Shared Care Guidance

Shared Care Guidelines for the use of Ketamine in Palliative Care Initiated by Palliative Care Specialists

Approved: July 2020 Review: July 2023

This guideline sets out details of the respective responsibilities of GPs and specialist services within shared care prescribing arrangements and is intended to provide sufficient information to enable GPs to prescribe ketamine for palliative care patients (largely with cancer related pain) that has been initiated by a palliative care specialist within a shared care setting.

An electronic version of this document can also be viewed / downloaded from the North of Tyne and Gateshead Area Prescribing Committee Website at:

http://www.northoftyneapc.nhs.uk/documents/guidelines-and-statements/

Endorsed for use within North Tyneside, Northumberland, North Cumbria, Newcastle and Gateshead by the North of Tyne, Gateshead and North Cumbria APC	
Review date	Medicines Use and Guideline Group recommended review date: July 2023
Membership of the guideline development group	The following were consulted on the review of the 2020 approved guidance: • Dr Alexa Clark, Consultant in Palliative Medicine, NuTH Community Specialist Palliative Care Team • Dr Rachel Quibell, Consultant in Palliative Medicine, NuTH • Catherine Horne, Prinicipal Pharmacist, NuTH • Dr Leena Srivastava, Consultant in Palliative Medicine, Gateshead Health

Ketamine in Palliative Care Shared Care Guideline

Introduction and Background

Ketamine is an anaesthetic agent that has been shown to have potent analgesic properties at low doses through inhibition of the N-methyl-D-aspartate (NMDA) receptor. It is used as an adjuvant analgesic in patients with neuropathic pain that is poorly responsive to opioids, particularly in patients with allodynia, hyperalgesia or hyperpathia. Inflammatory, ischaemic limb and procedure-related pain unresponsive to standard treatments may also respond to ketamine. It is used to control pain not successfully settled with strong opioids, anticonvulsants and antidepressants in line with the WHO analgesic ladder.

Although the use of ketamine in the treatment of pain is unlicensed there is considerable experience with its use. Use in the management of pain in palliative care is recommended in the Scottish Palliative Care Guidelines and the Palliative Care Formulary.

Following discussion by the Shared Care Group and Area Prescribing Committee it has been agreed that ketamine is suitable for prescribing under a shared care arrangement for patients receiving specialist palliative care treatment for pain. This decision has taken into account the unlicensed status of ketamine in the treatment of pain, any risks associated with its use, the fact that any problems with ketamine usually become apparent during the dose titration and stabilisation phases of treatment (undertaken by specialist care services in an inpatient setting) and the needs of patients. At present the prescribing of ketamine under a shared care arrangement for the treatment of chronic pain in other patients has not been approved.

Like many medicines used in palliative care the use of ketamine is not licensed for use as an adjuvant analgesic in the UK and prescribers should be aware of this.

As with many other drugs used in the treatment of pain there is a risk of abuse, but as with opioids this risk is very low when it is prescribed in palliative care. Ketamine is a controlled drug under the Misuse of Drugs Act, and in November 2015 was re-classified to a class 2 drug.

If a GP practice is concerned about the shared care agreement, the palliative care team can provide educational liaison to help address the concerns.

If a GP has concerns about prescribing ketamine for an individual patient then it is recommended that he/she should discuss possible options with the palliative care specialist.

If a GP refuses to participate in this shared care agreement then the palliative care specialist should not ask the GP to participate in a shared care arrangement for that patient again, unless there is a significant change in circumstances.

Referral Criteria
Patients with pain that has not been successfully treated with strong opioids, anticonvulsants (e.g. gabapentin) and antidepressants (e.g. amitriptyline) and who have responded to ketamine.

Palliative Care Specialist / Secondary Care Responsibilities

- To assess the suitability of the patient for a trial of ketamine.
- To provide information, discuss and agree treatment with the patient. To initiate treatment at the appropriate dose and route of administration.
- To titrate the dose and stabilise the patient including treatment of adverse
- effects and initiate opioid dose reduction if required. When the dose of ketamine is increased the opioid dose is usually reduced.
- To monitor blood pressure whilst initiating/titrating treatment (it may increase).
- To ensure that LFTs are checked, prior to commencing, after 2 weeks of ketamine, and monthly thereafter.
- To assess and reduce ketamine if possible after 2-3 weeks of treatment.
- To assess patient and implement a switch to a different route of administration or preparation, where appropriate.
- The use of this drug is exceptional and it is expected that the initiating palliative care specialist will liaise with the patient's GP (and where appropriate district nurse/ community pharmacist) to "share" the patient's care, informing them of any changes to the patient's ketamine prescription and other medicines. This includes communication by letter including completion of Appendix 1 – "Shared Care Request". A direct conversation should take place between the specialist and a GP member of the practice to discuss the arrangement.
- To prescribe 28 days supply of medication on discharge to ensure continuity of supply. The prescription must state the strength of vial or solution to be used.
- To supply information (including this shared care protocol) to the GP, and to the district nurse and/or community pharmacist nominated by the patient as appropriate.
- To review the patient's therapy at regular intervals and at the request of the patient or GP.
- To monitor for side effects at regular intervals
- To stop treatment when it is no longer appropriate.

