Northamptonshire Healthcare
NHS Foundation Trust

Guidance on the use of Methadone at Cynthia Spencer and Cransley Hospices – MMG017

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Why we need this guidance?

Methadone is a drug with complex pharmacology and it is recommended that it should be initiated only by specialists familiar with its use. This guidance aims to support clinicians working within the hospices to safely prescribe and administer methadone for severe pain.

Which stakeholders have been involved in the creation of this guidance?

- Specialist Palliative Care Clinicians
- Medicines Management Committee

Key duties

- **The Chief Operating Officer and the Director of Nursing, AHPs & Quality** are responsible for ensuring the implementation of this guidance across the clinical areas.
- **Hospice members of staff**
  (including Responsible Clinician and Multi-disciplinary Team) - All clinical hospice members of staff have a responsibility for ensuring that they have an awareness of the guidance.

Guideline detail

Consultant's advice must be sought prior to initiating methadone

Indications

Common indications:

1. Neurotoxicity with morphine at any dose (e.g. hyperalgesia, allodynia, myoclonus) which does not respond to a reduction in morphine and switching to another easier-to-use opioid (e.g. fentanyl, hydromorphone, oxycodone) is not possible or has been tried
2. Neuropathic or mixed nociceptive-neuropathic pain not responding to an NSAID + morphine + adjuvant analgesics, e.g. an anti-depressant ± anti-epileptic

Pharmacokinetics

Methadone is a synthetic strong opioid with mixed properties. It is a μ-opioid receptor agonist, possible δ–opioid receptor agonist, NMDA–receptor channel blocker and a pre-synaptic blocker of serotonin re-uptake. Methadone is a highly lipophilic drug and when given repeatedly, it creates an extensive tissue reservoir, with only about 1% of the drug in the blood. It is highly protein bound and with the large volume distribution, contributes to a long plasma half-life ranging from 5 – 130 hours. This half-life increases with patient age. It takes 4 – 7 days to reach steady state and accumulation is a potential problem. It is mainly metabolised in the liver and about half of the drug and its metabolites are excreted via the intestines and half by the kidneys. Renal and hepatic impairment do not affect methadone clearance. The oral bioavailability is 80% (range 40 - 100%). Onset of action is thought to be within 30 minutes after oral administration, 15 mins following intramuscular route.

Contraindications

- Concurrent administration of MAOI (Mono-amine oxidase inhibitor) drugs, including moclobemide, or for 2 weeks after stopping
- Hypersensitivity to methadone or its excipients

Cautions

Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:

- history of cardiac conduction abnormalities
- advanced heart disease or ischaemic heart disease
- liver disease
- family history of sudden death
- electrolyte abnormalities i.e. hypokalaemia, hypomagnesaemia
- concomitant treatment with drugs that have a potential for QT prolongation

- concomitant treatment with drugs which may cause electrolyte abnormalities
- concomitant treatment with cytochrome P450 CYP 3A4 inhibitors

Important DRUG Interactions

Increase in plasma methadone

SSRI's (serotonin specific reuptake inhibitors), MAOIs, cimetidine, ciprofloxacin, diazepam (high dose), itraconazole, fluconazole, voriconazole

Decrease in plasma methadone

Carbamazepine, phenytoin, phenobarbital, rifampicin and St John's wort, antiretrovirals, tobacco smoking

Preparations of methadone

METHADONE IS A SCHEDULE 2 CONTROLLED DRUG.

Oral	-	5mg scored tablets 1mg/ml solution
Injection	-	1ml, 2ml and 5ml ampoules of 10mg/ml

Dosing guidelines

Switching from another strong opioid to methadone, especially when that opioid has been at a high dose (e.g. > 600mg oral morphine equivalent per day) increases the risk of side effects due to methadone's complex pharmacokinetics. The following regime tries to account for this by giving a larger dose initially to saturate the body stores, and then reducing the dose to produce an effective and side effect-free maintenance phase. Therapeutic analgesic effect is often not attained until after 3 to 5 days of dosing and that is why initial regime is complex.

