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 RCT's 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 bupivacaine.. It's 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.

- **<u>Translational Gap between Basic Scientific Experiments to Clinical Research</u>**

A. Mismatch in Pain Evaluation tools (simple VAS scores VS specific modality changes)
B. Inability to measure behavioural end points in basic science
C. Measures of sensitization-thermal hyperalgesia VS mechanical allodynia
D. 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)

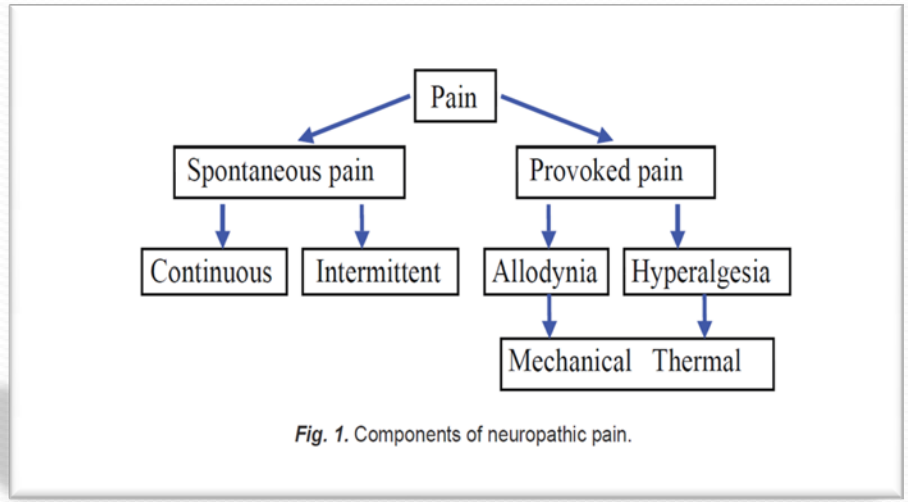


Fig. 1. Components of neuropathic pain.

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)

- **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***

- **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.

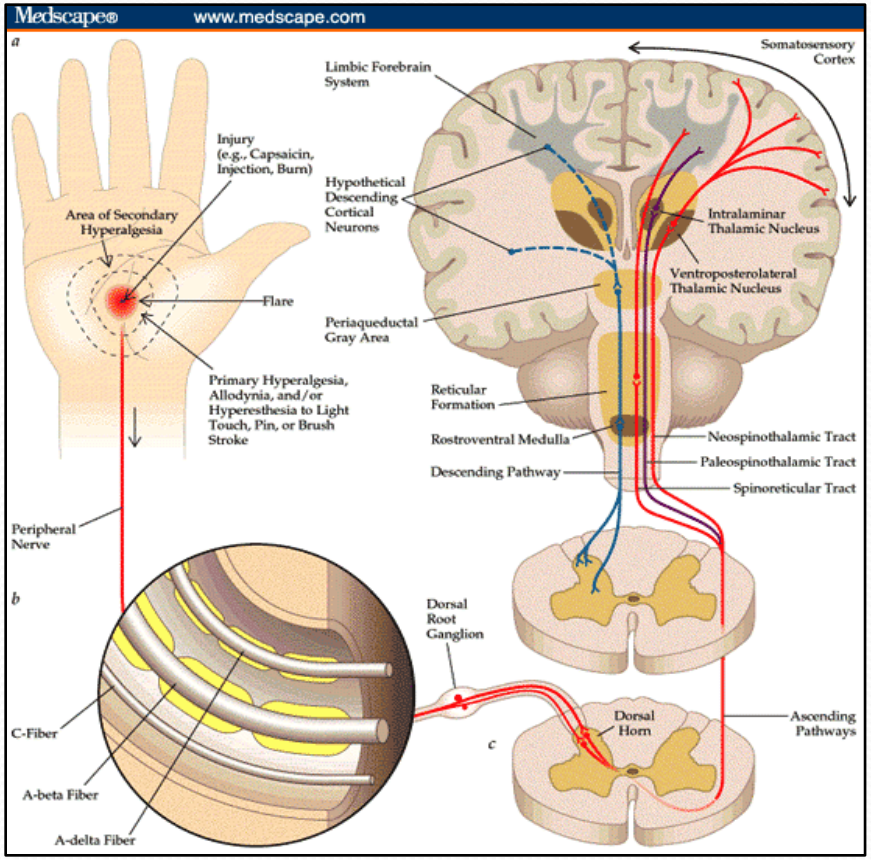
IASP: Hyperalgesia may include both a decrease in threshold and an increase in supra-threshold response.

