

## Oral Methadone Dosing for Chronic Pain A Practitioner's Guide

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### Contents


1. Introduction
2. History of Methadone
3. Pharmacokinetics
4. Pharmacodynamics
5. Dosing: Opioid-Naïve Patients
6. Dosing: Opioid-Tolerant Patients
7. Titration & Monitoring
8. Formulations & Costs
9. Drug Interactions
10. Special Situations
  - Elderly
  - Renal / Hepatic Failure
  - Pregnancy/Lactation
  - HIV/AIDS
11. Patient Cautions & Warnings
12. Conclusion
- References



***Methadone can offer significant advantages over other opioids for the management of chronic pain.***

### 1. Introduction

Methadone has emerged as a good choice for the management of cancer pain and chronic non-cancer pain both as a first-line medication and as a replacement opioid. Particular cautions must be observed as methadone's pharmacokinetics and pharmacodynamics are unique among opioids. Milligram for milligram, however, methadone is much more powerful than morphine, although there is significant interindividual variability in the response to methadone. In the initiation of chronic opioid therapy with methadone or the transition from a different opioid, careful day-to-day monitoring is essential. Methadone can interact with a large number of medications; therefore, drug-drug interactions must be considered. Finally, compared with other opioids, methadone can offer a very significant cost-savings advantage. This paper provides practical clinical guidance for all healthcare providers, whether or not they are already familiar with prescribing methadone for pain.



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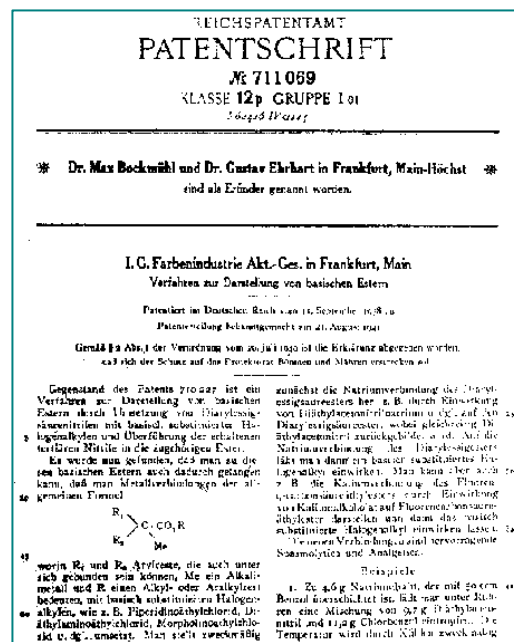
## 2. History of Methadone

A complete account of methadone may never be known, since much of the early history relies on translated documents, interviews, and personal accounts. It is usually agreed that the synthesis of methadone occurred in the late 1930s in Germany, discovered by IG Farbenindustrie researchers Max Bockmühl and Gustav Ehrhart in the course of ongoing research into compounds with both analgesic and spasmolytic properties. Contrary to rumor, there is no evidence this research was ever part of a Nazi attempt to replace war-time opium supplies, and only small quantities were given to the Wehrmacht (Preston, 2003).

Initially called Hoechst 10820 in the 1941 patent application (see **Image**), it later became known as Polamidon® (sometimes spelled Palamidon). The analgesic properties were unexpected because of its chemical structure, but this quality was discovered during initial testing. Methadone was not employed significantly as an analgesic during WWII due to poor initial dosing choices and an inadequate understanding of methadone’s pharmacologic properties (Chen, 1948).

With the end of the war, the patent, trade name, and research documents became the property of the Allies. The rights to produce Polamidon were purchased by Eli Lilly for one dollar, and commercial production in the United States was started in 1947 (Moll, 1990). One circulating myth is that the Lilly product, Dolophine®, was named to honor Adolf Hitler and that the drug was originally called Adolophine in Germany. In actuality, the name Dolophine was derived from the French *dolor* (pain) and *fin* (end). The American Medical Association originally assigned Polamidon the generic name “methadon” (Council, 1947).

Early clinical trials in the US and UK found methadone to be at least as potent as morphine. Since that time, numerous evaluations of methadone, from case reports to placebo-controlled clinical trials, have established it as an effective analgesic in cancer pain and chronic non-cancer pain with a potency significantly greater than morphine.



