EDUCATION MODULE

PRESCRIBING OPIOIDS FOR PATIENTS WITH DOSAGE ≥100 MME/DAY*

*This module provides information about high milligram morphine equivalent (MME) dose 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.*

Background

1. There is considerable and unpredictable variation among individuals in the clinical response to opioids at any given dosage, and therefore there is no completely safe opioid dose.

    a. Nonetheless, the risks for serious opioid-related toxicity, such as overdose and death, increase steadily with the average daily opioid dose.
    b. Compared to opioid doses <20 MME/day, the risk of overdose is increased by 1.3 to two-fold at opioid doses between 20 and 50 mg MME per day, and by up to nine-fold at doses ≥100 MME/day.[1-5]

2. Interindividual variability in the effectiveness, tolerability, or toxicity of a given opioid dose is also due to differences in important patient-specific characteristics such as age, body surface area, co-occurring organ dysfunction (liver, kidney, lung), levels of tolerance to the opioid's respiratory depressant and/or analgesic effects, pharmacogenetics (cytochrome P450 drug-metabolizing enzymes), and drug-drug interactions.[6-8]

3. Some states require clinicians to implement clinical protocols prior to initiating opioids or at specific dosage levels. Clinicians should be aware of rules related to MME thresholds and associated clinical protocols established by their states.[1]

4. There is a dearth of evidence to guide opioid analgesic tapering strategies. Outcome data from limited studies of successful voluntary tapers from long-term, high-dose opioid regimens suggest that pain and function are not substantially worsened or improved. Tapering strategies are an area of active clinical investigation with new findings emerging daily.[9,10]

    a. Commonly, tapering involves dosage reduction of 10% per week. However, patients taking higher dosages of opioid analgesics for a longer duration often require very slow tapering (5% to 10% decrease per month). [1,2,11]
    b. Additional research is needed to identify the opioid tapering processes that are associated with the best patient outcomes in terms of general functioning, psychosocial functioning, mood, pain-related disability, and adverse outcomes assessed in the short, medium, and long-term.[2]

Risk-mitigation interventions to consider regarding opioid dosage

1. Current guidelines recommend that primary care clinicians use caution when prescribing opioids at any dosage, and carefully reassess evidence of individual benefits and risks if considering dosage escalation to ≥50 MME/day. Furthermore, clinicians should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage beyond this level. The rationale should be based upon individualized clinical assessment of benefits (pain and function) and risks.[1,2,11,12]

2. For established patients already taking high dosages for chronic non-cancer pain (e.g., ≥90 MME/day), decisions about tapering opioid dosage should be based upon individualized clinical assessment of benefits (i.e., sustained and meaningful improvements in pain and function) versus the risks for harm (i.e., overdose, addiction). Strongly consider tapering opioid therapy to a reduced dose, or discontinuation if pain or functional benefits are small or if risks are high (e.g., it the patient is using another CNS depressant medication or substances), particularly if the patient has experienced a severe adverse outcome or an overdose event.[1,13]

    a. If pain relief is inadequate in patients treated with high opioid doses, check the PDMP and conduct urine drug testing to assess adherence by confirming the presence of the prescribed opioid(s) and to detect undisclosed use of non-prescribed controlled medications or illicit drugs. (See 'Follow Up' section in the "**Considerations for Safe and Responsible Opioid Prescribing**" module)

        i. Consider the possibility of opioid-induced hyperalgesia (OIH) if the patient appears to be adherent to the opioid treatment regimen but pain paradoxically increases as the opioid dosage increases in the absence of disease progression.[14,15]
        ii. OIH presents as heightened sensitivity to pain and/or expansion of pain to sites beyond the original site, such as generalized pain.[14,15]
        iii. Dose reduction or switching/rotating to another opioid or non-opioid medication may improve the patient's symptoms.[14,15]
        iv. Improvement in pain with reduction of dose is diagnostic of OIH.[14,15]

    b. Consider consultation or co-management with a pain medicine specialist regarding the need for high opioid dosage and to optimize pain management with non-pharmacologic and non-opioid pharmacologic treatments as appropriate, particularly as opioid dosage is tapered.[1]

