# Methadone

## Maximizing Safety and Efficacy for Pain Control in Patients with Cancer

Mary Lynn McPherson, PharmD, MA, MDE, BCPS, CPE[a,*],
Ryan C. Costantino, PharmD, BCPS, BCGP[b],
Alexandra L. McPherson, PharmD, MPH[b]

**KEYWORDS**

• Methadone • Analgesics • Pain management • Cancer pain • Opioid

**KEY POINTS**

- Methadone is an important opioid option in the management of cancer pain. The pharmacodynamics and pharmacokinetics are dissimilar from other opioids.
- Not all patients are appropriate candidates for methadone; providers should perform a risk assessment before initiating methadone therapy.
- Opioid-naïve patients, or patients receiving up to 40 to 60 mg oral morphine equivalents a day should begin methadone at no higher than 7.5 mg a day.
- Opioid-tolerant patients should convert to methadone using a 10:1 or 20:1 (oral morphine/oral methadone) equivalent regimen.
- Providers and informal caregivers must carefully monitor the patient's response to methadone, both therapeutic and potential toxicity.

### INTRODUCTION

Methadone is an important therapeutic option in the management of patients who have cancer with pain. Compared with other opioids, methadone offers advantages such as low cost, long half-life (allowing 2 or 3 times daily dosing), lack of active metabolites (advantageous in patients with renal impairment), availability as a high-concentrate oral solution (useful in patients with dysphagia), and benefit in more

None of the authors have any relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in article or with a company making a competing product.

[a] Advanced Post-Graduate Education in Palliative Care, Online Master of Science and Graduate Certificates in Palliative Care, University of Maryland School of Pharmacy, 20 North Pine Street, S405, Baltimore, MD 21201, USA; [b] Pain Management/Palliative Care, University of Maryland School of Pharmacy, 20 North Pine Street, Baltimore, MD 21201, USA
* Corresponding author.
*E-mail address:* mmcphers@rx.umaryland.edu

Hematol Oncol Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.hoc.2018.01.004 **hemonc.theclinics.com**

complex pain situations.[1] Methadone demands close attention to dosing, both in opioid-naïve and opioid-tolerant patients. Failure to respect best practices in methadone dosing and monitoring may result in serious toxicity or fatality. In recent years, methadone has been reported to cause a growing and disproportionately higher rate of opioid-induced deaths.[2] It is unclear what percentage of these deaths are due to inappropriate prescribing and monitoring of methadone, versus individual misuse or abuse.

## PHARMACODYNAMICS AND PHARMACOKINETICS

Methadone is an opioid agonist, binding to the mu-, kappa-, and delta-opioid receptors.[3] Methadone also acts as an N-methyl-D-aspartate (NMDA) antagonist; the NMDA receptor is thought to be associated with opioid tolerance and central hypersensitivity, and to decreased clinical effectiveness of opioids for pain.[4] Methadone is a racemic mixture of 2 enantiomers (R-methadone and S-methadone). A basic and lipophilic opioid, methadone has high oral bioavailability (67%–95%). Onset of action after oral administration is about 30 minutes, with a peak effect at 2.5 hours. Methadone has a long and variable half-life (8–90 hours) but is approximated at 24 hours. Due to its lipophilicity, methadone is widely distributed throughout the body. It exhibits a high degree of protein binding. Methadone is extensively metabolized by the liver (cytochrome P [CYP]2B6, CYP2C19, CYP3A4, and CYP2D6) to pharmacologically inactive metabolites, which are then excreted by the kidneys.[3,5] The extensive hepatic metabolism of methadone predisposes to the numerous drug interactions involving methadone (see later discussion).

## EFFICACY OF METHADONE IN CANCER PAIN

Mercadante and colleagues[6] evaluated the effectiveness of oral long-acting morphine, transdermal fentanyl, and oral methadone in cancer pain not responsive to codeine or tramadol. Subjects had mixed nociceptive-neuropathic cancer pain, and the 3 opioids were similarly effective in controlling pain (>30% reduction in pain).

Porta-Sales and colleagues[7] evaluated the efficacy and safety of methadone as a second-line opioid for patients in an outpatient cancer clinic. One hundred forty-five patients were switched to methadone because of poor pain control (77.9% of cases), opioid side effects (2.1%), or both (20%). The outcome measure was worst pain on day 28, and methadone was shown to be statistically superior ($P<.0001$). The median worst pain score decreased from 9 to 6 and no increase in opioid toxicity was noted.

Rhondali and colleagues[4] switched 19 subjects with cancer in an inpatient palliative care unit with refractory pain to methadone. The visual analog scale severity rating decreased by 4 points by day 7 after rotating to methadone, with almost 90% of patients reporting moderate to greater than moderate pain relief.

Reddy and colleagues[8] evaluated overall survival in patients with cancer after rotation to methadone. They compared 76 subjects switched to methadone with 88 subjects switched to other opioids on a follow-up clinic visit. In contrast to the Centers for Disease Control and Prevention report,[2] there were no significant differences between the 2 groups in subject characteristics, performance status, morphine-equivalent daily dose, pain scores, or median overall survival.

## RISK ASSESSMENT AND APPROPRIATENESS OF METHADONE THERAPY

In 2014, the American Pain Society (APS) and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, published methadone safety