

UNIVERSITY OF WISCONSIN-MADISON SCHOOL OF PHARMACY

## Methadone Dosing for Analgesia

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### Why this Presentation?

- Over 50% of methadone prescribed in the US is for analgesia
- Methadone has toxicities and pharmacokinetics unique to opioids
- Mortality associated with increased use of methadone is increasing



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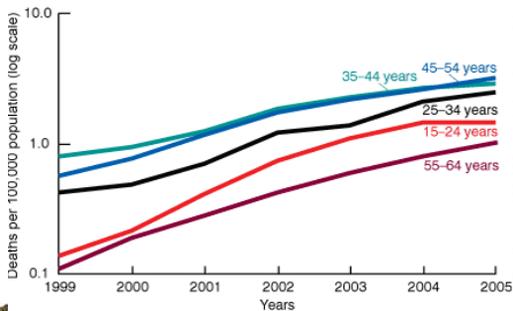
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### Increase in Methadone-related Deaths



SOURCE: CDC/NCHS, data from the National Vital Statistics System.

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## Increase in Opioid-related Deaths

- Narcotic-related deaths have played the largest role in the increase in all poisoning deaths from 1999 to 2005.
- They accounted for 56 percent of all poisoning deaths in 2005, increasing from 50 percent in 1999.
- Their absolute numbers increased 84 percent over the 7 years.
- Methadone-related deaths have increased more than other narcotic-related deaths.




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## Why do we use Methadone?

- A mu-opioid receptor agonist
  - Hence, an opioid analgesic
  - A phenylheptylamine, unlike morphine
- *in vitro* evidence of antagonism of the NMDA receptor
  - Argues for the use of methadone for the treatment of pain with neuropathic component
  - Limited clinical data to support this use.




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## Why do we use Methadone?

- Its long elimination half life (1-3 days) allows every 8-12 hour dosing
- It is available as a liquid (and tablets, IV)
- It is metabolized to inactive metabolites, so is useful in patients with poor kidney function
- It is relatively inexpensive




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## Methadone Pharmacology



- Methadone is currently administered as a racemic mixture
- R- isomer is the mu-opioid agonist
  - Metabolized by CYPs 3A4, 2C19, 2D6
- S- isomer is the NMDA antagonist
  - A CYP2B6 substrate
  - Primary cause of QTc prolongation




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## Methadone Pharmacology



- Both isomers have a very high tissue distribution (4 L/kg) and a modest clearance of ~ 5 L/hr
  - Elimination half life is long and variable
  - Steady state requires patience and caution
    - Concentration plateau takes 5 – 14 days
  - Renal elimination is slowed by an alkaline urine pH, but isn't major elimination route




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## Who are our Candidates for Methadone Treatment?



- True allergy to other pure mu-opioids
- Patients with mod-severe renal impairment
- Adverse effects from other opioids
  - Hallucinations, myoclonic jerks, dysphoria
- Pain refractory to other opioids
- Cases where cost is an issue
- Benefit from long-acting opioid
  - Especially those with G/J-tube access (liquid)

McPherson L. Demystifying opioid conversion calculations




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## Methadone has advantages in patients with renal dysfunction



- Other opioid glucuronide metabolites are renally excreted, but not all are active:
- Inactive glucuronides are found with:
  - Oxycodone
  - Hydrocodone
  - Tapentadol
- Active glucuronides are found with:
  - Morphine (M3G: neuroexcitatory; M6G: analgesia)
  - Hydromorphone (H3G: likely neuroexcitatory)




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## Methadone has characteristics of an extended-release formulation



- Extended Release Formulations
  - Tablets
    - Morphine, Oxycodone, Oxymorphone, Hydromorphone
  - Controlled-release granules
    - Morphine
  - Patches
    - Fentanyl, Buprenorphine, Hydromorphone
- Extended Effect (due to pharmacokinetics)
  - Methadone




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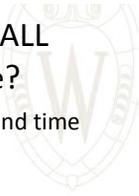
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## Why shouldn't we Start ALL Patients on Methadone?



- Highly variable elimination half-life and time to steady state
  - Impairs speed of titration
- Variable conversion ratio from other opioids
- Prolongation of QTc, risk of Torsades
- Multiple drug interactions
- Social stigma




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## Relative Contraindications for Considering Methadone Treatment

- Patients with very limited prognosis (hours to days)
- Other medications take that would affect P450 enzyme activity or increase risk of QTc prolongation
- Pts with history of arrhythmias or syncope
- Poor adherence, poor cognition, unreliable

McPherson L. Demystifying opioid conversion calculations  
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## What are our options for extended effect, chronic pain control in a patient unable to swallow meds?

