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Dr. Edwin A. Salsitz has been an attending physician in the Mt. Sinai Beth Israel, Division of Chemical Dependency, since 1983, and is an Assistant Professor of Medicine at the Icahn School of Medicine at Mount Sinai. He is the principal investigator of the Methadone Medical Maintenance (office-based methadone maintenance) research project. Dr. Salsitz is certified by the American Board of Addiction Medicine (ABAM), as well as by the Board of Internal Medicine and Pulmonary Disease. He has published and lectures frequently on addiction medicine topics.
Disclosure of Relevant Financial Relationships

Content of Activity: ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care

<table>
<thead>
<tr>
<th>Name</th>
<th>Commercial Interests</th>
<th>Relevant Financial Relationships: What Was Received</th>
<th>Relevant Financial Relationships: For What Role</th>
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<tbody>
<tr>
<td>Edwin A. Salsitz, MD, DFASAM</td>
<td>None</td>
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</table>
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 multidisciplinary 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-rems.org
## Founding Partners

- American Pain Society (APS)
- American Academy of Hospice and Palliative Medicine (AAHPM)
- American Association of Nurse Practitioners (AANP)
- American Academy of Physician Assistants (AAPA)
- American Osteopathic Association (AOA)
- American Society of Addiction Medicine (ASAM)
- California Academy of Family Physicians (CAFP)
- Healthcare Performance Consulting (HPC)
- Interstate Postgraduate Medical Association (IPMA)
- Nurse Practitioner Healthcare Foundation (NPHF)

## Strategic Partners

- Physicians Institute for Excellence in Medicine which coordinates 15 state medical societies
- Medscape
- American Academy of Family Physicians
- American College of Emergency Physicians *(New in 2015)*
# Content Development/Planner/Reviewer Disclosures

The following individuals disclose no relevant financial relationships:

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
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<tbody>
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<td>Executive Director, Interstate Postgraduate Medical Association, Madison, WI</td>
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</tr>
<tr>
<td>Phyllis Zimmer, MN, FNP, FAAN</td>
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<td>CME/CE Director, Medscape, LLC, New York, NY</td>
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<td>Scientific Director, Medscape, LLC, New York, NY</td>
</tr>
<tr>
<td>Cynthia Singh</td>
<td>Director, Grants and Foundation Development, American College of Emergency Physicians</td>
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<tr>
<td>Lori Foley</td>
<td>Director, Strategic Partnerships, American College of Emergency Physicians, Irving, TX</td>
</tr>
</tbody>
</table>
Acknowledgement

Presented by American Society of Addiction Medicine, 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/lwgCEUI/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>
</tr>
</thead>
<tbody>
<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>• Embeda® 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></td>
</tr>
<tr>
<td>• Methadose™ methadone hydrochloride tablets</td>
<td></td>
</tr>
<tr>
<td>• MS Contin® morphine sulfate CR tablets</td>
<td></td>
</tr>
<tr>
<td>• Nucynta® ER tapentadol ER tablets</td>
<td></td>
</tr>
<tr>
<td>• Opana® ER oxymorphone hydrochloride ER tablets</td>
<td></td>
</tr>
<tr>
<td>• OxyContin® oxycodone hydrochloride CR tablets</td>
<td></td>
</tr>
<tr>
<td>• Targiniq™ oxycodone hydrochloride/naloxone hydrochloride ER tablets</td>
<td></td>
</tr>
<tr>
<td>• Zohydro® hydrocodone bitartrate ER capsules</td>
<td></td>
</tr>
</tbody>
</table>
This course is not intended to advocate for the use of Extended-Release/Long-Acting (ER/LA) Opioids, but to ensure the proper education about safe prescribing practices should a medical provider determine that ER/LA Opioids are the best course of treatment.
WHY PRESCRIBER EDUCATION IS IMPORTANT

Introduction
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**
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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>2.4</td>
</tr>
<tr>
<td>Pain relievers</td>
<td>1.9</td>
</tr>
<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>
<td>0.6</td>
</tr>
<tr>
<td>LSD</td>
<td>0.4</td>
</tr>
<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>
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</tbody>
</table>

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
Balance Risks Against Potential Benefits

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

**Benefits Include**

- Analgesia (adequate pain control)
- Improved Function

**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
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.:**

<table>
<thead>
<tr>
<th>Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Cellulitis</td>
</tr>
<tr>
<td>STIs</td>
</tr>
<tr>
<td>Trauma, burns</td>
</tr>
<tr>
<td>Cardiac disease</td>
</tr>
<tr>
<td>Pulmonary disease</td>
</tr>
</tbody>
</table>
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

Past use

Current use

- Query state PDMP where available to confirm patient report
- Contact past providers & obtain prior medical records
- Conduct UDT

Dosage

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

General effectiveness

Nonpharmacologic strategies & effectiveness
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

