

SPAGG

Coversheet for Specialist Palliative Audit and Guideline Group Agreed Documentation

This sheet is to accompany all documentation agreed by SPAGG. This will assist maintenance of the guidelines as well as demonstrating the governance process undertaken prior to members seeking local approval in their areas of work.

Document Title	Methadone for adults with pain in palliative care
Document Date	June 2020
Document Purpose and Intended Audience	To provide guidance to healthcare professionals in how to utilise methadone safely and appropriately for palliative patients with pain who are either not responding to standard opiates or who are suffering from unacceptable side effects.
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References	See section 11
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SPAGG Guidelines

Methadone for Adults with Pain in Palliative Care

**Coversheet for Specialist Palliative Audit and
Guideline Group (SPAGG)
Agreed June 2020**

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1. Scope of the guideline

- 1.1 This guideline has been produced to support the use of methadone for analgesia in patients with a life-limiting illness.
- 1.2 Titration to methadone is not appropriate in the last days of life and therefore is not discussed in this guideline.
- 1.3 This guideline does not cover the use of methadone for symptoms other than pain.
- 1.4 This guideline does not cover the use of methadone in patients with drug dependence.

2. Guideline background

- 2.1 There are no NICE guidelines on the use of methadone for pain therefore the specialist palliative audit and guidelines group (SPAGG) have developed these guidelines to ensure safe and consistent practice in line with local expert opinion.
- 2.2 A small number of patients with cancer experience pain that cannot be controlled by using the analgesic ladder even when anti-epileptics and anti-depressant drugs are added to opioid drugs.
- 2.3 Methadone has pharmacological specificities described in [Appendix 1](#). In particular a long half-life and titration to an effective dose is often complex, therefore dose titration and modification should be carried out under the care and supervision of a specialist palliative care or pain team¹.
- 2.4 Recent guidelines and consensus papers have been published. We recommend that specialists and those wishing to safely prescribe methadone read these excellent documents. We have attempted to take account of their recommendations and cited some of them. They cannot be fully replicated for local guidelines as they operate in different clinical and health care systems than our^{1,2}.

3. Guideline statements

- 3.1 The use of methadone for analgesia requires the involvement of a specialist palliative care team at all stages, even once pain control seems satisfactory long after initial titration.
- 3.2 Patients with uncontrolled pain should be referred either to a specialist palliative care or pain team.
- 3.3 The use of methadone is **specifically indicated** for the management of pain in patients that:
 - 3.3.1 Gain inadequate analgesia with or without unacceptable side effects following appropriate dose escalation of morphine and/or other opioids
 - 3.3.2 Experience tolerance to the analgesic effects of other opioids leading to opioid dose escalation and loss of analgesic benefit over time
 - 3.3.3 Are already receiving methadone for an indication other than pain.
- 3.4 **The type of pains which we found in our cases series to be particularly responsive to methadone** include:
 - 3.4.1 Tumours affecting the chest wall and pleura such as peripheral lung cancer or mesotheliomas,
 - 3.4.2 Pelvic tumours such as cervical cancers, invasive prostate cancers, bladder cancer, ano-rectal cancer or pelvic bone tumours,
 - 3.4.3 Complex retro peritoneal and pancreatic cancer that may involve nerve plexuses.In those circumstances it may be wise to consider methadone earlier in the disease process as a second line opioid and before massive dose escalation has taken place.
- 3.5 Conversion to methadone requires careful monitoring and where possible should take place in a specialist palliative care inpatient unit. Under specific circumstances with the involvement of the specialist palliative care or pain team, the conversion may be undertaken at home or in another care environment, but the method used will be adapted to the environment with appropriate risk assessment and added safeguards.

- 3.6 Careful patient selection before prescribing methadone should take place according to an expert consensus white paper²:
- 3.6.1 **Potentially appropriate** candidates for methadone in palliative care
- *Moderate to severe pain (especially as a second-line opioid choice)*
 - *Pain refractory to other opioids*
 - *True phenanthrene (e.g., morphine) allergy*
 - *Significant renal impairment*
 - *Need for a long-acting opioid (particularly as an oral concentrate solution)*
 - *High opioid tolerance*
 - *Poorly controlled opioid-induced adverse effects with other opioids*
 - *History of dysphagia, inability to swallow, or feeding tube placement (NB: convenience of liquid long acting opioid)*
- 3.6.2 **Potential inappropriate** candidates for methadone in palliative care include:
- Patient lives alone, or poor cognitive functioning, without a responsible caregiver
 - Lack of knowledgeable practitioner on transfer
 - History of opioid/medication nonadherence
 - History of substance misuse or Substance Use Disorder (patient or family)
 - Multiple risk factors for methadone toxicity (e.g., clinical instability, multiple transitions in care, history of transplant)
 - History of QTc prolongation or at high risk for such (*see below in 3.7*)
 - Prognosis less than projected time to methadone steady state (i.e., five to seven days)
 - Obstructive or central sleep apnoea
 - Determined to be medically inappropriate after risk assessment
- 3.7 Consideration should be made of the **risk of long QT syndrome** ([appendix 2](#)) in exceptional cases this recommendation can be waived. (See reference [2](#) table 3 p 639).
- 3.7.1 Between 450ms and 500ms, the requirement for methadone and risk of cardiac arrhythmia should be re-evaluated. If a decision in favour of a trial of methadone is taken, monitoring of ECG should be part of the close clinical management of titration.
- 3.7.2 If the QTc is above 500 milliseconds, methadone should not be started until this has been corrected (when possible).
- 3.7.3 When the initial QT interval is deemed normal (QTc<450ms), it is not possible to state how often the ECG should be repeated due to lack of evidence. An emerging consensus is to repeat the ECG within a month of completing the titration. Other times that may be appropriate are when a drug known to prolong QT interval is introduced, once the daily dose of methadone is over 100mg or when a substantial (e.g. doubling) methadone dose increase occurs.
- 3.8 When patients are given the opportunity of taking methadone, they must be given adequate information for a joint decision to start methadone to be taken. See [section 9](#) of this guideline.
- 3.9 Methadone prescribing responsibilities should only be passed onto the primary care team when the patient has been stabilised and with support of shared care guidelines ([appendix 3](#))^{1,2} and in areas where shared care has been approved.
- 3.10 **Conversion from other opioids to subcutaneous methadone.**
- 3.10.1 It is not normally advised to convert to subcutaneous methadone from any opioid other than oral methadone.
- 3.10.2 Although it is not impossible to prescribe subcutaneous methadone alongside another opioid, this is not covered by this guideline.
- 3.10.3 Conversion is a prolonged process requiring considerable input from the patient to achieve successful conversion to oral methadone, therefore changing a patient in the final few days of life to subcutaneous methadone from other opioids is not advised.

