

# Prescribing Methadone, A Unique Analgesic

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Opioids are effective for a wide spectrum of painful conditions, and their risks are limited to well-known and manageable side effects, without organ toxicity [1]. Opioids remain the mainstay of cancer pain treatment [2], with two main limitations to their use:

1. With chronic opioid use, some patients may become tolerant to their analgesic effect and require dose escalation to maintain analgesia, with a consequent increase in the risk of side effects such as sedation and constipation.

2. Certain types of pain, such as neuropathic pain, may be less responsive to opioids [3].

Although opioid receptors remain the best available target in pain treatment, other receptors and systems, such as the N-methyl-D-aspartate (NMDA) receptors and the catecholamine system, are known to play an important role in maintaining chronic pain states and modulating responses to analgesics [4]. Methadone has unique pharmacodynamic properties, with activity at both the opioid and NMDA receptors and inhibition of catecholamine uptake [1, 5, 6]. Numerous papers have addressed methadone's "rediscovery" as an effective and safe analgesic, with emphasis on its NMDA-antagonist activity and improved dosing guidelines [7–9]. At one large cancer center, the number of methadone prescriptions increased 12-fold over the past 3 years, underscoring the increasing importance ascribed to methadone by experts in cancer pain management [10].

## Why Methadone Is a Unique Analgesic: A Close Look at Its Pharmacodynamics

Aside from its agonistic activity at the mu opioid receptor [1], methadone has other actions that possibly contribute to its unique analgesic activity. For instance, it exerts antagonistic activity at the NMDA receptor [5], and this counteracts opioid tolerance in experimental models of pain [11], possibly explaining the lesser escalation in opioid dosage required in patients treated with methadone compared with those given morphine [12, 13]. The NMDA antagonistic activity also results in increased efficacy against hyperalgesia and may explain methadone's greater

effectiveness against neuropathic pain and other chronic pain states not responsive to other therapies [11, 14]. This characteristic of methadone also may explain the exacerbation of pain seen in some patients switched from methadone to other opioids [15].

Methadone is a racemic mixture of *d*- and *l*-methadone. Both *d*-methadone and *l*-methadone share antagonistic activity at the NMDA receptor, but *l*-methadone is thought to be responsible for most of the activity at the opioid receptor [16]. A clinical program to test the analgesic activity of *d*-methadone is in progress. If *d*-methadone proves to be analgesic in humans, the contribution of the NMDA antagonistic activity to methadone's analgesia will be better elucidated.

Methadone inhibits the reuptake of both norepinephrine and serotonin [6]. Medications that share this effect have been the backbone of the treatment of neuropathic pain [17], which is the predominant mechanism in many patients with chronic pain syndromes, such as those suffering from postherpetic neuralgia and peripheral neuropathy. Neuropathic pain is also a frequent cause of cancer pain [18, 19]. Furthermore, there is experimental evidence that methadone's activity at opioid receptors may be broader than that of other opioids [20]. In addition to methadone's NMDA receptor and catecholamine actions, this broader spectrum of activity at opioid receptors may help explain the increasing number of reports from case series describing improved pain relief after rotation to methadone [21–26].

## Clinical and Pharmacokinetic Considerations When Prescribing Methadone

Opioid rotation is a routine maneuver in the management of both cancer pain and non-cancer-

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related pain, and methadone is often an important part of this rotation strategy [3, 14, 27]. Methadone has a long and variable half-life (13–58 hours) [28], and thus patients must be carefully monitored for rising blood levels to avoid over-medication with repeated dosing. A search of the literature shows three reports of opioid toxicity with oral methadone [29–31]. It appears that in all three cases methadone was started at too high a dose or was given too frequently at fixed intervals.

One of the authors of this paper (R.W.H.), an early investigator of methadone [32, 33] and the former head of the Analgesic Studies Program at Memorial Sloan-Kettering Cancer Center, has reported that in his experience of over 30 years as chief of the Memorial Hospital Pain Clinic, no serious problems were encountered with the use of methadone, even as a first-line analgesic. He attributes the avoidance of the problems reported by others to the fact that, when methadone was initiated or substituted for other opioids, a PRN regimen (patient-controlled titration) was always employed first, rather than by-the-clock administration, as appears to be the custom with analgesic prescribing today [34].

### Suggested Formulas for Converting to Methadone

Recent data show that, when oral or parenteral methadone is administered in proper doses and intervals, it is a very safe drug for both inpatients and outpatients [13, 26, 35]. When performing opioid rotations, aside from calculating the initial dose of the second opioid, it is paramount to consider the clinical scenario, including the reasons for the opioid rotation and patient characteristics such as age, renal and liver function, mental status, and pulmonary function.