Musculoskeletal Exam
- Inspection
- Palpation
- Percussion
- Auscultation
- Provocative maneuvers

Neurologic exam

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

<table>
<thead>
<tr>
<th>Tool</th>
<th># of items</th>
<th>Administered By</th>
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</thead>
<tbody>
<tr>
<td><strong>Patients considered for long-term opioid therapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORT Opioid Risk Tool</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>DIRE Diagnosis, Intractability, Risk, &amp; Efficacy Score</td>
<td>7</td>
<td>clinician</td>
</tr>
<tr>
<td><strong>Characterize misuse once opioid treatments begins:</strong></td>
<td></td>
<td></td>
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<tr>
<td>PMQ Pain Medication Questionnaire</td>
<td>26</td>
<td>patient</td>
</tr>
<tr>
<td>COMM Current Opioid Misuse Measure</td>
<td>17</td>
<td>patient</td>
</tr>
<tr>
<td>PDUQ Prescription Drug Use Questionnaire</td>
<td>40</td>
<td>clinician</td>
</tr>
<tr>
<td><strong>Not specific to pain populations:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAGE-AID Cut Down, Annoyed, Guilty, Eye-Opener Tool, Adjusted to Include Drugs</td>
<td>4</td>
<td>clinician</td>
</tr>
<tr>
<td>RAFFT Relax, Alone, Friends, Family, Trouble</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>DAST Drug Abuse Screening Test</td>
<td>28</td>
<td>patient</td>
</tr>
<tr>
<td>SBIRT Screening, Brief Intervention, &amp; Referral to Treatment</td>
<td>Varies</td>
<td>clinician</td>
</tr>
</tbody>
</table>
# Opioid Risk Tool (ORT)

**Mark each box that applies**

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
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</thead>
<tbody>
<tr>
<td><strong>1. Family Hx of substance abuse</strong></td>
<td></td>
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</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Illegal drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>2. Personal Hx of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>3. Age between 16 &amp; 45 yrs</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>4. Hx of preadolescent sexual abuse</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>5. Psychologic disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADD, OCD, bipolar, schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Administer**

- On initial visit
- Prior to opioid therapy

**Scoring (risk)**

- **0-3:** low
- **4-7:** moderate
- **≥8:** high
# 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 w/ 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 with history 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

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
- Oxycodone ER dosing changes for children ≥ 11 yrs (see Unit 6)

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

Challenge: The Friday Afternoon Patient

Red Flag: Adjusting a prescription without performing appropriate evaluation or screening

It is 4 pm on Friday and you are four patients behind schedule. Mr. Kingston asks you to increase his current dosage of hydrocodone, because he says it is not relieving his pain. It would take you two minutes to say yes.

Action: Check your local PDMP. Employ practice management strategies that maximize efficiency.

- Patient-administered screening tools
- Office staff to administer and score tools, document results, and communicate to the prescriber
Ms. Van Buskirk says she needs opioids to manage her pain until she can have surgery. She reports continued delays in getting to surgery. You phone the surgeon and discover that no date has been set and that she has cancelled several appointments.

**Red Flag:** Patient may be stalling to continue an opioid regimen

**Action:** Set expectations for time limitations. Offer non-medicine and non-opioid options for pain management. Consider referral to addiction specialist.
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
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/2106cfrt.htm](http://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm)
- United States Code (USC) - Controlled Substances Act, Title 21, Section 829: prescriptions

State

- Database of state statutes, regulations, & policies for pain management
  - [www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management](http://www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management)
# Initiating Treatment

*Prescribers should regard initial treatment as a therapeutic trial*

<table>
<thead>
<tr>
<th>May last from several weeks to several months</th>
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</thead>
<tbody>
<tr>
<td>Decision to proceed w/ long-term treatment should be intentional &amp; based on careful consideration of outcomes during the trial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progress toward meeting therapeutic goals</th>
<th>Presence of opioid-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in underlying pain condition</td>
<td>Changes in psychiatric or medical comorbidities</td>
</tr>
<tr>
<td>Identification of aberrant drug-related behavior, addiction, or diversion</td>
<td></td>
</tr>
</tbody>
</table>

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

## ER/LA Opioid-Induced Respiratory Depression

### More likely to occur

- In elderly, cachectic, or debilitated patients
  - **Contraindicated** in patients with respiratory depression or conditions that increase risk
- If given concomitantly with 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 with first dose
- Instruct patients to swallow tablets/capsules whole
  - Dose from cut, crushed, dissolved, or chewed tablets/capsules may be fatal, particularly in opioid-naïve individuals

---

Initiating & Titrating: Opioid-Naïve Patients

Drug & dose selection is critical

Monitor patients closely for respiratory depression

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

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)

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

Check ER/LA opioid product PI for minimum titration intervals

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

**The ER/LA Opioid Analgesics Risk Evaluation & Mitigation Strategy. Selected Important Safety Information. Abuse potential & risk of life-threatening respiratory depression.**