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

Allodynia: 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 (Wang J, Goffer Y, Xu D, Tukey DS, Shamir DB, Eberle SE, Zou AH, Blanck TJJ, Ziff EB: A single subanesthetic dose of ketamine relieves depression-like behaviors induced by neuropathic pain in rats. ANESTHESIOLOGY 2011; 115:812–21).

Generation----Modulation---Perception—Behaviour

Where does Ketamine have predominant actions?

Depression and Pain

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

A LARGE population of patients concomitantly experiences chronic pain and depression or symptoms of depression (52% in pain clinics, or 85% in chronic facial pain dental clinics, for example).[1] How these two syndromes coexist, interact, reinforce each other, and/or are maintained is poorly understood. It is not known whether pain itself can directly cause depression; if so, whether depression or its symptoms start concurrently with pain or develop while pain is perpetuated is not clear. Is it possible that the treatment of a depressive mood is sufficient to allow patients in chronic pain to return to normal activities and enjoy activities that used to make them happy? In this issue of ANESTHESIOLOGY, difficult to mimic or determine in rodent models or rodent behaviors. Therefore, the return to normal behavior after ketamine under stress situations may not necessarily reflect a more proper response to such stimuli, or the preference for sucrose solution over water may not necessarily reflect the regain of pleasure for enjoyable activities. Nevertheless, these models are affected by clinically used antidepressants, and Wang *et al.* observed that these depression-like behaviors in rats were blocked by ketamine, a drug that reduces symptoms of depression in patients.[3] This finding is indicative of the potential benefits of treating symptoms of depression in patients in pain.

JPET

RIMENTAL THERAPEUTICS

Effects of Ketamine on Sensory Perception: Evidence for a Role of N-Methyl-D-Aspartate Receptors[1]

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Accepted for publication November 12, 1991

ABSTRACT

The chiral forms of ketamine were applied as probes for N-methyl-D-aspartate receptor-mediated neurotransmission in humans. Both enantiomers, in clinically relevant concentrations, displaced [^{3}H]dizocilpine (MK 801) from specific binding sites (phencyclidine sites) in membrane fractions of brain homogenates. (*S*)-Ketamine was at least 4 times as potent as (*R*)-ketamine in this respect. In healthy volunteers, the most obvious effect of subanesthetic doses of both enantiomers was altered sensory perception. (*S*)-Ketamine was 4 times as potent as (*R*)-ketamine in reducing pain perception and in causing auditory and visual disturbances. Both enantiomers caused proprioceptive disturbances (feelings of detachment from the body) and slightly reduced the ability to recall objects seen after administration of the drugs. The ability to recall objects seen immediately before drug exposure was unaffected. The results are in accordance with the hypothesis that inhibition of sensory perception by ketamine in subanesthetic concentrations is due to N-methyl-D-asparate receptor blockade. It is suggested that N-methyl-D-asparate receptor-mediated transmission is involved in the processing of sensory information in the human brain.

