Reduced PPI over the study period. 2. Improved GPR over the study period.	1. No change in opioid use during infusion.	1. Four patients reported feeling drowsy on days 1 and 2. 2. One patient reported hallucinations. 3. One patient reported nausea.

Abbreviations: AROM, active range of motion; BDI, Beck Depression Inventory; BP, blood pressure; CCPT, Connor’s Continuous Performance Test; CRPS, complex regional pain syndrome; DN4, Douleur Neuropathique 4 Score; ESAS, Edmonton Symptom Assessment Scale; ESS, Epworth Sleep Scale; FIQ, Fibromyalgia Impact Questionnaire; GPR, Global Pain Relief; HP, habitual pain; HVLT, Hopkins Verbal Learning Test; HR, heart rate; ICU, intensive care unit; IU, international units; IM, intramuscular; IP, inpatient; MgSO₄, magnesium sulfate; MSO₄, morphine sulfate; MMSE, Mini-Mental Status Examination; MPQ, Short-form McGill Pain Questionnaire; NRS-11, 11-point numerical rating scale; NPIS, Numeric Pain Intensity Scale; OP, outpatient; PHN, postherpetic neuralgia; PO, oral; PONRT, prospective observational nonrandomized trial; PPI, present pain intensity; PPT, pressure point pain measured at the infraspinatus; PRCT, prospective; randomized control trial; PRI, Pain Rating Index; Prn, pro re nata; PRNCT, prospective randomized noncontrolled trial; RASQ, Radboud Skills Questionnaire; RS, repeated stimulation; WAQ, Walking Ability Questionnaire; WHYMPI, West Haven-Yale multidimensional pain inventory; VAS, visual analog scale.

Ketamine Infusion Centers

- Most are owned by either Psychiatrist or Anesthesia Professionals
- Can be a stand alone center or in combination with a physician office practice
- Average square feet needed will be around 2,000sq/feet
- Ideally need a consultation room, waiting room for family, and 2-4 infusion rooms

Ketamine Infusion Centers

- Most free standing centers are set up as physician office extension
- Need a DEA number to order drugs and some supplies
- Need to establish protocols for handling scheduled drugs
- Security is a big concern
- AANA Ketamine clinic check list:
 - [https://www.aana.com/docs/default-source/practice-aana-com-web-documents-\(all\)/ketamine-infusion-therapy-checklistf8fb24731dff6ddbb37cff0000940c19.pdf?sfvrsn=cc0549b1_6](https://www.aana.com/docs/default-source/practice-aana-com-web-documents-(all)/ketamine-infusion-therapy-checklistf8fb24731dff6ddbb37cff0000940c19.pdf?sfvrsn=cc0549b1_6)

Ketamine for Chronic Pain Protocol

Mix Either 100mg
Ketamine/100cc or
250mg/100cc



Calculate initial
dose of 1.2mg/kg



Run initial infusion
at 0.6mg/kg/hour



Administer adjuncts
as needed
(Versed/Zofran)



Monitor for at least
30 minutes prior to
D/C

Asses VAS Pain score:

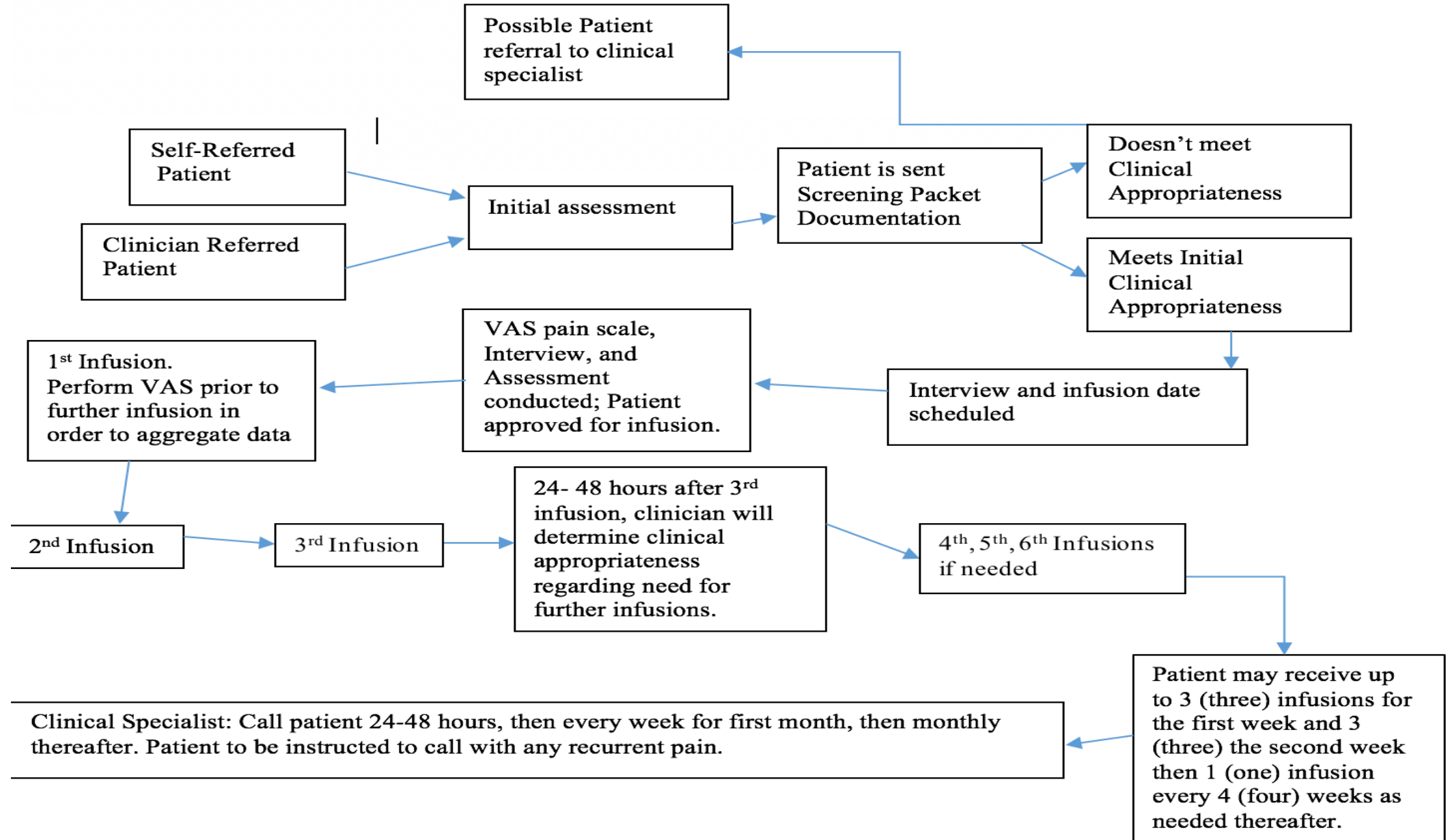
Before Each Infusion

After Each Infusion

Weekly for First Month

Monthly for First Year

Life Cycle of a CRPS Patient



Title: Ketamine Infusion Protocol for Chronic Pain Disorders		
Section: Ketamine Infusion		
Date Written: 07/07/2017		Revision Date:
Status: Approved	Effective Date: 07/07/2017	Page 1 of 3

|

Protocol:

1. MIXING KETAMINE

- Ketamine will be mixed in a 100ml or 250ml bag of saline at a concentration of 100mg /100ml or 250mg/250 ml bag.

2. DOSAGE

- Ketamine 1.2mg per kg of patient body weight

3. INFUSION RATE

- Infuse at a rate of 0.6mg per kg per hour as tolerated.
 - Rate may be changed at the discretion of the CRNA based on patient's tolerance of the infusion.