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**

---


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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
Equianalgesic Dose Tables (EDT)

Many different versions:
- Published
- Online
- Online Interactive
- Smart-phone apps

Vary in terms of:
- Equianalgesic values
- Whether ranges are used
- Which opioids are included:
  May or may not include transdermal opioids, rapid-onset fentanyl, ER/LA opioids, or opioid agonist-antagonists
## Example of an EDT for Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Dose</th>
<th>Usual Starting Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC/IV</td>
<td>10 mg</td>
<td>2.5-5 mg SC/IV q3-4hr (◆1.25 – 2.5mg)</td>
</tr>
<tr>
<td>PO</td>
<td>30 mg</td>
<td>5-15 mg q3-4hr (IR or oral solution) (◆2.5-7.5 mg)</td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>20 mg</td>
<td>5-10 mg q3-4 (◆2.5 mg)</td>
</tr>
<tr>
<td><strong>Hydrocodone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>30 mg</td>
<td>5 mg q3-4h (◆2.5 mg)</td>
</tr>
<tr>
<td><strong>Hydromorphone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 mg</td>
<td>7.5 mg</td>
<td>0.2-0.6 mg SC/IV q2-3hr (◆0.2mg)</td>
</tr>
<tr>
<td></td>
<td></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**

<table>
<thead>
<tr>
<th>Did Not Consider</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic dosing</td>
<td>High opioid doses</td>
<td>Other routes</td>
</tr>
<tr>
<td>Different pain types</td>
<td>Comorbidities or organ dysfunction</td>
<td>Gender, ethnicity, advanced age, or concomitant medications</td>
</tr>
<tr>
<td>Direction of switch from 1 opioid to another</td>
<td>Inter-patient variability in pharmacologic response to opioids</td>
<td>Incomplete cross-tolerance among mu opioids</td>
</tr>
</tbody>
</table>
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>Does not have these characteristics</td>
</tr>
<tr>
<td>Elderly or medically frail</td>
<td>Is switching to a different administration route of same drug</td>
</tr>
</tbody>
</table>

*75%-90% reduction for methadone

Calculate equianalgesic dose of new opioid from EDT

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Collaborative for REMS Education

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

No progress toward therapeutic goals

- 1 or 2 episodes of increasing dose without prescriber knowledge
- Sharing medications
- Unapproved opioid use to treat another symptom (e.g., insomnia)

Intolerable & Unmanageable AEs

- Use of illicit drugs or unprescribed opioids
- Repeatedly obtaining opioids from multiple outside sources
- Prescription forgery
- Multiple episodes of prescription loss

Pain level decreases in stable patients

Nonadherence or unsafe behavior

- Aberrant behaviors suggestive of addiction &/or diversion

- Use of illicit drugs or unprescribed opioids
- Repeatedly obtaining opioids from multiple outside sources
- Prescription forgery
- Multiple episodes of prescription loss
Challenge: The Broken Stereotype

Red Flag:
Making assumptions about a patient’s risk factors without objective evidence

Ms. Yeun seems like a “good” patient. She has never abused opioids previously. She has been in the practice a long time, has never been a problem, and in fact, is rather enjoyable. She always brings Christmas cookies for the staff around the holidays.

Action: Require all patients receiving opioids to follow a treatment plan and adhere to defined expectations. Evaluate risk in all patients. Use patient-provider agreements, contracts, or other tools.
Challenge: The Early Refill

**Red Flag:**
Patient requests an early refill every month.

You have prescribed Mr. Arias a long-acting opioid for low back pain and a short-acting PRN opioid for breakthrough pain. Every month he requests a refill for both prescriptions 3-8 days early. Upon questioning, Mr. Arias tells you that he takes both pills whenever he feels he needs them.

**Action:** Make sure that patients understand each medication’s dosage, time of day, and maximum daily dose. Ask them to repeat these instructions back to you. Avoid clinical terms such as “PRN” that the patient may not understand.
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
MANAGING THERAPY WITH ER/LA OPIOID ANALGESICS

Unit III
Informed Consent

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

<table>
<thead>
<tr>
<th>Analgesic &amp; functional goals of treatment</th>
<th>The potential for &amp; how to manage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectations</td>
<td>• Common opioid-related AEs (e.g., constipation, nausea, sedation)</td>
</tr>
<tr>
<td>Potential risks</td>
<td>• Other serious risks (e.g., abuse, addiction, respiratory depression, overdose)</td>
</tr>
<tr>
<td>Alternatives to opioids</td>
<td>• AEs after long-term or high-dose opioid therapy (e.g., hyperalgesia, endocrinologic or sexual dysfunction)</td>
</tr>
</tbody>
</table>
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 |
| Instructions for disposal when no longer needed |

