ST MICHAEL'S HOSPICE

CLINICAL CARE GUIDELINES

USE OF KETAMINE – PALLIATIVE CARE SHARED CARE GUIDELINES

(PLUS ALGORITHM AND INFORMATION SHEET)

Herefordshire Shared Care Protocol.
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PALLIATIVE CARE SHARED CARE GUIDELINES - KETAMINE

Pain in a palliative care setting not responding to opioids and adjuvant therapy

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

- This document outlines the process for shared care of palliative care patients taking **ketamine** within the Hereford region and is approved by Herefordshire CCG.
- It outlines the suggested roles and responsibilities of specialists and primary care teams within the patients care.
- The protocol is designed to support GP's with this unlicensed use of Ketamine and minimise disruption for the patients for whom it is necessary.
- **Please note this is an unlicensed indication for ketamine – see section on page 2. For unlicensed uses of drugs-the doctor who prescribes the medication legally assumes responsibility for the drug and the consequences of its use.**
- GP's are not obliged to take part. If the GP is not confident to undertake the roles described, the total clinical responsibility for use of ketamine in the diagnosed condition remains with the specialist.
- If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable**.**
- Sharing of care requires communication between the specialist, GP, pharmacist and patient. All parties should be aware of any plan to share care.
- Patients taking ketamine for this indication are under regular follow-up in secondary care, where it is expected that monitoring will occur.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Fax:	Email address:
Specialist: St Michaels Hospice	01432 851000	01432 851022	Tony Blower or ward doctors (please telephone for advice.)
Hospital Pharmacy Dept: Dispensary	01432 364024	01432 364055	
Hospital Pharmacy Dept: Medicines Information	01432 364017	01432 364055	meds.infowvt@nhs.net
Lead Palliative Care Clinical Nurse Specialist	01432 851356	01432 853076	**Wye Valley NHS Trust SPC team - Community** (Please telephone for advice.)
Consultant in Palliative Medicine based at Hereford County Hospital	01432 364414	01432 364108	**Wye Valley NHS Trust SPC team - Hospital** (Please telephone for advice.)

RESPONSIBILITIES AND ROLES

Specialist responsibilities
1 Initiate treatment with ketamine. 2 Discuss the benefits and side effects of treatment with the patient. 3 Ask the GP whether he or she is willing to participate in shared care, and agree with the GP as to who will discuss the shared care arrangement with the patient. 4 Regularly review the patient's condition and communicate promptly with the GP when treatment is changed. 5 Assess analgesic control and look for adverse effects. Advise patients to promptly report any new urinary tract symptoms or abdominal pain. Monitor for these at least monthly using Ketamine monitoring chart. 6 Advise the GP on when to adjust the dose, stop treatment, or consult with the specialist. 7 Report adverse events to the MHRA via the yellow card scheme (https://yellowcard.mhra.gov.uk/) and GP. 8 Ensure that clear backup arrangements exist for GPs to obtain advice and support. 9 Notify nominated community pharmacy of need to set up supply following initiation to allow continued supply. 10 Inform prescribing GP of nominated community pharmacy and recommend GP does prescription 1week before existing supplies run out to avoid break in supply. 11 Provide 2 weeks supply of ketamine on discharge.

General Practitioner responsibilities
1 Reply to the request for shared care as soon as practicable. Prescribe ketamine at the dose recommended by the specialist team for supply by nominated community pharmacy. Recommend do prescription 1 week before previous prescription runs out to avoid risk of break in supply. **PLEASE NOTE that Ketamine is a controlled drug and that full CD writing requirements apply** 2 Adjust the dose as advised by the specialist. Advise patients to report any new urinary or abdominal symptoms. Monitor for these and report urgently. 3 Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment. Advise patient. 4 Refer back to specialist if the patient's condition deteriorates, as advised. Be mindful of potential for urinary and hepatobiliary toxicities. 5 Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises. 6 Report adverse events to the specialist and MHRA via the yellow card scheme (https://yellowcard.mhra.gov.uk/)

Patient's role
1 Report to the specialist or GP if he or she does not have a clear understanding of the treatment. 2 Share any concerns in relation to treatment with ketamine. 3 Inform specialist or GP of any other medication being taken, including over-the-counter products. 4 Report any other adverse effects or warning symptoms to the specialist or GP whilst taking ketamine.

SUPPORTING INFORMATION (see SPC and BNF for complete details)

Licensed indications

This shared care protocol covers prescribing for an unlicensed indication of ketamine, although the use of ketamine for this indication is well established in specialist palliative care. Such prescriptions are written at the discretion of the individual prescriber. The prescriber is responsible for discussing the use of an unlicensed medication with the patient.