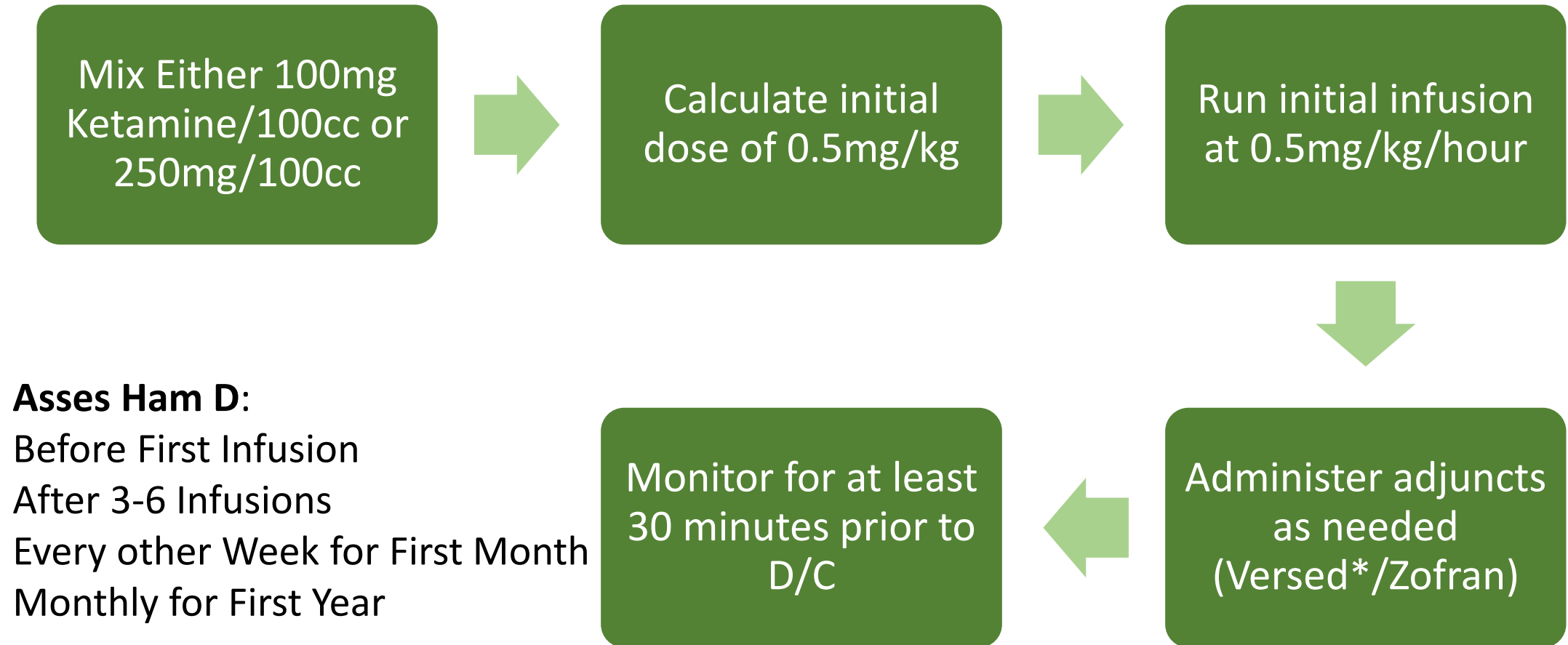
4. ADJUNCT MEDICATION

- Midazolam may be administered at the CRNAs discretion at a dosage of 1-2 mg prior to starting or at any time during the infusion for anxiety or other unpleasant psychological effects.