3.11 **Methods of methadone titration.**

There are several methods of methadone titration based on the level of expertise of the clinician involved, the availability of the patient for review and assessment and the urgency of achieving optimal pain relief. They can be categorised according to:

- the aim of the process which is **either** to reduce the use of another opioid **or** to discontinue the other opioid and achieve a complete switch, and
- the timeframe of titration which is to achieve it within two weeks **or** over a longer duration.

3.11.1 **Method 1: Stop and Start, complete switch**

This is method that has been popularised by Makin-Morley in the 1990's¹² It is based on a 'de novo' titration of methadone that takes partial account of the dose of the previous opioid used but is mainly determined by the ability of the patient to signal when the pain is returning to administer the next dose of methadone whilst observing the patient very closely throughout the process for signs of opioid toxicity.

In the hands of experts, **it can allow a rapid titration and control of the pain** within a few days of starting methadone and can be completed in most cases within 10 days to two weeks. It requires clear safeguards including opioid side-effects monitoring, frequent reviews by nursing staff to ensure patient is not left in pain and side-effects are closely monitored and documented. It also requires a strong commitment of the medical team to daily reviews (sometimes several times per day) and availability out of hours to advice, including face to face reviews.

It can only be done as an in-patient in a specialist unit. For teams that are not so experienced, it is possible to use this method but additional measures such a lower starting methadone dose and allowing the use of another opioid for pain breakthrough will reduce the risks but will inevitably delay the titration process.

3.11.2 **Method 2: Start low, Go slow**

This method involves continuing with the previous opioid both in the form of background pain relief and management of breakthrough pain episodes. The aim may be simply to spare the use of the other opioid and stop the titration when both patient and clinician believe the current level of pain relief is satisfactory. However, in most cases, it should be possible to complete the switch in full over time.

This method is **suitable for outpatient titration**, or as an inpatient, when the patient's ability to cooperate to the titration process is limited by anxiety and difficulties to report and verbalise pain levels.

Sometimes, the patient and the clinician agree that inpatient titration is not desirable, or the degree of urgency to improve pain control is considered low. If that method is adopted, patients must be warned that it can take several weeks until they start benefitting from clinically significant pain relief.

The basic principle of this method is the slow upwards titration of methadone and the down titration of the previous (or alternative) opioid(s). It is not possible to give detailed guidance on how frequently dose changes can be made as it depends on the frequency of clinical review. A minimum of 5 days is required to ascertain the tolerance of a given dose before a dose increase should be considered. The first week is the critical time to evaluate tolerance to methadone and once the exposure exceeds 4 weeks, the risk of significant toxicity following dose increases becomes low, allowing for more substantial dose increases if required.