BACKGROUND

- Most pain in patients with malignant disease will respond to opioids (sometimes at high doses) with or without adjuvant therapies.
- A small minority of patients, often those with neuropathic pain, are resistant to such measures, either due to intolerable side effects or lack of effect[1].
- Ketamine is a NMDA-receptor-channel blocker and a dissociative anaesthetic which has analgesic properties in sub-anaesthetic doses. Ketamine has other actions which may also contribute to its analgesic effect, including interactions with other calcium and sodium channels, cholinergic transmission, noradrenergic and serotoninergic re-uptake inhibition (intact descending inhibitory pathways are necessary for analgesia) and μ,δ and κ opioid-like effects[1,2].
- Oral ketamine undergoes extensive first-pass hepatic metabolism to norketamine. As an analgesic, norketamine is equipotent with parenteral ketamine. Less than 10% of ketamine is excreted unchanged, half in the faeces and half renally. Long-term use of ketamine leads to hepatic enzyme induction and enhanced ketamine metabolism [1,2].
- Ketamine also appears to have an antidepressant effect in patients with major depression[2].
- Such use of ketamine is not covered by the product licence and should only be initiated by a Specialist in Palliative Medicine[3].
- Ketamine potentates the action of opiates and therefore careful monitoring of opiate requirement is necessary at initiation and on dose increments[1,2].

PLACE IN THERAPY[4,5]

- Ketamine is a reserve line agent used in the management of neuropathic, ischaemic limb pain and refractory limb pain, and should only be used once the following drugs have been tried and tested:
  - Paracetamol
  - NSAID
  - Adjuvants e.g. amitriptyline, Gabapentin
  - Opioids
  - Dexamethasone if appropriate

Clinical features suggestive of ketamine sensitive pain[1]

- Allodynia
- Hyperalgesia
- Prolongation of evoked pain response

CONTRA-INDICATIONS[2]

- Absolute
  - Intra-cranial hypertension

- Glaucoma
- Seizures
- patients receiving MAOI's

- Relative
  - Hypertension
  - cardiac failure
  - previous cardiovascular events or cerebrovascular accidents.

SIDE EFFECTS[1,2]

Chronic Ketamine use may cause urinary and hepatobiliary toxicities. Urothelial toxicity may present early as haematuria, dysuria, bladder instability symptoms and progress to renal toxicity and failure. Ketamine urethelial toxicity needs to be considered if unexplained urinary symptoms develop. Seek specialist advice if symptoms develop. We need to be vigilant and monitor regularly for these side effects. The monitoring chart helps to facilitate this.

- Most commonly seen:
  - Vivid dreams
  - Hallucinations
  - Hypersalivation
  - Sedation/cognitive side effects/perceptual changes
  - Opioid toxicity from potentiation.
- Rare side effects:
  - Psychosis
  - Hypertension
  - Tachycardia

Ketamine is commonly given with Midazolam or Haloperidol to reduce the psychotomimetic effects. Ketamine does not depress respiration but by potentiating the action of opioids on pain, opioid toxicity may develop requiring a reduction in opioid dose[5].

Pregnancy and breast feeding*:* Not recommended for use in pregnancy or lactation[5].

DOSAGE AND ADMINISTRATION

- **Each vial of Ketamine injection is for single use only and must not be reused according to the SMH and the WVT Injectable Medicines Policy[14]. Once used opened vials to be stored in CD Cupboard awaiting destruction.**

- Opioids are usually continued at the previous dose but may need to be reduced if large dose of opioid, opioid induced hyperalgesia present, clinical concern over risk of opioid toxicity, the patient gets good pain relief from the ketamine or shows signs of opioid toxicity. Consider switching from sustained release to immediate release preparations. Consider an opioid dose reduction, for example by 30% particularly if on an opioid with a long half life or a transdermal preparation[5,6,7].
- Consider premedication and ongoing medication with haloperidol or a benzodiazepine to prevent or treat side effects [2,8] .
- Ketamine should only be started in a specialist inpatient setting[6,7,8].
- Dose alterations of ketamine should be undertaken in the inpatient unit **or after outpatient review**.

- Treatment should be commenced or changed before 2pm to monitor for side effects before bedtime [8]
- Ketamine is administered orally or subcutaneously. Conversion from oral to subcutaneous is 1:1[2].

- **Suggested Oral Regimen** [2,8]

  A single test dose of 10mg may be used to assess for possible side effects

Starting Dose	10-25mg TDS - QDS & PRN
Rate of Increase	10-25mg QDS daily

  Usual maximum dose 100mg QDS, maximum reported dose 200mg QDS

  - Analgesia may be achieved at low doses and higher doses may not be needed.
  - Delay dose increases if side effects a problem.
  - Dose increases should be stopped at 100mg QDS and response assessed over the next few days as the active metabolite norketamine will start to contribute to analgesia[2]
  - Doses above 100mg QDS are rarely required[2].
  - Ketamine injection may be given via the oral route. In this instance, the open vial may be kept in the fridge for up to 7 days[2]. However the oral solution should be used in preference if available.
  - An oral solution with a shelf life of 1 year is also available in various flavours including peppermint and butterscotch (see supply information)[2].

- **Suggested Sub-Cutaneous Regimen[2,8]**
  - **Ketamine should always be diluted with sodium chloride 0.9%[2].**
  - Ketamine can be mixed with diamorphine, morphine, haloperidol, levomepromazine, metoclopramide and midazolam. Additions of any other drugs should only be done with specialist advice[2].
  - Ketamine can be irritant therefore it is good practice to dilute the ketamine as much as possible. It is common practice if needed to add dexamethasone 1mg to the syringe driver to help manage this irritation[2].
  - Careful consideration by the specialist is given to duration of use of ketamine in discussion with the patient balancing risks/ benefits and prognosis in their individual situation. Prolonged analgesia may follow a course of ketamine.