- Do not store in medicine cabinet
- Keep locked (e.g., use a medication safe)
- Do not share or sell medication

| Commitments to return for follow-up visits |
| Comply w/ appropriate monitoring |
| Frequency of prescriptions |
| Enumerate behaviors that may lead to opioid discontinuation |
| An exit strategy |
## Monitor Patients During Opioid Therapy

<table>
<thead>
<tr>
<th>Therapeutic risks &amp; benefits do not remain static</th>
<th>Identify patients</th>
<th>Periodically assess continued need for opioid analgesic</th>
</tr>
</thead>
</table>
| Affected by change in underlying pain condition, coexisting disease, or psychologic/social circumstances | • Who are benefiting from opioid therapy  
• Who might benefit more with restructuring of treatment or receiving additional services (e.g., addiction treatment)  
• Whose benefits from treatment are outweighed by risks | 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>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>most common AE; does not resolve with time</td>
</tr>
<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>
<tr>
<td>Drowsiness &amp; sedation</td>
<td>tend to wane over time</td>
</tr>
<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>
<tr>
<td>Nausea &amp; vomiting</td>
<td>tend to diminish over days or weeks</td>
</tr>
<tr>
<td></td>
<td>Oral &amp; rectal antiemetic therapies as needed</td>
</tr>
<tr>
<td>Pruritus &amp; myoclonus</td>
<td>tend to diminish over days or weeks</td>
</tr>
<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 with 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 with 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

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

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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
**Interpretation of UDT Results**

**Positive Result**

- Demonstrates recent use
  - Most drugs in urine have detection times of 1-3 d
  - Chronic use of lipid-soluble drugs: test positive for ≥1 wk

- **Does not diagnose**
  - Drug addiction, physical dependence, or impairment

- **Does not provide enough information to determine**
  - Exposure time, dose, or frequency of use

**Negative Result**

- **Does not diagnose diversion**
  - More complex than presence or absence of a drug in urine

- **May be due to maladaptive drug-taking behavior**
  - Bingeing, running out early
  - Other factors: eg, cessation of insurance, financial difficulties
Be aware

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

Testing technologies & methodologies evolve

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

Opioid metabolism may explain presence of apparently unprescribed drugs
Examples of Metabolism of Opioids

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

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

*6-MAM=6-monoacetylmorphine
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
Mr. Lee’s daily function has improved significantly over the past two years. You suggest titrating his dosage down or trying alternative pain management options. He is extremely resistant and tells you “Nothing else relieves my pain.”

**Action**: Work with your patient to set treatment goals and expectations. Select and document a therapy plan or use a patient-provider agreement. Evaluate Mr. Lee for potential addiction; consider referral to psychiatry or addiction medicine.
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
COUNSELING PATIENTS & CAREGIVERS ABOUT THE SAFE USE OF ER/LA OPIOID ANALGESICS

Unit IV
Use Patient Counseling Document to help counsel patients

Download:

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

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
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
Co-Prescribing Naloxone

**Naloxone:**
- An opioid antagonist
- Reverses acute opioid-induced respiratory depression but will also cause withdrawal and reverse analgesia
- Administered intramuscularly and subcutaneously
- Intranasal formulation currently under consideration with the FDA

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

**What to do:**
- Encourage patients to create an ‘overdose plan’
- Involve and train family, friends, partners and/or caregivers
- Check expiration dates and keep a viable dose on hand
- In the event of known or suspected overdose, administer Naloxone and call **911**.
When to Consider Co-Prescribing Naloxone:

Those at a higher risk for opioid overdose including...

- Taking opioid high-doses for pain (50 mg/day equiv)
- Receiving rotating opioid medication regimes (at risk for incomplete cross tolerance)
- On opioid preparations with increased overdose risk
- With respiratory disease (COPD, emphysema, asthma)
- With renal or hepatic impairment
- Concurrent benzodiazepine use
Protecting the Community

**Caution Patients**

- Sharing ER/LA opioids with 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 with ER/LA opioid

**Know Your Poison Center’s Number.**

1-800-222-1222

You could save a life.
Source of Most Recent Rx Opioids Among Past-Year Users (2011-2012)

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

Educate Parents: Not in My House

**Step 1: Monitor**

- Note how many pills in each prescription bottle or pill packet
- Keep track of refills for all household members
- If your teen has been prescribed a drug, coordinate & monitor dosages & refills
- Make sure friends & relatives—especially grandparents—are aware of the risks
- If your teen visits other households, talk to the families about safeguarding their medications
Rx Opioid Disposal

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

Decreases amount of opioids introduced into the environment, particularly into water

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 26, 2015

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
Red Flag:

You decide not to request routine risk assessment for fear of creating conflict.

Mrs. Jorgensen has been your patient for eight years and has never caused any problems. When you ask her to undergo urine drug testing, she becomes upset and accuses you of not trusting her.

