

Position Statement on the use of ketamine in the management of chronic non-cancer pain

Background Paper

“The surge in use, lack of large-scale, methodologically sound studies to guide treatment, and absence of treatment standards to include safe-use recommendations, strongly portend the need for guidelines to inform safe practice.”

Cohen SP et al, Regional Anesthesia and Pain Medicine 2018; 43: 521-546

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LITERATURE REVIEW

Section I. KETAMINE AS AN ANALGESIC IN CHRONIC PAIN

The adult literature falls into 3 epochs:

- A. Recent reviews
- B. Post-2011 reports
- C. Pre-2011 reports
- D. Paediatric literature

It should be noted that the definition of neuropathic pain was changed in 2011¹. It is very likely that many of the “neuropathic syndromes” studied in articles published before 2011 (if not also later) would not satisfy the current definition.

A. Recent reviews

A-1. Orhurhu V, Orhurhu MS, Bhatia A, Cohen SP. Ketamine Infusions for Chronic Pain: A Systematic Review (SR) and Meta-analysis of Randomized Controlled Trials. *Anesth Analg* 2019;129(1):241-254.

- Cochrane-style SR and meta-analysis
- 696 studies screened; 7 included; 6 at high risk of bias
- 211 participants in total (range n=16-60)
- small effect in favor of ketamine up to 2 weeks but not beyond that
- no strong evidence of long term benefit
- ketamine-related adverse outcomes reported in the trials included nausea, vomiting, psychotomimetic effects, headache, fatigue, and sedation (relative risks calculated)
- “Compared to low-dose ketamine studies and investigations that evaluated non-complex regional pain syndrome conditions, a small but nonsignificant greater reduction in pain scores was found among studies that either utilized high-dose ketamine therapy ($P = .213$) or enrolled complex regional pain syndrome patients ($P = .079$).”
- “Based on the quality of the evidence from studies in this review and the strength of effect, it is recommended that IV ketamine be used, on a case-by-case basis, as a primary analgesic in patients with chronic pain refractory to more conventional treatments (GRADE: weak recommendation; low evidence)”

A-2. Cohen SP et al., Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional Anesthesia and Pain Medicine* 2018; 43,(5):521- 545 [268 refs]²

Synopsis

- (i) “Which patients and chronic pain conditions should be considered for ketamine infusions?”

Chronic neuropathic³ pain is the most widely investigated indication for IV ketamine. Specific diagnostic categories that have been studied in RCTs include neuropathic pain of mixed diagnoses, traumatic spinal cord injury, post herpetic neuralgia (PHN) and phantom limb pain (PLP). Conditions with features of neuropathic pain have also been studied including complex regional pain syndrome, fibromyalgia, and chronic ischaemic pain.

¹ IASP taxonomy reference

² Note the caveat to this publication: “Because this document has neither been presented to nor approved by either the American Society of Anesthesiologists Board of Directors or House of Delegates, it is not an official or approved statement or policy of the Society. Variances from the recommendations contained in the document may be acceptable based on the judgment of the responsible anesthesiologist.”

³ It is unclear whether pre- or post-2011 definitions were used.

The messages are mixed:

- “The variations in dose and duration of infusion limited the identification of a definitive dose-response relationship between ketamine and pain scores.” (p. 530)
- “Overall, we conclude that there is moderate evidence to support higher dosages of ketamine over longer time periods, and more frequent administration, for chronic pain.” (p. 533)
- “In summary,
 - For spinal cord injury pain, there is weak evidence supporting ketamine infusions (0.42 mg/kg per hour to 0.4 mg/kg ranging from 17 minutes to 5 hours for 7 consecutive days) for short-term improvements in pain (grade C recommendation, low level of certainty).
 - For CRPS, there is moderate evidence supporting ketamine infusions (22 mg/h for 4 days or 0.35 mg/kg per hour over 4 hours daily for 10 days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty).
 - For mixed neuropathic pain, PLP, PHN, fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there was weak or no evidence supporting ketamine infusions for immediate improvements in pain (grade D, low level of certainty).
 - Conclusion: Excluding CRPS, there was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain.” (p. 531)

(ii) “What are the contraindications for ketamine infusions?”