## 3. Pharmacokinetics

While methadone can be administered by a number of routes – oral, rectal, intravenous, intramuscular, subcutaneous, epidural, and intrathecal – it is most commonly given orally in either tablets or solution. Oral methadone is readily absorbed and very long-acting; by comparison, its bioavailability is nearly 3 times that of morphine and its half-life is about 10 times greater than morphine (see **Table**).

Methadone is highly lipophilic and is quickly distributed to tissues including the brain, gut, kidney, liver, muscle, and lung (Eap et al., 2002). Between doses, plasma concentrations are maintained by this tissue reservoir. Methadone also binds readily to plasma proteins and the unbound fraction – the pharmacologically active portion of the drug – averages 12%; however, this is variable, which may account for some of the differences in patient response to methadone (Inturrisi et al., 1987).

Methadone	
Bioavailability	~80% (79 ± 11.7%)
Half-life	~30 hrs. (30.4 ± 16.3)
Morphine	
Bioavailability	~30% (26 ± 13%)
Half-life	~3 hrs. (2.7 ± 1.2)

*Gourlay et al., 1986*

**Methadone plasma levels may take up to 10 days to stabilize.**

Peak plasma concentration occurs on average 2.5-4 hours following ingestion (Eap et al., 2002). While the half-life of methadone may be 30 hours, the duration of analgesia is much shorter. The mismatch of half-life and duration of analgesia is potentially life threatening if patients start out using methadone every 4 to 6 hours as they might use morphine, oxycodone, or hydrocodone. (Säwe, 1986). Although methadone analgesic effects typically last only 4 to 6 hours when it is initiated (Beaver et al., 1967), as a rule, this will extend to 8 to 12 hours with repeated dosing. Therefore, adequate pain control is most often maintained with 2 or 3 daily methadone doses. Some patients may require 4 daily doses while others, particularly elderly patients, may only require once-a-day dosing.

Because of its long half life, plasma levels of methadone may take up to 10 days to stabilize (Säwe, 1986). There must be a cautious balance between inadequate analgesia due to insufficient dosing and systemic toxicity due to excessive dose during the titration phase. Patients should be advised of methadone’s slow onset of action and gradual enhancement of analgesia over time.

Methadone undergoes biotransformation to inactive metabolites in the liver. Both methadone and its metabolites are eliminated in urine and feces. *Also see Section 9, Drug Interactions, below (page 8).*

#### 4. Pharmacodynamics

Methadone binds to Mu ( $\mu$ ), Kappa ( $\kappa$ ), and Delta ( $\delta$ ) opioid receptors, producing analgesia as well as typical opioid side effects (see **Table**).

While methadone has a potency equivalent to morphine specifically for  $\mu$ -opioid receptors, the clinical effectiveness of methadone increases with chronic dosing (Davis and Walsh, 2001). As noted above, peak plasma concentration of methadone occurs on average 2.5 to 4 hours following an oral dose (Eap et al., 2002). There is no predictable relationship between methadone plasma level and pain relief. Inturrisi et al. (1987) discovered the steady-state concentration of methadone required to produce an adequate analgesic effect in different patients ranged from 0.04 ug/mL (400 ng/mL) to 1.13 ug/mL (1130 ng/mL).

Methadone inhibits re-uptake of serotonin and norepinephrine, which are typical tricyclic antidepressant actions. Methadone is also an antagonist of N-methyl-D-aspartate (NMDA) receptors (Davis and Walsh, 2001), which can help prevent central sensitization and reduce opioid tolerance.

Clinically speaking, frequent or large methadone dose changes are not usually necessary after the initial titration phase. Loss of analgesia from a previously stable dose may reflect the addition of another medication affecting the metabolism of methadone and consequent serum levels of the analgesic.

Receptor	Clinical Effects
Mu ( $\mu$ )	Analgesia Euphoria Respiratory depression Physical dependence Miosis Decreased gastric motility
Kappa ( $\kappa$ )	Analgesia Sedation Respiratory depression
Delta ( $\delta$ )	Analgesia Dysphoria Hallucinations
Adapted from: Warfield and Fausett, 2002	

**Author’s Clinical Example:**

Recently, I had a patient with chronic low back pain that had been stable on methadone (20 mg po TID) for some time. He contacted me, very concerned because his pain had gotten much worse during the past few weeks. We reviewed all the changes in his life and could not find anything in particular that would affect his pain levels. In our conversation, he did recall that his psychiatrist started him on a new medication (Tegretol®) for his mood. Tegretol (carbamazepine) is a strong inducer of two enzymes (CYP3A4 and CYP2B6) that metabolize methadone and can lower serum methadone levels. We coordinated an increased dose of methadone to compensate, and his pain level returned to tolerable. (See **Sec. 9, p. 8** below for a brief discussion of methadone-drug interactions.)

