

# PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

## Methadone Conversion: Revisiting a Prior Case

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*This month, we revisit one of the first Palliative Pearls cases published in [March 2016](#). We have incorporated guidance from recently published literature along with revisions for your enrichment.*

### PATIENT CASE

CT is a 62-year-old woman with metastatic breast cancer experiencing aching pain in her chest with shooting pains down her arm that has become increasingly uncontrolled over the past 2 weeks. She also has oral thrush that developed a few days ago. She has a history of asthma, exacerbated by her breast cancer, and recently completed a 6-day steroid taper. You note that she was treated with fluconazole 2 months ago for a prior case of oral thrush. You decide to recommend methadone to better manage her pain and an antifungal course. What is your starting dose of methadone? Which antifungal do you recommend?

### Current pain medications:

- Morphine sustained-release 160mg PO Q12H
- Morphine oral solution 20mg/mL; 1.5ml (30mg) PO Q4H PRN (~6 doses per day; pain decreases from 8 to 5 rating on VAS after each breakthrough dose)

### METHADONE BENEFITS

Methadone is active at mu-opioid and NMDA receptors and inhibits the reuptake of serotonin and norepinephrine. These actions make methadone ideal for patients experiencing **mixed pain**, including somatic (muscle, bone, and tissue), visceral (organ) and neuropathic pain. Methadone therapy is also **inexpensive**, and its **unique pharmacokinetics** make routine use of even the oral liquid formulations useful for patients with long-acting pain management needs.

### METHADONE DISADVANTAGES

Specific enzymes are responsible for **methadone metabolism** and can be affected by a number of medications. Methadone is metabolized in the intestines as well as the liver by the cytochrome P-450 enzyme system (CYP450), primarily by enzymes CYP2B6 and CYP3A4. Medications that induce (speed up or increase) or inhibit (slow down or decrease) metabolism of methadone do so by affecting one of these enzymes. The Indiana University School of Medicine has a useful website listing medications considered inducers and inhibitors of specific CYP enzymes for reference.<sup>1,2</sup>

Methadone may prolong the QTc interval, resulting in a **potentially fatal cardiac arrhythmia**, torsades de points (TdP). This potential is increased when methadone is used in patients with risk factors for QTc interval prolongation and/or taking other medications that also prolong the QTc interval. The lists below are not all-inclusive however the CredibleMeds online resource hosts in-depth listings and may be referenced for additional information.<sup>3</sup>

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### Risk factors for QTc prolongation include:<sup>1,3</sup>

- Hypokalemia or hypomagnesemia
- Impaired liver function
- Structural heart disease
- Genetic predisposition

### Examples of medications with known risk for TdP:<sup>3</sup>

- Antiarrhythmics
- Conventional antipsychotics (e.g., haloperidol)
- Escitalopram (Lexapro<sup>®</sup>) and citalopram (Celexa<sup>®</sup>)
- Fluconazole (Diflucan<sup>®</sup>)
- Fluoroquinolone antibiotics (e.g., ciprofloxacin)
- Macrolide antibiotics (e.g., azithromycin)
- Ondansetron (Zofran<sup>®</sup>)

## METHADONE DOSING

In **opioid naïve** patients, consider starting methadone at a low dose, 2.5mg orally every 8 hours.<sup>1,4</sup> While this is conservative, and typically a safe starting dose, in older and debilitated patients, an extended frequency interval of “every 12 hours” may be necessary.

There are countless **methods to estimate methadone dosing needs** in patients taking other opioids. The method used in the case below is conservative and was developed for use as a standard method for a hospice pharmacy clinical consult service. Several published methods were incorporated in its development with the objective of producing consistent recommendations from the pharmacy team. This method is not superior to other methods that can be used. No matter the method chosen, the key steps for safe and effective methadone dosing include starting low with slow titration, allowing time for the initial dose or increase in dose to come to its full effect (about 5-7 days) before making a change and monitoring.

