Leicester, Leicestershire & Rutland

Palliative Care Prescribing

Drugs for Specialist Recommendation Only

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Version 3
Date: January 2014
Review January 2017

Endorsed by Leicestershire Medicines Strategy Group
Shared care has been defined as the mechanism of sharing patient care between primary and secondary care providers.

Within a palliative care setting input into patient care may be from many health professionals. During ongoing care medical support and information may be sought from palliative care clinicians.

**Palliative Care Clinician Responsibilities**
- Liaison with general practitioner (GP) to share patient care and ongoing problems
- Responding to issues raised by the GP caring for the patient
- Advising GP on therapies which may be of benefit for individual palliative care problems. Many of these drugs may not be licensed for the specific situation although the product will have a licence for other indications outside a palliative care setting.
- Reviewing patient at appropriate clinic if referred.

**GP Responsibilities**
- Monitor the patients overall well-being and raise any concerns with the palliative care consultant
- Prescribing medication listed below following discussion or liaison with palliative care
- Ensuring advice is sought from palliative care on any issue causing concern.
- Altering dosage or therapy following palliative care advice and the guidelines below

**Drugs covered by the guidelines – WE RECOMMEND THESE SHOULD ONLY BE STARTED BY OR IN LIASON WITH A PALLIATIVE CARE DOCTOR.**
- Atropine Eye Drops (used orally)
- Fentanyl sublingual tablets
- Furosemide subcutaneous infusion/bolus
- Ketamine
- Ketorolac
- Methadone
- Methylaltrexone
- Methylphenidate
- Midazolam
- Octreotide
- Olanzapine
- Ondansetron/Granisetron

For information regarding **Alfentanil** see [ICP Drug Prescribing in Advanced Kidney Disease (Appendix 1)]

It is also recognised that other drugs commonly used in palliative care syringe drivers are not licensed once mixed in a syringe driver. Guidance on such combinations can be found in [Guide to Prescribing in Advanced Malignancy]

**Contact Support and Advice**
[Guide to Prescribing in Advanced Malignancy] Dr Nicky Rudd, Dr Caroline Cooke.
Palliative Care Formulary version 4
LOROS advice line 0116 2318415
UHL Specialist Palliative Care Teams on Ex 5414 (LRI); Ex 3540 (GH); Ex 4680 (LGH)
GUIDELINES FOR THE USE OF ATROPINE EYE DROPS ORALLY

Indications
Drooling, due to reduced swallowing e.g. in motor neurone disease, may be improved with antimuscarinic medication, including Atropine Eye Drops 1% taken orally.

Atropine (as eye drops) are often used alone but may be used in combination with other antimuscarinics (given orally, subcutaneously or by enteral or transdermal routes) to achieve the required balance of saliva production.

Pharmacology
Atropine is a tertiary amine that exerts its effect on saliva production via its antimuscarinic action (both locally and via oesophageal vagal fibres). The dose required to reduce saliva is typically less than that which affects other muscarinic receptors.

Pharmacokinetics
Atropine is readily absorbed orally and sublingually and has a plasma half-life of 4 hours.

Dosage and administration
One to four drops of Atropine Eye Drops 1% is used up to 4 times day and titrated to effect.

Cautions
Use with caution in myasthenia gravis, where tachycardia may be an issue (heart failure, angina) and bladder outflow obstruction.

Monitoring
No specific monitoring is indicated.

Drug Interactions
Antimuscarinic drugs may impair the effect of prokinetic drugs e.g. domperidone, metoclopramide.

Side Effects
Dry mouth, blurred vision, tachycardia, constipation, retention of urine, reduced sweating.

Cost
10ml £13.25
Fentanyl is rapidly absorbed through the tissues of the mouth (cheeks, under tongue, palate). This allows rapid onset of action. Any fentanyl that is swallowed has much less effect.

**Indications**

Analgesia and:
- For patients with swallowing difficulty
- For patients who need rapid onset analgesia (e.g. for incident pain or dressings)
- For patients who need short lived breakthrough analgesia (e.g. for incident pain or dressings)
- For patients with poor gastrointestinal absorption
- For patients who are intolerant of other opioids

**Dosage and administration**

- There are 4 licensed products: Abstral (sub-lingual tablet); Effentora (buccal/sublingual tablet); PecFent and Instanyl (intra-nasal sprays).
- In Leicestershire, only Abstral has been evaluated and approved for use by the UHL Therapeutics Advisory Service and LMSG and only then after discussion with a palliative care specialist.
- Onset of action is from 10-15 minutes
- Time to peak plasma concentration about 20-40 minutes
- Duration of action about 1-3 hours – can use up to hourly if needed but may accumulate.