M.D. SIGNATURE _____

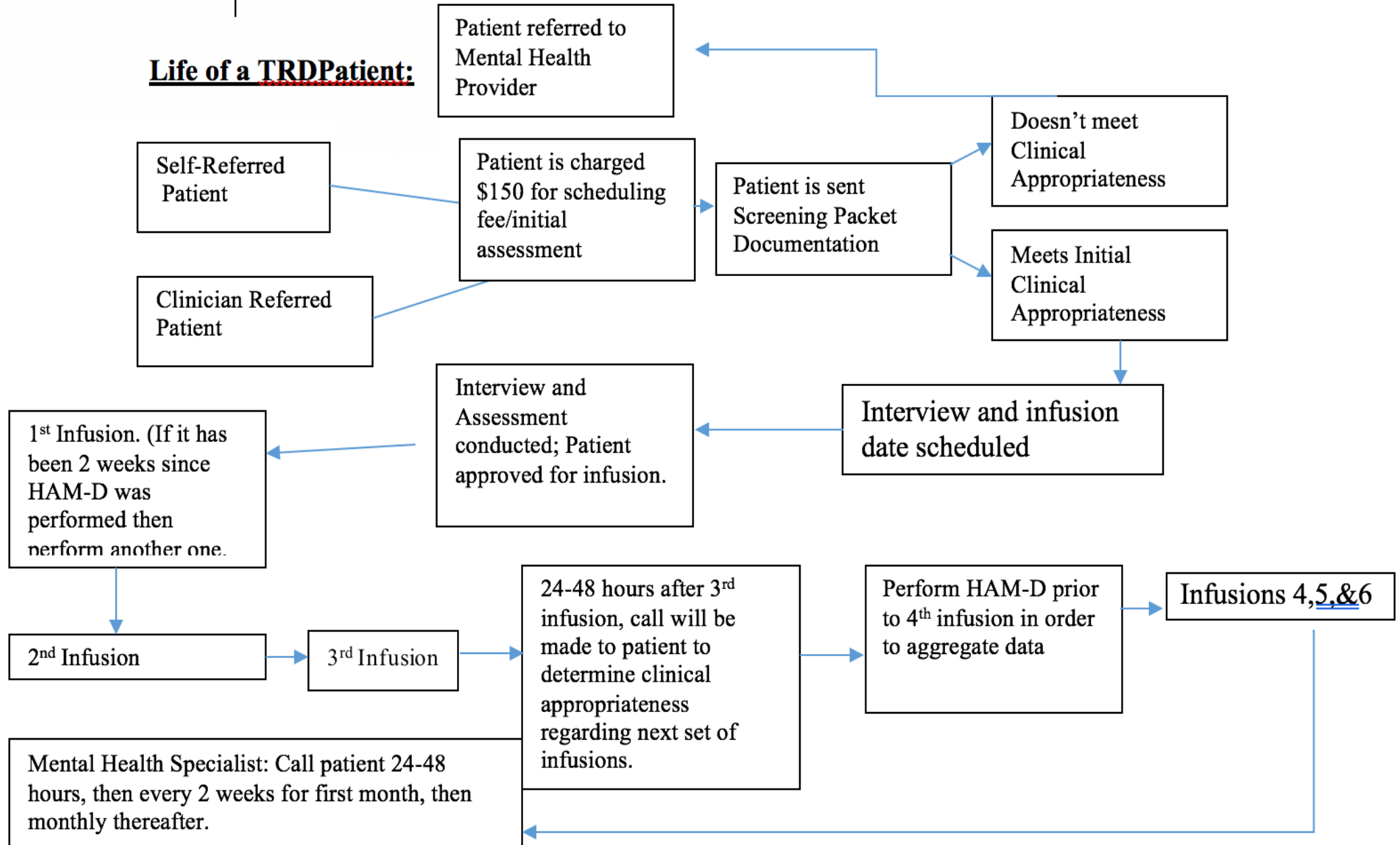
DATE _____

Ketamine for Depression Protocol



*Avoid versed if at all possible

Life of a TRDPatient:



TRD Infusion Protocol:

1. Make sure patient has a patent and secure IV access according to IV access policy.
2. Prepare ketamine bag for infusion.
 - a. Dilute ketamine in a bag of 100ml of Normal Saline to achieve concentration of 100mg/ml of Ketamine.
 - b. Begin infusion at 0.5mg/kg/hour and infuse for one hour per an electronic infusion pump.
3. At the discretion of the CRNA, patients who are very anxious may receive 1-2mg Midazolam prior to infusion begins. This must be given by the CRNA.
4. Patients who experience unpleasant psychological affects that are not well tolerated during the infusion may be given 1-2mg Midazolam by the CRNA at the CRNA's discretion. The infusion may be held for 5 minutes by the CRNA to allow the midazolam to begin to take affect before restarting the infusion.
5. If the patient continues to not tolerate unpleasant psychological side effects or if the patient becomes too sedated to remain in constant verbal contact during the infusion, the CRNA may decrease the rate of infusion or may discontinue the infusion at his/her discretion. The goal is to infuse ketamine for a period of one hour without achieving a state of deep sedation or anesthesia.
6. Patients should be communicated with verbally at a minimum of every ten minutes with the patient being able to voice satisfaction with the progress of the treatment, which shall be documented as well as level of consciousness documented every ten minutes as well.
7. If patient becomes too sedated to communicate appropriately, anesthesia must evaluate to determine if the infusion rate needs to be reduced or terminated.
8. Only anesthesia can start the infusion or change the rate of the infusions.
9. Patient vital signs (BP, HR, Resp Rate, SpO2) shall be monitored and documented prior to infusion for a baseline and at least every ten minutes during the infusion.