3. The recommended MME/day dosage thresholds are based on overdose risk when opioids are prescribed for pain and should not guide dosing of OUD pharmacotherapy (i.e., methadone, buprenorphine).[1,16]

4. Prescribe take-home naloxone for patients treated with opioid dosage >90 MME/day and consider it for all patients taking ≥50 MME/day to reverse life-threatening respiratory depression if an overdose occurs. 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.[1,2] (See 'Follow Up' section in the "**Considerations for Safe and Responsible Opioid Prescribing**" module)

Special considerations: tapering opioid dosage

1. No single approach to tapering opioid dosage is appropriate for all patients or situations, and the evidence to date is sparse regarding optimal tapering regimens and outcomes. The rate of opioid taper should be based primarily on safety considerations. Successful tapering can be a slow process that requires preparation, collaborative decision-making with the patient, monitoring, and follow-up. The goal is effective analgesia with acceptable tolerability and minimal signs and symptoms of opioid withdrawal.[1,2,11]

2. When safety permits, a gradual taper allows time for neurobiological, psychological, and behavioral adaptations that increase the likelihood of successful dose reduction.[1,2]

    a. In order to minimize withdrawal symptoms, the speed of the taper should be inversely correlated with the duration of treatment.[1,2,9]
        i. A reasonable initial rate of decrease for patients on long-term therapy for chronic pain may be 10% per week. However, patients taking higher dosages of opioid analgesics for a longer duration often require very slow tapering (5% to 10% decrease per month) and pauses in the taper -- without reversing -- to enable gradual accommodation to lower opioid dosages.
        ii. Consider faster tapering in patients who have experienced an overdose or who have been treated with lower opioid doses and/or shorter duration of therapy.
    b. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped when taken less than once a day.

3. Opioid withdrawal symptoms associated with tapering are distressing and uncomfortable but not life-threatening. Opioid withdrawal syndrome is characterized by cognitive and emotional symptoms, as well as signs and symptoms of autonomic hyperactivity such as restlessness, anxiety, insomnia, hypertension, tachycardia, tremor, mydriasis, diaphoresis, piloerection, shivering, abdominal cramps, nausea, diarrhea, anorexia, dizziness, myalgias or arthralgias, rhinorrhea, sneezing, lacrimation, and yawning.[17]

    a. Use non-opioid, non-benzodiazepine adjunctive agents such as the α2-adrenergic agonists clonidine and lofexidine as needed to manage the increased sympathetic activity associated with withdrawal. Antiemetics and NSAIDs may also be helpful.[9,11,13]

4. Key predictors of opioid tapering dropout or relapse include high pain scores, high opioid dosages, failing to anticipate and address taper failure, and depression.[9]

5. Watch for signs of unmasked mental health disorders (depression, PTSD, panic disorder, anxiety) or OUD during opioid tapering, especially in patients treated with long-term or high-dose opioids.[1,13]

6. All patients with suspected OUD as the indication for tapering, or which emerges during tapering, should be evaluated and considered for OUD treatment (e.g., methadone or buprenorphine). Consider consulting or co-management with, or referral to a specialist in addiction medicine or an interdisciplinary program, particularly for the initial diagnosis and treatment plan if local resources are available.[1,9]

7. Consider sequential tapers for patients concurrently treated with benzodiazepines and opioid analgesics who require tapering to reduce the risk of overdose. It may be safer and more practical to taper opioids first, as benzodiazepine withdrawal entails more risk relative to opioid withdrawal, and tapering opioids can be associated with anxiety. Consider co-management with a behavioral/mental health specialist.[1,13] (See **"Benzodiazepine"** module)

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. Opioid Dose 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)
3. Opioid Tapering Tools:
    a. Opioid Taper Decision Tool (VA)
    b. Opioid Tapering Template (Canada)
4. Sample protocol to justify opioid dose >90 MME/day
5. How to Discuss Stopping Opioid Therapy with the Patient

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