KETAMINE IN CHRONIC PAIN
ORAL and TOPICAL USE

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Objectives of the Talk

1. A relook at ketamine as an ANALGESIC, and NMDA receptors role in Pain

2. A Review of Literature for Peripheral/Topical Ketamine Use: does ketamine have peripheral actions?

3. A review of literature and closer look at RCTs of oral Ketamine use

4. Pharmaco-kinetic and Pharmaco-dynamic Considerations pertinent to oral treatment

5. Oral Treatment: Initiation, Dose conversion and long term treatment

6. A possible treatment algorithm to incorporate ketamine use in chronic pain

7. Challenges and Limitations
Possible Mechanisms of Ketamine’s Analgesia

1. NMDA antagonism

2. Other Possible Mechanisms of Ketamine Actions

- **Opioid**: It is said to be an antagonist at mu and agonist at kappa receptors (Sinner and Graf, White 1982).

- Ketamine is known to produce local anesthetic effect similar to lidocaine and bupivacaïne. Its LA potency is supposed to be comparable to Procaine (Pederson-Anesthesiology).

- Activation or increase in the activity of descending monoaminergic system (serotonergic).

- Effects on muscarinic cholinergic receptors are not shown to be responsible for analgesia.
Ketamine and Analgesia—several questions

- The role of Ketamine as a perioperative analgesic in established but the mechanisms are not entirely clear
- **How does it cause analgesia?**
  - Anti-nociception?
  - Dissociative at higher level?
  - Behavioural?
- Are NMDA receptors involved in nociceptive pain?
- **Does Nociceptive pain lead to sensitization** and other changes seen with neuropathic pain?
- **NMDA receptor mechanism is not supported by normal (physiological) pain response** such as that following transient noxious stimulation and tissue damage (Mao, 1999).

In general, blockade of NMDA receptors does not change baseline nociceptive response to either heat or mechanical stimulation or baseline spontaneous pain behaviours in experimental animals. Thus, **NMDA receptor antagonists are most likely to reduce the gain of pain intensity but not to remove a normal pain response.** That is, an NMDA receptor antagonist per se is unlikely to act as an analgesic.
How does the changes which occur in Neuropathic Pain differ from Nociception pain apart from being persistent nociception?

Are there CENTRAL EFFECTS OF Ketamine which are not purely analgesic but they seem so because of its effect on pain related behaviour?

Some of the studies have found that ketamine can have an effect on pain disability indices, despite there being not much decrease in actual pain, either spontaneous or evoked.

The most obvious effect of subanesthetic ketamine in human volunteers was altered perception (Oye 1991). This also involves decreasing pain perception.

Translational Gap between Basic Scientific Experiments to Clinical Research

- Mismatch in Pain Evaluation tools (simple VAS scores VS specific modality changes)
- Inability to measure behavioural end points in basic science
- Measures of sensitization- thermal hyperalgesia VS mechanical allodynia
- Spontaneous pain (clinically predominant) VS Evoked pain elements (stimulus-induced nociception such as thermal hyperalgesia is the most predominant test method used in basic research to assess a persistent pain state)

Mao J. Translational pain research: bridging the gap between basic and clinical research Pain 97 (2002) 183–187
Neuropathic Pain: an analysis of its characteristics
(Contrary to nociceptive pain, which results from physiological activation of nociceptors)

- Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.

- Neuropathic pain is characterized by spontaneous and provoked pain, by other positive symptoms such as paresthesias and dysesthesias, and by negative signs (sensory deficits) reflecting the neural damage.

- How can we differentiate those neuropathic pain conditions which does not have Positive or Negative Symptoms

NMDA antagonists act preferentially on the evoked pain modalities.

Basic research suggest that the NMDA receptor mechanism may be more sensitive to thermal hyperalgesia than mechanical allodynia (Tal and Bennett, 1994)
Central sensitization: Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. It is characterised by increased spontaneous activity, decrease in response threshold, enlarged receptive field (RF) areas, and an increase in responses evoked by large and small calibre primary afferent fibers (Jun Li, 1999; Cook, 1987).

Wind-up is a progressive, frequency-dependent facilitation or increase in the magnitude of C-fiber evoked responses, of the responses of a neurone observed on the application of repetitive (usually electrical) stimuli of constant intensity.

Hyperalgesia, primary: Hyperalgesia at the site of injury. It is often believed that primary hyperalgesia is mainly due to sensitization of nociceptive nerve endings.

Hyperalgesia, secondary: Hyperalgesia in an area adjacent to or remote of the site of injury. This form of hyperalgesia is not caused by sensitization of nociceptive nerve endings but solely due to changes in the processing of sensory information in the central nervous system.

While the induction of secondary hyperalgesia requires activity in nociceptive nerve fibers, its maintenance is independent of an afferent barrage as local anesthetic block of the injured site preempts but does not reverse secondary hyperalgesia.
Hyperalgesia: Increased pain sensitivity

It Is Not Synonymous With Central Sensitization; however hyperalgesia is one of its by product.

**IASP: Hyperalgesia may include both a decrease in threshold and an increase in supra-threshold response.**

In many cases it may be difficult to know whether or not the test stimulus is capable of activating nociceptors.

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**Alldynia:** Pain in response to a non-nociceptive stimulus

It is now reserved to those forms of pain only that are clearly caused by excitation of low-threshold (A delta) sensory nerve fibers.

**This term should only be used, when it is known that the test stimulus is not capable of activating nociceptors.**

At present, dynamic tactile allodynia to tangential stroking stimuli, e.g., brushing the skin is the only established one.
It has been suggested that depression or symptoms of depression (transient or chronic) are an integral part of the affective or emotional component and a consequence of acute and chronic pain conditions and the mechanisms by which pain and depression are maintained differ and are partly independent.