4. Conversion to oral methadone – [Titration method 1: Stop and Start](#)

- 4.1 This method of switching to methadone **must be done in a specialist inpatient unit**.
- 4.2 Perform baseline ECG to assess QTc interval
- 4.3 Patient must be given verbal explanations about the purpose of the switch and the potential potency of the drug necessitating frequent assessment especially during the first week of titration. This should be backed up by written information when appropriate. See [section 9](#) of this guideline.
- 4.4 Support of those close to the patient should be sought and assurance given that ongoing support will be available if discharge to usual place of residence is likely.
- 4.5 Start monitoring the patient's potential opioid side effects using a monitoring chart prior to the methadone titration and during the conversion period ([appendix 4](#)).
- 4.6 The choice of the first dose of methadone should be decided according to the following criteria:
 - 4.6.1 It should never exceed 30mg but 20mg may be a safer maximum for less experienced teams. This dose applies to any previous opioid intake of more than 500mg morphine equivalent per day.
 - 4.6.2 If the patient has been taking less than 500mg of oral morphine (or equivalent) per 24hours, consider giving 20mg if the previous opioid total daily dose was equivalent to 200-500mg of oral morphine per day, 10mg if 100-200mg or 5mg if less than 100mg. These doses can be reduced by up to 50% by less experienced clinicians or when individual patients had experienced intolerable opioid side-effects at low doses (see [appendix 5](#)).
 - 4.6.3 The first methadone dose should be given early in the morning to replace the twice daily opioid preparation. It can be given immediately after transdermal fentanyl patches are removed or an opioid drug syringe driver disconnected.
- 4.7 Prescribe the same dose of methadone to be given ad libitum (as often as necessary) up to every 3 hours. Some centres with less experience of monitoring methadone titration use only 50% of the initial dose. This may delay achieving satisfactory analgesia if the requirement ends up fairly high but preferable in some cases, as long as the patient is aware of this.
- 4.8 Prescribe PRN alternative analgesia for if the pain returns during the 3-hour window, paracetamol 1gr QDS. Some centres using lower starting doses of methadone may prefer to use the previous fast-acting opioid.
- 4.9 It is essential that the patient is frequently reviewed by the nursing or medical staff and given the next dose of methadone as soon after 3 hours as the pain returns or if it persists.
- 4.10 Patients should be reviewed at least daily by a senior doctor. The doctor should consider
 - any evidence of opioid side-effects especially excessive drowsiness,
 - whether the patient still experiences pain during the 3-hour window especially after the second day of titration,
 - how frequently methadone has been required throughout the previous 24hrs and globally since the start of the titration
- 4.10.1 If 1 or 2 doses were only required in the previous 24 hour or on average since starting titration, the ad libitum dose needs reducing respectively by 50% or 30%
- 4.10.2 If 5 or more doses were required, the ad libitum dose can be increased by 30 to 50%
- 4.11 Once the patient's pain is controlled and the average daily dose requirement has been stable (usually between day 5 and day 10) they can be converted to a regular daily dosing regimen in 3 to 4 divided doses.

For example, to convert to a three times daily dose: Calculate the total amount of oral methadone used in the previous 48 hours and divide this amount by 6 to prescribe a three times daily regular dose of methadone.

- 4.12 For pain breakthrough, once a regular regimen is in place, the next methadone dose can be given early allowing for a maximum frequency of 4 hours. During this 4-hour interval, the use of a non-opioid analgesic is recommended. In exceptional circumstances and under medical supervision, if the pain experienced by the patient is too severe to allow them to wait for the effect of the next oral dose of methadone and the above is ineffective, 1/3 of the next oral methadone dose can be given subcutaneously. The next oral dose does not need to be delayed beyond 30 minutes of the injection as absorption by the subcutaneous route is clinically significant within 15 minutes.

5. Conversion to oral methadone – Titration method 2: Start low, Go slow

- 5.1 This method of switching to methadone is better suited to the outpatient set up but still requires close monitoring and availability of clinicians out of hours. It should only be started when this availability can be anticipated, and appropriate senior backup is available.
- 5.2 It can be done as an inpatient as an alternative to the first method in cases when patient's collaboration is limited by various factors, but this is not recommended in the last weeks of life. In those cases, adjuvant prescription can be sometimes considered, preferably as an inpatient.
- 5.3 On day one, a starting dose of 5mg methadone once daily or 2.5mg twice daily should be well tolerated in opioid tolerant patient. Anybody taking on less than 60mg of oral morphine per 24 hours should start at a lower dose of 2.5mg daily or less at least for the first 5 days.
- 5.4 Close monitoring during the first 5 days after introducing methadone is essential, observing for any signs of opioid toxicity. After day 6, if there has been no evidence of opioid side-effects and additional pain relief is required, the dose can be doubled safely (5 mg methadone twice daily if 5mg daily is the initial dose).
- 5.5 Clinicians with less experience should prescribe half the above doses (2.5mg once daily initially and 2.5mg twice daily in the second week). This is a prudent approach for patients who are fearful of side-effect or sensitive to opioids in general.
- 5.6 The dosage of the concomitant opioid should be reduced rapidly if side-effects such as excessive sedation occur in the context of fair or satisfactory pain control during methadone titration.
- 5.7 Further face-to-face assessment should be scheduled within 5 to 7 days to decide on the subsequent dose increase as necessary.
- 5.8 If there is any clinically evident improvement in analgesia, then the next dose increase should be no more than a 50% increase. The other opioid background analgesia can also be reduced especially if the breakthrough frequency requirements are low.
- 5.9 If there are no changes in analgesia and there is no occurrence or worsening of opioid side-effects, a larger dose increase (75% to maximum 100%) can be decided after a minimum of two weeks of methadone exposure but close monitoring should continue.
- 5.10 If pain relief is already noticeable and there is some evidence of drowsiness, then reduction of the other opioid being administered alongside methadone should be carried out. Dose reductions can and should be done very quickly especially when pain relief is maintained.
- 5.11 The rate of reduction of the original opioid for each patient should be discussed and agreed with a Specialist Palliative Medicine consultant, experienced in the titration of methadone.
- 5.12 The regular dosing regimen of methadone, as with the other titration method, should be decided with the patient to maximise convenience and minimise side-effects. As a rule, it is better to administer methadone 3 to 4 times a day rather than twice daily to minimise blood level variations and potential side-effects.