Action: Describe UDT as a routine part of medication monitoring rather than a “drug test”. Create an office policy for performing UDT on all ER/LA opioid patients. Practice by following universal precautions. Use a patient-provider agreement to clarify expectations of treatment.
Challenge: The Daughter’s Party

**Red Flag:**
Patients do not safeguard their opioid medications correctly

Your patient’s daughter, Jody, stole her father’s opioids from his bedside drawer to take to a “fishbowl party”. Her best friend consumed a mix of opioids and alcohol and died of an overdose.

**Action:** Always counsel patients about safe drug storage; warn patients about the serious consequences of theft, misuse, and overdose. Tell your patients that taking another person’s medication, even once, is against the law.
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!
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

<table>
<thead>
<tr>
<th>Limitations of usage</th>
<th>Dosage reduction for hepatic or renal impairment</th>
<th>Relative potency to oral morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reserve for when alternative options (e.g., non-opioids or IR opioids) are ineffective, not tolerated, or otherwise inadequate</td>
<td>See individual drug PI</td>
<td>• Intended as general guide</td>
</tr>
<tr>
<td>• Not for use as an as-needed analgesic</td>
<td></td>
<td>• Follow conversion instructions in individual PI</td>
</tr>
<tr>
<td>• Not for mild pain or pain not expected to persist for an extended duration</td>
<td></td>
<td>• Incomplete cross-tolerance &amp; inter-patient variability require conservative dosing when converting from 1 opioid to another</td>
</tr>
<tr>
<td>• Not for acute pain</td>
<td></td>
<td>– Halve calculated comparable dose &amp; titrate new opioid as needed</td>
</tr>
</tbody>
</table>
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

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

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

- 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

Use in opioid-tolerant patients

- See individual PI for products which:
  - Have strengths or total daily doses only for use in opioid-tolerant patients
  - Are only for use in opioid-tolerant patients at all strengths

Contraindications

- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis)
- See individual PI for additional contraindications
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.
Challenge: The Patient in the ER

**Red Flag:** You are woken by a telephone call at 2 am reporting that your patient, Mr. Diallo, is in the ER with apparent respiratory depression.

**Action:** Be familiar with risk factors for respiratory depression and know when opioids are contra-indicated. Anticipate possible risks and develop contingency plans. Teach patients, family, and caregivers about respiratory depression and its symptoms.
SPECIFIC DRUG INFORMATION FOR ER/LA OPIOID ANALGESIC PRODUCTS

Unit VI
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></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key instructions**

<table>
<thead>
<tr>
<th>Use in opioid-tolerant patients</th>
<th>Product-specific safety concerns</th>
<th>Relative potency to morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Specific information about product conversions, if available**

<table>
<thead>
<tr>
<th>Specific drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<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
### 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 antiarrythmics, 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  

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# 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 Blue Print, 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
# 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*)

<table>
<thead>
<tr>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Every 72 h (3 d)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use product-specific information for dose conversion from prior opioid</td>
</tr>
<tr>
<td>• Hepatic or renal impairment: use 50% of dose if mild/moderate, avoid use if severe</td>
</tr>
<tr>
<td>• Application</td>
</tr>
<tr>
<td>‒ Apply to intact/non-irritated/non-irradiated skin on a flat surface</td>
</tr>
<tr>
<td>‒ Prep skin by clipping hair, washing site w/ water only</td>
</tr>
<tr>
<td>‒ Rotate site of application</td>
</tr>
<tr>
<td>‒ Titrate using a minimum of 72 h intervals between dose adjustments</td>
</tr>
<tr>
<td>‒ Do not cut</td>
</tr>
<tr>
<td>• Avoid exposure to heat</td>
</tr>
<tr>
<td>• Avoid accidental contact when holding or caring for children</td>
</tr>
<tr>
<td>• Dispose of used/unused patches: fold adhesive side together &amp; flush down toilet</td>
</tr>
</tbody>
</table>
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

*Not currently available due to voluntary recall.*
## Hydromorphone Hydrochloride ER Tablets (Exalgo)

### Dosing interval

- Once a day

### Key instructions

- Use conversion ratios in individual PI
- Start patients with moderate hepatic impairment on 25% dose prescribed for patient with normal function
- Renal impairment: start patients with moderate on 50% & patients with severe on 25% dose prescribed for patient with normal function
- Titrate in increments of 4-8 mg using a minimum of 3-4 day intervals
- Swallow tablets whole (do not chew, crush, or dissolve)
- Do not use in patients with 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.
### 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
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)

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>• Every 8 h or every 12 h</th>
</tr>
</thead>
</table>
| 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)

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

- **Dosing interval**
  - Every 12 h

- **Initial dose in opioid non-tolerant patients**: 10 mg every 12 h
- **Titrate using a minimum of 1-2 d intervals**
- **Hepatic impairment**: start with ⅓-½ usual dosage
- **Renal impairment (creatinine clearance <60 mL/min)**: start with ½ usual dosage
- **Consider other analgesics in patients with 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, with 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 with GI obstruction**

### Relative potency: oral morphine

- Approximately 2:1 oral morphine to oxycodone oral dose ratio
Oxycodone Hydrochloride CR Tablets (OxyContin) Extended Release Tablets, con’t
10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80 mg

Key instructions

For Adults:
• Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in adult patients in whom tolerance to an opioid of comparable tolerance has been established.
• When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose.

