CLINICAL GUIDELINE TITLE	**Ketamine low-dose for the treatment of complex pain in adult inpatients**

1) SUMMARY

Low-dose ketamine for complex pain should only be commenced, prescribed, titrated and discontinued by the anaesthetic or pain services.

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 or chronic pain.

For further information about ketamine and chronic pain please see NICE advice statement [ESUOM27] published in February 2014 [1].

2) INTRODUCTION

This document provides guidance on the administration of low-dose ketamine for adult inpatients with uncontrolled complex pain.

Ketamine is classified as a Schedule 2 controlled drug and is therefore subject to safe custody requirements and the need to keep a controlled drug register (has to be stored in the controlled drug cupboard) and needs a two person signature for administration.

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

Allodynia - pain due to a stimulus that does not normally provoke pain [2], such as normal touch.

Hyperalgesia - increased pain from a stimulus that normally provokes pain [2], often described as an exaggerated response to a pain stimulus.

Opioid induced hyperalgesia – a state of abnormal pain sensitivity caused by exposure to opioids [3].

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 administered 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 [4], but in practice they may fulfil more than one criterion:

- 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 pre-emptively for patients who are statistically at high risk of developing chronic post-surgical pain [5].

5) FULL GUIDELINE

5.1 Indications for use

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 persistent post-surgical pain has recently become the subject of debate [5,6,7]. 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 and chemotherapy [5]. 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 [8]. 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 [9,10]. Central sensitization changes the way that the nerves deal with subsequent painful stimuli [8] 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) [7].

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.

Five systematic reviews support the use of ketamine for the management of pain after surgery [11,12,13,14,15].

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 [4]:

- 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

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.

5.2 Ketamine trial

An intravenous ketamine trial should be undertaken prior to starting ketamine; this allows pain to be treated quickly and determines whether the patient will respond to ketamine. The bioavailability of oral ketamine is low, as it undergoes extensive first pass metabolism with only 17-24% of racemic ketamine reaching the systemic circulation [16]. If a patient fails to respond to an oral dose, it is difficult to know whether this is a failure of the medication or under prescribing.

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

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 on moving or coughing obtained from the patient before the start of the trial. A verbal pain rating scale of none, mild, moderate or severe pain is used in the Trust.

Bolus doses of 2.5mg of ketamine can be administered every 5 minutes, until pain is mild on movement or a maximum of 10mg ketamine has been given. If the patient's pain responds to the intravenous trial, they should be prescribed an oral ketamine regimen. Occasionally patients are unable to take oral medications or their medical condition may warrant the use of intravenous or sub-cutaneous ketamine.

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

5.3 Oral ketamine

Where possible we prefer 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 to sign for the medication.

5.4 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 or if their medical condition warrants it. These infusions should ideally be used in high dependency areas, where it can be prescribed and administered under the care of an anaesthetist or intensive care specialist.

On the infrequent occasions that intravenous or subcutaneous low-dose ketamine is required for patients in general wards, this must be prescribed and set up by either an anaesthetist or a member of the pain service. Intravenous or subcutaneous infusions that are made up in ward areas will ideally be changed every 24 hours [17]. But infusion bags may be left for 72 hours in exceptional circumstances.

When intravenous ketamine is administered in ward areas a Blue Bodyguard 575 smart pump, which is pre-programmed to provide a continuous intravenous ketamine infusion, must be used. The infusion should run at a rate of 0.1mg per kg per hour [18]. Therefore a patient who weighs 70kg will receive 7mg ketamine per hour. This can be increased to a maximum of 0.2mg per kg per hour if necessary without the risk of dissociation. Higher doses may cause the patient to dissociate and are therefore not advised.

When ketamine is administered in high dependency areas a syringe driver may be used. If the patient transfers to the wards with intravenous rather than oral ketamine, the ketamine infusion should be administered via the Blue Bodyguard 575 smart pump, as detailed above and the pain service must be alerted.

As there are no ready-made ketamine infusion bags, nurses from the pain service or an anaesthetist must supervise the preparation of intravenous or subcutaneous ketamine infusions for ward patients when the infusion bag has expired or needs to be changed. A standard bag containing a solution of 2mg ketamine 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 drugs and paracetamol.

5.5 Monitoring of patients

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 the ketamine trial, unless they are unwell, or have previously been given large doses of intravenous opioid. If pain is relieved by ketamine then patients who have recently been given strong opioids may experience opioid related side-effects, such as a reduced respiratory rate, hallucinations, light headedness, vivid dreams etc. These patients may require oxygen therapy until the adverse effects of the opioid have worn off. Ketamine at low doses does not produce dissociative side-effects.

