Ketamine for Chronic and Refractory Pain

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More than 40 people die every day from overdoses involving prescription opioids.¹

Since 1999, there have been over 165,000 deaths from overdose related to prescription opioids.²

4.3 million Americans engaged in non-medical use of prescription opioids in the last month.³
Prescriptions for opioid pain medication were written by healthcare providers in 2013.

Nearly 2M

Americans, aged 12 or older, either abused or were dependent on prescription opioids in 2014.

As many as 1 in 4 patients receiving long-term opioid therapy in primary care settings struggle with opioid use disorder.
**Figure 3:** Opioid-related drug overdose deaths per 100,000, 1999-2014, Massachusetts and US
The Numbers Persist......Why??

.... “A cultural change contributing to physicians' dilemma is the “all suffering is avoidable” ethos that pervades many aspects of modern life. Many Americans today believe that any kind of pain, physical or mental, is indicative of pathology and therefore amenable to treatment.” – NEJM 2012 Lembke A.

.... “One patient summed it up in this way: “I know I'm addicted to (opioids), and it's the doctors' fault because they prescribed them. But I'll sue them if they leave me in pain.”
The Alternatives:

NSAIDS

Acetaminophen

Neuropathic Pain Medications
- Gabapentin (1993)
- Savella (2009)
- TCA (1960s)
- Cymbalta (2004)
- Effexor ER (2008)
- Topamax (1979)

Topical Therapies – Lidocaine, Voltaren gel, Compound Creams
Physical/Aqua Therapy

TENS

Cognitive Behavioral Therapy

Stress Management

Functional Restoration Programs

Acupuncture

Massage Therapy

Reiki

Complementary and Alternative Medicine....ETC
Image Guided and Landmark Based Interventional Therapy
AND A RETURN TO AN OLD DRUG:

KETAMINE
The NMDA Receptor: A Target for Chronic Pain Management

- Excitatory Amino Acid Receptor Class
- Extracellular Domain
  - NR1 subunit binds Glycine
  - NR2 subunit binds Glutamate
- Membrane domain
  - High Ca2+ permeability
  - Voltage dependent Mg block
- Activation of the NMDA receptor by continuous C polymodal afferents in the dorsal horn is thought to play a central role in the development of hyperalgesia and central sensitization. This activation is mediated by the excitatory neurotransmitters glutamate and aspartate.
In this study flexor motor neuron responses in rats were elicited by standardized painful pinch to the toes q5mins after administering mustard oil which selectively excites the C nociceptors. Following the pain input caused by the mustard oil the pain response to toe pinch tends to remain exaggerated for approximately 60 minutes indicating the presence of central sensitization.

Pretreatment with NMDA antagonist CPP or MK-801 prior to administering mustard oil prevents central sensitization.

Administration of the NMDA receptor antagonist after application of Mustard oil reverses it.
IP injection of MK-801 prior to unilateral transection of the superior caudal trunk which innervates the tail in rats was shown to delay the onset of mechanical and thermal allodynia for least four days after the injury.
Rats were injected with CFA which produces intense inflammation, behavioral hyperalgesia typically develops 3-5h after injection.

Rats were tested for mechanical sensitivity utilizing a series of calibrated von Frey filaments.

Pre CFA median von frey thresholds were 8.5gm for the ipsilateral and contralateral sides.

24hrs post CFA administration von frey threshold was significantly reduced to a mean value of 1.2gm.
So what exactly is Ketamine???
First synthesized in 1962 by Calvin Stevens at Parke-Davis Co (Pfizer) as an alternative anesthetic to PCP

First utilized in humans by Corssen and Domino in 1965
- CI – 581, 20 male prison inmate volunteers
- vivid dreams, being in outer space, “death”
- Potent analgesic and amnestic

Introduced to clinical practice in 1970

It is classified by the WHO as an essential medicine (1985) due to its safety as an anesthetic agent, recommended that ketamine should not be controlled under the international drug control conventions
Ketamine Pharmacology

Ketamine is a derivative of phencyclidine and approximately 1/10th as potent but retains many of its psychomimetic properties.

S[+] vs R[-] Enatiomer

Varied routes of administration

Orally administered ketamine undergoes extensive 1\textsuperscript{st} pass metabolism resulting in a bioavailability $\sim 16\%$. 

![Diagram showing the chemical structure of ketamine and its metabolites]
Metabolism:

$1^\text{o}$ metabolic pathway involves N demethylation via the cytochrome P450 system to norketamine a pharmacologically active metabolite.

