Oral Methadone in Analgesia in palliative care

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AS AND FILED IN NOTES

Patient Name : **Date of Birth:** **NHS No:**

Name of Referring Consultant: **Contact number:**

INTRODUCTION – Indication and Licensing

Methadone is a strong opioid which is used for the management of complex pain in advanced illness when standard treatments (conventional opioids; co analgesics; steroids etc) have failed.

It has a more complex pharmacology than other strong opioids, which means that it should only be initiated and titrated with specialist palliative care support as patients can become rapidly toxic because it can form an extensive reservoir in the body tissues, and the mechanism for it to disrupt or be disrupted by other common drugs are not understood.

It can also affect (extend) the QT interval i.e. there is risk of unintentional overdose, and of death.

However, if effective it can really make a huge difference to pain control and a patient may then remain relatively stable on a fixed dose for many months.

It is licenced for pain. The key reference for use in palliative care is the Palliative Care Formulary (PCF – see latest edition Ed 7 pub 2020. Saint Francis Hospice has consolidated the chapter into a Methadone in Palliative Care guideline, updated at least 3 yearly. This can be supplied on request.

PATIENT PATHWAY- *brief explanation of why planned arrangements for prescribing and monitoring between primary and secondary care are appropriate*

Clinical Speciality / Indication	Prescribing Initiated by	Prescribing Continued by *(detail when suitable for transfer to occur)*	Monitored by *(detail when suitable for transfer to occur IF APPROPRIATE)*	Duration of treatment
Palliative Medicine. For management of complex pain in advanced illness when conventional analgesics have failed.	**EITHER** Consultant in Palliative Medicine <u>if a full opioid switch</u> (always in the hospice); may also be initiated as a co-opioid in the hospice. **OR** GP under guidance from Consultant in Palliative Medicine whilst patient is at home: as co-opioid only	**->** GP, at hospice discharge (the dose will have been stabilised after initiation/titration phase. **->** GP, with continued support from specialist palliative care team + specialist palliative senior clinician review as needed	Specialist Palliative Care (SPC) Team	As long as effective – Methadone for pain is usually initiated in the last year of life, and maintained until end of life. If pain becomes prominent again this will trigger either a specialist palliative care senior clinician visit or hospice admission

State when a review of outcome of treatment will be made to determine whether treatment will stop or continue. State who will do this assessment-usually the hospital.

Note the above table should describe the local pathway. For patients out of area this may differ and some GPs may prefer to monitor and in some cases perform their own phlebotomy. Add a statement to describe this where it applies.

ORAL DOSE AND ADMINISTRATION

The oral dose will be individually tailored to the patient. Methadone may be the baseline opioid (and will have replaced the conventional opioids previously tried) or may be a co-opioid, working alongside a conventional opioid.

PLEASE NOTE: THE FORMULATION WILL BE SPECIFIED BY SPECIALIST PALLIATIVE CARE; incidents have occurred because of confusion between different strength oral solutions. Specialist palliative care favour either 5mg tablets or 1mg/1ml oral solution. Only very rarely will an oral concentrate be specified.

Initiation dose: variable.
If initiated as a methadone switch (in the hospice) the initial dose will depend on the dose of the conventional opioid previously used.
If initiated as a co-opioid the starting dose may be as small as 5mg nocte; largest start dose will be 10mg bd; depends on patient vulnerabilities (such as frailty), also on the dose of the baseline opioid and requires guidance from a physician experienced in methadone for pain control. (See Palliative Care Formulary PCF ed 7 pub 2020).
Maintenance dose (to be continued by GP):

- Usual regimen is variable, but rarely higher than a total of 60mg / 24 hours. The regime will usually be a twice daily regime; less commonly it will be a three times daily regime. BNF guidance is lacking; use in palliative care is led by the Palliative Care formulary.
- Important points of patient education are included in the Patient Information Leaflet, but of highest importance is highlighting of the risk of unintentional overdose.
- The Patient Information leaflet has been developed by Saint Francis Hospice (with thanks to the PCF, also regional audit, clinical incident review and clinical experience).

