

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

PREAMBLE

- A. This document articulates the position of the Faculty of Pain Medicine on the use of ketamine in the management of patients with chronic non-cancer pain (CNCP).
- B. This position acknowledges that there is wide variation both in clinical practice and in reported effectiveness.
- C. This document is not a guideline for the use of ketamine in CNCP, but offers guidance in this controversial arena, based on the literature and expert consensus, in order to inform the judgement of practitioners and to promote safety and quality for their patients.
- D. This paper consists of three sections:
 - 1. Ethical considerations
 - 2. Evidence for benefit and harm
 - 3. Safety considerations

1. ETHICAL CONSIDERATIONS

- 1.1 The use of ketamine in the management of patients with CNCP is “off-label”, defined in Australia by the Therapeutic Goods Administration¹ (TGA) as:
“[when] a medicine is used in ways other than specified in the Australian Therapeutic Goods Administration approved product information (PI), including when the medicine is prescribed or administered:
- for another indication
 - at a different dose
 - via an alternate route of administration
 - for a patient of an age or gender outside the registered use.”
- and defined in New Zealand by Medsafe² as:
“the use of an approved medicine under the direction or supervision of a healthcare professional for any of the following.
An unapproved:
- indication
 - age group
 - dosage
 - route or form of administration.”
- 1.2 The only indications for ketamine, as are listed in both the TGA-approved PI and Australian Medicines Handbook (AMH) and in the New Zealand data sheet, are:
- as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation
 - for the induction of anaesthesia prior to the administration of other general anaesthetic agents;
 - to supplement low-potency agents, such as nitrous oxide
- 1.3 According to the Council of Australian Therapeutic Advisory Groups (CATAG) taxonomy³, the use of ketamine in CNCP is “**conditional**”, the criteria for which are:
- the quality of evidence is ‘low’ to ‘moderate’; *but*
 - potential benefits appear greater than potential harms; *and*
 - there is reasonable justification for use in certain types of patients
 - as defined by pre-specified criteria (e.g. disease type and severity, age, standard treatments that have been tried and failed), and
 - who receive treatment according to an agreed protocol; *and*
 - the condition of such use should involve systematic reporting of effectiveness and safety outcomes so that an evidence base can be developed
- 1.4 It follows that practitioners who use ketamine in the treatment of CNCP *must obtain written informed consent from their patients* (or their legal guardians) in which it is emphasised that this use is “conditional off-label” and subject to the development of evidence.

¹ TGA.gov.au

² Medsafe.govt.nz

³ Council of Australian Therapeutic Advisory Groups. Rethinking medicines decision-making in Australian Hospitals. Guiding principles for the quality use of off-label medicines. Council of Australian Therapeutic Advisory Groups; 2013

2. EVIDENCE FOR BENEFIT AND HARM

2.1 Rationale

The rationale for the use of ketamine is putative, the possibilities including:

- harnessing an intrinsic analgesic effect of the drug
- inducing reversal of suspected central sensitisation of nociception
- facilitating reduction in opioid usage

2.2 Patient selection

2.2.1 The reported purposes of ketamine use in adults and children with CNCP include:

- reduction in opioid dose
- enhancement of effectiveness of multidisciplinary pain management
 - reduction in pain and suffering
 - improvement in function

2.2.2 Ketamine has been considered in those patients with CNCP⁴:

- who are taking doses of opioid that are considered to reflect poor opioid-responsiveness⁵ of pain; and/or
- who have been experiencing clinically significant side-effects of opioids; and/or
- whose use of opioids has been associated with aberrant drug-seeking behaviour; and/or
- who are considered to have a dual diagnosis of pain and opioid use disorder

2.2.3 Ketamine should not be used in patients with CNCP who also have:

- poorly controlled cardiovascular disease
- poorly controlled psychoses
- severe hepatic impairment
- elevated intracranial or intraocular pressure

2.3 Efficacy⁶

In the literature there is a paucity of evidence of only moderate quality concerning the use of ketamine in adults with CNCP. For children with CNCP, evidence is lacking.

