

***Opioids and their Role in the Management of Chronic Non-Cancer Pain (CNCP):
Initiating Long-Acting Opioids (LAO)***

Key Message 3:

- **LAO should NOT be used for:**
 - Treatment of acute pain
 - Treatment on an as-needed basis
 - Initial opioid therapy for CNCP
- Patients with CNCP should NEVER be on more than 1 LAO at a time.
- When initiating long-term opioid therapy, the total daily morphine milligram equivalent (MME) dose should be calculated and should generally not exceed MME ≥ 90 /day.

In 2014, the Food and Drug Administration (FDA) recommended that all extended-release/long-acting (ER/LA) opioid formulations be reserved for “management of pain severe enough to require daily, around-the-clock, long-term opioid treatment” when “alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.”^{1,2}

The FDA has approved risk evaluation and mitigation strategies (REMS) for ER/LA opioids. The REMS are continually updated and available at REMS@FDA (<https://www.accessdata.fda.gov/scripts/cder/remis/>).

- Choosing an ER/LA agent with more stable, predictable pharmacokinetics and pharmacodynamics is preferred to minimize the risk of overdose.¹
- ER/LA agents with abuse deterrent properties are available to reduce the likelihood that the formulation will be crushed, snorted or dissolved in order to inject for the purposes of misuse or abuse.
- When switching to an ER/LA formulation from a short-acting opioid, prescribers should refer to product labeling and reduce the total daily dosage to account for incomplete opioid cross tolerance.¹
 - Incomplete opioid cross tolerance can occur due to variability in opioid binding.
 - The American Pain Society guideline recommends a dose reduction between 25-50%.³ Refer to the FDA product labels for specific dosing recommendations for these products.
- Use extra caution when using ER/LA opioids in patients with hepatic or renal insufficiency.¹ Prescribers also may consider longer dosing intervals to prevent drug accumulation.
- Methadone should not be the first choice when selecting an ER/LA opioid and should only be prescribed by clinicians who are familiar with its use and risks:¹
 - Methadone is associated with cardiac arrhythmias, along with QT interval prolongation, and requires close monitoring.
 - Methadone has a complicated pharmacokinetic and pharmacodynamic profile, which can lead to more inter-patient variability than other opioids.

Centers for Disease Control and Prevention (CDC) checklist when considering long-term opioid treatment for CNCP:⁴

- Set realistic goals for function and pain.
- Verify use of non-opioids first.
- Discuss risks and benefits with patient.
- Evaluate risk of harm or misuse by checking:
 - Patient specific risk factors
 - Prescription monitoring program (New York State Internet System for Tracking Over-Prescribing [I-STOP])
 - Urine drug screen (UDT)
- Set criteria for stopping/continuing opioids.
- Assess baseline pain and function.
- Schedule initial reassessment.
- Prescribe the lowest dose and shortest duration based on reassessment schedule.

Morphine Milligram Equivalent (MME)^{1, 3-9}

- MME represents doses at which equivalent analgesic effects may be observed for morphine and other opioids. MME can help determine the appropriate dose when switching from one opioid to another, or converting from an SAO to an LAO.
- Reassess individual patient benefits and risks when increasing dosage to ≥ 50 MME/day.
- Avoid increasing dosage to ≥ 90 MME/day.
- **Caution should be used when dosage ≥ 50 MME/day.**
 - Patients should be reassessed for treatment efficacy, adherence and aberrant behaviors.
 - Patients receiving ≥ 100 mg/day of morphine equivalent had a 9-fold increased risk of overdose. Most overdoses were medically serious and 12% were fatal.
 - A recent population-based study of patients that received opioids for CNCP and were followed for up to 13 years, showed:⁸
 - One in 550 patients died from an opioid-related overdose at a median of 2.6 years from their first opioid prescription.
 - **One in 32 patients** who escalated to opioid dosages > 200 MME died from an opioid-related overdose.