(Romero-Sandoval, E. Alfonso: Anesthesiology, 2011)

Ketamine, in doses that did not affect evoked pain-related behaviors (10–20 mg/kg), effectively reduced depression-like behaviors (immobility using the forced swim test, and reduced sucrose preference using the sucrose preference test).

Ketamine’s effects on depression-like behaviors lasted at least 5 days, far outlasting its presence in meaningful concentrations in blood or tissue.

Importantly ketamine did not relieve the hypersensitivity to tactile stimuli after peripheral nerve injury and yet recovered the rats’ normal response to physically react to certain situations and the ability to choose a sweet solution (supposedly pleasurable) over plain water.


Where does Ketamine have predominant actions?

Generation----Modulation---Perception—Behaviour
Depression and Pain

Does Ketamine Improve the Quality of Life of Patients in Chronic Pain by Targeting Their Mood?

A large population of patients comorbidity experiences chronic pain and depression or symptoms of depression (52% in pain clinics, at 93% in chronic pain clinics). There is overlap, acute, or chronic, in the terms, and for many there is a combination of both. The future of pain control is to target both the treatable and the treatable. It is difficult to elicit or determine in patients with chronic pain or chronic pain with depression. Therefore, the return to normal behavior after antidepressant treatment is not reflected in clinical practice. The return to normal behavior after ketamine administration may not reflect the return to normal behavior in patients. The results of this study indicate that ketamine treatment is effective in the treatment of depression and in the treatment of pain. The return to normal behavior after ketamine treatment is not reflected in clinical practice.

BETWEEN BEDSIDE AND BENCH

Lifting the mood with ketamine

James W Murrough & Dennis S Charney

Major depression is one of the most disabling and costly medical illnesses worldwide. Despite the large public health burden, the pace of therapeutic discovery for depression has markedly lagged behind other areas of medicine. Current treatments for depression target mostly components of the serotonergic or noradrenergic neurochemical systems and are limited in efficacy, showing only a delayed onset of therapeutic benefit of at least two to four weeks. In contrast, studies showing a rapid-onset antidepressant effect for the anesthetic agent ketamine—a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist—even in people with treatment-resistant depression (TRD), have engendered a new wave of clinical and basic science research focused on the glutamate system and the NMDA receptor complex in mechanisms of depression and its treatment.

An initial series of studies showed that a variety of NMDA receptor antagonists—the competitive antagonist 2-amino-7-phosphonoheptanoic acid, the noncompetitive antagonist dizocilpine and a partial agonist at the glycine modulatory site of the NMDA receptor called 1-amino-2-naphthalene-acetic acid—induced antidepressant-like effects similar to the tricyclic antidepressant imipramine in inescapable stress animal models of depression. Subsequently, a series of studies by the same group showed that chronic—but not acute—

Effects of Ketamine on Sensory Perception: Evidence for a Role of N-Methyl-D-Aspartate Receptors

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Abstract

The direct action of ketamine was examined as a probe for N-methyl-D-aspartate receptor-meditated neurotransmission in humans. Both ketamine, in clinically relevant concentrations, displaced [3H]ketamine (5 nM) from specific binding sites (phosphorylase a) in membrane fractions of both homogenates. In both cases, only a small fraction of the total binding at these concentrations was labeled by ketamine. The results of this study support the hypothesis that the direct action of ketamine is mediated by direct inhibition of the neurotransmitter release from the presynaptic terminal. The results are consistent with previous reports that a direct action of ketamine is mediated by direct inhibition of the neurotransmitter release from the presynaptic terminal.

Ten in-patients with neuropathic pain participated in this single-blind, placebo-controlled study after giving written informed consent.

Changes in pain perception were assessed using a numerical rating scale for pain. Behavioral changes, including psychotomimetic effects, were assessed using the Brief Psychiatric Rating Scale (BPRS). Electroencephalograms (EEG) and electrooculograms (EOG) were recorded continuously throughout the testing period.

Pain reduction was significantly correlated with ketamine-induced changes in hallucinatory behavior and excitement as measured by the BPRS.

Cortical neural networks that exhibit a high representational activity develop higher-order, self-referential representations as a result of self-organizing processes. The neural assemblies instantiate mental representations; hence consciousness depends on the rate at which large active assemblies are generated. The formation of assemblies involves the activation of the NMDA receptor channel complex which controls different forms of synaptic plasticity including rapid changes of the connection strengths. The various causes of unconsciousness (e.g., anaesthetics or brain stem lesions) have a common denominator: they directly or indirectly inhibit the formation of assemblies.
KETAMINE blocks the NMDA channel by 2 distinct mechanisms;

1) it blocks the open channel and thereby reduces channel mean open time—this is the well known “frequency dependent” mechanism

2) and 2) it decreases the frequency of channel opening by an allosteric mechanism (Orser 1997).
NMDARs display a number of unique properties:

1. The receptor controls a cation channel that is highly permeable to monovalent ions and calcium.

2. Simultaneous binding of glutamate and glycine, the co-agonist, is required for efficient activation of NMDAR (co-incidence detector).

3. At resting membrane potential the NMDAR channels are blocked by extracellular magnesium and open only on simultaneous depolarization and agonist binding, thus both depolarization of the postsynaptic neuron and presynaptic release of glutamate and glycine are required for maximum current flow through the NMDAR channel.

NMDA receptors are heteromeric protein complexes, and three families of NMDAR subunits have been identified: NR1, NR2 and NR3.