“In summary, ketamine should not be used in patients with

- poorly controlled cardiovascular disease and should be avoided in
- individuals with certain poorly controlled psychoses (grade B evidence, moderate level of certainty).
- For hepatic dysfunction, it should be avoided in individuals with severe impairment but may be administered judiciously with proper monitoring in people with moderate disease (grade C evidence, low level of certainty).
- In patients with elevated intracranial and intraocular pressure, there is grade C evidence that ketamine should not be used or used only in lower dosages with extreme caution (low level of certainty).
- Serial ketamine infusions should not be undertaken in patients with an active substance abuse problem and should be used along with universal precautions to monitor for abuse (grade C evidence, low level of certainty).”

(iii) “Is there any evidence for a therapeutic dose cutoff threshold, dose-response relationship, longer (ie, continuous versus boluses), more frequent (repeat) infusions, or higher dosages to be more effective for chronic pain?”

Conclusions: “[T]here is moderate evidence to support higher dosages of ketamine over longer time periods, and more frequent administration, for chronic pain.

“[I]t is reasonable to start dosing with a single, outpatient infusion at a minimum dose of 80 mg lasting more than 2 hours and reassess before initiating further treatments, (grade C recommendation, low level of certainty).”

(iv) “Is there any role for oral ketamine or another NMDA receptor antagonist as a follow-up treatment in lieu of repeat infusions?”

Conclusion: “Overall, we conclude that there is low-level evidence to support the use of oral ketamine (150 mg/d or 0.5 mg/kg every 6 hours) and other NMDA-receptor antagonists such as dextromethorphan (0.5–1 mg/kg every 8 hours) as follow-up therapy following IV infusions, and moderate evidence to support intranasal ketamine (1–5 sprays of ketamine 10 mg, 0.2–0.4 mg/kg (S)- ketamine, and single dose ketamine 25 mg every 6 hours as needed) as a treatment for breakthrough pain.”

- (vii)⁴ What preemptive medications should be available for administration as rescue medications to treat possible adverse events related to ketamine infusions?

Conclusion: “Overall, we conclude there is limited direct evidence supporting the preemptive use of benzodiazepines and α_2 agonists and no evidence to support antidepressant, antihistamine, or anti-cholinergic premedicants prior to the initiation of subanesthetic ketamine for chronic pain treatment (grade C recommendation, low level of certainty).” (p. 537)

- (viii) “What constitutes a positive treatment response for chronic pain?”

Conclusion: “[G]iven the refractory nature of [pain in] patients who receive ketamine infusions, we recommend that a positive outcome be considered as 30% pain relief or greater in conjunction with patient satisfaction and/or more objective indicators of meaningful benefit,

In terms of duration of benefit, patient expectations and satisfaction should be considered, but based on the cumulative risks and costs of treatment, greater than 3 weeks following a single outpatient infusion and greater than 6 weeks following an inpatient or series of infusions are a reasonable designation.” (p. 537)

A-3. Bell RF, Kalso EA. Ketamine for pain management. Pain Reports PR9 3 (2018) e674 <http://dx.doi.org/10.1097/PR9.0000000000000674> [63 refs.]

