Pan Birmingham NHS
Cancer Network

Guidelines for the use of Methadone for Adults with Pain in Palliative Care

Date Approved by Network Governance	**October 2012**

Date for Review	**October 2015**

1. Scope of the Guideline

1.1 This guideline has been produced to support the use of methadone for analgesia in palliative patients.

1.2 Titration to methadone is not appropriate in the last days of life and therefore is not discussed in this guidance.

2. Guideline Background

2.1 There are no NICE guidelines on the use of methadone for pain therefore the Pan Birmingham Cancer Network Specialist Palliative Audit and Guidelines Group have developed these guidelines to ensure safe and consistent practice in-line with local expert opinion.

2.2 A small number of patients with cancer experience pain that cannot be controlled using the analgesic ladder even when anti-epileptics and anti-depressant drugs are added to opiates[1]. Methadone may help in the pain management of these patients.

2.3 Methadone has a long half-life and titration to an effective dose is often complex therefore dose titration and modification should be carried out under the care and supervision of a specialist palliative care or pain team.

3. Guideline Statements

3.1 The use of methadone for analgesia requires the involvement of the specialist palliative care team at all stages.

3.2 Patients with uncontrolled pain should be referred either to a specialist palliative care or a pain team.

3.3 The use of methadone should be reserved for the management of pain in patients that:

a. gain inadequate analgesia with or without unacceptable side effects following appropriate dose-escalation of morphine and/or other opioids
b. experience tolerance to the analgesic effects of other opioids
c. are receiving methadone for another indication

3.4 Conversion to methadone requires careful monitoring and where possible should take place in a specialist palliative care in-patient unit. Under exceptional circumstances with the involvement of the specialist palliative care or pain team the conversion may occasionally be undertaken at home or in another care environment.

3.5 Consideration should be made of the risk of long QT syndrome (see appendix 6)

3.6 Methadone prescribing responsibilities should only be passed onto the primary care team when the patient has been stabilised and with the support of shared care guidelines (see appendix 4)[1,2] and in the areas where shared care has been approved.

3.7 Conversion from other opioids to sub-cutaneous methadone:

3.7.1 It is not advised to convert to sub-cutaneous methadone from any opioid other than oral methadone and is not covered by this guideline.

3..7.2 Conversion is a prolonged process requiring considerable input from the patient to achieve successful conversion to oral methadone, so changing a patient in the final few days of life to sub-cutaneous methadone from other opioids is not advised.

4. Conversion to oral methadone.

4.1 For conversion from oral opioids see Appendix 1.

4.2 For conversion from topical opioids see Appendix 2.

4.3 For conversion from subcutaneous opioids see Appendix 3.

5. Management of Breakthrough Pain

5.1 For patients in severe pain and requiring analgesia within the 3 hour interval between methadone doses, options are[15]:-

- Taking the previously used opioid (at 50-100% of the prn dose before switching) with a minimum of hourly intervals.
- If neurotoxicity with pre-switch opioid then use an appropriate dose of an alternative strong opioid.

6. Conversion to sub-cutaneous methadone from oral methadone

6.1 The following conversion ratio should be utilised:[3,6]

Oral : Sub-cutaneous

2 : 1

6.2 The continuous sub-cutaneous infusion should be started at the calculated dose eight hours after the final dose of oral methadone has been taken.

6.3 Following conversion all patients should be monitored for signs of toxicity or pain. Should either of these occur the methadone dose should be modified accordingly.

Methadone is an irritant and can cause local site reactions. These reactions can be reduced by:

a) using sodium chloride 0.9% as the diluent[2]
b) maximising the dilution of the methadone by using a 20 or 30 ml syringe[2]
c) add dexamethasone 0.5 mg to the syringe[5]

6.4 Do not mix methadone with any other drug in the same syringe unless unavoidable and on specialist advice.

6.5 Breakthrough pain for patients receiving sub-cutaneous methadone should be managed as for oral methadone **– see Appendices.**

7. Conversion of Methadone to Other Opioids

This should only be undertaken by Specialist Palliative Care teams and is not covered in the remit of this guidance. Please refer to SPCT or Specialist Pain Teams.

8.0 Opioid withdrawal symptoms[3,5,6,12]

8.1 Opioid withdrawal syndrome is important to recognise and manage due to its unpleasant symptoms and due to a small but significant risk of death.

