North Central London
Joint Formulary Committee

Shared Care Guideline
Methadone for Treatment of Pain
In Adult Palliative Care

Dear GP

The information in the shared care guideline has been developed in consultation with Primary Care and it has been agreed that this medication it is suitable for shared care.

Sharing of care assumes communication between the specialist, GP, and patient. The intention to share care should be explained to the patient by the Consultant when treatment is initiated. It is important that patients are consulted about treatment and agree with it.

Contents

1.0 Introduction

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing methadone for the treatment of pain in adult palliative care. This shared care is not used for the use of methadone for cough in palliative care (due to the differences in dosing and management); for this indication, individualised shared care arrangements should be considered.

Background Information

Methadone is a synthetic strong opioid agonist at the mu- and delta-opioid receptors and is also an NMDA antagonist.[1,2] Methadone is a highly lipophilic drug that is subject to considerable tissue distribution and sequestration, and it has a characteristically long half-life in plasma of around 24 hours (but ranging from 8 to 75 hours). Methadone is mainly metabolized in the liver to several inactive metabolites. It is then excreted via the intestine and kidneys. However renal and hepatic impairment does not significantly affect methadone clearance. Tissue accumulation of methadone occurs when repeated doses are given and there is potential for toxicity, especially during the initial titration period. Also, there is a considerable inter-individual variation in methadone pharmacokinetics, which translates to the dose conversion and titration is difficult to predict accurately.

Methadone should only be started in the palliative care setting by specialists experienced in its use. Patients will usually be admitted to a specialist palliative care unit when switching from another opioid to methadone or the switch will be undertaken by the specialist team. This enables a controlled dose titration period. Where the switch to methadone is successful (i.e. improved pain relief and/or reduced toxicity), methadone can be considered for prescribing in primary care with the patient remaining under the supervision of the relevant specialists.

Progressing to a stable, optimal dose usually takes approximately 4 weeks or longer. Once achieved, a shared care arrangement with you will be requested. It will clarify responsibilities between the specialist and general practitioner (GP) for managing the prescribing of methadone such as:

- Who will prescribe;
- Who will monitor;
- Any tests required (e.g. blood tests), the exact names/nature of the tests, why they are needed, the frequency of testing, the location in which these will be carried out and action to be taken for any abnormal results
- Which clinician will be responsible for receipt and review of the results;
- Who will communicate any necessary changes in dose to the patient and the GP;

Please note that for some conditions and/or drugs, a Patient-Held Monitoring and Dosage Record booklet is required, in which case, in addition to all the above, the shared care guideline should also clarify who is responsible for recording the test results in this booklet.

2.0 Shared Care criteria

Patients who are stabilised on methadone, for pain control who are under palliative care services within the NCL region and have been monitored appropriately at baseline, and after initiation of treatment with no problems that have been identified during this period.

3.0 Shared care responsibilities

3.1 Consultant and /or Specialist Nurse

Send a letter to the GP along with shared care criteria and the transfer form requesting shared care for this patient. Indication, dose and frequency to be decided by the hospital team.

1) Initiate treatment and prescribe until the GP formally agrees to share care (until the patient is stabilised or according to Section C for local minimum supply durations). Treatment should only be initiated if the GP has agreed to shared care before starting.
2) Discuss the shared care arrangement with the patient.
3) Provide results of any baseline tests and any additional tests and recommended frequency of monitoring with the GP. The consultant must also explain what the recommended tests are, why they are needed, and the location in which these tests will be carried out.
4) Inform the GP of blood test results and actions to take in case of abnormal results, and advise the GP on when to adjust the dose, stop treatment, or consult with the specialist team.
5) Periodically review the patient's condition and communicate promptly with the GP when treatment is changed. Counsel the patient on any dose changes that are made during specialist appointments or reviews.
6) Evaluate adverse effects reported by the GP or patient.
7) Report adverse events to the MHRA (via the yellow card scheme) and the GP.
8) Inform GP of patients who do not attend appointments/reviews
9) Ensure that clear backup arrangements exist for GPs to obtain advice and support.
10) Initial assessment of the appropriateness of Methadone will be undertaken by the specialist.
11) Consider and assess for the risk of long QT syndrome e.g. those with:
    - ➢ a history of cardiac conduction abnormalities
    - ➢ a family history of sudden death
    - ➢ advanced heart disease or ischaemic heart disease
    - ➢ liver disease
    - ➢ electrolyte abnormalities
    - ➢ concurrent treatment with drugs which:
        - ▪ may cause electrolyte abnormalities
        - ▪ have the potential to prolong QT
        - ▪ inhibit CYP3A4 cytochrome isoenzymes.
12) Obtain informed consent; ensure the patient understands the dosing, the benefits, side effects, intended outcomes, and possible drug interactions of treatment. Provide the patient with a patient information leaflet (PIL).
13) Undertake any baseline monitoring prior to initiation of Methadone (tests may need to be obtained via the GP under certain circumstances especially when the patient is not an inpatient. This is due to the palliative care community teams lacking direct access to community phlebotomy):