Methadone is not often recommended as the **breakthrough medication** to complement a scheduled methadone regimen as this has potential for excess methadone accumulation and unintentional overdose.<sup>1</sup> Short-acting opioids such as morphine, oxycodone or hydromorphone are beneficial when initiating methadone, allowing methadone to come to steady-state (full effect) without the interference of unscheduled breakthrough medication.

## CASE ASSESSMENT

- CT is experiencing uncontrolled, somatic pain (muscle aches and pain) and neuropathic pain (shooting). Methadone can manage different types of pain.
- CT has oral thrush likely due to corticosteroid use. A potential drug-drug interaction exists between azole antifungals, such as fluconazole (Diflucan<sup>®</sup>), which causes increased

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concentrations of methadone and additionally prolongs the QTc interval. Nystatin suspension is considered a safer alternative.

### CASE RECOMMENDATIONS

**Total Daily Usage of Current Opioids:** Morphine PO 500mg/day that, until recently, controlled her pain

**New Opioid Requested:** Methadone tablets

**New Dose and Interval:** Using a conversion ratio based on milligrams of oral morphine equivalents (provided below), 500mg/day of Morphine is deemed equivalent to 33mg/day of Methadone, using a 15:1 conversion ratio. Place an order for Methadone 10mg tablet; 1 tablet PO Q8H. Maintain current breakthrough regimen with Morphine concentrate with increased dose of 2ml (60mg) PO Q4H PRN.

- Daily Oral Morphine Milligram Equivalents (OME) = Morphine: Methadone
- <30mg OME = 2:1 (2mg morphine = 1mg methadone)
- 30-90mg OME = 4:1 (4mg morphine = 1mg methadone)
- 100-299mg OME = 8:1 (8mg morphine = 1mg methadone)
- 300-499mg OME = 12:1 (12mg morphine = 1mg methadone)
- 500-999mg OME = 15:1 (15mg morphine = 1mg methadone)
- 1,000-1,999mg OME = 20:1 (20mg morphine = 1mg methadone)
- 2,000-3,999mg OME = 30:1 (30mg morphine = 1mg methadone)

**Oral thrush therapy:** Nystatin suspension; Swish and swallow 5ml PO Q.I.D. x 10 days

**Monitor** for therapeutic effectiveness (pain severity rating, breakthrough doses used) and toxicity (increased sedation or confusion, difficulty arousing patient)

**Assess, and Titrate** dose if needed, after 5-7 days. Note: more frequent dose increases may result in adverse effects/overdose.

### CONSIDERATIONS IN HOSPICE/PALLIATIVE CARE

Appropriate candidates for methadone include those with:<sup>1</sup>

- A true morphine allergy
- Financial constraints with other opioid therapy
- High pill burden or opioid-induced adverse effects due to high dose opioids (e.g., hallucinations, myoclonus)
- Uncontrolled pain despite increasing opioid doses and opioid rotation trials
- Significant renal impairment
- Neuropathic pain
- Difficulty swallowing or presence of a PEG tube in a patient that requires long-acting pain medication to manage pain (with routine dosing methadone can take on long-acting properties even with the liquid formulation).

Patients who may NOT be appropriate candidates includes those with:<sup>1</sup>

- Limited prognosis
- Taking several medications that interact with methadone
- A history of syncope, arrhythmias, QTc prolongation

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- Poor cognition
- Adherence issues to medication
- No stable practitioner to oversee methadone titration and adjustments
- No caregiver or an unreliable caregiver to assist with monitoring

Hospice patients often present with mixed pain making methadone ideal in appropriate candidates. They have frequently changing medication profiles making it important to review often for potential drug-drug and drug-disease interactions and before initiating any new therapy.

### FOR ADDITIONAL INFORMATION ON THIS TOPIC, PLEASE REVIEW THE FOLLOWING:

Enclara Pharmacia's On Demand Educational Webinar, "Methadone: A Review for Hospice Clinicians". Click [here](#) to log in.