- IV or SubQ infusion
  - Morphine, hydromorphone, fentanyl, methadone
- Per G- or J-tube
  - Methadone solution
    - **CAUTION! (1mg/ml, 2mg/ml, and 10mg/ml solutions are available. Be careful and check!)**
  - Kadian® controlled release granules
    - Can clog small bore tubes
- Fentanyl and other patches

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## The Economies of Methadone

Drug	Daily Oral Dose	Daily Dosage	Monthly Cost
Morphine Sulfate ER	600 mg	6 X 100mg	\$682
Oxycodone ER	400 mg	5 x 80mg	\$1960
Fentanyl TTS	300 mcg/hr	100mcg/hr (replace q3D)	\$545
Methadone	60 mg	6 x 10mg	\$102

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## Can we start Methadone in an Opioid-naïve Patient?



- Yes
- 2.5 mg methadone PO 1 – 3x daily
  - Once daily usually best for frail elderly
  - 2.5 mg Q12H or Q8H for others
  - 5-7.5mg methadone approximates 15-40mg oral morphine
- Breakthrough (Rescue) med?
  - Some use methadone
  - Most use morphine, oxycodone, hydromorphone




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## Starting Methadone



- Non-naïve patients
  - The equianalgesic ratio of methadone to morphine IS NOT LINEAR, but VARIES
  - You will see ratios of 4:1 – 40:1, depending upon the dose
  - As a rule, the larger the equivalent morphine dose, the higher the conversion ratio




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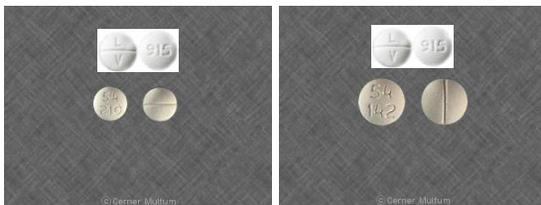
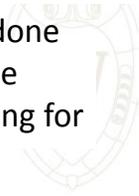
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QUICK...Which is methadone (Q8H) and which is the morphine IR for Q2Hr dosing for breakthrough pain?




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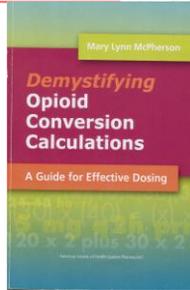
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## Recommended Reading

- McPherson MLM. Demystifying opioid conversion calculations: a guide to effective dosing. ASHP Bethesda 2009.




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## FDA-Approved Dolophine® Label

Total Daily MEDD*	Estimated Daily Oral Methadone Dose as % of MEDD
< 100mg	20 – 30% (3.3:1 – 5:1 ratio)
100 - 300mg	10 – 20% (5:1 – 10:1 ratio)
300 - 600mg	8 – 12% (8:1 – 12:1 ratio)
600 - 1000mg	5 – 10% (10:1 – 20:1 ratio)
>1000mg	< 5% (> 20:1 ratio (?))

MEDD: Morphine Equivalent Daily Dose

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## Ripamonti and Mercadente Models

Oral MEDD	30 – 90mg	90 - 300mg	>300mg
Ripamonti (1998)	4:1	6:1	8:1
Mercadente (2001)	4:1	8:1	12:1

MEDD = Morphine Equivalent Daily Dose (Oral)

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### Friedman Methadone Conversion

- Less than 1000 mg MEDD and < 65years:
  - Use a 10:1 oral morphine / methadone ratio
- Less then 1000 mg MEDD and ≥ 65 yrs OR 1000-2000 mg MEDD:
  - Use a 20:1 oral morphine / methadone ratio
- More than 2000 mg MEDD:
  - Consider 30:1 oral morphine/methadone
  - High MEDD may represent hyperalgesia
  - High MEDD may affect Pgp opioid transport




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### Modified Friedman (Hutson)

Morphine Equivalent Daily Dose (mg)	Morphine to Methadone Ratio	
	At or Under 65 yr and Not frail	Over 65 or Frail
< 300 mg/day	5:1	10:1
300 – 1000 mg/day	10:1	20:1
1001 – 2000 mg/day	20:1	30:1
2001 -	30:1	40:1

The starting dose of methadone for inpatients or closely monitored patients should not exceed 90mg/day. For most outpatients, the starting dose should not exceed 45 mg/day.