- “There is only very limited evidence for the use of ketamine in chronic noncancer pain and concerns and a lack of safety data concerning long-term or repeated treatment. Importantly, there is no strong evidence to support the current practice of treating chronic noncancer pain with repeated intravenous infusions. [11] [SEP]”
- Ketamine has dose-dependent adverse effects, and there are good arguments for avoiding high doses.” [11] [SEP]

B. Post-2011

B-1. Maher DP, Chen L, Mao A. Intravenous ketamine infusions for neuropathic pain management: a promising therapy in need of optimization. *Anaesthesia & Analgesia* 2017;124:661-74

- Review paper 26 articles, 16 prospective randomized placebo controlled trials, 4 prospective observational non randomized studies, 4 retrospective studies and 1 prospective randomized non placebo controlled study.
- Duration of Infusion-shorter duration infusions all resulted in lowered VAS but of short duration. Studies using 4-5 days duration achieved pain relief from 6 weeks to 6 months.
- Total infusion dose. Several studies with doses from 324-6800mg over several days normalized to 70kg patient had reductions in pain from 4 weeks to 6 months.
- Infusion rate. 0.1-0.5mg/kg/hr. The higher rates were undertaken in ICU with monitoring but showed a longer benefit. However the lower infusions continued for higher duration also showed longer duration of benefit, hence the total cumulative dose appeared important. Side effects were the same regardless of dose of infusion.
- Coadministration: midazolam, clonidine, calcitonin or oral gabapentin reported benefits but with specific pain syndromes.
- Conclusion: higher total infused dosages of ketamine and longer infusions were associated with longer durations of pain relief.

B-2. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *The Lancet Neurology* 2015; 14:162-173.

- Ketamine and other NMDA-antagonists: inconclusive recommendations for use or recommendations against use based on the GRADE classification

C. pre-2011 reports

⁴ Guideline questions (v) and (vi) in this publication are not included in this synopsis.

- C-1.** (a) Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. (Review) *Expert Opin Pharmacother* 2010; 11:2417-2429.
(b) Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits (Review) *Br J Clin Pharmacol* 2013; 77:357–367. [These two papers are very similar.]
- Search: 1992-2010
 - Studies found: 36 RCTs, 6 since 2008; 21 intravenous; > 0.15 mg/kg ketamine
 - Syndromes treated (text refers to them as “neuropathic”): acute and chronic migraine (2), breakthrough non-cancer pain (1), central neuropathic pain (2), chemotherapy- induced neuropathy (1), chronic neuropathic pain (various causes) (9), complex regional pain syndrome (3), fibromyalgia (3), painful limb ischaemia (3), peripheral nerve injury (traumatic) (4), phantom limb pain (1), post-herpetic neuralgia (1), spinal cord injury (2), temporomandibular pain (2), trigeminal neuropathic pain (1), whiplash (3)
 - Conclusion: “*There is evidence that long term treatment of chronic pain (particularly in pain with a neuropathic component) with ketamine will cause prolonged pain relief, although the evidence comes from just a limited number of RCTs (n = 3). Of importance is that no effect on functionality or on depressive symptoms was observed. Still, although ketamine treatment is linked to a variety of side effects (which include CNS-related symptoms (development of a schizoid-like state, somnolence, dizziness, drug high, memory defects), cardiovascular stimulation and in a minority of patients liver injury), it is the impression of the treating physicians (and of many of the patients) that the benefits outweigh the risks in specific patient populations.*”
 - Comment: Majority of studies demonstrated > 50% reduction of pain intensity; effect did not persist beyond 48 h following infusion. Infusion duration ranged from 30 min to 2 h; no consensus on administration protocol.
- C-2.** Bell RF. Ketamine for chronic non-cancer pain (Topical review). *Pain* 2009; 141:210-214
- 29 controlled trials with 579 patients; 18 intravenous; duration in 21 trials <4h
 - syndromes treated: chronic neuropathic pain (incl phantom limb) pain, whiplash-associated pain, TMJ arthralgia, atypical odontalgia, breakthrough pain, migraine prophylaxis
 - Comment: “In summary, while the current literature provides evidence for acute relief of chronic non-cancer pain, information supporting the efficacy and tolerability of ketamine in the long-term treatment of chronic pain is extremely limited.”
- C-3.** Visser E, Schug SA. The role of ketamine in pain management. *Biomed Pharmacother* 2006; 60:341-8.
- Comment: “The place of ketamine in the treatment of chronic pain and the effects of long-term medicinal use remain unclear.”
- C-4.** Hocking G, Cousins MJ. Ketamine in Chronic Pain Management: An Evidence Based Review. *Anesthesia and Analgesia* 2003; 97: 1730.
- Search: 1996-August 2002
 - Studies found: 11 controlled; many uncontrolled
 - Syndromes treated: central pain, complex regional pain syndrome, fibromyalgia, ischaemic pain, pain of neuropathic origin, acute-on-chronic neuropathic pain, orofacial pain, phantom/stump pain, post-herpetic neuralgia
 - Mode: Parenteral i.v. or s.c. 0.125-0.3mg/kg/hr; oral: 30-1000mg/day. Start 0.5mg/kg, median daily dose 200mg
 - Comment: “The magnitude of reported benefit from ketamine in chronic pain is often little more than what could be expected by a placebo effect. It is therefore unlikely that ketamine will become a regular treatment option for patients with chronic pain, unless there is greater interest in performing good quality studies in this area to further delineate the target population and dose response for specific diagnoses. Until this takes place, ketamine will remain a third line drug that is administered on the basis of weak evidence in patients who have failed to respond to routine pharmacotherapy.”