10. Anesthesia personnel shall be notified immediately of any significant deviation from the baseline vital signs.

11. Anesthesia personnel must stay in the facility during all infusions and until the patient as fully recovered from the infusion therapy.

12. At the conclusion of the infusion, anesthesia personnel must document the total amount of ketamine infused in the record.

13. All drug waste shall be witnessed and documented by two licensed personnel.

14. Patient can be discharged if all criteria are met after 30 minutes post infusion with post infusion instructions given to patient and caregiver.

Ketamine Infusion Therapy

Considerations Checklist

Ketamine infusion therapy involving the administration of a single infusion or a series of infusions for the management of psychiatric disorders (e.g., major depressive disorder, post-traumatic stress disorder) or chronic pain has grown over several decades. Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that has traditionally been used for the induction and maintenance of anesthesia. As ketamine infusion clinics in healthcare facilities become available, certified registered nurse anesthetists (CRNAs) are providing ketamine therapy services as part of the patient's management.

This checklist provides considerations for administration of ketamine infusion therapy and is not intended to be all inclusive.

- ☐ Review and complete applicable elements of the [Considerations for Adding New Activities to Individual CRNA Scope of Practice](#)
- ☐ State scope of practice
 - Establish [State Association of Nurse Anesthetists](#) (SANA) relationship(s), as appropriate, with SANA board of directors, committees, and lobbyist/lawyer.
 - Review applicable state nursing, medical, drug and facility statutes and regulations to identify existing and anticipated practice barriers.
 - Verify whether the state board of nursing or other relevant board has issued a related opinion applicable to RNs and/or CRNAs
- ☐ Determine employment arrangement (*AANA member login required*)
 - Employee of facility or independent contractor
 - [Starting Your Own Business Checklist](#)
 - [CRNA Independent Contractor Agreement Checklist](#)
 - [CRNA Employment Agreement Checklist](#)
 - Establish contract for services
 - [Anesthesia Services Agreement Checklist](#)
 - [Anesthesia Services Agreement](#) (template; adapt to employment needs)
 - Malpractice insurance
 - Who will provide insurance?
 - Verify coverage for specific procedures
- ☐ Considerations for clinic infrastructure, operations, and policies
 - Market assessment
 - Is there a need for this service in your area?
 - What type of patient volume can you expect?
 - Identify competitors within your area.
 - What are your barriers?
 - What are the costs?

- Process for referrals
 - Establish relationships with primary care and specialty clinicians
 - Will local clinicians refer to a CRNA?
 - What clinicians can make referrals (e.g., MD, APRN, PA)?
 - Patient scheduling process
- Identify clinic personnel and outline roles
- Accreditation
 - Who accredits the facility?
 - What are the applicable standards?
- Identify requirements for credentialing within the facility
- Evaluate staff
 - Education, skills, and expertise
 - Is additional training required for clinic staff?
 - Develop competency evaluation
- Clinic location and equipment
 - Accessibility to patients
 - Comfortable infusion rooms
 - Recovery area
 - Determine cost-benefit of equipment based on patient safety and clinic needs
 - Required equipment
 - Standard equipment
 - Monitoring equipment
 - Emergency equipment readily available
 - Crash cart
 - Emergency airway management
- Patient eligibility
 - Consultation with primary and and/or specialty clinicians
 - Understand contraindications to ketamine
 - Patient selection criteria
 - Physical status 1 & 2 are typically candidates for ketamine infusion
 - Physical status 3 & 4 may be considered, but require additional precautions
- Documentation
 - Electronic or paper record
 - Procedure-specific forms
 - Document pertinent information on the patient's healthcare record in an accurate, complete, legible, and timely manner
 - Informed consent
 - Include risks, benefits, and potential side effects, as well as alternative therapies and their risks, benefits, and potential side effects
 - Manage treatment expectations

