Joint Session ACOFP/AOA: ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care

Katherine Galluzzi, DO, CMD, FACOFP dist.
Annette T. Carron, DO
ACOFP FULL DISCLOSURE FOR CME ACTIVITIES

Please check where applicable and sign below. Provide additional pages as necessary.
Name of CME Activity: 2015 AOA/ACOFP Osteopathic Medical Conference & Exposition (OMED)

Dates and Location of CME Activity: October 17 - October 21, 2015 Orange County Convention Center Orlando, Florida
Topic: Joint Session ACOFP/AOA: ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care Monday, October 19, 2015 3:00-5:00pm

Name of Speaker/Moderator: Katherine Galluzzi, DO CMD, FACOFP dist.

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- [ ] Others, please list:

Please indicate the name(s) of the organization(s) with which you have a financial relationship or interest, and the specific clinical area(s) that correspond to the relationship(s). If more than four relationships, please list on separate piece of paper:

<table>
<thead>
<tr>
<th>Organization With Which Relationship Exists</th>
<th>Clinical Area Involved</th>
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</tbody>
</table>

*If you checked "Speakers’ Bureau" in item B, please continue:
- Did you participate in company-provided speaker training related to your proposed topic?  
  Yes: No:  
- Did you travel to participate in this training?  
  Yes: No:  
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  Yes: No:  
- Did the company pay the travel/lodging/other expenses?  
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  Yes: No:  
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Signature: ___________________________ Date: 8/28/15
Katherine Galluzzi, DO CMD, FACOFP dist.

Please fax this form to ACOFP at 866-328-1835, or e-mail to joank@acofp.org as soon as possible.
Deadline: Friday, September 11, 2015
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Name of Speaker/Moderator: Annette Carron, DO

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Signature: ____________________________ Date: 9/18/15
Annette Carron, DO

Please fax this form to ACOFP at 866-328-1835, or e-mail to joank@acofp.org as soon as possible.
Deadline: Friday, September 11, 2015
ER/LA OPIOID REMS:
Achieving Safe Use While Improving Patient Care

Presented by CO*RE Collaboration for REMS Education
www.core-rems.org

Faculty Information

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Botsford Hospital, Farmington Hills, MI
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AOA Board-Certified Family Physician
Chairman, Department of Geriatrics
Philadelphia College of Osteopathic Medicine

DISCLOSURE:
Drs. Carron and Galluzzi have nothing to disclose.
On July 9, 2012, the Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications.

Founded in June, 2010, the Collaborative on REMS Education (CO*RE), a multi-disciplinary team of 10 partners and 3 cooperating organizations, has designed a core curriculum based on needs assessment, practice gaps, clinical competencies, and learner self-assessment to meet the requirements of the FDA REMS Blueprint.

www.core-rem.org
### Content Development/Planner/Reviewer Disclosures

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<table>
<thead>
<tr>
<th>Name</th>
<th>Position/Institution</th>
</tr>
</thead>
<tbody>
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<tr>
<td></td>
<td><strong>COI NOTE:</strong> While Dr. Cardarelli is PI on a Pfizer grant, his employing institution (U of KY) receives those funds to compensate for Dr. Cardarelli’s time.</td>
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<tr>
<td>Catherine Underwood, MBA, CAE</td>
<td>Chief Executive Officer, American Pain Society, Chicago, IL</td>
</tr>
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<td>Vice President, Professional Development, American Society of Addiction Medicine</td>
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<td>Penny Mills, MBA</td>
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</tr>
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<td>Executive Director, Interstate Postgraduate Medical Association, Madison, WI</td>
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<td>Director, Strategic Partnerships, American College of Emergency Physicians, Irving, TX</td>
</tr>
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</table>
Acknowledgement

Presented by the American Osteopathic Association, a member of the Collaborative on REMS Education (CO*RE), 13 interdisciplinary organizations working together to improve pain management and prevent adverse outcomes.

This educational activity is supported by an independent educational grant from the ER/LA Opioid Analgesic REMS Program Companies. Please see [http://ce.er-la-opioidrems.com/ligCEUL/rem/ pdf/List_of_RPC_Companies.pdf](http://ce.er-la-opioidrems.com/ligCEUL/rem/pdf/List_of_RPC_Companies.pdf) for a listing of the member companies. This activity is intended to be fully compliant with the ER/LA Opioid Analgesic REMS education requirements issued by the US Food & Drug Administration.

Products Covered by this REMS

<table>
<thead>
<tr>
<th>Brand Name Products</th>
<th>Generic Products</th>
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<tr>
<td>• Avinza® morphine sulfate ER capsules</td>
<td>• Fentanyl ER transdermal systems</td>
</tr>
<tr>
<td>• Butrans® buprenorphine transdermal system</td>
<td>• Methadone hydrochloride tablets</td>
</tr>
<tr>
<td>• Dolophine® methadone hydrochloride tablets</td>
<td>• Methadone hydrochloride oral concentrate</td>
</tr>
<tr>
<td>• Duragesic® fentanyl transdermal system</td>
<td>• Methadone hydrochloride oral solution</td>
</tr>
<tr>
<td>• <em>Embeda®</em> morphine sulfate/naltrexone ER capsules</td>
<td>• Morphine sulfate ER tablets</td>
</tr>
<tr>
<td>• Exalgo® hydromorphone hydrochloride ER tablets</td>
<td>• Morphine sulfate ER capsules</td>
</tr>
<tr>
<td>• Hysingla® ER (hydrocodone bitartrate) ER tablets</td>
<td>• Oxycodone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• Kadian® morphine sulfate ER capsules</td>
<td>• Zohydro® hydrocodone bitartrate ER capsules</td>
</tr>
<tr>
<td>• Methadose™ methadone hydrochloride tablets</td>
<td>• Targiniq™ oxycodone hydrochloride/naloxone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• MS Contin® morphine sulfate CR tablets</td>
<td>• OxyContin® oxycodone hydrochloride CR tablets</td>
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<tr>
<td>• Nucynta® ER tapentadol ER tablets</td>
<td>• OxyContin® oxycodone hydrochloride/naloxone hydrochloride ER tablets</td>
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<td>• Opana® ER oxymorphone hydrochloride ER tablets</td>
<td>• Zohydro® hydrocodone bitartrate ER capsules</td>
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<td>• OxyContin® oxycodone hydrochloride CR tablets</td>
<td>• OxyContin® oxycodone hydrochloride/naloxone hydrochloride ER tablets</td>
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<td>• Zohydro® hydrocodone bitartrate ER capsules</td>
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</tbody>
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* Not currently available due to voluntary recall (still approved); † No longer marketed (still approved)
WHY PRESCRIBER EDUCATION IS IMPORTANT

Introduction

Opioid Misuse/Abuse is a Major Public Health Problem

Improper use of any opioid can result in serious AEs including overdose & death

This risk can be greater w/ ER/LA opioids

ER opioid dosage units contain more opioid than IR formulations

Methadone is a potent opioid with a long, highly variable half-life

In 2012

37 million Americans age ≥12 had used an opioid for nonmedical use some time in their life

In 2011

488,004 ED visits involved nonmedical use of opioids

- Methadone involved in 30% of prescription opioid deaths

In 2011

41,340 Americans
DIED FROM DRUG POISONINGS
Nearly 17,000 deaths involved prescription opioids

In 2008

For every 1 death there are:

- 10 treatment admissions for abuse
- 32 ED visits for misuse or abuse
- 130 people who abuse or are addicted
- 825 nonmedical users


First-Time Use of Specific Drugs Among Persons Age ≥ 12 (2012)

Number in millions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>2.4</td>
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<tr>
<td>Pain relievers</td>
<td>1.9</td>
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<tr>
<td>Tranquilizers</td>
<td>1.4</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>0.9</td>
</tr>
<tr>
<td>Stimulants</td>
<td>0.7</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.6</td>
</tr>
<tr>
<td>Inhalants</td>
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<tr>
<td>LSD</td>
<td>0.4</td>
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<tr>
<td>Sedatives</td>
<td>0.2</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.2</td>
</tr>
<tr>
<td>PCP</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Prescribers of ER/LA Opioids Should Balance:

The benefits of prescribing ER/LA opioids to treat pain

The risks of serious adverse outcomes

ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.