There is no consensus on:

- protocol with respect to
 - dose
 - duration of infusion
- outcome
 - measures
 - duration

2.4 Adverse effects⁷

- “Ketamine is associated with myriad adverse effects including psychomimetic, cardiovascular, and gastrointestinal effects, resulting from its action on a variety of receptors, which include NMDA, acetylcholine, opioid, ion channels, monoamine, and histamine.” (Cohen et al, 2018, p. 536)
- “Ketamine overdose is associated with loss of consciousness, respiratory

⁴ The common indication here is opioid reduction and/or improved risk management.

⁵ As per College document PS01(PM)(2020) ; clause 2.1.5

⁶ For details of the variability in this space, refer to Section I of the Background paper, especially under Cohen et al (2018)

⁷ See Background paper for detail

depression, tachycardia, hypertension, and severe psychomimetic events including positive and negative signs of schizophrenia.” (Cohen et al, 2018, p.537)

- Potential for addiction
- Lack of safety data concerning long-term or repeated treatment (Bell & Lalso, 2018, p.e674).

2.5 Unanswered questions

Questions remaining to be addressed in the literature include but are not limited to:

- Does ketamine infusion lead to analgesia of meaningful magnitude and duration?
- Does ketamine infusion facilitate improvement in function?
- Does ketamine infusion lead to significant reduction in opioid use?
- Does ketamine infusion prevent relapse of opioid misuse?
- What is the optimal ketamine infusion dosage regimen?
- How does ketamine infusion compare with controlled opioid reduction?
- Are there groups of patients or conditions for which ketamine infusion might be more certain to be beneficial and cost-effective? If so, what is the best practice protocol?
- What, if anything, is the role of oral ketamine in chronic non-cancer pain?
- What are the potential harms of ketamine infusion in adults and in children?

3. SAFETY CONSIDERATIONS

3.0 Practitioners who are considering the use of ketamine in patients with CNCP should be familiar with the following principles that have been compiled from the literature and from expert consensus.

3.1 **Comprehensive assessment of the patient in a sociopsychobiomedical framework is a fundamental presumption.**

3.2 Context of ketamine infusion

3.2.1 Infusion of ketamine (subcutaneous or intravenous) should be delivered in in-patient settings that are staffed by experienced nurses and doctors who understand the pharmacology of the drug, the infusion and monitoring equipment being used, the protocol being followed and the age-group being treated.

3.2.2 Daily review by attending specialist pain medicine physician or appropriate delegate should be undertaken to monitor for efficacy and adverse side-effects and to oversee engagement in and progress with other therapies as agreed pre-admission.

3.2.3 Record-keeping must comply with legislation concerning storage, dispensing, administration and disposal of S8 drugs (in Australia) or Schedule 3 Class C Part 4 drugs (in New Zealand)

3.3 Necessary elements of protocol for ketamine infusion

3.3.1 Standardised concentration within the facility

3.3.2 Route and giving-set instructions that reduce the risk of

- inadvertent delivery of bolus
- line infection
- drug misuse or diversion

3.3.3 Type and frequency of observations

3.3.4 Clear direction regarding management of common adverse effects

3.3.5 Threshold for

- raising concern
- escalating to emergency response

3.4 Concomitant opioid management

3.4.1 An opioid treatment plan should be negotiated with the patient prior to admission for ketamine infusion.

3.4.2 Conversion of current opioids (oral, transdermal) to one opioid species⁸ should be made prior to administration of ketamine.

3.5 Discharge plan, follow-up plan and communication strategy⁹

3.5.1 Before discharge from in-patient care, there must be clear advice to patient, general practitioner(s) and appropriate other(s), including

- checklist for early adverse events, management instructions and emergency contacts
- change in opioid regimen following infusion
- updated pain management plan

3.5.2 Contingency plan for management of recurrence of pain

3.5.3 Routine 24-48 hour post-discharge telephone follow-up

3.5.4 Clear delegation of follow-up and management of medium-to-longer term adverse events

3.5.5 Serious adverse events should be reported to the TGA or Medsafe.

⁸ See PS01(PM)(2020) clause 2.2.2 and FPM Opioid Calculator app

⁹ As per Procedures in Pain Medicine Clinical Standard PS11(PM)(2020), Quality Statement 10

Disclaimer: The material in this Appendix is provided as illustration only.

