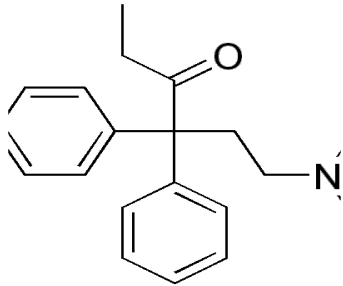


The Place for Methadone Therapy in the Hospice Setting

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Methadone Background



1940s

- Antispasmodic
- Analgesic

1960s

- Opioid Addiction
- Heroin Addiction

2000s

- Chronic Pain

Methadone Pharmacology

- ❖ Potent μ -opioid receptor agonist
 - Similar to Morphine, greater efficacy
- ❖ Non-opioid analgesic mechanisms of action
 - N-methyl-D-aspartate (NMDA) antagonism ¹
 - Inhibits reuptake of serotonin¹
- ❖ Extremely lipophilic
 - Good bioavailability & offers a variety of administration routes ²
- ❖ Metabolized in liver ²
- ❖ Minimum renal excretion (<10%)³

Advantages of Methadone

- ❖ Long-acting (8-12hrs)²
- ❖ Good absorption^{4,5}
 - Both oral and sublingual administration
- ❖ Hospice favorable dosage forms:
 - Liquid and crushable tablets
- ❖ Relatively safe in patients with renal/liver impairment ²
- ❖ Synthetic opioid with distinct chemical structure¹
 - Great for opioid rotation
- ❖ Efficacy toward neuropathic pain
- ❖ Very inexpensive



Favorable Methadone Dosage Forms

❖ Oral Tablets:

- 5mg, 10mg (may be crushed)
- 40mg dispersible tablet (restricted usage methadone maintenance detox clinics, hospitals only)

❖ Oral solution: 5mg/5ml, 10mg/5ml, 10mg/ml

❖ Sterile solution for injection 10mg/ml (IV, SC)

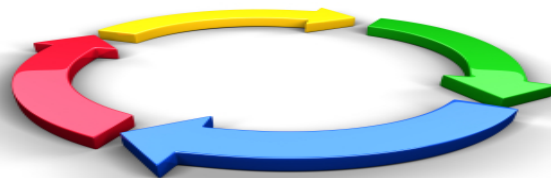
❖ Suppository (compounded)

Great Choice for Renal Impairment ⁶

Drug Name	Renal Dysfunction	Liver Dysfunction
Meperidine	NOT recommended	NOT recommended
Codeine	NOT recommended	NOT recommended
Morphine	Use cautiously	Use cautiously
Oxycodone	Use cautiously	Use cautiously
Hydromorphone	Use cautiously	Use cautiously
Oxymorphone	Use cautiously	Use cautiously
Hydrocodone	Use cautiously	Use cautiously
Methadone	Safe	Use cautiously
Fentanyl	Safe	Safe

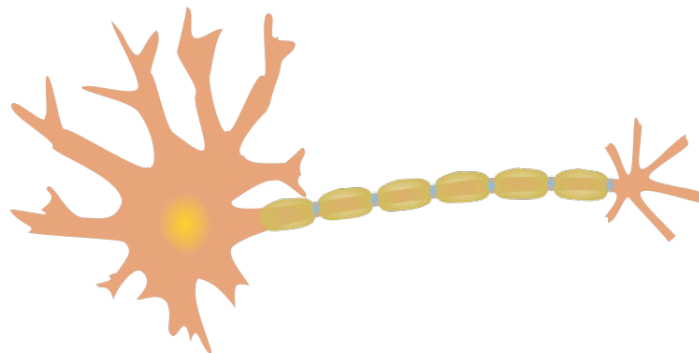
Great Choice for Opioid Rotation

- ❖ Tolerance develops to other opioids
- ❖ Intolerable side effects
 - Neurotoxicity of Morphine and Hydromorphone in renal impairment
 - Morphine's "pseudo-allergy" related to histamine release
- ❖ Methadone is a good alternative
 - Synthetic opioid
 - Different structural class vs. Morphine vs. Fentanyl



Great Choice for Neuropathic Pain

- ❖ Neuropathic pain occurs in 40% of cancer patients⁷
- ❖ More effective for neuropathic pain than other opioids.
- ❖ Additional non-opioid analgesic activity:
 - Inhibition of the NMDA receptor
 - Inhibition of serotonin re-uptake (SSRI)



