LINCOLNSHIRE Clinical Commissioning Groups in association with UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE:
Ketamine for use in palliative care for the management of pain unresponsive to standard therapies and as a third/fourth-line choice for the management of chronic neuropathic pain that has failed to respond to alternative treatments.

This protocol does not cover the use of ketamine injection prescribed to be administered sublingually. All prescribing of sublingual ketamine will be retained by United Lincolnshire Hospitals.
This protocol only covers the oral administration of ketamine.

General Principles

Shared Care Responsibilities:
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (BNF 74, September 2017 – March 2018, pg.5)

Aims:
(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.
(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.
(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.
(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from members of the Optum Medicines Management and Optimisation Team.

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Principles of shared care

NHS England published Guidance - Responsibility for Prescribing between primary, secondary and tertiary care – January 2018.
Key recommendations from guidance:

1.0 Introduction

1.1 Shared Care Prescribing guidelines are local policies to enable General Practitioners to accept responsibility for the prescribing and monitoring of medicines/ treatments in primary care in agreement with the initiating service.
1.4 Where possible shared acre should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared acre policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER (AMBER 1 for Lincolnshire) through the traffic light system. … However it should be remembered that the provision of shared care prescribing guidelines does not necessarily mean that the GP has to agree to accept clinical and legal responsibility for prescribing; that they should only do so if they feel clinically confident in managing that condition.

2.3 reasonable predictable clinical situation

2.3.1 Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stale or predictable.

2.4 Agreement of shared care between consultant and GP

2.4.1 Referral to the GP should only take place once the GP has agreed in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that the supply arrangements have been finalised. The secondary/ tertiary provider must supply an adequate amount of the medication to cover the transition period. The patiet should then be informed to obtain further prescriptions from the GP.

2.7 Clear definition of responsibility

2.7.1 The areas of care for which each clinician has responsibility should be clearly defined.

2.8 Clinical responsibility

2.8.1 Clinical responsibility for prescribing is held by the person signing the prescription who must also ensure adequate monitoring.

2.9 Communication network & emergency support

2.9.1.Telephone details and (if appropriate) secure email addresses of both parties should be exchanged and recorded. This will enable the practice to access timely advice, guidance and information if problems arise, and will also enable secondary care clinicians to easily contact the GP if necessary. This should include out of hours contact numbers, how to access the on-call duty doctor. Patients and their carers should also be provided with contact details for support and help if required both in and out of hours.
2.9.2 People who are being treated on the advice of a secondary acre team, but are no longer being seen in that setting , may still need a review should problems arise. The appropriate level of care or advice should be available from the secondary care team in a timely manner without necessarily requiring a new referral.

6.0 Monitoring

6.0.1 All appropriate monitoring arrangements must be fulfilled. The person delivering that aspect of the shared care agreement should ensure that the resources to do this are in place in the clinical setting in which they are delivered.

Drug Details

Approved Name: Ketamine
Brand Name: Ketalar (solution for injection)
Form and Strength: oral solution available as an unlicensed special and solution for injection administered orally.
Both the chronic pain management service and the palliative care service prefer to use the ketamine oral solution first line.

Specialist Responsibilities

Ketamine treatment should only be initiated by:
either a consultant / specialist experienced in palliative care
or a medical specialist / consultant experienced in chronic pain management.
The specialist secondary/tertiary care service will:

1. Send a letter to the GP requesting that the GP participates in shared care. As part of the communication the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef. The palliative care team have stated that their prefer method of communication is via a telephone call to the patient's GP to discuss the ongoing management of the patient.
2. Ensure that the patient receives initial supplies of ketamine from the hospital until the GP formally agrees to share care.
3. Provide a comprehensive assessment of the patient.
4. Discuss treatment options with the patient to include an explanation of the unlicensed use of ketamine for the management of pain/neuropathic pain unresponsive to standard treatments, obtaining consent to treatment.
5. Ensure that the patient is aware of possible side effects on mood and behavioural effects of ketamine.
6. Before initiation of treatment baseline blood tests should be undertaken to assess renal & hepatic function.
7. Initiate treatment with ketamine or provide the GP with clear instructions as to the initial dose of including details of any dose titration that might be required and when the patient will next be reviewed in clinic. **All dose titration and alteration of dose should only be undertaken by or at the direction of the appropriate specialist (palliative care / chronic pain).**
8. Periodically review the patient's clinical condition, frequency of the review will be dependant on individual patient circumstances and for what clinical condition ketamine is being prescribed for.
9. Communicate promptly any changes in ketamine dose or any other ongoing pain clinic intervention to the GP.
10. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
11. Follow up any adverse drug reactions reported by the GP and report back to the GP.
12. Provide support to the GP and advice if treatment needs to be discontinued.