The patient will be issued the Patient Information Leaflet as methadone is initiated. It will be given to the patient by the supporting Consultant in Palliative Medicine.

MONITORING STANDARDS FOR MEDICATION

Note: be clear about what needs monitoring, normal parameters, how often and by whom. What results warrant referral back to the hospital team?
Blood tests:
Most people starting methadone will have had a blood test as they will have been suffering complex pain, possibly some toxicity on a conventional opioid and efforts will have been made to investigate for any reversible cause for high symptom burden (e.g. electrolyte disturbance). However, initiation does not require a blood test, and ongoing monitoring does not require blood tests.
ECG:
People for whom methadone is suggested will need a baseline ECG before initiation if they are not within the last few weeks of life (i.e. if their prognosis is likely longer), if they are still 'for CPR', if there are other treatment options for the pain, if there is a family history of sudden death or personal history of arrhythmia. When any of these apply the baseline ECG is needed to identify whether there is any QTc interval prolongation. If there is, then any other medication which may be prolonging the QTc interval will need to be reviewed. Whether to risk starting methadone needs full discussion. As methadone for complex pain, the decision around whether to do a baseline ECG will be made and done there if the patient is in the hospice.
The date of the ECG and QTc interval will be recorded within the hospice discharge summary.
If the patient is at home then the Palliative Medicine Consultant will discuss with GP as to whether and where easiest to achieve a baseline ECG. The hospice is able to support practices if struggling to arrange an ECG for patients.
The date of the ECG and QTc interval should be recorded in both the GP and the Palliative Care records.
Repeat ECG will be only required if the baseline QTc is prolonged (repeat after 2m), or the dose requires significant incremental uplift over time, (a pragmatic approach is OPD ECG which the hospice will organise, no more than 6 monthly).

Parameter	QTc interval
Target level	Not applicable
Frequency of monitoring	Baseline (unless within last few weeks of life/DNACPR) then 6 monthly
Action	Repeat ECG will be only required if the baseline QTc is prolonged (after 2m), or the dose requires significant incremental uplift over time

When the hospice does an ECG the QTc result will be sent to the GP for their records.
Note that no hospital monitoring is required.

KEY ADVERSE EFFECTS & ACTIONS

Adverse effects	**Symptoms/signs** *(specify what would prompt action)*	**Actions (***what action should the GP take if identified in primary care)*
Opioid side effects	Constipation (99% have)	Regular Laxatives will almost always be needed with any regular opioid (Senna +/- docusate are recommended to start with).
	Transient sleepiness with dose changes (resolves within 2-3 days)	Patient will be closely monitored by SPC team if symptomatic of pain, and after dose changes. The SPC team to direct any dose change (both of methadone and any other co=opioid). Consider other cause e.g. electrolyte disturbance/ increased disease load/opioid toxicity if somnolence persists Do contact SPC for advice/support if needed. .
	Nausea/vomiting (not likely as the patient will be already opioid familiar – suspect other cause)	Suspect other cause for nausea – investigate as appropriate. Symptom control as required, with anti emetics. (call SPC for advice if needed)
	Dry mouth (very common with all opioids)	Mouth care, lubricants (call SPC for advice if needed)
Opioid toxicity	Sleepiness/ somnolence; confusion. At worst, as with all opioids, reduced respiratory depression or death – but sleepiness/somnolence will proceed	Ring Specialist Palliative Care for advice
Some case reports of duodenal perforation possibly related to longer term use of oral solution	Epigastric pain/indigestion	PPI Discuss with SPC – may need move to different form of methadone
Note case reports of sudden death largely linked to use in opioid dependence and probable unintentional overdose but also note potential to prolong QTc interval and rare risk of developing a serious ventricular arrhythmia (Torsades de Pointes). Linked mainly with doses much higher than are used for complex pain in advanced disease	Cardiac Arrest	V unlikely as mode of dying. Advance Care Planning to include discussion regarding CPD status. Monitoring by ECG to identify those at risk (i.e. those with pre-existing QTc interval prolongation)