Learning Objectives

- Describe appropriate patient assessment for treatment with ER/LA opioid analgesics, evaluating risks and potential benefits of ER/LA therapy, as well as possible misuse.

- Apply proper methods to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, applying best practices including accurate dosing and conversion techniques, as well as appropriate discontinuation strategies.

- Demonstrate accurate knowledge about how to manage ongoing therapy with ER/LA opioid analgesics and properly use evidence-based tools while assessing for adverse effects.

- Employ methods to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.

- Review/assess general and product-specific drug information concerning ER/LA opioid analgesics and identifying potential adverse effects of ER/LA opioids.
Misuse, abuse, divergence and overdose of ER/LA opioids is a major public health crisis.

**YOU and YOUR TEAM can** have an immediate and positive impact on this crisis while also caring for your patients appropriately.

**ASSESSING PATIENTS FOR TREATMENT WITH ER/LA OPIOID ANALGESIC THERAPY**

**Unit 1**
### Balance Risks Against Potential Benefits

#### Conduct thorough H&P and appropriate testing

**Benefits Include**
- Analgesia (adequate pain control)
- Improved Function

#### Comprehensive benefit-to-harm evaluation

**Risks Include**
- Overdose
- Life-threatening respiratory depression
- Abuse by patient or household contacts
- Misuse & addiction
- Physical dependence & tolerance
- Interactions w/ other medications & substances
- Risk of neonatal withdrawal syndrome w/ prolonged use during pregnancy
- Inadvertent exposure/ingestion by household contacts, especially children

---

**Adequately DOCUMENT**

all patient interactions, assessments, test results, & treatment plans

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Clinical Interview: Patient Medical History

**Illness relevant to (1) effects or (2) metabolism of opioids**

1. Pulmonary disease, constipation, nausea, cognitive impairment
2. Hepatic, renal disease

**Illness possibly linked to substance abuse, e.g.:**

- Hepatitis
- HIV
- Tuberculosis
- Cellulitis
- STIs
- Trauma, burns
- Cardiac disease
- Pulmonary disease


Clinical Interview: Pain & Treatment History

**Description of pain**

- Location
- Intensity
- Quality
- Onset / Duration
- Variations / Patterns / Rhythms

**What relieves the pain?**

**What causes or increases pain?**

**Effects of pain on physical, emotional, and psychosocial function**

**Patient’s pain & functional goals**

Clinical Interview: Pain & Treatment History, cont’d

### Pain Medications

<table>
<thead>
<tr>
<th>Past use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
</tr>
<tr>
<td>• Query state PDMP where available to confirm patient report</td>
</tr>
<tr>
<td>• Contact past providers &amp; obtain prior medical records</td>
</tr>
<tr>
<td>• Conduct UDT</td>
</tr>
</tbody>
</table>

#### Dosage

- For opioids currently prescribed: opioid, dose, regimen, & duration
- Important to determine if patient is opioid tolerant

#### General effectiveness

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### Nonpharmacologic strategies & effectiveness

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### Perform Thorough Evaluation & Assessment of Pain

- Seek objective confirmatory data
- Components of patient evaluation for pain
- Order diagnostic tests (appropriate to complaint)

- General: vital signs, appearance, posture, gait, & pain behaviors
- Neurologic exam
- Musculoskeletal Exam
  - Inspection
  - Palpation
  - Percussion
  - Auscultation
  - Provocative maneuvers
- Cutaneous or trophic findings
Assess Risk of Abuse, Including Substance Use & Psychiatric Hx

**Obtain a complete Hx of current & past substance use**

- Prescription drugs
- Illegal substances
- Alcohol & tobacco
  - Substance abuse Hx does not prohibit treatment w/ ER/LA opioids but may require additional monitoring & expert consultation/referral
- Family Hx of substance abuse & psychiatric disorders
- Hx of sexual abuse

**Social history also relevant**

Employment, cultural background, social network, marital history, legal history, & other behavioral patterns

---

Risk Assessment, cont’d

**Be knowledgeable about risk factors for opioid abuse**

- Personal or family Hx of alcohol or drug abuse
- Younger age
- Presence of psychiatric conditions

**Understand & use addiction or abuse screening tools**

- Assess potential risks associated w/ chronic opioid therapy
- Manage patients using ER/LA opioids based on risk assessment

**Conduct a UDT**

- Understand limitations
Risk Assessment Tools: Examples

Patients considered for long-term opioid therapy:

<table>
<thead>
<tr>
<th>Tool</th>
<th># of items</th>
<th>Administered By</th>
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<tbody>
<tr>
<td>Opioid Risk Tool (ORT)</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>SOAPP® Screener &amp; Opioid Assessment for Patients w/ Pain</td>
<td>24, 14, &amp; 5</td>
<td>patient</td>
</tr>
<tr>
<td>Diagnosis, Intractability, Risk, &amp; Efficacy Score (DIRE)</td>
<td>7</td>
<td>clinician</td>
</tr>
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</table>

Characterize misuse once opioid treatments begins:

<table>
<thead>
<tr>
<th>Tool</th>
<th># of items</th>
<th>Administered By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Medication Questionnaire (PMQ)</td>
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<td>patient</td>
</tr>
<tr>
<td>Current Opioid Misuse Measure (COMM)</td>
<td>17</td>
<td>patient</td>
</tr>
<tr>
<td>Prescription Drug Use Questionnaire (PDUQ)</td>
<td>40</td>
<td>clinician</td>
</tr>
</tbody>
</table>

Not specific to pain populations:

<table>
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<th>Administered By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut Down, Annoyed, Guilty, Eye-Opener Tool, Adjusted to Include Drugs (CAGE-AID)</td>
<td>4</td>
<td>clinician</td>
</tr>
<tr>
<td>Relax, Alone, Friends, Family, Trouble (RAFFT)</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>Drug Abuse Screening Test (DAST)</td>
<td>28</td>
<td>patient</td>
</tr>
<tr>
<td>Screening, Brief Intervention, &amp; Referral to Treatment (SBIRT)</td>
<td>Varies</td>
<td>clinician</td>
</tr>
</tbody>
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Opioid Risk Tool (ORT)

Mark each box that applies

1. **Family Hx of substance abuse**
   - Alcohol
   - Illegal drugs
   - Prescription drugs

2. **Personal Hx of substance abuse**
   - Alcohol
   - Illegal drugs
   - Prescription drugs

3. **Age between 16 & 45 yrs**

4. **Hx of preadolescent sexual abuse**

5. **Psychologic disease**
   - ADD, OCD, bipolar, schizophrenia
   - Depression

Scoring Totals:

Administer

- On initial visit
- Prior to opioid therapy

Scoring (risk)

- 0-3: low
- 4-7: moderate
- ≥8: high

Collaborative for REMS Education
Screener & Opioid Assessment for Patients with Pain (SOAPP)®

Identifies patients as at high, moderate, or low risk for misuse of opioids prescribed for chronic pain

How is SOAPP® administered?

- Usually self-administered in waiting room, exam room, or prior to an office visit
- May be completed as part of an interview with a nurse, physician, or psychologist
- Prescribers should have a completed & scored SOAPP® while making opioid treatment decisions

The SOAPP® Version 1.0 Tutorial: https://painedu.org/soapp-tutorial_01.asp

When to Consider a Trial of an Opioid

Potential benefits are likely to outweigh risks

Failed to adequately respond to nonopioid & nondrug interventions

Continuous, around-the-clock opioid analgesic is needed for an extended period of time

Pain is chronic and severe

No alternative therapy is likely to pose as favorable a balance of benefits to harms

When to Consider a Trial of an Opioid, cont’d

60-yr-old w/ chronic disabling OA pain

- Nonopioid therapies not effective, IR opioids provided some relief but experienced end-of-dose failure
- No psychiatric/medical comorbidity or personal/family drug abuse Hx
  - High potential benefits relative to potential risks
  - Could prescribe opioids to this patient in most settings w/ routine monitoring

30-yr-old w/ fibromyalgia & recent IV drug abuse

- High potential risks relative to benefits (opioid therapy not 1st line for fibromyalgia)
- Requires intensive structure, monitoring, & management by clinician w/ expertise in both addiction & pain
  - Not a good candidate for opioid therapy

Selection of patients between these 2 extremes requires:

Careful assessment & characterization of patient risk

Structuring of care to match risk

In patients w/ Hx of substance abuse or a psychiatric comorbidity, this may require assistance from experts in managing pain, addiction, or other mental health concerns

In some cases opioids may not be appropriate or should be deferred until the comorbidity has been adequately addressed
  - Consider referral

Referring High-Risk Patients

Prescribers should

Understand when to appropriately refer high-risk patients to pain management or addiction specialists

Also check your state regulations for requirements

Special Considerations: Elderly Patients

Does patient have medical problems that increase risk of opioid-related AEs?