Functional NMDAR channels require a combination of NR1 (essential) and at least one of the NR2 subunits (Zhou 2011, Petrenko 2003).

It also has been acknowledged that the NR1 subunit is necessary for the NMDA receptor-coupled channel activity and the NR2 subunit is likely to modulate the properties of such channel activities.
Ketamine induces both an open and closed blockade of NMDA receptor by acting 2 distinct sites: one located within the channel pore and the other associated with the hydrophobic part of the membrane protein. The closed channel actions result from membrane associated site.

The predominance of closed channel blockade at low concentrations of ketamine suggests that its analgesic properties might result from the closed rather than open channel blockade. Drugs like memantine and amantadine, have no appreciable anesthetic or analgesic properties and inhibit NMDARs by purely open channel blockade.

This dual mechanism may be clinically relevant in treating patients with low dose and high dose ketamine, and may in fact act through different pathways apart from molecular mechanisms.

Multiple Mechanisms of Ketamine Blockade of N-methyl-D-aspartate Receptors
Opioids, Tolerance and Hyperalgesia

- A growing body of evidence now points to a **general interaction between the NMDA and opioid receptor systems in many aspects of pain and pain modulation.**

- The clinical interactions between NMDA and opioid receptors could occur in 2 directions. Thus, any condition which would result in activation of NMDA receptors within the CNS could modulate opioid receptors causing reduced efficacy of opioid analgesia; conversely, repeated treatment with opioids could set up a condition mimicking ongoing nociceptive input through interactions between opioid and NMDA receptors.

- Apparently, a common factor in both directions is the activation of NMDA receptors.

- Most likely **kappa receptors** are responsible for these effects.
Peripheral Ketamine Effects (2 mechanisms which could be responsible)

1. Ketamine and Peripheral NMDA antagonism

BASIC STUDIES

- There is a role of peripheral excitatory amino acids modulated by NMDA receptors in pain and analgesia.

- The analgesic effect of these drugs most likely occurs as a result of a blockade of NMDA receptors located on unmyelinated axons in the skin.

- Nociceptive behaviors observed following intraplantar injection of complete Freund’s adjuvant, capsaicin or formalin can be attenuated by local intraplantar injection of MK-801. (Davidson 1998)

- Approximately 20% of the unmyelinated cutaneous axons at the dermal-epidermal junction immunostain for the NMDAR1 subunit of the NMDA receptor.

- The decrease in formalin induced pain by at least two mechanisms: A. reduce primary afferent activity which would ultimately reduce central sensitization of dorsal horn cells and, or, B. reduce the phase-2 inflammatory response.
Peripheral administration of NMDA, AMPA or KA results in pain behaviors in rats

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Key Words: Glutamate; Non-NMDA; CNQX; MK-801; Ionotrophic; Allodynia; Hyperalgesia

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The Role of *N*-Methyl-\(d\)-Aspartate (NMDA) Receptors in Pain: A Review

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There is accumulating evidence to implicate the importance of *N*-methyl-\(d\)-aspartate (NMDA) receptors to the induction and maintenance of central sensitization during pain states. However, NMDA receptors may also mediate peripheral sensitization and visceral pain. NMDA receptors are composed of NR1, NR2 (A, B, C, and D), and NR3 (A and B) subunits, which determine the functional properties of native NMDA receptors. Among NMDA receptor subtypes, the NR2B subunit-containing receptors appear particularly important for nociception, thus leading to the possibility that NR2B-selective antagonists may be useful in the treatment of chronic pain. (Anesth Analg 2003;97:1108–16)

Clinical Studies


Warncke T, Jorum E, Stubhaug A: Local treatment with the *N*-methyl-\(d\)-aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action. Neurosci Lett 1997; 227:1-4
Peripheral Analgesic Effects of Ketamine in Acute Inflammatory Pain

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Background: This study examined the analgesic effect of local ketamine infiltration, compared with placebo and systemic ketamine, in a human model of inflammatory pain.

Methods: Inflammatory pain was induced by a burn (at 47°C for 7 min; wound size, 2.5 × 5 cm) on the calf in 15 volunteers on 3 separate days with 7-day intervals. They received either (1) subcutaneous infiltration with ketamine in the burn area (local treatment) and contralateral placebo injections, or (2) subcutaneous ketamine contralateral to the burn (systemic treatment) and placebo in the burn area, or (3) placebo on both sides. The study was double-blinded and the order of the treatments was randomized. Hyperalgesia to mechanical and heat stimuli was examined by von Frey hairs and contact thermodes (3.75 and 12.5 cm²), and pain was rated using a visual analog scale (0–100).

Results: The burns produced significant hyperalgesia. Local ketamine infiltration reduced pain during the burn injury compared with systemic treatment and placebo (P ≤ 0.01). Heat pain thresholds were increased by local ketamine treatment compared with placebo immediately after injection (P ≤ 0.03), and so were the mechanical pain thresholds (P = 0.02). Secondary hyperalgesia and suprathreshold pain responses to heat and mechanical stimuli were not significantly affected by local ketamine. No difference between local ketamine and placebo could be detected 1 h and 2 h after the burn.

Conclusions: Ketamine infiltration had brief local analgesic effects, but several measures of pain and hyperalgesia were unaffected. Therefore, a clinically relevant effect of peripheral ketamine in acute pain seems unlikely. (Key words: N-methyl-D-aspartate receptor antagonist; psychophysics; thermal injury.)