GP Responsibilities

Ketamine should only be prescribed by or in conjunction with:
Either a consultant / specialist experienced in palliative care
Or a medical specialist / consultant experienced in chronic pain management.

The GP will:

1. Notify the consultant in writing, without undue delay, if they agree to share care
2. Continue prescribing ketamine according to written instructions provided by the specialist service (palliative care/chronic pain)
3. Liaise with the community pharmacist or practice dispensary to ensure arrangements are in place for the regular supply of oral ketamine solution. More details on how to obtain a supply can be found on page 4.
4. Monitor the patients overall health and wellbeing.
5. Monitor patients blood pressure every three months or at intervals agreed with appropriate specialist.
6. Monitor the patient for adverse drug reactions and remain vigilant to the risk of potential drug interactions.
7. Be alert to increased frequency of requests for supply from the patient. These may be indicative of either potential abuse of ketamine or failing to achieve an adequate response to treatment in either case the appropriate specialist service should be contacted for advice.
8. Carry out any investigations that are communicated and deemed appropriate.
9. Refer back to the specialist service if condition deteriorates as advised by the appropriate specialist.
10. Discontinue treatment (where necessary) on the advice of the appropriate specialist.

Referral Criteria for transfer of care to GP

1. Patients, over 18 years of age, who have been stabilized on ketamine on an appropriate dose.
2. The appropriate specialist will have carried out an assessment of efficacy

Licensed Indications

Ketamine is licensed as an anaesthetic agent. Within the context of this shared care guideline it can be used under specialist supervision in palliative care patients in combination with opioids for those patients who have lost an analgesic response to high dose morphine.
It can also be used in palliative care setting for the relief of neuropathic pain unresponsive or poorly responsive to first line analgesics.
In the management of chronic pain it can also be used in patients suffering from neuropathic pain or nociceptive pain unresponsive to two or three alternative treatments.

Recommended Dosage and Administration

Ketamine is administered usually orally, dosing regimens can vary, the general principle is to start with a low dose and titrate upwards according to response.

Chronic Pain management

Examples of commonly used dose regimens.

1) Initiate at a dose of 5-10mg four times daily increasing in increments of 5-10mg. Usual daily dose is 10-60mg four times daily.

or

2) Initiate using a single daily dose of 10-20mg increasing frequency to twice daily and then thrice daily according to response.
Usual dose range 60-80mg three times daily.

Palliative care (Doses from Palliative Care Formulary)

Initial dose 10-25 mg three – four times daily and when required
If necessary increase dose in steps of 10-25 mg up to a dose of 50mg four times daily.
Maximum reported dose of 200mg four times daily. (rarely used)

All dose titration will be the responsibility of the appropriate specialist service Ketamine injection can also be administered sublingually. Lincolnshire PACEF has not approved the use of ketamine administered sublingually to be suitable for primary care prescribing or monitoring. Any patient requiring ketamine by this route will have all supplies of ketamine prescribed and dispensed from United Lincolnshire Hospital Pharmacy Departments.

Background Pharmacology

Ketamine is an N-methyl – D-aspartate (NMDA) receptor antagonist. Ketamine also interacts with cholinergic and opiate receptors and possible inhibits the synaptic re-uptake of mono-amines.
Powerful synergism arises from the combination of morphine with low doses of ketamine.

Preparations Available

Ketamine oral solution.

This is an unlicensed special 50mg/5ml, it is normally available flavoured with ginger, lemon or anise. It is available nationwide from Martindale Pharmaceuticals. Requests usually take 3 working days.
Tel No 0800 137627.
Ketamine is classed as a schedule 2 controlled drug and is subject to the full controlled drug requirements related to prescriptions, safe custody, the need to keep registers etc.(For further details please refer to BNF (prescriptions requirements), ULHT medicines policy and the Lincolnshire Controlled Drug Policy.