8.2 Patients should be monitored for signs of opioid withdrawal. Opioid withdrawal syndrome may resemble a severe flu-like illness, characterized by rhinorrhoea, sneezing, yawning, lacrimation, abdominal cramping, leg cramping, piloerection (goose bumps), nausea, vomiting, diarrhoea, and dilated pupils. Some patients may also experience anxiety, restlessness, irritability and insomnia.

8.3 Disorientation, hallucinations, and seizures, which are characteristic of delirium tremens, are not seen in opioid withdrawal.

8.4 If a patient should experience signs of opioid withdrawal they should be promptly referred back to the specialist palliative care or pain team. Management options include:

a) administration of breakthrough doses of the previous opioid
b) benzodiazepines can be added to control insomnia and muscle cramps

9.0 Patient Information and Counselling

The NICE guidance on Opioids in Palliative Care (CG140)[16] states that patients should be asked about any concerns of being prescribed strong opioids, that verbal and written information should be offered to patients and carers and that they are offered frequent review of their pain control and side-effects.

Responsibility for the communication around the use of Methadone for pain control in palliative care is with the specialist palliative care team.

10 Other issues

10.1 As with all opioids, a risk assessment of home circumstances may be undertaken and help to establish practical plans concerning supply and availability of methadone in the community and the patient's place of care.

10.2 For the management of methadone overdose please see Pan Birmingham Cancer Network Guidelines for the Use of Naloxone in Palliative Care Adult Patients.

10.3 For further drug and general information on methadone see Appendix 5.

10.4 A simple summary of the guidelines for conversion of oral opiates to oral methadone is shown in Appendix 1.

10.5 Further information on the use of methadone can be obtained from your local specialist palliative care team.

Monitoring of the Guideline

Adherence to the Network guidelines may from time to time be formally monitored.

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References

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Approval Signatures

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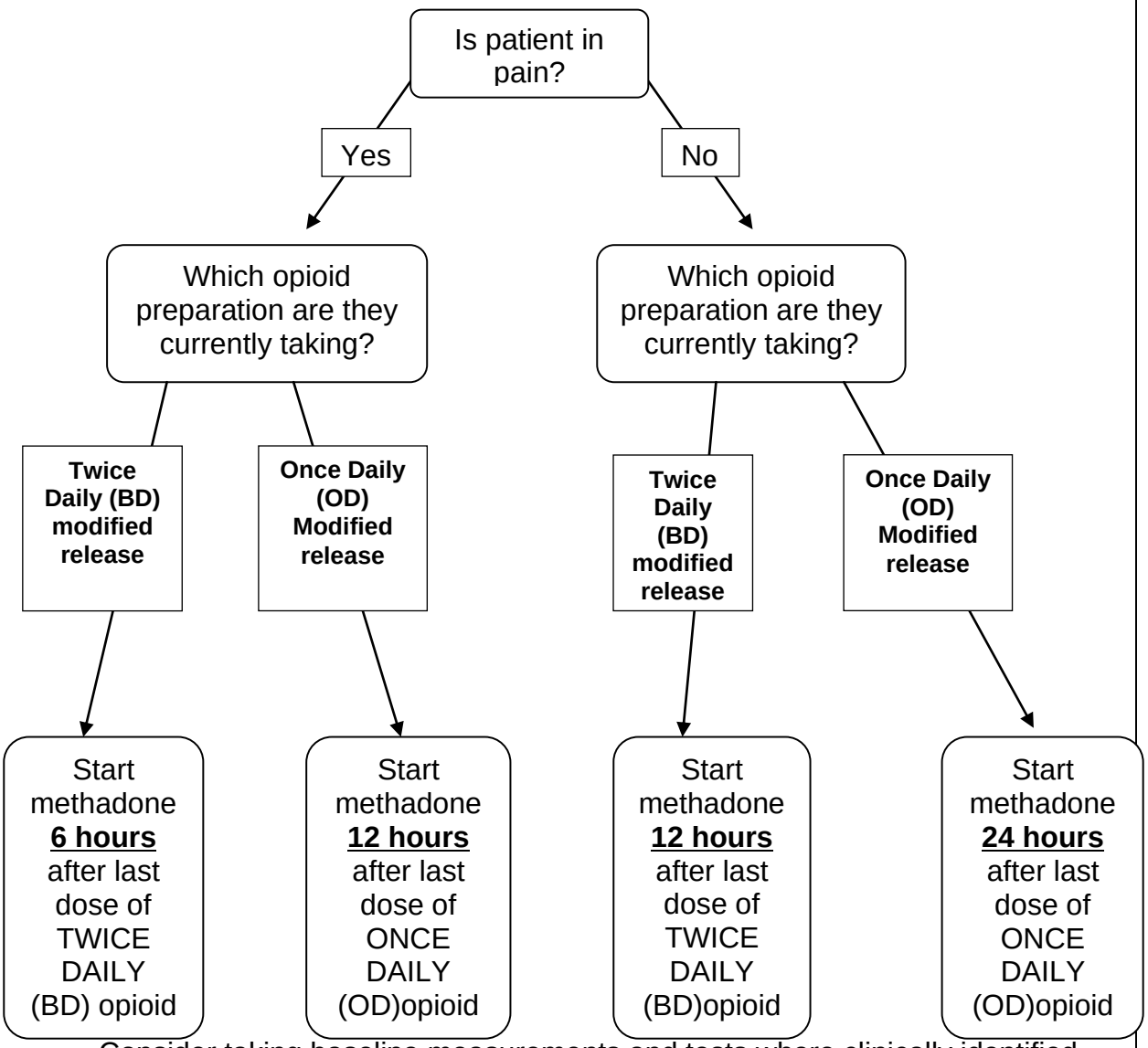
Appendices