6. Conversion of subcutaneous methadone from oral methadone

- 6.1 This should be done if there is inability of continuing with the oral route because of nausea and vomiting or difficulties to swallow methadone in progressive disease.
- 6.2 The conversion ratio should be 50-66% of previous oral dose (2:1 or 3:2 conversion) based on oral bio-availability.⁵
- 6.3 The continuous subcutaneous infusion should be started at the calculated dose between 8 and 24 hours after the last dose of oral methadone has been taken because blood levels take a long time to drop reflecting methadone long half-life.
- 6.4 Following switching of route of administration, all patients should be monitored for signs of pain or opioid side-effects using an opioid monitoring chart (appendix 6). Should either of these occur the methadone dose should be modified accordingly.
- 6.5 Subcutaneous methadone is an irritant and can cause local site reactions. These reactions can be reduced by:
 - 6.5.1 Adding dexamethasone 0.66mg to the syringe containing methadone^{1,5}
 - 6.5.2 Maximising the dilution of the methadone by using a 30ml syringe
 - 6.5.3 Using sodium chloride 0.9% as the diluent ²
 - 6.5.4 Avoid mixing methadone with any drug other than dexamethasone in the same syringe whenever possible due to lack of compatibility data.
- 6.6 Breakthrough pain for patients receiving subcutaneous methadone should be managed with caution due to potential for accumulation. Up to two doses of 1/6 of the 24-hour dose is safe but beyond that an alternative short-acting opioid may be preferable. It should be noted that patients well pain controlled on regular methadone rarely face complex pain at the end of life.

7. Conversion of methadone to other opioids

- 7.1 It is not recommended and rarely required clinically but if this is required for other reasons, patients and health care professionals should be warned that it could result in the return of severe pain.
- 7.2 This should only be undertaken by specialist palliative care teams and is not covered in the remit of this guidance. Please refer to SPCT or specialist pain teams.

8. Opioid withdrawal symptoms ^{3,5,6,12}

- 8.1 Opioid withdrawal syndrome is important to recognise and manage due to its unpleasant symptoms and due to a small but significant risk of death.
- 8.2 Patients should be monitored for signs of opioid withdrawal. Opioid withdrawal syndrome may resemble a severe flu-like illness characterised by rhinorrhoea, sneezing, yawning, lacrimation, abdominal cramping, leg cramping, piloerection, nausea, vomiting, diarrhoea and dilated pupils. Some patients may also experience anxiety, restlessness, irritability and insomnia.
- 8.3 Disorientation, hallucinations and seizures which are characteristic of delirium tremens are not seen in opioid withdrawal.
- 8.4 If a patient should experience signs of opioid withdrawal, they should be promptly referred to the specialist palliative care or pain team. Management options include:
 - use of methadone in the same way as for analgesia
 - administration of breakthrough doses of the previous opioid
 - a benzodiazepine can be added to control insomnia and muscle cramps.

9. Patient information and counselling

- 9.1 The NICE guidance on Opioids in Palliative care (CG140)¹⁴ states that patients should be asked about any concerns of being prescribed strong opioids, that verbal and written information should be offered to patients and carers and that they are offered frequent review of their pain control and side effects.
- 9.2 Responsibility for the communication around the use of methadone for pain control in palliative care is with the specialist palliative care team.
- 9.3 All patients should be offered a copy of the patient information leaflet ([appendix 6](#)).
- 9.4 In March 2015 new legislation came in to force which allows the police to perform roadside testing for strong opiates including methadone¹⁵. Patients should be counselled about this and advised to carry information of their medication for example a repeat prescription sheet. If the medication, including methadone is being taken in accordance with medical advice and the patient's driving is not impaired no action will be taken by the police. It remains an offence if driving is impaired and patients should be counselled not to drive if their ability is impaired e.g. drowsiness by the medication.

10. Other issues

- 10.1 As with all opioids a risk assessment of home circumstances may be undertaken and help to establish practical plans concerning supply and availability of methadone in the community and patient's place of care.
- 10.2 For the management of methadone overdose please see the SPAGG guideline on 'The Use of Naloxone in Palliative Care Adult Patients'.
- 10.3 For further drug and general information on methadone see [appendix 3](#) and in [reference 11](#)
- 10.4 Further information on the use of methadone can be obtained from your local specialist palliative care team.
- 10.5 Nursing staff involved in the care of patients undergoing methadone conversion should have received formal training on monitoring such patients.
- 10.6 Monitoring of the guideline
Adherence to the guideline may from time to time be formally monitored.

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Appendix 1: General drug information about methadone

- a. Methadone has a long and very variable half-life of 30-110 hours. The effect of dose increases could be clinically noticeable up to five days after they are implemented.
- b. Further drug information is available from the summary of product characteristics and
- c. Drug and food interactions with methadone

Methadone is metabolised by the group of enzymes known as cytochrome P450. This is a highly complex group of enzymes that is often induced or inhibited by a number of other conventional and herbal medications as well as some foods (see below). This enzyme induction or inhibition may result in pain in previously stable patients, or accumulation and therefore toxicity in others. For a comprehensive list of interacting drugs, refer to: www.atforum.com/pdf/Drug_Interactions.pdf

- d. Clinical suggestions for minimizing methadone drug Interactions¹¹: (page9 of 33)

1. Maintain an accurate, updated profile for each patient that includes all prescribed drugs and OTC products (including herbal remedies and dietary supplements).

2. Use alternative, non-interacting, drugs whenever possible.

Usually, there are differences in the interactive properties of at least some members of any drug class. For example, the macrolide antibiotic erythromycin is a strong CYP3A4 inhibitor, likely to possibly interact with methadone, whereas the macrolide azithromycin does not appear to have this effect.