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### Methadone TO Morphine

- VERY LITTLE information on this
  - DO NOT use 1:10 ratio (or higher)
  - Recommendation:
    - 1:3 ratio to be conservative**
- eg. From 15mg Q8H methadone go to 45mg q8H extended release morphine




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## Timing of Conversions



- Rapid method (with close observation)
  - Stop infusion; Start methadone 3 hours later
  - or, Give first dose of methadone instead of next dose of CR morphine or oxycodone
- Tapered method (gentler, better for outpatient)
  - More often used with high MEDD conversions
  - Give 1/3 of equivalent dose of methadone and drop MEDD by 1/3
  - Repeat daily x3, dropping original drug by 1/3 of original dose daily, replacing with methadone




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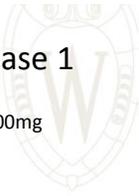
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## Methadone Conversion: Case 1



Example: A patient is to be converted from 600mg Morphine SR (200mg Q8H)

Scheduled Dose:

Methadone 20mg Q8H (10:1 ratio)

Rapid Taper:

No need to taper morphine, just switch

Rescue Dose:

Methadone 10mg PO Q4H PRN, or  
Morphine 60-120 mg PO Q2H PRN




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## Methadone Conversion



Example: A patient is to be converted from 600mg Morphine SR (200mg Q8H)

Scheduled Dose (10:1) = Methadone 20mg Q8H

Slow Taper (better for Outpatient Transition):

Day 1: 120mg Morphine SR & 5mg Methadone, Q8H

Day 2: 60mg Morphine SR & 10mg Methadone, Q8H

Day 3: 30mg Morphine SR & 15mg Methadone, Q8H

Day 4: Stop Morphine SR, Give 20mg Methadone Q8H

Rescue: 60-120mg Morphine IR, Q2H PRN

[OR: Methadone 5mg Q3-4H, PRN]




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## Case 2



- Patient BR is receiving a basal SC hydromorphone infusion at a rate of 2.5 mg/hr, and has had an average of an additional 30mg over 24hrs from patient or RN boluses. We are asked to convert him to oral methadone for a neuropathic pain component and for cost considerations. What should his initial regimen be?




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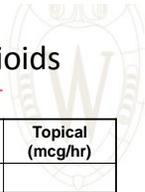
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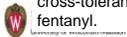
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## Converting between Opioids



Drug	IV/SC (mg)	Oral (mg)	Topical (mcg/hr)
Morphine	10	30	
Oxycodone	-	20-30	
Hydromorphone	1.5	7.5	
Oxymorphone	1	10	
Methadone	50% of Oral	~3	
Fentanyl	0.015 (15mcg)		15 (0.015 mg/h)

After determining conversion dose, reduce by 25-33% for incomplete cross-tolerance, EXCEPT for conversion of morphine to methadone or fentanyl.




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## Case 2:



- What is the daily oral morphine equivalent of the hydromorphone IV?
- 2.5 mg/hr x 24hr = 60mg basal
- + 30mg from PID & RN = 90mg IV hydromorphone
- Using a 1:20 ratio, this would equal 1800mg oral morphine per day.
  - Lower by 25-33% for incomplete cross-tolerance to 1200mg/day MEDD




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### Case #2 - Methadone



- Calculating an daily morphine equivalent dose of 1800 mg, the methadone regimen should be (with appropriate rescue dosing):
  - 210mg, as 70mg PO every 8 hours
  - 150 mg, as 50mg PO every 8 hours
  - 90 mg, as 30mg PO every 8 hours
  - 30 mg, as 10mg PO every 8 hours




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### Comparison of Methadone Conversions from 1800mg MEDD

Method	Ratio	Daily Methadone
Ripamonti	8:1	225 mg
Mercadente	12:1	150 mg
FDA-approved PI	20:1	90 mg
Friedman	20:1	90 mg

Many clinicians will limit the initial daily methadone dose to 90mg (30mg TID) if calculations suggest a higher initial dose.