**How to use:**
See product information for titration and discuss with a palliative care specialist.

**Cautions in Use**
For full list, see Abstral SPC
Drowsiness, dizziness, nausea.

**Contraindications**
As per opioids.

**Monitoring**
Assess analgesic response and any side effects to initial dose and titrate to effect as discuss with a palliative care specialist.

**Drug Interactions**
As per opioids.
Side Effects
As per opioids.

Cost
Abstral £50 per 10 tablet pack for all strengths. Following dose titration ensure correct strength is prescribed.

References
1. Fentanyl [www.palliativedrugs.com](http://www.palliativedrugs.com)
GUIDELINES FOR THE USE OF SUBCUTANEOUS FUROSEMIDE

Indications
Patients with heart failure are often prescribed diuretics as part of their drug treatment. If they become more symptomatic (e.g. increasing oedema, weight and/or breathlessness) while taking oral diuretics, treatment with parenteral (normally intravenous) furosemide may be helpful. In the past this has usually necessitated admission to an acute hospital. Giving furosemide via the subcutaneous (s/c) route may be an alternative way of managing these patients, especially when admission to hospital may be deemed inappropriate, for instance at the end of life. It may also allow discharge from hospital for those patients require ongoing treatment with parenteral diuretics.

Furosemide is effective when given subcutaneously to healthy volunteers and has similar local complication rates as subcutaneous saline. In one survey, it was used by up to 69% of centres caring for an elderly population, but its effectiveness was not examined. In theory, the dose used subcutaneously should be the same as the dose used intravenously, unless there is a reaction at the site of administration that prevents absorption. It was as well tolerated locally when given subcutaneously as normal saline. Some practitioners have given it 20mg (2ml) s/c prn, whilst others have infused it. The subcutaneous route is unlicensed but should be seen as a legitimate aspect of clinical practice.

Dosage and administration
Consult with cardiology, medical or palliative medicine consultant or SpR to discuss suitability of initiation of treatment. Liaise with GP and district nursing services.

Start with the same dose s/c as the patient was previously taking orally, or you would be using if the patient was going to have intravenous Furosemide

In patients who are dying and who are drinking less, reducing the dose of diuretic in line with fluid status may be appropriate.

Continuous Subcutaneous Infusion
Administer the dose by continuous subcutaneous infusion via a McKinley T34 (24 hour) syringe driver diluted with water for injection. It may be infused over 24 hours. If a large dose is required, two syringe drivers may be used concurrently. There is limited data on drug compatibility so it is not recommended to mix furosemide with other drugs at present. Avoid using oedematous areas as infusion sites due to possible reduced absorption, and monitor the site as you would for any other subcutaneous infusion.

Bolus dosing
Some practitioners have given it 20mg (2ml) s/c prn.

Cautions in Use
Use with caution in hypotension, impaired micturition, gout, diabetes or prostatic enlargement.
Avoid using oedematous areas as infusion sites due to possible reduced absorption.
Relative Contraindications
Hypovolaemia, dehydration, severe hyponatraemia or hypokalaemia. Comatose or precomatose states associated with liver cirrhosis. Renal failure due to nephrotoxic or hepatotoxic drugs. Anuria.

Monitoring
Monitor clinical symptoms and signs (breathlessness, weight, oedema) as normal. Measuring serum urea and electrolytes if appropriate (e.g. if worsening renal function would not change your management, consider not measuring). Adjust the dosage accordingly. Hospital at home may be an appropriate service if close monitoring is needed.
Monitor the site as you would for any other subcutaneous infusion for signs of irritation or infection.
For further advice, please contact your local clinical nurse specialist in heart failure or LOROS (0116 2318415).

Drug Interaction
Diuretic effect may be antagonised by concomitant use of corticosteroids. Diuretic effect may be antagonised by Ketorolac. Increase risk of nephrotoxicity with NSAIDs.

Side Effects
Mild gastrointestinal disturbances, hyperglycaemia, electrolyte disturbances, tinnitus and deafness. Hypersensitivity reactions including rashes and anaphylaxis.

Cost
10mg/ml amp. 5ml= 66p 25ml=£2.50

References


This would normally be started in a secondary care setting by a palliative care specialist.

**Indications**

Ketamine is an anaesthetic agent, but in the palliative care setting it can be used for neuropathic, ischaemic, inflammatory or myofascial pain that is not responding to strong opioid analgesia. It should be noted that ketamine is unlicensed for pain control.