Orally administered ketamine is associated with higher serum levels of norketamine as compared to other routes of administration.

IV ketamine has a hepatic extraction of 0.9 accounting for its relatively short ½ life of approximately 2-3 hrs. Norketamine ½ life approx 4hrs.

In contrast long term ketamine administration for management of chronic pain is associated with significantly longer ½ lives upwards of 11 days.
Ketamine and Descending Inhibition

Using fMRI low dose ketamine has been demonstrated to activate descending inhibitory pain pathways arising from supraspinal sites (anterior cingulate gyrus, orbital frontal cortex, insula and brain stem) and to inhibit dorsal horn nociceptive neurons.

Ketamine has also been found to play a role in conditioned pain modulation.

Conditioned pain modulation is characterized by the central inhibition of a focal pain stimulus by administering a noxious stimulus in a remote location.

In a patient population with chronic neuropathic pain this phenomenon was not demonstrated. After administration of ketamine this response was found to be more robust than after administering either placebo or morphine.
Anti Depressant Effect

• Clinical studies show sub-anesthetic doses of ketamine produces antidepressant effect with 1 hr
• Ketamine has a positive effect in otherwise therapy resistant patients
• Li et al (2010)
  • Inhibition of NMDA receptor activates the mammalian target of rapamycin mTOR increasing the expression of synaptic proteins and the density of dendritic spines producing antidepressant effect within 1 day
Currently the most frequent use of ketamine is in the management of severe acute episodes of refractory neuropathic pain many times in situations in which high dose opioid therapy has contributed to the development of opioid induced hyperalgesia.

There is significant literature which demonstrates a reduction in opioid requirements when ketamine is administered peri-operatively, however there have been no rigorous studies examining the effectiveness of ketamine in controlling chronic episodes.
Non Specific Pain of Neuropathic Origin


Randomized double blind cross over trial – it enrolled 8 pts with chronic post traumatic pain of varying etiologies, however, all utilized neuropathic pain descriptors and experienced widespread mechanical allodynia.

Ketamine gtt over 2hrs (mean dose 58mg), Alfentanil gtt and placebo

Mean Peak Relief Score Ketamine pain/allodynia 60-65%

Max et al 1995
Central Pain Syndrome

Characterized by pain that is largely described as constant, burning, tingling, pressing and lacerating.

It is a neurological condition caused by damage to or dysfunction of the central nervous system.

Etiologies are varying and include stroke, MS, epilepsy, brain or spinal cord trauma and Parkinson’s disease.

Allodynia tends to be a prominent feature, pain is characteristically worsened with movement, emotions, and temperature changes.

Randomized double blind cross over study which enrolled 9 patients with central dyesthesia following spinal cord injury.

Pain in these patients was evoked by non noxious stimulation (allodynia), as well as, by repeated pricking of the skin to induce wind up. The severity of continuous and evoked pain was examined pre and post IV infusion of Ketamine, alfentanil, or placebo.
Change in continuous pain after infusion of ketamine (6 µg/kg/min after a bolus dose of 60 µg/kg), alfentanil (0.6 µg/kg/min after a bolus dose of 7 µg/kg)

Change in allodynia after infusion of ketamine
Change in wind-up-like pain after infusion of ketamine

Both continuous and evoked pain were markedly reduced by blockade of the NMDA receptor by ketamine and activation of u opioid receptor by alfentanil, however, neither significantly altered sensory thresholds for pain.
Polomano et al 2013 – Effect of Low Dose IV Ketamine on Peripheral and Central Pain from Major Limb Injuries Sustained in Combat

Retrospective study – 19 hospitalized patients with neuropathic pain following major limb injuries, with inadequate pain control despite multi modal analgesia.

Patients received a 3day infusion of ketamine at doses ≤ 120µg/kg/h

Outcomes Measures

Daily Present (PPI)
Average pain intensity (API)
Worst pain intensity (WPI)
Global Pain Relief (GPR) – 1 “no relief” to 5 “complete relief”

Significant reduction in daily present and improvement in global pain relief was found.

Higher baseline WPI was associated with a significant decrease in WPI but lower baseline WPI was not, WPI was also found to be more significantly decreased in patient without phantom limb pain.

Essentially what they found was pts demonstrated favorable response patterns over time when risk stratified by baseline pain score and presence or absence of phantom limb pain.
Fisher and Hagen (1999)

32yo Male with bilateral LE motor and sensory impairment following traumatic insertion of a metal into the thecal sac after an MVA.