**5. Methadone Dosing: Opioid-Naïve Patients**

With methadone, the general rule is to “**Start Low and Go Slow.**” For patients not currently taking opioids regularly, the College of Physicians and Surgeons of Ontario recommends a starting dose of 2.5 mg po every 8 hours (CPSO, 2000). While this is a conservative and typically safe starting dose, for a frail or elderly patient an initial dose of 2.5 mg po once daily might be necessary. Revised product information (Methadone PI 2006) recommends no more than 2.5 to 10 mg every 8-10 hours, slowly titrated to effect. This is in stark contrast to the earlier package insert (PI), which implied that induction doses of up to 80 mg/day were allowable; however, this *could be hazardous* in opioid-naïve patients.

*The general rule for methadone dosing is, “Start Low, Go Slow.”*

Acceptable guidelines for methadone titration are lacking, so increases should be based on the patient’s response (see **Example Table**). An increase of 2.5 mg per dose every 5-7 days has been recommended in the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (VA/DoD, 2003).

Example: Methadone Titration Plan Opioid-Naïve Patient		
Wk	Dose	Total Dose/Day
1	2.5 mg po BID	5 mg
2	5 mg po BID	10 mg
3	7.5 mg po BID	15 mg
4	10 mg po BID	20 mg
5	10 mg po TID	30 mg
6	20 mg po BID (10 mg po QID)	40 mg

**Author’s Comment:**

In starting methadone, or any opioid, we use an Opioid Treatment Agreement. The first part of this agreement outlines the risks of chronic opioid therapy along with the expected side effects. In the clinic, we go through this point-by-point. We also discuss what to expect with methadone and the dangers of using it differently than prescribed. As a rule, we start opioid-naïve patients on 2.5 mg po BID and direct them to call the clinic weekly.

Regarding titration: If the patient is receiving tolerable pain relief on the current dose we hold-the-course and do not increase the dose. In patients experiencing a side effect like somnolence, we ask if they can tolerate it for a few more days to see if it goes away. For patients receiving partial relief with no significant side effects, we will raise the dose. When tolerable pain relief is not achieved, we will generally increase the dose, and if a patient indicates that pain relief does not last for 12 hours, we increase the dose *frequency* (BID>TID>QID) as necessary.

If after several increases or other adjustments the patient is still not receiving at least partial relief, the pain syndrome is likely unresponsive to methadone and we begin tapering methadone to explore other therapies.

## 6. Methadone Dosing: Opioid-Tolerant Patients

Most equianalgesic tables published to date indicate that a 15 mg oral dose of morphine is approximately equivalent to a 10 mg oral dose of methadone. For a single dose, this may be true; however, with repeated dosing methadone may have a much greater analgesic effect. Relying on these “single dose tables” to transition a patient to methadone from one or more other opioids can result in a substantial methadone overmedication, possibly overdose, that may not become apparent for a number of days.

From retrospective studies, a number of conversion ratios have been developed (See **Tables** below). In each study, the final equianalgesic dose ratio, or EDR, correlates with the total daily opioid dose before switching to methadone.

### Selected EDRs (Equianalgesic Dose Ratios): Morphine-to-Methadone Conversion

Morphine Dose (mg/d)	30-90	90-300	300+
Morphine:Methadone EDR	4:1	6:1	8:1
Ripamonti et al., 1998			

Morphine Dose (mg/d)	30-90	90-300	300+
Morphine:Methadone EDR	4:1	8:1	12:1
Mercadante et al., 2001			

**IMPORTANT NOTE:**  
*These ratios should NOT be used in reverse — that is, for converting from methadone to morphine.*

Morphine Dose (mg/d)	<100	101-300	301-600	601-800	801-1000	>1001
Morphine:Methadone EDR	3:1	5:1	10:1	12:1	15:1	20:1
Ayonrinde, 2000						

In the sample calculation on the next page, the Ayonrinde EDRs have been used. These ratios provide a reasonable approximation at the lower doses and tend to place a cap on the upper doses. As an example, 300 mg, 600 mg, and 900 mg of oral morphine will each predict a 60 mg dose of methadone. However, these EDRs are not without their faults: Ayonrinde’s ratios predict a patient using 100 mg of morphine will require about 33 mg of methadone, while a person using 110 mg of morphine requires only 22 mg of methadone.