    ➢ Measure electrolytes and correct them as appropriate – especially for hypokalaemia, hypomagnesemia, hypocalcaemia & hypophosphatemia.
14) Perform baseline ECG as required:

    ➢ QT interval prolongation and, rarely, a serious ventricular arrhythmia (torsade de pointes) have been observed during treatment with methadone. Generally, the latter is associated with, but not limited to, higher-dose treatment (> 100mg/24h).
15) Consider using a Opioid Toxicity Monitoring chart when making changes to methadone dosing (which can be completed by the patient at home). The chart can be continued throughout treatment, but the specialist may decide to stop formal monitoring in patients on an established stable dose with no concerns. An example Opioid Toxicity Monitoring chart

can be seen in the CNWL guidance (Appendix 3) – it is recommended any chart should contain:

- ➢ Respiratory rate
- ➢ Conscious Level
- ➢ Symptoms of opioid-induced neurotoxicity:
  - ▪ Myoclonus, myoclonic jerks
  - ▪ Hallucination
  - ▪ Delirium/Confusion.

16) Prescriptions for Methadone during the initial dose titration are to be written by the specialist unless the GP agrees to take on the prescribing of the first dose.
17) Prescription of a further 14 days of Methadone to be supplied once a stable dose has been achieved and shared care agreed upon with the GP.
18) When prescribing, state the formulation, strength, and number of milligrams to be taken with the frequency and the total quantity to be supplied in words and figures.
19) Notify the community pharmacist nominated by the patient so community supplies can be obtained and the clinical details for safe dispensing provided (see CNWL guidelines).
20) Stop the methadone treatment if it is no longer considered to be appropriate.
21) To arrange a named Palliative Care physician to monitor the efficacy and tolerability and adjust dose where required on an ad hoc basis as required. If the dose is altered, additional closer monitoring should be undertaken for two weeks following the dose alteration.
22) To arrange timely reassessment of the patient if the GP raises a concern.
23) Ask the GP whether he or she is willing to participate in shared care by emailing the shared care request letter (continue to prescribe until GP has agreed to take over prescribing).
24) Ensure all documentation is sent to the GP; must include a clinical letter stating indication for pain management and contact details for urgent queries, the patient's dosage regimen including formulation, outcomes of reviews, and dose amendments as appropriate.

3.2 General Practitioner

Complete the transfer form and send it back to the palliative care specialist confirming acceptance/ rejection of shared care for the patient. If GP is unable to agree to shared care, inform the palliative care specialist stating reasons within ***14 days*** of receipt of the request. If no response is received within 14 days, the Consultant will assume the GP has accepted shared care.