Ketamine is a potent NMDA receptor channel blocker. The NMDA glutamate receptor is a calcium channel in the dorsal horn of the spinal cord that is involved in central sensitisation.

**Dosage and administration**

**Orally**
- Start at 10 to 25mg tds-qds and prn (max hourly)
- Increase dose in steps of 10-25mg up to 50mg qds
- Maximum reported dose is 200mg qds

Oral ketamine tastes very bitter, discuss with pharmacy for alternative preparations.

**Subcutaneously**
- Start at 10 to 25mg prn (<500 micrograms/kg)
- If necessary increase dose in steps of 25-33%

**Continuous Subcutaneous Infusion**
- Start at 1 to 2.5mg/kg/24hours. Typically 100 to 300mg over 24 hours
- If necessary increase by 50-100mg daily.

With higher doses consider reducing the dose of morphine if the patient becomes drowsy.

If a patient experiences hallucinations the dose of ketamine should be reduced and given diazepam 5mg stat and 5mg at night, or midazolam 5mg sc stat and 5 to10mg via CSCI or haloperidol 2 to 5mg po stat and 2 to 5mg at night. **These medications can be prescribed in anticipation.**

Ketamine can irritate the skin and so it should be diluted in the largest volume of saline possible. If it is to be mixed with other drugs in the same syringe driver compatibilities should be checked.

**Conversion of oral ketamine to subcutaneous ketamine** for pain control
- Initially use a 1:1 conversion.
- Review as individual patients may vary and require further titration.
Prescribing-controlled drug requirements
Ketamine should be prescribed and supplied as a controlled drug. The oral solution is available via pharmacy from Martindale Pharmaceuticals. Available formulations include 10mg/ml in a 20ml vial, 50mg/ml in a 10ml vial and 100mg/ml in a 10ml vial.

Pharmacokinetics
Oral Ketamine undergoes extensive first pass hepatic metabolism to norketamine. It is thought that oral and subcutaneous doses are equipotent. In some studies it has been reported that the maximum blood concentration of norketamine is greater after oral administration than after injection and it is thought that the extensive first pass metabolism is responsible for this. Some times when converting from a parenteral dose to an oral dose after several weeks a smaller oral dose can be used. Ketamine can be used safely in patients with renal impairment.\textsuperscript{1,3}

Cautions in Use
Epilepsy, hypertension, cardiac failure, symptomatic angina, cerebrovascular disease. Urinary tract toxicity – urinary tract symptoms (frequency, urgency, incontinence, dysuria and haematuria) can be caused by ketamine. The underlying pathophysiology is not clear and usually patients are on significant doses for many months before developing toxicity. If symptoms do occur with no evidence of bacterial infection then the ketamine should be stopped.\textsuperscript{1,2}

Contraindications
Any situation in which an increase in blood pressure or intracranial pressure would be hazardous, acute intermittent porphyria\textsuperscript{1,2} and hypersensitivity

Monitoring
Ensure skin site does not show signs of irritation. If irritated check dilution and compatibility.

Drug Interaction
Plasma concentration is increased by diazepam.\textsuperscript{1}

Side Effects
The most common side effects are tachycardia, intracranial hypertension, confusion, delirium, vivid dreams, hallucinations and feelings of detachment from the body.\textsuperscript{1,4}

Cost
200mg vial £5, 500mg vial £8.77, 1g vial £16.10

References
1. Ketamine. \url{www.palliativedrugs.com}
4. Binns A. Ketamine in Palliative Care. \url{www.medicineau.net.au}. 
GUIDELINES FOR THE USE OF KETOROLAC

**Indications**
Severe cancer pain poorly responsive to the maximum doses of other Non Steroidal Anti-Inflammatory Drugs (NSAIDs) combined with a strong opioid. Ketorolac can offer significant analgesia when other NSAIDs have not, particularly in bony or inflammatory cancer pains. Patients are counselled that it may have more side effects. The usual aim is to use for 2 weeks or less pending other treatments (e.g. radiotherapy) but it has been used for up to six months without undesirable side effects.

**Dosage and administration**
20 to 30mg tds can be given by subcutaneous injection but is better tolerated by continuous subcutaneous infusion (CSCI).

60mg/24 hours by CSCI (maximum dose in patients over 65 or under 50kg). Can be increased by 15mg/24h up to 90mg/24h maximum.

Co-prescribe a gastro-protective drug H2 antagonist or PPI ranitidine 300mg or lansoprazole 30mg daily.

**Cautions in Use**
Caution in patients with renal cardiac or hepatic impairment. Ketorolac may impair renal function. The dose should be kept as low as possible and renal function monitored. Use with caution in patients with a history of peptic ulceration.