3. If a potentially interacting drug is used with methadone, it is better to adjust the methadone dose based on patient response rather than in advance based on an expected interaction.

The magnitude of drug interactions varies dramatically from patient to patient, and it is unlikely that the elected methadone dosage adjustment would exactly offset the actual effect of the second drug.

4. Signs/symptoms of either opioid withdrawal or overmedication (e.g., sedation), and their severity, can help gauge serum methadone level (SML) adequacy in the presence of an interacting drug. Adjustments of methadone or concomitant drug(s) may be appropriate to overcome such adverse reactions.

5. If there are concerns about adverse effects of increased methadone concentrations, patients should be advised in advance of physical signs/symptoms of overmedication that might occur and what to do. It may be desirable to temporarily monitor SMLs in certain cases.

6. Whenever possible, avoid concurrent administration of drugs with overlapping adverse-effect profiles. Otherwise, signs/symptoms of major variations in methadone concentration may be confused with side effects of concomitantly administered drugs, and vice versa.

7. Consider pre-existing disease states.

For example, conditions associated with impaired renal or hepatic function may significantly alter drug metabolism and excretion. Patients with pre-existing cardiovascular conditions – particularly those with congestive heart failure or left ventricular systolic dysfunction – may be more sensitive to potential arrhythmogenic effects of certain drugs (including methadone).

8. In some cases, adverse drug reactions can be resolved by prescribing a medication with or without food, by altering dosing schedules, or by splitting doses into smaller increments.

9. Unreported or seemingly inconsequential factors may play a role in drug interactions. *For example, grapefruit juice or smoking cessation can hinder metabolism and increase methadone serum levels.*

10. Patients may not adhere to prescribed medication regimens, which could affect adverse reactions, and the more complicated the regimen the less likely that the patient will adhere to it. This can be important in methadone-maintained patients prescribed multiple medications

Appendix 2: Minimising the risk of cardiac toxicity with methadone

- a. Consideration of burden vs. benefit is crucial and, in those with life limiting illness the potential benefit of controlling otherwise refractory pain may far outweigh the risks, even when monitoring for arrhythmia is impractical. ECG monitoring is generally not required in the last days of life.
- b. Pre-treatment one off ECG monitoring is recommended for all patients even those without recognised risk factors for QT prolongation.
- c. ECG is mandatory in the presence of other risk factors for QT interval prolongation including:
 - A history of cardiac conduction abnormalities
 - Advanced heart disease or ischaemic heart disease
 - Liver disease
 - A family history of sudden death
 - Electrolyte abnormalities that could alter cardiac conduction
 - Concurrent treatment with drugs which:
 - May cause electrolyte abnormalities
 - Have a potential to prolong QT including anti-arrhythmic drugs such as Amiodarone, psychotropic drugs including haloperidol, macrolide antibiotics including clarithromycin and erythromycin, domperidone. A full list can be found at <http://www.azcert.org> or <https://crediblemeds.org>
- d. The ultimate decision on ECG monitoring for each patient should be made by the consultant responsible for the methadone initiation.
- e. Monitoring of serum electrolytes is generally recommended in patients taking diuretics or at risk of hypokalaemia e.g. vomiting or diarrhoea.
- f. If the QT interval is prolonged >500msec
 - Other drugs known to be possibly involved should be withdrawn if possible
 - Discussion with a local cardiologist should be sought to help assess risk of arrhythmia to aid weighing up or risk vs. burden of treatment.

Appendix 3: Proposed shared care responsibilities for the prescribing and monitoring of methadone in palliative patients

Palliative medicine specialist responsibilities

- Assess patient suitability for pain control with methadone and obtain informed consent
- Consider and assess for the risk of long QT syndrome ([appendix 4](#))
- Initiate and titrate the dosage regimen for methadone
- Assess response and side effects and prescribe for minimisation of side effects
- Arrange shared care with the general practitioner when the patient is managed on a stable regimen. Written communication with the general practitioner must include:
 - A copy of the shared care guideline
 - A contact for urgent queries out of hours and a letter stating that patient takes methadone for pain
 - A detailed letter outlining the individual patient's dosing regimen
- If shared care is not agreed or in place in the locality, arrangements must be made prior to discharge as to how prescribing and obtaining methadone will continue
- Notify hospice or hospital pharmacist and forward details to the community pharmacist nominated by the patient so community supplies can be obtained
- Notify community and specialist nurses
- Ensure that all patients when discharged to their general practitioner for management have at least 14 days' supply to ensure continuity of supply at home
- When prescribing state, the formulation, strength and colour and the number of milligrams to be taken with frequency, the total quantity in words and figures (e. g. methadone oral blue 10mg/ml solution, 20mg TDS, supply one hundred and fifty (150) millilitres)
- Review the patient's response and continuing appropriateness of methadone at regular intervals. This may be facilitated by the Community Specialist Palliative Care Team.
- Stop the treatment when it is no longer considered to be appropriate.

General Practitioner responsibilities

- Referral to specialist when symptoms fail to respond to the management of analgesia or when change in the administration route may be indicated
- Review of the patient at regular agreed intervals to monitor control of symptoms
- Identify adverse effects and report them to the specialist in palliative medicine
- Continue prescribing methadone (where agreed locally) and ensure supply through designated community pharmacy
- When prescribing state the strength of the liquids, tablets or ampoules to be used in addition to the dose prescribed.
- Liaise with community and specialist nurses.