BETWEEN BEDSIDE AND BENCH

■ BENCH TO BEDSIDE

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 serotonin or norepinephrine neurochemical systems and are limited in efficacy, showing also 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-aminocyclopropanecarboxylic acid—induced antidepressant-like effects similar to the tricycle antidepressant imipramine in inescapable stress animal models of depression[1]. Subsequently, a series of studies by the same group showed that chronic—but not acute—

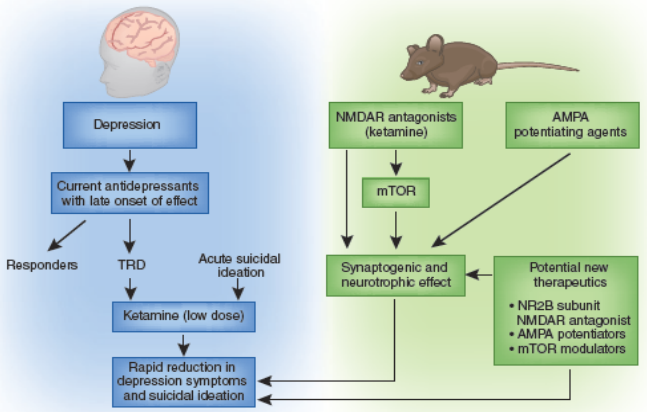
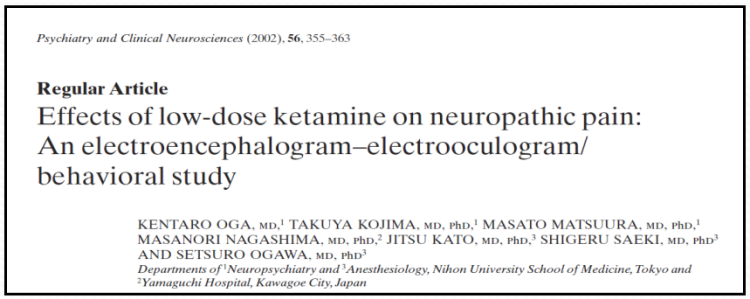


Figure 1 The rapid-acting antidepressant effects of ketamine and the potential role of synaptogenic and neurotrophic mechanisms in depression. Left, low-dose ketamine has been shown to exert a rapid antidepressant effect, and it may be effective at reducing acute suicidal ideation, even in people with TRD. Right, in parallel, studies in rats are shedding new light on the molecular effects of ketamine and other glutamate NMDA receptor (NMDAR) antagonists on depression. The antidepressant effect of NMDAR antagonists may result from enhancing the activity of the glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and activating the mammalian target of rapamycin (mTOR) intracellular signaling pathway, which ultimately leads to increased synapse-related proteins and neural trophic support. These findings suggest new molecular targets to treat people with severe depression.

Murrough JW, Charney DS: Cracking the moody brain: Lifting the mood with ketamine. Nat Med 2010; 16:1384 –5

There are several reasons to suggest that Ketamine does more than just providing pharmacological analgesia!



Psychiatry and Clinical Neurosciences (2002), **56**, 355–363

Regular Article

Effects of low-dose ketamine on neuropathic pain: An electroencephalogram–electrooculogram/ behavioral study

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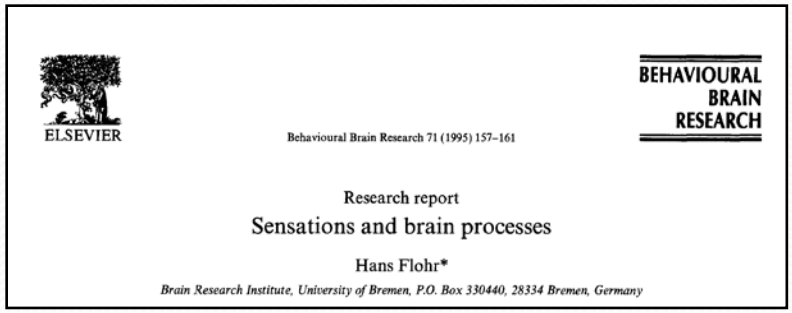

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Behavioural Brain Research 71 (1995) 157–161

BEHAVIOURAL BRAIN RESEARCH

Research report

Sensations and brain processes

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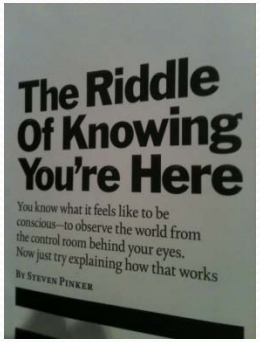
•Ten in-patients with neuropathic pain participated in this single-blind, placebo-controlled study after giving written informed consent.