1) Monitor the patient's overall health and well-being
2) Prescribe the drug treatment as described (but not alter the dose unless advised to do so by the specialist). The term "as directed" **SHOULD NOT** be used
3) Ensure that the patient understands the dosing
4) Ensure the patient understands that he/she must report the warning symptoms as listed under "adverse effects"
5) Ensure compatibility with concomitant medication
6) Monitor results at recommended frequencies as described under "clinical monitoring" and inform the Consultant if abnormal
7) Adjust the dose as advised by the specialist (where applicable) and counsel the patient on any dose changes

8) Refer back to a specialist if the patient's condition deteriorates, or if there are concerns over patient compliance, or on any aspect of patient care of concern to the GP that may affect treatment.
9) Stop treatment on the advice of a specialist or immediately if an urgent need arises
10) Help in monitoring the progression of the disease and inform the palliative care specialist of any changes to medication (see Table 2).
11) Reply to the request for shared care as soon as practicable, preferably within 14 working days, by emailing back the shared care letter.
12) If declining this request, please indicate the reason for declining.
13) Prescribe the Methadone at the dose recommended, from the agreed date, by the strength and formulation as defined by the consultant.
14) Be aware of key drug interactions with Methadone and seek advice if needed prior to initiating any medications which can interact with Methadone.
15) Report adverse events to the MHRA on a Yellow Card at www.mhra.gov.uk/yellowcard and to the specialist and appropriate Medicines Optimisation team.
16) All requests for repeat prescriptions should ideally be reviewed individually prior to issuing them.

3.3 Patient responsibility

1) Take medicines as agreed
2) Inform the palliative care specialist and GP of any changes in address or telephone numbers
3) Attend all appointments with GP and specialist.
4) Report to the specialist or GP if he or she does not have a clear understanding of the treatment. Be aware of further information must be provided if driving a motor vehicle or you plan to travel outside the UK.
5) Agree to any required routine blood monitoring health checks for the duration of treatment.
6) Share any concerns in relation to treatment with methadone
7) Inform the specialist or GP of any other medication being taken, including over-the-counter products/ alternative therapies.
8) Report to the GP or specialist as soon as possible should his/her condition significantly worsens.
9) Report any adverse effects or warning symptoms to the specialist or GP.
10) The patient may also choose to report any adverse drug reaction direct to the MHRA on a Yellow Card, available at pharmacies, GP surgeries, or from the Yellow Card hotline (freephone 0808 100 3352 during business hours). The form can also be downloaded from www.mhra.gov.uk/yellowcard

3.4 Integrated Care Boards

1) To provide feedback to Trusts from the standard letter, via the shared care forum.
2) To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3) To support NHS Trusts in resolving issues that may arise as a result of shared care.

4.0 Indications

Methadone is only used as a third-line opioid for patients with complex pain that is poorly responsive to other opioids, or where these opioids have resulted in intolerable side effects. However, in patients who are already using it as replacement therapy for substance misuse, it may be considered earlier than as a 3rd line option.

Methadone can be useful for the following problems:

- inadequate analgesia with conventional strong opioids, e.g. for patients whose opioid dose is rapidly escalating but with incomplete benefit, or for those for whom dose increase is limited by toxicity symptoms
- opioid induced neurotoxicity (hyperalgesia, allodynia +/- myoclonus, sedation, delirium, complex neuropathic pain
- in the treatment of difficult pain in patients with end-stage renal disease where other opioids are not effective or unsuitable (eGFR < 30mls/min)
- in true morphine allergy
- as analgesia for patients already using methadone for opioid dependency

National Institute for Health and Clinical Excellence (NICE)

There are no NICE guidelines on the use of methadone for pain; however, the use of methadone as an analgesic is well-established within palliative medicine. See the Palliative Care Formulary (PCF7) third edition.

Licensing: Not all preparations are licensed for use as an analgesic in moderate to severe pain. However, it is initiated by specialists due to difficulties with dose titration and risks of accumulation. The specialist will initiate this product during the titration period which should then be maintained throughout treatment at a dose recommended by them. One of a number of preparations may be used, depending on route and dosage.

Prescribing: When used for this indication Methadone should be prescribed on an FP10 prescription in the same way as other schedule 2 controlled drugs – the restrictions and prescription forms used for the management of addiction do not apply.

5.0 Dose and Administration

Dose and administration

The initial dose and regime will be recommended by the palliative care specialist (along with the initial prescription), and all relevant details will be sent to the GP (such as GP the rationale for methadone treatment, the correct dose, formulation and quantity). Any dose adjustments recommended by the specialist will be communicated to the GP in writing to enact from the next prescription (it will also be communicated verbally/in writing to the patient in cases of an immediate adjustment).