For a particular individual, the EDR is only a predicted value and the actual EDR may be quite different. For example, Ripamonti et al. (1998) actually reported a range of 2.5:1 to 8.8:1 (median 3.7:1) when converting to oral methadone for patients using 30-90 mg of oral morphine daily.

The initial step in transitioning to methadone requires calculating the patient’s daily oral morphine equivalent dose. For both long-acting and breakthrough opioid medications the daily dosage of each is multiplied by the appropriate ratio of equianalgesic doses (**Table**, APS 2003). The results are summed to produce the Total Daily Oral Morphine Equivalent Dose, and, from this, the equianalgesic dose of methadone is calculated using the appropriate EDR (see the **Example** on the next page).

Table: Approximate EDRs for Selected Opioids		
OPIOID	EQUIVALENT DOSE	CONVERSION FACTOR
Codeine	200 mg	0.15
<i>Morphine</i>	<i>30 mg</i>	<i>1.00</i>
Hydromorphone	7.5 mg	4.00
Oxycodone	20 mg	1.50
Hydrocodone	30 mg	1.00
Source: APS 2003		

**Step One: Calculate the Daily Oral Morphine Equivalent Dose...****Current Opioid Use (example):**

60 mg of sustained release oxycodone q8h, with  
4 mg of hydromorphone for breakthrough pain (4 doses per day)

**Daily Total Opioids:**

oxycodone sustained release 60 mg x 3 = 180 mg/day  
hydromorphone 4 mg x 4 = 16 mg/day

**Convert to Morphine Equivalents:**

oxycodone 180 mg/day x 1.5 [30 mg morphine / 20 mg oxycodone]  
= 270 mg oral morphine/day  
hydromorphone 16 mg/day x 4.0 [30 mg morphine / 7.5 mg hydromorphone]  
= 64 mg oral morphine/day

**Total Daily Oral Morphine Equivalent Dose = 334 mg** [270 + 64]

**Step Two: Divide the Total Daily Oral Morphine Equivalent Dose by the Appropriate EDR (Equianalgesic Dosing Ratio)...**

**Total Daily Oral Morphine Equivalent Dose = 334 mg**

**Morphine:Methadone EDR = 10:1** [from Ayonrinde, 2000]

334 mg morphine = 33.4 mg methadone  
q8h dosing = 33.4 mg methadone / 3 = 11.13 mg

**Predicted Methadone Dose = approx. 10 mg po q8h**

**Author's Comment:**

In practice, most patients who we transition to methadone are outpatients, using less than 200 mg of morphine or the equivalent per day. Using Ayonrinde EDRs, I estimate their equianalgesic dose of methadone. From this, I develop a conservative starting dose of methadone, with the expectation that we will reach the predicted dose in 1 or 2 titrations. Because of the limited milligram strengths of methadone tablets available, there are inevitable compromises in the starting dose and the incremental titrations.

For example: If the predicted methadone dose is 35 mg/day, I would likely start this patient on 10 mg methadone po TID (30 mg total/day). After 5-7 days, if this dose proves inadequate, I would increase the dose to 15 mg po TID (or 10 mg po QID). We try to avoid complicated dosing regimens that require splitting pills, but sometimes this is necessary (eg, 2.5 mg po BID in example on p. 4).

As noted earlier, there must be a cautious balance between inadequate analgesia, due to insufficient dosing, and systemic toxicity, due to excessive dose. In general, I find that patients are tolerant of this approach and understand that we are starting low and dosing adjustments can be made week-to-week.