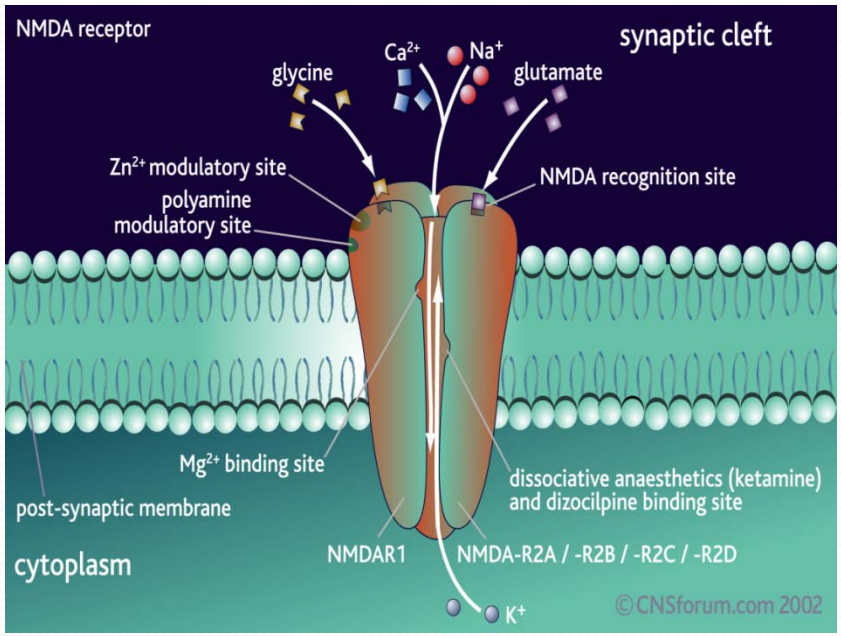
•Changes in pain perception were assessed using a numerical rating scale for pain. Behavioral changes, including psychotomimetic effects, were assessed using the Brief Psychiatric Rating Scale (BPRS). Electroencephalograms (EEG) and electrooculograms (EOG) were recorded continuously throughout the testing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



Time Magazine Special issue-Your Brain: A User's Guide, 2011



KETAMINE blocks the NMDA channel by 2 distinct mechanisms;

1) ***it blocks <u>the open channel</u>*** *and there by 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 coagonist, is required for efficient activation of NMDAR (co-incidence detector).