D. Paediatric literature

D-1. Masaracchia MM, Sites BD, Lee J, Thomas JJ, Fernandez PG. Subanesthetic ketamine infusions for the management of pediatric pain in non-critical care settings: An observational analysis. *Acta Anaesthesiol Scand*. 2019 Oct;63(9):1225-1230. doi: 10.1111/aas.13429. Epub 2019 Jul 16. PMID: 31313291.

- Retrospective uncontrolled
- N = 172
- Aged 0-21 years
- Receiving low-dose ketamine infusions (≤ 0.3 mg/kg/hour) in inpatient care units
- Pain score reduction in order of -2/10
- No change in opioid use
- 52 incidences of some side effect (neurologic excitability [10.4%]; over-sedation [7.4%]; rapid response team alerts [1.1%]), none resulted in termination of the infusion or escalations in care.

D-2. Sheehy KA, Muller EA, Lippold C, Nourai M, Finkel JC, Quezado ZM. Subanesthetic ketamine infusions for the treatment of children and adolescents with chronic pain: a longitudinal study. *BMC Pediatr*. 2015;15:198. Published 2015 Dec 1. doi:10.1186/s12887-015-0515-4

- Longitudinal cohort study of consecutive patients treated
- N = 63 patients / 277 ketamine infusions.
- Aged 12-17 years
- 0.1–0.3 mg/kg/h that lasted for 4–8 h per day, up to a maximum of 16 h in total over a maximum of three consecutive days on outpatient basis
- Statistically significant change in pain score from baseline but not clinically signif (SML)
- “In 37 % of infusions (N = 99 out of 277), ketamine yielded a greater than 20 % reduction in pain scores compared to baseline” and “in 12 % of infusions (N = 9 out of 77 [who were on opioids]), patients had greater than 20 % reduction in morphine-equivalent intake”

Section II. KETAMINE AS PRE-EMPTIVE ANALGESIC OR AS “OPIOID-SPARING”

Pain of acute nociception

Ketamine has an established place in the perioperative management of acute pain (at subanaesthetic doses <0.5 mg/kg), where it has consistently been shown to be opioid sparing and to decrease nausea and vomiting while adding only a mild side-effect profile of its own. The optimal dose is unresolved.

Pre-emptive analgesia in acute nociception

A significant body of evidence has tested the hypothesis that pre-emptive administration of ketamine might prevent the development of pain (both acute and chronic) by preventing the sensitisation of neuronal circuits. Although positive findings were reported from animal studies, data from human trials have not shown a clear pre-emptive benefit. However, the acute analgesic effects of ketamine can outlast the expected duration of the effect of the drug (>5.5 half-lives), suggesting that ketamine has a preventive effect. This is also supported by data that show perioperative ketamine reduces the incidence of chronic postsurgical pain.