General Practitioner's Responsibilities

- **The GP may decline this request for clinical or operational reasons.**
- To contact the specialist to confirm he/she is happy to accept the shared care arrangement by **returning the completed form in Appendix 1.**

- To prescribe ketamine for the patient when required, to enable the patient to receive a continuing supply.
- To monitor the patient for continued effectiveness of ketamine and adverse effects.
- To seek further information and advice from the palliative care specialists.
  - If there are any concerns regarding the ongoing effectiveness of ketamine, or side effects in particular urinary tract symptoms, new abdominal pain or increased BP.
  - If the patient develops a cardiac arrhythmia
  - If there are other problems with its use.
  - When a change of administration route may be indicated
  - For patient who are not stable or pain is not well controlled.
- Judgment is needed on an individual case basis, taking into account all of the factors. Please seek advice from palliative care team, if adjustment in dose or route of administration, or a change in treatment is required
- To liaise with community and specialist nurses and the community pharmacy as appropriate.
- Ketamine is a CD 2 drug and should be prescribed accordingly
- To monitor patient's pulse, blood pressure, urinary tract symptoms and LFTs if requested by Palliative Care Specialist

Ketamine – Information Sheet

Drug	Ketamine	
Indication	Treatment of neuropathic pain that has not responded adequately to other medication including strong opioids, anticonvulsants (e.g. gabapentin) and tricyclic antidepressants. Patients may also have had a trial of high dose dexamethasone. Inflammatory, ischaemic, procedure related pain or other pains that may respond to Ketamine in patients who have not responded to treatment with conventional analgesic.	
Formulations and strengths available	Solution in vials administered orally or by SC infusion over 24hours. 200mg in 20ml (10mg/ml) vial 500mg in 10ml (50mg/ml) vial 50mg in 5ml and 250mg in 5ml oral solutions (unlicensed) available from pharmaceuticals specials manufacturers. See additional information below.	
Usual initiation and maintenance dose	Oral, 10mg four times daily initially, increasing to a maximum 100mg four times daily according to response (lower or higher doses occasionally needed). SC infusion 50mg/ 24 hours in a syringe driver titrated according to response. Max 500mg over 24 hours. Frail patients may be started at a lower oral/SC dose (25-30mg/24 hours)	
Usual dose range	40mg to 500mg /24hours (taken in divided doses if not administered by continuous SC infusion).	
Dose for breakthrough pain	Usual opioid breakthrough medication. Occasionally oral ketamine or sublingual/buccal ketamine is used as required. Usual Buccal dose 2.5-5 mg (using 50mg/5ml solution). However this is on an individual case basis and should be a palliative care specialist decision.	
Likely duration of treatment	Ongoing. Ketamine use will be assessed and reduced if possible after 2-3 weeks treatment by the palliative care specialist.	
Cost	200mg in 20ml (10mg/ml) vial £5.06 500mg in 10ml (50mg/ml) vial £8.77 50mg in 5ml oral solution (unlicensed) Cost and pack size variable Example prices: £77.48 per 200m. Prices vary considerably, larger pack sizes proportionally cheaper per ml. Purchasing via third party specials supplier will incur additional costs.	
Adverse Effects	**Problem**	**Management**
Common	Vivid dreams, hallucinations, dysphoria, and sedation are the most commonly reported problems, though rarely the patient can develop a psychosis.	Incidence of psychotic effects can be reduced by using drugs such as midazolam, diazepam or haloperidol. If the patient experiences dysphoria or hallucinations, the Palliative Medicine Specialist should be contacted for advice and to agree possible dose reductions in the ketamine and to arrange review. If immediate action is needed, the dose of ketamine should be reduced and midazolam or haloperidol prescribed as an interim measure e.g. 2.5-5mg midazolam subcutaneously or 1.5-3mg haloperidol orally or subcutaneously.