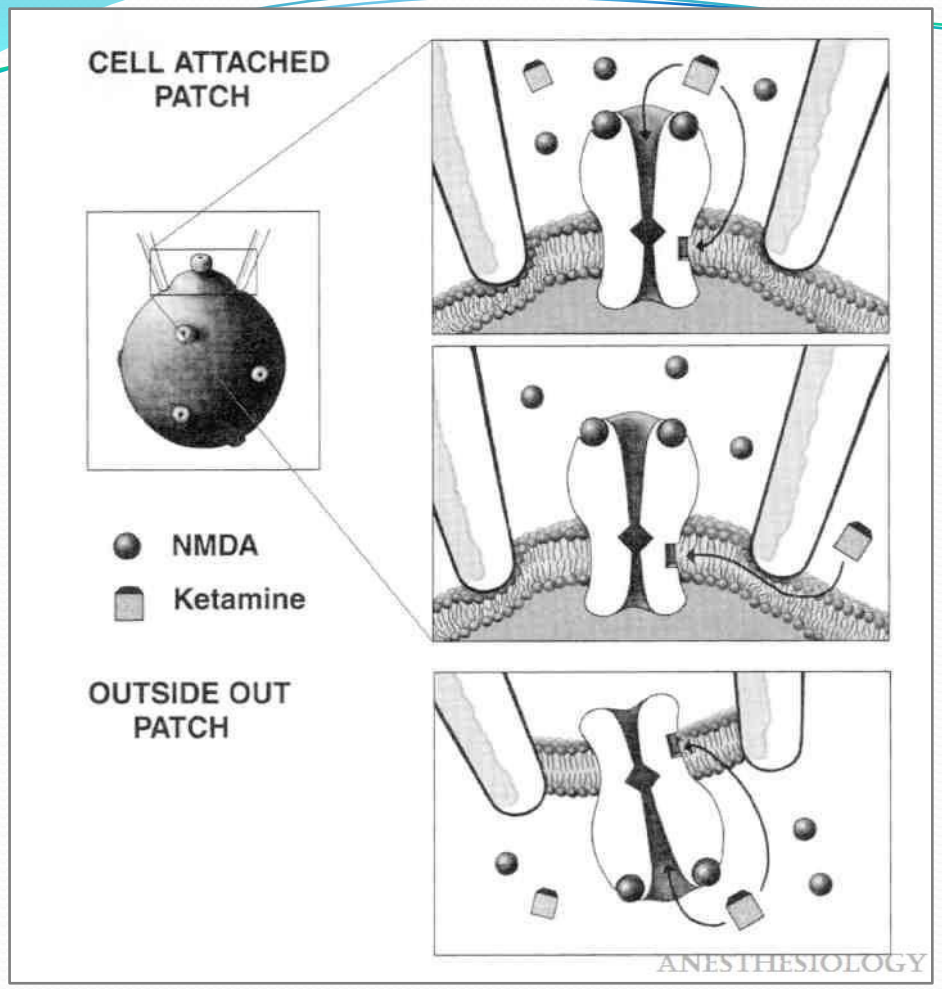
3. At resting membrane potential the NMDAR channels are blocked by extracellular magnesium and open only on simultaneous depolarization and agonist binding, thus both depolarization of the postsynaptic neuron and presynaptic release of glutamate and glycine are required for maximum current flow through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

Figure 11



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 my infact act through different pathways apart from molecular mechanisms.

Multiple Mechanisms of Ketamine Blockade of N-methyl-D-aspartate Receptors

Orser, Beverley A.; Pennefather, Peter S.; MacDonald, John F.

Anesthesiology. 86(4):903-917, April 1997.

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.
  Carlton SM. Peripheral excitatory amino acids. Curr Opin Pharmacol 2001; 1:52-6).

- 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.
  (R.E. Coggeshall, S.M. Carlton, Ultrastructural analysis of NMDA, AMPA and kainate receptors on unmyelinated and myelinated axons in the periphery, J. Comp. Neurol. 764 1997. 126–132).

- 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.
  (J. Haley, A.F. Sullivan, A.H. Dickenson, Evidence for spinal *N*methyl-D-aspartate receptor involvement in prolonged chemical no-ciception in the rat, Brain Res. 518 1990. 218–226).

neuroReport

NeuroReport 7, 895–900 (1996)

Peripheral administration of NMDA, AMPA or KA results in pain behaviors in rats

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THE present study investigated the role of *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptor subtypes in peripheral pain transmission. Activation of NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate acid (KA) receptors in glabrous skin of the rat hindpaw resulted in mechanical allodynia and mechanical hyperalgesia. These agonist-induced pain behaviors were attenuated following peripheral injection of appropriate antagonists (MK-801 and CNQX). Thus, activation of NMDA, AMPA or KA receptors at the level of the peripheral nerve terminal can produce nociceptive behavior. These data suggest that topical application of glutamate receptor antagonists may be useful in treating pain disorders. Since all three receptor subtypes are involved in peripheral pain transmission, however, it will be necessary to antagonize multiple glutamate receptor subtypes to achieve effective pain relief.

