CLINICAL GUIDELINE TITLE	Low-dose Ketamine for the treatment of complex pain in adults inpatients

1) SUMMARY

This document provides guidance on the administration of low-dose ketamine for adult inpatients with uncontrolled complex pain. Ketamine has been reclassified as a Schedule 2 controlled drug and therefore has to be stored in the controlled drug cupboard and needs a two person signature for administration.

2) INTRODUCTION

Low-dose ketamine for complex pain should only be commenced, prescribed, titrated and discontinued by the anaesthetic or pain service. This guideline does not cover the administration of ketamine as an anaesthetic agent or for the relief of procedural pain in areas such as Accident and Emergency. It does not cover the use of ketamine in palliative care.

3) DEFINITIONS

Complex pain – pain which does not respond to conventional analgesia, such as strong opioids. This is normally due to pain arising from complex pathophysiology, producing a mixture of neuropathic and nociceptive pain.

Ketamine trial – an accepted term used in the scientific literature to denote an intravenous trial of ketamine to establish efficacy.

Low-dose ketamine – sub-anaesthetic doses of ketamine

4) SCOPE

This document describes the indications for using low-dose ketamine for adult inpatients with complex pain. It describes how an intravenous trial of ketamine can be administered, by specified staff, to establish efficacy. It explains how low-dose oral ketamine suspension can be adminisered by nursing staff on the general wards.

Low-dose ketamine is reserved for patients whose pain does not respond to conventional analgesia, such as opioids. Patient should have one of the following criteria for ketamine to be considered (Schug 2004), but in practice they may fulfil more than one criteria:

- Neuropathic pain, including phantom limb pain
- Patient with hyperalgesia or allodynia
- Patients who have responded poorly to opioids
- Patients with a history of taking opioids preceding injury or surgery

There is an indication to use low-dose ketamine preemptively for patients who are statistically at high risk of developing chronic post-surgical pain (Macrae 2001).

This document does not cover the use of ketamine in chronic pain in the outpatient setting where its use is controversial. The NICE advice statement [ESUOM27] published in February 2014, states that the evidence for the use of ketamine in chronic pain is limited and the quality is poor in the trials that do exist. Adverse effects were frequently reported and there were also cases of

haemorrhagic cystitisassociated with long-term use. The summary of product characteristics (SPC) states that 'ketamine is not indicated nor recommended for long term use'.
https://www.nice.org.uk/advice/esuom27/chapter/key-points-from-the-evidence

5) FULL GUIDELINE

The aim of acute pain management is not only to relieve the immediate pain and suffering experienced by the patient, but also to prevent the development of chronic or persistent pain. The concept of chronic post-surgical pain has only recently become the subject of debate (Crombie et al. 1998; Macrae 2001; Kehlet et al. 2006). Although certain types of surgery are considered high risk for developing chronic post-surgical pain (for example, amputation, thoracotomy and mastectomy), there are other common risk factors. These include uncontrolled pre or post-operative pain, nerve damage or recent radiotherapy or chemotherapy (Macrae 2001). It is therefore vital to control acute pain, but there are patients who do not respond to conventional analgesia, such as strong opioids.

The development of persistent pain is thought to be due to changes that occur in the dorsal horn of the spinal cord, in particular the activation of the N-methyl-D-aspartate (NMDA) receptor (Woolf & Mannion 1999). In normal pain transmission the NMDA receptor is dormant, but when the dorsal horn is bombarded by pain signals and there is intense activity in the synapse, the NMDA receptor becomes active. Active NMDA receptors are thought to be responsible for central sensitization, the mechanism by which pain becomes persistent (Schmid et al. 1999; Petrenko et al. 2003; Schug 2004). Central sensitization changes the way that the nerves deal with subsequent painful stimuli (Woolf & Mannion 1999) and shows itself by enlarging the sensitive area of the skin that causes pain stimulation and producing symptoms of allodynia (pain from normal touch) and hyperalgesia (intense pain from minor painful stimuli) (Kehlet et al. 2006).

Ketamine is an anaesthetic agent, but in low doses can be effective as an analgesic without inducing anaesthesia. It is used to manage pain in complex patients and works by blocking the NMDA receptor, antagonising the effects of the excitatory neurotransmitter glutamate.

Four systematic reviews would support the use of ketamine for the management of pain after surgery (McCartney et al. 2004; Subramaniam et al. 2004; Bell et al. 2006; Laskowski et al. 2011).