Adverse Effects

For further information on adverse effects please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Adverse effects are more common with higher doses of ketamine; these may resolve if the dose of ketamine is reduced. Prescribers are advised to contact the appropriate specialist service if the patient is experiencing troublesome adverse effects, as adjustment of the ketamine dose and/ or review of concomitant therapies may be required.

Common or very common

Anxiety, behaviour abnormal, confusion, diplopia, hallucination, muscle tone increased, nausea, nystagmus, skin reactions, sleep disorders, tonic clonic movements, vomiting.

Uncommon

Appetite decreased, arrhythmias, hypotension, respiratory disorders.

Rare or very rare

Apnoea, cystitis, cystitis haemorrhagic, delirum, dysphoria, flashback, hypersalivation.

Frequency unknown

Drug induced liver injury.

Management of adverse effects

Hallucinations, nightmares, vivid dreams and other transient psychotic effects.

These are most commonly seen at the higher doses used in anaesthesia.
Consider review of concurrent opioid dose if applicable as adverse effect may be due to opioid toxicity. If patient not drowsy more likely to be due to ketamine.
Haloperidol orally 0.5mg-1mg twice daily may be of benefit.

Drowsiness

May require review of opioid dose if taking concurrently, may require reduction of ketamine dose.

Ketamine dysphoria

This can be prevented by co-prescribing oral haloperidol 0.5mg-1mg at start of treatment. This can be stopped once patient is stable on ketamine dose.

Hypertension, tachycardia

May require ketamine dose to be reduced or treatment discontinued. Seek advice from specialist if patient develops moderate to severe hypertension e.g. BP > 160/100mmHg or rise of >20/10mmHg whilst taking ketamine.

diplopia, nystagmus

May require ketamine dose to be reduced or treatment discontinued

Urinary tract toxicity

Symptoms of cystitis, haematuria and supra-pubic pain have been linked to ketamine especially in doses over 400mg/24 hours. Irreversible damage leading to renal failure has occurred. If patient has urinary symptoms with no evidence of bacterial infection, the ketamine should be stopped and urology referral made.

Nausea

Give regular antiemetics. If nausea persists after two drugs consider the additional of dexamethasone. Avoid the use of neuroleptic drugs such as droperidol or chlorpromazine.

Excessive salivation and drooling

This could be treated with hyoscine tablets 300mcg up to three times daily (unlicensed use). If problem continues consider reducing ketamine dose or discontinuation of therapy.

Increased muscle tone or involuntary movements
If troublesome contact consultant for advice. May require discontinuation of treatment.
Liver toxicity
This is rare. Liver function should be monitored regulary or if the patient develops new abdominal pain. Contact specialist for further if this occurs. May require discontinuation of treatment.

Drug Interactions

For detailed information on drug interactions, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk
Below is a summary of some of the key interactions.

Potentiation of CNS depression increasing risk of respiratory depression
The use of ketamine with other central nervous system (CNS) depressants e.g. ethanol, phenothiazines, sedating H_1 blockers, can potentiate respiratory depression and or increase the risk of respiratory depression. Reduced dose of ketamine may be required with concurrent administration of other anxiolytics, sedatives and hypnotics.

Thyroid hormones
Concomitant use of thyroid hormones increase risk of developing hypertension and tachycardia.

Antihypertensive agents
Concomitant use of antihypertensive agents increase risk of hypotension.

Sympathomimetics (directly or indirectly acting)
Sympathomimetics and vasopressin may enhance sympathomimetic effects of ketamine.

Theophylline and aminophylline
When ketamine given with theophylline or aminophylline a significant reduction in seizure threshold may be observed and unpredictable extensor type seizures have been reported.

Memantine
Avoid concomitant use as increased risk of CNS toxicity.

Warfarin
Ketamine may affect the hepatic metabolism of warfarin, advise increasing the frequency of INR monitoring.

5HT1 agonists
Ketamine should not be used with specific migraine treatments such as sumatriptan, zolmitriptan etc or ergotamine as increased risk of adverse effects.

Antiepileptics

Ketamine may also increase hepatic metabolism of carbamazepine, phenytoin but clinical importance unclear.