Appendix 1 – Conversion from oral opioids to oral methadone

Plan for converting from ORAL opioids to ORAL Methadone

Day 0 (pre-Methadone)

- Plan start time of Methadone on Day 1



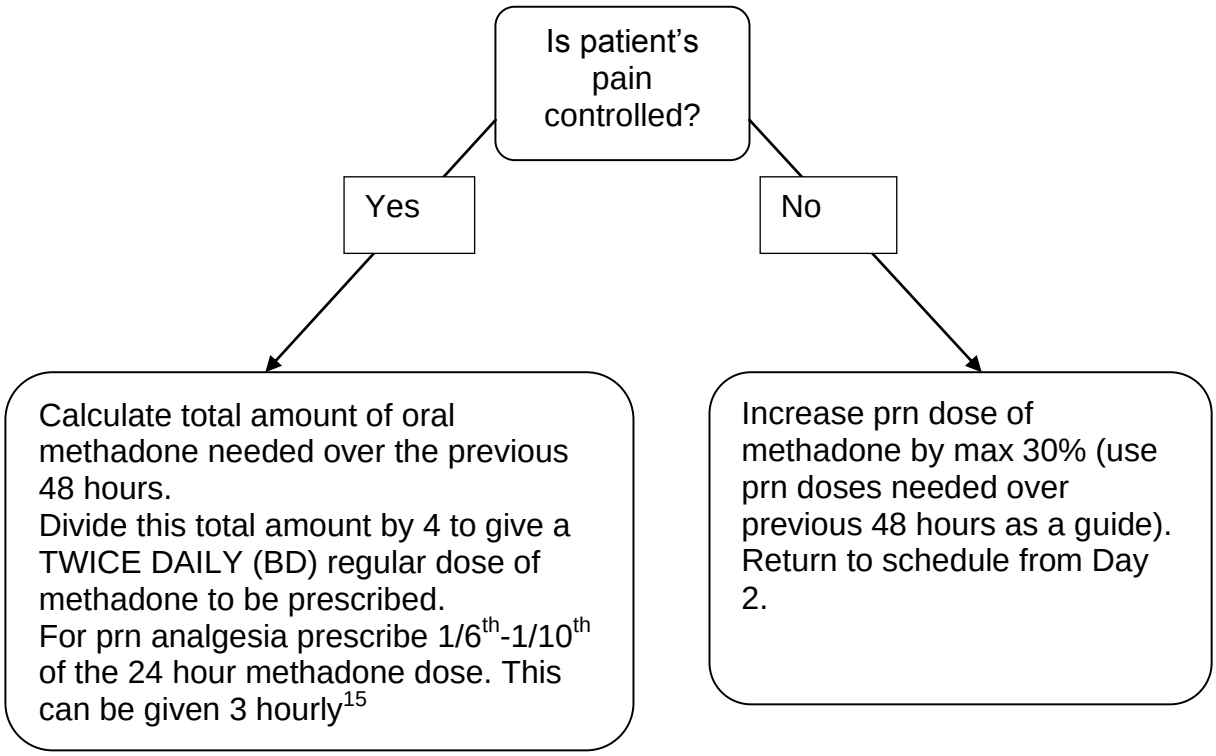
- Consider taking baseline measurements and tests where clinically identified

Day 1

- Prescribe single loading dose of methadone to be given at start time identified at Day 0
  - Dose of methadone = 1/10th of the previous total daily dose of ORAL morphine. The titration dose of methadone should be no more than a MAXIMUM of 30mg.

