Methadone Dosing, Titration, and Ongoing Monitoring

Dosing and Titrations

- Critical Period: The first few days of methadone treatment are critical due to methadone accumulation and high overdose risk.
- Safety Check: At each dose determination, collaborate with staff to observe for and be mindful of concomitant use of illicit drugs, alcohol, medical conditions that may compromise respiratory function, prescribed medications that are sedating, or prescribed medications that may increase methadone's effective plasma level.
- Initial Dose Determination: Based on pharmacology of methadone, patient characteristics, and current level of opioid tolerance (quantity, potency, and route of opioid use and time elapsed since last use).

Dose	Information
Healthy Patient At least moderate opioid tolerance Demonstrates at least early signs of opioid withdrawal	
Induction: Day 1 Goal: Reduce withdrawal for 3-4 hours after the dose. The 1st dose of methadone should not be expected to completely suppress opioid withdrawal, and the dose is too high if it does.	10-30 mg; observe the patient for 2-4 hours for sedation or relief from withdrawal symptoms. Maximum dose is 30 mg. Lower doses: those 55 or older, taking sedating or interacting medications with methadone, patients with medical conditions such as asthma, COPD, obesity, sleep apnea, hypokalemia or hypomagnesemia. *For patients for whom methadone history is not known, start as if the dosing is initial induction and increase if objective signs/symptoms of withdrawal are observed.
Induction: Day 2	Screen the patient for signs of overmedication, including sedation, unusual energy with or without euphoria, or feeling completely well for 24 hours after the 1st dose. If these signs are present- reduce the dose by 20-30%. If complete suppression of withdrawal was achieved 2-4 hours after dosing on Day 1, delay any dose increase for another day or 2. If the patient did not experience complete suppression of withdrawal within 2-4 hours of dosing on Day 1, it is safe to increase the dose by 5 mg.

Funding for SMI CalAdviser was made possible by the State of California Department of State Hospitals (DSH) (the Department), but does not necessarily represent the views of the Department or any of its employees except to the extent, if any, that it has formally been approved by the Department.

Dose	Information
Induction: Day 3	A patient's response to the previous day's dose serves as a guide to the determination of subsequent doses. Helpful question to ask patient: Did the dose completely controlled symptoms of withdrawal for 2-4 hours after dosing? Continue this way until steady state is reached at Day 5.
Tolerance is Unclear **Patient who has a low level of tolerance**	
Induction: Day 1 Goal: Reduce withdrawal for 3-4 hours after the dose. The 1st dose of methadone should not be expected to completely suppress opioid withdrawal, and the dose is too high if it does.	5 mg; observe the patient for 2-4 hours for sedation or relief from withdrawal symptoms.
Induction: Day 2	Screen patient for sedation, euphoria, and duration of suppression of urges to use opioids or opioid withdrawal. Adjust or continue the dose in increments of 2.5 and 5 mg as necessary.
Induction: Day 3	Patient's response to the previous day's dose serves as a guide to the determination of subsequent doses. The rate of titration and the doses used will be slower and lower.
No Tolerance	
Induction: Day 1 Goal: Reduce withdrawal for 3-4 hours after the dose. The 1st dose of methadone should not be expected to completely suppress opioid withdrawal, and the dose is too high if it does.	2.5 mg; observe the patient for 2-4 hours for sedation or relief from withdrawal symptoms.
Induction: Day 2 and forward	No evidence of sedation on Day 1, continue 2.5 mg daily for 5 days until steady state is achieved. Evidence of sedation on Day 1, the dose can be lowered to 2 mg and continued for 5 days, until steady state is achieved.

Special Populations (rapid metabolizers or concurrent pain management)

- May require split dosing to alleviate withdrawal between doses
- Two methods:
    - 5-10 mg of the morning dose can be transferred to the evening. Continue to make transfers in increments of 5-10 mg every 5-7 days until the patient feels comfortable and without symptoms of withdrawal between doses.
    - Divide the daily dose in half, given ½ in the morning and the other in the evening. This may cause the patient to experience some amount of withdrawal after the morning dose.
- If split dosing cannot be continued:
    - Evening dose will need to be slowly added back to the morning dose in 5-10 mg increments every 3-5 days.
    - If sedation is observed after the morning dose, return the morning dose to the last tolerated dose and taper the evening dose to discontinuation.
    - Discontinuing the split dose in a patient who is a rapid metabolizer will make it impossible to achieve a therapeutic dose.