1. McPherson ML. Methadone: A Complex and Challenging Analgesic, But It's Worth It! In: Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, 2<sup>nd</sup> ed. Bethesda, MD: American Society of Health-System Pharmacists, Inc; 2018.
2. Indiana University School of Medicine, Department of Medicine. Clinical Pharmacology Drug Interactions: Cytochrome P450 Drug Interactions Flockhart Table™. Accessed June 4, 2019. Available from: <https://drug-interactions.medicine.iu.edu/main-table.aspx>
3. CredibleMeds. Resources for Healthcare Providers: QT Drug Lists. Accessed June 4, 2019. Available from: <https://crediblemeds.org/healthcare-providers/>
4. McPherson ML, Walker KA, Davis MP, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. *J Pain Symptom Manage* 2019;57:635-645.
5. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust*. 2000;173:536-540.
6. Brown R, et al. Methadone: Applied pharmacology and use as adjunctive treatment in chronic pain. *Postgrad Med J*.2004;80:654-659. Available from: <http://pmj.bmj.com/content/80/949/654.full?ck=nck>
7. Bruera E, Pereira J, Watanabe S, et al. Opioid rotation in patients with cancer pain: A retrospective comparison of dose ratios between methadone, hydromorphone and morphine. *Cancer*. 1996;78:852-857.
8. Cruciani RA. Methadone: to ECG or not to ECG...That is still the question. *J Pain Symptom Manage*. 2008 Nov;36(5):545-52
9. Gazelle G, Fine PG. Fast Facts and Concepts #75: Methadone for the treatment of pain. 2015 June. Available from: <http://www.mypcnow.org>
10. Friedman LL, Rodgers PE. Pain management in palliative care. *Clin Fam Prac*. 2004;6:371-393.
11. Jamero, et al. The Emerging Role of NMDA Antagonists in Pain Management. *US Pharm*. 2011;36(5):HS4-HS8.
12. King S, Forbes K, Hanks GW, et al. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: A European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med*. 2011 Jul;25(5):525-52.
13. Manfredonia JF. Prescribing methadone for pain management in end-of-life care. *J Am Osteopath Assoc*. 2005 Mar;105(3 Suppl 1):S18-21.

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14. Mercadante S, Caraceni A., Conversion ratios for opioid switching in the treatment of cancer pain: A systematic review. *Palliat Med.* 2011 Jul;25(5):504-15.
15. Mercadante S, Ferrera P, et al. Switching from oxycodone to methadone in advanced cancer patients. *Support Care Cancer.* 2012 Jan;20(1):191-4
16. Mercadante S, Casuccia A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol.* 2001;19:2898-2904.
17. Morley JS, Makin MK. UK Hospice Model. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev.* 1998;5:51-8.
18. Morley, Bridson, Nash. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliat Med.* 2003;17:576-587.
19. Plonk WM. Simplified methadone conversion. *J Palliat Med.* 2005;8:478-479.
20. Pollock AB, Tegeler ML, et. al. Morphine to methadone conversion: an interpretation of published data. *Am J Hosp Palliat Care.* 2011 Mar;28(2):135-40.
21. Ripamonti C, Groff L, Brunelli C, et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Onco.* 1998;16:3216-3221.
22. von Gunten CF. Fast Facts and Concepts #86: Methadone: Starting dose information. 2015 June. Available from: <https://www.mypcnow.org>
23. Weissman DE. Fast Facts and Concepts #171: Methadone for neuropathic pain. 2015 July. Available from: <http://www.mypcnow.org>
24. Weschules DJ, Bain KT. A systematic review of opioid conversion ratios used with methadone for the treatment of pain. *Pain Med.* 2008;9(5):595–612.
25. Wong E, Walker KA. A review of common methods to convert morphine to methadone. *J Community Hosp Intern Med Perspect.* 2012;2(4): doi: 10.3402/jchimp.v2i4.19541. Published online 2013 Jan 7. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3715153/>