- Prescribe prn doses of methadone which need to be given when the pain returns at a minimum interval of 3 hours between methadone doses.
  - Dose = 1/3rd of the loading dose to a MAXIMUM of 10mg methadone.
  - [The dose will be equivalent to 1/30th of the previous total daily dose of

<table>
<tr><td></td><td>ORAL morphine].

• Prescribe prn doses of alternative analgesia for if the pain returns within the 3 hourly interval for the methadone – see point 5 in the main guideline for recommendations.</td></tr>
<tr><td>Days 2 to 5</td><td>• Continue to review patient and their analgesia needs
○ If patient becomes over sedated reduce dose of methadone by 33-50%.
○ If reducing the dose of methadone, remember to reduce any prn doses of additional analgesia.
○ Monitor respiration rate 4 hourly for 24 hours. If respiratory rate <8 reduce dose of analgesia further, refer to Pan Birmingham Cancer Network Guidelines for the use of Naloxone in Palliative Care.</td></tr>
<tr><td>Day 6</td><td> 
</td></tr>
<tr><td>Pre-Discharge</td><td>Consider who will be prescribing methadone in the community.
Liaise with GP regarding doses, monitoring and follow up.
Book review by community palliative care team within 5 working days of discharge.
Liaise with community pharmacist over discharge medication and how prescriptions will be ordered/prescribed in the future.</td></tr>
<tr><td>Maintenance</td><td>The patient and/or their relative/carer should contact the Specialist Palliative Care Team to discuss any issues.
Methadone dose will need to be increased if patient is requiring more than 2 prn analgesia doses/24 hours.
Due to the long half-life of methadone, all patients receiving methadone should be monitored for signs of opioid toxicity, these may take up to one month to manifest following a dose increment
If patient becomes over sedated, action should be taken as advised in Day 6.</td></tr>
</table>

Appendix 2 – Conversion from topical opioids to oral methadone

<table>
<tr><th colspan="2">Plan for converting from TOPICAL opioids to ORAL Methadone</th></tr>
<tr><td>Day 0 (pre-Methadone)</td><td>

Plan start time of Methadone on Day 1

Start methadone <u>12 hours</u> after opioid patch has been removed

Consider taking baseline measurements and tests where clinically identified

</td></tr>
<tr><td>Day 1</td><td>

Prescribe single loading dose of methadone to be given at start time identified at Day 0

Dose of methadone = 1/10th of the previous total daily dose of ORAL morphine. The titration dose of methadone should be no more than a MAXIMUM of 30mg.

Prescribe prn doses of methadone which need to be given when the pain returns at a minimum interval of 3 hours between methadone doses.
Dose = 1/3rd of the loading dose to a MAXIMUM of 10mg methadone.

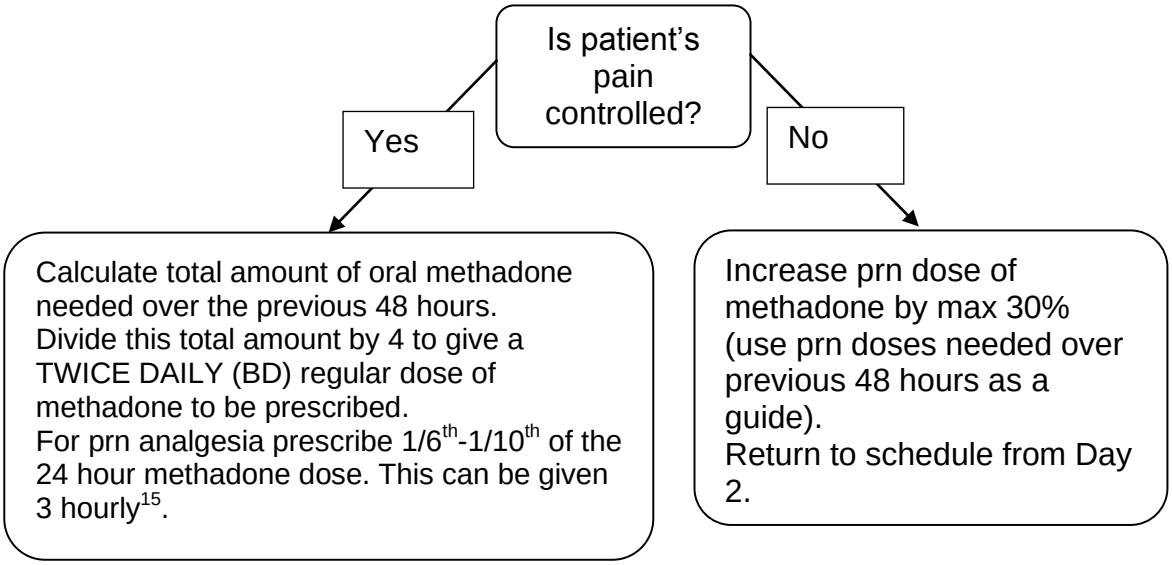
[The dose will be equivalent to 1/30th of the previous total daily dose of ORAL morphine].