Adverse Effects (continued)	**Problem**	**Management**
Less common	*Cardiovascular side effects*: Dose dependent increases blood pressure and heart rate may occur. Excessive salivation/ secretions. *Urinary Tract Symptoms* Dysuria, haematuria, urinary frequency *Upper GI symptoms* Vomiting or epigastric pain	Seek advice, if hypertension occurs. These problems are not normally serious in patients where the dose has been titrated by the palliative care specialists. Please discuss with palliative care specialist, as ketamine may need to be withdrawn Please discuss with palliative care specialist, as ketamine may need to be withdrawn
	Opioid toxicity	Normally avoided by reducing opioid dose prior to commencing ketamine.
Other Side Effects	Increased muscle tone, involuntary movements, dizziness and nausea. Liver toxicity – rare Neuropsychiatric toxicities	If troublesome, ketamine should be withdrawn. Contact palliative care specialist for advice. Liver function should be monitored regularly or if the patient develops new abdominal pain. Please contact palliative care specialist for advice. Ketamine may need to be withdrawn Depression, mild psychosis and memory problems have been reported when taken in large doses as a drug of abuse

Cautions/Contraindications	**Ketamine should be avoided in patients with:** Raised intracranial pressure. Severe systemic hypertension. Raised intra-ocular pressure. Recent history of epilepsy. Recent history of psychosis. Known hypersensitivity to the product. Use in pregnancy and lactation is not recommended. **Ketamine should be used with caution in patients with:** Intracranial space occupying lesion. Cardiac arrhythmia. On strong opioids (patients on long-acting opioids will usually be changed to a short acting opioid and the dose reduced during the ketamine dose titration phase). Pre-existing controlled hypertension, ischaemic heart disease, cardiac failure, previous cardiovascular events and cerebrovascular accidents. Thyroid dysfunction (increased risk of cardiovascular adverse effects)
Drug Interactions	Avoid concomitant use with memantine (increased risk of CNS toxicity). May increase risk of seizures with theophylline. Plasma concentrations of ketamine may be increased by diazepam. Use with other CNS depressant drugs may increase CNS depressant effects and may increase the risk of respiratory depression. Ketamine may affect hepatic metabolism of some other drugs e.g. warfarin, carbamazepine, phenytoin, but clinical importance unclear. Increased risk of hypertension and tachycardia in patients taking thyroid hormones.
Renal Impairment	No additional caution required.
Liver Impairment	Dose reduction is occasionally required in severe hepatic impairment and ketamine may cause hepatic toxicity. Therefore any changes in liver function should be discussed with the specialist.
Pregnancy and breast feeding	Use not recommended.
Monitoring	LFTs monthly if requested by specialist palliative care. Patients need monitoring in terms of effectiveness of analgesia. Pulse and Blood pressure should be monitored after any change in dose. Monitor for urinary tract symptoms. If problems are encountered in terms of ineffective analgesia or side effects, the specialist palliative care team should be informed.

Use with Other Analgesics	Ketamine may be used safely with analgesics such as paracetamol, aspirin, NSAIDs and weak opioids such as codeine. Ketamine is commonly used in conjunction with strong opioids, but is likely to reduce required dose of strong opioids. If opioid dose needs increasing or if patient has symptoms of opioid toxicity the palliative care specialists should be contacted. Ketamine should not be used with specific migraine treatments such as the $5HT_1$ agonists (sumatriptan, zolmitriptan etc.) or ergotamine – increased risk of adverse effects. Contact palliative care team for advice

Ketamine Induced Hypertension
If patient develops moderate to severe hypertension (e.g. BP > 160/100 mmHg or rise of > 20 mmHg) while taking ketamine, seek advice from palliative care specialist on the possibility of reducing dose/withdrawing ketamine.

Quantities for Prescribing
The following advice is provided to help minimise wastage and minimise costs taking into account:

- the clinical needs of the patient
- the time to obtain this product
- the differences in costs between different pack sizes and strengths

Patients whose pain is well controlled and the dose of ketamine is stable

Oral solution	• 28 days supply of ketamine oral solution may be prescribed, bearing in mind pack sizes available • Where practicable prescribe packs that are prepared in bulk by the manufacturer *These are generally available more rapidly and will have a longer shelf life than other strengths / pack sizes.*
Vials	• One week's supply per prescription, as the product has a 7 day shelf-life after preparation for oral use

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Ketamine Therapy in Palliative Care Pain
Community Pharmacist Information Leaflet

Introduction
When used to help provide pain relief in palliative care, ketamine is usually administered orally, but can be administered by continuous subcutaneous infusion.

Ketamine is available as:

- Vials which are licensed for injection, but which can also be administered orally (an unlicensed use)
- Oral solutions containing 50mg in 5ml and 250mg in 5ml are unlicensed, but are available as a "Special"[1].