5.1 Indications

Low-dose ketamine should not to be used routinely for all patients. It should be restricted to patients who have activated NMDA receptors. Patients should be selected for a trial of intravenous low-dose ketamine if they fulfil one or more of the following criteria (Schug 2004):

- Neuropathic pain, including phantom limb pain
- Patient with hyperalgesia or allodynia
- Patients who have responded poorly to opioids
- Patients with a history of taking opioids preceding injury or surgery

An intravenous trial of low-dose ketamine will quickly identify whether the patient has an active NMDA receptor and is going to respond to this medication. If the patient responds, then it will relieve pain within minutes.

5.2 Contra-indications

Contra-indications to low-dose ketamine are few. Most of the contra-indications noted in the Summary of Product Characteristics (SPC) are related to giving ketamine in high doses. But the following contra-indications should apply to the administration of low-dose ketamine:

- Allergy to ketamine
- Previous history of ketamine abuse
- Pregnancy
- Schizophreniform psychosis.

Ketamine is metabolised by the liver and hepatic clearance is required to terminate its effect. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. Dose reductions should be considered in these patients. On the rare occasions that this happens dosing advice should be sought from the pain service on an individual patient basis.

5.3 Intravenous ketamine trial

A ketamine trial should only be undertaken by an anaesthetist, the consultant nurse for the pain service, the lead nurse for the pain service, or clinical nurse specialists in the pain service, who have previously been deemed competent by the consultant or lead nurse. The decision to prescribe ketamine for patients in ward areas must be made in conjunction with the pain service, who can fully assess the patient's suitability for this treatment. Please see check list in Appendix 1.

Ten milligrams of intravenous ketamine should be diluted to a strength of 1mg of ketamine per mL, in a 10mL syringe. The 10mL syringe of ketamine should be clearly labelled.

A syringe of 20mL of saline, which will be used for flushing the intravenous line, should also be drawn up and clearly labelled. The ketamine trial should have been explained to the patient and a verbal pain rating score, at rest and moving (or coughing), obtained from the patient before the start of the trial. A verbal pain rating scale of no pain, mild pain, moderate pain or severe pain is used in the Trust. If the patient has difficulty understanding a verbal pain rating score, then a numeric score of 0 to 10 can be used.

Bolus doses of 2.5mg of ketamine can be administered every 5 minutes, until pain is mild on movement or a maximum of 10mg of ketamine has been given. If the patient's pain responds to the intravenous trial, they should be prescribed an oral ketamine regimen. On the rare occasions that patients are unable to take oral medications then either intravenous or sub-cutaneous ketamine can be considered.

In low doses ketamine will not affect the vital signs, as its sympathomimetic effects of raising blood pressure and pulse rate only occurs with anaesthetic doses. Patients do not have to be monitored during administration unless they are unwell, or have previously been given large doses of intravenous opioid. If pain is relieved by ketamine and patients have recently been given strong opioids, they may experience opioid related side-effects, such as a reduced respiratory rate, hallucinations, light headedness, vivid dreams etc. Ketamine at low doses does not produce dissociative side-effects.

The ketamine audit sheet must be completed for all patients who have a ketamine trial and pain scores should continue to be monitored with routine observations.

5.4 Oral ketamine

Where possible we would choose to administer ketamine orally, as there is less likelihood for error. Patients can be prescribed oral ketamine suspension, which is available from pharmacy. Oral doses usually start at either:

25mg ketamine, 6 hourly **or**
50mg ketamine, 6 hourly

Ketamine will be titrated further by the pain service to a maximum of 400mg per day (100mg 6 hourly). Some patients can experience breakthrough pain when ketamine is administered 6 hourly, as it wears off within the six-hour time period. Low-dose ketamine is best administered 4 hourly for these patients and can be titrated to a dose of 75mg every 4 hours (a total of 450mg of ketamine per day).

Oral ketamine can be administered by the general nursing staff, but as it is a Schedule 2 controlled drug, it requires two nurses to administer and sign for the medication. The administration of low-dose oral ketamine suspension does not require any additional monitoring of the patient's vital signs.

5.5 Intravenous or subcutaneous ketamine infusions

Please note that intravenous ketamine comes in three strengths, 10mg/mL, 50mg/mL and 100mg/mL.

Intravenous or subcutaneous low-dose ketamine infusions can be administered if the patient is unable to take oral medications and therefore cannot be prescribed oral ketamine suspension. These infusions should ideally be used in high dependency areas, where it can be prescribed and administered under the care of an anaesthetist.