Cost Effective Long-Acting Opioid

Approximate cost of a 15 day supply of equivalent doses (based upon AWP)

Drug	Dosage	Cost
Methadone	5mg q12h	<u>\$8</u>
Fentanyl Patch	50mcg Q72h	\$132
Morphine ER tablet	60mg Q12h	\$186
Oxymorphone (Opana ER)*	20mg Q12h	\$255
Morphine capsule (Kadian, Avinza)*	100mg q24h	\$296
Oxycodone ER (Oxycontin)*	40mg Q12h	\$300
Zohydro ER	60mg q12h	\$552
Exalgo	32mg Daily	\$915

* Only some select strengths have become generically available, still relatively high cost

Concerns about Methadone

- Negative connotation
Opioid detox. use, drug addicts
- Respiratory depression
May persist longer than the analgesic effects during initial dosage period
- Cardiac effects with high doses
QT prolongation
- Drug interactions
CYP substrate
- No high strength tablets available
5mg and 10MG
- Unfamiliar Kinetics
Biphasic analgesic duration

♠ Require More Patient Educations

- ❖ Emphasize severe pain is the indication
- ❖ Provide rationale of using Methadone
- ❖ Educate on monitoring parameters to ensure successful Methadone therapy



Methadone Side Effects

- ❖ Constipation
- ❖ Sedation
- ❖ Nausea/vomiting
- ❖ Confusion, delirium (reported to be less with Methadone)
- ❖ Hypotension
- ❖ Respiratory depression (more prolonged with Methadone)

♠ Take the same precautions as you use any other opioids

Opioid Respiratory Depression

- ❖ General risk factors for all opioids:
 - Opioid naïve patient
 - Rapid escalation of the opioid dosage (especially long-acting opioids)
 - Presence of sleep apnea
 - Frail elderly and severely debilitated patients
 - Combination with other drugs that contribute to respiratory depression (benzodiazepines, phenobarbital, sedative-hypnotic drugs, alcohol, muscle relaxant)
- ❖ Little difference in risk among opioids w/ equi-analgesic doses ²
 - Less common with oral opioid therapy
- ❖ Tolerance to respiratory depression develops rapidly ⁸

♠ Methadone should be used as long-acting opioid

Potential Methadone Cardiac Side Effects

- ❖ EKG changes: possible prolonged QT interval
 - Potential for serious arrhythmia (torsade de pointes). Rare.
 - Not usually associated with low dose methadone (< 200mg/day)⁹
 - No clinical confirmation of this effect with oral methadone; only IV¹⁰
- ❖ Patient Risk Factors for prolonged QT interval:
 - Cardiac hypertrophy or conduction disorder
 - Methadone doses > 200mg/day (Warning – methadone package insert labeling)
 - Low potassium & or magnesium levels (use caution with diuretic therapy)
 - Combination with other drugs that prolong QT interval
 - ❖ Tricyclic antidepressants, Anti-arrhythmics, Antipsychotics, Macrolide
 - ❖ some 35 other drugs have FDA approved warnings for this

♠ QT Prolongation is not usually a concern at low methadone dose when treating pain

Methadone Drug Interactions

- ❖ Primary means of metabolism: demethylation by CYP-3A4
- ❖ CYP-3A4 activity varies considerably among patients
 - methadone bioavailability varies and difficult to predict interactions
- ❖ Generally of a delayed onset, and of moderate severity ⁶
- ❖ Short-term changes in methadone blood levels not often associated with clinically significant changes
 - Due to large volume of distribution

**♠ Start Methadone at low dose and titrate to effect slowly
base on clinical response**

Some drugs that may increase activity of Methadone ⁶ (by decreasing the metabolism of Methadone)

- ❖ SSRI's
 - Prozac(Fluoxetine), Paxil (Paroxetine), Luvox (Fluvoxamine).
 - Newer SSRI's not as significant (Citalopram, Escitalopram)
- ❖ Elavil (Amitriptyline)
- ❖ Antifungals
 - Fluconazole, Ketoconazole
- ❖ Antibiotics:
 - Ciprofloxacin, Erythromycin, Clarithromycin
- ❖ Chronic alcohol consumption



[Methadone]

Some drugs that Decrease activity of Methadone⁶ (by increasing the metabolism of Methadone)

