venebio

EDUCATION MODULE

PRESCRIBING METHADONE FOR CHRONIC PAIN*

*This module provides information about methadone as a risk factor for opioid overdose and specific risk-reduction guidance. It **supplements** but does not replace the general best practices for opioid prescribing presented in the "**Considerations for Safe and Responsible Opioid Prescribing**" module. Also, see the **"Substance Use Disorder"** module regarding methadone prescribed as pharmacotherapy for opioid use disorder.*

Background

1. Methadone is a synthetic opioid that is indicated for: a) the management of pain severe enough to require daily, around the clock, long-term opioid treatment and for which alternative opioid and non-opioid treatment options are inadequate, and b) the management of opioid withdrawal and for maintenance treatment of opioid use disorder (OUD). (See also: FDA label)

Methadone and opioid overdose

1. Even at label-recommended doses, opioid analgesics carry the risk of overdose as well as misuse, abuse, OUD, and death.[1]
2. Prescribing methadone is complex and requires a cautious, highly individualized approach. Methadone possesses unique pharmacokinetics with extensive inter-individual variability, making it difficult to safely titrate methadone, and increasing the risk of overdose, particularly during initiation of therapy, following dose escalation, as well as in older people, individuals on complex medication regimens, or in people with severely impaired renal or hepatic function.[2-4]

    a. Methadone is a very long-acting opioid with a mean elimination half-life of approximately 24-36 hours (range, 8 to 59 hours). However, **methadone's duration of analgesic action is typically 4 to 8 hours**.[4,5] (see also: FDA label)
    b. Steady-state plasma concentrations and full analgesic, and toxic effects are not usually attained until after 3 to 5 days of oral dosing due to slow absorption and onset of action, long half-life, and cumulative effects over time.[4,5] (See also: "**ER/LA**" module)
    c. Methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects, particularly in the early dosing period.[6] (see also: FDA label
        i. **Tolerance to methadone-induced respiratory depression is slow to develop and may never be complete**.[7,8]
        ii. Fatal overdose has occurred due to the respiratory or cardiac effects of methadone, and too-rapid titration (including repeat self-administration by the patient due to waning analgesic effects) without appreciation for the accumulation of methadone over time. (See also: FDA label)
    d. **Methadone is not a first choice for a long-acting opioid to treat chronic pain.**[2,9]

3. Incomplete cross-tolerance between mu-opioid agonists coupled with complex metabolic pathways makes determination of dosing during opioid conversion to, or from, methadone particularly complex.[7,8]

    a. Even in individuals with a high degree of opioid tolerance (i.e., those receiving long-term, high-dose treatment with other mu-agonist opioids), fatal methadone overdose has occurred during conversion to methadone or during initiation of methadone treatment of OUD. (See also: FDA label)
    b. Adults are considered opioid-tolerant if they have been receiving a total daily opioid dosage equivalent to at least 60 mg of oral morphine (60 MME/day) for one week or longer. (FDA REMS 2018[1], see 'Treatment' section 5a in the *"***Considerations for Safe and Responsible Opioid Prescribing***"* module. This dosage is comparable to:
        - 25 mcg transdermal fentanyl per hour
        - 30 mg oral oxycodone per day
        - 60 mg oral hydrocodone per day
        - 8 mg oral hydromorphone per day
        - 25 mg oral oxymorphone per day
    c. The risk is particularly high when a patient concurrently consumes other respiratory and CNS depressants such as alcohol or benzodiazepines. (See 'Treatment' section 5a in the *"***Considerations for Safe and Responsible Opioid Prescribing***"* module)

4. Methadone undergoes hepatic N-demethylation to inactive metabolites by several cytochrome P450 (CYP) isoforms, primarily CYP2B6, CYP3A4, as well as CYP2D6, CYP2C19, and CYP2C9.[10-13] (see also: FDA label)

    a. Concurrent use of methadone with drugs that inhibit its metabolism can increase plasma levels of methadone and the risk of unintentional overdose (see risk-mitigation strategies below).