**Contraindications**
Contraindicated in patients with hypersensitivity to aspirin or other NSAID, coagulation defects or severe heart failure.

**Monitoring**
Check for signs of gastrointestinal side effects and skin reactions at site of infection.

**Drug Interactions**
Furosemide (reduced diuretic response and increased risk of nephrotoxicity), ACE inhibitors (increased risk of renal impairment). Do not give concomitantly with other NSAID

**Side Effects**
Bleeding and pain at injection sites (others as for NSAIDs – increased risk of GI side effects compared with other NSAIDs).

**Cost**
10mg/ml 94p and 30mg/ml £1.14 per amp.

**References**
GUIDELINES FOR THE USE OF METHADONE

ONLY TO BE INITIATED BY SPECIALIST PALLIATIVE CARE NORMALLY IN A SECONDARY CARE SETTING

Indications

- Poorly controlled pain where intolerable side effects (nausea, vomiting, sedation, hallucinations) have prevented dose escalation of another opioid.
- Refractory pain or difficult pain syndromes (especially neuropathic pain).
- Renal impairment. (Remember to consider other opioids e.g. fentanyl)
- Paradoxical pain with other strong opioids.

Patients are usually admitted to a specialist palliative care unit when switching from another opioid to methadone. This is to enable a controlled titration period. It is a highly lipophilic drug with a long half life and repeated use leads to an extensive tissue reservoir.

Patients will usually be discharged on a twice daily dose with a prn dose that can be used up to 3 hourly.

Occasionally methadone is added on top of an existing opioid as they can act in synergy.

Pharmacokinetics

Methadone is a highly lipophilic drug and with repeated use it forms an extensive tissue reservoir. This along with being highly protein bound contributes to a long plasma half-life ranging from 8-75 hours. This half life increases with patient age. It is mainly metabolised in the liver and about half of the drug and it metabolites are excreted via the intestines and half by the kidneys. However renal and hepatic impairment do not significantly affect methadone clearance. Its oral bioavailability is 80% however this may range from 40-80%. Onset of action is thought to be within 30 minutes, however patients have reported this to be up to an hour after oral administration.

Dosage and administration

- Switching to methadone will be under the care of palliative care team in the hospice or acute trust. The previous opioid will be stopped abruptly.
- A dose of methadone 1/20 of the 24 hour oral morphine dose (up to a maximum of 30mg) will be prescribed on a 3 hourly prn basis.
- The patient may take a regular dose every 3 hours prn. Peak concentration may take up to 3 hours hence 3 hourly prn limit.
- During the titration period (3 hourly methadone prn), if the patient has pain in between the 3 hourly doses, they may be given 1/5 the 3 hourly prn dose (minimum 1 mg) up to every hour.
- By days 5 or 6, if the dosing has become stable, the amount of methadone taken over the previous 24 hours is noted and converted into a regular b.d. dose, with the provision for extra doses, that are ½ the b.d. dose, to be available 3 hourly prn. Please note that some patients may require a lower prn dose e.g. one ¼ of the b.d. dose.
- If prn medication is still required, increase the dose of methadone by ½ to 1/3 every 4 to 6 days.
Example: For a patient on morphine 200mg per 24 hours, initial 3 hourly prn is 200mg/20 = 10mg, and hourly is 10mg/5 = 2mg. By day 6, if taking 60mg of methadone in 24 hours then the b.d. dose is 60mg/2 = 30mg, with 30mg/2 = 15mg as a prn dose.

Example: For a patient on morphine >600mg per 24 hours. The initial 3 hourly prn is 30mg, and the hourly dose is 30/5 = 6mg

Synergy of methadone with a concurrent opioid
There is increasing evidence anecdotally and in animal models that methadone can work in synergy with other strong opioids.\(^5\,^6\)

The following regime is suggested and agreed by consultant consensus:

- Add 5mg methadone b.d. along side the regular long acting opiate.
- Increase as necessary on a weekly basis

Conversion to subcutaneous route
As stated previously oral bioavailability of methadone ranges from 40-80%. Traditionally a conservative conversion ratio has been used of 2:1 from the oral to subcutaneous route. However some centres are now using 2/3 of the oral dose subcutaneously.\(^1\,^7\)

Example: Total 24 hour dose of oral methadone is 40mg therefore subcutaneous dose is 20mg. The prn dose may be up to ¼ of the total 24 hour subcutaneous dose, i.e. 5mg in this case.