DRUG INTERACTIONS

Methadone is metabolized by several cytochrome P450 iso-enzymes, mainly CYP3A4 and CYP2B6, with CYP2D6, CYP2C9, CYP2C19 and CYP1A2 also involved to varying degrees; this differs between the enantiomers with CYP3A4 and CYP2B6 preferentially metabolizing *R*-methadone and *S*-methadone respectively. Caution is needed with concurrent use of drugs that inhibit or induce these enzymes. Clinically relevant and well-established CYP-related drug–drug interactions are listed in the table below. Note particularly that **carbamazepine**, **phenobarbital**, **phenytoin**, **rifampicin** and **St John's wort** increase the metabolism of methadone, and may reverse previously satisfactory pain relief or even precipitate withdrawal symptoms. Conversely, methadone overdose has occurred when such inducers have been stopped, including after cessation of smoking (polycyclic aromatic hydrocarbons in tobacco smoke are CYP1A2 inducers).

Symptomatic bradycardia has been reported in a patient on **thalidomide** given methadone.

Avoid concurrent use with other drugs that prolong the QT interval.
Risk of serotonin toxicity when used in combination with other serotoninergic drugs, e.g. **selegiline**, SSRIs.
The concurrent use of MAOIs and methadone is contra-indicated in the SPC.

Methadone increased by	*Methadone decreased by*	*Increased by methadone*	*Decreased by methadone*
SSRIs	Carbamazepine	Desipramine	Amprenavir
Cimetidine	Phenobarbital	Zidovudine (AZT)	
Ciprofloxacin	Phenytoin		
Diazepam (high-dose)	Rifampicin		
Itraconazole	St John's wort		
Fluconazole	Antiretroviral, e.g. abacavir, amprenavir, efavirenz,		
Voriconazole	lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir,		
	telaprevir, tipranavir		
	Tobacco smoking		

This only lists the key important ADRs-For comprehensive information on cautions, contra-indications and interactions, please refer to the current British National Formulary and Summary of Product Characteristics.

PREGNANCY AND BREAST FEEDING

If is recommended that the patient should not become pregnant whilst on the drug-add a statement that both men and women will be counselled about contraception and what to do if pregnancy occurs. The counselling should be documented in the patient notes.

Patients will be screened to ensure those who may become or who are pregnant and those who are breastfeeding are excluded.
Methadone is retained in breast milk and crosses the placenta. However, if a situation does arise whereby someone with advanced life limiting illness is pregnant or breast feeding and is in pain, methadone would be avoided, in favour of standard opioids.
For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital (or in this case, hospice) specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations are normal before commencing treatment. Give the patient a patient held booklet for result monitoring if appropriate.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first month of treatment or until patient is stabilised). An exception (in the case of methadone for pain) is when a small dose of methadone is initiated at home as a co-opioid (very safe), when the GP is asked to prescribe. (Option 'OR' on P1)
5. Send a letter to the GP requesting shared care for this patient.
6. To produce a notification to be forwarded to the community pharmacy advising that the prescribing for this patient is not part of a substance misuse therapy programme
7. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
8. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated (unless otherwise covered by letter eg from Rheumatology Clinical Nurse Specialist or Pharmacy Drug Monitoring Service).
9. Where the GP is not performing the phlebotomy, the blood test form MUST be annotated to request that blood results are also copied to the GP
10. Evaluation of any reported adverse effects by GP or patient.
11. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient and inform GP.
12. Inform GP of patients who do not attend clinic appointments.
13. Counsel the patient on contraception and what to do if pregnancy occurs. Document in the notes.
14. Ensure that backup advice is available at all times.
15. Ensure that the patient has received a flu vaccine prior to commencing treatment that is likely to cause immunosuppression. Document this in the patient notes and inform the GP it has been given

General Practitioner

1. Reinforce the patient's understanding of the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA, where appropriate.
5. Help in monitoring the progression of disease
6. Maintain a patient held monitoring booklet where used
7. Prescribe the drug treatment as described.