Prescribe prn doses of alternative analgesia for if the pain returns within the 3 hourly interval for the methadone - see point 5 in the main guideline for recommendations.

</td></tr>
<tr><td>Days 2 to 5</td><td>

Continue to review patient and their analgesia needs

If patient becomes over sedated reduce dose of methadone by 33-50%.
If reducing the dose of methadone, remember to reduce any prn doses of additional analgesia.
Monitor respiration rate 4 hourly for 24 hours. If respiratory rate <8 reduce dose of analgesia further, refer to Pan Birmingham Cancer Network Guidelines for the use of Naloxone in Palliative Care.

</td></tr>
<tr><td>Day 6</td><td>


</td></tr>
</table>

Before discharge	Consider who will be prescribing methadone in the community. Liaise with GP regarding doses, monitoring and follow up. Book review by community palliative care team within 5 working days of discharge. Liaise with community pharmacist over discharge medication and how prescriptions will be ordered/prescribed in the future.
Maintenance	The patient and/or their relative/carer should contact the Specialist Palliative Care Team to discuss any issues. Methadone dose will need to be increased if patient is requiring more than 2 prn analgesia doses/24 hours. **Due to the long half-life of methadone, all patients receiving methadone should be monitored for signs of opioid toxicity, these may take up to one month to manifest following a dose increment.** If patient becomes over sedated, action should be taken as advised in Day 6.

Appendix 3 – Conversion of subcutaneous opioids to oral methadone

<table>
<tr><th colspan="2">Plan for converting from SUBCUTANEOUS opioid infusions to ORAL Methadone</th></tr>
<tr><td>Day 0 (pre-Methadone)</td><td>

Plan start time of Methadone on Day 1

Start methadone <u>4 hours</u> after opioid infusion has been stopped

Consider taking baseline measurements and tests where clinically identified

</td></tr>
<tr><td>Day 1</td><td>

Prescribe single loading dose of methadone to be given at start time identified at Day 0

Dose of methadone = 1/10th of the previous total daily dose of ORAL morphine. The titration dose of methadone should be no more than a MAXIMUM of 30mg.

Prescribe prn doses of methadone which need to be given when the pain returns at a minimum interval of 3 hours between methadone doses.