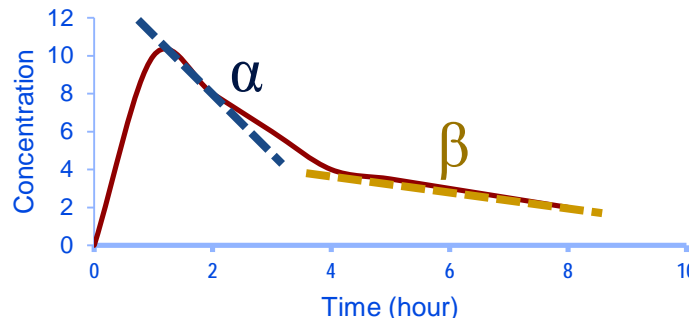
- ❖ Rifampin
- ❖ Carbamazepine (Tegretol)
- ❖ Phenytoin (Dilantin)
- ❖ Phenobarbital
- ❖ Risperidone (Risperdal)
- ❖ Protease Inhibitors
- ❖ Acute high dose alcohol use

[Methadone]



Methadone Kinetics⁶

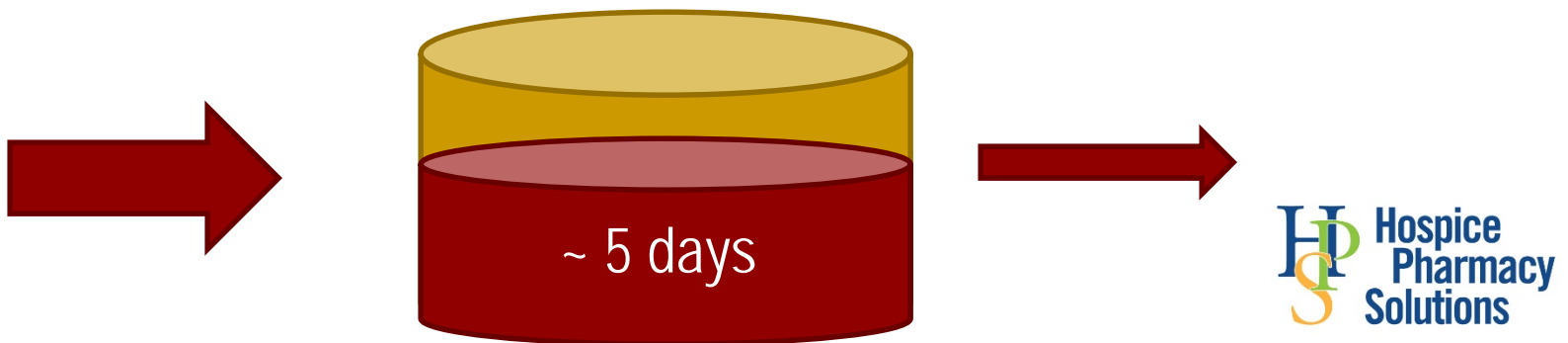
- ❖ Time until detected in plasma after oral dose: 30 min.
- ❖ Time to reach maximum plasma conc. (T_{max}): 2.5 – 4.5 hr
- ❖ Plasma protein binding: 60 – 90%
 - Only unbound drug is active
- ❖ Lipid solubility:
 - 98% of drug that reaches central compartment is rapidly transferred to tissues
 - 2% remains in blood compartment
- ❖ Plasma half-life (T_{1/2}) is bi-phasic:
 - Initial or alpha phase: 2 – 4hr (distribution phase – about 5 days)
 - Maintenance or beta phase: 10 – 40 hrs (big differences b/w individuals)



Methadone Distribution & Biphasic Analgesic Duration

- ❖ Extensive tissue distribution
 - High degree of drug-tissue binding (only “unbound” drug is active)
- ❖ Reservoir of drug is created during distribution phase
 - Steady-state reached in 5 days on average (distribution phase complete)
- ❖ Duration of analgesic effect is biphasic – correlates w/ above
 - 4 -6 hours when therapy initiated
 - 8 -12 hours after repeated routine dosing

(average of 5 days to reach steady-state level, longer for liver impairment)



♠ Not Recommended for Opioid Naïve Patients

- ❖ Avoid starting any LA opioid in an opioid naïve patient
 - Including Methadone
- ❖ Initial opioid responses may be unpredictable and vary from patient to patient
- ❖ Risk of toxicity may be magnified and extended if using a LA opioid to initiate therapy
- ❖ Patient may be considered as "*no longer opioid naïve*" after 5 days of opioid therapy with 60mg/day of morphine or equivalent opioid.

