Opioid Analgesic Dosing Guideline

Washington State Pharmacy and Therapeutics Committee

The Use of Opioid Analgesic Agents for Chronic Pain

Opioid analgesic agents are safe and equally effective if prescribed appropriately and administered in equipotent doses. Equipotency can be complicated because opioids differ in half-life, binding affinity, route of administration, metabolism and potential for side effects. In addition to the differences in the opioids themselves, an individual patient's response to opioid analgesics is variable and difficult to anticipate because of genetic differences that influence analgesia and side effect profiles.

Genetic differences exist in:

- Metabolism of opioids and their active metabolites
- Opioid receptor variablilty
- Binding affinity of opioids and active metabolites to the receptors that affect analgesia
- Binding affinity of opioids and active metabolites to the receptors that affect side effects

Therefore, the selection of an opioid analgesic for chronic pain is largely empiric. In addition, patients must be monitored and reassessed frequently, as the potential for adverse outcomes and abuse exists with all opioid analgesics.

The risk of abuse or adverse outcomes with any opioid analgesic increases with:

- Active alcohol and/or substance abuse
- History of alcohol and/or substance abuse
- History of chronic use of benzodiazepines
- Borderline personality disorder
- Mood disorder and other mental illness
- Off work for more than 6 months
- Poor response to narcotic analgesic agents in the past
- Drug seeking behaviors including:
    - Selling prescription drugs
    - Forging prescriptions
    - Stealing or borrowing drugs
    - Frequently losing prescriptions
    - Aggressive demand for narcotics
    - Injecting oral/topical narcotics
    - Unsanctioned use of opioids
    - Unsanctioned dose escalation
    - Injecting oral or topical narcotics
    - Concurrent use of illicit drugs
    - Failing to undergo diagnostic tests
    - Concurrent abuse of illicit drugs

Methadone Dosing Recommendations for the Treatment of Chronic Pain

Traditionally methadone has been associated with the treatment of heroin addiction. However, methadone is an analgesic alternative for treating refractory pain. Pharmacokinetic properties of methadone require initiation at a low dosage with gradual titration to effect to reduce the potential for side effects and adverse outcomes. Risk of toxicity due to overdose increases greatly if the dosage is increased too rapidly.

Special pharmacokinetic properties of methadone

- Long elimination half-life (128hrs) coupled with a
- Much shorter duration of analgesic effect (6-8 hours) results in
- Risk of drug accumulation and adverse effects
- Half-life does not predict duration of analgesia
- Analgesic effects may require initial dosing interval of 6 hours.
- Repeated dosing will result in tissue accumulation and may require dosing intervals of 8-12 hours or reduction in dose with chronic utilization.

Benefits of methadone

- Duration of analgesia 6-8 hours or longer
- Effective in pain that is non-responsive or refractory to other opioid analgesic agents because of incomplete cross tolerance
- No active metabolites
- Low cost (long acting morphine is also a lower cost alternative to the more expensive long acting opioid analgesic agents)

Toxicities related to methadone can occur when conversion doses are too high, titration is too rapid and/or short dosing intervals (≤4hrs) are used.

Methadone toxicities

- Drowsiness,
- Sedation
- Nausea,
- Constipation
- Respiratory depression
- Bradycardia,
- Tachycardia,
- Hypotension
- QTc prolongation
- Urticaria

Methadone is generally well tolerated when

- Initiated at a low dose
- Dosage is increased slowly
- Appropriate conversion ratios are utilized
- Appropriate monitoring is performed
- Patient education is provided

Methadone should be used with caution in

- Patients with significant liver, renal or pulmonary disease or electrolyte imbalances
- Elderly patients

Drugs that increase methadone concentrations:

- SSRIs (particularly fluoxetine and fluvoxamine)
- Fluconazole, Ketoconazole
- Acute alcohol ingestion

Drugs that decrease methadone concentrations:

- Carbamazepine
- Nevirapine
- Risperidone
- Ritonavir
- Phenytoin
- Rifampin
- Chronic alcohol ingestion

Methadone increases concentrations of TCA’s and Zidovudine

Recommended Methadone Dosing Guidelines

For opioid naïve patients start at 2.5 to 5mg bid to tid
increase by 2.5 to 5mg per day every 1-2 weeks

For patients taking chronic opioid analgesic agents:

Narcotic Analgesic Estimated Conversion Tables
(Narcotic conversions are not simple calculations and these are simplified guidelines)

Morphine Dose	**Morphine : Methadone** Estimated Ratios	**Methadone Dose**
30-90mg/day	4 :1	10-20mg/day
90-300mg/day	8 :1	10-40mg/day
300-600mg/day	10 :1	30-60mg/day
600-800mg/day	12 :1	50-60mg/day
Oxycodone Dose	**Oxycodone : Methadone** Estimated Ratios	**Methadone Dose**
10-60mg/day	2 :1	5-30mg/day
60-100mg/day	4 :1	15-25mg/day
> 100mg/day	6 :1	

Oxycontin Dose	**Long-acting Morphine Dose**	**Fentanyl Patch**	**Methadone Dose**
10mg bid	15mg bid		2.5mg tid to 5mg bid
20mg bid	30mg bid	25mcg/hr	5mg tid or 10mg bid
40mg bid	60mg bid	25mcg/hr	5mg qid or 10mg bid
60mg bid	30mg 3 tabs bid	50mcg/hr	5mg qid or 10mg tid
80mg bid	60mg 2 tabs bid	75mcg/hr	10mg tid to 10mg qid

- Educate the patient not to exceed the prescribed dose of methadone.
- Provide additional breakthrough medication on an as needed basis.
- After 7-10 days, adjust the dose as needed by 5-10mg per day.
- Patient variability makes converting difficult and the patient's clinical situation may require a smaller or larger conversion dose.
- A larger dose may be required if the patient's pain is not already well controlled.
- In general when converting do not exceed 40mg daily.
- Converting to methadone doses of greater than 40-50mg/day should be discussed with providers who specialize in the management of chronic pain.

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Washington State Department of Labor and Industries. Guidelines for outpatient prescription of oral opioids for injured workers with chronic, noncancer pain.
http://www.lni.wa.gov/omd/PdfDoc/MedTreat/2002MTG86to108.pdf

Opioid and Chronic Non-Malignant Pain: A Clinicians' Handbook.
Section 6: Converting from one long-acting opioid to another.
http://www.ohsu.edu/ahec/pain/painmanual.html

Cyngery is a PDA program designed to assist with narcotic analgesic conversions. When converting it is important to designate the chronic dosing conversions. You may find the chronic dosing conversions of methadone to be on the lower end of the spectrum.
Methadone PDA conversion:
http://www.cynergygroup.com/Demo/cgi-bin/calc/disclaimer.asp