Pain described as “constant achiness and jabbing”, (+) allodynia, Rates 5/10 with circadian increase to 8/10.

Multiple inpatient hospitalizations with pain crises managed with high dose parenteral opioids.

Home Medication Regimen
- Codeine 150mg BID
- Valium 7.5mg qD
- Baclofen 80mg qD
- Amitriptyline 75mg qD
- APAP PRN

Pt transitioned to oral ketamine 25mg TID he required no other scheduled analgesics, Baseline pain score now a 3/10 with no circadian increase, allodynia had also resolved.
Vick and Lamar (2001)

68 yo female s/p ICH, SAH involving the basilar cistern resulting in bilateral CN VI palsy, lethargy and quadriparesis, she did have a full recovery but developed persistent right sided burning body pain.

Home Medication Regimen
   MS Contin 450mg/day
   MSIR
   Gabapentin 300mg/day
   Notriptyline 100mg/day

Failed PT, ESI, SGB, Anti Convulsants, Amantadine and IV/nasal Lidocaine

After establishing that patient was a ketamine responder with IV ketamine she was transitioned to a PO regimen of 50mg TID and Valium 5mg. Subsequently she rated her pain a 3/10, pain control was described as satisfactory and pain intensity described as tolerable.
Complex Regional Pain Syndrome

Complex regional pain syndrome as defined by the IASP guidelines includes features of

1. Allodynia, hyperalgesia, hyperpathia, and other abnormalities in pain processing
2. Vasomotor and sudomotor dysfunction
3. Neurogenic edema
4. Trophic changes which can result in motor impairment.

288 records were identified of these 45 studies were included in the analysis, records excluded included those that were unrelated, animal studies, basic science, non systematic reviews, did not pertain to CRPS/RSD, did not pertain to ketamine or were editorials/commentaries/letters.

Level 1 Evidence n=6
Level 2 Evidence n=5
Level 3 Evidence n=13
Level 4 Evidence n=21
Azari et al 2012 – systematic review specifically examining the safety and efficacy of ketamine for patients with CRPS

Evaluated 3 RCTs, 7 observational studies and 9 case studies/reports
Identified Level 2B evidence (weak/moderate quality evidence) to recommend routine use of ketamine in CRPS, further study is required

Cochrane Review 2013

“low quality evidence that a course of IV ketamine maybe effective for CRPS related pain....effect did not appear to be sustained beyond 4-11 weeks post treatment....ketamine and other NDMA receptor antagonists might represent a promising therapy and target for future studies”

.....little evidence for the use of oral ketamine

33 patients were identified who underwent inpatient ketamine infusion for management of CRPS, patients had an average age of 40 and average duration of CRPS symptoms of approximately 28 months.

Average rate of ketamine infusion was 23.4mg/hr, Max 50mg/hr Min 15mg/hr

Following an initial course of therapy complete pain relief was achieved in 25 (76%), partial relief in 6 (18%) and no relief in 2 (6%) of patients.

An average of 54% of patients experienced ≥ 3mo of pain relief, 31% of patients ≥ 6mo

12 pts underwent a 2nd course of therapy due to relapse 100% achieved complete relief. 58% of these patients had relief for at least 1 year and almost 1/3 remained pain free beyond 3 yrs
Fibromyalgia

After osteoarthritis fibromyalgia is the most commonly diagnosed rheumatic disorder. It can be thought of as a centralized pain state characterized by central sensitization and hyperalgesia.

fMRI studies reveal activation of pain processing areas in the brain with application of light pressure or heat stimulus in fibromyalgia patients.

It is diagnosed in part with a patient self report survey which records a wide spread pain index and notes symptom severity including consideration of fatigue and depression.
Sorensen et al 1995

Double blind placebo controlled trial in which 31 Fibromyalgia patients were divided into three groups. Responders classified as reporting decreased pain intensity of greater than 50%.

31 patients

9 patients IV Morphine
No Significant Change

11 patients IV Lidocaine
Decreased pain during and after infusion

11 patients IV Ketamine
Significant reduction in pain intensity during and after test period; endurance increased and tenderness at tender points decreased

This study also provides evidence for the role of the NMDA receptor in fibromyalgia and suggests that central sensitization is present in fibromyalgia and tender points may actually represent secondary hyperalgesia.

Double blind placebo controlled crossover trial – 29 female fibromyalgia patients were enrolled to assess the effect of ketamine on muscle pain at rest, muscular hyperalgesia, temporal summation of muscle pain, and pain referral pattern.

Ketamine 0.3mg/kg or isotonic NS was administered over 30 minutes.