When to Consider Methadone in Hospice

- ❖ Long-acting opioid is required to manage pain
 - > 4 breakthrough doses for > 5 days
- ❖ Severe neuropathic pain
- ❖ Poor pain relief/tolerance to other opioids
 - > 200mg oral Morphine/day
- ❖ Unacceptable side effects that could be signs of opioid neurotoxicity or pseudo-allergy
 - Hyperalgesia, myoclonus, allodynia
- ❖ Chronic Renal Failure -- may be the opioid of choice
 - No toxic metabolites as there is with Morphine and Hydromorphone
- ❖ When a low cost, long-acting opioid is indicated



Implications for Methadone Dosing

- ❖ Duration of analgesic effect:
 - Before distribution phase complete: 4 - 6hrs
 - After distribution phase complete: 8 - 12hrs
- ❖ Recognize the initial increased risk of Methadone accumulation¹¹
 - First week – avoid frequent dosage intervals if possible¹²
- ❖ Prefer fixed routine methadone dose: Q8h or Q12h interval¹²
- ❖ Avoid Methadone dose increases more frequently than q 5 days
- ❖ Anticipate need for PRN analgesic for BTP during first 5 days
 - Use short-acting opioid (Morphine, Oxycodone, etc) PRN for BTP
 - Methadone is generally not recommended for BTP¹²



Typical Methadone Regimen for Pain

Methadone 5mg PO Q12h routine

Morphine (solution or IR tab) PO 10 or 20mg Q2 – 4h prn BTP

- ❖ Reassess PRN usage after 5 days & increase Methadone dose if indicated
- ❖ Increase Methadone dose base on PRN morphine required during 24h period on day 5 of distribution phase
- ❖ Monitor daily during initial week of therapy ¹¹
 - Respiratory depression
 - Signs of over sedation
 - Breakthrough pain

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Several Published Methadone Conversion Methods

- ❖ MD Anderson Med Cntr Guidelines (Ayonrinde & Bridge)
 - ❖ United Kingdom Model (Morely & Makin)
 - ❖ Edmonton Model aka Canadian Model (Bruera)
 - ❖ Italian Method (Ripamonti)
 - ❖ CDC Guideline for Prescribing Opioids for Chronic Pain (Dowell, etc)
-

All *except* MD Anderson guidelines use Q4h dosing initially, then gradually lengthen dosage interval

- High risk for accumulation/toxicity

Most methods are based on “Oral Morphine Equivalents”

- Some do not account for differences in cross tolerance among opioids at higher doses

HPS Methadone Conversion Guideline

- ❖ Based on MD Anderson Cancer Center guidelines
- ❖ Fix dose at long routine interval (8 -12h) from day 1
- ❖ Does NOT rely on PRN Methadone usage
- ❖ Use of a short-acting opioid for BTP (i.e. Morphine)
- ❖ Sliding scale equivalency ratios
- ❖ Works well for patients on low or high dose opioid therapy
- ❖ Less risk of Methadone accumulation/toxicity



HPS Methadone Conversion Guideline

**Step 1: Calculate the total daily Oral Morphine Equivalent (OME)
from all opioids**

Morphine Conversion Factor Chart (Step 1)

Drug	Multiply current dose by this factor to equal oral Morphine dose
Hydromorphone oral	4
Hydromorphone IV	20
Oxycodone	1.5
Morphine IV, SC	3
Methadone	See methadone guidelines
Hydrocodone	1
Codeine	0.15
Fentanyl patch	<u>25mcg/hr</u> patch roughly = 50mg Oral Morphine/day (ratio of 1:100)

HPS Methadone Conversion Guideline

Step 1: Calculate the total daily Oral Morphine Equivalent (OME) from all opioids



Step 2: Convert total daily OME to total daily oral Methadone dose

"Sliding Scale" Methadone Conversion (Step 2)

Hospice Pharmacy Solutions Conversion Guide ^(13,14)

Total Daily Oral Morphine Dose	Morphine to Methadone Ratio
<100mg	5:1
101-750mg	10:1
751-1500mg	12:1
>1500mg	15:1

Adapted from MD Anderson Cancer Center guidelines, Ayonrinde and Bridge (Med J Aust 2000), and Ripamonti (Cancer Pain & Palliative Care 1999)

HPS Methadone Conversion Guideline

Step 1: Determine the total daily Oral Morphine Equivalent (OME) from all opioids