Respiratory depression more likely in elderly, cachectic, or debilitated patients

- Altered PK due to poor fat stores, muscle wasting, or altered clearance
- Monitor closely, particularly when
  - Initiating & titrating ER/LA opioids
  - Given concomitantly w/ other drugs that depress respiration
- Reduce starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients
- Titrate dose cautiously

Older adults more likely to develop constipation

- Routinely initiate a bowel regimen before it develops

Is patient/caregiver likely to manage opioid therapy responsibly?
Special Considerations: Pregnant Women

Managing chronic pain in pregnant women is challenging, & affects both mother and fetus

Potential risks of opioid therapy to the newborn include:
- Low birth weight
- Premature birth
- Hypoxic-ischemic brain injury
- Neonatal death
- Prolonged QT syndrome
- Neonatal opioid withdrawal syndrome

Given these potential risks, clinicians should:
- Counsel women of childbearing potential about risks & benefits of opioid therapy during pregnancy & after delivery
- Encourage minimal/no opioid use during pregnancy, unless potential benefits outweigh risks

If chronic opioid therapy is used during pregnancy, anticipate & manage risks to the patient and newborns

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Special Considerations: Children (<18 years)

Safety & effectiveness of most ER/LA opioids unestablished

Pediatric analgesic trials pose challenges
Transdermal fentanyl approved in children aged ≥2 yrs

Most opioid studies focus on inpatient safety

Opioids are common sources of drug error

Opioid indications are primarily life-limiting conditions

Few children with chronic pain due to non-life-limiting conditions should receive opioids

When prescribing opioids to children:

Consult pediatric palliative care team or pediatric pain specialist or refer to a specialized multidisciplinary pain clinic

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Unit 1

Pearls for Practice

Document EVERYTHING
Conduct a Comprehensive H&P
General and pain-specific
Assess Risk of Abuse
Compare Risks with Expected Benefits
Determine Whether a Therapeutic Trial is Appropriate

INITIATING THERAPY, MODIFYING DOSING, & DISCONTINUING USE OF ER/LA OPIOID ANALGESICS

Unit II
Federal & State Regulations

Comply w/ federal & state laws & regulations that govern the use of opioid therapy for pain

Federal

• Code of Federal Regulations, Title 21 Section 1306: rules governing the issuance & filling of prescriptions pursuant to section 309 of the Act (21 USC 829)
  - www.deadiversion.usdoj.gov/21cfr/cfr/2106cfr.htm
• United States Code (USC) - Controlled Substances Act, Title 21, Section 829: prescriptions
  - www.deadiversion.usdoj.gov/21cfr/21usc/829.htm

State

• Database of state statutes, regulations, & policies for pain management
  - www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management

Initiating Treatment

Prescribers should regard initial treatment as a therapeutic trial

May last from several weeks to several months

Decision to proceed w/ long-term treatment should be intentional & based on careful consideration of outcomes during the trial

- Progress toward meeting therapeutic goals
- Presence of opioid-related AEs
- Changes in underlying pain condition
- Changes in psychiatric or medical comorbidities
- Identification of aberrant drug-related behavior, addiction, or diversion

ER/LA Opioid-Induced Respiratory Depression

**Chief hazard of opioid agonists, including ER/LA opioids**
- If not immediately recognized & treated, may lead to respiratory arrest & death
- Greatest risk: initiation of therapy or after dose increase

**Manifested by reduced urge to breathe & decreased respiration rate**
- Shallow breathing
- CO₂ retention can exacerbate opioid sedating effects

**Instruct patients/family members to call 911**
- Managed w/ close observation, supportive measures, & opioid antagonists, depending on patient’s clinical status

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ER/LA Opioid-Induced Respiratory Depression

**More likely to occur**
- In elderly, cachectic, or debilitated patients
  - **Contraindicated** in patients w/ respiratory depression or conditions that increase risk
- If given concomitantly w/ other drugs that depress respiration

**Reduce risk**
- Proper dosing & titration are essential
- **Do not overestimate** dose when converting dosage from another opioid product
  - Can result in fatal overdose w/ first dose
- Instruct patients to swallow tablets/capsules whole
  - Dose from cut, crushed, dissolving, or chewed tablets/capsules may be fatal, particularly in opioid-naïve individuals

---


Initiating & Titrating: Opioid-Naïve Patients

Drug & dose selection is critical

Some ER/LA opioids or dosage forms are only recommended for opioid-tolerant patients

- ANY strength of transdermal fentanyl or hydromorphone ER
- Certain strengths/doses of other ER/LA products (check drug PI)

Monitor patients closely for respiratory depression

Especially within 24-72 h of initiating therapy & increasing dosage

Individualize dosage by titration based on efficacy, tolerability, & presence of AEs

Check ER/LA opioid product PI for minimum titration intervals

Supplement w/ IR analgesics (opioids & nonopioid) if pain is not controlled during titration

Initiating: Opioid-Tolerant Patients

If opioid tolerant – no restrictions on which products can be used

Patients considered opioid tolerant are taking at least

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/hr
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day
- An equianalgesic dose of another opioid

Still requires caution when rotating a patient on an IR opioid to a different ER/LA opioid

For 1 Wk Or Longer

IMPORTANT
Opioid Rotation

Definition:
Change from an existing opioid regimen to another opioid w/ the goal of improving therapeutic outcomes or to avoid AEs attributed to the existing drug, e.g., myoclonus

Rationale:
Differences in pharmacologic or other effects make it likely that a switch will improve outcomes
• Effectiveness & AEs of different mu opioids vary among patients
• Patients show incomplete cross-tolerance to new opioid
  – Patient tolerant to 1st opioid can have improved analgesia from 2nd opioid at a dose lower than calculated from an EDT

Equianalgesic Doses

Opioid rotation requires calculation of an approximate equianalgesic dose

Equianalgesic dose is a construct derived from relative opioid potency estimates
• Potency refers to dose required to produce a given effect

Relative potency estimates
• Ratio of doses necessary to obtain roughly equivalent effects
• Calculate across drugs or routes of administration
• Relative analgesic potency is converted into an equianalgesic dose by applying the dose ratio to a standard
### Example of an EDT for Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>SC/IV</th>
<th>PO</th>
<th>Parenteral</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
<td>2.5-5 mg SC/IV q3-4hr (1.25 – 2.5mg)</td>
<td>5-15 mg q3-4hr (IR or oral solution) (2.5-7.5 mg)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20 mg</td>
<td>NA</td>
<td>5-10 mg q3-4 (2.5 mg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30 mg</td>
<td>NA</td>
<td>5 mg q3-4h (2.5 mg)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
<td>0.2-0.6 mg SC/IV q2-3hr (0.2mg)</td>
<td>1-2 mg q3-4hr (0.5-1 mg)</td>
</tr>
</tbody>
</table>

### Limitations of EDTs

*Single-dose potency studies using a specific route, conducted in patients w/ limited opioid exposure*

**Did Not Consider**

- Chronic dosing
- High opioid doses
- Other routes
- Different pain types
- Comorbidities or organ dysfunction
- Gender, ethnicity, advanced age, or concomitant medications
- Direction of switch from 1 opioid to another
- Inter-patient variability in pharmacologic response to opioids
- Incomplete cross-tolerance among mu opioids
Utilizing Equianalgesic Doses