The Faculty of Pain Medicine does not endorse any of the protocol elements mentioned.

For more detail, refer to the Background Paper.

A. The following table, extracted from Cohen et al (2012) (p.527), shows 6 different combinations of dosing and follow-up in adult patients enrolled in research trials of ketamine infusion for CNCP:

KETAMINE REGIMEN	FOLLOW-UP
• 80mg over 5 hours per day for 1 week	4 weeks
• 0.4mg/kg over 1 hour with 48 hour minimal interval between infusions	48 hours
• Up to 100mg over 4 hours for 10 consecutive weekdays	9-12 weeks
• 0.43mg/kg/hr over 4.2 days	12 weeks
• 0.5mg/kg over 30 minutes	8 weeks
• 0.6mg/kg over 4 hours	2-9 days

B. Regarding **doses**, Cohen et al (2018) conclude as follows (p. 538):

- “(1) Bolus: up to 0.35 mg/kg
 (2) Infusion: 0.5 to 2 mg/kg per hour, although dosages up to 7 mg/kg per hour have been successfully used in refractory cases in ICU settings

(3) There is evidence for a dose-response relationship, with higher dosages providing more benefit. Total dosages be at least 80 mg infused over a period of >2 h.”

[Level of evidence: All Grade C, low certainty]

However, in a more recent systematic review, Orhurhu et al (2019) concluded that the difference in pain score reduction between studies that utilised lower-dose and those that studied higher-dose ketamine infusions was not statistically significant (p. 241).

C. Regarding criteria for response, acceptable duration of benefit, and frequency of repeat infusions, Cohen et al (2018) recommend (p. 537):

- (a) Positive outcome: “30% pain relief or greater, in conjunction with
- patient satisfaction and/or
 - more objective indicators of meaningful benefit, such as
 - a 12.8% improvement in Oswestry Disability Index score in a patient with back pain or
 - a 20% or greater reduction in opioid use”
- (b) Duration of benefit:
- “...greater than 3 weeks following a single outpatient infusion and
 - greater than 6 weeks following an inpatient or series of infusions...”
- (c) Frequency of infusion:
- “... a consecutive ‘series’ of infusions should not be administered by rote, but rather tailored to patient response....
 - ...limiting these to no more than 6 to 12 treatments per year...”

[Level of evidence: Grade C, low to moderate certainty]

- D. Regarding pre-emptive management of side-effects, Cohen et al (2018) conclude (p. 537):
- “...there is limited direct evidence supporting the preemptive use of benzodiazepines and $\alpha 2$ agonists and
 - no evidence to support antidepressant, antihistamine, or anti-cholinergic premedicants prior to the initiation of subanesthetic ketamine for chronic pain treatment”

[Level of evidence: Grade C, low certainty]

APPENDIX II: ORAL KETAMINE IN CNCP

The literature reports low-level evidence to support the use of oral ketamine as follow-up therapy following infusion, with variable and short duration of effect. The consensus dose for adults in the literature is 150mg per day or 0.5mg/kg every six hours. There is insufficient evidence in relation to short- and long-term adverse effects.

The Faculty of Pain Medicine does not support the use of oral ketamine outside a research context.

This document is accompanied by a background paper PS12(PM) BP which provides more detailed information regarding the rationale and interpretation of the Position Statement.

ANZCA AND FACULTY OF PAIN MEDICINE PROFESSIONAL DOCUMENTS

POLICY – A document that formally states principle, plan and/or course of action that is prescriptive and mandatory.

STATEMENT – A document that describes where the college stands on a particular issue. This may include areas that lack clarity or where opinions vary. A statement is not prescriptive.

GUIDELINE – A document that offers advice on a particular subject, ideally based on best practice recommendations and information, available evidence and/or expert consensus. A guideline is not prescriptive. Note that, in contrast to policy, guidelines use “should” (advises) and avoid “must” (mandated).

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