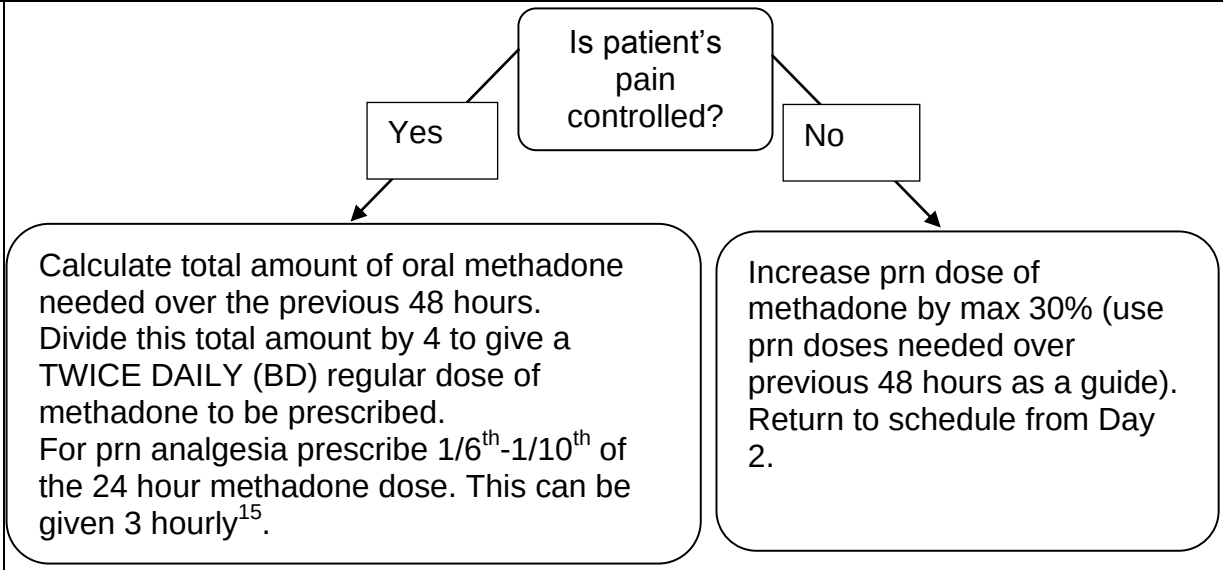
Dose = 1/3rd of the loading dose to a MAXIMUM of 10mg methadone.
[The dose will be equivalent to 1/30th of the previous total daily dose of ORAL morphine].

Prescribe prn doses of alternative analgesia for if the pain returns within the 3 hourly interval for the methadone - see point 5 in the main guideline for recommendations.

</td></tr>
<tr><td>Days 2 to 5</td><td>

Continue to review patient and their analgesia needs

If patient becomes over sedated reduce dose of methadone by 33-50%.
If reducing the dose of methadone, remember to reduce any prn doses of additional analgesia.
Monitor respiration rate 4 hourly for 24 hours. If respiratory rate <8 reduce dose of analgesia further, refer to Pan Birmingham Cancer Network Guidelines for the use of Naloxone in Palliative Care.

</td></tr>
<tr><td>Day 6</td><td>


</td></tr>
</table>

Before discharge	Consider who will be prescribing methadone in the community. Liaise with GP regarding doses, monitoring and follow up. Book review by community palliative care team within **5** working days of discharge. Liaise with community pharmacist over discharge medication and how prescriptions will be ordered/prescribed in the future.
Maintenance	The patient and/or their relative/carer should contact the Specialist Palliative Care Team to discuss any issues. Methadone dose will need to be increased if patient is requiring more than 2 prn analgesia doses/24 hours. **Due to the long half-life of methadone, all patients receiving methadone should be monitored for signs of opioid toxicity, these may take up to one month to manifest following a dose increment.** If patient becomes over sedated, action should be taken as advised in Day 6.

Appendix 4 - Proposed Shared Care responsibilities for the prescribing and monitoring of methadone in palliative patients.

Shared care responsibilities for the prescribing and monitoring of methadone in palliative patients

Palliative medicine specialist responsibilities

- Assess patient suitability for pain control with methadone and obtain informed consent.
- Consider risk of long QT syndrome (Appendix 6)
- Initiate and titrate the dosage regimen for methadone.
- Assess response and side effects, and prescribe for minimisation of side-effects.
- Arrange shared care with General Practitioner when patient is managed on a stable regimen. Written communication with General Practitioner must include:
  - A copy of Shared Care Guideline
  - A contact for urgent queries out-of-hours
  - A detailed letter outlining individual patients dosing regimen
- If shared care is not agreed or in place in the locality, arrangements must be made prior to discharge as to how prescribing and obtaining methadone will continue
- Notify Hospice or Hospital Pharmacist to forward details to the Community
- Pharmacist nominated by the patient so Primary Care supplies can be obtained.
- Notify Community and Specialist Nurses.
- Ensure that all patients when discharged to their General Practitioner for management have at least fourteen days supply to ensure continuity of supply at home.
- When prescribing state the number of milligrams to be taken, the formulation, strength and colour **e.g. Methadone oral 20mg bd (blue 10mg/ml liquid).**
- Review the patient's response and continuing appropriateness of methadone at regular intervals. This may be facilitated by Community Specialist Palliative Care team.
- Stop the treatment when no longer considered to be appropriate.