Incomplete cross-tolerance & inter-patient variability require use of conservative dosing when converting from one opioid to another

Equianalgesic dose a starting point for opioid rotation

Intended as General Guide

Calculated dose of new drug based on EDT must be reduced, then titrate the new opioid as needed

Closely follow patients during periods of dose adjustments

Follow conversion instructions in individual ER/LA opioid PI, when provided

Guidelines for Opioid Rotation

Reduce calculated equianalgesic dose by 25%-50%*

Select % reduction based on clinical judgment

<table>
<thead>
<tr>
<th>Closer to 50% reduction if patient is</th>
<th>Closer to 25% reduction if patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Receiving a relatively high dose of current opioid regimen</td>
<td></td>
</tr>
<tr>
<td>• Elderly or medically frail</td>
<td></td>
</tr>
<tr>
<td>• Does not have these characteristics</td>
<td></td>
</tr>
<tr>
<td>• Is switching to a different administration route of same drug</td>
<td></td>
</tr>
</tbody>
</table>

*75%-90% reduction for methadone
Guidelines for Opioid Rotation, cont’d

If switching to **methadone**:

- Standard EDTs are less helpful in opioid rotation to methadone
- In opioid tolerant patients, methadone doses should not exceed 30-40 mg/day upon rotation.
  - Consider inpatient monitoring, including serial EKG monitoring
- In opioid-naïve patients, methadone should not be given as an initial drug

If switching to **transdermal**:

- **Fentanyl**, calculate dose conversion based on equianalgesic dose ratios included in the PI
- **Buprenorphine**, follow instructions in the PI

Guidelines for Opioid Rotation, cont’d

Have a strategy to frequently assess analgesia, AEs and withdrawal symptoms

Titrate new opioid dose to optimize outcomes & safety

Dose for breakthrough pain (BTP) **using a short-acting, immediate release preparation** is 5%-15% of total daily opioid dose, administered at an appropriate interval

If oral transmucosal fentanyl product is used for BTP, begin dosing lowest dose irrespective of baseline opioid dose

NEVER use ER/LA opioids for BTP
## Breakthrough Pain in Chronic Pain Patients

<table>
<thead>
<tr>
<th>Patients on stable ATC opioids may experience BTP</th>
<th>Therapies</th>
<th>Consider adding</th>
</tr>
</thead>
</table>
| Disease progression or a new or unrelated pain   | • Directed at cause of BTP or precipitating factors  
• Nonspecific symptomatic therapies to lessen impact of BTP | • PRN IR opioid trial based on analysis of benefit versus risk  
  - Risk for aberrant drug-related behaviors  
  - High-risk: only in conjunction w/ frequent monitoring & follow-up  
  - Low-risk: w/ routine follow-up & monitoring | • Nonopioid drug therapies  
• Nonpharmacologic treatments |

## Reasons for Discontinuing ER/LA Opioids

<table>
<thead>
<tr>
<th>No progress toward therapeutic goals</th>
<th>Intolerable &amp; Unmanageable AEs</th>
<th>Pain level decreases in stable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonadherence or unsafe behavior</td>
<td>Aberrant behaviors suggestive of addiction &amp;/or diversion</td>
<td></td>
</tr>
</tbody>
</table>
| • 1 or 2 episodes of increasing dose without prescriber knowledge  
• Sharing medications  
• Unapproved opioid use to treat another symptom (e.g., insomnia) | • Use of illicit drugs or unprescribed opioids  
• Repeatedly obtaining opioids from multiple outside sources  
• Prescription forgery  
• Multiple episodes of prescription loss |
Treat Initiation of Opioids as a Therapeutic Trial

Anticipate ER/LA Opioid-Induced Respiratory Depression

*It can be immediately life-threatening*

Be Conservative and Thoughtful In Dosing

*When initiating, titrating, and rotating opioids*

*First calculate equinalgesic dose, then reduce dose appropriately*

Discontinue ER/LA opioids slowly and safely
Informed Consent

Before initiating a trial of opioid analgesic therapy, confirm patient understanding of informed consent to establish:

- Analgesic & functional goals of treatment
- Expectations
- Potential risks
- Alternatives to opioids

The potential for & how to manage:

- Common opioid-related AEs (e.g., constipation, nausea, sedation)
- Other serious risks (e.g., abuse, addiction, respiratory depression, overdose)
- AEs after long-term or high-dose opioid therapy (e.g., hyperalgesia, endocrinologic or sexual dysfunction)

Patient-Prescriber Agreement (PPA)

Document signed by both patient & prescriber at time an opioid is prescribed

- Clarify treatment plan & goals of treatment w/ patient, patient’s family, & other clinicians involved in patient’s care
- Assist in patient education
- Inform patients about the risks & benefits
- Document patient & prescriber responsibilities
Consider a PPA

Reinforce expectations for appropriate & safe opioid use

- Obtain opioids from a single prescriber
- Fill opioid prescriptions at a designated pharmacy
- Safeguard opioids
  - Do not store in medicine cabinet
  - Keep locked (e.g., use a medication safe)
  - Do not share or sell medication
- Instructions for disposal when no longer needed

- Commitments to return for follow-up visits
- Comply w/ appropriate monitoring
  - E.g., random UDT & pill counts
- Frequency of prescriptions
- Enumerate behaviors that may lead to opioid discontinuation
- An exit strategy

Monitor Patients During Opioid Therapy

Therapeutic risks & benefits do not remain static

Affected by change in underlying pain condition, coexisting disease, or psychologic/ social circumstances

Identify patients

- Who are benefiting from opioid therapy
- Who might benefit more w/ restructuring of treatment or receiving additional services (e.g., addiction treatment)
- Whose benefits from treatment are outweighed by risks

Periodically assess continued need for opioid analgesic

Re-evaluate underlying medical condition if clinical presentation changes
Monitor Patients During Opioid Therapy, cont’d

Periodically evaluate:

- Pain control
  - Document pain intensity, pattern, & effects
- Functional outcomes
  - Document level of functioning
  - Assess progress toward achieving therapeutic goals
- Health-related QOL
- AE frequency & intensity
- Adherence to prescribed therapies

Patients requiring more frequent monitoring include:

- High-risk patients
- Patients taking high opioid doses

Anticipate & Treat Common AEs

<table>
<thead>
<tr>
<th>Constipation</th>
<th>most common AE; does not resolve with time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Initiate a bowel regimen before constipation develops</td>
</tr>
<tr>
<td></td>
<td>• Increase fluid &amp; fiber intake, stool softeners, &amp; laxatives</td>
</tr>
<tr>
<td></td>
<td>• Opioid antagonists may help prevent/treat opioid-induced bowel dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drowsiness &amp; sedation</th>
<th>tend to wane over time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Counsel patients about driving, work &amp; home safety as well as risks of concomitant exposure to other drugs &amp; substances w/ sedating effects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nausea &amp; vomiting</th>
<th>tend to diminish over days or weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral &amp; rectal antiemetic therapies as needed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pruritus &amp; myoclonus</th>
<th>tend to diminish over days or weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment strategies for either condition largely anecdotal</td>
</tr>
</tbody>
</table>
Monitor Adherence and Aberrant Behavior

*Routinely monitor patient adherence to treatment plan*

- Recognize & document aberrant drug-related behavior
  - In addition to patient self-report also use:
    - State PDMPs, where available
    - UDT
      - Positive for nonprescribed drugs
      - Positive for illicit substance
      - Negative for prescribed opioid
  - Family member or caregiver interviews
  - Monitoring tools such as the COMM, PADT, PMQ, or PDUQ
  - Medication reconciliation (e.g., pill counts)

**PADT=Pain Assessment & Documentation Tool**

Address Aberrant Drug-Related Behavior

*Behavior outside the boundaries of agreed-on treatment plan:*

- Behaviors that are **less** indicative of aberrancy
  - Unsanctioned dose escalations or other noncompliance w/ therapy on 1 or 2 occasions
  - Unapproved use of the drug to treat another symptom
  - Openly acquiring similar drugs from other medical sources

- Behaviors that are **more** indicative of aberrancy
  - Multiple dose escalations or other noncompliance w/ therapy despite warnings
  - Prescription forgery
  - Obtaining prescription drugs from nonmedical sources
Prescription Drug Monitoring Programs (PDMPs)

