ER/LA OPIOID REMS:
Achieving Safe Use While Improving Patient Care

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

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DISCLOSURE:

It is the policy of the AAFP that all individuals in a position to control content disclose any relationships with commercial interests upon nomination/invitation of participation. Disclosure documents are reviewed for potential conflicts of interest and if identified, they are resolved prior to confirmation of participation. Only these participants who have no conflict of interest or who agree to an identified resolution process prior to their participation were involved in this CME activity.

Dr. Gianutsos has returned a form indicating that he has no affiliation or financial interest in any organization(s) that may have a direct interest in the subject matter of his CME presentation.

All other individuals in a position to control content for this activity have indicated they have no relevant financial relationships to disclose.
On July 9, 2012, the Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications.

Founded in June, 2010, the Collaborative on REMS Education (CO*RE), a 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-rem.org
Acknowledgement

Presented by the American Academy of Family Physicians, a member of the Collaborative on REMS Education (CO*RE), 10 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 Analgesics REMS Program Companies (RPC). Please see www.er-la-opioidREMS.com for a listing of the member companies.

This activity is intended to be fully compliant with the ER/LA Opioid Analgesics REMS education requirements issued by the U.S. Food & Drug Administration.
# Products Covered by this REMS

## Brand Name Products

- Avinza® morphine sulfate ER capsules
- Butrans® buprenorphine transdermal system
- Dolophine® methadone hydrochloride tablets
- Duragesic® fentanyl transdermal system
- *Embeda® morphine sulfate/naltrexone ER capsules
- Exalgo® hydromorphone hydrochloride ER tablets
- Kadian® morphine sulfate ER capsules
- Methadose™ methadone hydrochloride tablets
- MS Contin® morphine sulfate CR tablets
- Nucynta® ER tapentadol ER tablets
- Opana® ER oxymorphone hydrochloride ER tablets
- OxyContin® oxycodone hydrochloride CR tablets
- †Palladone® hydromorphone hydrochloride ER capsules

## Generic Products

- Fentanyl ER transdermal systems
- Methadone hydrochloride tablets
- Methadone hydrochloride oral concentrate
- Methadone hydrochloride oral solution
- Morphine sulfate ER tablets
- Morphine sulfate ER capsules
- Oxycodone hydrochloride ER tablets

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* Not currently available due to voluntary recall (still approved);
† No longer marketed (still approved)

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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
Rate of unintentional drug overdose deaths
United States, 1970–2007

* Per 100,000 population.
Scope of Opioid Mortality Epidemic

Number of unintentional drug overdose deaths
United States, 1999–2007

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

Prescription opioids are second only to marijuana in rates of new users for non medical reasons

In 2011,

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

In 2010,

425,247 ED visits involved nonmedical use of opioids

- Methadone involved in 30% of prescription opioid deaths

New Users of Specific Drugs Among Persons Age ≥ 12 (2011)

In 2009

39,147 Americans died from drug poisonings

Nearly 14,800 deaths involved prescription opioids

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

Learning Objectives

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

- Safely initiate therapy, modify dose, rotate opioids, and discontinue use of ER/LA opioid analgesics, applying best practices.

- Safely manage ongoing therapy with ER/LA opioid analgesics and properly use evidence-based tools while assessing for adverse effects.

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

- Understand general and product-specific information concerning ER/LA opioid analgesics and identify potential adverse effects of ER/LA opioids.
ASSESSING PATIENTS FOR TREATMENT WITH ER/LA OPIOID ANALGESIC THERAPY

Unit 1
Balance Risks Against Potential Benefits

Conduct thorough H&P and appropriate testing

**Potential benefits Include**

- Analgesia (adequate pain control)
  - Evidence regarding benefit of ER/LA opioid therapy for long term analgesia in chronic non cancer pain is limited
  - Average reduction in pain scores ~ 30%
- Improved Function
  - Evidence regarding benefit of ER/LA opioid therapy for improving function in chronic non cancer pain is limited

**Comprehensive benefit-to-harm evaluation**

**Risks Include**

- Overdose: ER/LA dosage units contain more opioid than IR drugs
- Abuse by patient or household contacts
- Misuse & addiction
- Physical dependence & tolerance
- Interactions w/ other medications & substances
- Inadvertent exposure 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.:

- Hepatitis
- HIV
- Tuberculosis
- Cellulitis
- STIs
- Trauma, burns
- Cardiac disease
- Pulmonary disease
Clinical Interview: Pain & Treatment History

Description of pain

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

What relieves the pain?

What causes or increases pain?

