# Clinical Resource Guide:
# Methadone Use in the Hospice Setting

## INTRODUCTION TO METHADONE

Methadone is a synthetically derived Schedule II controlled substance developed in the 1940s, widely renowned for its utilization later in the management of opioid use disorder (OUD). Despite continuing to be used for OUD, methadone was initially developed as an analgesic, and has increased in popularity amongst palliative care and hospice providers for the management of persistent pain. The versatility, potency, multiple mechanisms of action and low cost make it an attractive therapeutic option, but complex pharmacokinetics, multiple reported conversion factors, and significant drug interaction profile may prevent some providers from prescribing the medication. This Pharmacist Corner was created to serve as a resource to hospice administrators and clinicians by providing guidance on the following:

***Pharmacist Corner Objectives***

1. Describe the role of methadone when used for pain in the hospice/palliative care setting
2. Identify the analgesic mechanisms by which methadone produces analgesia
3. Summarize benefits of methadone therapy compared to other opioid analgesics
4. Determine appropriate patients for methadone initiation/trial
5. List the equianalgesic conversion ratios for transitioning from other opioids to methadone
6. Identify drug-drug interactions and alternatives to therapy when encountered

## METHADONE MECHANISMS OF ACTION

Methadone has activity as an opioid receptor (mu and delta) agonist, acts as a N-methyl D-aspartate (NMDA) antagonist, and has been found to have serotonin-norepinephrine reuptake inhibition activity. These multiple mechanisms of action result in a broader spectrum of analgesic activity for methadone compared to other opioid analgesics. The activity as a NMDA receptor antagonist is attributed to improvement in neuropathic pain, a unique characteristic of methadone within the opioid class. While methadone inhibits the reuptake of serotonin and norepinephrine, it is not as potent as duloxetine or venlafaxine, and thus does not result in increased risk of serotonin syndrome when used with selective serotonin reuptake inhibitors (SSRIs), a serotonin-norepinephrine reuptake inhibitors (SNRIs), or a tricyclic antidepressants

 

(TCAs). However, because methadone and many of these agents are metabolized via similar enzymatic pathways, medication interactions can occur when used in combination (see COMMON DRUG-DRUG INTERACTIONS WITH METHADONE).

## ROLE OF METHADONE IN THE PALLIATIVE CARE OR HOSPICE SETTING

In the palliative care and hospice setting, methadone is used primarily as an analgesic, with pain relieving benefit documented in the treatment of neoplasm-related pain, neuropathic pain and even chronic, non-malignant pain. Additionally, in patients with a history of OUD, methadone can also be used to manage opioid cravings/withdrawal symptoms, making it a viable option in patients with pain and a history of OUD.

## BENEFITS OF METHADONE THERAPY

As an analgesic, methadone has advantages over other available opioids making it an attractive option when treating pain in patients with severe or life-limiting illnesses. Notably, methadone has a long duration of action, and is available in multiple dosage forms, including a liquid that can more easily be administered to patients with pain or difficulty swallowing. Even in patients who are NPO, the oral concentrated solution can be administered buccally or sublingually. Concentrations of up to 20mg/ml allow for small volumes to be administered, decreasing burden to the patient. The high lipophilicity of methadone results in increased absorption of the medication via the sublingual or buccal routes compared to morphine or oxycodone solutions. The chemical structure of methadone also differs enough from the phenanthrene (morphine, oxycodone, hydromorphone, etc) class of opioids, that it can safely be used as an alternative if a patient has a true phenanthrene allergy. Another benefit of methadone therapy is the lack active metabolites, making it a viable option for use in patients with significant renal insufficiency or failure.

| Benefits of Methadone Therapy |
|---|
| 1. Long duration of action |
| 2. Available in multiple formulations for ease of dosing (tablets, liquid, IV) |
| 3. Highly lipophilic, resulting in increased absorption sublingually, buccally |
| 4. Can be used in patients with renal severe renal impairment |
| 5. Activity against neuropathic pain (NMDA receptor antagonism) |
| 6. Can be used safely in patients with phenanthrene allergy |
| 7. Inexpensive |

 

## DETERMINING APPROPRIATENESS OF METHADONE THERAPY

Candidates for therapy:

- True morphine (or another full mu opioid agonist) allergy
- Significant renal impairment
- Significant component of neuropathic pain in assessment
- History of opioid-induced adverse effects
- Pain not adequately managed by other opioids
- Patients unable to swallow tablets, but with persisting pain

Patients who should not be considered for therapy:

- Patient with very limited prognosis (≤ 1 week to live) due to time needed to titrate
- Significant drug interactions and no viable alternatives for interacting medications
- Patients with history of syncope, arrhythmias or significant QTc prolongation (≥500ms)
- Limited support, concern for compliance with medication regimen

## INITIATING METHADONE IN AN OPIOID-NAÏVE PATIENT

| Methadone Initiation for Opioid-Naïve Patient | |
|---|---|
| Recommended starting dose | 2.5mg po every 8-12 hours |
| Immediate-release opioid therapy | Recommend initiation/continuation of immediate-release opioid RX |
| Time prior to titration | 4-5 days |

## CONVERTING TO METHADONE

Multiple ratios for converting from another opioid to methadone have been proposed over the years, ranging from 3:1 to 20:1 (mg of morphine equivalent: mg methadone). This range and inconsistencies between proposed ratios has led to much variability in calculated doses, contributing to confusion and concern among prescribers. However, in 2019 a consensus paper was published by a group of hospice and palliative care subject matter experts outlining the rationale for the following conversion factor recommendation:

| Methadone Conversion in an Opioid-Tolerant Patient | |
|---|---|
| **24 Hour Morphine Usage** | **Morphine : Methadone Ratio** |
| < 60mg | See opioid-naïve dosing recs |
| MEDD: 60-200mg *AND* pt ≤ 65 years of age | 10:1 |
| MEDD > 200mg or pt > 65 years of age | 20:1 |