Ketamine responders were characterized as those who expressed a 50% reduction in two consecutive VAS scores as compared to baseline and were not placebo responders.
VAS scores of ketamine responders progressively declined during the 30 minute infusion session as compared to baseline.

Reaction time in sensory testing administered during the ketamine infusion was increased by 102ms +/- 27ms as compared to baseline, testing done maximally after 30 minutes following cessation of the infusion revealed an average increase in reaction time of 15ms +/- 12.

Additionally the mean pressure tolerance threshold from three paired tender points was significantly increased with ketamine as was the pain threshold at the trapezius muscle indicating that main effect of ketamine was found at high intensity pressure stimulation.
Ischemic Pain

Ischemic pain can be acute or chronic and can be largely divided into three major categories

1. Vascular pain which originates from the vessel wall
2. Somatic pain related to tissue ischemia
3. Nerve pain caused by ischemia of the nerve trunks

Chronic pain is generally mixed nociceptive. Activation of peripheral nociceptors facilitates the release of vasoactive neuropeptides such as substance P, somatostatin and CGRP which contributes to neurogenic inflammation and neuropathic pain due to ischemic degeneration of the nerves.

8 patients with lower extremity rest pain secondary to arteriosclerosis obliterans were administered subanesthetic doses of ketamine 0.15, 0.30, 0.45mg/kg, morphine 10mg served as a control. These were administered at a 5 minute infusion on four separate days.

Ketamine 0.30 mg/kg provided 7/8 and 0.45mg/kg provided 8/8 patient total pain relief at the conclusion of the five minute infusion period. The effect was sustained at 10 minutes then declined steadily to reach a median value of 50% at the end of 60 minutes.

At 10 minutes post infusion only the 0.45mg/kg dose was statistically significantly different from morphine
Orofacial Pain

Orofacial pain covers a wide variety of disorders and is a general term used to describe pain localized to the region above the neck, anterior to the ear, and below the orbitomeatal line as well as pain within the oral cavity.

Etiologic classification can be broken down into two major categories

1. Primarily somatic originating from musculoskeletal or visceral structures and transmitted via an intact pain transmission and modulation system. These include periodontal pain, tempromandibular disorders or pain from the salivary glands.

2. Primarily neuropathic which can be attributed to abnormal pain signal processing due to for example surgical or traumatic injury to a peripheral nerve

7 female patients with chronic pain attributable to nerve damage in the trigeminal distribution refractory to conventional therapies including treatment with analgesics, antiepileptics and nerve blocks.

Patients received ketamine as either an IM, IV, or single dose followed by continuous infusion on an individual basis.

3 patients with >5 yrs of pain had no relief following ketamine administration
1 patient reported relief only during the infusion
3 patients all with <3 yrs of pain reported consistent and prolonged pain relief lasting more than 12 hours.
Rabben et al 1999

Double Blind Crossover Trial – enrolled 30 patient with trigeminal neuralgia

IM protocol
  IM injection of 1.0mg/kg meperidine or 0.4mg/kg ketamine with midazolam

9 patients reported no significant decrease in pain with either ketamine or meperidine

8 patients displayed analgesic effect many hours after ketamine administration; 6/8 preferred ketamine

9 patients reported short term analgesic effect 3/8 preferred ketamine
Ketamine for Refractory Headache: A Retrospective Analysis (Schwenk et al, Regional Anesthesia and Pain Medicine 2018)

Retrospective analysis of 61 (59 migraine, 2 cluster HA) patients admitted over 3 years for 5 days of IV therapy which included continuous ketamine gtt (upper limit 1mg/kg/hr).

48 (77%) of patients were immediate responders defined as a patient with a $\geq 2$ point decrease in VAS from start to final pain score in the hospital.

Max improvement occurred on mean day 4.56.

Sustained response defined as sustained 2 point improvement in VAS occurred in 40% of patients at visit 1 (mean 38.1 days).

39% at visit 2 (mean 101.3 days)

No differences regarding demographics, opioid use, or fibromyalgia between immediate responders and non responders.
Phantom Limb Pain

Phantom limb pain is characterized by cortical sensory perception of an amputated body part.

The peripheral afferent theory of phantom limb pain centers around the neuroma as the primary pain generator which then functions as a driver for the development of secondary central changes.
Parkes et al (1973)

45 patients with phantom limb pain were administered ketamine vs saline placebo peri-operatively. No statistically significant difference was observed at 3 days, 3 months or 6 months. However there was a strong trend towards a significant rate of pain reduction, with a p value of 0.28 at 6 months, where 47% of the group who received ketamine continued to have phantom limb pain vs 71% in the control group.