KETAMINE is a rapidly acting anesthetic and analgesic agent, which has been used for more than 30 yr in general anesthesia practice. However, recent research suggests new clinical uses, such as for pain relief by peripheral application. The presence of ionotropic glutamate receptors, such as N-methyl-D-aspartate (NMDA) receptors, on peripheral sensory axons could be the basis of peripheral ketamine-induced analgesia. Peripheral administration of ligands to these receptors evoked nociceptive behaviors in rats, and local administration of the NMDA antagonists, MK-801 and ketamine, and non-NMDA glutamate receptor antagonists has reduced nociceptive behaviors in rats.

Only a few human studies of the peripheral analgesic effect of ketamine exist. A study of acute postoperative pain in a limited number of patients suggested that ketamine enhanced local anesthetic and analgesic effects of bupivacaine by a peripheral mechanism. Further, subcutaneous injection of ketamine reduced human hyperalgesia after an experimental burn, and the authors of that study suggested a long-lasting analgesic effect (7 days) based on observations in six persons. However, two other studies in humans (n = 5 and n = 3) suggest brief local anesthetic effects (maximum duration, 20 min) when using ketamine for subcutaneous infiltration.

Therefore, our aim was to examine the analgesic effect of local ketamine infiltration, compared with placebo and systemic ketamine, in a human model of in-
Peripheral Ketamine Effects

2. Local Anesthetic Effect (through blockade of Cations

- In clinical studies, ketamine has been used for intravenous regional, spinal, and epidural anesthesia and for regional pain treatment.

- The local anesthetic effect has been related to a depression of the potential-sensitive Na\(^+\) and K\(^+\) currents in the peripheral nerve, as shown in voltage-clamp investigations.

- The concentrations necessary, however, were much greater than those in clinical systemic administration of general anesthesia and could only be reached by local application (Brau 1997).

- Ketamine blockade of sodium and potassium channels in peripheral nerve membranes shows no stereoselectivity.

Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients

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Abstract

Patients with unilateral ($n = 14$) and bilateral ($n = 4$) hemoirrhaphy participated in this study. With bilateral hemoirrhaphy, at the end of the surgery, the wound was infiltrated with a solution of bupivacaine 0.5\% and ketamine 0.3\% on one side and a solution of bupivacaine 0.5\% only, on the other. With unilateral hemoirrhaphy, the patients were randomly assigned to one of two groups ($n = 7$). One group at the end of the surgery received the infiltration with a solution of bupivacaine 0.5\% and ketamine 0.3\%, the other group received the infiltration with a solution of bupivacaine 0.5\% only. The duration of the local anesthetic (response to a von Frey filament) and postoperative analgesic (time to mild spontaneous pain) effects of the infiltrations, as well as wound pain threshold 24 h after surgery (pressure algometry), were determined. In patient with unilateral hemoirrhaphy, the addition of ketamine for wound infiltration enhanced the duration of infiltration anesthesia ($206 \pm 76 \text{ versus } 343 \pm 108 \text{ min, } P < 0.02$) and analgesia ($240 \pm 45 \text{ versus } 420 \pm 151 \text{ min, } P < 0.03$). Similar enhancement of the local anesthetic effect was observed in patients with bilateral hemoirrhaphy. The increase in pain threshold to pressure on the wound with the addition of ketamine was evident in bilateral hemoirrhaphy patients and also with a combination of bilateral and unilateral results ($1.39 \pm 0.40 \text{ versus } 2.35 \pm 0.92 \text{ kg, } P < 0.02$). In the group of five volunteers, the subcutaneous infiltration with 0.3\% ketamine produced a local anesthetic effect lasting only 10–20 min. The results indicate that ketamine acting via a peripheral mechanism can profoundly enhance anesthetic and analgesic actions of a local anesthetic administered for infiltration anesthesia.

The study involved 5 patients ranging from 25 to 70 years of age. The dose used ranged from 0.093 mg/kg to 9.33 mg/kg. All reported significant relief of pain and wished to continue the therapy. The average (NAS) score pre-application was 8.8 and post 1.6.

The authors proposed that part of the effect of topical ketamine might lie in interruption of afferent transmission via interactions with local Na+-K+ channels that may reduce centrally mediated hyperexcitability.

### Table 1 Responses of case studies

<table>
<thead>
<tr>
<th>Patient case</th>
<th>Pain diagnosis</th>
<th>Ketamine dose (mg/kg)</th>
<th>NAS (preapplication)</th>
<th>NAS (postapplication)</th>
<th>Reduction in pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RSD</td>
<td>0.37</td>
<td>9–10</td>
<td>4</td>
<td>55–60</td>
</tr>
<tr>
<td>2</td>
<td>RSD</td>
<td>0.20</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Postherpetic neuralgia</td>
<td>0.32</td>
<td>8</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>Post laminectomy syndrome, radiculopathy</td>
<td>0.24</td>
<td>8.5</td>
<td>0 (calf)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (back)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–2 (hip)</td>
<td>76–88</td>
</tr>
<tr>
<td>5</td>
<td>RSD</td>
<td>0.13</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

NAS, numeral analogue scale; RSD, Reflex Sympathetic Dystrophy.
### TOPICAL STUDIES