### ORAL DOSING

The rotation from oral morphine to oral methadone can be accomplished in one step following the guidelines delineated in Table 1 [7, 27]. These guidelines recommend that for patients on lower morphine doses (ie, 30–90 mg), the ratio of morphine to methadone should be 4:1; eg, a patient who is receiving a daily dose of 60 mg of morphine should be started on approximately 15 mg of methadone daily. For patients on higher doses of morphine, the ratio should be 12:1 or greater; eg, a patient receiving 400 mg of morphine should be started on approximately 35 mg of methadone.

When methadone is used for analgesia, it is generally administered three times a day, although four times daily, twice daily, and even once daily regimens have been described.

### INTRAVENOUS DOSING

Some patients with difficult-to-control pain may benefit from parenteral methadone [24]. Again, careful conversion and monitoring are essential. One recent report related experience with two patients who were sedated shortly after being rotated to intravenous (IV) methadone at too high a dose relative to the previous opioid dosage [24]. In both of these patients, dose reduction resulted in prompt resolution of sedation. When continuous infusion of methadone or another opioid is started at an appropriate dose and the patient is given an opportunity to self-titrate with PCA (patient-controlled analgesia), opioid overdose is rarely encountered [26].

Methadone has a very high oral bioavailability [8, 9]; therefore, when converting from IV to oral methadone, the prudent approach is to perform a 1:1 conversion, keeping in mind that some patients will require upward titration close or equal to a 1:2 ratio. When instead performing the opposite rotation from oral methadone to IV methadone, the prudent approach is to perform a 2:1 conversion, keeping in mind

**Table 1**

Suggested Safe and Effective Starting Doses When Rotating Patients from Oral Morphine to Oral Methadone<sup>7,27</sup>

MORPHINE DOSE	CONVERSION RATIO	EXAMPLE
30–90 mg	4:1	30 mg morphine ≈ 7 mg methadone
91–300 mg	8:1	300 mg morphine ≈ 35 mg methadone
> 300 mg <sup>a</sup>	12:1	400 mg morphine ≈ 35 mg methadone

<sup>a</sup>If previous morphine dose is *much* higher than 300 mg, the dose ratio will be higher than 12:1.

**Table 2**

Suggested Safe and Effective Starting Doses When Rotating Patients from Other IV Opioids to IV Methadone with Patient-Controlled Analgesia<sup>21,24,26</sup>

INITIAL OPIOID	BASAL <sup>a</sup>	NEW OPIOID	BASAL <sup>a</sup>	DEMAND <sup>b</sup>	CAB <sup>c</sup>
Morphine	10 mg	Methadone	1 mg	1 mg	5 mg
Hydromorphone	1.5 mg	Methadone	0.3 mg	0.3 mg	5 mg
Fentanyl	250 µg	Methadone	1.25 mg	1.25 mg	5 mg

<sup>a</sup>Continuous hourly infusion. Decrease the initial dose of methadone by 25%–50% for high previous opioid doses (eg, 50 mg/h of morphine) and increase the dose by 25%–50% for low doses (eg, 5 mg/h of morphine).

<sup>b</sup>Dose available every 15 minutes by the patient pressing the demand button on the infusion pump.

<sup>c</sup>Clinician-activated bolus: dose administered by nurse upon request if pain persists despite the self-administration of demand doses.

## Rotating Opioids

### EXAMPLE 1

A 46-year-old man is receiving hydromorphone 5 mg/h by continuous infusion (CI) and needs to be switched to methadone. The initial CI dose of methadone should be 1 mg/h, with 1 mg every 15 minutes available via PCA and 5–15 mg administered by the nurse should the pain persist despite PCA use. After 12 hours, but not before, the CI dose can be titrated upward by 50%–100%, depending on the patient's pain, side effects, and PCA-CAB use. Once the pain is well controlled, the patient can be switched from IV to oral methadone with a 1:1 conversion. If this patient were taking 30 mg of IV methadone in 24 hours, the initial oral dose would be 10 mg TID, with 5 mg every 4 hours as needed. It should be kept in mind that the patient may need a higher oral dose, approaching 15–20 mg TID.

### EXAMPLE 2

A 45-year-old woman is receiving morphine 30 mg/h CI and needs to be switched to methadone. The initial CI dose of methadone should be 3 mg/h, with 3 mg every 15 minutes available via PCA and 10–15 mg administered by the nurse should the pain persist despite PCA use. After 12 hours, but not before, the CI dose can be titrated upward by 50%–100%, depending on the patient's pain, side effects, and PCA-CAB use. Once the pain is well controlled, the patient can be switched from IV to oral methadone with a 1:1 conversion. If this patient were taking 60 mg of IV methadone in 24 hours, the initial oral dose would be 20 mg TID, with 10 mg every 4 hours as needed.

that some patients switched to this lower IV dose may require upward titration close or equal to a 1:1 ratio.