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### Question #2 - Methadone



- Calculating an daily morphine equivalent dose of 1800 mg, the methadone regimen should be (with appropriate rescue dosing):
  - 210mg, as 70mg PO every 8 hours
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  - 90 mg, as 30mg PO every 8 hours
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## Methadone Caveats



- Conversions from other opioids are NOT proportional
- Reaching steady state takes ~ 1 week
- Clearance will vary with adding/removing other drugs that affect its P450 enzymes (3A4, 2B6)
- QTc interval will likely increase with higher doses
  - Avoid use with other QTc prolonging drugs
  - Some MDs will get an ECG before/during Tx




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## Timing of Conversions



- Rapid method (with close observation)
  - Stop infusion; Start methadone 3 hours later
  - or, Give first dose of methadone instead of next dose of CR morphine or oxycodone
- Tapered method (gentler, better for outpatient)
  - More often used with high MEDD conversions
  - Give 1/3 of equivalent dose of methadone and drop MEDD by 1/3
  - Repeat daily x3, dropping original drug by 1/3 of original dose daily, replacing with methadone




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## Rapid Conversion



- Stop IV hydromorphone infusion
- Wait 3 hours, and give first dose of 30mg methadone
- Continue through the rest of the day at 30mg q8h
- Rescue / Breakthrough: Most convenient will be IV PID doses of hydromorphone (2.5 mg q10min)
  - Could also give 15mg methadone q4h




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## Tapered Conversion



- Day 1
  - Decrease hydromorphone infusion from 2.5 to 1.6mg/hr
  - 3 hours later start 10mg methadone q8 hours
- Day 2
  - Decrease hydromorphone infusion from 1.6 to 0.8mg/hr
  - 3 hours later start 20mg methadone q8 hours




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## Tapered Method (continued)



- Day 3
  - Stop hydromorphone infusion
  - 3 hours later start 30mg methadone q8 hours
- Rescue/Breakthrough
  - Hydromorphone 2.5mg q10 min IV PID
  - Morphine 120-240 mg PO Q2 hours
  - Methadone 50% of Scheduled dose, given orally Q3-4 hours
    - Cognition? Caregiver helping with PRNs?




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## Can we Give Methadone IV?



- Yes, bioavailability is 30-100%
- Use 100% bioavailability when transitioning from IV to PO methadone
  - 36 mg IV/day >> 36 (45) mg PO/day
- Use a more conservative 2:1 ratio when converting from PO to IV methadone
  - 45 mg PO/day >> 24 mg IV/day




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## Opioid Respiratory Depression



- Treatment
  - Ventilate
  - Stop infusion / remove patch, if present
  - Administer 50-100 mcg boluses naloxone Q5 min
    - Naloxone is a pure mu antagonist
      - Higher doses (400 mcg) are more likely to reverse BOTH respiratory depression AND pain control




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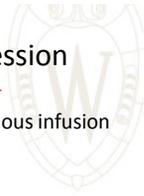
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## Opioid Respiratory Depression



- For sustained-release products, a continuous infusion of naloxone is indicated
  - Dilute 2 mg in 500 ml NS
  - Initial rate (mcg/hr) is approximately 67% of the bolus size needed for initial resuscitation
  - Titrate rate to clinical effect; may require additional boluses as the infusion rate is increased.




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## Opioid Respiratory Depression



- Example
  - If we needed to administer 200mcg of naloxone to reverse apparent opioid-induced respiratory depression
  - We should immediately start a naloxone infusion of about 120mcg/hr.
  - Duration of infusion will depend on the half-life of the opioid causing the toxicity




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## Drugs Implicated in TdP

- Antiarrhythmics
  - Class IA and III
- Promotility agents
  - Cisapride\*
  - Erythromycin
- Antibiotics
  - Erythromycin
  - Clarithromycin
  - Pentamidine
  - Antimalarials
- Antidepressants
  - TCA > SSRIs
- Antipsychotics
  - Phenothiazines
  - Butyrophenones
    - Haloperidol
    - Droperidol
  - Ziprasidone (GEODON)
- Supplements
  - Licorice
- Opioids
  - **Methadone**
  - Oxycodone ?

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## Methadone and LQTS/TdP

- Multiple series reporting prolonged QTc and some cases of Torsades in patients receiving methadone
  - Most were opioid replacement patients or IV
    - Doses tend to be higher than for pain
  - Few cases were for pain treatment
- Quality and generalizability of reports varies
  - Case report/series
  - Cross-Sectional, Retrospective, or Prospective




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## Other Possible Risk factors for Methadone LQTS

- Exposure to cardiotoxic chemotherapy
  - Taxanes, anthracyclines, high dose cyclophosphamide
- Hypokalemia
  - NG suction
  - Chronic diarrhea
  - History of Cisplatin treatment
- Bradycardia (perhaps drug-induced)




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### What about other opioid effects?