Effects of pain on physical, emotional, and psychosocial function

Patient’s pain & functional goals

Clinical Interview: Pain & Treatment History, cont’d

Pain Medications

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

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
- Neurologic exam
- Musculoskeletal Exam
  - Inspection
  - Palpation
  - Percussion
  - Auscultation
  - Provocative maneuvers
- Cutaneous or trophic findings

Assess Risk of Abuse, Including Substance Use & Psychiatric Hx

Obtain a complete Hx of current & past substance use

- Prescription drugs
- Illegal substances
- Alcohol & tobacco
  - While recent substance abuse does not prohibit treatment w/ ER/LA it is outside of the scope of primary care requires extensive monitoring & may require expert consultation/referral
- Family Hx of substance abuse & psychiatric disorders
- Hx of physical or sexual abuse

Social history also relevant

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

Intersection of Pain, Addiction and Mental Health Disorders

- Addiction
- Mental Health: Anxiety, Depression, PTSD, Axis 2
- Chronic Pain
Opioid guidelines and actual prescribing patterns

<table>
<thead>
<tr>
<th>Chronic opioid guidelines</th>
<th>Chronic opioid reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use chronic opioid therapy (COT) for intractable pain</td>
<td>• 3-4x more likely to be on chronic opioid therapy with depression or other mental health disorders (Braden 2009, Edlund 2010)</td>
</tr>
<tr>
<td>• Caution with substance abuse history</td>
<td>• 4-5x more likely: alcohol or non-opioid abuse history (Weisner 2009, Edlund 2010)</td>
</tr>
<tr>
<td>• Caution with mental health disorders</td>
<td>• 5-10x more likely: opioid abuse or dependence (Weisner 2009, Edlund 2010)</td>
</tr>
</tbody>
</table>

Chou et al The Journal of Pain, 10:2, 2009, 113-130
Characteristics of COT patients

• 30-40% recipients use sedative-hypnotics most days. 13% drink alcohol within 2 hours of opioid use (Saunders 2012)

• Opioid use concentrated (Edlund 2010):
  In commercially insured, 5% patients use 70% opioids
  In publicly insured, 5% patients use 48% opioids

• MH and SA disorders concentrated in high dose users (Morasco 2010, Seal 2012, Kobus 2012, Merrill 2012)

• Patients with MH and SA disorders are more likely to receive:
  • Higher daily doses, high potency Schedule II opioids
  • Concurrent sedative-hypnotics (Saunders 2012)
Adverse Selection

Adverse selection is the practice of prescribing opioids more commonly and at higher doses to the highest risk population.

Why does adverse selection occur?

- Providers want to help patients in pain but may have few tools other than Rx pad.
- Patients with MH and SA disorders and multiple pain problems may be more distressed and more persistent in demanding opioid initiation and dose increases.

Assess Risk Carefully

**Be knowledgeable about risk factors for opioid abuse**
- Personal or family Hx of alcohol or drug abuse
- Presence of psychiatric conditions
- Younger age

**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 UDT**
- Understand limitations

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## Risk Assessment Tools: Examples

<table>
<thead>
<tr>
<th>Tool</th>
<th># of items</th>
<th>Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients considered for long-term opioid therapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORT</strong> Opioid Risk Tool</td>
<td>5</td>
<td>By patient</td>
</tr>
<tr>
<td><strong>SOAPP®</strong> Screener &amp; Opioid Assessment for Patients w/ Pain</td>
<td>24, 14, &amp; 5</td>
<td>By patient</td>
</tr>
<tr>
<td><strong>DIRE</strong> Diagnosis, Intractability, Risk, &amp; Efficacy Score</td>
<td>7</td>
<td>By clinician</td>
</tr>
<tr>
<td><strong>Characterize misuse once opioid treatments begins:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PMQ</strong> Pain Medication Questionnaire</td>
<td>26</td>
<td>By patient</td>
</tr>
<tr>
<td><strong>COMM</strong> Current Opioid Misuse Measure</td>
<td>17</td>
<td>By patient</td>
</tr>
<tr>
<td><strong>PDUQ</strong> Prescription Drug Use Questionnaire</td>
<td>40</td>
<td>By clinician</td>
</tr>
<tr>
<td><strong>Not specific to pain populations:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CAGE-AID</strong> Cut Down, Annoyed, Guilty, Eye-Opener Tool, Adjusted to Include Drugs</td>
<td>4</td>
<td>By clinician</td>
</tr>
<tr>
<td><strong>RAFFT</strong> Relax, Alone, Friends, Family, Trouble</td>
<td>5</td>
<td>By patient</td>
</tr>
<tr>
<td><strong>DAST</strong> Drug Abuse Screening Test</td>
<td>28</td>
<td>By patient</td>
</tr>
<tr>
<td><strong>AUDIT</strong> Alcohol Use Questionnaire</td>
<td>Varies</td>
<td>By patient</td>
</tr>
</tbody>
</table>
# Opioid Risk Tool (ORT)