 

EXAMPLE CALCUATION: 69-year-old male with metastatic renal cell carcinoma

Pain medication regimen
-Morphine SR 60mg po every 8 hours
-Morphine IR 15mg po every 4 hours prn breakthrough pain
-Morphine oral solution 20mg/ml take 10mg (0.5ml) po every 2 hours prn pain/dyspnea

Step 1: Determine total daily oral morphine equivalent
-Will need to know how many prn morphine IR and oral liquid doses used/day
-For calculation one, assume patient uses all three morphine SR doses, plus 4 doses of morphine IR and 2 doses of morphine oral liquid/day
-Total daily oral morphine equivalent: 60+60+60+15+15+15+15+10+10=260mg

Step 2: Convert to methadone equivalent
-Since patient > 65 years of age, use 20:1 ratio
-Morphine 260mg = methadone 13mg/day

Step 3: Determine starting methadone dose and frequency
-Could initiate at either 5mg po every 12 hours (10mg/day) or 5mg po every 8 hours (15mg/day)

Step 4: Determine starting time:
-Initiate methadone in place of morphine SR at time next due

Step 5: Continue immediate-release opioid to ensure patient has option available for breakthrough pain

## COMMON DRUG-DRUG INTERACTIONS WITH METHADONE

Pharmacodynamic Drug Interactions

Pharmacodynamic drug interactions increase or decrease the therapeutic effectiveness or adverse effects of another medication. When methadone is given in combination with CNS depressing medications or substances, such as other opioids, benzodiazepines, antidepressants or alcohol, anticipate increased risk of CNS depressing side effects (confusion, drowsiness, impaired motor skills).

Pharmacokinetic Drug Interactions

Pharmacokinetic drug interactions affect or alter the absorption, distribution, metabolism or elimination of the medication. The primary enzymes responsible for the metabolism of methadone are CYP2B6 and CYP3A4. Some medications may reduce, or inhibit, the activity of one of these enzymes, while others increase, or induce, the activity of these enzymes. When the patient is co-prescribed another medication with inducing or inhibiting effects on an

 

enzyme essential to methadone metabolism, consider the following outlined in the table below:

| Effect of Enzyme Inhibition and Inducers on Methadone Metabolism | | | |
|---|---|---|---|
| **Clinical Scenario** | **Result of Interaction** | **Patient Impact** | **Considerations** |
| Methadone in combination with an inhibitor | Metabolism of methadone slowed, resulting increased serum level | Patient at increased risk of methadone overdose or side effects | If converting to methadone and patient on an inhibitor, consider up to 25% methadone dose reductions |
| Methadone in combination with an inducer | Metabolism of methadone increased, resulting in decreased serum level | Patient at increased risk of not achieving analgesia due to decreased serum levels | Encourage use of immediate-release opioid in addition to methadone, recommend titration once steady state reached |

Most common drug interactions include:

*Amiodarone*: Inhibitor, resulting in increased serum concentrations
*Antibiotics/Anti-infectives*
- Ciprofloxacin, clarithromycin, erythromycin, fluconazole, itraconazole, ketoconazole

*Antidepressants*
- Amitriptyline, citalopram, desipramine, fluoxetine, fluvoxamine, paroxetine, sertraline

## SUMMARY

Methadone is an opioid analgesic with potential to provide significant pain relief, especially in patients with severe, life-limiting illnesses. The low cost, multiple mechanisms of analgesic activity, long duration of action, versatility of formulation, safety in patients with significant renal impairment and tolerability in patients with a true morphine (phenanthrene class) allergy make it a great option to treat pain in the hospice and palliative care settings. A recently published consensus statement provides simplified dose conversions instructions.

Despite appropriateness of use for many hospice patients with pain and improved dosing guidance, the use of methadone requires close attention to detail, patient/family/caregiver education and monitoring to ensure safety and efficacy of proposed treatment plan. For questions regarding patient-specific scenarios, please call BetterRX for a Clinical Pharmacy Consultation.

 

## References

1.) McPherson, ML. Demystifying opioid convers calculations: a guide for effective dosing. American Society of Health-Systems Pharmacists, Inc., Bethesda, MD. 2018
2.) McPherson ML, Walker KA, Davis MP, Ray JB etc. Safe and appropriate use of methadone in hospice and palliative care: expert consensus whitepaper. Journal of Pain and Symptom Management. 2019; 57(3): 635-645
3.) Greenblatt DJ. Drug interactions with methadone: time to revise the product label. Clin Pharmacol Drug Dev. 2014; 3(4): 349-251
4.) Mercadante S, Sapio M, Serretta R et al. Patient-controlled analgesia with oral methadone in cancer painL preliminary report. Ann Oncol. 1996; 7:613-617.
5.) Strickland Jennifer. Palliative Pharmacy Care. Ch 20 Equianalgesic Opioid Rotation. American Society of Health-Systems Pharmacists, Inc., Bethesda, MD 2009.
6.) Davis MP, Dalal S et al. Essential Practices in Hospice and Palliative Medicine, 5th Edition, Pain assessment and management. American Academy of Hospice and Palliative Medicine, Chicago, IL. 2017.

 