Please note:

Caution is required when there has been a rapid dose escalation of the pre-switched opioid. The safest option would be calculate the initial dose of methadone using the pre-escalation dose.

As per Palliative Care Formulary (PCF) Quick Prescribing Guide: Use of methadone for cancer pain. See Appendix 1 for dosing sheet.

N.B Round doses up to nearest convenient tablet size or volume

1. Stop the previous opioid abruptly

2. Give a loading dose of oral (PO) methadone 1/10th of the previous total 24 hour oral morphine dose, *up to a maximum of 30mg*

- If switching from immediate release (I/R) morphine – give the first dose of methadone ≥ 2 hours (pain present) or 4 hours (pain-free) after the last dose of morphineModified release (M/R) morphine – give the first dose of methadone ≥ 6 hours (pain present) or 12 hours (pain free) after the last dose of a 12 hour preparation

3. Prescribe 'as required' (PRN) dose of methadone that is **1/30th of the previous total 24 hour oral morphine** (1/3rd of loading dose) equivalent dose *up to a maximum of 30mg* using the methadone dosing sheet.

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

4. Allow the patient to take the PRN dose NO MORE FREQUENTLY THAN 3 HOURLY. (Peak concentration may take up to 3 hours, hence 3 hourly PRN limit)

5. For patients in severe pain requiring analgesia before the 3 hour interval, options are:

   - Taking the previously used opioid 1 hourly PRN (at 50 - 100% of the PRN dose before switching)
   - If neurotoxicity with pre-switched opioid, use an appropriate dose of an alternative strong opioid
   - Ketamine (discuss with consultant)

6. On day 6, the amount of methadone taken in total over the previous 48 hours is noted and divided by 4 to give a regular twice daily (BD) dose. The 3 hourly PRN dose will be 1/6 - 1/10th of the 24 hour dose. **Please note that some patients may require a lower PRN dose.**

7. If ≥ 2 doses/day of PRN methadone continues to be needed, the dose of regular methadone should be increased once a week, guided by PRN use.

8. If a patient:

   - Becomes over sedated, reduce the dose generally by 33 – 50%
   - Develops opioid abstinence symptoms, give PRN doses of the previous opioid to control these

Example 1: For a patient on morphine equivalent 300mg per 24 hours

Initial loading dose would be: 30mg

3 hourly PRN dose: 10mg (1/3 of loading dose)

On day 6, the amount of methadone taken in total over the previous 2 days is noted and divided by 4. This will give a 12 hourly dose

The 3 hourly PRN dose will be 1/6 - 1/10th of the 24 hour dose

(eg. methadone 80mg in the previous 48 hours – 20mg BD and 5mg 3 hourly PRN)

Example 2: For a patient on morphine > 600mg per 24 hours. The loading dose will be limited to 30mg and 3 hourly PRN dose will be 30mg

Synergy of methadone with a concurrent opioid

Occasionally some clinicians may opt to add a small dose of methadone alongside the current opioid. When there is evidence of opioid toxicity, the dose of morphine (or equivalent) is reduced. This regime does not negate the importance of close supervision. (N.B. There is limited evidence to support of the use of methadone in this way)

Subcutaneous use (s/c)

If a patient is on a stable dose of oral methadone, a conversion of 2 **:** 1 should be used when substituting oral with subcutaneous methadone (i.e. to convert oral → s/c methadone, divide the oral dose in half) Given the wider bioavailability range, some patients may experience a deterioration in pain control. The subcutaneous infusion **should not** be started within 12 hours of taking the last oral dose of methadone, although PRN dosing should be available.

This may be a slightly conservative conversion given the wide range in the quoted oral bioavailability for methadone (40 - 100%).

For PRN doses, $1/6^{th}$ – $1/10^{th}$ of the total daily sub-cutaneous dose may be given subcutaneously (as with stable oral dosing).

