EDUCATION MODULE

PRESCRIBING EXTENDED-RELEASE OR LONG-LASTING (ER/LA) OPIOIDS*

*This module provides information about ER/LA opioids 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. ER/LA-formulated opioids (see Table 1) are reserved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment when alternative treatment options [e.g., non-opioid analgesics or immediate-release (IR) opioids] are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. ER/LA opioids are not indicated for "as needed" treatment of breakthrough pain.[2,3]

Opioid products classified as ER/LA

Generic Name	*ER/LA Branded-product Examples*
Buprenorphine buccal film	***Belbuca***
Buprenorphine transdermal system	***Butrans***
Hydromorphone ER	***Exalgo***
Hydrocodone ER	***Hysingla ER, Vantrela ER, Zohydro***
Fentanyl transdermal system	***Duragesic***
Methadone	***Dolophine***
Morphine sulfate ER	***MS Contin, Kadian, Morphabond,***
Morphine sulfate ER	***Arymo***
Morphine sulfate ER - naltrexone	***Embeda***
Oxymorphone ER	***Opana ER***
Oxycodone ER	***OxyContin, Xtampza ER***
Oxycodone ER/naloxone	***Targiniq ER***
Oxycodone ER/naltrexone	***Troxyca ER***
Tapentadol ER	***Nucynta ER***

From the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics[1]

ER/LA opioids and opioid overdose

1. Patients treated with ER/LA opioid formulations have a greater risk for unintentional overdose and death compared to those taking IR formulations.[4-7]

2. The risk of overdose is particularly high (by five-fold) during the first 2 to 4 weeks after initiation of ER/LA opioid therapy for chronic, non-cancer pain in opioid-naïve individuals.[5,6]

3. Crushing, chewing or dissolving an ER/LA product may disable its time-release mechanism; ingesting/snorting/injecting the contents may result in rapid release and absorption of a potentially fatal dose of opioid.[1]

Risk-mitigation interventions to consider when prescribing ER/LA opioids
[Refer to the full prescribing information (FDA label) for important product-specific details]

1. When initiating opioid therapy to manage chronic non-cancer pain, prescribe an IR formulation, particularly in individuals who are either opioid-naïve or not opioid-tolerant.[2,8]
    a. 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 2017 and 'Treatment' section 5a in the "**Considerations for Safe and Responsible Opioid Prescribing"** module).

    b. 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

2. Do not prescribe ER/LA analgesics "as needed" (PRN) for breakthrough pain or for pain that is acute, mild, or not expected to persist for an extended duration.[1,2]

3. Selecting an ER/LA opioid with predictable pharmacokinetics and pharmacodynamics is preferred to minimize the risk of unintentional overdose.[2]
    a. Safe prescribing of methadone and transdermal fentanyl is especially challenging due to their complex pharmacokinetics and pharmacodynamics.[1,2] (See "**Methadone**" and "**Fentanyl**" modules)

4. Breakthrough pain may occur in patients with chronic pain treated with ER/LA opioids. It may result from disease progression or a new or unrelated pain while on a stable around-the-clock opioid regimen or occur during titration after initiating an ER/LA opioid.[9]
    a. Do not treat breakthrough pain with an ER/LA opioid.[9]

    b. Supplement the ER/LA opioid with 'rescue doses' of an IR analgesic (opioid or non-opioid) and non-pharmacologic treatments.[9]

    c. If an IR opioid is used as a supplemental rescue dose, begin at 5% to 15% of the total daily opioid dose and administer at an appropriate interval.

    d. The safety of supplemental IR opioids for breakthrough pain when ER/ LA opioids are used to treat chronic non-cancer pain is unknown. Assess and monitor closely for benefit versus risk, including potential misuse.[2,8,10]

5. If switching, converting, or rotating from one opioid to an ER/LA opioid, calculate a safe and reasonably effective starting dose for the new ER/LA opioid. Use conservative dosing to avoid unintentional overdose of the new opioid due to incomplete cross-tolerance and individual variability in pharmacokinetics between the two opioids.[1,11,12] (See 'Treatment' section #7 in the "**Considerations for Safe and Responsible Opioid Prescribing**" module for details)

6. Do not abruptly discontinue ER/LA opioids.
    a. To safely reduce or discontinue an ER/LA opioid analgesic, gradually taper the dose to minimize signs and symptoms of withdrawal in patients who are physically dependent.[1] (See "**High MED**" module)

7. Educate the patient and caregivers about the safe and appropriate use, storage and disposal of ER/LA opioids. Warn them that manipulating an ER/LA opioid product as described below may result in rapid release and absorption of a potentially fatal dose of opioid.[1]
    a. *Solid oral dosage forms* (tablets, capsules) should be swallowed whole, one tablet at a time, and with sufficient water so that they are swallowed completely and without choking.
        i. Patients who intentionally alter an oral ER/LA product to disable the time-release mechanism by crushing, chewing, breaking, cutting, or dissolving it before ingesting, snorting, or injecting the contents should be evaluated for active opioid use disorder (by DSM-5 criteria) and referred for treatment.
        ii. Some ER opioid products may rapidly release opioid (dose dump) when exposed to alcohol, and some drug levels may increase without dose dumping when exposed to alcohol. Refer to individual product prescribing information.
        iii. For persons who require ER opioids but cannot swallow a capsule whole, several product formulations allow for the contents of capsules to be sprinkled on applesauce and administered either orally or, in some cases, via feeding tube. Refer to individual product prescribing information

    b. *Transdermal patches* should be protected from external heat and sunlight to avoid the risk of increased opioid absorption. Closely monitor patients with fever for over-sedation or respiratory depression. Transdermal patches should not be cut, torn, or damaged prior to use. (See "**Fentanyl"** module)

8. Closely monitor the patient for respiratory depression or over-sedation during initiation of an ER/LA opioid, and after each dosage escalation.
    a. 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.[2,13-15]

9. 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.[2,8,13] (see also: FDA Label)

10. Consider prescribing take-home naloxone to patients treated with opioids to reverse life-threatening respiratory depression if an overdose occurs.
    a. 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.

b. 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.[2,16] (See 'Follow Up' section in the "**Considerations for Safe and Responsible Opioid Prescribing**" 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. FDA Blueprint for prescriber education for extended-release and long-acting opioid analgesics. Updated May 2017.
3. **ER/LA Opioid analgesic REMS Education**
4. **Opioid 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)

References

1. FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (Jan. 2018) https://www.regulations.gov/contentStreamer?documentId=FDA-2017-D-2497-0683&attachmentNumber=1&contentType=pdf
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16. U.S. Department of Veterans Affairs. VA/DoD clinical practice guideline for opioid therapy for chronic pain. Washington, DC: US Department of Veterans Affairs; 2017. https://www.healthquality.va.gov/guidelines/pain/cot/