Therapeutic Methadone Dose: Achieve a therapeutic dose which suppresses physical signs and symptoms of opioid withdrawal between doses, minimizes intrusive thoughts/dreams about opioids and urges to use or cravings, has minimal side effects such as sedation, sweating, constipation, and decreased libido, and blocks euphoria produced by opioids.

- Dose adjustments should be made using “start low and go slow”.
- Patients typically reach 24-hour coverage of physical symptoms within the first few weeks of treatment.
- For patients with at least moderate opioid tolerance, dose adjustments of 5 mg can be made every 3-5 days as needed.
- For patients with no or low tolerance, make dose adjustments of 2.5 to 5 mg weekly as needed.
- Methadone can induce its own metabolism via CYP3A4. The eventual dose will be higher than the initial dose.

Monitoring

- Observed random urine or saliva toxicology- performed at least monthly
- Regular assessment of bowel functioning
- Monthly weight and BMI
- Methadone peak and trough plasma levels as clinically indicated
- ECG annually or as clinically indicated
- Regular pregnancy testing in women of childbearing age
- Therapeutic Methadone Blood Levels:
    - **Methadone has a long half-life and accumulation in the tissues - even with holding the dose constant over several days, the patient’s methadone serum level will rise each day until it reaches steady state.

- Example: Patient is treated with 10 mg for the first few days of induction, the serum level on Day 2 will reflect the 10 mg from the Day 2 dosing plus 5 mg that remained in the body from the Day 1 dosing. On Day 3, the serum level will reflect 10 mg from Day 3 plus 5 mg remaining in the body from Day 2 plus 2.5 mg remaining in the body from Day 1.

- Typical peak plasma concentrations: 800-1000 ng/mL
- Typical trough levels: 400-500 ng/mL
- Obtain serum methadone levels after a patient has steady state, which occurs after 5-7 consecutive days at the same dose.
- Once daily dosing: A trough level is drawn before the daily dose and about 24 hours after the previous dose.
- Divided Doses: Level drawn before the morning dose
- Peak level is drawn 3-4 hours after taking the daily dose

- Adverse Reactions to Monitor For:
  - Constipation
  - Sedation
  - Sweating
  - Sexual dysfunction or decreased libido
  - Drowsiness
  - Amenorrhea
  - Weight Gain
  - Edema of the extremities
  - Opioid-induced androgen deficiency resulting in decreased testosterone and bone loss

Drug Interactions

Medication	Recommendations
Benzodiazepines or other CNS Depressants	Stopping benzodiazepines, muscle relaxants, and other sedating medications prior to treatment with methadone is preferred. If they can't be stopped, decreasing to the lowest possible dose with increased monitoring may be appropriate. Concomitant use with sedating antipsychotics: adjust the dose to maximize efficacy and minimize sedation before starting methadone.
Concomitant use of CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, azole antifungals, and certain antiretrovirals)	Can increase plasma concentration of methadone resulting in sedation and prolonged opioid effects. After stopping a CYP3A4 inhibitor, methadone plasma concentration will decline. Consider titrating the methadone dose until stable drug effects are achieved.

Medication	Recommendations
Concomitant use of CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, and some antiretrovirals)	Can decrease plasma concentration of methadone resulting in decreased efficacy or the onset of opioid withdrawal. If CYP3A4 inducer is stopped, methadone increases over 4-6 weeks. Monitor for signs of sedation or respiratory depression. If the patient appears sedated, reduce the methadone dose by 2.5 mg to 10 mg per day. Doses of 20 mg per day or less should be decreased by 2.5 to 5 mg per day. Doses of >20 mg per day can be decreased by 5 to 10 mg per day.
Anticholinergic Drugs	May increase risk of severe constipation. Monitor patient carefully. Consider prophylactic laxatives. If constipation does not respond to laxative polypharmacy, treat with naloxegol or naldemedine.
Antiarrhythmics	Monitor cardiovascular status carefully.
Drugs acting on the mu opioid receptor	May precipitate severe opioid withdrawal.

Additional Resource for Drug Interaction: https://chi.ucsf.edu/

Tapering and Discontinuing Methadone

- Patients should stay in treatment for as long as they continue to benefit and develop no contraindications.
- Tapers should be flexible and tailored to the individual.
- Tapers typically occur over several months or longer to give the patient time to acclimate to the lower dose and reduce discomfort from opioid withdrawal and cravings.
- One approach: Decrease the methadone dose by 5-10% every 1-2 weeks. Once the dose reaches 20-40 mg, the patient may begin to experience more urges to use opioids. The patient can continue to taper the methadone at a slower rate.

See this resource for more details on naloxone administration and monitoring

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