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

REVIEW ARTICLE

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

Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I: Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: A study in postoperative patients. Neurosci Lett 1996; 215:5-8

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

Anesthesiology
1998; 89:58–66

Peripheral Analgesic Effects of Ketamine in Acute Inflammatory Pain

Juri L. Pedersen, M.D., Tina S. Galle,† Henrik Kehlet, M.D., Ph.D.‡*

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 cm^2), 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 ($P \leq 0.01$). Heat pain thresholds were increased by local ketamine treatment compared with placebo immediately after injection ($P \leq 0.03$), 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.[1] Peripheral administration of ligands to these receptors evoked nociceptive behaviors in rats,[1–3] and local administration of the NMDA antagonists, MK-801 and ketamine, and non-NMDA glutamate receptor antagonists has reduced nociceptive behaviors in rats.[3–5]

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.[6] 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.[7] 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.[6,8] 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.

- Durrani Z, Winnie AP, Zsigmond EK, Burnett ML: Ketamine for intravenous regional anesthesia. Anesth Analg 1989; 68:328-32 .
  Amiot JF, Bouju P, Palacci JH, Balliner E: Intravenous regional anaesthesia with ketamine. Anaesthesia 1985; 40:899-901.
  Dowdy EG, Kaya K, Gocho Y: Some pharmacologic similarities of ketamine, lidocaine, and procaine. Anesth Analg 1973; 52:839-42 .
- Brau ME, Sander F, Vogel W, Hempelmann G: Blocking mechanisms of ketamine and its enantiomers in enzymatically demyelinated peripheral nerve as revealed by single-channel experiments. Anesthesiology 1997; 86:394-404

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Neuroscience Letters 215 (1996) 5–8

NEUROSCIENCE LETTERS

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) herniorrhaphy participated in this study. With bilateral herniorrhaphy, 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 herniorrhaphy, 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 herniorrhaphy, the addition of ketamine for wound infiltration enhanced the duration of infiltration anesthesia (206 ± 76 versus 343 ± 108 min, $P < 0.02$) and analgesia (240 ± 45 versus 420 ± 151 min, $P < 0.03$). Similar enhancement of the local anesthetic effect was observed in patients with bilateral herniorrhaphy. The increase in pain threshold to pressure on the wound with the addition of ketamine was evident in bilateral herniorrhaphy patients and also with a combination of bilateral and unilateral results (1.39 ± 0.40 versus 2.35 ± 0.92 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.

Crowley KL, Flores JA, Hughes CN, Iacono RP. Clinical application of ketamine ointment in the treatment of significant allodynia and hyperalgesia associated with chronic neuropathic pain. J Pharm Comp 1998;2:123 27.

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

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

NAS, numeral analogue scale; RSD, Reflex Sympathetic Dystrophy.

Topical Ketamine Gel: Possible Role in Treating Neuropathic Pain
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TOPICAL STUDIES

Author	Design	Patient population and numbers	Design/Methodology	Outcomes	Withdrawal/Side Effects
Barton (2011)	DB RCT PLC	N=208; Chemotherapy associated peripheral neuropathy for >1 month	Topical Gel of 10 mg baclofen, 40 mg amitryptyline and 20 ug ketamine vs placebo 10ml applied daily x 4 weeks	Statistically significant improvement in motor neuropathy symptoms on CIPN-20 questionnaire; trend towards improvement in sensory neuropathy symptoms	No significant difference in adverse events between placebo and treatment
Lynch (2003)	DB RCT PLC; subsequent open-label prospective in "ketamine responders" subgroup	N=20; Chronic neuropathic pain	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	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	2 patients experienced "minor" side effects
Lynch (2005)	DB RCT PLC	N=92; Diabetic neuropathy, Post-Heraptic neuralgia or Posttraumatic neuralgia	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	No statistically significant difference in pain reduction on NRS-PI scale between study arms; all arms generated 1-1.5 decrease in spontaneous pain	1 episode of local skin irritation; 1 swollen feet; 2 episodes of drowsiness
Vranken (2005)	DB RCT PLC	N=33 Central Neuropathic Pain	Iontopatch administered 50 mg ketamine vs 75 mg ketamine vs placebo (NS) over 24hr x 5 days	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	3 patients in ketamine arms reported sedation, 1 each of nausea/vomiting, confusion, dizziness, vivid dreams,

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**.