Cautions in Use
Careful observation of the Respiratory Rate must be maintained – see Toxicity

The subcutaneous infusion should not be started within 12 hours of taking the last oral dose of methadone, although prn dosing should be available.

Subcutaneous methadone can irritate the skin. It should therefore be diluted as much as possible in saline. If other drugs are to be used in the same syringe driver, compatibilities should be checked. The addition of dexamethasone 0.5mg may be helpful.

Toxicity
Methadone has a similar side effect profile to other strong opioids including constipation, nausea, sedation, cognitive impairment and hallucinations. The most important side effect not to miss is respiratory depression.\(^1\,^8\)

Management of Respiratory Depression\(^1\)
If the respiratory rate is above 8 per minute and the patient is easily rousable and not cyanosed, a watch and wait policy can be adopted. Omit the next dose of methadone.
If the respiratory rate is less than 8, the patient is barely rousable or unconscious or cyanosed:

- Dilute an ampoule of naloxone 400 microgram/ml in 10ml of saline
- Give 2.5-5ml (100-200mcg) boluses IV every 2-3 minutes until respiratory rate is satisfactory.
- If unable to give IV then the same dose can be given SC or IM undiluted e.g. 0.5-1ml.
- Methadone lasts longer than naloxone and so an infusion may need to be set up.
- Initial infusion rate may be set at 60% of the initial effective intravenous bolus dose, and given over an hour. This may have to be titrated according to response.  

Example: Improved respiratory rate observed after 200mcg. An infusion rate can be set at 120mcg/hr.

It is important to titrate against the respiratory rate and not consciousness level as total reversal may lead to pain and agitation.

**Contraindications**
Hypersensitivity. No other absolute contraindications provided it is carefully titrated against the patient's pain.

**Monitoring**
Renal and hepatic impairment do not affect methadone clearance. Monitor for respiratory depression as above.
The CHM recommends that patients with the following risk factors for QT interval prolongation are carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or taking drugs which can prolong the QT interval; patients requiring more than 100mg methadone daily should also be monitored.

**Drug Interactions – key importance for primary care prescribers**
Amitriptyline, SSRIs, cimetidine, macrolide antibiotics, ciprofloxacin, ketoconazole and fluconazole will increase plasma methadone. Carbamazepine, phenytoin, phenobarbital, risperidone and rifampicin will decrease plasma methadone. Methadone increases zidovudine levels.

**Ensure you check for interactions before stopping or starting other medication as reactions are clinically significant.**

**Side Effects**
Nausea, vomiting (especially at initiation), constipation and drowsiness, respiratory depression, hypotension and muscle rigidity. Other side effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, headache, vertigo, dysphoria.

**Cost**
Methadone solution 1mg/ml. £1.35 per 100ml.
Injection 50mg/ml amp £2.05 per 1ml amp.
References
2. Palliative care formulary 2nd ed
8. Keen JC. Methadone in palliative care guidelines. St Columba’s Hospice Edinburgh
GUIDELINES FOR THE USE OF METHYLNALTREXONE

Indication:
In opioid-induced constipation in advanced illness in patients receiving palliative care who are unresponsive to usual the usual stimulant and softening laxative measures, on the recommendation of a palliative care specialist. Laxatives tried should include lactulose, senna, docusate sodium, sodium picosulfate, danthron, laxido. Consider if
- Titration & switching of laxatives & rectal measures is ineffective or inappropriate and
- Opioids are thought to be a significant cause of their constipation.

Pharmacology & Pharmacokinetics
Methylnaltrexone blocks opioids action on the gastrointestinal tract (a ‘mu receptor antagonist’). However, it does not penetrate the blood brain barrier, so should not interfere with their analgesic effect.
Pharmacokinetic properties
- Absorption: Peak plasma concentration 30mins after SC injection
- Distribution: Does not readily cross the blood brain barrier
- Metabolism and elimination: Around 1/3 is metabolised to either inactive or partially active compounds. These, plus the un-metabolised parent drug, are predominantly renally excreted. Half-life is ~8 hours.
Therefore dose reduction is advised in renal impairment, and caution is advised with severe renal and severe hepatic impairment – dose adjustment above.
Discuss use in such patients with a consultant.

Dose and Administration
Continue regular laxatives alongside methylnaltrexone
Prescribe subcutaneously once & review response before giving further doses. 25% of patients usually respond within 30 minutes and a further 25% within 4 hours.

Dose is according to weight (if in doubt, use lower dose):
- Use 0.15mg per kg for patients below 38kg.
- Give 8mg on alternate days if 38-62kg and assess.
- Give 12mg on alternate days if over 62kg and assess

If patients are very obese start at 12mg dose and assess response. Consult palliative care consultant for advice.
Consider a lower test dose with colostomy, diverticulosis, or faecal impaction
The intervals between administration can be varied but should not be given more than once a day.