Pharmacist

1. The pharmacist to be alerted by letter (in the case of methadone for pain) to ensure they understand the purpose of methadone. Otherwise they are at risk of thinking that the methadone is being prescribed as part of an opioid programme.

CCG

2. To provide feedback to trusts via Area Prescribing Committee
3. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
4. To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy
5. Take/ administer the medication as prescribed
6. Undertake any monitoring as requested by the GP and/or specialist

Costs

Drug Product	Cost in primary care
Methadone	50 x 5mg tablets £2.84 1mg/1ml oral solution 500mls between £4.30 and £6.10 dep on brand Dose is highly individual but based on a typical dose of 20mg bd + 5mg prn likely monthly cost = tablets: approx. £14.20 or oral solution: approx. £12.00

Based on BNF edition……..Accessed on line 9.10.2020

Give the cost of a 1 month course of treatment for each drug listed

RESOURCES AVAILABLE

SAINT FRANCIS HOSPICE	
Consultant via switchboard Registrar on-call out of hours	**Via Hospice Advice Line 01708 758643 24/7** N/A
Clinical Nurse Specialist (where appropriate)	**Via Hospice Advice Line 01708 758643 24/7**
Drug Monitoring Clinic Pharmacist (where appropriate)	N/A
BHR CCGs Medicines Management Team	0203 182 3133

References

1. SFH audits:
   i) Methadone as a co-opioid: 2 years reflective audit of practice in Saint Francis Hospice 2009
   ii) A re-audit of Methadone use in Saint Francis Hospice (presented June 2016)
2. The Palliative Care Formulary 7th Edition (2020) 'for further information on the use of methadone in palliative care, https://www.medicinescomplete.-com/#/content/palliative/methadone
3. BNF online accessed 29.10.2020 See Methadone -> Palliative Care ->
4. Oxford Textbook of Palliative Medicine 4th Edition. Ed G Hanks et al. (2011)
5. Methadone prescribing guidelines Author Dr Craig Gannon, Princess Alice Hospice (2011)
6. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Anschersen et al. Addiction 2009; 104:993-9
7. Care Quality Commission Patient Safety Newsletter Vol 1 No 1 Nov 15
8. Cochrane Database of Systematic Reviews:
   - 2007, Issue 4. Nicholson AB. Methadone for cancer pain.
   - 2013 Pier Paolo Pani et al (Editorial Group: Cochrane Drugs and Alcohol Group). QTc interval screening for cardiac risk in methadone treatment of opioid dependence
   - 2017 Methadone and Cancer Pain
     http://onlinelibrary.wiley.com/wol1/doi/10.1002/14651858.CD003971.pub4/full

Refer to the NHS Barking and Dagenham, Havering and Redbridge CCG website to obtain the latest version of this guideline

Template approved by Area Prescribing Committee (APC)
Guideline written by Dr Corinna Midgley Saint Francis Hospice on October 2020.
Approved by BHR CCGs APC on December 2020 v1 Review date: December 2022 (2 years).

SHARED CARE AGREEMENT letter for signatories: **Will be on SFH headed paper**

Shared care agreement – Methadone in the community for palliative care patients

Date

GP address

Dear Dr GP

Re: Patient name and address and DOB

Thank you for taking the time to speak with me on the phone about the introduction of methadone for patient's name.

Patient name suffers from diagnosis which causes significant pain.

Then (– the Consultant will delete as appropriate):

EITHER

1. He/she was admitted to Saint Francis Hospice inpatient unit for better pain management.

After consideration, we trialled Methadone for pain control. Methadone has achieved better pain control. H/she is happy to continue with this medication.

We plan to discharge Patient name on Date on:

Patient name will be discharged with a two week supply of methadone along with all his/her other medication.

Or

2. He/she does not want admission to Saint Francis Hospice inpatient unit. Given the complex pain which has been resistant to or poorly controlled by other more standard opioids/co analgesics we would like to try a trial of Methadone as a co-opioid.