GP responsibilities

- Referral to Specialist when symptoms fail to respond to the management of analgesia or when change of administration route may be indicated.
- Review of the patient at regular agreed intervals to monitor control of symptoms.
- Identify adverse effects and report them to the Specialist in Palliative Medicine.
- Continue prescribing methadone (where agreed locally) and ensure supply through designated community pharmacy.
- When prescribing state the strength of liquid, tablets or ampoules to be used in addition to the dose prescribed.
- Liaise with community and specialist nurses.

Community pharmacist responsibilities

- To order and supply methadone and complete and maintain appropriate records.

Methadone is available in the following commercial formulations:

- Methadone 5mg tablets
- Methadone liquid 10mg/ml (blue and bitter tasting)
- Methadone liquid 20 mg/ml (caramel/brown colour and bitter tasting)
- Methadone injection 10 mg/ml (1 ml, 2 ml, 3.5 ml and 5 ml ampoules available)

Appendix 5 – General drug information about Methadone

A 5.1 General points

- There is no directly applicable conversion ratio either from morphine to methadone or vice versa.
- Methadone has a long half life of 30 to 110 hours and dose increases should occur no more frequently than every five days.[3]

A 5.2 preparations

Methadone is available in a number of commercial formulations however not all of these are licensed for pain relief. The following preparations are most commonly used for analgesia:

- Methadone 5mg tablets
- Methadone liquid 10mg/ml (blue and bitter tasting)
- Methadone liquid 20mg/ml (caramel colour and bitter tasting)
- Methadone injection 10mg/ml (1ml, 2ml, 3.5ml and 5ml ampoules available)

When prescribing methadone please ensure that the number of milligrams of methadone and frequency are documented and also the formulation and colour are included on the prescription e.g. methadone oral 20 mg bd (blue 10 mg/ml liquid). Methadone is a controlled drug and prescriptions should meet the CD requirements.

Further drug information

Available from:
Summary of Product Characteristics- Methadone (1mg/ml, 10mg/ml, 20mg/ml and injection). Available at: http://emc.medicines.org.uk/

A 2.3 drug and food interactions with methadone

Methadone is metabolised by the group of enzymes known as cytochrome P450. This is a highly complex group of enzymes that is often induced or inhibited by a number of other conventional and herbal medications as well as some foods (see below). This enzyme induction or inhibition may result in pain in previously stable patients, or accumulation and therefore toxicity in others.

For a comprehensive list of interacting drugs, refer to:
www.atforum.com/pdf/Drug_Interactions.pdf

Appendix 6 – Reducing cardiac risk with Methadone

Minimizing the risk of cardiac toxicity with methadone

A6.1 Consideration of burden vs. benefit is crucial and, in those with life-limiting illness, the potential benefit of controlling otherwise refractory pain may far outweigh the risks, even when monitoring for arrhythmia is impractical. ECG monitoring is generally irrelevant in the last days of life.

A6.2 In people with a longer prognosis an ECG may be performed before starting methadone and when the dose is stabilized in the presence of other risk factors for QT interval prolongation including:

6.2.1 A history of cardiac conduction abnormalities
6.2.2 Advanced heart disease or ischemic heart disease
6.2.3 Liver disease
6.2.4 A family history of sudden death
6.2.5 Electrolyte abnormalities
6.2.6 Concurrent treatment with drugs which:

- may cause electrolyte abnormalities
- have a potential to prolong QT including anti-arrhythmic drugs such as Amiodarone, psychotropic drugs including Haloperidol, Macrolide antibiotics including clarithromycin and erthromycin as well as Anti-malarial drugs and Domperidone a more extensive list is available at http://www.azcert.org/
- inhibit CYP3A4

A 6.3 ECG monitoring is recommended in patients without recognized risk factors for QT prolongation, before dose titration above 100mg/day PO and 1 week after such up-titration (an arbitrary dose, based on expert opinion).

A 6.4 The decision on ECG monitoring for each patient should be made by the consultant responsible for the methadone initiation.

A6.5 Monitoring of serum electrolytes, e.g. potassium, magnesium, is generally recommended in patients taking diuretics or at risk of hypokalaemia, e.g. because of vomiting or diarrhoea.

A6.5 If the QT interval is prolonged >500msec:-

- An alternative opioid should be considered
- Discussion with a local cardiologist should be sought to help assess risk of arrhythmia to aid weighing up or risk vs. burden of treatment.