On the infrequent occasions that intravenous or subcutaneous low-dose ketamine is required for patients in general ward areas, this should be prescribed and set up by either an anaesthetist or a member of the pain service. Intravenous or subcutaneous infusions that are made up on the wards will need to be changed every 24 hours.

Intravenous ketamine should be administered via a Blue Bodyguard 575 smart pump, which is pre-programmed to provide a continuous intravenous ketamine infusion. The infusion should run at a rate of 0.1mg per kg per hour (Hocking et al. 2007). Therefore a patient who weighs 70kg will receive 7mg Ketamine per hour. This can be increased up to 0.2mg per kg per hour if necessary, without the risk of dissociation. Higher doses than this may cause the patient to dissociate and are therefore not advised.

Nurses from the pain service or an anaesthetist must supervise the preparation of intravenous or subcutaneous ketamine solution for ward patients, when the intravenous infusion runs out. A standard bag containing a solution of 2mg per mL should be prepared for intravenous administration.

Low-dose subcutaneous ketamine should be administered via a Blue Bodyguard 575 smart pump, which is pre-programmed to provide a continuous subcutaneous infusion. A standard solution of 5mg per mL should be prepared for sub-cutaneous administration. If the patient should require more than 2mL per hour because of their weight, then a stronger concentration will be required.

Ketamine can be given in combination with other types of analgesia, including weak or strong opioids, non-steroidal anti-inflammatory and paracetamol.
The administration of low-dose ketamine, as an intravenous or subcutaneous infusion, will not require any additional monitoring of the patient's vital signs.

5.6 Stopping ketamine

Our audit data shows that by starting low-dose ketamine, we can prevent some patients having to take medications for persistent pain. However some patients who are difficult to manage may need to start another medication for neuropathic pain such as an anti-convulsant (gabapentin, pregabalin), whilst taking low-dose ketamine. These medications can be titrated to therapeutic doses whilst the patient continues to take ketamine. Ketamine should be discontinued prior to the patient's discharge from hospital and alternative medication for neuropathic pain should be established, if required.

It is advisable to discontinue strong opioids prior to stopping ketamine, as patients can experience rebound hyperalgesia, if ketamine is stopped first (Macintyre et al. 2010). If patients are taking therapeutic doses of neuropathic medications, then ketamine can be discontinued prior to stopping strong opioids.

Ketamine can be stopped abruptly, but in practice is normally stepped down to ensure that the patient does not experience a return of pain. Ketamine is not an addictive medication when given for pain relief and it does not cause physical or mental problems on withdrawal.

5.7 Adverse effect of low-dose ketamine

The Cochrane review of the use of low-dose ketamine for acute post-operative pain described the adverse effects of low-dose ketamine as being mild or absent (Bell et al. 2006) or no different than the administration of opioid alone (Hocking et al. 2007). Patients should not experience dissociation with low doses, but if higher doses are administered then dissociation is corrected by the administration of midazolam (please see sedation policy for advice on the administration of midazolam).
http://source/prdcont/groups/intranet/@corporate/@policies/documents/ppgs/id_028908.pdf.

The pain service audit data of 147 patients analysed in 2015, shows that some patients may experience feeling lightheaded during the administration of the intravenous ketamine trial (11%) or continue to feel lightheaded during oral ketamine administration (9%). Patients may experience opioid side-effects if pain is relieved by ketamine and their opioid dose may need to be reduced. These side-effects may include vivid dreams (0.1%), hallucinations (7%) and sedation (3%). Ketamine is known to reduce opioid consumption (Subramaniam et al. 2004). Most patients (73%) experienced no side-effects.

6) IMPLEMENTATION

Training required for staff	√Yes ☐ No
If yes, who will provide training:	Yes, a competency is required for Clinical Nurse Specialists in the pain service to enable them to deliver a ketamine trial. Training will be provided by: Dr Gillian Chumbley, Consultant Nurse, Pain Service Ms Rachel Townsend, Lead Nurse, Pain Service
When will training be provided?	When the nurse has been deemed experienced enough by the consultant or lead nurse to take on this extended role.
Date for implementation of guideline:	Not applicable

7) MONITORING / AUDIT

When will this guideline be audited?	Continuous audit of ketamine administration
Who will be responsible for auditing this guideline?	Dr Gillian Chumbley, Consultant Nurse, Pain Service
Are there any other specific recommendations for audit?	No