Step 2: Convert total daily OME to total daily oral Methadone dose

Step 3: Divide total daily Methadone dose in to 2 to 3 divided doses

Step 4: Provide a PRN short-acting opioid at 10% to 20% of OME and used q2-4h prn

Step 5: Monitor for 5 days and adjust Methadone dose according to PRN opioid usage

Converting back *from* Methadone

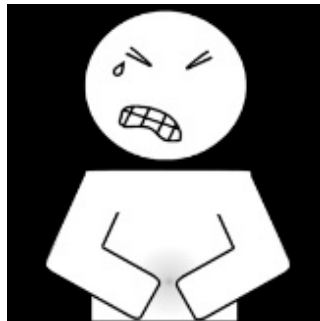
- ❖ Conversion we have described here is ONLY for conversion of other opioids TO Methadone
- ❖ Conversion FROM Methadone to another opioid must take into account the extensive half-life of Methadone (related to tissue binding and wide distribution)



Case Study

Ima Payne:

- ❖ 71 year old female with lung cancer, mets to the bone, and painful diabetic neuropathy
- ❖ Current pain meds:
 - Fentanyl patch 150mcg Q72h
 - PRN Hydrocodone/Acetaminophen 5/325 (14 tabs daily)
- ❖ Has persistent c/o severe burning, shooting pains in her legs, despite current pain meds



Decision to convert

A decision is made to convert from fentanyl to methadone to try and achieve a better response to her pain.

Rationale:

- Neuropathic pain is not responding to current meds
- She can swallow tablets
- Fentanyl is used at high dose and is expensive
- She is receiving 4550mg acetaminophen/day
- May not be a candidate for TCA therapy due to age

Step 1: Determine Total Daily Oral Morphine Equivalent

Oral Morphine Conversion Factor Chart:

Drug	Multiply current dose by this factor to equal oral Morphine dose
Hydromorphone oral	4
Hydromorphone IV	20
Oxycodone	1.5
Morphine IV, SC	3
Methadone	See Methadone Guidelines
Hydrocodone	1
Codeine	0.15
Fentanyl patch	<u>25mcg/hr</u> patch roughly = 50mg Oral Morphine/day (ratio of 1:100)

Step 1: Determine Total Daily Oral Morphine Equivalent

From the morphine conversion factor chart:


- ❖ Fentanyl
 - $150\text{mcg/hr} = 150\text{mcg}/25\text{mcg} = 6$
 - $6 \times 50\text{mg oral morphine/day} = 300\text{mg oral morphine/day}$

- ❖ Hydrocodone/APAP 5mg/325mg
 - $14 \text{ tabs} = 70\text{mg hydrocodone} \times 1 = 70\text{mg oral morphine/day}$

- ❖ Total daily oral morphine equivalent = 370mg

Step 2: Convert OME to Daily Methadone Dose

Using the oral morphine equivalent, determine the appropriate conversion ratio from the table:

Total Daily Oral Morphine Dose	Morphine to Methadone Ratio
<100mg	5:1
 101-750mg	10:1
751-1500mg	12:1
>1500mg	15:1

Methadone Conversion Continued

Step 2: Convert oral Morphine equivalent to methadone:

From the oral Morphine to Methadone conversion chart:

- Ratio is 10:1 for this patient's current dose of 570mg/day
- $370\text{mg}/10 = 37\text{mg}$ total daily Methadone dose

Step 3: Divide total daily dose by 2 = 18.5mg Q12h

- Round down to nearest 5mg increment = Methadone 15mg Q12h
- Initiate methadone 12 hours after fentanyl patch removed¹⁵

Methadone Conversion Continued

Step 4: Provide PRN opioid for breakthrough pain

- Morphine IR tablet 30mg q2h prn
- Oxycodone IR tablet 20mg q2h prn, if morphine allergy

Step 5: Titrate Methadone dose base on PRN opioid use on day 5. Example:

- 5 doses of Oxycodone IR used in 24 hours on day 5
- Total 100mg Oxycodone daily = 150 OME
- 150 OME = 15mg add'l Methadone per day (45mg total)
- Increase Methadone dose to 20mg q12h

Methadone Bottom Line

- ❖ Methadone is an analgesic of indisputable value that continues to gain acceptance for chronic severe pain management.
- ❖ Methadone has no active metabolites
- ❖ Methadone is an inexpensive long-acting opioid with a rapid onset of action available in various dosage forms.
- ❖ Methadone is an excellent long-acting opioid alternative from both a clinical and economic perspective.



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