Cautions in use
Reduce dosage by half in severe renal failure. Not recommended in end-stage renal impairment requiring dialysis. No dosage adjustment is required in mild to moderate hepatic impairment although it has not been studied in severe impairment.

Consider hyoscine butylbromide 20mg SC in case of severe colicky pain
**Contraindications**
Known or suspected mechanical gastrointestinal obstruction
When constipation is unrelated to opioid use
Known allergy to methylnaltrexone or the product constituents

**Monitoring & Adverse effects**
Bowel action can occur quickly (within 30-60mins) and can be diarrhoea, so consider incontinence sheets, commode at bedside if appropriate.
If giving via a SC line, flush with sodium chloride 0.9%. Rotate site if reaction occurs.

Adverse effects:
Very common (>1 in 10) Abdominal pain, nausea, flatulence, diarrhoea
Common (>1/100 – 1/10) Dizziness, injection site reactions

**Drug interactions**
No significant interactions have been noted to date.

**Cost**
£ 21 for 1 ampoule of 12mg in 0.6ml

**References**
1. Summary of product characteristics (see [http://emc.medicines.org.uk/](http://emc.medicines.org.uk/))
2. Thomas J et al *Methylnaltrexone for opioid-induced constipation in advanced illness.*
5. Further information: Methylnaltrexone (Relistor) UKMi London New drugs Group APC/DTC Briefing Document July 2008
This should be initiated by or after discussion with a specialist in palliative care.

**Indications**
Methylphenidate is a CNS stimulant used in palliative care for opioid related sedation, fatigue and depression (sometimes in combination with other antidepressants).

**Pharmacology**
Its mechanism of action is by blockade of pre-synaptic dopamine reuptake.

**Pharmacokinetics**
The immediate release formulation has an onset of action of 20 to 40 minutes and duration of action of 3 to 6 hours. It is normally given bd, on waking and at lunchtime, to reduce any potential for insomnia.

**Dosage and administration**
Start at 5mg bd (on waking and lunchtime) or 2.5mg bd if particular concern about side effects.

Titrated up by 5mg bd steps every 3 days, titrating benefit against any side effects, to a maximum dose of 20mg bd. Occasionally higher doses are required (e.g. 30mg bd, 20mg tds).

**Cautions**
Psychosis, significant cardiovascular disease.

**Interactions**
May antagonise anti-epileptic effect of phenytoin and action of anti-hypertensives. Inhibits metabolism of TCAs and warfarin.

It is normally well tolerated (better than TCAs).

**Side effects**
Very common (>10%) include nervousness and insomnia (responds to dose reduction).
Common (>1% but <10%) include headache, dizziness, palpitations, arrhythmias, hypertension, nausea and vomiting, anorexia, dry mouth, rash, pruritis, fever, arthralgia.

**Monitoring**
For adverse effects eg: anxiety, agitation, sleeplessness; hypo/hypertension, arrhythmias, palpitations;
For drug interactions with methylphenidate particularly: warfarin and phenytoin

**Cost and supply**
It is a controlled drug (CD)
Methylphendiate tablets 5mg – 30 tabs £2.67 10mg – tabs £7.08.
Ritalin 10mg (scored) 30 tabs £5.57
References


British National Formulary 64 Sept 2012
GUIDELINES FOR THE USE OF BUCCAL MIDAZOLAM

Indications
Midazolam is a short acting benzodiazepine – it can be given by the buccal route as an alternative to rectal diazepam for patients prone to prolonged generalised seizures (lasting longer than 5 minutes), clusters of seizures or status epilepticus. Rectal diazepam whilst licensed can be practically difficult to administer, socially unacceptable and have variable bio absorption. Midazolam is as effective as rectal diazepam, is absorbed rapidly through the buccal cavity, and has practical advantages of ease and social acceptability in administration.

Pharmacology & Pharmacokinetics
The solution is placed against the gums and cheeks for best absorption. If swallowed absorption of the solution may be less effective.

Dosage and administration
A preparation of Midazolam specifically intended for the buccal route is available. The dose for adults and children over 10 years is 10mg. The solution comes in a 2ml (10mg) pre-filled syringe. Half this amount should be dripped into the spaces between the lower gums and the cheek on one side of the mouth. The remaining liquid should be dripped between the lower gums and cheek on the other side of the mouth. If necessary, the whole dose can be given just on one side of the mouth.