Mark each box that applies

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

Scoring Totals:

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
SOAPP®: Available in 4 Formats to Assess Misuse Risk

<table>
<thead>
<tr>
<th>SOAPP® 1.0 24Q version (original)</th>
<th>14Q version</th>
<th>5Q (short-form) version</th>
<th>SOAPP-R 24Q version (revised)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 questions (14 used to score tool)</td>
<td>14 questions*</td>
<td>5 questions*</td>
<td>24 questions</td>
</tr>
<tr>
<td>Add ratings for 14 &quot;screening&quot; questions</td>
<td>Add ratings for each question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 min. to complete 10 &quot;unscored&quot; questions provide background</td>
<td>&lt;8 min. to complete</td>
<td>&lt;5 min. to complete</td>
<td>&lt;10 min. to complete</td>
</tr>
</tbody>
</table>

*Questions from SOAPP V.1.0 Patients rate all questions on scale of 0-4
When to Consider a Trial of an Opioid

- Pain is moderate to severe
- *Failed to adequately respond to nonopioid & nondrug interventions*
- Continuous, around-the-clock opioid analgesic is needed for an extended period of time
- Potential benefits are likely to outweigh risks
- *Consider referral to pain or addiction specialist for patients where risks outweigh benefits*
- 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
• Active substance abuse disorder
• High potential risks relative to benefits (opioid therapy not 1st line for fibromyalgia)
• 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 a 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 1/4 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: Children

*For pediatric patients, <18 years:*

- Safety & effectiveness of most ER/LA opioids* unestablished
  - Pediatric analgesic trials pose challenges
- 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

* Transdermal fentanyl approved in children aged ≥2 yrs

Case:

Peter
25-Year-Old Male
Case:

Peter

New to area, presents at 4:45 PM on Friday

- Chronic left knee pain from a MVA 5 yrs ago
- Wants oxycodone ER & oxycodone IR for “rescue”

Hx

- 3 knee surgeries—last was 18 mo ago
- Persistent ambulatory dysfunction—granted disability
- Prior therapies: medications, supporting devices, & PT
  - Only oxycodone ER works
    - Allergic to acetaminophen & NSAIDs
    - Morphine & codeine make him throw up
  - PT sessions not helpful

Physical examination of knee

- No erythema, swelling, or bruising; surgical scars present
- Left quadriceps has signs of atrophy compared to right side
- Limited ROM on flexion of left knee
Peter: Assess Abuse Risk w/ 5-Q SOAPP

<table>
<thead>
<tr>
<th>How often:</th>
<th>Never=0</th>
<th>Seldom=1</th>
<th>Sometimes=2</th>
<th>Often=3</th>
<th>Very often=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have mood swings?</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you smoke a cigarette within an hr after you wake up?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>3. Have you taken medication other than the way that it was prescribed?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have you used illegal drugs (e.g., marijuana, cocaine) in past 5 yrs?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. In your lifetime, have you had legal problems or been arrested?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total Score: 7**

(Cutoff is 4)=high risk for prescription opioid misuse

After further questioning:
- Admits smoking 1 cigarette pack/d for 10 yrs
- Claims occasional marijuana use, not for last 2 yrs
Peter: Assess Abuse Risk

Ask for contact details of prior regular physician
  • No info w/ him—can get it on Monday if you give him a prescription now

Ask Peter to provide a urine sample for testing
  • He accuses you of not trusting him
  • Explain it is your office policy for a new patient being considered for a controlled substance
    – He goes with your nurse

Access your state’s PDMP: 6-month report
  • Received 28 prescriptions from 4 physicians, using 5 pharmacies
    – Left quadriceps has signs of atrophy compared to right side
  • Some paid for w/ insurance, others w/ cash
Peter: UDT & Results

POC immunoassay cup tests for THC, cocaine, opiates, methamphetamine, & amphetamine

- Only detects naturally occurring opiates—morphine & codeine
- **Semisynthetic oxycodone not reliably detected**
  - Included in some, but not all panels—always check

Peter’s test:
- POSITIVE for THC
- NEGATIVE for other substances

Sample sent to laboratory, w/ request for a pain management profile that includes oxycodone

- Adulterant panel, THC, cocaine, opiates, & oxycodone
Peter: What Now? Should You:

1. Write a 4-day supply of ER & IR oxycodone, to last until you contact his previous prescriber on Monday.

2. Not write a prescription today, since he lied about prescribers & drug use. Untreated addiction prevents you from addressing his pain; refer to a pain management physician w/ addiction expertise.