The administration of low-dose oral ketamine suspension does not require any additional monitoring of the patient's vital signs.

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 must 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 opioid induced hyperalgesia if ketamine is stopped first [19]. If patients are taking therapeutic doses of neuropathic medications, then ketamine can be discontinued prior to stopping strong opioids.

Ketamine can be stopped immediately, but in practice is normally stepped down to ensure that the patient does not experience a return of the 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 effects 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 [13], or no different than the administration of opioid alone [18]. Patients should not experience dissociation with low doses, but if higher doses are administered then dissociation is corrected by the administration of midazolam (*please refer to the sedation policy for advice on the administration of midazolam*).

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%). Most patients (73%) experienced no side-effects. 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%). Systematic reviews of ketamine have demonstrated an opioid sparing effect [12,13,14,15].

In a recent randomised control trial comparing ketamine to saline placebo conducted in the Trust, the ketamine group reported feeling more lightheaded ($p=0.02$) and experienced more vivid dreams ($p=0.001$), but no patient withdrew from the study because of these side-effects [20].

Ketamine is known to have an abuse potential [21]. Adverse effects following chronic abuse include haemorrhagic cystitis [22], cholestasis and biliary dilatation [23]. These symptoms are not seen in patients using ketamine in small doses for short duration, but these issues need to be considered when using ketamine in a chronic setting and may limit its indications [24]. For these reasons patients who have used ketamine in the acute setting are not discharged home with ketamine. As mentioned previously, ketamine should be discontinued prior to the patient's discharge from hospital and alternative medication for neuropathic pain should be established, if required.

6) IMPLEMENTATION

Training required for staff	√ Yes ☐ No
If yes, who will provide training:	The pain service
When will training be provided?	The use of ketamine in the Trust is taught on the Pain Study Day each month. Nurses in the pain service are taught about ketamine on the Pain Study Day and by senior members of the team. Their competency in the administration of a ketamine trial and the non-medical prescribing of ketamine is assessed by the Consultant Nurse, Lead Nurse or Senior Clinical Nurse Specialists for the Pain Service.
Date for implementation of guideline:	

7) MONITORING / AUDIT

When will this guideline be audited?	On-going continuous audit of the administration of ketamine
Who will be responsible for auditing this guideline?	Dr Gillian Chumbley – Consultant Nurse, Pain Service Pauline Chinn - Lead Nurse, Pain Service Nicola Bourne – Lead Nurse, Pain Service
Are there any other specific recommendations for audit?	None

8) REVIEW

Frequency of review	**Please indicate frequency of review:** *THREE YEARS* **Person and post responsible for the review:** Dr Gillian Chumbley – Consultant Nurse, Pain Service Pauline Chinn - Lead Nurse, Pain Service Nicola Bourne – Lead Nurse, Pain Service

9) REFERENCES

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10) GUIDELINE DETAIL

Start Date:	**17th July 2019**
Approval Dates	Theatre Q&S Group 04/06/19 SCC Q&S Directorate group: DATE Drugs and Therapeutics Committee: 2nd July 2019
Has all relevant legislation, national guidance, recommendations, alerts and Trust action plans been considered, and included as appropriate in the development of this guideline?	**Please list ALL guidance considered:** Please see reference list
Have all relevant stakeholders been included in the development of this guideline?	**Please list all (name and role):** Anaesthetists & Nurses in the Inpatient pain service (SCC) Dr Stewart Berry, Clinical Director Theatres, Anaesthetics & Pain Anaesthetists at CX, HH & SMH
Who will you be notifying of the existence of this guidance?	**Please give names/depts:** It will be advertised on the intranet
Related documents	
Author/further information	Dr Gillian Chumbley , Consultant Nurse, Pain Service (SCC). gillian.chumbley@nhs.net Dr Nicola Stranix, Consultant Anaesthetist (SCC) Jaimi Patel, Lead Pharmacist Anaesthetics and Pain (SCC)
Document review history	**Next review due: 2nd July 2022** V2.2 – revised guideline V3.0 – finalised version
THIS GUIDELINE REPLACES:	Low-dose Ketamine for the treatment of complex pain in adults inpatients (October 2015)

11) INTRANET HOUSEKEEPING

Key words	Ketamine, pain, complex pain, postoperative pain
Which Division/Directorate category does this belong to?	Pain Service (SCC)
Which specialty should this belong to when appearing on the Source?	Pain Service (SCC)

12) EQUALITY IMPACT OF GUIDELINE

Is this guideline anticipated to have any significant equality-related impact on patients, carers or staff? No