Methadone for Pain; Prescribing Guidelines, 2011

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Methadone is a strong opioid with an established role in the relief of cancer pain. Though methadone has many positive characteristics e.g. a broad spectrum of analgesic activity (opioid and non-opioid) and a favourable profile in renal failure, these do not justify early selection in the management of pain in view of; methadone's complex pharmacokinetics (an unusually long, unpredictable, and varying half-life of typically ~8 - 80h which can lead to difficult initiation, titration and significant accumulation); a specific cardiac toxicity (QT interval prolongation); and complex / potentially serious drug interactions (P450 CYP3A4). Consequently, the availability of alternative strong opioids and co-analgesics may present more suitable options. Careful patient selection to identify those suitable for starting methadone is paramount. If there is any doubt regarding a patient's suitability or the required titration procedure for methadone, the case should be discussed with a consultant. Additionally the availability of experienced staff to provide the necessary support during initiation should be confirmed before a patient is switched to methadone (ideally in the inpatient setting). There is no conversion ratio to move from morphine to methadone, though once stabilised, typically far smaller methadone doses around 5 -10X less than morphine are needed (but can be 20 -30X smaller).

Indications for methadone in the palliative care setting:

The specific indication for prescribing methadone needs to be clearly documented in the patient's records

1. **Chronic, moderate to severe malignant nociceptive pain**
   Typically only as a third line opioid;
   1st line; morphine
   2nd line; oxycodone or fentanyl or buprenorphine
   3rd line; methadone
   - **Dose limiting opioid side effects;** where increases in second-line opioid dose have delivered analgesia but with intolerable adverse effects. Opioid-induced myoclonus is a good predictor of benefit from switching; similarly other neurotoxicities are relevant e.g. opioid-induced hyperalgesia and allodynia
   - **Rapid opioid tolerance;** where increases in second-line opioid dose have delivered only short periods of analgesia requiring rapid dose escalation. High doses particularly above an EDDM of 500mg are a positive predictor of likely benefit
   - **Refractory cancer pains;** in difficult cancer pain syndromes where "all standard" analgesic options (optimised simple / second-line opioid / coanalgesic combinations) have failed

2. Pain relief in **severe renal failure**
   - Methadone has no active metabolites and limited accumulation in plasma as a result of enhanced faecal elimination in renal failure
   - Particularly helpful for patients on dialysis – as methadone is not removed by dialysis
   - However, don't start methadone in final terminal stages of severe renal failure; use Alfentanil / Fentanyl

3. **True morphine allergy;** though rare, methadone's different structure prevents cross-anaphylaxis with either morphine or oxycodone

4. **Other pain states:** Methadone may also prove valuable in other settings, though the evidence is less clear:
   - Neuropathic pain - mixed results, no robust evidence though increasingly positive, thus more "traditional" approaches should be explored first.
   - Chronic non-malignant pain

5. **Anti-tussive agent:** well-established role as cough linctus (2mg/5ml; initially 1-2mg QDS reducing to BD – this formulation should not be used for analgesia)

Some clinical settings are not as suitable for switching to methadone, consider avoiding methadone in;

- Acute, unstable or escalating pain states – e.g. just following radiotherapy for bone pain; reducing pain could lead to dangerous toxicity
- Acute or chronic confusional states (if pain history appears unreliable) – may lead to inadvertent overdose
- Only the parenteral route available for initiation of Methadone – less practical for PRN
- Moribund / a predicted prognosis of less than one week – no time to get to steady state
- Psychogenic pain – relatively opioid / methadone resistant; may lead to unnecessary dose escalation/toxicity
- Spurious opioid responsiveness (steep rate on increase seen in round-the-clock opioid dose as PRN relief due to sedation rather than true analgesic benefit) – may lead to unnecessary dose escalation and toxicity
- Patients where compliance would be questioned (potential under- or over-use) – may lead to inadequate dosing and increasing pain or unnecessary dose escalation and toxicity
- Allergy to methadone - analphylaxis

Cautions:

Methadone already carries the risk of specific dose-related toxicity (prolongation of QT interval and prolonged respiratory depression) compounded by a potential to accumulate. Though the magnitude of the risk is yet to be established, additional caution, including the need to consider ECG monitoring, follows the disproportionate risks when inadvertent drug accumulation / specific QT interval toxicity appear more likely:

- When doses are higher than Methadone100mg daily (EMEA cut-off, but possibly significant risks at doses >60mg)
- Long QT intervals are seen in;
  - Cardiac co-morbidity; ischaemia, hypertrophy, arrhythmias etc...
  - Hypothyroidism, bradycardia, HIV antivirals), (genetic – rare)
  - Hypocalcaemia, hypokalaemia, hypomagnesaemia
- Respiratory co-morbidity; severe COPD, acute asthma, pre-existing respiratory depression, obesity (if hypoxia / hypercapnia)
- Drug interactions
  - Drugs that increase methadone levels (P450 CYP3A4 inhibition) e.g. SSRIs; Ciprofloxacin; Clarithromycin; Fluconazole and HIV antivirals e.g. indinavir, nelfinavir, ritonavir
  - Drugs that may also prolong QT interval e.g. Amitriptyline, Clarithromycin, diuretics, Domperidone, Fluconazole, Haloperidol, Octreotide, Ondansetron, Pregabalin, Tamoxifen & SSRIs
  - Drugs that reduce methadone levels (P450 CYP3A4 induction) e.g. Phenytoin; Carbamazepine; Phenobarbital
- Elderly – as longer half-lives are seen, though ad libitum titration should automatically adjust doses proportionately
- Partially or non-opioid responsive pains
- Patients intolerant to WHO step 2 opioids or low dose WHO step 3 opioids

Initiation of methadone - ad libitum titration: a fixed dose given at patent-determined intervals

Ad libitum titration is required because of marked dose changes during titration and wide inter-patient variability preventing sufficiently reliable equi-analgesic dose predictions. Adequate specialist supervision is paramount for methadone titration (ideally as an in-patient).

Starting dose: first calculate the "fixed dose" to be used ad libitum:
Calculate the "fixed dose" of methadone for titration as **1/10th of the equivalent daily dose of morphine** (EDDM) up to a **maximum dose of 30mg**. If opioid doses have escalated rapidly prior to the switch, consider using the pre-escalation dose to calculate the "fixed" dose (or something in-between). Methadone can be administered orally/PEG or occasionally rectally, and subsequently converted to CSCI/24h if required.
Always prescribe methadone doses as mg (not ml, to prevent confusion)
Prepare patients that any significant benefits (better analgesia/reduced toxicity) may take 24 to 48 hours

Preparations for pain:

PO	Oral "concentrate" 10mg/ml (blue) and 20mg/ml solution (brown); bitter – "Methadose" Rosemont); 1mg/ml solution (non-proprietary); 5mg tablets
PR	30mg, 50mg, 100mg Suppositories (Martindale special order) 50mg Suppositories (Boots special order)
CSCI	10 mg/ml as 1-mL, 2-mL, 3.5-mL and 5-mL vials; 2ml vials of 25 mg/ml and 1ml vials of 50 mg/ml (non-proprietary)

1) Titration phase; the "ad libitum" regime, using a "fixed dose" PRN

a) Stop all other opioids before giving the first "fixed dose" of methadone (**1/10th EDDM up to 30mg**) any transient opioid overlap is probably irrelevant and possibly even helpful, on switching. If concerns, delay Methadone first dose, 2 - 4h after IR opioid or 6 - 12h after M/R opioid – depending on pain

b) **Repeat the "fixed dose" at the patient's request**, on the recurrence of the targeted pain (even "slight discomfort") but **not within 3 hours of the last "fixed dose"** (in view of real risk of accumulation).

c) If there are concerns of higher potential toxicity (e.g. unusually rapid escalation to the conversion dose), **consider** using the initial 1/10th of EDDM only as a **"loading dose"**, thereafter use a lower dose **"fixed dose"** of **1/30th of EDDM** (again, up to a maximum dose of 30mg)

d) Use non-opioid analgesia as back-up in between; consider paracetamol, NSAIDs and non-drug measures. Avoid using other opioids if possible, as this could prolong the titration phase, however the patients most recent prior short-acting opioid can be used if necessary

e) If effective analgesia is not achieved within the first 72 hours despite all 8 doses of methadone per day, providing there is no opioid toxicity, the "fixed dose" can be increased by ~33 - 50% (e.g. limit up to 50mg and then 75mg, ideally still within the 1/10th of EDDM limit) to ensure maximal loading and clarify dose-effect. However, discontinue titration if unexpected pain escalation occurs during titration to suggest the switch to methadone has failed

f) If opioid toxicity such as sedation occurs, the "fixed dose" can be decreased by ~33 - 50% (e.g. from 30mg to 20mg and then 15mg)

g) If effective analgesia is achieved in the first 72 hours with only 1 or 2 doses of methadone per day, the "fixed dose" can be decreased by ~33 - 50% (e.g. from 30mg to 20mg and then 15mg)

h) An ideal PRN dose of Methadone would result in good relief without toxicity using between 4 and 8 doses a day.