Ketamine Oral Solution
Community pharmacists can obtain supplies of ketamine oral solution as a special.

It can usually be supplied within a period of about 3-4 working days. However to ensure continuity of supply in the event of any delay, the patient should be advised to obtain repeat prescriptions and take them to the community pharmacy that he/she uses 28 days before the next supply is needed.

The prices below are typical costs per 100ml if purchased direct from a specials manufacturer (usual pack sizes 100ml to 500ml). Prices may vary considerably between manufacturers; purchasing via a third party specials supplier will incur additional costs.

Concentration	**per 100ml**
50mg in 5ml	£25 - £100
250mg in 5ml	£100 - £500

Batch-produced strengths and pack sizes are the most cost-effective and tend to have longer shelf life. Other strengths can be made to order, but may be more expensive and have a shorter shelf life.

Ketamine Injection Vials
Oral Use
Ketamine injection can be taken using an oral syringe (neat).

- A sufficient quantity of ketamine for up to one week should be withdrawn and dispensed into a medicine bottle.
- The bottle should be labelled with a **7 day expiry** and **store in the refrigerator**.

[1] Made by a licensed specials manufacturer in premises that are inspected by the Medicines & Healthcare Products Regulatory Agency. Their pharmaceutical quality should therefore be of a good standard and in many ways similar to that of a licensed product.

Ketamine injection preparations available

10mg/ml	x 20ml	£5.06
50mg/ml	x 10ml	£8.77

Supply Arrangements

Community pharmacies can order ketamine injection via their usual controlled drugs wholesale account.

N.B. Pfizer only distributes its products through Alliance. Panpharma generic Ketamine 50mg/ml injection is available via Mawdsleys. Hameln brand generic Ketamine 50mg/ml injection available via major wholesalers from January 2020.

Ketamine for Subcutaneous Administration
District Nurse information leaflet

Prescribing

When used to help provide pain relief in palliative care, ketamine is usually administered orally, but may also be administered by continuous subcutaneous infusion.
If prescribed subcutaneously best practice dictates that this should be documented on the NESCN Community Prescription Chart (or local chart), and the ketamine stock balance should be documented on the Controlled Drugs stock balance chart.

Supply

Ketamine injection is available in single use vials – 10mg/ml (20ml vial) and 50mg/ml (10ml vial); 50mg/ml vials are normally used.

Preparation of subcutaneous infusion

- Dilute ketamine injection with sodium chloride 0.9% and initiate syringe driver as per local guidelines.
- Check syringe driver daily for turbidity or discolouration.
- Syringe stability may be affected by factors that accelerate drug degradation such as heat and light. Avoid placing the syringe close to the body or under bedclothes. Protect from light where possible, particularly syringes that include levomepromazine.
- Rotate the infusion site daily to prevent necrosis. Dexamethasone 0.5mg - 1mg may be added to the infusion if irritation is a problem.

CSCI compatibility with other drugs

- There are 2-drug compatibility data for ketamine in 0.9% saline with **alfentanil**, **clonazepam**, **dexamethasone** (low-dose for local irritation), **diamorphine**, **haloperidol**, **hydromorphone**, **levomepromazine**, **metoclopramide**, **midazolam**, **morphine sulfate** and **oxycodone**.

Once the vials have been opened they must be discarded (single use only). Refer to the Shared Care Protocol for shared care responsibilities and for additional information.

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Private and Confidential

Ketamine Shared Care Request/Confirmation

- **Consultant to complete first section of form and send to patient's GP.**
- GP to complete second section of form and return to palliative medicine consultant within 28 days.

A copy of the full shared care guideline can be viewed at www.northoftyneapc.nhs.uk

Consultant .....

Address .....

Contact number .....

.....

Patient Details (use printed label if preferred)

Name .....

Address .....

Postcode ..... **Sex** .....

NHS. No. ..... **DOB** .....

Treatment Requested for Prescribing in Accordance with an Approved Shared Care Arrangement:

Drug Name ..... **Dose** ..... **Frequency** .....

Other Information (if appropriate) .....

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Signed (Palliative medicine consultant).....
Name (print) ..... **Date** .....

To be completed by GP

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ☐
Or
I ACCEPT the proposed shared care arrangement with the caveats below ☐
Or
I DO NOT ACCEPT the proposed shared care arrangement for this patient ☐

My caveats / reason(s) for not accepting include:

.....

Signed ..... **Name (print)** ..... **Date** .....
(Patient's GP)

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the palliative medicine consultant and the patient's GP