Being aware that not many GPs are familiar with the use of methadone for difficult to manage neuropathic cancer pain, we have a **SHARED CARE AGREEMENT** between the GP and Hospice services. A letter will go to the patient's pharmacy to highlight the purpose of methadone and the preparation to be used.

1. The medical team at SFH will take on the responsibility of supervising the Methadone titration and its effective use;
2. The GP surgery will take on the responsibility of prescribing the drug;
3. The pharmacy will take on the responsibility of ordering and dispensing Methadone

If any concerns please contact the Hospice Advice Line on 01708 758643

Of note:

The patient has / has not had an ECG to check for QTc interval prolongation

Date …….. QTc interval measurement …….
(normal Qtc <450msec (males) and <460msec (females))

Explanation if not having an ECG……..

……

ECG follow up plan: …….

……

SPECIALIST PALLIATIVE CARE CONTACT DETAILS: ……

SPECIALIST PALLIATIVE CARE SENIOR CLINICIAN REVIEW PLAN: …….

HOW METHADONE IS BEING USED. This will be specified to clarify:

a) whether Methadone is being used as the only baseline opioid or as a co-opioid in conjunction with a more conventional baseline opioid.
b) whether Methadone is being used for breakthrough pain (i.e. prn)
c) what else can be used for breakthrough pain, if methadone prn is no effective or if pain comes back within 3 hours (the patient cannot take methadone prn more frequently than max 3 hourly).

Note that a regular dose will almost invariably be different from a prn dose, but the form of the drug ie oral solution or tablet will likely be the same.

d) An ongoing management plan will be supplied e.g.

- a plan to increased, reduce or keep steady and a plan to increase, reduce or keep steady any other opioid being in use
- what s/c injectables are in place
- what to do towards EOL/if oral methadone becomes unmanageable

FORM OF METHADONE: **THIS FORM ALWAYS TO BE PRESCRIBED**

……

DOSES OF METHADONE: if not applicable the regular or the prn sentence will be deleted:

Regular Methadone: dose

Prn Methadone: dose and max frequency

Patient name is fully aware of her medication and how to use it. He/She has full mental capacity and has been involved in all decisions around her medication and other treatments. He/She has our 24/7 advice line number (01708 758643).

Patient name has been given a Patient Information Leaflet YES NO Date ……..

Name of Specialist Palliative Care Team

Methadone for complex pain in advanced or progressive disease: Shared Care Guidance

SHARED CARE AGREEMENT LETTER

Re: Patient's Name…………….………………………………

Date of Birth………………………………………………

Hospice Number…………….………………………………

Name of GP ………………………….. Address ……………………………….

…………………………………..

………………………………….

Dear GP

Please sign below and return this letter to the Hospice Consultant named to confirm agreement to the shared care arrangements for this patient.

Many thanks

Hospice Consultant	GP
Signature……………………..	Signature…………………………..
Name …………………………..	Name …………………………….
Hospice base ………………..	Practice ………………………….
………………………………….	…………………………………….
………………………………….	…………………………………….
Date………………………….	Date……………….……………..

If you are not taking on shared care for this patient please state the reason why and return this letter to the Hospice Consultant.

………

………

………

………

PHARMACIST UPDATE **Will be on SFH headed paper**

Methadone in the community for palliative care patients

Date

Dear Pharmacist/Pharmacy

Re: **Patient name and address and DOB**

GP address

Thank you for taking the time to speak with me on the phone about the introduction of methadone for patient's name.

Patient name suffers from diagnosis which causes significant pain.

This is to confirm that they have been prescribed methadone for the purpose of pain control in advanced disease, and not as part of an opioid maintenance or replacement regime.

Currently the dose is

Additional opioids being prescribed;

FORM OF METHADONE: **THIS FORM ALWAYS TO BE PRESCRIBED**

……

If any concerns please contact the Hospice Advice Line on 01708 758643