Community pharmacist responsibilities

- To order and supply methadone and complete and maintain appropriate records
- Preparations: methadone is available in several commercial formulations however not all of these are licensed for pain relief. The following preparations are most commonly used for analgesia:
 - a. [Methadone 5mg tablets](#)
 - b. [Methadone liquid 10mg/ml](#) (blue and bitter tasting)
 - c. [Methadone liquid 20mg/ml](#) (caramel colour and bitter tasting)
 - d. [Methadone injection 10mg/ml](#) (1ml, 2ml, 3.5ml and 5ml ampoules)
 - e. [Methadone injections 50mg/ml \(1ml ampoules\)](#)
- We recommend using only one formulation of methadone at a time, either tablets, oral solution or injections to avoid confusion between volume and milligrams.

Appendix 4: Opioid Monitoring chart

Use of opioid monitoring chart

Opioid toxicity is the development of unacceptable symptoms or signs (principally cognitive impairment or respiratory depression) due to opioid drugs or opioid metabolites.

These symptoms and signs include: confusion, sedation, hallucinations, myoclonus, respiratory depression with respiratory rate less than 10/min or reduction from baseline respiratory rate of more than 6 breaths per min.

Starting opioid monitoring

A baseline set of observations for 24 hours, or at least one set in daytime and one set in the night should be recorded prior to a switch to an alternative opioid drug. Subsequent observations should be every 4 hours, or more frequently if instructed by medical staff. During the night, it is not expected that the patient will be deliberately woken to record observations unless specifically instructed to.

Abnormal observations should be reported to the medical staff. Subsequent doses of opioid may be withheld.

Severe toxicity

If respiratory rate is 8/min or less and / or the patient barely rousable or unconscious, the patient should be constantly stimulated and oxygen administered. Naloxone may be administered

Naloxone administration

The aim is to give small doses to reverse respiratory depression, but to avoid reversal of analgesia and opioid withdrawal. Dilute 400mcg of naloxone in 10mls saline. Administer 2.5mls (100mcg) IV every 2 mins until the respiratory status is satisfactory. Repeated doses may be necessary as naloxone has a half-life of 30-80 mins. An infusion is likely to be necessary because of the long half-life of methadone. The infused dose/hour is based on the previous naloxone requirement. See also specific [SPAGG guidelines on the use of naloxone](#).

OPIOID MONITORING CHART

Patient Name: _____ Unit Number: _____ Date of Birth: _____

Observations	Baseline				Baseline				Baseline				Baseline			
	Date:		Time:		Date:		Time:		Date:		Time:		Date:		Time:	
	Day		Night		Day		Night		Day		Night		Day		Night	
Resp Rate/min																
Myoclonus																
Awake/Asleep																
IF AWAKE																
Conscious Level:																
Alert:																
Responsive to voice:																
Responsive to pain:																
Unresponsive:																
Hallucinations																
Confusion																
Other Comments																
Doctor contacted																
Nurses initials																

Appendix 5: Flowchart of conversion to methadone (Method 1 stop and start)

Day 0 Pre-methadone	Check baseline ECG, renal and liver function Check patient understanding and likely concordance with medications Commence opioid monitoring chart																								
Day 1	<p>A. Stop regular opioid (oral/transdermal/syringe driver)</p> <ul style="list-style-type: none">Remove patchDisconnect syringe driverOmit long acting oral opioid <p>B. Give first dose of methadone at the morning drug round or whenever pain starts on that day</p> <table><tr><th>Previous EDD Morphine</th><th>Specialist First & ad libitum dose¹</th><th colspan="2">Safer dosing Alternative²</th></tr><tr><th></th><th></th><th>First dose</th><th>Ad libitum</th></tr><tr><td>> 500mg</td><td>30mg</td><td>20mg</td><td>10mg</td></tr><tr><td>200-500mg</td><td>20mg</td><td>10mg</td><td>5mg</td></tr><tr><td>100-200mg</td><td>10mg</td><td>5mg</td><td>2.5mg</td></tr><tr><td><100mg</td><td>5mg</td><td>2.5mg</td><td>1mg</td></tr></table> <p>C. Prescribe ad libitum dose of methadone to be given for when the pain returns after a 3-hour period (see above table)</p> <p>D. Prescribe alternative PRN analgesia for if the pain returns within the 3-hour window</p> <ul style="list-style-type: none">Paracetamol orPreviously used opioid at 50-100% of the PRN dose used prior to methadone conversion with a minimum of hourly intervals	Previous EDD Morphine	Specialist First & ad libitum dose ¹	Safer dosing Alternative ²				First dose	Ad libitum	> 500mg	30mg	20mg	10mg	200-500mg	20mg	10mg	5mg	100-200mg	10mg	5mg	2.5mg	<100mg	5mg	2.5mg	1mg
Previous EDD Morphine	Specialist First & ad libitum dose ¹	Safer dosing Alternative ²																							
		First dose	Ad libitum																						
> 500mg	30mg	20mg	10mg																						
200-500mg	20mg	10mg	5mg																						
100-200mg	10mg	5mg	2.5mg																						
<100mg	5mg	2.5mg	1mg																						
Days 2-5	Senior medical review of the patient daily or more frequently if required If the patient becomes sedated/drowsy/, hallucinate or has a reduced respiratory rate (<8 resp/mn), reduce the dose of methadone by 33-50% If there is no evidence of toxicity dose adjustments may be required to prevent under or overdosing: <ul style="list-style-type: none">If 1 or 2 doses per 24h, reduce by 50% or 30% respectivelyIf 5 doses or more, increase by 30%																								
Days 5-10	If pain uncontrolled or dosing requirement irregular, continue ad libitum titration until stable requirement for at least 48h If pain is controlled the patient can be switched to a regular TDS or QDS dosing regimen (see section 5)																								
Pre-discharge	Arrange community prescribing and shared care with the GP and community pharmacist Book review with the community palliative care team within 5 days of discharge. Medical reviews by experienced physician within 2 weeks is essential.																								
Maintenance	Give patient a letter to state that they are on methadone for pain control to show to other healthcare professionals when consulted. Advice to the patient that they should contact the specialist palliative care team with any queries regarding pain control. Patient can never be discharged from specialist palliative care whilst remaining on methadone.																								