48 states have an operational PDMP
1 state & DC have enacted PDMP legislation, not yet operational
1 state has no legislation

Individual state laws determine
- Who has access to PDMP information
- Which drug schedules are monitored
- Which agency administers the PDMP
- Whether prescribers are required to register w/ the PDMP
- Whether prescribers are required to access PDMP information in certain circumstances
- Whether unsolicited PDMP reports are sent to prescribers

PDMP Benefits

Record of a patient’s controlled substance prescriptions
- Some are available online 24/7
- Opportunity to discuss w/ patient

Provide warnings of potential misuse/abuse
- Existing prescriptions not reported by patient
- Multiple prescribers/pharmacies
- Drugs that increase overdose risk when taken together
- Patient pays for drugs of abuse w/ cash

Prescribers can check their own prescribing Hx
PDMP Unsolicited Patient Threshold Reports

*Reports automatically generated on patients who cross certain thresholds when filling prescriptions. Available in some states.*

- E-mailed to prescribers to whom prescriptions were attributed
- Prescribers review records to confirm it is your patient & you wrote the prescription(s) attributed to you
- If inaccurate, contact PDMP
- If you wrote the prescription(s), patient safety may dictate need to discuss the patient w/ other prescribers listed on report
  - Decide who will continue to prescribe for the patient & who might address drug abuse concerns.

Rationale for Urine Drug Testing (UDT)

*Help to identify drug misuse/addiction*
- Prior to starting opioid treatment

*Assist in assessing adherence during opioid therapy*
- As requirement of therapy w/ an opioid
- Support decision to refer

*UDT frequency is based on clinical judgment*

- Depending on patient’s display of aberrant behavior and whether it is sufficient to document adherence to treatment plan
- Check state regulations for requirements
Main Types of UDT Methods

**Initial testing** w/ IA drug panels:
- Classify substance as present or absent according to cutoff
- Many do not identify individual drugs within a class
- Subject to cross-reactivity
- Either lab based or at POC

**Identify specific drugs** &/or metabolites w/ sophisticated lab-based testing; e.g., GC/MS or LC/MS*
- Specifically confirm the presence of a given drug
  - e.g., morphine is the opiate causing a positive IA*
- Identify drugs not included in IA tests
- When results are contested

Detecting Opioids by UDT

**Most common opiate IA drug panels**
- Detect “opiates” morphine & codeine, but doesn’t distinguish
- Do not reliably detect semisynthetic opioids
  - Specific IA panels can be ordered for some
- Do not detect synthetic opioids (e.g., methadone, fentanyl)
  - Only a specifically directed IA panel will detect synthetics

**GC/MS or LC/MS will identify specific opioids**
- Confirm presence of a drug causing a positive IA
- Identify opioids not included in IA drug panels, including semisynthetic & synthetic opioids
- Identify opioids not included in IA drug panels, including semisynthetic & synthetic opioids

* GC/MS= gas chromatography/ mass spectrometry
IA=immunoassay
LC/MS= liquid chromatography/ mass spectrometry
Be aware

**Testing technologies & methodologies evolve**

**Time taken to eliminate drugs**
- Document time of last use & quantity of drug(s) taken

**Differences exist between IA test menu panels vary**
- Cross-reactivity patterns
  - Maintain list of all patient’s prescribed & OTC drugs
  - Assist to identify false-positive result
- Cutoff levels

**Opioid metabolism may explain presence of apparently unprescribed drugs**

Examples of Metabolism of Opioids

- **Codeine** → **Morphine** → **6-MAM** → **Heroin**
  - $t_{1/2} = 25-30$ min
  - $t_{1/2} = 3-5$ min

- **Hydrocodone** → **Hydromorphone**
- **Oxycodone** → **Oxymorphone**

*6-MAM = 6-monocetylmorphine*
Interpretation of UDT Results

**Use UDT results in conjunction w/ other clinical information**

**Investigate unexpected results**
- Discuss w/ the lab
- Schedule appointment w/ patient to discuss unexpected/abnormal results

**Chart results, interpretation, & action**

**Do not ignore the unexpected positive result**
- May necessitate closer monitoring &/or referral to a specialist

---

ER/LA Opioid Use in Pregnant Women

**No adequate & well-controlled studies**
- Only use if potential benefit justifies the risk to the fetus

**Be aware of the pregnancy status of your patients**
- If prolonged use is required during pregnancy:
  - Advise patient of risk of neonatal withdrawal syndrome
  - Ensure appropriate treatment will be available

---

Be Ready to Refer

Be familiar w/ referral sources for abuse or addiction that may arise from use of ER/LA opioids

SAMHSA substance abuse treatment facility locator

http://findtreatment.samhsa.gov/TreatmentLocator/faces/quickSearch.jspx

SAMHSA mental health treatment facility locator


Unit 3

Pearls for Practice

Anticipate and Treat Common Adverse Effects

Use Informed Consent and Patient Provider Agreements

Use UDT and PDMP as Valuable Sources of Data About your Patient

However, know their limitations

Monitor Patient Adherence, Side Effects, Aberrant Behaviors, and Clinical Outcomes

Refer Appropriately if Necessary
Use **Patient Counseling Document** to help counsel patients

**Download:**

**Order hard copies:**
www.minneapolis.cenveo.com/pcd/SubmitOrders.aspx

---

**COUNSELING PATIENTS & CAREGIVERS ABOUT THE SAFE USE OF ER/LA OPIOID ANALGESICS**

**Unit IV**

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**Table: Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics**

<table>
<thead>
<tr>
<th>Field</th>
<th>Example Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Name:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Patient Specific Information:</strong></td>
<td></td>
</tr>
</tbody>
</table>

---

**Text:**

- **DO:**
  - Read the Medication Guide.
  - Take your medicine exactly as prescribed.
  - Store your medicine away from children and in a safe place.
  - Flush unused medicine down the toilet.
  - Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

- **Call 911 or your local emergency service right away if:**
  - You take too much medicine.
  - You have trouble breathing, or shortness of breath.
  - A child has taken this medicine.

- **Talk to your healthcare provider:**
  - If your dose does not control your pain.
  - About any side effects you may be having.
  - About all the medicines you take, including over-the-counter medications, vitamins, and dietary supplements.

- **DON'T:**
  - Don't give your medicine to others.
  - Don't take medicine unless it was prescribed for you.
  - Don't stop taking your medicine without talking to your healthcare provider.
  - Don't use, break, chew, dissolve, snort, or inject your medicine.
  - If you vomit your medicine, re-swallow the medicine.
  - Don't share alcohol while taking the medicine.

For additional information on your medicine, go to: www.drugabus.gov

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**FDA. EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY (REMS): Modified 08/2014.**

Counsel Patients About Proper Use

**Explain**

- Product-specific information about the prescribed ER/LA opioid
- How to take the ER/LA opioid as prescribed
- Importance of adherence to dosing regimen, handling missed doses, & contacting their prescriber if pain cannot be controlled

**Instruct patients/caregivers to**

- Read the ER/LA opioid Medication Guide received from pharmacy every time an ER/LA opioid is dispensed
- At every medical appointment explain all medications they take

Counsel Patients About Proper Use, cont'd

**Counsel patients/caregivers:**

- On the most common AEs of ER/LA opioids
- About the risk of falls, working w/ heavy machinery, & driving
- Call the prescriber for advice about managing AEs
- Inform the prescriber about AEs

Prescribers should report serious AEs to the FDA:

[www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)
or 1-800-FDA-1088
Warn Patients

Never break, chew, crush or snort an oral ER/LA tablet/capsule, or cut or tear patches prior to use

- May lead to rapid release of ER/LA opioid causing overdose & death
- When a patient cannot swallow a capsule whole, prescribers should refer to PI to determine if appropriate to sprinkle contents on applesauce or administer via feeding tube

Use of CNS depressants or alcohol w/ ER/LA opioids can cause overdose & death

- Use with alcohol may result in rapid release & absorption of a potentially fatal opioid dose
- Other depressants include sedative-hypnotics & anxiolytics, illegal drugs

