Guidance for the Prescribing of Oral and Subcutaneous Methadone (Amber-G)

Introduction

This document sets out guidance for the assessment and treatment of those patients prescribed methadone within specialist palliative care settings, and delineated responsibilities when care for the patient is initiated in Secondary Care and transferred to Primary Care for continuation.

It is intended to provide clear guidance to General Practitioners (GPs) and specialists regarding the procedures to be adopted when clinical responsibility for a patient's treatment using methadone is shared between secondary and primary care.

Background Information

Methadone is a synthetic strong opioid agonist at the mu- and delta- opioid receptors and is also an NMDA antagonist. Methadone is a non-acidic and 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 do 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 considerable inter-individual variation in methadone pharmacokinetics, which means that 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. This is to enable 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 in primary care with the patient remaining under the supervision of the relevant specialists.

Indications for use

- Poorly controlled pain where intolerable side effects (e.g., nausea, vomiting, sedation, hallucinations) have prevented dose escalation of another opioid
- Refractory pain or difficult pain syndromes (including neuropathic pain)
- Neurotoxicity with opioids at any dose (e.g. myoclonus, allodynia, hyperalgesia) which does not respond to a reduction in morphine dose

and switching to another easier-to-use opioid (e.g. fentanyl, hydromorphone, oxycodone) is not possible
- Renal impairment

It should be initiated only under consultant in palliative medicine supervision.

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. Palliative Care Formulary (PCF7) third edition.

Dosage

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 and this is rarely considered locally.

Local specialists generally choose to reduce the regular dose of opioid 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 all current patients under Doncaster and Bassetlaw consultants are prescribed less than 50mg daily. Methadone doses are generally split into twice daily dosing, although occasionally three times daily dosing is used.

Alternatively, PCF 7 favors a ‘stop and go’ approach (Morley-Makin method), i.e. the abrupt cessation of the opioid and introduction of methadone p.r.n over a period of five days. On day six, a regular twice daily oral maintenance dose can be calculated and commenced. Maintenance doses vary considerably, but most are <80mg/24h.

For information only (GPs will not be asked to prescribe parenteral methadone):

When switching from methadone PO to SC, a safe conversion is to halve the methadone PO dose. However, for some patients, particularly those receiving a small dose of methadone (<80mg/24h), a 1:1 conversion ratio may be more appropriate and subsequent upwards dose titration may be required.

Administration

Unless indicated otherwise, all preparations are classed as a controlled drug Schedule 2, and as such are subject to controlled drug prescription requirements and safe custody requirements. Methadone (non-proprietary)

Methadone Tablets 5mg preferred

Methadone Oral solution 1mg/ml (various volumes)

When prescribing methadone, all prescriptions should conform to the legal requirements for controlled drugs. Please ensure that the number of milligrams of methadone and the frequency are documented and that the formulation is included on the prescription, for example:

Methadone 5mg tablets 2 tablets twice daily

Total quantity: 50 (fifty) tablets

Adverse events

As for all strong opioids.

For a full list, see manufacturers' SPCs via www.medicines.org.uk

Prolonged QT interval:

Methadone can cause dose-related prolongation of the QT interval. There is the potential risk that co-administration with other drugs that also prolong the QT interval (e.g. amiodarone, erythromycin, quinine) may result in ventricular arrhythmias. Electrolyte disturbances must be corrected (e.g. hypokalaemia) because of the risk of prolonged QT prolongation. ECG monitoring is recommended for doses >100mg daily (unlikely in palliative care).
Where a patient is on a dose >100mg daily they will revert to the care of the consultant who will be responsible for the appropriate monitoring

Drug Treatment Summary

For contraindications or further information please see the current BNF http://www.bnf.org.uk/bnf/bnf/current/index.htm or summary of product characteristics for the individual drug http://www.medicines.org.uk/

Drug Dose & TLS Listing	Adverse Effects	Therapeutic Monitoring	Consultant / GP	Clinically relevant drug interactions
1. Methadone (Specialist Palliative Medicine)				
1.1 Methadone (AMBER-G)				
Initiation Dose Initiated under the consultant in palliative medicine (CiPM) supervision **Maintenance dose** A twice daily maintenance dose will be established by the CiPM. Maintenance doses vary considerably, but most are <80mg/24h, however in some cases higher doses may be required (see notes above).	Strong opioids tend to cause similar undesirable effects, albeit to varying degrees, the frequency is not defined, but reported undesirable effects include; ▪ Anorexia ▪ Asthenia ▪ Biliary pain ▪ Confusion ▪ Constipation ▪ Drowsiness ▪ Dry mouth ▪ Dyspepsia ▪ Exacerbation of pancreatitis ▪ Euphoria Insomnia ▪ Headaches ▪ Hyperhidrosis ▪ Myoclonus ▪ Nausea ▪ Pruritus ▪ Sexual dysfunction (e.g. amenorrhea, decreased libido, erectile dysfunction)	**Baseline assessment before initiation** ● Serum electrolytes ● ECG if history cardiac conduction abnormalities, advanced heart disease or ischemic heart disease, family history of sudden death, concomitant treatment with drugs that have the potential for QT-prolongation and/or drugs that may cause electrolyte abnormalities **Ongoing monitoring** ● Patients with recognised risk factors for QT-prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring >100mg daily. This includes electrolyte and ECG monitoring if appropriate. When reviewing the patients the CiPM will take into consideration the risks versus benefits of the treatment, and depending on the stage of the illness whether or not it is appropriate for ongoing ECG/electrolyte monitoring.		● Methadone is metabolised mainly by CYP3A4 and CYP2B6 ● Amiodarone may increase methadone concentration ● Antidepressants: Amitriptyline, SSRI: Fluoxetine, Paroxetine, Sertraline – may increase increase Methadone concentration ● Antiepileptics: Carbamazepine, Phenobarbital - reduces effect of methadone ● Antibiotics: Ciprofloxacin, Erythromycin - may increase methadone concentration ● Clopidogrel may increase methadone concentration ● **Fluconazole – may increase methadone concentration** ● Drugs which prolong the QT interval, potential risk with co-administration with other drugs that also prolong the QT interval. ● Antihypertensives increase risk hypotension ● CNS depressants- risk of excessive sedation ● Ketamine- there is potential opioid-sparing effect with ketamine and the doses of methadone may need reducing. ● Haloperidol & levomepromazine – may be an additive hypotensive effect and additive QT effect. ● Avoid Grapefruit juice- may increase dose methadone