¹ These doses are recommended for centres who have good experience of methadone titration and can provide very close clinical monitoring and supervision of patients.

² These doses are recommended to centres who are less familiar with methadone titration or when there is concern about the reliability of the patient in reporting pain because of anxiety or previous tendency to overdosing.

Methadone for pain relief

What is methadone?

This medicine is used for moderate to severe pain. It belongs to a large family of medicines called strong opioid medicines which are drugs similar to morphine. Common examples of other strong opioids are: morphine, diamorphine, oxycodone, fentanyl and buprenorphine.

Why is methadone better for me than other opioid medicines?

Certain types of cancer pain respond better to methadone. Cancers affecting the chest wall, deep in the belly especially around the pancreas and also cancers affecting the bone round your hips and the areas near your bottom can cause severe pain which can be treated with methadone.

All pains including some chronic non-cancer pains can be helped by methadone, especially when the dose of the other opioids has escalated over months or years and gradually lost their effects or caused more side-effects.

Your doctor may suggest switching to methadone, if you are experiencing uncontrolled pain despite taking bigger doses of strong opioids, or having ongoing side effects on strong opioids such as:

- Feeling more sleepy
- Feeling sick more of the time
- Restlessness, twitching or jerking
- Bad dreams
- Confusion and hallucinations (seeing or hearing things that are not really there and are not seen or heard by other people).

Although you could still get these unpleasant effects when you start with methadone, they will rarely carry on more than a few days. We expect you to feel a lot better on methadone once we know how much you need.

If methadone is so much better than other strong opioids, why do we bother using them?

Although methadone is a very good painkiller, it requires more experience in prescribing than morphine and other strong opioids, because the dose of methadone needed is very different from one person to another. This means that the doctors need to skilfully adjust your methadone dose, to stop you getting too sleepy whilst trying to control the pain, especially at the start of this treatment. It can also take much longer to find the right dose if the doctor is not available to review you frequently. In the right hands and started in the right environment, methadone be extremely effective in difficult to control pain.

Is methadone only used for people at the end of their life?

Like other strong opioid medicines, it is given for different sorts of moderate to severe pain that may be as a result of cancer or other illnesses. We have learnt over more than 20 years of prescribing methadone that it is best to change over to methadone long before the last few weeks of life. Indeed a few patients are known to have been on methadone for years. When methadone has been started successfully, it is best to continue on methadone indefinitely.

Isn't methadone a medicine that drug addicts take?

Apart from pain control, methadone is used to help wean people from illicit use of drugs such as heroin. In these situations, methadone prevents withdrawal symptoms (cold turkey) and reduces the urge to go back to using drugs. People go on having a better quality of life, whilst staying on methadone.

However, methadone is also prescribed widely for pain relief by healthcare professionals across the world- especially Britain, Ireland, Australia, USA and Canada. The prescription of methadone for pain relief requires expertise and is only prescribed under supervision by a few specialist centres. It is important to understand that you are having methadone for the reason of pain relief, and there is no other meaning to you being on methadone.

If I take methadone or other opioids, will I get addicted to them and be unable to stop taking them?

No, taking methadone or other opioids for pain will not make you an addict. It is quite normal for the dose to increase over time, although many people remain on a stable dose for long periods. Methadone seems to remain effective for years, and certain patients have even taken methadone for more than 10 years with excellent effect on pain and quality of life.

As with other medicines, you should not stop taking methadone or any opioids suddenly without discussing this with your doctor or nurse as your body needs time to adjust. If you no longer need to take opioids, your doctor or nurse will reduce the dose gradually.

How will I start taking methadone?

Methadone is very different to other painkillers like morphine. We cannot work out in advance the dose you will need. So, we therefore always start afresh and work out the dose you need with a method that does not rely on what you took before. Methadone must be monitored carefully when started, to reach the right dose safely. This is why switching to methadone is carried out in a specialist unit, such as a hospice. You will need to be sure that you can stay in the hospice for at least 2 weeks, although sometimes you may be able to go home more quickly.

What are the main side effects to look out for?

Opioids including methadone tend to make you constipated and most people will need to take laxatives. They can also sometimes make you feel sick when you first take them. Your doctor may give you something to stop this feeling, but it usually only lasts a few days. Opioids can make you feel sleepy for the first few days while you are getting used to them or when the dose is increased but our bodies can usually adapt gradually.

How do we find out how much methadone you need?