Example 3: Total 24 hour dose of oral methadone is 40mg; therefore subcutaneous dose is 20mg.

The PRN dose may be up to $1/6^{th}$ – $1/10^{th}$ of the total 24 hour subcutaneous dose, i.e. 2-3mg

Doses of subcutaneous methadone above 25mg can result in marked local inflammation, requiring regular site rotation.

Toxicity

- **See MMG021 Guidance on the use of Naloxone in the management of opioid-induced respiratory depression**
- **Always discuss with the consultant**
- **It is imperative the treatment plan is clearly communicated to all team members (including on-call doctors), especially to cover out-of-hours when doctors are not on site**

Methadone shares a similar side effect profile to the other strong opioids. The most important side effect not to miss is respiratory depression. Toxicity may develop insidiously if methadone accumulates.

If the patient's respiratory rate (RR) is > 8 breaths/min, easily rousable and not cyanosed – OBSERVE (and omit or reduce the next dose of methadone)

If RR is < 8 breaths/min, barely rousable, unconscious and/or cyanosed:

- Dilute naloxone 400micrograms (1ml) to 10ml with sodium chloride 0.9%
- Give 100 micrograms naloxone intravenously (IV) as a STAT dose
- Continue to give 20 – 100 micrograms naloxone IV every 2minutes until the patients' respiratory rate is satisfactory
- If unable to give IV, give STAT dose intramuscularly (IM) of 100 micrograms (undiluted), further doses can be given subcutaneously (SC) or IM undiluted – discuss with consultant as rate of absorption will be slower by these routes
- Further boluses and/or an infusion may be needed as methadone's half-life is considerably longer than naloxone IV (see separate Guidance on the use of Naloxone in the management of opioid-induced respiratory depression – MMG021)

It is important to titrate to respiratory function and not consciousness as total reversal of methadone may result in severe agitation and pain.

Training requirements associated with this Guideline

There is no mandatory training associated with this guideline.

Equality considerations

Refer to MMP001 Control of Medicines Policy

Havard Reference Guide

- Twycross, R. Wilcock, A & Howard P. 2014. Palliative Care Formulary (PCF) 6th edition. September 2017
- http://www.medicines.org.uk/emc/medicine/29897 - accessed 8th July 2015
- UKMI Q&A 227.2. What naloxone doses should be used in adults to reverse urgently the effects of opioids or opiates? June 2015.

Document control details

Author:	Reema Pal, Speciality Doctor, Specialist Palliative Care Natalie Fasham, Palliative Care Pharmacist
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1	15/03/2016	01/04/2016	01/04/2018	New guidance
2	15/05/2018	20/06/2018	15/05/2020	Minor Amendments

Appendix 1 – Methadone Prescription sheet

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Addressograph sticker here

Cynthia Spencer and
Cransley Hospices
Methadone Prescription Sheet

Allergies (with reaction if known)	

METHADONE STARTING SHEET

N.B. See latest Palliative Care Formulary (PCF) for more detailed information:

Previous equivalent 24 hour oral morphine dose	
Methadone loading dose (max 30mg) Calculated as 1/10th of previous oral morphine dose	
Methadone 3 hourly "PRN" dose (max 30mg) Calculated as 1/30th of previous oral morphine dose	

Reason, if any for deviating from guidance _____

METHADONE 3 HOURLY DOSE	**Time**	**Date**	**Date**	**Date**	**Date**	**Date**	**Date**	**Date**	**Date**
Prescriber (sign)	**0.00 - 3.00**								
Print	**3.00 - 6.00**								
DATE	**6.00 - 9.00**								
DOSE: mg	**9.00 - 12.00**								
PLEASE RECORD ACTUAL TIMES GIVEN	**12.00 - 15.00**								
	15.00 - 18.00								
MINMUM INTERVAL 3 HOURS	**18.00 - 21.00**								
	21.00 - 24.00								

Final twice daily dose = _____ **mg**

(To be prescribed on the main drug chart)