Fisher, K., Coderre, TJ., & Hagen, NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. *J Pain Symptom Manage*. 2000 Nov;20(5):358-73

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.**

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Br. J. Anaesth., (1981), 53, 805

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.

Observational Study

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 240 to 300 minutes after the 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 measure assessed 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 day 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, enantiomers

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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.

Study	Number of patients	Design (quality)	Pain type	Daily dosage/number of divided doses	Duration of treatment	Efficacy	Adverse effects
Rabben et al. (1999)	26	CO, PC, SB (III)	Secondary trigeminal neuralgia	4 mg/kg/1 (at night) after KET IM 0.4 mg/kg vs. pethidine 1.0 mg/kg single dose	3 days	Five patients significant but variable pain relief. Non-responders to KET IM no response to KET PO.	Dizziness, sedation, dry mouth, blurred vision, altered hearing, sensory illusions
Haines and Gaines (1999)	21	CO, PC (III)	Neuropathic pain	20 up to 100 mg/1 (dose escalation), average 45 mg/1 (PC)	1 week (run-in) + 3 × 1 week KET vs. 1 week PL	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	Light headedness, dizziness, tiredness, headache, nervous floating feeling, bad dreams
Lauretti et al. (1999)	15	RCT (III)	Chronic cancer pain	1 mg/kg/2 (patients randomized to one of 4 groups ($N = 15$): morphine (control), morphine + KET PO, + nitroglycerin or + dipyrone)	1 month	After day 15 daily morphine consumption was statistically significant reduced in KET-group due to analgesic and/or opioid-sparing effect	Hallucinations; less somnolence compared to control group
Furuhashi-Yonaha et al. (2002)	8	CO, PC (III)	Neuropathic pain (CRPS, phantom pain, PHN, visceral pain)	2 mg/kg/4, in long-term treatment 25–136 mg per day (positive response to KET IV test-dose)	1 week, in long-term treatment 9–54 months	Statistically significant reduction of VAS score (average 30%) after 1 week of. 4/8 patients received long-term treatment. No tolerance	Nightmares and dizziness, headache
Enarson et al. (1999)	21	CS, R (IV)	Central and peripheral neuropathic pain	100 mg, adjusted to 40–500 mg (average 220 mg)/number of divided doses not mentioned	<10 days up to > 1 year	7/21 ↓ pain. 3/7 responders continued in long-term treatment	Dissociative feeling, somnolence, insomnia, sensory changes
Rabben and Oye (2001)	13	CS (IV)	Neuropathic orofacial pain	4 mg/kg/1 (at night) (after KET IM 0.4 mg/kg test-dose)	3 days	8/13 patients reduced pain intensity or complete analgesia	Anxiety and hallucinations, 'near death' experience, dizziness

ORAL STUDIES

Author/ Year	Design	Patient population and numbers	Design/Methodology	Outcomes	Withdrawal/Side Effects
Haines (1999)	DB RCT PLC	N=9; Patients with refractory neuropathic pain; previous responders to oral ketamine (from previous arm of study)	Ketamine (solution up to 100mg po) vs Placebo (peppermint mixture) qweekly x 3 weeks	No significant change in VAS pain scores after 3 weeks	17/21 in original study experienced adverse events, 4 light-headed, 4 dizziness, 3 headache; only 9 patients made it to RCT arm
Lauretti (1999)	DB RCT PLC	N=60; Cancer patients with pain not ameniable to NSAIDs or Tramadol	Ketamine (0.5 mg/kg PO q12h) vs Moprhine (10 mg po Q12hr max 20 mg) vs Dipyrone (500 mg po q6h) vs nitroglycerin (5 mg TD)	Similar VAS scores amoung all groups; all decreased VAS score for breakthrough pain	7 patients reported diminished appetite and tiredness; 4 constipation, 2 hallucination and somnolence
Ishizuka (2007)	DB RCT PLC	N=30; Cancer patients with pain not ameniable to NSAIDS, Tramadol or codeine	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)	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	5 patients experienced nausea and dizziness; 4 vomited, 6 constipation; 3 pruritis; 2 dizziness and disorientation