1. When you are admitted to the in-patient unit, we will normally observe you during the first day, reviewing your pain control and any side effects of your existing painkillers. You will continue to take your pain medicine as you would have done at home with any other painkillers you were taking including medicine for pain breakthrough. We use a special sheet called 'Opioid monitoring chart' to record any possible side-effects related to your pain medicine. We will do an electrocardiogram (ECG) in order to make sure your heart rhythm will not be affected by methadone.
2. When we start methadone, you will normally stop any strong opioid drug(s) you are already on. You will normally be prescribed a fixed amount of methadone chosen by the medical team. Methadone can be given in a liquid or tablet form according to your preference.

3. It can take up to **3 hours** to get the full effect of each dose of methadone because it takes time for methadone to get through the bowels into your body. This is why we don't give methadone more often than every 3 hours but, if you still have pain after 3 hours, we will give you another dose and so on until the pain is controlled.
4. You can take a top-up dose of another painkiller during the 3-hour gap if you are in too much pain but after 3 hours, it is better to have methadone.
5. **You must tell us as soon as the pain is coming back**, so we can give you methadone in time but please do not ask for methadone if you don't have pain even if it is more than 3 hours that you had the last dose.
6. We continue checking regularly for any possible side effects of your pain medicines whilst we are giving you methadone. We follow a strict method with frequent checks by senior doctors with experience in prescribing methadone.
7. During the first week on methadone, we need to watch you closely looking for pain relief obtained or any side-effects. Side effects can vary through the day. We check every day how much methadone you have needed so far and decide whether we should change the dose we give you each time.
8. Usually after 5 to 8 days of you telling us when the pain is coming back, we can decide how much methadone you need each day. We give it to you 3 or 4 times a day, but you can have your methadone dose a little earlier if the pain comes back before you are due your next dose. If it is less than 4 hours since you last had methadone, we will give you a top-up dose of another painkiller instead.
9. We usually keep you a few more days in the hospice once you are on the regular dose of methadone to make sure everything is all right.
10. When you go home, we will give you an appointment to see the Consultant from the hospice within the next week or two.
11. We will need to do an ECG (heart tracing) again to check for any possible risks of irregular heartbeat. If it is OK, we don't need to do it again unless the dose of methadone has to be increased a lot. If the reading of the ECG gives reasons for concern, we may need to check the ECG more often but we may also in rare cases, have to reduce the amount of methadone you take.

Is there a maximum dose of methadone?

No, there is no maximum dose that can be prescribed. If it is taken for pain as prescribed, the dose can be increased gradually to match your pain. People can be on large amounts of methadone for a long time without significant problems. Long term, you should remain under the care of a specialist doctor who is an expert in methadone, but your GP can prescribe the repeat prescriptions of methadone.

Can I start taking other medications whilst I am on methadone?

Your methadone specialist will have reviewed your medication when starting you on it. Other medications may react with methadone to decrease its pain relief effects, or increase its side effects. Please ensure any healthcare professional who gives you medication advice is aware you are taking methadone for pain control. If you start a new drug, even for a short course, it is wise to check with your doctor whether it could cause methadone to have more or less effect and get in touch with your specialist pain doctor to ask if the methadone dose needs changing. For this reason, it is important that you contact your healthcare professional before you start, or stop, any other medications you are on.

Can I drive if I am taking methadone?

Driving may be possible but there are many factors to consider and your doctor or nurse will advise you. Please remember that as in any other situation you should only drive if you feel it is completely safe for you to do so. In 2015, new drug-driving laws came into place and the police can now carry out roadside testing for strong opioids. If you are taking a strong opioid (which includes methadone) and are tested for this whilst driving, no action is taken if the medication is in accordance with medical advice and you are safe to drive. It is useful to keep information of your medication with you when driving, such as your repeat prescription sheet.

However, it remains an offence to drive if your driving is impaired by the medication (e.g. drowsiness). **It is your responsibility not to drive if this is the case.** If you have any further questions you can discuss this with your healthcare team.

What should I do if I am sick or am not able to swallow methadone?

Methadone stays in your body longer than other medications. This means that you may not straightaway feel the pain coming back. It is sometimes possible to continue giving you methadone when you are just occasionally sick. Methadone can be given by injection or using a syringe driver if needed. Your doctor may decide to prescribe the injections for you to keep at home just in case it is required.

Can I drink alcohol if I am taking methadone?

Yes you can drink small amounts (e.g. a small glass of wine, beer or spirits) but it may make you feel more sleepy.

How do I store methadone at home?

Keep the medicines in their original containers, clearly labelled and stored safely at room temperature in a dry place. Make sure that they are well out of reach and sight of children. The label should provide storage instructions but check with your pharmacist if you are unsure.

What should I do with any opioids that are no longer needed?

Opioids that are no longer needed should be returned to the pharmacist for safe disposal. Do not flush them down the toilet or throw them away.

Further prescribing of methadone and follow up

When you are discharged home or when you start methadone as an outpatient, you will be given a letter explaining that you are on methadone for pain, **not** because you are on a methadone programme for drug addiction. The letter is addressed to any health care professional and explains that the dose of methadone should only be changed in consultation with your specialist hospice consultant.

Your GP or your specialist doctor will provide you with further prescriptions of methadone. It is very important that you never run out of your medication. You should not stop taking this drug unless on the advice of a palliative care doctor or nurse as this would be likely to make you feel ill for a few days afterwards. This is called a withdrawal reaction. You could also get a severe return of pain.