**NOTE: Existing opioid analgesia is typically discontinued the evening before starting methadone.**

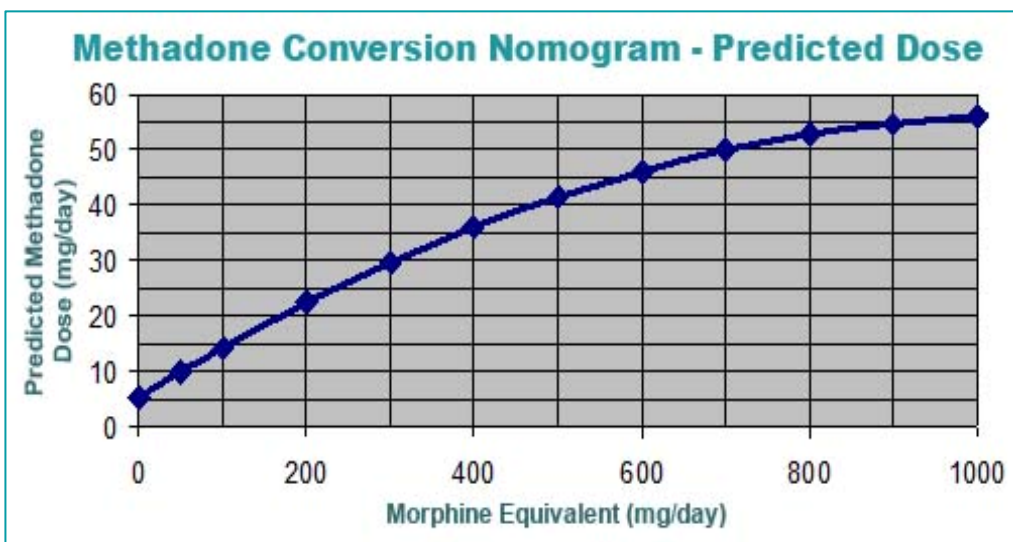
**Methadone is usually started in the morning to help gauge its effects during the day.**

To simplify calculation of the predicted equianalgesic dose of methadone and remove the EDR's inconsistencies (discussed earlier), a Methadone Conversion Nomogram was created. For each of the Ayonrinde EDRs, the predicted methadone dose at the lower limit was calcu-

lated and the dose was limited if it exceeded the predicted dose at the next higher limit (only 800 mg was affected). Additionally, a data point at 1200 mg was calculated.

A curve was fitted to these points using the lowest sum of squared absolute error. The resultant curve can be expressed by the quadratic equation:  $Y=5.3956+.09401X-.0000435X^2$ , and the fitted curve is shown in the **Graph**.

The nomogram is used by locating the current morphine oral equivalent dose along the X-axis, moving up to the curve, and reading the corresponding methadone-dose value along the Y-axis.



For instance, in Step 2 of the above example, the total oral morphine equivalent dose was 334 mg/day. Approximately locating this value on the bottom

axis of the nomogram and reading up to the curve would roughly indicate 30 mg/day of oral methadone or a predicted dose of 10 mg po q8h, as in the example.

## 7. Titration & Monitoring

As noted earlier, there are few published recommendations for methadone titration. In the outpatient setting, dosing increases should not be made more frequently than every 5-7 days.

For opioid naïve patients started on 2.5 mg of methadone BID or TID, an increase of 2.5 mg per dose was recommended in the VA/DoD Guidelines (2003). After several titrations, this milligram dose increase may not be meaningful relative to the previous dose and may need to be increased. An example titration plan for an opioid naïve patient was shown above (Sec. 5).

For patients transitioned from other opioids (<200 mg/day of morphine oral equivalent), an increase of 5 mg per dose is recommended in the VA/DoD Guidelines (see example in **Table**).

For patients previously receiving 200-500 mg/day of morphine oral equivalent, the recommended increase is equal to the initial methadone starting dose (VA/DoD, 2003).

Example: Methadone Titration Plan Opioid-Tolerant Patient		
Wk	Dose	Total Dose/Day
1	5 mg po TID	15 mg
2	10 mg po TID	30 mg
3	15 mg po TID	45 mg
4	20 mg po TID	60 mg
5	25 mg po TID	75 mg

Patients must be monitored for side effects during the transition to methadone, particularly respiratory depression, as this remains the chief hazard associated with methadone. A recent change in prescribing guidelines noted: “Methadone’s peak respiratory depressant effects typically occur later, and persist longer than the peak analgesic effects, particularly in the early dosing period.” Even correctly calculated doses of methadone may be too high in some patients. Daily progress reports via telephone from the patient or family members can help assure both the practitioner and patient that the transition is being completed safely.

Transitioning patients on higher doses of opioids (>300 mg morphine) to methadone is most safely completed in a hospital setting. There are protocols for rapid transition to metha-

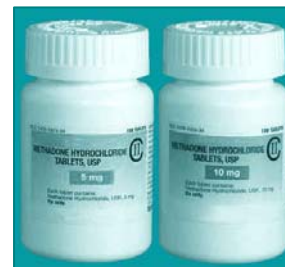
done that use loading doses (Ayonrinde, 2000), variable dosing intervals (Morley and Makin, 1998), and daily dose adjustments (VA/DoD, 2003).

