

*Sue Ryder*

Patient Name:
Address:
DOB:
NHS No:
GP:

## METHADONE for refractory pain: SHARED CARE PROTOCOL

(this protocol *does not* describe the use of methadone in substance misuse – see separate guidance)

**Produced by: Paul Howard, Consultant in Palliative Medicine**

**Authorised by: Berkshire West CHQPSG**

**Date: June 2013**

**Reviewed: January 2015**

This shared care protocol is produced to support the combination of the best of both primary and secondary care for the benefit of the patient. It supports, but does not replace, discussion and agreement on an individual patient basis about transfer of care. Agreement by the GP should be confirmed (verbal or written) before transfer of care.

### Responsibilities for care and clinical monitoring

#### Consultant responsibilities

<b>Initiation</b>	<ul style="list-style-type: none"> <li>Initial assessment of appropriateness of methadone</li> <li>Informed consent to start methadone and baseline observations and tests</li> <li>Initial dose titration, including adjusting concurrent analgesia as needed</li> </ul>
<b>Prescribing</b>	<ul style="list-style-type: none"> <li>Prescription of methadone during initial dose titration</li> <li>Prescription of further 14 days of methadone once stable dose achieved and shared care agreed</li> </ul>
<b>Monitoring</b>	<ul style="list-style-type: none"> <li>To arrange a named pain or palliative care team member (physician or nurse specialist) to monitor efficacy, tolerability and adjust dose where required</li> <li>To arrange additional timely re-assessment if the GP raises concern</li> </ul>
<b>Communication</b>	<ul style="list-style-type: none"> <li>To discuss shared care arrangement with GP and send a copy of this document (including completed clinical summary page) to GP</li> <li>To inform GP of outcome of re-assessments</li> <li>To provide 24hr advice (via on-call palliative care consultant or anaesthetist as appropriate)</li> </ul>

#### General Practitioner responsibilities

<b>Initiation</b>	<ul style="list-style-type: none"> <li>None</li> </ul>
<b>Prescribing</b>	<ul style="list-style-type: none"> <li>Prescription of methadone once the patient is established on an effective dose and shared care has been agreed (the back page 'pharmacist information' can be torn off and sent with the FP10)</li> </ul>
<b>Monitoring</b>	<ul style="list-style-type: none"> <li>For adverse effects (similar to morphine, but accumulation can cause delayed onset sedation/toxicity in patients established on a stable dose)</li> <li>For drug interactions with methadone: <ul style="list-style-type: none"> <li>↑Methadone toxicity with enzyme inhibitors e.g. azole antifungals: (fluconazole is least problematic, or use nystatin), ciprofloxacin, cimetidine, SSRIs; quinidine and grapefruit juice (↑absorption)</li> <li>↓effect with enzyme inducers (e.g. carbamazepine, phenytoin, , rifampicin, St John's wort, some anti-retrovirals) – use alternatives or monitor for ↓effect</li> <li>Additive QT prolongation with other QT prolongers</li> <li>MAOI (monoamine oxidase inhibitors): methadone is an SSRI - avoid</li> </ul> </li> </ul>
<b>Communication</b>	<ul style="list-style-type: none"> <li>To inform specialist of concerns about inadequate pain control or adverse effects</li> </ul>

## Summary of the clinical condition

*(The specialist completes the summary section below, including advice for a particular patient that differs to the standard shared care arrangements. Copies of the entire shared care document, including this summary, are kept in the clinical notes, sent to the GP and offered to the patient)*

- **Diagnosis**

- Underlying disease:
  
  
  
  
  
  
  
  
  
  
- Pain mechanism (e.g. neuropathic pain):

- **Current regimen**

- Dose and frequency:
  
  
  
  
  
- Route:
  
  
  
  
  
- Formulation and strength of preparation (**beware of confusion between different strength preparations**):
  
  
  
  
  
- Date initiated:
  
  
  
  
  
- Date current regimen reached:

- **Relevant co-morbidities, abnormal baseline observations or tests, or other factors relevant to the use of methadone:**

<b>When GP could assume responsibility</b>
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- |   |
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| <ul style="list-style-type: none"><li>• The patient has been initiated on the treatment by a consultant in pain or palliative medicine and it is considered clinically appropriate to transfer care.</li></ul> <p style="text-align: center;">AND</p> <ul style="list-style-type: none"><li>• Shared care has been agreed in accordance with these guidelines between the consultant and the GP</li></ul> |
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## Methadone for refractory pain

### Background information and common problems

#### Key differences from morphine

- Methadone has several additional actions that are helpful for morphine-poorly responsive pains
- It can accumulate – it takes one or more weeks to reach steady state after dose adjustments
- It has clinically important drug interactions
- Thus toxicity can develop unexpectedly after taking an apparently well tolerated stable dose

#### Licensing status and obtaining supplies in the community

Methadone is a Schedule 2 Controlled Drug. It is prescribed on an FP10 in the same way as other controlled drugs – **the restrictions and prescription forms used in addiction do not apply**. Writing “please label ‘for pain’” on the FP10 avoids confusion about the indication.