For Pediatric Patients (11 years and older)
• For use only in opioid tolerant pediatric patients already receiving and tolerating opioids for at least five (5) consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least 2 days immediately preceding dosing with Oxycodon ER. Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage
• If needed, pediatric dose may be adjusted in 1 to 2 day intervals.
• When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% of the current daily dose.

IMPORTANT:
• Opioids are rarely indicated or used to treat pediatric patients with chronic pain.
• The recent FDA approval for this oxycodone formulation was NOT intended to increase prescribing or use of this drug in pediatric pain treatment. Review the product information and adhere to best practices in the literature.
Dosing interval

- Every 12 h

Key instructions

- Opioid-naïve 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/ ⅓-⅔ usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start w/ ½ 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
# Hydrocodone Bitartrate ER Capsules (Zohydro ER)

<table>
<thead>
<tr>
<th><strong>Dosing interval</strong></th>
<th>• Every 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key instructions</strong></td>
<td>• Initial dose in opioid non-tolerant patient is 10 mg</td>
</tr>
<tr>
<td></td>
<td>• Titrate in increments of 10 mg using a min of 3-7 d intervals</td>
</tr>
<tr>
<td></td>
<td>• Swallow capsules whole (do not chew, crush, or dissolve)</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>• Alcoholic beverages or medications containing alcohol may result in rapid release &amp; absorption of a potentially fatal dose of hydrocodone</td>
</tr>
<tr>
<td></td>
<td>• CYP3A4 inhibitors may increase hydrocodone exposure</td>
</tr>
<tr>
<td></td>
<td>• CYP3A4 inducers may decrease hydrocodone exposure</td>
</tr>
<tr>
<td><strong>Opioid-tolerant</strong></td>
<td>• Single dose &gt;40 mg or total daily dose &gt;80 mg for use in opioid-tolerant patients only</td>
</tr>
<tr>
<td><strong>Product-specific safety concerns</strong></td>
<td>• None</td>
</tr>
<tr>
<td><strong>Relative potency: oral morphine</strong></td>
<td>• Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio</td>
</tr>
</tbody>
</table>
## Naloxone (Narcan)

| Dosing interval | IM or SQ: onset 2-5 minutes, duration >45 min  
|                 | IV: onset 1-2 min, duration 45 minutes |
| Key instructions | Monitor respiratory rate  
|                   | Monitor level of consciousness for 3-4 hours after expected peak of blood concentrations  
|                   | Note that reversal of analgesia will occur |
| Drug interactions | Larger doses required to reverse effects of buprenorphine, butorphanol, nalbuphine, or pentazocine |
| Opioid-tolerant  | Assess signs and symptoms of opioid withdrawal, may occur within 2 min – 2 hrs  
|                  | Vomiting, restlessness, abdominal cramps, increased BP, temperature  
|                  | Severity depends on naloxone dose, opioid involved & degree of dependence |
| Product-specific safety concerns | Ventricular arrhythmias, hypertension, hypotension, nausea & vomiting  
|                                 | As naloxone plasma levels decrease, sedation from opioid overdose may increase |
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
CHRONIC PAIN, CHRONIC OPIOIDS: IS MY PATIENT ADDICTED?

ASAM Unit VII
Edwin Salsitz, MD, DFASAM
From: **Wide Variation in Controlled Substance Prescribing Patterns**

Complex Interactions

- Opioids
- Pain
- Addiction
Pain

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” (IASP 1994)

“Pain is whatever the experiencing person says it is, existing whenever he says it does.” (McCaffrey 1968)

“Pain is viewed as a biopsychosocial phenomenon that includes sensory, emotional, cognitive, developmental, behavioral, spiritual and cultural components.” (IASP website)
Addiction

Public Policy Statement:
Definition of Addiction  ASAM 2011
Short Definition of Addiction:

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.

This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.
Pain and Addiction

No Objective Measurements
Physical Dependence

“Physical dependence is the physiological adaptation of the body to the presence of an opioid. It is defined by the development of withdrawal symptoms when opioids are discontinued, when the dose is reduced abruptly or when an antagonist (e.g., naloxone) or an agonist-antagonist (e.g., pentazocine) is administered.”

“Physical dependence is a normal and expected response to continuous opioid therapy. Physical dependence may occur within a few days of dosing with opioids, although it varies among patients. Physical dependence (indicated by withdrawal symptoms) does not mean that the patient is addicted.”