Warn Patients, cont’d

Misuse of ER/LA opioids can lead to death

- Take exactly as directed*
- Counsel patients/caregivers on risk factors, signs, & symptoms of overdose & opioid-induced respiratory depression, GI obstruction, & allergic reactions
- Call 911 or poison control 1-800-222-1222

*Serious side effects, including death, can occur even when used as recommended

Do not abruptly stop or reduce the ER/LA opioid use

- Discuss how to safely taper the dose when discontinuing
Consider Prescribing Naloxone

**Naloxone:**
- An opioid antagonist
- Antidote to acute opioid toxicity
- Instruct patients to use in event of known or suspected overdose, **in addition to calling emergency services**

**Available as:**
- Naloxone kit (w/ syringes & needles)
- EVZIO™ (naloxone HCl) auto-injector

**Candidates for naloxone include those:**
- Taking high-doses of opioids
- Taking opioid preparations that may increase risk for overdose; eg, ER/LA opioids
- Undergoing opioid rotation
- Discharged from emergency medical care following opioid intoxication/poisoning
- Legitimate medical need for analgesia, coupled with suspected/confirmed substance abuse

**Encourage patients to:**
- Create an “overdose plan”
- Involve friends, family members, partners, &/or caregivers


Protecting the Community

**Caution Patients**
- Sharing ER/LA opioids w/ others may cause them to have serious AEs – Including death
- **Selling or giving away ER/LA opioids is against the law**
- Store medication safely and securely
- Protect ER/LA opioids from theft
- Dispose of any ER/LA opioids when no longer needed – Read product-specific disposal information included w/ ER/LA opioid

Know Your Poison Center’s Number.

1-800-222-1222
Source of Most Recent Rx Opioids Among Past-Year Users (2011-2012)

- Free: friend/relative: 0.2%
- 1 doctor: 1.8%
- Bought/took: friend/relative: 4.3%
- Other: 14.9%
- Drug dealer/stranger: 19.7%
- >1 doctor: 54.0%
- Bought on Internet: 5.1%


Rx Opioid Disposal

New “Disposal Act” expands ways for patients to dispose of unwanted/expired opioids

Collection receptacles
Call DEA Registration Call Center at 1-800-882-9539 to find a local collection receptacle

Mail-back packages
Obtained from authorized collectors

Local take-back events
• Conducted by Federal, State, tribal, or local law enforcement
• Partnering w/ community groups

Voluntarily maintained by:
• Law enforcement
• Authorized collectors, including:
  • Manufacturer
  • Distributer
  • Reverse distributer
  • Retail or hospital/clinic pharmacy
  • Including long-term care facilities

Last DEA National Prescription Drug Take-Back Day on September 27, 2014


Other Methods of Opioid Disposal

If collection receptacle, mail-back program, or take-back event unavailable, throw out in household trash

- Take drugs out of original containers
- Mix w/ undesirable substance, e.g., used coffee grounds or kitty litter
  - Less appealing to children/pets, & unrecognizable to people who intentionally go through your trash
- Place in sealable bag, can, or other container
  - Prevent leaking or breaking out of garbage bag
- Before throwing out a medicine container
  - Scratch out identifying info on label

FDA lists especially harmful medicines – in some cases fatal w/ just 1 dose – if taken by someone other than the patient

- Instruct patients to check medication guide

Flush down sink/toilet if no collection receptacle, mail-back program, or take-back event available

- As soon as they are no longer needed
  - So cannot be accidentally taken by children, pets, or others
- Includes transdermal adhesive skin patches
  - Used patch worn for 3d still contains enough opioid to harm/kill a child
  - Dispose of used patches immediately after removing from skin
- Fold patch in half so sticky sides meet, then flush down toilet
- Do NOT place used or unneeded patches in household trash
  - Exception is Butrans: can seal in Patch-Disposal Unit provided & dispose of in the trash
Establish Informed Consent

Counsel Patients about Proper Use

*Appropriate use of medication*
*Consequences of inappropriate use*

Educate the Whole Team

*Patients, families, caregivers*

Tools and Documents Can Help with Counseling

*Use them!*

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**GENERAL DRUG INFORMATION FOR ER/LA OPIOID ANALGESIC PRODUCTS**

**Unit V**
General ER/LA Opioid Drug Information

Prescribers should be knowledgeable about general characteristics, toxicities, & drug interactions for ER/LA opioid products:

- ER/LA opioid analgesic products are scheduled under the Controlled Substances Act & can be misused & abused
- Respiratory depression is the most serious opioid AE
  - Can be immediately life-threatening
- Constipation is the most common long-term AE
  - Should be anticipated

For Safer Use: Know Drug Interactions, PK, & PD

- CNS depressants can potentiate sedation & respiratory depression
- Use w/ MAOIs may increase respiratory depression
  - Certain opioids w/ MAOIs can cause serotonin syndrome
- Methadone & buprenorphine can prolong QTc interval
- Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol
  - Some drug levels may increase without dose dumping
- Can reduce efficacy of diuretics
  - Inducing release of antidiuretic hormone
- Drugs that inhibit or induce CYP enzymes can increase or lower blood levels of some opioids
Opioid Tolerant

Tolerance to sedating & respiratory-depressant effects is critical to safe use of certain ER/LA opioid products, dosage unit strengths, or doses

Patients must be opioid tolerant before using
  - Any strength of transdermal fentanyl or hydromorphone ER
  - Certain strengths or daily doses of other ER products

Opioid-tolerant patients are those taking at least
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hr
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - An equianalgesic dose of another opioid

FOR 1 WK OR LONGER

Key Instructions: ER/LA Opioids

Individually titrate to a dose that provides adequate analgesia & minimizes adverse reactions

Times required to reach steady-state plasma concentrations are product-specific

Refer to product information for titration interval

Continually re-evaluate to assess maintenance of pain control & emergence of AEs
Key Instructions: ER/LA Opioids, cont'd

During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids

If pain increases, attempt to identify source, while adjusting dose

When an ER/LA opioid is no longer required, gradually titrate dose downward to prevent signs & symptoms of withdrawal in physically dependent patients

Do not abruptly discontinue

Common Drug Information for This Class

Limitations of usage
- Reserve for when alternative options (eg, non-opioids or IR opioids) are ineffective, not tolerated, or otherwise inadequate
- Not for use as an as-needed analgesic
- Not for mild pain or pain not expected to persist for an extended duration
- Not for acute pain

Dosage reduction for hepatic or renal impairment
See individual drug PI

Relative potency to oral morphine
- Intended as general guide
- Follow conversion instructions in individual PI
- Incomplete cross-tolerance & inter-patient variability require conservative dosing when converting from 1 opioid to another
  - Halve calculated comparable dose & titrate new opioid as needed
Transdermal Dosage Forms

Do not cut, damage, chew, or swallow

- Exertion or exposure to external heat can lead to fatal overdose
- Rotate location of application
- Prepare skin: clip - not shave - hair & wash area w/ water
- Monitor patients w/ fever for signs or symptoms of increased opioid exposure
- Metal foil backings are not safe for use in MRIs

Drug Interactions Common to this Class

**Concurrent use w/ other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma**
- Reduce initial dose of one or both agents

**Avoid concurrent use of partial agonists* or mixed agonist/antagonists† with full opioid agonist**
- May reduce analgesic effect &/or precipitate withdrawal

**May enhance neuromuscular blocking action of skeletal muscle relaxants & increase respiratory depression**

**Concurrent use w/ anticholinergic medication increases risk of urinary retention & severe constipation**
- May lead to paralytic ileus

* Buprenorphine; † Pentazocine, nalbuphine, butorphanol
Drug Information Common to This Class

<table>
<thead>
<tr>
<th>Use in opioid-tolerant patients</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• See individual PI for products which:</td>
<td>• Significant respiratory depression</td>
</tr>
<tr>
<td>– Have strengths or total daily doses only for use in opioid-tolerant patients</td>
<td>• Acute or severe asthma in an unmonitored setting or in absence of resuscitative equipment</td>
</tr>
<tr>
<td>– Are only for use in opioid-tolerant patients at all strengths</td>
<td>• Known or suspected paralytic ileus</td>
</tr>
<tr>
<td></td>
<td>• Hypersensitivity (e.g., anaphylaxis)</td>
</tr>
<tr>
<td></td>
<td>• See individual PI for additional contraindications</td>
</tr>
</tbody>
</table>