Precautions and Contraindications

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Contraindications

Ketamine use should be avoided in patients with:

- acute porphyrias
- eclampsia & pre-eclampsia
- head trauma
- raised intracranial pressure,
- hypertension,
- Severe cardiac disease
- History of stroke / Previous cerebrovascular accident disease

Pregnancy and breast feeding – use not recommended.

Cautions

Ketamine should be used with caution in patients with;

- Intracranial space occupying lesion
- cardiovascular disease including : Cardiac arrhythmias, Cardiac failure and Ischaemic heart failure
- fixed cardiac output
- acute circulatory failure – shock – hypovolaemia
- hepatic impairment. Manufacture advises consider dose reduction as increased risk of accumulation.
- hypertension
- dehydration
- elderly patients
- history of head injury
- history of hallucinations
- history of nightmares
- history of respiratory tract infections
- history of thyroid dysfunction
- Increased cerebrospinal fluid pressure
- on long –acting opioid.
- History of previous addictive behaviour
- predisposition to seizures
- psychotic disorders
- raised intraocular pressure

Use with caution in elderly patients, more sensitive to adverse effects and often achieve therapeutic effects with much lower doses.

Monitoring

Palliative care patients

All patients receiving ketamine initiated by the palliative care team will be reviewed monthly in clinic or receive a domiciliary visit or a telephone review depending on the wishes of the patient and the severity of their underlying condition. A 24 hour telephone advice line is provided by St Barnabas Hospice for both patients and health care professionals.

Chronic pain patients

Ongoing review will be provided by the Chronic Pain Management Team. Frequency of review will be determined by co-existing co-morbidities, concurrent treatment and

patient's response to ketamine. Once stable and responding to treatment patients will receive a minimum of an annual review.
GPs can refer patients back to the team for review on request.

Blood Pressure Monitoring All patients

For both patient group regular blood pressures monitoring should be undertaken. Normally weekly during first four weeks of treatment, reducing to a minimum of once every three months.
If patient previously receiving regular blood monitoring then recommended to increase by a factor of two the frequency blood pressure is monitored. For example if every 3 months prior to ketamine therapy then monitor once ever 6 weeks,

Liver Function Tests (LFTs)

Monthly if requested by palliative care or chronic pain specialist.

Urinary Tract Symptoms

All patients should be monitored for development of urinary tract symptoms

Indication of Likely Cost of Therapy in Primary Care (November 2018)

	Strength	Cost (£)
Ketamine oral solution	50mg5/ml	£110.79 /200ml
Ketamine oral suspension	50mg/5ml	£95.54/200ml
Ketamine injection	100mg/ml	£16.10* (10ml)

Information Given to the Patient

Chronic pain management service
Patient will be provided with contact details for the pain management team and instructed to seek advice if necessary.

Contact Details

Chronic Pain Management Team

Pilgrim Hospital, Boston
Pain Management Clinic Secretaries – 01205 446612

Lincoln County Hospital, Lincoln
Pain Management Clinic Secretaries – 01522 573691
Or
Pain Management Nurse Specialist – 01522 512512 ext 3717

Palliative Care

St Barnabas Lincolnshire Hospice
Tel 01522 511566

References

1. BNF 70 September 2015 – March 2016.
2. NHS Lothian Shared care protocol. Ketamine. Complex pain in palliative care patients. Version 9 April 2009. Due for review April 2011.
3. All Gwent Palliative Medicine Consultants Group. Specialist Guidelines for using ketamine. July 2010.
4. Pan – Birmingham NHS Cancer network. Guidelines for the use of ketamine in palliative care. Current version approved by network review group 13/5/09.

Additional references for January 2016 update
5) North of Tyne Area prescribing Committee. Shared care guidance. Shared care Guidelines for the use of ketamine in palliative care initiated by palliative care specialists. March 2014
6) Royal Cornwall Hospitals NHS Trust. Clinical guideline for the use of ketamine as an analgesic agent in chronic pain and palliative care. September 2015.
Additional References for November 2018 update
7) BNF accessed online November 2018
8)Summary of Product Characteristics Ketalar 10mg/ml injection (Pfizer ltd) last updated on emc 27th June 2018.

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