- No evidence of clinically significant QTc prolongation:
  - Morphine
  - Codeine
  - Fentanyl
  - Tramadol
- Dose-dependent QTc prolongation with
  - Oxycodone




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### Expert Panel Recommendations

Krantz 2009



- Disclosure
 

Clinicians should inform patients of the arrhythmia risk when they prescribe methadone
- Clinical History
 

Clinicians should ask patients about any history of structural heart disease, arrhythmias, or syncope




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### Expert Panel Recommendations

Krantz 2009



- Screening
 

Obtain a pretreatment ECG for ALL patients to measure QTc interval, and a follow-up ECG within 30 days and annually.

Additional ECGs are recommended if the methadone dosage exceeds 100mg/day, OR if patients have unexplained syncope




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## Expert Panel Recommendations

Krantz 2009



### • Risk Stratification

If the QTc is > 450ms but < 500ms, discuss the potential risk and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500ms, consider stopping or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy



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## Expert Panel Recommendations

Krantz 2009



### • Drug Interactions

– Clinicians should be aware of interactions between methadone and other drugs that possess QTc-interval prolonging effects, or that slow the elimination of methadone



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## Methadone Drug Interactions

### • CYP3A4 Inhibitors

- Fluconazole
- Fluoxetine
- Fluvoxamine
- Nefazodone
- Paroxetine
- Venlafaxine
- Erythromycin/Clarithro
- Ciprofloxacin

### • CYP2B6 Inhibitors

- Fluoxetine
- Fluvoxamine
- Haloperidol
- Nefazodone
- Paroxetine
- Sertraline
- Ticlopidine
- Clopidogrel

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## Methadone Drug Interactions

- CYP2D6 Inhibitors
  - Bupropion
  - Cinacalcet
  - Fluoxetine
  - Paroxetine
  - Duloxetine
  - Sertraline
  - Terbinafine
  - Amiodarone
  - ...
- CYP3A4 Inducers
  - Carbamazepine
  - Glucocorticoids
  - Phenytoin
  - Rifampin

**Adding or removing inducers or inhibitors can change the clearance of methadone, and the effects at steady state will not be known for days to weeks, even on stable methadone doses**

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## Modifiable Concerns

- Avoid or Correct Concurrent
  - Hypokalemia
  - Medications
    - Erythromycin / Clarithromycin
    - Ondansetron
    - Haloperidol
    - Ziprasidone (Geodon)
    - Tricyclic antidepressants, perhaps SSRIs
    - Enzyme inhibitors (CYP3A4 and 2D6)
    - Cardiac Chronotrophs




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## Indications for Considering Methadone Treatment

- True allergy to other pure mu-opioids
- Patients with renal impairment
- Opioid-induced adverse effects
  - Hallucinations, myoclonic jerks
- Pain refractory to other opioids
- Cases where cost is an issue
- Benefit from long-acting opioid
  - Especially those with G/J-tube access



McPherson L. Demystifying opioid conversion calculations

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## Relative Contraindications for Considering Methadone Treatment



- Patients with very limited prognosis (hours to days)
- Other medications take that would affect P450 enzyme activity or increase risk of QTc prolongation
- Pts with history of arrhythmias or syncope
- Poor adherence, poor cognition, unreliable

McPherson L. Demystifying opioid conversion calculations




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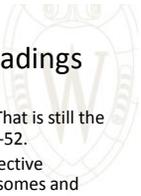
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## References and Suggested Readings



- **Cruciani AR.** Methadone: To ECG or not to ECG. That is still the question. *J Pain Symptom Manage* 2008; 36: 545-52.
- **Chang Y, Fang WB, Lin SN, Moody DE.** Stereo-selective metabolism of methadone by human liver microsomes and cDNA-expressed cytochrome P450s: a reconciliation. *Basic Clin Pharmacol Toxicol.* 2011 Jan;108(1):55-62.
- **Fanoë S, Jensen BB, Sjogren P.** Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity *in vitro*. *Br J Clin Pharmacol* 2009; 67: 172-79.




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## Thank You

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