Unit 5

Pearls for Practice

Patients MUST be opioid-tolerant in order to safely take most ER/LA opioid products

Be familiar with drug-drug interactions, pharmacokinetics and pharmacodynamics of ER/LA opioids

Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
### Specific Characteristics

**Know for opioid products you prescribe:**

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>Formulation</th>
<th>Strength</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key instructions</td>
<td>Use in opioid-tolerant patients</td>
<td>Product-specific safety concerns</td>
<td>Relative potency to morphine</td>
</tr>
<tr>
<td>Specific information about product conversions, if available</td>
<td>Specific drug interactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For detailed information, refer to online PI: DailyMed at [www.dailymed.nlm.nih.gov](http://www.dailymed.nlm.nih.gov) Drugs@FDA at [www.fda.gov/drugsatfda](http://www.fda.gov/drugsatfda)
Morphine Sulfate ER Capsules (Avinza)

**Dosing interval**
- Once a day

**Key instructions**
- Initial dose in opioid non-tolerant patients is 30 mg
- Titrate in increments of not greater than 30 mg using a minimum of 3-4 d intervals
- Swallow capsule whole (do not chew, crush, or dissolve)
- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately
- MDD:* 1600 mg (renal toxicity of excipient, fumaric acid)

**Drug interactions**
- Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose
- P-gp* inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold

**Opioid-tolerant**
- 90 mg & 120 mg capsules for use in opioid-tolerant patients only

**Product-specific safety concerns**
- None

* MDD=maximum daily dose; P-gp= P-glycoprotein

Buprenorphine Transdermal System (Butrans)

**Dosing interval**
- One transdermal system every 7 d

**Key instructions**
- Initial dose in opioid non-tolerant patients on <30 mg morphine equivalents & in mild-moderate hepatic impairment: 5 mcg/h
- When converting from 30 mg-80 mg morphine equivalents, first taper to 30 mg morphine equivalent, then initiate w/ 10 mcg/h
- Titrate in 5 or 10 mcg/h increments by using no more than 2 patches of the 5 or 10 mcg/h system(s) w/ minimum of 72 h prior between dose adjustments. Total dose from all patches should be ≤20 mcg/h
- Maximum dose: 20 mcg/h due to risk of QTc prolongation

**Application**
- Apply only to sites indicated in PI
- Apply to intact/non-irritated skin
- Prep skin by clipping hair; wash site w/ water only
- Rotate application site (min 3 wks before reapply to same site)
- Do not cut

- Avoid exposure to heat
- Dispose of patches: fold adhesive side together & flush down toilet

* MDD=maximum daily dose; P-gp= P-glycoprotein
Buprenorphine Transdermal System (Butrans) cont’d

**Drug interactions**
- CYP3A4 inhibitors may increase buprenorphine levels
- CYP3A4 inducers may decrease buprenorphine levels
- Benzodiazepines may increase respiratory depression
- Class IA & III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk of QTc prolongation & torsade de pointe

**Opioid-tolerant**
- 7.5 mcg/h, 10 mcg/h, 15 mcg/h, & 20 mcg/h for use in opioid-tolerant patients only

**Drug-specific safety concerns**
- QTc prolongation & torsade de pointe
- Hepatotoxicity
- Application site skin reactions

**Relative potency: oral morphine**
- Equipotency to oral morphine not established

Methadone Hydrochloride Tablets (Dolophine)

**Dosing interval**
- Every 8 to 12 h

**Key instructions**
- Initial dose in opioid non-tolerant patients: 2.5 – 10 mg
- Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose & death. Use low doses according to table in full PI
- Dosage adjustments using a minimum of 1-2 d intervals
- High inter-patient variability in absorption, metabolism, & relative analgesic potency
- Opioid detoxification or maintenance treatment only provided in a federally certified opioid (addiction) treatment program (CFR, Title 42, Sec 8)

**Drug interactions**
- Pharmacokinetic drug-drug interactions w/ methadone are complex
  - CYP 450 inducers may decrease methadone levels
  - CYP 450 inhibitors may increase methadone levels
  - Anti-retroviral agents have mixed effects on methadone levels
- Potentially arrhythmogenic agents may increase risk for QTc prolongation & torsade de pointe
- Benzodiazepines may increase respiratory depression

*NOTE:* While the dosing information below reflects the 8/20/14 FDA Blueprint, the CO*RE Expert Clinical Faculty believe it to be too aggressive and perhaps a risky approach. CO*RE Expert Clinical Faculty discourages methadone for opioid naïve patients as an initial drug and recommends 4-5 d intervals for dosing adjustments.
Methadone Hydrochloride Tablets (Dolophine) cont’d

**Opioid-tolerant**
- Refer to full PI

**Drug-specific safety concerns**
- QTc prolongation & torsade de pointe
- Peak respiratory depression occurs later & persists longer than analgesic effect
- Clearance may increase during pregnancy
- False-positive UDT possible

**Relative potency: oral morphine**
- Varies depending on patient’s prior opioid experience

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Fentanyl Transdermal System (Duragesic) 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr
("These strengths are available only in generic form)

**Dosing interval**
- Every 72 h (3 d)

**Key instructions**
- Use product-specific information for dose conversion from prior opioid
- Hepatic or renal impairment: use 50% of dose if mild/moderate, avoid use if severe
- Application
  - Apply to intact/non-irritated/non-irradiated skin on a flat surface
  - Prep skin by clipping hair, washing site w/ water only
  - Rotate site of application
  - Titrate using a minimum of 72 h intervals between dose adjustments
  - Do not cut
- Avoid exposure to heat
- Avoid accidental contact when holding or caring for children
- Dispose of used/unused patches: fold adhesive side together & flush down toilet
### Fentanyl Transdermal System (Duragesic), cont’d

#### Key instructions

**Specific contraindications:**
- Patients who are not opioid-tolerant
- Management of:
  - Acute or intermittent pain, or patients who require opioid analgesia for a short time
  - Post-operative pain, out-patient, or day surgery
  - Mild pain

#### Drug interactions

- CYP3A4 inhibitors may increase fentanyl exposure
- CYP3A4 inducers may decrease fentanyl exposure
- Discontinuation of concomitant CYP P450 3A4 inducer may increase fentanyl plasma concentration

#### Opioid-tolerant

- All doses indicated for opioid-tolerant patients only

#### Drug-specific safety concerns

- Accidental exposure due to secondary exposure to unwashed/unclothed application site
- Increased drug exposure w/ increased core body temp or fever
- Bradycardia
- Application site skin reactions

#### Relative potency: oral morphine

- See individual PI for conversion recommendations from prior opioid

---

### Morphine Sulfate ER-Naltrexone Tablets (Embeda)

#### Dosing interval

- Once a day or every 12 h

#### Key instructions

- Initial dose as first opioid: 20 mg/0.8 mg
- Titrate using a minimum of 1-2 d intervals
- Swallow capsules whole (do not chew, crush, or dissolve)
- Crushing or chewing will release morphine, possibly resulting in fatal overdose, & naltrexone, possibly resulting in withdrawal symptoms
- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately

#### Drug interactions

- Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose
- P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold

#### Opioid-tolerant

- 100 mg/4 mg capsule for use in opioid-tolerant patients only

#### Product-specific safety concerns

- None
Hydromorphone Hydrochloride ER Tablets (Exalgo)

**Dosing interval**
- Once a day

**Key instructions**
- Use conversion ratios in individual PI
- Start patients w/ moderate hepatic impairment on 25% dose prescribed for patient w/ normal function
- Renal impairment: start patients w/ moderate on 50% & patients w/ severe on 25% dose prescribed for patient w/ normal function
- Titrate in increments of 4-8 mg using a minimum of 3-4 d intervals
- Swallow tablets whole (do not chew, crush, or dissolve)
- Do not use in patients w/ sulfite allergy (contains sodium metabisulfite)