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Patient population and numbers</th>
<th>Design/Methodology</th>
<th>Outcomes</th>
<th>Withdrawal/Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barton (2011)</td>
<td>DB RCT PLC</td>
<td>N=208; Chemotherapy associated peripheral neuropathy for &gt;1 month</td>
<td>Topical Gel of 10 mg baclofen, 40 mg amitryptyline and 20 ug ketamine vs placebo 10ml applied daily x 4 weeks</td>
<td>Statistically significant improvement in motor neuropathy symptoms on CIPN-20 questionnaire; trend towards improvement in sensory neuropathy symptoms</td>
<td>No significant difference in adverse events between placebo and treatment</td>
</tr>
<tr>
<td>Lynch (2003)</td>
<td>DB RCT PLC; subsequent open-label prospective in &quot;ketamine responders&quot; subgroup</td>
<td>N=20; Chronic neuropathic pain</td>
<td>Topical ketamine cream (0.5%) vs topical amitryptyline cream (0.1%) vs combination cream vs placebo 5 ml daily x 2 days; subsequent 7 day open label trial of combination cream</td>
<td>No difference on McGill Pain Questionnaire or VAS between treatment arms in 2 day trial; open-label arm showed significant decrease in pain by day 3-7</td>
<td>2 patients experienced &quot;minor&quot; side effects</td>
</tr>
<tr>
<td>Lynch (2005)</td>
<td>DB RCT PLC</td>
<td>N=92; Diabetic neuropathy, Post-Heraptic neuralgia or Posttraumatic neuralgia</td>
<td>Topical ketamine cream (0.1%) vs Topical amitryptyline cream (0.2%) vs combination cream vs Placebo (emulsant only); all creams 4ml TID x 3 weeks</td>
<td>No statistically significant difference in pain reduction on NRS-PI scale between study arms; all arms generated 1-1.5 decrease in spontaneous pain</td>
<td>1 episode of local skin irritation; 1 swollen feet; 2 episodes of drowsiness</td>
</tr>
<tr>
<td>Vranken (2005)</td>
<td>DB RCT PLC</td>
<td>N=33 Central Neuropathic Pain</td>
<td>Iontopatch administered 50 mg ketamine vs 75 mg ketamine vs placebo (NS) over 24hr x 5 days</td>
<td>No significant difference between any groups in change of VAS scores after 7 days; significant improvement in PDI, EQ-5D and SF-6 scores in the 75 mg ketamine group</td>
<td>3 patients in ketamine arms reported sedation, 1 each of nausea/vomiting, confusion, dizziness, vivid dreams,</td>
</tr>
</tbody>
</table>
SUMMARY OF PRESENT EVIDENCE-for topical

- There is some evidence to argue for peripheral NMDA activation via glutamate.
- The potency of local anesthetic action needs more investigation.
- Animal studies have shown the decreased pain behaviours with peripheral ketamine, can it still be systemic?
- Human studies have not been conclusive.
- The topical application is not used on its own in any study (in any RCT’s).
- It is difficult to say that there is any good evidence for topical ketamine application (Class III). Proper well designed studies with adequate patients are needed.
Oral Ketamine

- The oral ketamine therapy can have significant advantages in terms of patient comfort and ease of use.

- It is preferred more commonly in cancer or palliative care patients.

- Clinicians usually test the patients for ketamine responsiveness by other parenteral route or intranasal or even sublingually.

- Positive correlation was found between a long pain history and lack of analgesic effect and also between a short pain-history and a long-term analgesic effect of low-dose ketamine. (Rabben & Oye 1999, Matheisen).

- The observation that oral administration is associated with higher serum concentrations of the main metabolite of ketamine, norketamine, compared to other routes of administration has led to the speculation that norketamine contributes to the analgesic effects of ketamine.

Pharmacokinetics and Pharmaco-dynamic Considerations

- The oral bioavailability of ketamine after a single oral dose is about one fifth of the availability after an intravenous injection. On the other hand, the bioavailability of norketamine is similar between the two types of administrations, with much higher peak plasma concentrations (200 ng/ml) reached after oral administration (Grant et al., 1981).

- Analgesic effects of ketamine observed with plasma levels of 100–200 ng/ml (sum of S- and R-isomer) following intramuscular and intravenous administration. Effective analgesia following oral dose occurs at much lower concentrations of ketamine (40 ng/ml).

- The elimination half-life is 2–3 h for ketamine (Grant et al., 1981) and approximately 4 h for norketamine (Product information leaflet, 1999).

- A recent study it has shown that norketamine binds to the PCP site of the NMDA receptor at low micro-molar concentrations in the rat brain and spinal cord.

PHARMACOKINETICS AND ANALGESIC EFFECTS OF I.M. AND ORAL KETAMINE

I. S. Grant, W. S. Nimmo and J. A. Clements

SUMMARY

The pharmacokinetics and analgesic effects of i.m. and oral ketamine in a dose of 0.5 mg kg\(^{-1}\) were determined in six healthy volunteers. Analgesia was measured by the submaximal effort tourniquet test. Following both routes of administration, ketamine prolonged the period of pain-free ischaemic exercise. Pain thresholds were increased at 15 min and 30 min after i.m. injection and at 30 min after oral ketamine. The plasma ketamine concentration associated with analgesia was 150 ng ml\(^{-1}\) following the i.m. dose, but only 40 ng ml\(^{-1}\) after the oral dose. Oral administration was, however, associated with much greater concentrations of the metabolite norketamine, which may have contributed to the analgesic effect.
Pharmacodynamic Profiles of Ketamine (R)- and (S)- with 5-Day Inpatient Infusion for the Treatment of Complex Regional Pain Syndrome

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**Background:** Ketamine might be effective in blocking central sensitization of pain transmission neurons through its effect on NMDA receptors in refractory Complex Regional Pain Syndrome (CRPS) patients. At higher doses, ketamine infusions can be associated with significant risks; outpatient therapy requires return visits for a 10-day period with variable efficacy and duration.

**Objective:** This study determined the efficacy of a 5-day moderate dose, continuous racemic ketamine infusion. The pharmacodynamic responses to racemic ketamine and norketamine were examined.