Bandschapp O, Girard T, Ruppen W. Intra- and postoperative intravenous ketamine does not prevent chronic pain: A systematic review and meta-analysis. *Scand J Pain*. 2015;7(1):42-54. doi:10.1016/j.sjpain.2014.12.005, 10.1016/j.sjpain.2014.12.005.

Lumanauw DD, Youn S, Horeczko T, Yadav K, Tanen DA. Subdissociative-dose Ketamine Is Effective for Treating Acute Exacerbations of Chronic Pain. *Acad Emerg Med*. 2019;26(9):1044-1051. doi:10.1111/acem.13755, 10.1111/acem.13755

- RCT n = 106 adults with acute exacerbation of CNCP presenting to ED setting
- 0.5 mg/kg ketamine, 0.25mg/kg ketamine, or placebo infused over 20 minutes
- VAS at 20, 40, 60 mins plus phone FU NRS at 24 and 48 hours
- significantly improved acute pain management but no diff at 24-48 hrs after infusions;
- significantly more AEs incl one SAE in ketamine gr

Ketamine as an agent to reduce opioid dose in chronic pain:

Kapural L, Kapural M, Bensitel T, Sesslet DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. *Pain Physician* 2010; 13: 389-394

- retrospective chart review, n=18, with controls
- 10-100 mg/hr, 3+ hrs, 3-6 weeks; co-administered with midazolam
- 11 patients completed 3-6 weekly ketamine infusions 5 of 11 maintained <50% baseline opioid use at 6/12
- no differences in pain scores between ketamine and control groups

Quinlan J. The use of a subanesthetic infusion of intravenous ketamine to allow withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance and hyperalgesia: Outcome at 6 months. *Pain Med* 2012; 13: 1524 [Letter]

- retrospective, >6/12 post infusion, 11 responses of 15
- 2.5-40 mg/hr SC; 5 days
- 8/11 “better” at 2/12; 3/11 “well” and off opioids at 6/12

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PROPOSED MECHANISMS FOR THE ANALGESIC EFFECT OF KETAMINE

1. Inhibition of the N-methyl-D-aspartate (NMDA) -receptor

Ketamine is a non-competitive antagonist of the NMDA-receptor at subanaesthetic concentrations.

A central issue is whether all the clinically relevant analgesic effects of ketamine are related to NMDA-receptor antagonism.

- If so, pain relief would only be expected in situations where there is sensitization of the central nervous system.
- main role of ketamine at lower concentrations is as an antihyperalgesic/ antiallodynic or tolerance-protective drug [Visser & Schug, 2006]

2. Intrinsic analgesic effect

At higher (anaesthetic) concentrations ketamine has been reported to interact with

- opioid receptors (central and spinal), although this activation is not reversed by naloxone
- monoamine systems: agonistic effect on α - and β -adrenergic receptors; enhancement of dopamine activity (possibly relevant to euphorogenic, addictive and psychotomimetic properties)
- cholinergic: antagonism at CNS muscarinic and nicotinic receptors

Possible other actions:

- effect on purinergic and adenosine receptor systems
- local anaesthetic effects

3. Central antinociceptive effects

Enhancement of descending inhibition (enhanced or re-activated expression of descending inhibition, conditioned pain modulation), anti-inflammatory effects [Niesters, 2013]

Reduction of temporal summation in the nociception reflex model.

4 (a) Attenuation of acute opioid tolerance

"Opioid sparing" due to "attenuation of acute opioid tolerance" [Kissin et al. 2000] (Problems of definition)

4 (b) Prevention of opioid-induced hyperalgesia

Animal data indicate that NMDA receptor antagonists prevent development of opioid-induced hyperalgesia although the significance of that role is debated.

5. Cytokine effects

Inhibition of tumor necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6) gene expression in lipopolysaccharide (LPS)-activated macrophages has been reported.

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Specific syndromes - headache

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