Nikolajsen et al (1994)

Double blind saline controlled study which enrolled 11 patients with PLP. Administered an IV ketamine bolus 0.1mg/kg over 5 min following by an infusion of 7µg/kg/min. All 11 pts responded with decreased phantom limb and stump pain as assessed by VAS, and the McGill Pain Questionnaire. Pressure thresholds were significantly increased, pain evoked by tapping on dysesthetic skin areas or wind up like pain was also reduced significantly by ketamine.

No effect was observed on thermal stimulation.
Post Herpetic Neuralgia

Post herpetic neuralgia occurs after reactivation and resolution of shingles associated with varicella zoster.

The etiology of this pain is not well understood.

It can be associated with allodynia which maybe related to formation of new connections involving central pain transmission neurons.

Other patients with PHN may experience severe spontaneous pain without allodynia possibly secondary to increased spontaneous activity of de-afferented central neurons or reorganization of central pain transmission neurons.

Alternative theories include possible loss of large inhibitory fibers with associated increase in the number of small excitatory fibers.
Eide et al (1994)
8 pts with post herpetic neuralgia were enrolled. Pain and sensory thresholds were examined before and after administration of ketamine, morphine and saline.

Sensory thresholds were unchanged with administration of ketamine however, in 4 patients ketamine normalized abnormal heat pain sensations likely due to a central effect.

Allodynia was significantly reduced by both ketamine and morphine. This study also demonstrated significant worsening of pain evoked by repeated pricking of the affected skin after administration of morphine. In contrast wind up pain was significantly reduced with Ketamine.

This same group performed a second open prospective study of 5 pts who were established ketamine responders. Patients were administered continuous SC ketamine in increasing doses (0.05, 0.075, 0.10 or 0.15mg/kg/hr) over the course of one week.

Allodynia was maximally reduced 59-100% at 1 one week with 0.05mg/kg/hr ketamine gtt and wind up was maximally reduced 60-100% at one week with 0.15mg/kg/hr ketamine gtt.

Relief of continuous pain as evaluated by VAS was demonstrated at the infusion rate of 0.05mg/kg/hr but was most pronounced at 0.15. All patients reported that ketamine reduced the severity of continuous pain as well as severity and number of attacks of spontaneous pain.
In Tsuneyoshi et al 7 patient with post herpetic neuralgia were enrolled and received a low dose ketamine drip at 0.2mg/kg/hr. Course of infusion therapy was tailored to 4-24d depending on patient response.

85% of patient (6/7) reported a positive response.

After administration of the first dose adequate pain relief was obtained within one hour and VAS scores remained low (5-20mm) for at least 8 hrs, near return to baseline was observed at 24hrs.

5 year retrospective analysis, identified 49 patients with refractory pain for at least six months who were being managed with outpatient ketamine infusions, diagnoses were varied and included CRPS, intractable HA, chronic back pain, somatic pain, fibromyalgia, central neuropathic pain, PHN, and cervical radiculopathy.

Of the 49 patients only 29 could be contacted by phone for follow up. All patients reported a significant reduction in VAS score of 5.9 or 77% pain relief.

27% reported pain relief lasting several hours after the infusion.

73% reported pain relief for more than 1-2 days.

38% experienced relief lasting more than three weeks.
A Bernoulli statistical model was then used to calculate the probability that a random patient suffering from chronic pain would respond to treatment.

To carry out the confidence interval calculation

1. they used a standard approximation of the outcomes in a repeated Bernoulli trial to a normal distribution
2. the second assumption was that the patients were statistically independent

These calculations showed a 59-85% probability that a patient with severe pain would have a positive response either short or long term to ketamine infusion, furthermore there was a 23-51% probability that this pain relief in this random patient would last for more than three weeks.

If however one assumes that the remainder of the patient who could not be contacted for f/u did not have long term relief the calculation show a 13-31% probability that pain relief would last for more than three weeks.

Ultimately this study provides support for consideration of ketamine as a third line agent in the treatment of refractory chronic pain of varying etiologies.
Palliative Care Guidelines (ESMO)

Ketamine for the palliative treatment of neuropathic pain should be done under the care of a specialist.

Ketamine maybe considered for management of complex neuropathic and vascular pain syndromes where opioids have become ineffective.

Ketamine should only be administered after combination of opioid and oral adjuvants have become ineffective.

