

General Properties¹

- Synthetic opioid developed over 60 years ago
- Affects mu, kappa, delta, and NMDA receptors (useful in neuropathic pain due to effect at NMDA)
- Routes of administration include oral, rectal, IV & SQ
- Oral tablets available as 5mg and 10mg tablets; oral solution available as 5mg/5ml, 10mg/5ml and 10mg/ml. All are available at low cost.
- Fat soluble, is quickly and widely distributed throughout the body, retained in tissues, and slowly released back into plasma during redistribution and elimination
- Functions as a long-acting opioid (both tablets and oral solutions) after repeated, regular use due to its long elimination half-life (range: 5-130 hours, average: 20-35 hours); steady state achieved in 4-10 days
- Metabolism takes place primarily in the liver via the cytochrome P450 (CYP450) enzyme system
 - Multiple medications cause significant drug interactions²

Drug Interactions²

CYP450 Inducers (decrease methadone concentrations)	CYP450 Inhibitors (increase methadone concentrations)
Anti-tuberculosis agents (rifampin, rifabutin)	Azole antifungals (itraconazole, fluconazole, ketoconazole)
Anticonvulsants (phenobarbital, phenytoin, carbamazepine)	SSRI antidepressants (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram)
Anti-retrovirals (nevirapine, efavirenz, amprenavir, ritonavir)	Antibiotics (clarithromycin, erythromycin, ciprofloxacin)
Recommendation: Encourage the use of rescue medication	Recommendation: Empirically reduce methadone dose by 25% or more

Adverse Effects²

- Common adverse effects: sedation, dry mouth, constipation, dizziness, nausea
- Serious adverse effects: respiratory depression, apnea, severe hypotension, seizures

Cardiac Effects³

- Increased risk for QT interval prolongation and Torsade de Pointes (TdP)
- More common in larger doses, but also observed with lower doses
- Use caution with cardiac arrhythmias, electrolyte abnormalities, hypotension, and other cardiac diseases
- Use caution when administering methadone with other QT prolonging agents
- Medications associated with QT prolongation and TdP:
 - Antiarrhythmics
 - Antiemetics
 - Quinolone antibiotics
 - Macrolide antibiotics
 - Antipsychotics
 - Tricyclic antidepressants

Candidates for Methadone Therapy¹

- Moderate to severe pain
- Patients with true morphine allergy
- Significant renal impairment
- Presence of neuropathic pain
- Pain refractory to other opioids (high opioid tolerance)
- Patients needing long-acting opioids and unable to swallow whole tablets but can utilize oral crushed tablets, liquid, or tablets administered rectally
- For opioid rotation in patients exhibiting signs of opioid neurotoxicity
- Cases where cost of other long-acting opioids is an issue

When to Avoid Methadone Therapy

- Limited prognosis < 1 week
- Drug-drug interactions
- History of arrhythmias or QTc prolongation
- Inability to take medications as prescribed
- Lack of practitioner for continued monitoring

Methadone in Opioid-Naïve Patients^{1,3}

Patients receiving less than 40-60 mg oral morphine equivalent per day are considered opioid-naïve
Hospice and palliative care experts recommend a starting dose of 2 to 7.5mg of oral methadone per day
Initial dose increases of no more than 5 mg/day every 5-7 days
When total daily dose (TDD) exceeds 30-40 mg/day, dose increase should be no more than 10 mg/day every 5-7 days

Initiation of Breakthrough Pain Medication¹

- Most practitioners do not use methadone for rescue dosing due to the prolonged half-life and increased risk for accidental overdose
- For the opioid-naïve: morphine 2.5-5mg po every 2-4 hours as needed or equipotent dose of another opioid
- Important to keep pain diary to document use of breakthrough pain medications

Methadone as Adjuvant Therapy

- Methadone may be used as an adjuvant, or co-analgesic, to other opioids because of its unique mechanisms of action
- Research suggests that patients with a short life expectancy still benefit from adjuvant use of methadone⁴
- Doses of 2.5mg every 8-12 hours can be added to the existing pain regimen when utilizing methadone as an adjuvant analgesic

Monitoring and Titration¹

- It takes several days to achieve full analgesic effect (important to reassure patient that it is normal and expected for them to have a need for breakthrough pain medications for the first few days after starting methadone)
- Respiration (depth, rhythm, rate)
- Opioid overdose signals (difficulty waking, loud snoring, slurring of speech)
- Cardiac monitoring: unexplained syncope or seizures
- Gradual titration: don't titrate earlier than 5-7 days (faster titration increases the risk of respiratory depression/severe sedation/overdose); should notice a gradual improvement in pain and decrease in breakthrough pain medications; titrate based on the amount of breakthrough pain medication required

Methadone Conversions Ratios used by Enclara Pharmacia

Note: Various equianalgesic dose ratios for methadone conversion exist, ranging from 3:1 to 10:1 at lower doses, and 8:1 to 20:1 at higher doses. Consensus guidelines suggest that experienced clinicians, in closely monitored settings, may use more aggressive titration methods. For patients on higher doses of opioids, experts recommend using conservative ratios (15:1 to 20:1) and further decreasing calculated dose by 75-90%. For all conversion methods, the higher the oral morphine equivalent (OME), the lower the percentage of methadone required to give an equianalgesic effect. Enclara pharmacists use the following equianalgesic dose ratios:

OME Daily Dose (mg/day)	Initial Equianalgesic Ratio (M:ME)
<60	Recommend opioid naïve dosing
60-99	4:1
100-299	8:1
300-360	12:1
>360	Recommend TDD of 30mg**

**Initial recommendations of methadone are limited to 30mg per day regardless of previous opioid usage

References

1. McPherson ML. Methadone: A complex and challenging analgesic, but it's worth it! Demystifying opioid conversion calculations: A guide for effective dosing. 2nd edition. ASHP, Inc, Bethesda; 2018: 148.
2. Clinical Pharmacology [Internet]. Tampa (FL): Elsevier [April 22, 2024]
3. Chou R, Cruciani RA, et. al. Methadone Safety: A Clinical Practice Guideline from the American Pain Society and College on Problems of Drug Dependence, in Collaboration With the Heart Rhythm Society. *The Journal of Pain*. 2014; 321-337
4. Chalker, Cameron, Hannah O'Neill, and Faith Cranfield. "Efficacy of low-dose and/or adjuvant methadone in palliative medicine." *BMJ Supportive & Palliative Care* 12.e6 (2022): e730-e7