Contraindications
Known hypersensitivity to the drug or any excipients. Acute narrow angle glaucoma.

Monitoring & Adverse effects
The most common reported side effect is drowsiness; in some cases this may be severe. All patients receiving midazolam are likely to be drowsy for several hours after administration. Agitation and disorientation may occur but are rare. No specific monitoring is necessary.

Drug interactions
Erythromycin, other macrolides and cimetidine inhibit metabolism of midazolam. This may result in prolonged duration of sedative side effect.

Cost
2 ml (10mg) prefilled syringe £22.88

References
1. BNF 66
GUIDELINES FOR THE USE OF OCTREOTIDE

Indications
The use of octreotide in palliative medicine is frequently beyond licence and indications include:

- Symptoms associated with unresectable/metastatic hormone secreting tumours, e.g. carcinoid, glucagonomas, insulinomas.
- Malignant bowel obstruction/high volume/intractable vomiting.
- Severe tumour related secretions.
- Intractable diarrhoea.
- High output gastrointestinal fistulae.
- Malignant ascites
- Bronchorrhoea (death rattle). 1,2,3

Pharmacology
Octreotide is a long acting-synthetic somatostatin analogue.1,2,3,4 Somatostatin is an inhibitory hormone found throughout the body. It suppresses the secretion of serotonin and endocrine secretions of the pancreas, stomach and intestine, including glucagon, gastrin, insulin, vasoactive intestinal peptide (VIP) and secretin. In type I diabetes mellitus octreotide decreases insulin requirements, however in type II diabetes mellitus octreotide suppresses both insulin and glucagon release and plasma glucose levels therefore remain unchanged or only slightly raised.1 The inhibition of gut hormones by octreotide reduces splanchnic and portal blood flow,1,4 gastrointestinal motility, gastric, pancreatic and small bowel secretions and increases water and electrolyte absorption.1,2,4 Octreotide also has a direct anticancer effect on solid tumours of the gastrointestinal tract, probably by blocking the action of epidermal growth factor (EGF) thus prolonging survival.4

Pharmacokinetics
Octreotide is poorly absorbed from the gastrointestinal tract. It is completely and rapidly absorbed after subcutaneous injection and is 65% plasma protein bound. It has inactive metabolites and is mainly excreted unchanged (32%) by the kidney.4 The onset of action is 30 minutes. Time to peak plasma concentration 30 minutes subcutaneously. Plasma half life 1.5 hours subcutaneously. Duration of action 8 hours.1,2,3

Dosage and administration
Octreotide is administered as subcutaneous bolus injections, bd to tds, or as a continuous subcutaneous infusion (CSCI). The dose varies according to indication and should be titrated according to response. The usual range is 50 – 1500mcg daily, although higher doses are occasionally used depending on the patient. Once improvement of the symptom is achieved reduction in dose can be tried.1,2,3

Continuous Subcutaneous Infusion
When given by CSCI 0.9% sodium chloride is used as the diluent. It normally mixes well depending on concentrations with dexamethasone (<1mg), midazolam, haloperidol, diamorphine, oxycodone, morphine, hyoscine butylbromide and metoclopramide. Precipitation may occur with cyclizine.1,2,4 If more than two drugs are to be mixed in the same syringe please seek further specialist advice.
Cautions
Insulinoma (may potentiate hypoglycaemia). In diabetes mellitus insulin or oral hypoglycaemic requirements may be reduced.

Monitoring
Clinical response (e.g. volume/frequency of vomiting/diarrhoea)

Drug Interactions
Octreotide has been reported to reduce the intestinal absorption of ciclosporin and delay the absorption of cimetidine. In diabetes mellitus insulin or oral hypoglycaemic requirements may be reduced. Concomitant administration of octreotide and bromocriptine increased the availability of bromocriptine. Limited data indicates that it may decrease the metabolic clearance of compounds known to be metabolised by cytochrome P450. Use with caution with carbamazepine, digoxin, warfarin and terfenadine.

Side Effects
The most common side effects are dry mouth, gastrointestinal disturbances including anorexia, nausea, flatulence (due to reduction in oesophageal sphincter tone), vomiting, abdominal pain, steatorrhoea (due to the inhibition of pancreatic enzyme secretion) and gallstone formation (due to biliary stasis). These may be reduced by timing the injections between meals or at bed time. Steatorrhoea may be overcome by the use of pancreatic enzyme supplements. Rarely hyperglycaemia has been reported with chronic administration and hypoglycaemia has also been reported. Rarely pancreatitis has been reported shortly after administration. Bolus injection is painful but less if the vial is warmed to room temperature.