**Drug interactions**
- None

**Opioid-tolerant**
- All doses are indicated for opioid-tolerant patients only

**Product-specific adverse reactions**
- Allergic manifestations to sulfite component

**Relative potency: oral morphine**
- ~5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in individual product information

Hydrocodone Bitartrate (Hysingla ER)

**Extended-Release Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120mg**

**Dosing interval**
- Once a day

**Key instructions**
- Opioid-naïve patients: initiate treatment with 20 mg orally once daily.
- During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved.
- Swallow tablets whole (do not chew, crush, or dissolve).
- Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction.
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
- Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.
Hydrocodone Bitartrate (Hysingla ER), cont'd

| Drug interactions | • CYP3A4 inhibitors may increase hydrocodone exposure.  
|                   | • CYP3A4 inducers may decrease hydrocodone exposure.  
|                   | • Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels.  
|                   | • The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER. |

| Opioid-tolerant | • 80 mg is only for use in opioid tolerant patients. |

| Drug-specific safety concerns | • Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction.  
|                             | • Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER.  
|                             | • In nursing mothers, discontinue nursing or discontinue drug. QTC prolongation has been observed with Hysingla ER following daily doses of 160 mg.  
|                             | • Avoid use in patients with congenital long QTC syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTC interval.  
|                             | • In patients who develop QTC prolongation, consider reducing the dose. |

| Relative potency: oral morphine | • See individual PI for conversion recommendations from prior opioid |

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Morphine Sulfate ER Capsules (Kadian)

| Dosing interval | • Once a day or every 12 h |

| Key instructions | • PI recommends not using as first opioid  
|                 | • Titrate using minimum of 2-d intervals  
|                 | • Swallow capsules whole (do not chew, crush, or dissolve)  
|                 | • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately |

| Drug interactions | • Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose of morphine  
|                  | • P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |

| Opioid-tolerant | • 100 mg & 200 mg capsules for use in opioid-tolerant patients only |

| Product-specific safety concerns | • None |
Morphine Sulfate CR Tablets (MS Contin)

| Dosing interval | • Every 8 h or every 12 h |
| Key instructions | • Product information recommends not using as first opioid.  
| | • Titrate using a minimum of 1-2 d intervals  
| | • Swallow tablets whole (do not chew, crush, or dissolve) |
| Drug interactions | • P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |
| Opioid-tolerant | • 100 mg & 200 mg tablet strengths for use in opioid-tolerant patients only |
| Product-specific safety concerns | • None |

Tapentadol ER Tablets (Nucynta ER)

| Dosing interval | • Every 12 h |
| Key instructions | • 50 mg every 12 h is initial dose in opioid non-tolerant patients  
| | • Titrate by 50 mg increments using minimum of 3-d intervals  
| | • MDD: 500 mg  
| | • Swallow tablets whole (do not chew, crush, or dissolve)  
| | • Take 1 tablet at a time w/ enough water to ensure complete swallowing immediately after placing in mouth  
| | • Dose once/d in moderate hepatic impairment (100 mg/d max)  
| | • Avoid use in severe hepatic & renal impairment |
| Drug interactions | • Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of a potentially fatal dose of tapentadol  
| | • Contraindicated in patients taking MAOIs |
| Opioid-tolerant | • No product-specific considerations |
| Product-specific safety concerns | • Risk of serotonin syndrome  
| | • Angio-edema |
| Relative potency: oral morphine | • Equipotency to oral morphine has not been established |
### Oxymorphone Hydrochloride ER Tablets (Opana ER)

#### Dosing interval
- Every 12 h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing

#### Key instructions
- Use 5 mg every 12 h as initial dose in opioid non-tolerant patients & patients w/ mild hepatic impairment & renal impairment (creatinine clearance <50 mL/min) & patients >65 yrs
- Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth
- Titrate in increments of 5-10 mg using a minimum of 3-7 d intervals
- Contraindicated in moderate & severe hepatic impairment

#### Drug interactions
- Alcohol & medications w/ alcohol may result in absorption of a potentially fatal dose of oxymorphone

#### Opioid-tolerant
- No product-specific considerations

#### Product-specific safety concerns
- Use with caution in patients who have difficulty swallowing or underlying GI disorders that may predispose to obstruction (e.g. small gastrointestinal lumen)

#### Relative potency: oral morphine
- Approximately 3:1 oral morphine to oxymorphone oral dose ratio

### Oxycodone Hydrochloride CR Tablets (OxyContin)

#### Dosing interval
- Every 12 h

#### Key instructions
- Initial dose in opioid non-tolerant patients: / 10 mg every 12 h
- Titrate using a minimum of 1-2 d intervals
- Hepatic impairment: start w/ 1/3-1/2 usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start w/ 1/2 usual dosage
- Consider other analgesics in patients w/ difficulty swallowing or underlying GI disorders that predispose to obstruction. Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth

#### Drug interactions
- CYP3A4 inhibitors may increase oxycodone exposure
- CYP3A4 inducers may decrease oxycodone exposure

#### Opioid-tolerant
- Single dose >40 mg or total daily dose >80 mg for use in opioid-tolerant patients only

#### Product-specific safety concerns
- Choking, gagging, regurgitation, tablets stuck in throat, difficulty swallowing tablet
- Contraindicated in patients w/ GI obstruction

#### Relative potency: oral morphine
- Approximately 2:1 oral morphine to oxycodone oral dose ratio
### Oxycodone Hydrochloride/Naloxone Hydrochloride ER Tablets (Targiniq ER)

**Dosing interval**
- Every 12 h

**Key instructions**
- Opioid-naive patients: initiate treatment w/ 10mg/5mg every 12 h
- Titrate using min of 1-2 d intervals
- Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h)
- May be taken w/ or without food
- Swallow whole. Do not chew, crush, split, or dissolve: this will release oxycodone (possible fatal overdose) & naloxone (possible withdrawal)
- Hepatic impairment: contraindicated in moderate-severe impairment. In patients w/ mild impairment, start w/ ⅓–⅓½ usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start w/ ⅓ usual dosage

**Drug interactions**
- CYP3A4 inhibitors may increase oxycodone exposure
- CYP3A4 inducers may decrease oxycodone exposure

**Opioid-tolerant**
- Single dose >40 mg/20 mg or total daily dose of 80 mg/40 mg for opioid-tolerant patients only

**Product-specific safety concerns**
- Contraindicated in patients w/ moderate-severe hepatic impairment

**Relative potency: oral morphine**
- See individual PI for conversion recommendations from prior opioids

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### Hydrocodone Bitartrate ER Capsules (Zohydro ER)

**Dosing interval**
- Every 12 h

**Key instructions**
- Initial dose in opioid non-tolerant patient is 10 mg
- Titrate in increments of 10 mg using a min of 3-7 d intervals
- Swallow capsules whole (do not chew, crush, or dissolve)

**Drug interactions**
- Alcoholic beverages or medications containing alcohol may result in rapid release & absorption of a potentially fatal dose of hydrocodone
- CYP3A4 inhibitors may increase hydrocodone exposure
- CYP3A4 inducers may decrease hydrocodone exposure

**Opioid-tolerant**
- Single dose >40 mg or total daily dose >80 mg for use in opioid-tolerant patients only

**Product-specific safety concerns**
- None

**Relative potency: oral morphine**
- Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio
Summary

Prescription opioid abuse & overdose is a national epidemic. Clinicians must play a role in prevention

Understand how to assess patients for treatment w/ ER/LA opioids

Be familiar w/ how to initiate therapy, modify dose, & discontinue use of ER/LA opioids

Know how to manage ongoing therapy w/ ER/LA opioids

Know how to counsel patients & caregivers about the safe use of ER/LA opioids, including proper storage & disposal

Be familiar w/ general & product-specific drug information concerning ER/LA opioids

IMPORTANT!

Thank you for completing the post-activity assessment for this CO*RE session.

Your participation in this assessment allows CO*RE to report de-identified numbers to the FDA.

A strong show of engagement will demonstrate that clinicians have voluntarily taken this important education and are committed to patient safety and improved outcomes.

THANK YOU!
Thank you!

www.core-rems.org