## 8. Formulations & Costs

Methadone is not under patent protection and generic versions of 5 mg and 10 mg methadone tablets provide impressive cost savings over other opioids. Prices vary; however, in some cases monthly costs to patients for oral methadone can be more than 30-fold *less than* equianalgesic doses of other generic or brand-name opioid analgesics.

Effective January 1, 2008, manufacturers of methadone voluntarily agreed to restrict the distribution of 40 mg methadone dispersible tablets to only those facilities authorized for detoxification and maintenance treatment of opioid addiction. Both the 5 mg and 10 mg tablet strengths will continue to be available to all authorized registrants including retail pharmacies (Methadone Advisory 2008).

Primarily in inpatient settings, methadone powder is available for pharmacy compounding of injectable solutions and larger-dose oral capsules, although this adds cost. Premixed oral liquid formulations are available for delicate titrations requiring precise dose increments.



## 9. Drug Interactions

Methadone is principally metabolized by two enzymes: CYP3A4 and CYP2B6, both members of the cytochrome P450 family (Leavitt, 2006). Many substances, including medications, illicit drugs, and OTC products may be substrates, inhibitors, or inducers of these CYP enzymes and significantly affect the serum levels of methadone. Other medications, especially the benzodiazepines, may act synergistically with methadone, increasing the apparent effect of methadone and likelihood for life threatening adverse events.

Certain medications may potentially influence the concentration of methadone indirectly. For example, topiramate is a carbonic anhydrase inhibitor and increases urinary pH (alkalinization; Topamax PI 2007). Alkalinization of urine has been shown to increase the half-life of methadone to an average of 42 hours (Baselt 2004). Therefore, when used concomitantly with topiramate, methadone may reach higher plasma levels.

These potential interactions must be considered when starting methadone therapy and also when medications are added or eliminated from a patient's regimen. The general rule for methadone dosing remains "start low, go slow."

*For a comprehensive, evidence-based listing, see:*

**Methadone-Drug\* Interactions (\*Medications, illicit drugs, & other substances).** By: Stewart B. Leavitt, MA, PhD; from *Pain Treatment Topics*, January 2006. Available at: [http://pain-topics.org/opioid\\_rx/methadone.php#methintr](http://pain-topics.org/opioid_rx/methadone.php#methintr). Access checked 2/22/08.

**Many substances can interact with methadone and must be considered when starting the opioid medication.**



## 10. Special Situations

### Elderly

Methadone clearance does not appear to be affected by age (Eap, 2002). However, there may be an exaggerated response to methadone in the elderly (Säwe, 1986). This group of patients also may have comorbid medical conditions (eg, COPD) and may use medications with potential to interact with methadone. These factors may suggest a lower starting dose in the elderly with titration as necessary.

## Renal and/or Hepatic Failure

Unlike morphine or meperidine, the metabolism of methadone produces no active or toxic metabolites. Only a minor fraction of methadone is cleared by the kidneys. Except in end-stage renal failure, it is usually unnecessary to adjust the dose of methadone because of renal disease.

For patients with severe chronic liver disease, the elimination half-life of methadone increases. However, mean plasma concentrations and dose-adjusted mean plasma concentration do not significantly differ from patients with mild or moderate liver disease (Säwe, 1986), and no dose adjustments are typically required for this degree of hepatic failure (Eap, 2002).

*For further information see:*

**Opioid Safety in Patients With Renal or Hepatic Dysfunction.** By: Sarah J. Johnson, PharmD.

From *Pain Treatment Topics*, Updated November 30, 2007. Available online at:

<http://pain-topics.org/pdf/Opioids-Renal-Hepatic-Dysfunction.pdf>. Access checked 2/20/08.



## Cardiac Conditions

QT interval prolongation and serious arrhythmia (*torsades de pointes*) have been observed during treatment with methadone. Updated methadone product information (Methadone PI 2006) included a “black box” warning noting, “Most cases involve patients being treated for pain with large, multiple daily doses of methadone.” Along with that, however, a majority of cases have involved multiple factors, including prior history of cardiac disease and/or the concurrent administration of other drugs known to affect cardiac rhythm and/or methadone metabolism.