Opioid Sites of Action in the Brain

- Anterior Cingulate Gyrus
- Prefrontal Cortex
- Nucleus Accumbens
- Arcuate Nucleus
- Amygdala
- Ventral Tegmental Area
- Locus Coeruleus
- Periaqueductal Gray Area
Substance Use Disorder  DSM-V

**Severity measured by number of symptoms; 2-3 mild, 4-6 moderate, 7-11 severe**

* These do not apply if the medication is prescribed
Pain and Addiction

Chronic Pain OR Addiction

- Depression and Anxiety
- Human Suffering
- Financial Problems
- Functional Disability
- Cognitive Disturbances
- Sleep Disturbances
- Secondary Physical Problems
- Family/Social Problems

Ann Quinlan-Colwell, PhD, PCSS-O Webinar 2011
Pain: Psychiatric Co-Morbidity

- 56 Articles (14D>P, 42P>D)
- 65% with Depression (Dep.) have significant Pain
- ~50% in Pain Clinic have Dep.
- Pain negatively affects Dep. Outcomes
- Dep. associated with decreased pain mgt.

Twelve-Month Prevalence of DSM-IV Independent Mood and Anxiety Disorders Among Respondents with DSM-IV Substance Use Disorders Who Sought Treatment in the Past 12 Months

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Respondents, % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any mood disorder</strong></td>
<td></td>
</tr>
<tr>
<td>Those With Any Drug Use Disorder</td>
<td>60.31 (5.86)</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td></td>
</tr>
<tr>
<td>Major Depression</td>
<td>44.26 (6.28)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>25.91 (5.19)</td>
</tr>
<tr>
<td>Mania</td>
<td>20.39 (5.17)</td>
</tr>
<tr>
<td>Hypomania</td>
<td>2.48 (1.67)</td>
</tr>
<tr>
<td><strong>Any anxiety disorder</strong></td>
<td>42.63 (5.97)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td></td>
</tr>
<tr>
<td>With agoraphobia</td>
<td>5.92 (2.19)</td>
</tr>
<tr>
<td>Without agoraphobia</td>
<td>8.64 (3.05)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>12.09 (3.48)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>22.52 (4.99)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>22.07 (5.18)</td>
</tr>
<tr>
<td>Any alcohol use disorder</td>
<td>55.16 (6.29)</td>
</tr>
</tbody>
</table>

*Data in parentheses are the percentages of respondents with the substance use disorders who sought treatment in the past 12 months.*
Pain and Addiction-Psychiatric Co-morbidity

Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use

Sullivan M.D., Arch Intern Med 2006;166:2087-2093


Odds Ratios: Major Depression—3.43  Dysthymia—6.51 Panic—5.37  GAD—2.56  Problem Drugs—3.57 Problem Alcohol—.73

Conclusion: Common mental health and drug disorders are associated with initiation and use of prescribed opioids. Attention to psychiatric disorders is important when considering opioid therapy
## Opioid Treatment for Pain: Risk of Addiction

<table>
<thead>
<tr>
<th>Voluminous literature including multiple systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates vary widely 0%-50%-- higher in those with addiction hx</td>
</tr>
<tr>
<td>Often not clear how the diagnosis of addiction is confirmed</td>
</tr>
<tr>
<td>Aberrant and Problematic Behaviors often considered to make a diagnosis of addiction</td>
</tr>
<tr>
<td>Diagnosis is often not clear when opioids are prescribed for pain by HCP—lack of education in addictive disease</td>
</tr>
<tr>
<td>Clinical expertise and individualization required. ASAM members uniquely qualified</td>
</tr>
</tbody>
</table>
Opioid Treatment for Pain: Risk of Addiction


Conclusions:
The results of this evidence-based structured review indicate that COT exposure will lead to abuse/addiction in a very small % of patients. This % can be dramatically decreased by preselecting CPPs for no previous/current hx of drug/alcohol abuse/addiction

- 24 studies COT, 26.2 mos. (n=2,507), average % addiction= 3.27%
- 17% of studies pre-selected for no current/past hx of addiction/abuse addiction in pre-selected 0.19% vs. 5.0% in non-selected
- Average % ADRBs =11.5% , pre-selected= 0.59%
- UDS, 5 studies n=15,442, ADRBs = 20% no opioid/other non-Rx opioid
- UDS, illicit drugs non-opioid, 14.5%

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Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Addiction

Martell, B. Ann Intern Med. 2007;146:116-127

Conclusion:

Opioids are commonly prescribed for chronic back pain and may be efficacious for short-term pain relief. Long-term efficacy (>16 weeks) is unclear. Substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24%.
Treating Pain in the Addicted Patient

- “Pain Patients with a coexisting SUD are among the most challenging patients in medicine.”
- Awareness of potential deception in pt’s history
- Universal Precautions
- ?? “Real Pain” may make opioids less rewarding/euphorogenic
- Screening Tests: ORT, SOAPP, others

- Untreated Pain is a trigger for relapse
- Address both pain and addiction
- Significant other to secure and dispense opioid meds
- Active recovery program
- UDS, pill counts, agreements, etc.