Ketamine is contraindicated in patients with:
- Intracranial HTN
- Delerium
- Recent Hx of Seizure and
- Psychosis

**A cochrane review found insufficient trials to determine the safety and efficacy of ketamine in relieving cancer pain.**
Adverse Effects....

Central Nervous System

Psychedelic effects associated with ketamine occur in a dose dependent manner. Both internal and external perception of reality are affected which can result in auditory or visual hallucinations, paranoid ideas, anxiety, inability to control thoughts, increased awareness of sound or color, and de-realization of time and space. Drug highs can be dysphoric or euphoric. Complete prevention is not possible however, they maybe attenuated with benzodiazepines or α2 adrenergic agonists.

Dizziness, blurred vision, vertigo, N/V, nystagmus, dysphasia, and impaired motor function

Impairment in working memory, encoding information into episodic memory and semantic memory

A single study examined the safety of high dose long term ketamine use in CRPS patients (anesthetic doses over 5 days) demonstrated no severe cognitive deficits
**Cardiovascular**

Direct negative ionotropic effect

Indirect stimulatory effect on the cardiovascular system through activation of the sympathetic nervous system which results in the systemic release of catecholamines, inhibition of norepinephrine reuptake at peripheral nerves and non-neuronal tissues such as the myocardium, as well as, norepinephrine release from sympathetic ganglia. Patients can develop tachycardia, systemic and pulmonary hypertension, increased CO and MVO$_2$.

**Hepatic**

There have been some reports in the literature demonstrating elevated liver function tests following anesthetic and sub anesthetic doses of ketamine. The etiology of this is poorly understood however it maybe related decreased hepatic O2 delivery, increased lipid peroxidation and formation of free radicals.

Noppers et al observed a significant increase in AST ALT and Alk phos following a 100h treatment trial in CRPS Type I pts such that the trial was terminated.
**Ketamine Cystitis**

20 – 30% of ketamine abusers will report bladder symptoms such as dysuria, frequency, nocturia, and urgency.

Symptomatic abusers are reported to have an average intake of 3000mg/day.

Cystoscopy can reveal epithelial inflammation, ulceration, neovascularization, and contact bleeding.
If you recall the Oral administration of ketamine is associated with higher serum levels of norketamine compared to other routes of administration. Analgesic effects of IV/IM ketamine have been observed at plasma concentrations of 100-200ng/mL, in contrast to oral ketamine at 40ng/mL.

Considering this and the relatively high plasma concentration of norketamine, norketamine is thought to play a large role in the analgesic effect observed with administration of oral ketamine.
22 studies which described a total of 166 patients receiving oral ketamine from 1994-2008.

No clear dose response relationship was observed with administration of oral ketamine which maybe related to several factors including variability in hepatic metabolism, variance in plasma levels of norketamine, reduced bioavailability, and the association of an anti hyperalgesic effects at low doses and anti nociceptive effects at higher doses.

Equianalgesic potency of ketamine SQ/ketamine PO ranged from 1:0.3 to 1:8.5 with median 1:1.

Effective daily dosing ranged from 45mg to 1000mg in a patient with post herpetic ophthalmic neuralgia once again no consistent dose response was established.

The number of divided doses needed for continuous analgesic also ranged from once daily to up to six times/day.

The duration of effect also varied from several to 24 hours.
90% of case reports present positive findings regarding the efficacy of ketamine, larger comparative controlled trials show an efficacy of approximately 25%.
Ketamine racemic

Oral Ketamine

Parental Ketamine

Single Test Dose

Continuous Treatment with IV infusion or SC Ketamine

Converted to Equipotent oral dose of ketamine

Equianalgesic potency of ketamine SC/PO 1:1
Oral Ketamine Dosing

Monitored placebo controlled IV trial of ketamine to assess therapeutic benefit
0.25 – 0.5mg/kg over 30 minutes
Initiate oral ketamine 0.5mg/kg

Ketamine naïve patient
0.5mg/kg oral racemic ketamine
0.25mg/kg oral S[+] ketamine

Dose Increases
0.25 mg/kg or 0.5mg/kg increments
Clinical Practice

Off Label

No commercially available oral formulation

Pharmaceutical quality ketamine is not readily available as a raw material

**Unclear whether long term use of ketamine in chronic pain patients produces dependence**
Conclusions

Limited number of RCTs provide evidence that long term treatment of chronic pain (neuropathic pain) with Ketamine will provide prolonged pain relief.

Oral ketamine currently has a limited role as an add on therapy in complex chronic pain patients.