	▪ Urinary retention ▪ Vertigo ▪ Visual disturbance ▪ Vomiting Excessive dose: ▪ Agitation ▪ Exacerbation of pain ▪ Hallucinations ▪ Miosis ▪ Paraesthesia ▪ Respiratory depression ▪ Restlessness	Review patient for continued need of medication and dose escalation retaining patients on doses >100mg daily Review patient on request from GP (if and when required) **General** ● Side Effects ● Symptom control ● Refer to the consultant in palliative medicine if escalating levels pain not controlled on maintenance dose methadone ● Refer to the CiPM if assessment of condition required ● Refer to the CiPM if unable to take oral methadone. This includes patients entering the terminal phase of their illness or for those patients unable to keep oral medication down due to nausea and vomiting	**Please note this is not a complete list – Please refer to the current BNF and SPC for further information**

Arrangements
Once a stable medication regime has been established, the physical monitoring and prescribing of oral methadone can be transferred to primary care.

Aspects of care for which the Consultant in Palliative Medicine is responsible

- Assess patient's suitability for pain control with methadone and obtain informed consent
- Initiation and stabilisation of methadone.
- Assess response and side effects.
- Arrange shared care with the General Practitioner when the patient is managed on a stable regime. Written communication with General Practitioner must include:
    - A copy of, or reference to (eg. hyperlink), this prescribing guidance
    - A contact for urgent queries out-of-hours
    - A detailed letter outlining individual patients dosing regime
- Notify Community Palliative Team and community nursing staff
- Ensure that all patients when discharged to their General Practitioner for management have at least one month supply to ensure continuity of supply at home.
- When prescribing, state the quantity to be taken, the formulation, strength and total quantity in words and figures.
  eg. Methadone 5mg tablets 2 tablets twice daily
  Total quantity: 50 (fifty) tablets
- Ensure that the patient/guardian/carer is fully informed of potential benefits and side effects of treatment.
- Ensure that the patient/guardian/carer is clear what is being monitored and by whom
- Ensure that the patient knows what significant adverse effects/events to report urgently and to whom they should report (consultant in palliative care or GP)
- Review the patient's response and continuing appropriateness of the methadone at regular intervals. Write to the GP after every assessment detailing whether the medication regime should remain the same or be changed. Specify any preparation, dose or frequency changes.
- Monitor side effects of medication.
- Report adverse events via the Yellow Card reporting system in the BNF or at yellowcard.mhra.gov.uk

Aspects of care for which GP can undertake

- Once stable, prescribe methadone and arrange ongoing monitoring as advised by and agreed with the consultant in palliative medicine.
- Refer to the consultant in palliative medicine should symptoms fail to respond, or when a change of dose may be indicated
- Review the patient at regular agreed intervals to monitor symptom control.
- Identify adverse drug reactions and report to the consultant in palliative medicine.
- Liaise with community nurses regarding ongoing patient care using agreed paperwork to support administration.

Aspects of care for which Primary Care Team is responsible

- Referral to consultant in palliative medicine when symptoms fail to respond to the management of analgesia or when change of administration route indicated.
- Ensure that the patient knows what significant adverse effects/events to report urgently and to whom they should report (consultant in palliative medicine or GP)
- Identify adverse effects and report to the consultant in palliative medicine.
- Amend prescription as per requests from the consultant in palliative care.
- Seek consultant in palliative medicine advice promptly as advised in the guidance or if signs/symptoms of changes occur.
- Report adverse events via the Yellow Card reporting system in the BNF or at yellowcard.mhra.gov.uk
- Stop treatment on advice of the consultant in palliative medicine (or immediately) if intolerable side effects occur provided that it is safer to do so than to continue therapy
- Seek consultant in palliative medicine advice promptly as advised in the guidance if patient unable to take oral methadone and needs to be converted to subcutaneous methadone

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the full prescribing data SmPC (via medicines.org.uk), the BNF and the current Palliative Care Formulary. Information is also available at www.palliativedrugs.com

The Consultants in Palliative Medicine are available during working hours through their secretaries and out of hours there is a consultant in palliative medicine available through DRI switchboard.

References

1. British National Formulary online (via https://www.medicinescomplete.com/#/browse/bnf)
2. Palliative Care Formulary (PCF7)
   Available from: www.palliativedrugs.com

Guidance Development

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December 2021