

The Use of Methadone in Palliative Medicine

For patients with palliative care needs, methadone should only be prescribed under the supervision of a specialist palliative care team
The use of methadone is complex, owing to its long half-life, accumulation after repeated doses and wide inter-individual variations.

Indications for Use

- Moderate to severe pain, neuropathic pain, cough

Pharmacokinetics

- Methadone is a synthetic opioid with mixed properties; it is a mu-opioid receptor agonist, an NMDA receptor channel blocker and a pre-synaptic blocker of serotonin reuptake.
- It is absorbed well from all routes of administration, with 80% oral bioavailability (range 40–100%).
- It has a high volume of distribution due to its lipid solubility, and is extensively protein-bound.
- The result is a long and unpredictable plasma half-life, leading to potential problems with accumulation. Initial doses will typically have a half-life of hours whereas, after stable dosing has been reached, the half-life may increase to some days.

Preparations

- Methadone 1mg/ml Oral Solution
- Methadone 10mg/ml Oral Solution—Available for hospital use only
- Methadone Injection 10mg/mL 1ml vials (Martindale) - unlicensed in Ireland

ORAL DOSE CONVERSION

When rotating strong opioids to methadone, various methods of rotation have been proposed.
The method favoured by OLH&CS is the Palliative Care Formulary 'Stop and Go' Approach.

PALLIATIVE CARE FORMULARY 'STOP AND GO' APPROACH

1. The initial opioid is discontinued when methadone is started. Calculate the total 24 hour oral morphine equivalent dose the patient has been taking.
2. Give a single **loading dose** of oral methadone **one-tenth** of the total 24 hour oral morphine equivalent dose up to a **maximum of 30mg** of methadone.
3. A three hourly '**as required**' dose of methadone **one-thirtieth** of the total 24 hour oral morphine equivalent dose is prescribed, up to a **maximum of 30mg** of methadone. If additional analgesia is required for breakthrough pain, i.e. for patients in severe pain, an alternative opioid may be prescribed 'as required' for second line use.
4. On **day six**, the amount of methadone taken in total over the previous 48 hours is calculated and divided by 4 to give a regular twice daily dose.
 - When considering the use of methadone, the difficulty of a subsequent switch from methadone to another opioid should be borne in mind.
 - When switching from a strong opioid other than morphine, the total equivalent daily dose of morphine is used.
 - If there has been recent rapid escalation of the pre-switch opioid dose, calculate the initial dose of methadone using the pre-escalation dose of the opioid.
 - The use of a loading dose aids tissue saturation and helps to reduce the number of PRN doses required, however, based on the clinical context a decision may be made to omit the loading dose (e.g. when converting from a transdermal patch).
 - The timing of the first dose of methadone is dependent on the clinical context. The Palliative Care Formulary advises the following when switching from modified-release morphine; give the first dose of methadone ≥ 6 h (pain present) or 12h (pain-free) after the last dose of the 12 hour preparation of morphine.

ORAL DOSE CONVERSION—WORKED EXAMPLES

Example 1: Patient receiving the equivalent of 120mg oral morphine in 24 hours

Loading dose = 12mg oral methadone

'As required' dose = 4mg oral methadone

Example 2: Patient receiving the equivalent of 450mg oral morphine in 24 hours

Loading dose = 30mg oral methadone (one-tenth equates to 45mg however this exceeds the maximum dose advised)

'As required' dose = 15mg oral methadone

Example 3: Patient receiving the equivalent of 1200mg oral morphine in 24 hours

Loading dose = 30mg oral methadone (one-tenth equates to 120mg however this exceeds the maximum dose advised)

'As required' dose = 30mg oral methadone (one-thirtieth equates to 40mg however this exceeds the maximum dose advised)

Management of Breakthrough Pain

Methadone prescribed for breakthrough pain can be taken up to a maximum of 3 hourly. For patients in severe pain and who need more analgesia within 3 hours, a second opioid may be prescribed for breakthrough pain.

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Subcutaneous Dose Conversion

When switching from oral to subcutaneous methadone one of two ratios can be used, **2:1 or 1:1**. Dose calculation and titration should be carefully individualised. The Palliative Care Formulary recommends a 2:1 conversion however notes that a 1:1 conversion ratio may be more appropriate for those receiving doses of less than 80mg/24h methadone.

For further information see 'How do you convert methadone from an oral dose to an equivalent subcutaneous dose?' Available on <http://www.olh.ie/7-departments/166-palliative-meds-info/>

Cautions

Methadone can cause QT prolongation. Caution is advised in patients at risk of QT prolongation. Subcutaneous administration can cause marked local inflammation necessitating site rotation.

Hepatic Impairment

Methadone is extensively metabolised in the liver. There is a lack of consensus on the need for dose adjustment in hepatic impairment. Dose reductions of up to 50% have been suggested in hepatic failure. Caution is advised and dose requirements should be individually titrated.

Renal Impairment

Dose reduction may be necessary in moderate to severe renal impairment. Reductions of 50-75% have been suggested where creatinine clearance is less than 10ml/min

Drug Interactions

Methadone has the potential for numerous and complex drug interactions, due to its metabolism via the Cytochrome P450 enzyme system.

Drugs that may **increase** the effect of methadone include:

- Amiodarone
- Ciprofloxacin
- Clarithromycin
- Clopidogrel
- Erythromycin
- Fluconazole
- SSRIs
- Voriconazole

Drugs that may **reduce** the effect of methadone include:

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin
- Anti-retrovirals

Methadone can interact with other drugs. Please consult with pharmacy for advice. Product information is available on www.hpra.ie

Issues for Discharge and Outpatients

Methadone **MUST** be prescribed on the designated methadone prescription form issued by the Minister for Health

For further information contact Pharmacy to request a copy of 'Methadone – From Hospital to Home – Practical Information'