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 Fitzzgibbon 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 T1/2 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.**

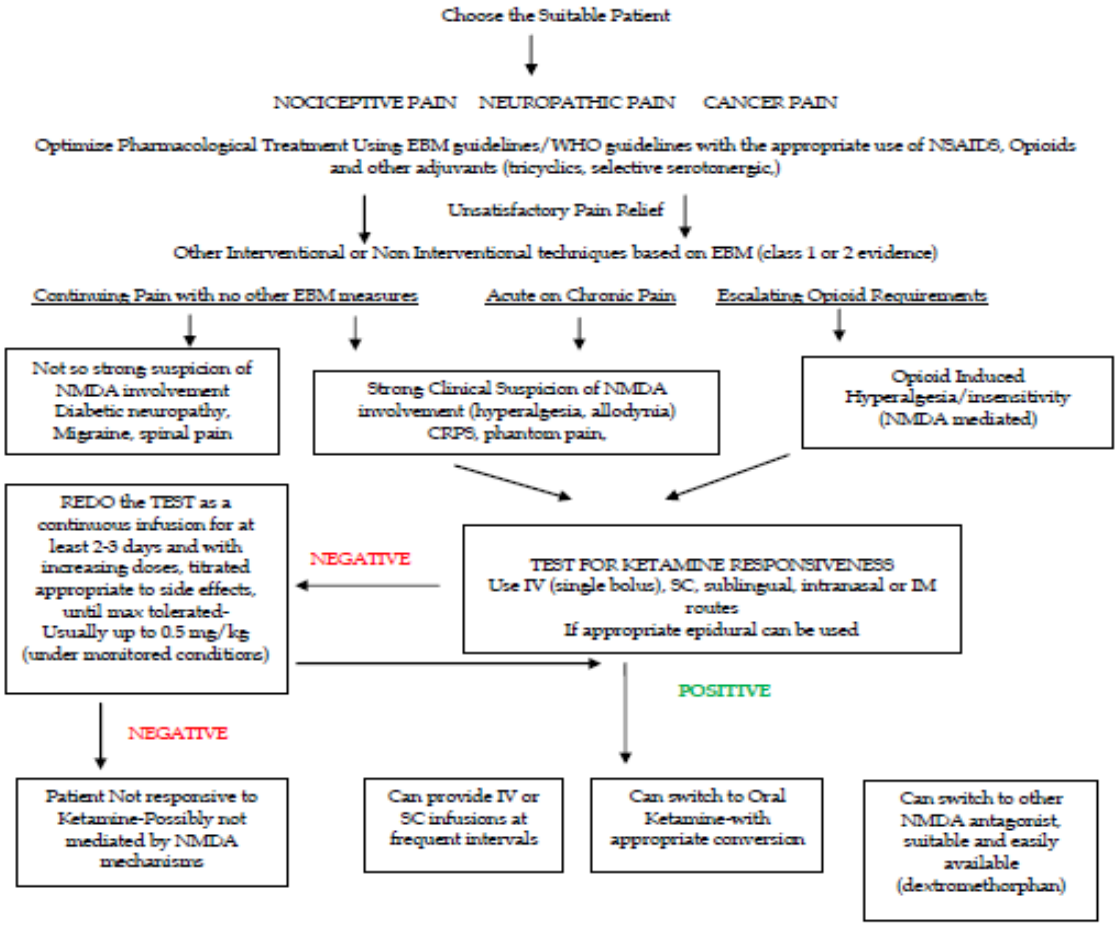
- Managing side effects

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



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.

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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-dependant, 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 ($93.5 \pm 11.1\%$, $89.4 \pm 17.0\%$, $79.3 \pm 25.3\%$; $P < 0.001$). 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 ($59.0 \pm 14.7\%$, $P < 0.004$; $50.2 \pm 10.6\%$, $P < 0.002$). 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.

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Successful pain relief in non-responders to spinal cord stimulation: The combined use of ketamine and spinal cord stimulation

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ABSTRACT

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.

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.

THANKS