In terms of switching from existing treatments, there is no straightforward conversion ratio between methadone and other opioids such as morphine. Accumulation can result in a delayed onset of toxicity. Thus, dose titration is extremely difficult and is usually undertaken in an inpatient setting where both nursing and medical staff are experienced in its use.

Several guidelines exist for switching from morphine to methadone, but all require practitioners to be experienced in the use of methadone and close observation of the patient, generally as an inpatient. Carefully controlled outpatient regimens can be used, but pain relief can take weeks rather than days to achieve. Local specialists generally choose to reduce the regular dose of opioids and gradually upwardly

titrate the methadone until an effective dose is reached and the current opioid has been discontinued (anecdotally, this usually ends with the patient being stabilised on a lower methadone dose). Maintenance doses vary considerably, but most are prescribed at less than 100mg daily. Methadone doses are generally split into twice daily dosing, although occasionally three times daily dosing is used.

Oral to subcutaneous conversion

For use during temporary or permanent loss of oral route (e.g. vomiting or end-of-life care). Discuss this with the pain or palliative care consultant. If required, subcutaneous methadone is given:

- via a 24-hour subcutaneous syringe driver;
- 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 a syringe driver;
- Using water or sodium chloride 0.9% can be used as a diluent.
- There is limited data on combining methadone with other drugs in syringe drivers: discuss with the pain or palliative care team

Preparations available

Table 1 - Approved Formulations of Methadone to Prescribe**

Oral formulations	Preferred option **Methadone oral solution 1mg/ml** Must specify sugar-free when specifically required* Usually green in colour The bottle containing the liquid methadone preparation should always be shaken before use. Patients should use a syringe to measure the liquid methadone preparation, to ensure the accuracy of the volume ingested. **Methadone tablets 5mg**	NB: concentrated oral solutions (10mg/ml and 20mg/ml) **are not** to be prescribed. Methadone linctus **is not** to be prescribed for pain control
Parenteral formulations	**Methadone injection** 10mg/1ml solution for injection ampoules Ampoules containing 1, 2, 3.5, or 5ml of solution are usually available.	Concentrated ampoules (50mg/ml) **are not** recommended and should not be used unless exceptionally high CSCI (continuous subcutaneous infusion) doses are required.

*Bitter taste can be masked. The oral solution can be diluted in water or any juice (except grapefruit) for enhanced palatability.

** other unlicensed formulations may be available from specialist manufacturers including suppositories that can be compounded for rectal administration.

6.0 Adverse Effects

Adverse effects with methadone are generally similar to morphine and other strong opioids. The important differences are: -

- Accumulation resulting in delayed toxicity (e.g. respiratory depression) can occur despite well-tolerated stable doses for days or weeks.
- Drug interactions resulting in unexpected toxicity can occur.

- Arrhythmias due to QT prolongation can occur. 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.

GPs are asked to monitor the patient for potential adverse effects. Table 2 (below) outlines the more common adverse effects and their appropriate management. A larger list of adverse effects can be seen below. Any adverse effects experienced which is not transient should be communicated to the initiating clinician.

Table 2 – Monitoring issues with methadone and their management

Problem	Explanation	Management
Drowsiness	This may indicate accumulation; it can herald respiratory depression and should thus prompt same-day assessment	If a delay in assessment cannot be avoided, consider asking the patient to omit or reduce their methadone and use top-up doses of shorter-action opioids, e.g. Oramorph, if needed
Electrolyte disturbance	This increases the risk of QT prolongation and arrhythmia	Correct the electrolyte imbalance
Use of different preparations	Concentrations of liquid preparations vary; significant dose changes can result from changes in concentration	Avoid unnecessary changes in the concentration of methadone liquid; ensure any change is effectively communicated to the patient and other team members
Respiratory depression	This can result from unrecognised accumulation	Provide basic life support while awaiting paramedic assistance; administer naloxone (small boluses of 100micrograms every 5 to 10 minutes) if available; naloxone is cleared more rapidly than methadone and so patients will require prolonged careful monitoring despite initially improving

Common – nausea, vomiting, constipation, dry mouth, biliary spasm, respiratory depression, drowsiness, muscle rigidity, hypotension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, dependence, confusion, urinary retention, ureteric spasm;