STEPS TO CALCULATE MME:

1. Determine the total daily amount of each opioid the patient takes.
2. Convert the current opioid dose to the oral MME. For each opioid, multiply the current 24-hour dose by the corresponding conversion factor (see table on page 3).
3. Add the 2 MME totals together to get the total MME/day that the patient is taking.

Additional tools to calculate MME may be found at:

<https://www.cdc.gov/drugoverdose/prescribing/clinical-tools.html>
<http://www.globalrph.com/narcotic.cgi>

MORPHINE EQUIVALENT FACTORS ⁹		
Major Group	Type of Opioid	Morphine equivalent conversion factor per oral mg of opioid
SAO, Less Potent	Codeine + (acetaminophen, ibuprofen, or aspirin)	0.15
	Hydrocodone + (acetaminophen, ibuprofen, or aspirin), Hydrocodone and homatropine	1.0
	Tramadol with or without aspirin	0.10
	Butalbital and codeine (with or without aspirin/ibuprofen/acetaminophen)	0.15
	Dihydrocodeine (with or without aspirin/ibuprofen/acetaminophen)	0.25
	Pentazocine (with or without aspirin/ibuprofen/acetaminophen)	0.37
SAO, More Potent	Morphine sulfate	1.0
	Codeine sulfate	0.15
	Oxycodone (with or without aspirin/ibuprofen/ acetaminophen)	1.5
	Hydromorphone	4.0
	Meperidine hydrochloride	0.1
	Fentanyl citrate transmucosal*	0.125
	Oxymorphone	3.0
LAO	Morphine sulfate sustained release	1.0
	Fentanyl transdermal	2.4
	Levorphanol tartrate	11.0
	Oxycodone HCL controlled release	1.5
	Methadone+	3.0

* Fentanyl transmucosal: mcg dose must be converted to mg; rough estimate of conversion factor provided above
+ Methadone: equianalgesic dosing ratios between methadone and other opioids are complex; typically, a mg to mg conversion is not adequate due to the complex and variable pharmacokinetics and pharmacodynamics. Methadone should only be prescribed by clinicians who are familiar with its use and risks.

MME Calculation Examples:

What is the MME for a patient taking hydrocodone/acetaminophen 5/320 mg by mouth every 4 hours?

- 1) Hydrocodone 5 mg x 6 (pills per day) = 30 mg per day
- 2) Hydrocodone morphine equivalent conversion factor = 1
- 3) 30 mg x 1 = 30 MME/day

What is the MME for a patient taking oxycodone 10 mg twice daily?

- 1) Oxycodone 10 mg x 2 (pills per day) = 20 mg per day
- 2) Oxycodone morphine equivalent conversion factor = 1.5
- 3) 20 mg x 1.5 = 30 MME/day

Discontinuation of Opioid Therapy:^{1, 3, 5-7}

Discontinuation of opioid therapy may be recommended for any of the following reasons:

- Severe, unmanageable adverse effects
- Serious non-adherence to the treatment plan or unsafe behaviors
- Misuse that is suggestive of addiction
- Lack of effectiveness of therapy to meet treatment goals
- Desire from the patient to discontinue therapy

Protocol for tapering opioid therapy:

- 1) *Decrease patient's dose by 20-50% per week; slow tapering will help to minimize adverse/withdrawal effects*
- 2) *Tapering schedules should be individualized for each patient – some literature suggests that the longer the person has been on opioids, the slower the taper should be*
- 3) *Monitor the patient frequently during tapering (e.g., at each dose change)*
- 4) *Consider the use of adjuvant agents such as antidepressants to manage irritability or sleep disturbances, or antiepileptics for neuropathic pain*
- 5) *Referral for counseling or other support during this period is recommended*

Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued. DO NOT treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids.

SUMMARY:

- Patients on opioid therapy require frequent monitoring, e.g., every 1-4 weeks, especially when changes to therapy are being made.
- LAOs should not be considered a first-line opioid option for CNCP, especially in opioid-naïve patients.
- Know and calculate your patient's MME. **Use caution at MME \geq 90 mg/day.**

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