Treating Pain in the Addicted Patient, cont’d

UDS—consider using opioids without confusing metabolic conversions to other non-prescribed opioid analgesics: oxycodone → oxymorphone (hydromorphone, methadone)

No poppy seeds

Opioid agreement

Avoid other potentially abusable medications: benzos, hypnotics, muscle relaxants, etc

Identify and treat psychiatric co-morbidity—common in both

This review does not discuss the management of pain, requiring chronic opioids, in the context of active or ongoing addiction.

Treating Pain in the Addicted Patient, cont’d

Methadone—FDA approved for both pain and addiction

Addiction dosing q 24 hours: Analgesic dosing q 6-8 hours

MMTPs/OTPs not authorized to treat pain

MMTPs not able to provide 3-4 doses per day for pain/addiction

MMTPs “take homes” take time

Prescribing methadone for addiction not legal—CSA

Buprenorphine pharmacotherapy: formulations approved for addiction and for pain. OBOT waived physicians

Judicious use of non-opioid medications

Psychosocial modalities: MI, CBT, Acupuncture, Meditation, etc.

Wachholtz, et al. Substance Abuse and Rehabilitation 2011:2 145--162
Pain and Addiction – ASAM REMS

Physical Dependence Does Not Necessarily Equal Addiction
“Dependence on opioid pain treatment is not, as we once believed, easily reversible; it is a complex physical and psychological state that may require therapy similar to addiction treatment, consisting of structure, monitoring, and counseling, and possibly continued prescription of opioid agonists. Whether or not it is called addiction, complex persistent opioid dependence is a serious consequence of long term pain treatment that requires consideration when deciding whether to embark on long term opioid pain therapy as well as during the course of such therapy.”
Pain and Addiction – ASAM REMS

Aberrant/Problematic Behavior

Does Not Necessarily Equal

Addiction

Does Not Necessarily Equal
Pain and Addiction – ASAM REMS

Chronic Pain

Does Not Necessarily Equal

Suffering

Does Not Necessarily Equal

Chronic Pain

Suffering
Treatment of Opioid Addiction

Medication Assisted: Therapy, Treatment, Recovery

Opioid Full/Partial Agonist Therapy: Methadone, Buprenorphine

Opioid Antagonist Therapy: Naltrexone Tablets and Depot I.M.

Medication Plus Psychosocial

Drug Free Recovery-Initially or Post-Medication
Conclusions: Known Knowns & Unknowns

- De Novo Iatrogenic addiction 0 – 50%
- Aberrant/Problematic Behaviors are common ~ 20%
- Risks are highest in those with current/past history of addiction – Multidisciplinary Team
- Monitoring patients, using Universal Precautions is helpful
- Follow the FSMBs guidelines to avoid any regulatory problems

- Is it a “Pain Case Gone Bad” or Addiction—often Grey Zone
- Suffering is common: “Terribly Sad Life Syndrome”*
- Challenging Clinical Cases—Requires Individualization Tx
- Buprenorphine: Therapeutic Option – Pain and Addiction**

Opioid Therapy for Chronic Pain in the United States: Promises and Perils

- 12 week studies: pain reduced 30% vs placebo
- Functional Improvement ±
- Majority of patients stop opioids: -efficacy + Aes
- COT: Less likely to return to work
- Patients with SUD or Mental Health Disorders are More likely to receive Long Term COT
- >90 days COT > long term: >120mgME > misuse
- “Adverse Selection” - The likelihood of a patient receiving COT increases as the associated risks increase

Sullivan, Howe: Pain, 154 (2013) S94-S100
Opioid Prescribing After Nonfatal Overdose and Association With Repeated Overdose


- Retrospective Cohort Study  n=2848   2000-2012
- Week before OD mean MED ↑ 187mg from 160mg (mean dose)
- 91% received 1 or more Opioid Rx after OD
- 1/3 receiving > 100mg MED per day after OD
- 7% had repeat OD (dose related)
- 70% Post OD Rx from same prescriber as before OD
- 7% received Buprenorphine Rx after OD
- 56% Benzo Rx before OD,   58% Benzo Rx after OD
- 59% Mental Health Dx in 90 days before OD
- 41% Substance Use Disorder in 90 days before OD
- 9% had a Dx of Drug Withdrawal 30 days after OD
Principle of Balance

**Dual obligation of governments and HCPs:**

- Establish system of controls to prevent abuse, misuse, & diversion of CS--opioids
- Ensure medical availability

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From: **Wide Variation in Controlled Substance Prescribing Patterns**
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