Methadone for Pain; Prescribing Guidelines, 2015

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Methadone is a strong opioid with an established role in relief of cancer pain. Though methadone has many positive characteristics e.g. 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 to 80h, leading to difficult initiation, titration and risk of accumulation); specific cardiac toxicity (QT interval prolongation); more concerns of respiratory depression; and complex / potentially fatal drug interactions (via P450 CYP3A4). Consequently, other strong opioids / co-analgesics will typically appear more suitable options. When considering methadone careful patient selection is paramount. Before starting methadone, all cases should be discussed with a consultant. When initiating methadone, confidence in the unique titration is paramount. Additionally the on-going availability of experienced staff to provide the necessary support should be confirmed before a patient is switched to methadone (ideally in inpatient setting). There is no conversion ratio to move from morphine to methadone, though once stabilised, typically far smaller daily methadone doses of 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**
   Methadone should typically be used as a third line opioid, i.e. after; 1st line, morphine; and 2nd line, oxycodone
   Methadone would be most appropriate in specific contexts, when:
   - **Dose limiting opioid side effects;** where increases in opioid doses have delivered analgesia but with intolerable adverse effects. Opioid-induced myoclonus is a good predictor of likely benefit if do switch; similarly other neurotoxicities are relevant markers of possible benefit e.g. opioid-induced hyperalgesia and allodynia.
   - **Rapid opioid tolerance;** where increases in opioid dose have delivered notable but short periods of analgesia, requiring rapid dose escalation. High doses particularly above EDDM of 500mg are positive predictors of benefit.
   - **Refractory cancer pains;** in difficult cancer pain syndromes where "all standard" analgesic options have failed (already optimised simple, opioid and co-analgesic combinations).

2. Pain relief in **severe renal failure**
   - Methadone has no active metabolites and there is limited plasma accumulation as a result of enhanced faecal elimination in renal failure.
   - Particularly helpful for patients on dialysis – as methadone is not significantly removed by dialysis.
   - However, don't start methadone in final 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, 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 after radiotherapy for bone pain, as reducing pain could lead to dangerous toxicity.
- Acute or chronic confusional states, or just if pain history appears unreliable – these 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 to two weeks – no time to get to steady state.
- Psychogenic pain – as relatively opioid / methadone resistant; may lead to unnecessary dose escalation/toxicity.
- Spurious opioid responsiveness (steep rate of increase in round-the-clock opioid dose, as PRN relief due to sedation rather than actual analgesia) – 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 – anaphylaxis.

Cautions:

Methadone already carries the risk of specific dose-related toxicity compounded by a potential to accumulate (prolongation of QT interval and prolonged respiratory depression). Though the magnitude of the risk in the hospice setting is yet to be established, additional caution is needed, including consideration of ECG monitoring, if the risks for inadvertent drug accumulation and / or specific QT interval toxicity appear disproportionate (as below), or mandatory ECG if any warning symptoms such as dizziness, palpitations and / or syncope:

- When doses are higher than Methadone100mg daily (EMEA cut-off, but possibly significant risks at doses >60mg).
- Long QT intervals are seen in;
  - i) Cardiac co-morbidity; ischaemia, hypertrophy, arrhythmias etc...
  - ii) Hypothyroidism, bradycardia, HIV (as on antivirals, see below), (genetic – rare).
  - iii) Hypocalcaemia, hypokalaemia, hypomagnesaemia.
- Respiratory co-morbidity; severe COPD, acute asthma, pre-existing respiratory depression, obesity (if sufficient to cause hypoxia / hypercapnia).
- Drug interactions (bold more serious, underlined if both risks; increased methadone levels and prolonged QT interval)
  - **i)** Drugs that **increase methadone levels** (P450 CYP3A4 inhibition) e.g. SSRIs; Ciprofloxacin; **Clarithromycin**; Diazepam; Fluconazole; Grapefruit; several HIV antivirals; Midazolam; and Quetiapine
  - ii) Drugs that may also **prolong QT interval** e.g. Amitriptyline, **Clarithromycin**, diuretics, **Domperidone**, Fluconazole, **Haloperidol**, Octreotide, Ondansetron, Pregabalin, Tamoxifen & SSRIs.
  - iii) 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.

Starting dose: first calculate the "fixed dose" to be used ad libitum:
The "fixed dose" of methadone to use in for titration is **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, needs flavouring – "Methadose" (from 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 on switching is not of clinical concern and possibly helpful. If concerns as already toxic, delay first Methadone dose, to be 2 - 4h after IR opioid or 6 - 12h after M/R opioid – depending on severity of pain.

b) **Repeat the "fixed dose" when patient requests more**, on the recurrence of the targeted pain (even "slight discomfort") but **not within 3 hours of the last "fixed dose"** (to mitigate against risk of accumulation).

c) Exceptionally, when additional concerns of higher risks of 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), though the delay may be counterproductive.

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.

2) Calibrating "fixed dose"

a) An ideal fixed dose of PRN Methadone for titration would result in good relief without toxicity using between 4 and 8 doses a day (so rapid relief, rapid titration and clear dose drop as then steady state and sure safe for RTC dosing).

b) If effective analgesia is not achieved within the first 48 hours despite all 8 doses of methadone each day, providing there is no opioid toxicity, the "fixed dose" can be increased by ~33 - 50% (limit up to 50mg and then 75mg, providing still within the 1/10th of EDDM limit) to ensure maximal loading and clarify dose-effect. However, discontinue titration if unexpected pain escalation during titration, to suggest the switch to methadone has failed.

c) 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).
d) If effective analgesia is achieved in the first 48 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).
e) 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.
f) As opioid adverse effects reduce, a reduction in constipation will often require a reduction in laxatives.

3) Waiting till drop in demand for PRN Methadone, when steady-state reached

Critical stage – firstly it confirms good candidate for switch (as confirms dose-response to methadone); 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 is stable for another 2 - 3 days, signifying steady-state (as risks of accumulation are minimised thereafter). If no clear dose drop is witnessed by day 10 to 14, consider abandoning the switch to methadone.

4) Calculating regular regimen

Once doses are relatively stable for 2 - 3 days after a clear drop in the 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).

5) Subsequent titration after initial 7-10 days stabilisation

Titrate the dose as with other opioids, increasing the dose by 33% 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).

6) 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).

7) Discharge arrangements

On discharge from the hospice the patient needs to be given a covering letter outlining the necessary advice for prescribing methadone and 24-hour point 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.

8) 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 1/10th 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).

9) 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 using 4-hourly IR opioid 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 using 4-hourly IR opioid 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).