5. Methadone's relative affordability ostensibly makes it an attractive alternative for certain patients. Yet despite representing <2% of opioid prescriptions for chronic pain (i.e., outside of opioid addiction treatment programs), methadone has been associated with approximately one-quarter to one-third of all U.S. opioid overdose deaths.[14-16] Moreover, methadone was involved in twice as many *single-drug* deaths as any other prescription opioids.[15]

Risk-mitigation interventions to consider when prescribing methadone for management of chronic pain.

[Beyond the general best practices for opioid prescribing described in the ***"Considerations for Safe and Responsible Opioid Prescribing"*** module*. See the* ***"Substance Use Disorder"*** module *regarding methadone prescribed as pharmacotherapy for OUD,* and refer to the full prescribing information (FDA label) for important product-specific details]

1. Do not prescribe methadone:

    a. Unless you are knowledgeable of its complex pharmacokinetics, additional monitoring requirements, and are experienced in using it to manage chronic pain.[2,9,17]
    b. As a first choice for a long-acting opioid.[2,9]

c. To treat acute pain or for patients with intermittent chronic pain requiring an opioid analgesic only "as needed" or for breakthrough pain.[2,9]
d. With other CNS and respiratory depressant such as benzodiazepine anxiolytics, non-benzodiazepine sedatives/hypnotics, barbiturates, muscle relaxants, or alcohol.[18] (see also: FDA label and the **"Substance Use Disorder"** module regarding concurrent use of benzodiazepines or other CNS depressants in patients receiving methadone for medication-assisted treatment of OUD)
e. For patients who have taken monoamine oxidase inhibitors within the past 14 days. (see: FDA label)

2. Before prescribing morphine, estimate the glomerular filtration rate using either the eGFR or creatinine clearance (ClCr) method. In patients with severe renal impairment (ClCr <10 mL/min), start with 25% to 50% of the dose that would be prescribed for patients with normal renal function.[3] (see also: FDA label; see ***"Renal Impairment"*** module)

3. In patients who are not opioid tolerant (see ***"Considerations for Safe and Responsible Opioid Prescribing"*** module), start with a low dose (e.g., 2.5 mg every 8 to 12 hours).

4. In methadone-treated patients, certain drug interactions can lead to an increase in methadone plasma levels that may result in fatal respiratory depression (overdose). Monitor methadone-treated patients using these drugs closely for respiratory depression and over-sedation. Consider consulting a specialist in pain medicine or clinical pharmacology with expertise in opioid pharmacology and drug-drug interactions.[2,11-13,20] (see also: FDA label and Drug Interactions Checker)

    a. Concomitant use of inhibitors of primarily CYP2B6 or CYP3A4, and also CYP2D6, CYP2C19, and CYP2C9, particularly when an inhibitor is added after a stable dose of methadone is achieved. Examples of inhibitors: 2B6-clopidogrel, voriconazole; 3A4-ketoconazole, clarithromycin; 2D6-paroxetine, fluoxetine, bupropion; 2C19-pantoprazole, lasoprazole; 2C9-fluconazole, amiodarone.
    b. Discontinuation of inducers of primarily CYP2B6 and CYP 3A4, and also 2D6, CYP2C19, or CYP2C9. Examples of inducers: 2B6-efavirenz; 3A4-rifampin, carbamazepine; 2D6-rifampin, dexamethasone; 2C19-ritonavir; 2C9-phenobarbital.
    c. Conversely, if an inhibitor is discontinued or an inducer is initiated, methadone plasma levels may decrease. Monitor for decreased opioid efficacy or withdrawal symptoms in patients who are physically dependent on methadone. (see: FDA label)
    d. Anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, and combination lopinavir+ritonavir are known to inhibit some CYPs, but *reduce* the plasma levels of methadone, possibly due to CYP induction activity.