Table 2 lists the parameters followed at Memorial Sloan-Kettering Cancer Center for IV opioid conversions to methadone with PCA and provides two examples. To avoid a delayed overdose in the face of methadone's long and variable half-life, these parameters are based on a conservative initial continuous infusion and a relatively liberal use of PRN doses via PCA. Based on our clinical experience and that of others, when IV methadone is administered at a constant infusion

rate, the analgesic and sedative effects will increase over the first 12 hours after starting or increasing an infusion. Therefore, the infusion should not be increased during this initial 12-hour period; instead, PRN doses can be administered liberally (every 15 minutes if necessary) to control the pain.

It should be noted that the rotation from IV hydromorphone to IV methadone is performed at even lower starting doses of methadone, relative to the rotation from morphine. This does not follow opioid equianalgesic charts and is based on empirical observations suggesting that higher starting methadone doses can result in overdose [24].

### Our Experience with Reverse Rotation

Clinical experience is making it apparent that the formula for rotating to methadone is not bi-directional. There is a paucity of reports describing rotations from methadone to other opioids, and thus the rotation parameters in this direction remain poorly defined. Such rotations are performed infrequently, and this indirectly underscores the agent's effectiveness: Patients treated with methadone rarely go back to other opioids. Nevertheless, this may sometimes be necessary. After reviewing the unsatisfactory outcomes of our patients rotated from methadone to other opioids in one step [15], we now proceed at Memorial Sloan-Kettering Cancer Center with a gradual switch over 3 days. We decrease the dose of methadone by one third each day while introducing the new opioid. Table 3 shows the conversion parameters that we currently use, in the absence of better data. These parameters are based solely on the experience of one of the authors (P.L.M.) and represent only a starting point for more observations and studies.

### The Question of Cardiac Toxicity

The clinical evidence for QTc prolongation and torsades de pointes stemming from oral methadone use remains limited to case reports [36], and a relationship was not confirmed in a recent retrospective study of patients with cancer pain [37]. In the latter study, the QTc interval of patients was the same on and off oral methadone, and two patients with a prolonged QTc interval > 500 ms when not receiving methadone had a normal QTc when taking oral methadone.

In contrast, a similar retrospective study of cancer patients treated with IV methadone for pain

showed a direct correlation between the methadone dose and QTc prolongation. This study also included original in vitro experimental data showing a synergistic block of cellular currents by the combination of methadone and chlorobutanol [38]. Parenteral methadone is available in the United States only as a commercial solution (Dolophine) containing racemic methadone (10 mg/mL) preserved with chlorobutanol (5 mg/mL). As Kornick et al [38] point out, chlorobutanol or chlorobutanol plus methadone, rather than methadone alone, may be the cause of cardiac toxicity in patients treated with IV methadone. Chlorobutanol has a very long half-life, extending beyond 10 days [39], and one report showed a serum concentration of 85 µg/mL (0.480 mM) of chlorobutanol in a patient receiving IV morphine preserved with 0.5% chlorobutanol [40]. Furthermore, in a controlled clinical trial that led to the discontinuation of chlorobutanol from heparin, chlorobutanol was found to decrease blood pressure in patients [41]. Chlorobutanol also causes significant negative inotropic effects on human atrial tissue, and this was the postulated cause of the hypotension seen in patients receiving oxytocin preserved with chlorobutanol [42]. In amphibian heart cells, chlorobutanol increases action-poten-

tial duration, lowers conduction velocity, and induces automaticity [43].

When using IV methadone in hospitalized patients at Memorial Sloan-Kettering Cancer Center, we routinely perform electrocardiograms before starting the infusion, 24 and 72 hours later, and again 24 and 72 hours after each increase in dose. We also monitor serum electrolytes, especially potassium, and avoid concomitant drugs that may prolong the QTc interval. We do not take such special precautions in patients treated with oral methadone, as the evidence for QTc prolongation and cardiotoxicity from oral methadone is lacking.

**Table 3**

**Suggested Safe and Effective Starting Doses When Rotating Patients from IV Methadone to Other IV Opioids Over 3 Days with Patient-Controlled Analgesia**

INITIAL OPIOID	BASAL <sup>a</sup>	NEW OPIOID	BASAL <sup>a</sup>	DEMAND <sup>b</sup>	CAB <sup>c</sup>
Methadone	1 mg	Morphine	1 mg	0.5 mg	1 mg
Methadone	1 mg	Hydromorphone	0.5 mg	0.25 mg	0.5 mg
Methadone	1 mg	Fentanyl	75 µg	35 µg	75 µg

<sup>a</sup>Continuous hourly infusion. Perform a gradual rotation by reducing the dose of methadone by one third over each of the 3 days.

<sup>b</sup>Dose available every 15 minutes by the patient pressing the demand button on the infusion pump.

<sup>c</sup>Clinician-activated bolus: dose administered by nurse upon request if pain persists despite the use of demand doses.

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