Costs
50 microgram £3.72
100 microgram £6.53 per amp.

References
1 Twycross R & Wilcock A Editors in Chief. Palliative Care Formulary (PCF4)
2 Octreotide in www.palliativedrugs.com
3 Octreotide Palliative Care Shared Care Guidelines. Interface Pharmacist Network Specialist Medicines www.ipnsm.hscni.net
4 Octreotide CCO formulary

Depot preparations
Depot preparations of octreotide 10 – 30mg given every 4 weeks are available. Alternatively lanreotide (Somatuline ® LA) 30mg given every 2 weeks (sometimes every 7 – 10 days) and lanreotide (Somatuline ® Autogel) 30 – 90mg given every 4 weeks could be used. In palliative care these long acting preparations are generally used when symptoms have first been controlled with subcutaneous octreotide. The most common problems for which they are used are in patients with chronic intestinal fistulae or intractable diarrhoea. They are given by deep intramuscular injection into the gluteal muscle.
Patients switching over to the depot medication may need to continue to receive subcutaneous octreotide for about two weeks and some patients may require additional rescue octreotide for up to 2 – 3 months because of the time to reach steady state lanreotide levels.4
Olanzapine has been used in palliative patients where its receptor activity and side effect profiles have been deemed to be beneficial over Levomepromazine. It is a potent D₁, D₂, D₃, D₄, 5HT₂A, 5HT₂C, 5HT₃ and 5HT₆ antagonist with activity at ACh, α₁-adrenergic and H₁ receptors.

**Indications**
Nausea and vomiting as a third line choice:

- For patients in whom Levomepromazine has been too sedating
- Where stimulation of appetite may be a useful side effect

**Dosage and administration**

- It comes in tablet, oro-dispersible tablet and injectable form
- As an anti-emetic start with 1.25 to 2.5mg stat, prn and at night
- If necessary increase to 5mg at night, maximum 5mg bd
- Time to peak plasma concentration 5-8 hours
- Duration of action about 12-48 hours. Plasma half-life 34 hours; 52 hours in the elderly. Unchanged in renal or hepatic impairment.

**How to use:**
See palliative care formulary for more information and discuss with a palliative care specialist.

**Cautions in Use**
For full list, see SPC.
Increased mortality in patients with dementia. Over-sedation has occurred with higher doses and with concomitant use of benzodiazepines. Significant cardiovascular disease.

**Contraindications**
As for antipsychotics, see BNF

**Monitoring**
No specific monitoring is required

**Drug Interactions** - see BNF

**Side Effects**
Sedation, extra-pyramidal, as for antipsychotics.

**Cost** (28 days)
Generic tabs 2.5mg £6.56; 5mg £13.11.
Orodispersible 2.5mg £21.85; 5mg £38.46.
Injection 10mg vial £3.48

**Reference** Palliative Care Formulary 4th Ed
5HT₃ antagonists were developed to counter highly emetogenic stimuli such as platinum based chemotherapy and certain radiotherapy regimes. They are also successfully used as 3rd or 4th line anti-emetics for intractable vomiting where usual approaches have failed.

**Indications**
- Nausea and vomiting in a palliative situation where other antiemetics including metoclopramide, haloperidol, cyclizine, levomepromazine and dexamethasone have not worked.
- Cholestatic or uraemic itch

**Dosage and administration**
- Ondansetron 8mg bd PO or SC (or 16mg over 24 hours by syringe driver)
- Granisetron 1-2mg od PO or SC
- Trial for 3 days – continue if effective, stop if not
- Typically they are used in combination with an antiemetic with multiple sites of activity eg Levomepromazine or Olanzapine +/- Dexamethasone
- Duration of action – Ondansetron 12 hours, Granisetron 24 hours

**How to use:**
See palliative care formulary for more information and discuss with a palliative care specialist.

**Cautions in Use**
Reduce dose of Ondansetron to 8mg in moderate or severe hepatic impairment. For full list, see SPC.

**Contraindications**
Not to be used intravenously with iv metoclopramide – risk of arrhythmia.

**Monitoring**
No specific monitoring is required

**Drug Interactions**
See BNF

**Side Effects**
Very common – headache. Common includes - constipation. See BNF for full list.
**Cost**

Ondansetron
Oral - 4mg, 10 tabs £1.88, 8mg, 10 tabs £35
Injection – 2mg/ml – 2ml £1, 4ml £11

Granisetron
Oral – 1mg 10 tabs £50.37
Injection – 1mg/ml, 1ml £1.60, 3ml £2.40

**Reference**

Palliative Care Formulary 4th Edition