

Methadone for Pain; Prescribing Guidelines, 2010

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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 (a long, unpredictable, and varying / increasing half-life of ~8 - 80h which can lead to significant accumulation) and the available range of alternative strong opioids and co-analgesics, which 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.

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 2.5-5ml QDS reducing to BD – this formulation should not be used for analgesia)

Cautions and exclusions:

Additional care is often needed, as the risks of inadvertent drug accumulation/toxicity are higher in several situations – though the specific titration of methadone (ad libitum) should automatically adjust doses safely:

- Cardiac co-morbidity (arrhythmias; can cause prolongation of QT interval, but not seen in with oral methadone in cancer patients)
- Drug interactions (e.g. increased effects of methadone with; MAOi; amitriptyline; SSRIs; ciprofloxacin; fluconazole; and cimetidine)
- The elderly
- Partially or non-opioid responsive pains
- Patients intolerant to WHO step 2 opioids or low dose WHO step 3 opioids

Some clinical settings are not suitable for switching to methadone, avoid in;

- Acute or chronic confusional states (if pain history appears unreliable)
- Only the parenteral route available for initiation of Methadone
- Moribund / a predicted prognosis of less than one week
- Psychogenic pain
- Spurious opioid responsiveness (sedation rather than true analgesic benefit)
- Patients where compliance would be questioned (potential under- or over-use)
- Respiratory depression
- Allergy to methadone

Initiation of methadone - ad libitum titration: a fixed dose given at patient-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 10mg/ml and 20mg/ml solution (blue, bitter – "Methadose" Rosemont), 1mg/ml, 5mg tablets
 PR 30mg, 50mg, 100mg Suppositories (?Martindale special order) 50mg Suppositories (Boots)
 CSCI 1ml, 2ml, 3.5ml, and 5ml vials of 10mg/ml

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) to ensure maximal loading and clarify dose-effect. However, discontinue the

titration if unexpected pain escalation occurs during titration to suggest the switch to methadone has failed

- f) 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. fro 30mg to 20mg and then 15mg)
- g) 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
- h) Opioid adverse effects need to be monitored and managed appropriately; typically a reduction in constipation requires a reduction in laxatives or if sedation occurs, reduce the "fixed dose" by 33-50%

2) Waiting till steady-state is confirmed

Continue with PRN administration of the fixed dose. Wait until the demand for methadone 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)

3) Calculating regular regimen

Once doses are relatively stable for 2 - 3 days after a 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 in a BD regime (a TDS regime or even a single nocte dose can suit some patients better)

4) Subsequent titration after initial 1-2 weeks 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).

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 up to 1 hour following methadone administration). If the next BD dose is imminent (next 1-2 hours) this can simply be brought forward.

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

7) Conversion from oral to parenteral Methadone

Titration with S/C methadone, though possible using the same fixed dose method, is not advisable. If paking 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)

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 for pain (empirical figures erring on under-dosing) while allow methadone rescue for any specific withdrawal side effects.
- 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)