Uncommon – restlessness, dyspnoea, hypoventilation, depersonalization, dysarthria, amnesia, incoordination, paraesthesia, malaise, agitation, tremor, muscle weakness, hypertension, dizziness, itching, bronchospasm, dysmenorrhoea, dry eyes, hyperprolactinaemia; and

Rare – QT interval prolongation, torsades de pointes, hypothermia, circulatory depression, cardiac arrest, hiccups, arrhythmia, paralytic ileus, haemoptysis, psychosis, seizures, shock, asystole, pyrexia, ataxia, muscle fasciculation, raised intracranial pressure

Effects on ability to drive and operate machinery: Methadone can affect the ability to drive or operate machinery. The time after which such activities can be safely resumed is patient-dependent. Patients should be informed of the impact on the ability to drive, and not to drive until it is known how methadone affects the individual. It is an offence to drive while under the influence of medicine.

Pregnancy and Breastfeeding: There is potential for adverse effects harming a foetus and neonate, including respiratory depression. A careful benefit/risk assessment must be made. It should not be used during labour. Specialist advice should be taken under these circumstances.

Methadone does not have black triangle ▲status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the CHM. Refer to summary of product characteristics (SPC)[2] for a full list of side effects – see references.

7.0 Cautions

Cautions in the prescribing of methadone include the following: -

- Significant sleep apnoea
- Raised intracranial pressure
- Prolonged QTc interval: >450 ms
- Concurrent administration of some drugs that might result in significant drug interactions or known to impact the clearance and/or protein binding
- Drinking alcohol (may result in increased plasma levels and fatal overdose) and benzodiazepines.
- Pain is suspected to have a strong psychological component as repeated demands for as-needed doses of methadone may lead to opioid toxicity.
- Methadone should also be used with caution in patients with a history of asthma, convulsive disorders, depressed respiratory reserve, hypotension, shock, prostatic hyperplasia, adrenocortical insufficiency, inflammatory or obstructive bowel disorders, myasthenia gravis or hypothyroidism.

For a full list of cautions, refer to the Summary of Product Characteristics.[3]

8.0 Clinical Monitoring

No specific routine monitoring is required for methadone by the GP other than general monitoring for side effects (see Table 2 in Section 6.0); Any suspected adverse reactions should be reported using the Yellow Card Scheme**.**

The clinical picture may require basic tests such as BP & pulse if the need arises. Certain patients may require additional tests for urea and electrolytes. GPs should review their patients as per their normal practice. The specialist may suggest additional investigations as required. The results should be discussed with the specialist if they are undertaken by the GP and are found to be abnormal.

Additional ECGs should only be required to be undertaken by the GP if the specialist team has produced an additional monitoring plan. However**,** on some occasions it can be desirable, e.g. when prescribing daily doses of methadone above 100mg or a new clinical situation arises such as a new major drug interaction due to medication changes. The specialist team may either request these to be undertaken directly via the GP or when the clinical issue is identified by the primary care team; the specialist team should be willing to provide the clinical advice on whether further ECG/s are required.

9.0 Contraindications

- Concurrent pentazocine, nalbuphine, and butorphanol administration - may precipitate withdrawal symptoms
- Patients with mild, intermittent, or short-duration pain that can be managed with other pain medications, acute unstable pain
- Relative contraindication: Prolonged QTc defined as >500 ms for males and >470 ms for females
- Conversion from other opioids to methadone is contraindicated if the patient is moribund or confused because initial titration requires significant patient involvement.
- Hypersensitivity to the active ingredient or any excipients
- Pheochromocytoma;

- Respiratory depression, obstructive airways disease and during an acute asthma attack;
- Acute alcoholism;
- Head injury and raised intracranial pressure;
- Concurrent administration with monoamine oxidase inhibitors or for two weeks after stopping;
- Use during labour (increased risk of neonatal depression);
- Children (serious risk of toxicity)
- Patients with ulcerative colitis (as methadone may precipitate toxic dilatation or spasm of the colon);
- Patients at risk of paralytic ileus;
- Patients dependent on non-opioid drugs;
- Patients with severe hepatic impairment (as it may precipitate encephalopathy);
- Patients with biliary and renal tract spasm.
- Outside of specialist palliative care units – Patients unable to engage with and participate in a tight and carefully monitored patient management plan