Currently, pretreatment ECGs are not required for all patients prescribed methadone analgesia. Caution is necessary, however, when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers (see Leavitt 2006, also noted above, for listings of drugs that might be of concern).

*For a discussion of these cardiac arrhythmias and further information see:*

**Methadone Cardiac Concerns.** By: Stewart B. Leavitt, MA, PhD; Mori J. Krantz, MD, FACC.

*Pain Treatment Topics* exclusive, from *Addiction Treatment Forum*, October 2003. Available

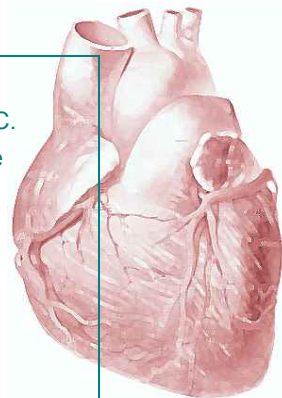
at: [http://pain-topics.org/opioid\\_rx/methadone.php#Cardiac](http://pain-topics.org/opioid_rx/methadone.php#Cardiac). Access checked 2/22/08.

**Also: FDA Advisory Raises Concerns About Methadone. Is Methadone Harmful to**

**Heart Health?** From: *Addiction Treatment Forum*. 2007(winter);16(1). Available at:

[http://atforum.com/SiteRoot/pages/current\\_pastissues/2007winter.html#clinicalconcepts](http://atforum.com/SiteRoot/pages/current_pastissues/2007winter.html#clinicalconcepts).

Access checked 2/22/08.



## Pregnancy/Lactation

Methadone is a Pregnancy Category C (uncertain safety) medication. If it is necessary to use during pregnancy for analgesia, this classification would suggest prescribing a minimal dose. Methadone does cross the placenta, and neonates can suffer from a withdrawal syndrome. Methadone is expressed in breast milk in very small quantities but is generally compatible with breastfeeding (AAP, 2001).

**HIV/AIDS**

Patients with HIV/AIDS are often taking a “cocktail” of antiviral medications, including protease inhibitors and reverse transcriptase inhibitors, and they may also be using antimicrobials to treat or prevent opportunistic infections. These classes of medications may have significant effects on methadone serum levels, and changing a patient’s HIV therapy can have an unpredictable effect. Methadone also may have an effect on anti-HIV medications, potentially making them less effective. Using methadone in patients with HIV/AIDS requires coordination with their HIV healthcare providers. (See Leavitt 2006, also noted above, for antiretroviral drugs that might interact with methadone serum levels.)

*Using methadone in patients with HIV/AIDS requires coordination with their HIV healthcare providers.*

**11. Patient Cautions & Warnings**

Since methadone is different than other opioids in its onset and effects, patients should be advised of several cautions and warnings when starting methadone:

- A)** Pain relief builds gradually over time and it usually takes 5 to 7 days to see how the patient will react to a particular dose.
- B)** Taking methadone as frequently as other opioids (such as Vicodin or Percocet) every 4 to 6 hours may produce a fatal overdose.
- C)** Non-prescribed use of methadone in combination with other opioids, other drugs, or alcohol may be fatal.
- D)** Patients should refrain from driving and other activities requiring balance or focused concentration until the effects of methadone are known, typically a week or longer.
- E)** Other medical providers must be aware the patient is taking methadone. Adding medications or changing dosing of other medications can affect methadone and should be coordinated with the methadone prescriber.
- F)** Methadone, like other opioids, can cause significant constipation. This should be anticipated and a laxative prescribed for the patient at the initiation of methadone therapy.



*More educational and cautionary information for patients is available: Methadone Safety Handout for Patients. In English and Spanish. From Pain Treatment Topics, Updated February 2008. Available online at: <http://pain-topics.org/pdf/MethadoneHandout.pdf>. Access checked 2/20/08.*

**12. Conclusion**

During the 70 years since its development oral methadone has demonstrated a favorable safety profile when properly prescribed and used. Methadone can provide effective and economical pain relief even when other analgesics – opioid or non-opioid – fail to do so. It is suitable for treatment of chronic cancer and non-cancer pain.

Since methadone is different than other opioids in its onset, effects, and metabolism, prescribers need an understanding of its pharmacokinetics and pharmacodynamics. The potential for methadone-drug interactions must be considered. Cautious prescribing of methadone and careful patient-response monitoring are essential. Finally, patients and their caregivers should be advised of several warnings regarding the proper and safe use of methadone.

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