  1. VIA CSCI[2]

Starting Dose	1-2.5mg/kg/24h (in practice 100-200mg/24hrs)
Rate of Increase	50-100mg/24h
Usual dose range	100-400mg/24hrs
Maximum Reported Dose	3.6g/24h

- **As Required Medication**
  - Typically ketamine 10-25mg p.r.n[2] (max 100mg/24hrs)
  - Or 4 hourly opioid dose [2]

MONITORING*:*

- Observe for opioid toxicity. (i.e. respiratory, depression, drowsiness, jerking). Ketamine would only ever be initiated within a specialist setting with use of opioid monitoring chart after initiation.
- Once analgesia established consider rationalising medications as appropriate e.g. reducing opioid/adjuvant agents etc.
- If analgesia is not achieved consider stopping ketamine.
- Once stabilised on an effective dose, pain and side effects need to be assessed on a regular basis. The syringe driver will need to be changed every 24 hours by the district nurse. Normal care and monitoring of the syringe driver should be followed as per Wye Valley Trust Syringe Driver Policy and West Midlands Palliative Care Guidelines[10,11].
- Chronic Ketamine use may cause urinary and hepatobiliary tract toxicities. At monthly consultant review monitor for changing urinary symptoms using the urinary questionnaire on the Ketamine Monitoring Chart. If new symptoms, dip urine and send MSU to exclude infection. In absence of infection consider ketamine related cystitis. Seek specialist advice and consider stopping ketamine. Abnormal LFTs have been seen in ketamine abuse and analgesic use. In abusers, abdominal pain has been reported and in some dilation or strictures of the common bile duct. When ketamine is stopped the LFTs, abdominal pain and biliary duct dilation generally improve
- Reassessment by the palliative medicine consultant should be at least monthly.

IMPORTANT SUPPLY INFORMATION

PLEASE NOTE Ketamine is a controlled drug and full CD writing requirements apply

The supply in recent years has been compromised and specific products / strengths may vary depending on availability. Always refer to the information provided with the specific product

- <u>Oral Solution</u>
  - Be aware this has to be specially ordered and can take up to several working days for delivery. Ongoing supply must be arranged by the nominated community pharmacy who is notified on discharge. Patients are discharged with 2 weeks supply after initiation. The community pharmacy needs an FP10 from the GP before they can re stock from the supplier. This may take several days so to avoid break in supply (which has occurred) it is strongly advised the GP does initial repeat prescription 1 week after discharge to prevent this ***Ketamine 50mg/5ml is the standard strength that is used and available to community pharmacists from e.g. Rosemont Pharmaceuticals on 0800 919 312.***
  - The parenteral preparation can be used orally – disguise taste with ribena.

- <u>Sub-cutaneous Infusion</u>
  - Ketamine injection is available in 10mg/ml, 50mg/ml and 100mg/ml concentrates.
  - **Labelling on all concentrations is very similar therefore caution is required.**

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Ketamine Monitoring Chart

Chronic ketamine use may cause urinary and hepatobiliary tract toxicity (*see monograph on palliativedrugs.com)*

Practitioners should:

- Advise patients to promptly report any new Urinary tract symptoms or abdominal pain
- Monitor for these toxicities, at least monthly

Name
Hospital Number
DOB
Address
(or affix sticker)

	Baseline	Visit 1	2	3	4	5
Date						
Ketamine dose (mg/24h)						

Urinary symptoms: enter score using questionnaire overleaf						
Urgency						
Frequency >2 hourly						
Nocturia						
Dysuria						
Haematuria						

If new or worsening symptoms, dip urine test
If dip test suggests possible infection, send MSU
In the absence of infection, consider ketamine-related cystitis
Consider stopping the ketamine (ideally withdraw over 2-3 weeks), and seeking the advice of a urologist

Liver function: enter value						
Date of test (if different from above)						
ALT/AST						
Bilirubin						
Alk Phos						
Albumin						

Abnormal LFTs have been seen with both ketamine abuse and analgesic use
In abusers, abdominal pain has been reported and, in some, dilation or strictures of the common bile duct.
When Ketamine is stopped, the LFTs, abdominal pain and biliary duct dilation generally improve

Appendix 1: Monitoring chart

Appendix 2:

Urinary symptom assessment

The urinary score gives a pre-treatment, baseline score against which subsequent raised scores warrant further evaluation.

During the past month, how often have you felt the strong urge to pass urine with little or no warning?	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always
During the past month, how often have you had to pass urine less than 2 hours after the last time?	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always
During the past month, how often do you typically get up at night to pass urine?	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always
During the past month, have you experienced pain or burning in your bladder	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always
During the past month, have you experienced passing blood or blood clots in your urine	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always

ALGORITHM FOR USE OF KETAMINE by Specialist Palliative medicine service