- Treatment and management
 - Consult ketamine package insert and current literature for drug-specific considerations, contraindications, dosages, side effects, etc.
 - Ketamine therapy is not a first line treatment
 - Consider only after failure of standard medical treatment
 - Pre-treatment consultation
 - History and physical
 - Patient receives medical clearance
 - General medical clearance
 - Specialty medical clearance (e.g., cardiac, neurological) as necessary based on history
 - Pre-procedure labs (e.g., liver function tests, creatinine)
 - Establish process for infusion and medication orders
 - Evaluate patient for contraindications to ketamine
 - Conduct anesthesia patient assessment and evaluation
 - NPO status
 - Administer pre-medication, as appropriate, to mitigate adverse events
 - Consider trial infusions to assess for responsiveness, efficacy, and tolerability of side effects, prior to prolonged daily treatment
 - Administration of ketamine (anesthesia professional)
 - Dosage
 - Volume
 - Frequency
 - Patient monitoring
 - Vital signs
 - Consciousness
 - Heart rate
 - Blood pressure
 - Respiratory rate
 - Oxygen saturation
 - Level of consciousness
 - End-tidal CO₂
 - ECG monitoring
 - Signs/symptoms of ketamine toxicity
 - Establish process of significant side effects
- Physician and/or anesthesia professional immediately available
- Recovery
 - Establish recovery criteria
 - Patient must be monitored until recommended recovery criteria are met
 - Establish recovery/discharge criteria
 - Recovery to pre-administration baseline levels

- Cardiovascular function
 - Airway patency
 - Oxygen saturation
 - Patient reflexes and speech
 - Respiratory rate
-
- Blood pressure
 - Patient is awake
 - Assess and treat nausea and vomiting
 - Patient and caregiver education
 - Patient sent home with appropriate driver/caregiver
-
- Follow-up
 - Treatment communication with patient care team, referring clinician, primary care clinician, etc.
 - Establish standardized testing tool for the facility to monitor progress
 - Psychological questionnaires
 - Pain assessment tools
 - Treatment regimen - # infusions administered over # days
 - Maintenance infusion(s)
 - Drug disposal and diversion prevention
 - Implement proper drug disposal and wasting measures consistent with federal, state, and local law to prevent drug diversion and misuse
 - AANA recommendations on drug diversion prevention can be found in [Addressing Substance Use Disorder for Anesthesia Professionals](#)
 - Continuous Quality Improvement
 - Tracking adverse events
 - Patient satisfaction
-
- ❑ Reimbursement
 - Verify insurance coverage (e.g., private, Medicare, Medicaid)
 - Many insurers may not cover treatment
 - Establish fee schedule
 - Establish collection method for self-pay patients
 - Know how clinic is billing for your services
 - Educate billing staff
 - Identify applicable billing codes
-
- ❑ AANA Resources
 - [Ketamine Infusion Therapy for Psychiatric Disorders and Chronic Pain Management, Practice Considerations](#)
 - [The Role of the CRNA on the Procedure Team](#)
 - AANA Professional Practice, practice@aana.com, 847-655-8870
 - Practice-related inquiries
 - AANA State Government Affairs, sga@aana.com, 847-655-1130

Future of Ketamine

- With so many off label uses being studied, some researchers are predicting that Ketamine will soon be listed as more than just an anesthetic.
- Researchers are also assessing similar compounds to Ketamine that could deliver similar results to Ketamine without the more untoward side effects and would be able to qualify for patent protection. Update 9/2/2018 J&J filed for FDA Marketing Application for Esketamine Nasal Spray for Depression.
- Approved early 2019 (Sparvato Trade name).
- Requires REMs certification for storage and monitoring.

The End: Q and A

Tracy P. Young, MSNA, MBA, CRNA