Methadone is licensed for use in severe pain. However, it is an amber drug (for initiation by specialists) due to difficulties with dose titration and accumulation. One of four preparations is used, depending on the dose and route:

- **Oral solution (1mg/ml)**
- **Oral solution (10mg/ml):** particularly to minimise the volume needed where higher doses are used (Methadose 10mg/ml from Rosemont Pharmaceuticals, tel: 0113 2441999 Fax: 0113 2460738)
- **Oral tablets (5mg)**
- **Subcutaneous:** Methadone for injection (10mg/ml) in 1ml, 2ml or 5ml ampoule sizes

#### Starting methadone

Methadone is used for pain refractory to usual measures (e.g. opioids combined with anti-epileptics and tricyclic antidepressants). Like ketamine, it reduces the hyperexcitability (central sensitisation) sometimes responsible for refractory pain by blocking NMDA-glutamate receptors.

Three approaches to dosing are used, depending on the setting. All require medical staff experienced in its use. There is no straightforward conversion ratio between methadone and other opioids such as morphine and accumulation can result in a delayed onset of toxicity.

- **Cross-tapering.** The previous opioid is gradually reduced and the methadone gradually increased. Takes time (weeks) but can often be done in the home setting.
- **Switching.** The previous opioid is stopped abruptly and the methadone commenced. Requires 24hr oversight and thus usually only possible in an inpatient specialist palliative care unit.
- **Parallel use.** A low dose of methadone is added alongside the existing opioid. Dosing is simpler but the patient is left with a more complex regimen to take.

#### Adverse effects

Methadone's adverse effects are generally similar to morphine and other strong opioids. The important differences are:

- **Accumulation resulting in delayed toxicity (e.g. respiratory depression).** This can occur despite well tolerated stable doses for days or weeks
- **Drug interactions resulting in unexpected toxicity.** Important examples are listed on page 1
- **Arrhythmias due to QT prolongation.** Case reports include fatal arrhythmias but mainly involve people treated for opioid addiction (dose regimens differ). The clinical significance in pain medicine is unclear but pre- and post-methadone initiation ECG monitoring can be used in patients at particular cardiovascular risk.

## Subcutaneous methadone

Consider prescribing subcutaneous methadone pre-emptively in patients at risk of losing the oral route (e.g. those approaching the end of life). Few community pharmacies stock parenteral methadone, so allow additional time if possible.

Subcutaneous methadone is given:

- via a 24 hour subcutaneous syringe pump
- at a dose **half** that of the previous 24 hour oral dose (e.g. methadone 20mg b.d. PO would be equivalent to 20mg over 24hrs via syringe pump)
- using water or sodium chloride 0.9% as a diluent
- data on combining methadone with other drugs in syringe drivers is given below

	<b>Compatible 2, 3 and 4 drug combinations</b>	<b>Diluent</b>
Methadone <i>plus</i> :	cyclizine	Water
	clonazepam	Sodium chloride 0.9%
	haloperidol	Water or sodium chloride 0.9%
	hyoscine butylbromide	Water
	levomepromazine	Water
	midazolam	Water or sodium chloride 0.9%
	ketamine	Water or sodium chloride 0.9%
Methadone <i>plus</i> :	clonazepam and haloperidol	Water or sodium chloride 0.9%
	clonazepam and levomepromazine	Sodium chloride 0.9%
	haloperidol and hyoscine butylbromide	Water or sodium chloride 0.9%
	haloperidol and midazolam	Water or sodium chloride 0.9%
	levomepromazine and hyoscine butylbromide	Water or sodium chloride 0.9%
	levomepromazine and midazolam*	Water or sodium chloride 0.9%
	midazolam and hyoscine butylbromide	Water or sodium chloride 0.9%
	Ketamine and midazolam	Water
Methadone <i>plus</i> :	haloperidol, midazolam and hyoscine butylbromide	Water
	levomepromazine, midazolam and hyoscine butylbromide	Sodium chloride 0.9%
	Haloperidol, ketamine and midazolam	Water

\*If the methadone dose is greater than 40mg, use a 30ml syringe to maximise the dilution. Dose-dependent crystallisation reported

## Appendix 3. Pharmacist information

(please detach this page and ask the patient to take it along with the FP10 to their community pharmacist)

### Dear pharmacist,

This patient is receiving methadone for refractory pain. This has been initiated by a specialist in pain or palliative medicine. Please find information below to facilitate its supply.

### Indication

Methadone is used for pain refractory to usual measures (e.g. opioids combined with anti-epileptics and tricyclic antidepressants). Like ketamine, it reduces the hyperexcitability (central sensitisation) sometimes responsible for refractory pain by blocking NMDA-glutamate receptors. It is used instead of, or in combination with, ketamine where the latter is insufficient or its use precluded. Methadone is widely prescribed by Specialist Palliative Care and Pain teams in Great Britain - further information may be obtained from:

- The pain or palliative care team
- Palliative Care Formulary 4<sup>th</sup> Edition. Twycross *et al* 2011, Radcliffe Medical Press

### Licensing status and Use by Non-Specialists

Methadone is licensed for use in severe pain. However, it is initiated by specialists due to difficulties with dose titration and accumulation.

One of four preparations is used, depending on the route:

- **Oral solution (1mg/ml)**
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