5. Closely monitor the patient for respiratory depression or over-sedation during methadone initiation and after dosage escalation. The risk for overdose is greatest at this time because tolerance to an opioid's respiratory depressant effects is slower to develop and less complete than tolerance to its analgesic or euphoric effects.[2,7,8,17]

    a. Follow up within 1 to 3 days after initiating or increasing the dose of methadone.[9,21] (**AAPM 2016, SAMHSA 2012**)

b. Slowly titrate the dose of methadone if necessary to achieve effective analgesia with acceptable tolerability and minimal adverse effects. Increase the methadone dose no more frequently than once per week (five half-lives) to ensure that the full effects of the previous dose are evident.[3,9]
    i. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days). (FDA label)
    ii. Total daily dose increases should not exceed 5 to 10 mg per week.[9]
c. If the dose of methadone is inadequate to manage the pain during a methadone dose titration, consider an immediate-release opioid as a supplemental ''rescue dose." Begin the immediate release opioid at its lowest effective dosage and prescribe no more than a 7-days' supply.[9]

6. Avoid concurrent use of other medications or substances that are central nervous system depressants, such as benzodiazepines, sedatives/hypnotics, and alcohol in morphine-treated patients. The combination can result in profound sedation, respiratory depression, coma, and death and should be restricted to the minimum required dosage and duration in patients for whom alternative treatment options are inadequate or contraindicated.[2,17,23] (see also: FDA label) (See *the* **"Considerations for Safe and Responsible Opioid Prescribing"** module and the **"Benzodiazepine"** module)

7. Consider prescribing take home naloxone to patients treated with methadone to reverse life-threatening respiratory depression if an overdose occurs. The long duration of action of ER/LA opioids compared with the short duration of naloxone increases the risk of recurrent respiratory and CNS depression that may require repeated doses of naloxone and prolonged surveillance. Educate the patient, family/household members, and caregivers about signs and symptoms of opioid overdose and train them to properly use naloxone if an opioid-related overdose is suspected.[2,3] (See 'Follow up' section in the "**Considerations for Safe and Responsible Opioid Prescribing**" module).

Special considerations: Cardiac safety

1. Cases of QT interval prolongation and serious, potentially fatal arrhythmia (*torsades de pointes*) have been observed during treatment with methadone.[13]

    a. These cases appear to be more commonly associated with, but not limited to, patients treated for pain with large, multiple daily doses and higher total daily dose (>200 mg/day).[24,25]
    b. In cases treated with lower doses, contributing factors included concurrent medications and/or clinical conditions such as hypokalemia.[24,25] (see also: FDA label)

2. Obtain a baseline electrocardiogram before initiating methadone therapy in patients with risk factors for prolonged QT interval, any prior ECG demonstrating prolonged QT, or a history suggestive of prior ventricular arrhythmia.[13]

3. Closely monitor patients with risk factors for developing prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia), a personal or family

history of cardiac conduction abnormalities, family history of sudden death, and those taking medications affecting cardiac conduction.[13] (see also: FDA label)

4. Evaluate patients who develop QT prolongation while on methadone treatment for the presence of modifiable risk factors (see Credible Meds for detailed information) such as concomitant medications that are known to increase the QTc interval, cause bradycardia, other arrhythmogenic effects, drugs that might cause electrolyte abnormalities, and drugs that might inhibit methadone metabolism.[13,25] (see also: FDA label)

Additional Resources

**The information presented in this module highlights some fundamental concepts of opioid prescribing for adult outpatients. It excludes certain populations (pediatrics, pregnancy, patients with active cancer or receiving palliative or end-of-life care) and settings (perioperative, emergency, in-patient). The information provided is intended to support safe and effective opioid therapy and minimize serious adverse outcomes, particularly overdose. It is not intended to be exhaustive nor substitute for consulting a medication's full prescribing information for complete details and warnings. Links and references to selected, more comprehensive clinical and prescribing resources are provided to facilitate safe and effective opioid prescribing.*

1. FDA-approved drug label information: FDA Online Label Repository or Daily Med (NIH/National Library of Medicine)
2. Flockhart Cytochrome P450 Drug Interaction Table.[20]
3. Drug Interactions Checker
4. Credible Meds - Resources focused on iatrogenic QT prolongation
5. Opioid Milligram Morphine Equivalent (MME) Calculators:
    a. New York City Department of Health and Mental Health (online interactive and mobile app)
    b. Washington State Agency Medical Directors' Group (online interactive and mobile app)
    c. CDC Factsheet: Calculating total daily dose of opioids for safer dosage (manual calculator and mobile app)

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