**Design:** Observational study

**Methods:** In this study, ketamine was titrated from 10-40 mg/hour in 16 CRPS patients, and maintained for 5 days. Pain was assessed daily. Ketamine and norketamine concentrations were obtained on Day 1 before starting the infusion; at 60 to 90 minutes; 120 to 150 minutes, 180 to 210 minutes, and at 300 minutes after initiation of the infusion on Days 2, 3, 4, and 5; and on Day 5 at 60 minutes after the conclusion of the infusion. The plasma concentrations of (R)-ketamine, (S)-ketamine, (R)-norketamine and (S)-norketamine were determined using an enantioselective liquid chromatography–mass spectrometry method.

**Results:** Ketamine and norketamine infusion rates stabilized 5 hours after the start of the infusion. The subjects showed no evidence of significant tachycardia, arterial oxygen desaturation, or hallucinatory responses. Subjects generally experienced minimal pain relief on day one followed by significant relief by day 3. Mean pain scores decreased from the 8-9 to 3-5 ranges; however, the analgesic response to ketamine infusion was not uniform. On day 5, there was little or no change in the pain response observed as the worst pain experienced over the last 24 hours in 37% of the subjects. (R)- and (S)-ketamine concentrations peaked at 240-300 min. (R)- and (S)-norketamine concentrations were lower and peaked on Day 2 of the infusion, as opposed to Day 1 for (R)- and (S)-ketamine. Significant pain relief was achieved by the second day of infusion and correlated with the maximum plasma levels of ketamine and norketamine. Pain relief continued to significantly improve over the 5 days infusion at concentrations of 200-225 ng/mL for (R)- and (S)-ketamine, and 90-120 ng/mL for (R)- and (S)-norketamine.

**Conclusions:** A 5-day ketamine infusion for the treatment of severe CRPS provided significant (P<0.05) pain relief by Day 3 compared to baseline. The pain relief experienced on Day 2 of the infusion continued to improve over the 5-day infusion period and correlated with the maximum plasma levels of ketamine and norketamine. We speculate that downstream metabolites of ketamine and norketamine might be playing a role in its therapeutic efficacy.