8) REVIEW

Frequency of review	**Please indicate frequency of review: 2 yearly review** January 2018 **Person and post responsible for the review:** Dr Gillian Chumbley, Consultant Nurse, Pain Service Ms Rachel Townsend, Lead Nurse, Pain Service

9) REFERENCES

- Bell, R. F., J. B. Dahl, et al. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev(1) 2006; CD004603.
- Crombie, I. K., H. T. Davies, et al. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76(1-2): 167-71.
- Hocking, G., E. J. Visser, et al. Ketamine: Does Life Begin at 40? Pain: Clinical Updates 2007; XV(3).
- Kehlet, H., T. S. Jensen, et al. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367(9522): 1618-25.
- Laskowski M.D., Stirling A., McKay W.P., Lim H.J. (2011) A systematic review of intravenous ketamine for postoperative analgesia. *Canadian Journal of Anesthesia* 58:911-923.
- Macintyre PE, Schug SA, et al. Acute Pain Management: Scientific Evidence. Melbourne, 2010. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.
- Macrae, W. A. Chronic pain after surgery. British Journal of Anaesthesia 2001; 87(1): 88-98.
- McCartney, C. J., A. Sinha, et al. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesthesia & Analgesia 2004; 98(5): 1385-400.
- Petrenko, A. B., T. Yamakura, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesthesia & Analgesia 2003; 97(4): 1108-16.
- Schmid, R. L., A. N. Sandler, et al. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999; 82(2): 111-25.
- Schug, S. A. "New Uses for an Old Drug: The Role of Ketamine in post-operative pain management. ASEAN Journal of Anaesthesiology 2004; 5(1): 39-42.
- Subramaniam, K., B. Subramaniam, et al. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesthesia & Analgesia 2004; 99(2): 482-95.
- Woolf, C. J. and R. J. Mannion. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999; 353(9168): 1959-64.

SUGGESTED READING

- Chumbley G. Ketamine in uncontrolled acute and procedural pain. The Nursing Standard 2010; **25**(15-17): 35-37.
- Chumbley G. New directions in acute pain management: ketamine. 2010. In Carr ECJ, Layzell M (Eds) Advancing Nursing Practice in Pain Management. Wiley-Blackwell, Oxford UK.

10) GUIDELINE DETAIL

Start Date:	February 2016
Approval Dates	Name of Divisional group: Surgery, Cancer and Cardiothoracic Date of ratification: 3rd February 2016
	Name of Directorate group:Theatres, Anaesthetic, Pain & Pre-assessment Quality & Safety Meeting Date of ratification: 08/12/15 Evidenced Based Practice Group – 14/12/15 Drugs & Therapeutics Committee – 8/12/15 (Chair's action 20/1/16)
Has all relevant legislation, national guidance, recommendations, alerts and Trust action plans been considered, and included as appropriate in the development of this guideline?	The misuse of drug regulations 2001
Have all relevant stakeholdersbeen included in the development of this guideline?	Dr Helgi Johannsson - Chief of service, Anaesthesia, Theatres, Pain Dr Nicola Stranix – Consultant anaesthetist for acute pain Dr Ashwin Kalbag – Consultant anaesthetist for acute pain Dr Marta Prestedge – Consultant anaesthetist for acute pain
Who will you be notifying of the existence of this guidance?	Anaesthetics, theatres and recovery, high dependency, all general wards, divisional director of nursing
Related documents	Sedation Policy Non-anaesthetic procedural sedation policy
Author/further information	Name: Dr Gillian Chumbley Title: Consultant Nurse, Pain Service Division: Surgery, Cancer and Cardiothoracic Site: Trustwide Telephone/Bleep: 0203 311 1000, bleep 5865 Trust email address: gillian.chumbley@imperial.nhs.uk
Document review history	October 2015 v3, replaces the 2011 guideline Next review in January 2018
THIS GUIDELINE REPLACES:	Low-dose ketamine for the treatment of complex pain in adults, clinical guideline 2011

INTRANET HOUSEKEEPING

Key words	Ketamine, low-dose ketamine, complex pain
Which Division/Directorate category does this belong to?	Surgery, Cancer and Cardiothoracic
Which specialty should this belong to when appearing on the Source?	Anaesthetics Pain Service

EQUALITY IMPACT OF GUIDELINE

Is this guideline anticipated to have any significant equality-related impact on patients, carers or staff?

Yes ☐ No √