i) Opioid withdrawal effects may be experienced – use a low dose, at most half the prior back-up dose, of the immediate release preparation of the most recent opioid used before switching to methadone
j) As opioid adverse effects reduce, a reduction in constipation will often require a reduction in laxatives

2) Waiting till steady-state is confirmed

Critical stage – firstly it confirms good candidate for switch (as dose-response to methadone seen); secondly confirms reached steady-state (so safe to consider move from PRN to RTC dosing); and thirdly it quantifies dose required RTC Continue with PRN administration of the fixed dose. Wait until the demand for methadone clearly reduces (typically around day 3 - 5, but it can take up to 10 days), and then stabilises for another 2 - 3 days, signifying steady-state (as risks of accumulation are minimised thereafter). If no clear dose drop is witnessed, consider abandoning the switch to methadone

3) Calculating regular regimen

Once doses are relatively stable for 2 - 3 days after a clear drop in 24-hour dose, calculate the mean total daily dose of methadone required over the preceding 48 hours, then divide this mean daily dose by 2 to find the regular dose for a BD regime (a TDS regime or a single nocte dose can suit some patients better)

4) Subsequent titration after initial 7-10 days stabilisation

Titrate the dose as with other opioids, increasing the dose by 33% - 50% as required (e.g. if PRN is required regularly on daily basis), ideally with increasing daily methadone no more than once weekly (if the increase doesn't reduce the demand for PRN, reduce round the clock methadone back to prior daily dose and consider other options).

5) As required PRN dosing

Once on a regular regimen, 10% of the daily methadone dose can be given PRN, though ideally not within 2-3 hours of the last regular or PRN dose (reassure that analgesia can increase for more than 1 hour following methadone administration). If next BD dose is imminent (next 1-2 hours) this can simply be brought forward (then resume normal timings).

6) Discharge arrangements

On discharge from the hospice the patient needs to be given a covering letter outlining the necessary advice in prescribing methadone and 24-hour points of contact for specialist advice. A copy should also be sent to the relevant lead clinician directly. Arrangements to supply the correct dose / concentration of methadone need to be place with the local pharmacist. Advise not to drink grapefruit juice and seek advice when any drug changes are made

7) Conversion from oral to parenteral Methadone

Titration with S/C methadone, though possible using the same fixed dose method, is not advisable. If patients on oral methadone lose the oral route, methadone for injection can be used as a CSCI, usually made up in **N/Saline** or if required, water for injections. Use 50% - 66% of the daily oral dose or rectal dose. Again use $1/10^{th}$ of 24-hour S/C methadone dose as S/C PRN 3-hourly. Though compatible with many other syringe driver medications, as site reactions can occur, set up in a separate pump where possible and change sites every 48 hours. If site problems do occur; first decrease concentration by increasing volume of diluent and site rotation every 24hours; then add Dexamethasone 1 - 2mg; then inject Hyalase 1500IU S/C into CSCI site (possibly better than into syringe). Alternatives to methadone e.g. oxycodone or fentanyl for use as S/C PRNs may suit better – faster action and less irritant, if appropriate clinically (no prior problems) and practical (volumes needed per injection)

8) Conversion from Methadone back to another opioid

a) Within 7 days of the switch (during titration): revert back to the pre-switch opioid at 66% - 75% of the prior EDDM and re-titrate (as empirical figures).
b) After chronic methadone administration: multiply methadone dose by 2 - 3 to estimate the "current" / "safe" EDDM, use half dose for 2 days and carefully re-titrate with "unlimited" back-up of new opioid for pain (empirical figures erring on under-dosing) while allow occasional methadone rescue for any specific withdrawal side effects not responding to the new opioid.
c) Additionally it is important to be guided by;
    (1) The prior conversion ratio to methadone
    (2) The perceived need for clinical caution (any dose escalating with methadone and any particular patient risks e.g. COPD)