**Key words:** ketamine, norketamine, CRPS, pharmacodynamics, chronic pain, enanptomers

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Review

Use of oral ketamine in chronic pain management: A review

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ABSTRACT

The analgesic effect of ketamine is primarily based on the antagonism of the N-methyl-D-aspartate (NMDA) receptor. Activation of NMDA receptors may play a crucial role in the pathogenesis of chronic pain. Little formal research has been performed on the efficacy and safety of ketamine in chronic pain, especially concerning long-term oral administration. This review provides an overview of the available clinical data on the use of oral ketamine in chronic pain management. A literature search was performed in MEDLINE, EMBASE and the Cochrane Library, resulting in 22 relevant articles. Because most retrieved articles were of a descriptive nature (e.g., case reports and case series) a quantitative analysis was not possible. There was no consistent dose–response relation. A recommended starting dosage in ketamine-naive patients is 0.5 mg/kg racemic ketamine or 0.25 mg/kg S-ketamine as a single oral dose. The dosage is increased by the same amount if required. For a continuous analgesic effect it is usually given 3–4 times daily. The injection fluid can be taken orally. When parenteral ketamine is switched to oral administration the daily dosage can be kept equal and, depending on clinical effect and/or adverse effects, is slowly increased. The pharmacologically active metabolite norketamine is believed to contribute to the analgesic effect of oral ketamine. Lack of evidence regarding efficacy, and the poor safety profile, do not support routine use of oral ketamine in chronic pain management. Oral ketamine may have a limited place as add-on therapy in complex chronic pain patients if other therapeutic options have failed.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Design (quality)</th>
<th>Pain type</th>
<th>Daily dosage/number of divided doses</th>
<th>Duration of treatment</th>
<th>Efficacy</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabben et al. (1999)</td>
<td>26</td>
<td>CO, PC, SB (III)</td>
<td>Secondary trigeminal neuralgia</td>
<td>4 mg/kg/1 (at night) after KET IM 0.4 mg/kg vs. pethidine 1.0 mg/kg single dose</td>
<td>3 days</td>
<td>Five patients significant but variable pain relief. Non-responders to KET IM no response to KET PO.</td>
<td>Dizziness, sedation, dry mouth, blurred vision, altered hearing, sensory illusions</td>
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<tr>
<td>Haines and Gaines (1999)</td>
<td>21</td>
<td>CO, PC (III)</td>
<td>Neuropathic pain</td>
<td>20 up to 100 mg/1 (dose escalation), average 45 mg/1 (PC)</td>
<td>1 week (run-in) + 3 x 1 week KET vs. 1 week PL</td>
<td>10/21 withdrew after run-in open-dose escalation period due to SE. 9/21 entered PC study. 3/9 patients reported to have benefit from KET</td>
<td>Light headedness, dizziness, tiredness, headache, nervous floating feeling, bad dreams</td>
</tr>
<tr>
<td>Lauretti et al. (1999)</td>
<td>15</td>
<td>RCT (III)</td>
<td>Chronic cancer pain</td>
<td>1 mg/kg/2 (patients randomized to one of 4 groups (N = 15): morphine (control), morphine + KET PO, + nitroglycerin or + dipyrone)</td>
<td>1 month</td>
<td>After day 15 daily morphine consumption was statistically significant reduced in KET-group due to analgesic and/or opioid-sparing effect</td>
<td>Hallucinations; less somnolence compared to control group</td>
</tr>
<tr>
<td>Furuhashi-Yonaha et al. (2002)</td>
<td>8</td>
<td>CO, PC (III)</td>
<td>Neuropathic pain (CRPS, phantom pain, PHN, visceral pain)</td>
<td>2 mg/kg/4, in long-term 1 week, in long-term treatment 25–136 mg per term treatment day (positive response to 9–54 months KET IV test-dose)</td>
<td>&lt;10 days up to &gt;1 year</td>
<td>Statistically significant reduction of VAS score (average 30%) after 1 week of. 4/8 patients received long-term treatment. No tolerance</td>
<td>Nightmares and dizziness, headache</td>
</tr>
<tr>
<td>Enarson et al. (1999)</td>
<td>21</td>
<td>CS, R (IV)</td>
<td>Central and peripheral neuropathic pain</td>
<td>100 mg, adjusted to 40–500 mg (average 220 mg)/number of divided doses not mentioned</td>
<td>&lt;10 days up to &gt;1 year</td>
<td>7/21 ↓ pain. 3/7 responders continued in long-term treatment</td>
<td>Dissociative feeling, somnolence, insomnia, sensory changes</td>
</tr>
<tr>
<td>Rabben and Oye (2001)</td>
<td>13</td>
<td>CS (IV)</td>
<td>Neuropathic orofacial pain</td>
<td>4 mg/kg/1 (at night) after KET IM 0.4 mg/kg test-dose</td>
<td>3 days</td>
<td>8/13 patients reduced pain intensity or complete analgesia</td>
<td>Anxiety and hallucinations, ‘near death’ experience, dizziness</td>
</tr>
<tr>
<td>Author/ Year</td>
<td>Design</td>
<td>Patient population and numbers</td>
<td>Design/Methodology</td>
<td>Outcomes</td>
<td>Withdrawal/Side Effects</td>
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<tr>
<td>Haines (1999)</td>
<td>DB RCT PLC</td>
<td>N=9; Patients with refractory neuropathic pain; previous responders to oral ketamine (from previous arm of study)</td>
<td>Ketamine (solution up to 100mg po) vs Placebo (peppermint mixture) qweekly x 3 weeks</td>
<td>No significant change in VAS pain scores after 3 weeks</td>
<td>17/21 in original study experienced adverse events, 4 light-headed, 4 dizziness, 3 headache; only 9 patients made it to RCT arm</td>
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<tr>
<td>Lauretti (1999)</td>
<td>DB RCT PLC</td>
<td>N=60; Cancer patients with pain not amenable to NSAIDs or Tramadol</td>
<td>Ketamine (0.5 mg/kg PO q12h) vs Morphine (10 mg po Q12hr max 20 mg) vs Dipyrone (500 mg po q6h) vs nitroglycerin (5 mg TD)</td>
<td>Similar VAS scores among all groups; all decreased VAS score for breakthrough pain</td>
<td>7 patients reported diminished appetite and tiredness; 4 constipation, 2 hallucination and somnolence</td>
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<td>Ishizuka (2007)</td>
<td>DB RCT PLC</td>
<td>N=30; Cancer patients with pain not amenable to NSAIDS, Tramadol or codeine</td>
<td>Oral morphine (10 mg PO q4-6h PRN) and ketamine (8mg PO q6-8h PRN) vs Oral morphine (10 mg PO q4-6h PRN) and placebo (PO q6-8 PRN)</td>
<td>Both arms showed significant decrease in pain by VAS scale; no statistical difference between treatment and placebo arm; no change in treatment arm's morphine requirements</td>
<td>5 patients experienced nausea and dizziness; 4 vomited, 6 constipation; 3 pruritis; 2 dizziness and disorientation</td>
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</table>
Dosage and Conversion

- The effective daily dosages ranged from (approximately) 45 mg to 1000 mg.

- The number of divided doses necessary for continuous analgesic effect also ranged from once daily up to a frequency of 6 times daily (on average 3–4 times daily).

- The duration of effect after a single dose (if there was any effect) ranged from a few hours to 24 h or more.

- In opioid naïve patients, the recommended starting dosage in ketamine naïve patients is 0.5 mg/kg racemic ketamine or 0.25 mg/kg S-ketamine as a single oral dose. Doses can be increased in steps of 0.5 or 0.25 mg/kg according to the efficacy and adverse effects, respectively (Blonk).

- For patients who have been on parenteral ketamine, the dose conversion is not simple—Benitez-Rosario 2003, Blonk suggest 1:1, however Fitzgibbon suggests 1/3, but Soto suggests the following:
  - Convert from intravenous to oral route using at least 15% of the total parenteral dose in up to 4 divided dose, having in consideration that the $T_1/2$ of oral ketamine has been reported as 5.1 to 5.6 hours.
  - After the intravenous infusion, reduce opiate by 25% daily, once adequate analgesia has been reached.
  - Titrate up by 0.3 mg/kg daily until adequate analgesia is achieved or side effects occur.
Challenges and Limitations of Ketamine Use in Chronic Pain

• **Unavailability**: the use of Ketamine for chronic pain is not approved and is off label. Because of its higher potency, the S (+) racemate of ketamine is approved for use in Europe where it is commercially available as a preservative-free formulation for the treatment of pain by oral, parenteral, and neuroaxial administration (Ben Ari, 2007).

• **Choosing the right patient**, in terms of responsiveness.

• **Choosing the right dose, duration and route** of administration: there are no fixed strategies.