For a full list of contraindications, refer to the Summary of Product Characteristics. [2]

10.0 Drug Interactions

- Avoid concurrent administration of MAOIs or within 2 weeks of discontinuation of their use
- Methadone is metabolised by hepatic CYP3A4 & CYP2B6 enzymes. Co-administration with drugs that are metabolised by or affect the activity of these pathways may lead to clinically relevant drug interactions including:
    - Drugs that may ↑ plasma concentration of Methadone: azole antifungals, amiodarone, ciprofloxacin, cimetidine, Erythromycin, SSRIs, quinidine, and grapefruit juice
    - Drugs which may ↓ plasma concentration of Methadone: carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort, some antiretrovirals
- An additive risk of QT prolongation with other drugs which can prolong QT interval (see appendix 1 of the BNF for a full list of drugs that can prolong QT interval).
- For a full list of drug interactions, refer to the CNWL guidance (Appendix 1: Drug Interactions with Methadone); alternatively, please refer to the relevant Summary of Product Characteristics (via https://www.medicines.org.uk/emc/) or BNF.

11.0 References

1. Howard, R. and Howard, P. (2012), What GPs need to know about palliative-care drugs: methadone. Prescriber, 23: 34-38. https://doi.org/10.1002/psb.959
2. Sunilkumar MM, Lockman K. Practical Pharmacology of Methadone: A Long-acting Opioid. Indian J Palliat Care. 2018 Jan;24(Suppl 1):S10-S14. doi: 10.4103/IJPC.IJPC_180_17 PMID: 29497249; PMCID: PMC5806300.
3. SPCs. Accessed at https://www.medicines.org.uk/emc/

12.0 Associated documents

Guidelines on the use of Methadone for Pain Control within CNWL Palliative Care Services

13.0 Contact Details

Address:	Address: UCLH & HCA Services office:

Camden and Islington Community Palliative Care Team Service office: 5th Floor South Wing St Pancras Hospital 4 St Pancras Way London NW1 0PE Please note, the Camden office's postal address is different. Please send any post or deliveries to: - Camden, Islington ELiPSe and UCLH & HCA Palliative Care Service University College Hospital 235 Euston Road, London NW1 2BU	2nd Floor Wing B Maple House 149 Tottenham Court Road London W1T 7NF
Telephone: The service is open seven days a week-9 am to 8 pm.	If you need to speak to the team: - South Camden and North-East Westminster telephone 020 3317 5777 Islington's telephone 020 3317 5777 (the team is based at Camden and Islington Community Palliative Care Team Service, St Pancras Hospital, 4 St Pancras Way, London, NW1 0PE) UCLH and HCA telephone 020 3447 7140
Out of hours:	Currently unavailable except for the hours specified above.

Document control

Date	Version	Amendments
November 2023	1.0	Share Care produced by CNWL specialists and NCL ICB Barnet borough Medicines Management Team Agreed by NCL Shared Care Group: 14th November 2023

Appendix 1: Methadone transfer form: from [Trust] to GP practice

Section A: to be completed by secondary care *Send to practice*

This document is to request the shared care pathway of your patient and comprises an agreement between the GP and named consultant. The patient will continue to be seen by the named consultant as regular follow up.

Fix address label here (ensure NHS no.on)	Clinic stamp *or give details below*

Department

Clinic phone

Consultant Email

Indication for prescription

Drug prescribed

Date Drug started Current dose

Relevant conditions

Monitoring variations

Date next blood test Next disease review due in months' time.

Section B: [Accept Shared Care] to be completed by practice *Send back **FAO referring consultant** above*

The above patient has been accepted into our monitoring service.

Practice date for next blood test		Practice stamp
Signed / Designation		
Date		

Section B: [Reject Shared Care] to be completed by practice *Send back **FAO referring consultant** above*

The above patient has not been accepted into our monitoring service.

Reason		Practice stamp
Signed / Designation		
Date		