• **There is no consistent dose–response relation.**

• Managing side effects
  
  **CNS**: sedation, somnolence, dizziness, sensory illusions, hallucinations, nightmares, dissociative feeling and blurred vision. Some Patients also complain of gastrointestinal adverse effects, such as nausea, vomiting, anorexia and abdominal pain. It is also known to **cystitis** and other **urinary complications** when used on a longer duration and in addicts.

• **Addiction**: It is used as a street drug because of its psychotomimetic properties. It can be obtained as powder by heating the injection fluid, and used through snorting or inhaling (Blonk, 2010).

• **Monitoring for long term effects** and change: Long term effects are unknown
5. A Practical Algorithm for Ketamine in Chronic Pain

Choose the Suitable Patient

NOICEPTE PAIN  NEUROPATHIC PAIN  CANCER PAIN

Optimize Pharmacological Treatment Using EBM guidelines/WHO guidelines with the appropriate use of NSAIDs, Opioids and other adjuvants (tricyclics, selective serotonergics).

Unsatisfactory Pain Relief

Other Interventional or Non-Interventional techniques based on EBM (class 1 or 2 evidence)

Continuing Pain with no other EBM measures

Not so strong suspicion of NMDA involvement
- Diabetic neuropathy
- Migraine, spinal pain

Strong Clinical Suspension of NMDA involvement
- Hypersalgia, allodynia
- CRPS, phantom pain.

Opioid induced Hyperalgiesia/insensitivity (NMDA mediated)

Testing Ketamine Responsiveness

Use IV (single bolus), SC, sublingual, intranasal or IM routes
- If appropriate epidural can be used

Testing Ketamine Responsiveness

NEGATIVE

Patient Not responsive to Ketamine-Possibly not mediated by NMDA mechanisms

Can provide IV or SC infusions at frequent intervals

Can switch to Oral Ketamine-with appropriate conversion

Can switch to other NMDA antagonist, suitable and easily available (dexamethorphan)

POSITIVE

For long term use

1. Monitor for Ketamine induced changes in cognition, memory and mood disturbances.
2. Monitor for Ketamine addiction, using the same guidelines as opioids.
3. Long term neuraxial use is not advised as it is supposed to be associated with side effects.
NEUROPATHIC PAIN SECTION

Original Research Article

Efficacy of Ketamine in Anesthetic Dosage for the Treatment of Refractory Complex Regional Pain Syndrome: An Open-Label Phase II Study

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ABSTRACT

Objective. Advanced complex regional pain syndrome (CRPS) remains very difficult to treat. While subanesthetic low-dose ketamine has shown promise in early localized CRPS, its use in advanced CRPS has not been as effective. Since ketamine’s analgesic potency and duration of effect in neuropathic pain are directly dose-dependent, we investigated the efficacy of ketamine in anesthetic dosage in refractory CRPS patients that had failed available standard therapies.

Methods. Twenty ASA I-III patients suffering from refractory CRPS received ketamine in anesthetic dosage over 5 days. Outcome criteria were pain relief, effect on the movement disorder, quality of life, and ability to work at baseline and up to 6 months following treatment.

Results. Significant pain relief was observed at 1, 3, and 6 months following treatment (93.5 ± 11.1%, 89.4 ± 17.0%, 79.3 ± 25.3%; P < 0.001). Complete remission from CRPS was observed at 1 month in all patients, at 3 months in 17, and at 6 months in 16 patients. If relapse occurred, significant pain relief was still attained at 3 and 6 months (59.0 ± 14.7%, P < 0.004; 50.2 ± 10.6%, P < 0.002). Quality of life, the associated movement disorder, and the ability to work significantly improved in the majority of patients at 3 and 6 months.

Conclusions. This open-label trial suggests benefit in pain reduction, associated CRPS symptoms, improved quality of life and ability to work following anesthetic ketamine in previously refractory CRPS patients. However, a randomized controlled trial will be necessary to prove its efficacy.
Successful pain relief in non-responders to spinal cord stimulation: The combined use of ketamine and spinal cord stimulation

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Although spinal cord stimulation (SCS) is an established therapy for chronic neuropathic pain, still 30% of patients do not respond adequately to trial stimulation. These so called “non-responders” do not receive a permanent implantation for pain relief.

The induction and maintenance of central sensitization plays a pivotal role in (chronic) neuropathic pain and is thought to be the resultant of the activation of the N-methyl-D-aspartate (NMDA) receptor in the dorsal horn. Blocking the NMDA receptor through the use of the non-competitive blocker ketamine has shown to attenuate neuropathic pain, although the undesirable side effects limit its use. The present study was performed to examine whether the combination of SCS with an individually determined sub-effective dose of intrathecal (i.t.) ketamine could convert non-responders into responders in rats with chronic neuropathic pain. Rats received a partial ligation of the sciatic nerve for the induction of neuropathic pain. Animals with tactile hypersensitivity to von Frey monofilaments (n = 15) received 30 min of SCS. Non-responders to SCS (n = 8) received their individually determined sub-effective i.t. dose of ketamine followed by 30 min of SCS. No side effects of the sub-effective dose of ketamine could be noted. The combined treatment of SCS and sub-effective dose of i.t. ketamine in non-responders resulted in a significant reduction of the withdrawal threshold in all previous non-responders to SCS, thereby converting them into responders to SCS.

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CONCLUSIONS

- More Research on specific subtypes of NMDA receptors.

- Meaningful interpretation of basic research: understanding its limitations and clinical applicability.

- Use appropriate measurement variables to know the clinical effects of ketamine.

- The level of evidence for Oral and Topical ketamine in chronic pain is Level 3. Although there are RCT’s, there are limited by number of patients, methodology and heterogeneity in indications.

- With the present evidence the best approach is to make it suit the responsiveness of the patient.