3. Write 30-day prescriptions for ER & IR oxycodone while you carry out diagnostic tests on his injury, obtain his prior medical records, & review test results.

Answer 2 is correct.
Peter: Case Summary

Several red flags raised:

- PDMP report revealed probable doctor shopping
- UDT positive for recent marijuana use, which he denied
- SOAPP score suggests risk for prescription drug misuse
- DEA identified modus operandi used by a drug-seeking patient
  - Wants appointment toward end of office hrs
  - Requests specific controlled substance
  - Claims nonopioid analgesics do not work or allergy
  - Reluctant to give name of primary physician
- Younger age

Peter may have a pain problem:

- Beyond your scope of practice to manage while his addiction is untreated
- Refer to pain management or addiction specialist
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/2106cfr.htm](http://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfr.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

May last from several weeks to months

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

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

ER/LA Opioid-Induced Respiratory Depression
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
- Some states have “Good Samaritan” laws allowing prescribing of naloxone to family, friends, caregivers

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

**Source:**
FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.
Initiating & Titrating: Non-Opioid Tolerant Patients

Drug & dose selection is critical

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

- Transdermal fentanyl, hydromorphone ER

Monitor patients closely for respiratory depression

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

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

Check ER/LA opioid product PI for minimum titration intervals

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

Initiating: Opioid-Tolerant Patients

*If opioid tolerant—no restrictions on which products can be used*

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

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

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Opioid Rotation

**Definition:**
Change from an existing opioid regimen to another opioid with 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 may 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

Mu Opioid Receptors & Incomplete Cross-Tolerance

Mu opioids bind to mu receptors

Many mu receptor subtypes:
Mu opioids produce subtly different pharmacologic response based on distinct activation profiles of mu receptor subtypes

May help explain:
Inter-patient variability in response to mu opioids
Incomplete cross-tolerance among mu opioids

Incomplete Cross-Tolerance

**Drug** | **Receptor Subtype Selectivity**
--- | ---
A | 1+3
B | 2+3
C | 1
D | 1+2+3

**Cross-tolerance if tolerant to drug:**

<table>
<thead>
<tr>
<th>Challenge drug:</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-</td>
<td>Partial</td>
<td>Partial</td>
<td>Yes</td>
</tr>
<tr>
<td>B</td>
<td>Partial</td>
<td>-</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>C</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>Partial</td>
<td>Partial</td>
<td>Partial</td>
<td>-</td>
</tr>
</tbody>
</table>

Reasons for Opioid Rotation

Poor opioid responsiveness:
- Dose titration yields intolerable/unmanageable AEs
- Poor analgesic efficacy despite dose titration

Other potential reasons:
- Patient desire or need to try a new formulation
- Cost or insurance issues
- Adherence issues
- Concern about abuse or diversion
- Change in clinical status requires an opioid with different PK
- Problematic drug-drug interactions

References:
Equianalgesic Doses

Opioid rotation requires calculation of an approximate equianalgesic dose

Equianalgesic doses 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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral</th>
<th>Parenteral</th>
<th>Conversion ratio to oral morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
<td>10 mg</td>
<td>Parenteral morphine: <strong>3 times</strong> as potent as oral morphine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg</td>
<td>NA</td>
<td>Oral oxycodone: ~<strong>1.5 times</strong> as potent as oral morphine</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>20 mg</td>
<td>NA</td>
<td>Oral hydrocodone: ~<strong>1.5 times</strong> as potent as oral morphine</td>
</tr>
</tbody>
</table>
| Hydromorphone| 7.5 mg| 1.5 mg     | Oral hydromorphone: ~**4-7 times** as potent as oral morphine  
Parenteral hydromorphone: **20 times** as potent as oral morphine |
| Fentanyl     | NA    | 15 mcg/hr  | Transdermal fentanyl: ~**80 times** as potent as morphine (based on studies converting from morphine to fentanyl) |

Periyakoil V. End of Life Online Curriculum. *Pain control: opioid conversion module*  

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Limitations of EDTs

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

Did Not Consider

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

Utilizing Equianalgesic Doses

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

Equianalgesic dose a starting point for opioid rotation

**Intended as General Guide**

- Calculated dose of new drug based on EDT must be reduced, then titrate the new opioid as needed
- Closely follow patients during periods of dose adjustments

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


Guidelines for Opioid Rotation

Calculate equianalgesic dose of new opioid from EDT

- Receiving a relatively high dose of current opioid regimen
- Elderly or medically frail

Select % reduction based on clinical judgment

- Closer to 50% reduction if patient is
- Does not have these characteristics
- Is switching to a different administration route of same drug

- Closer to 25% reduction if patient

Reduce calculated equianalgesic dose by 25%-50%*

*75%-90% reduction for methadone


Collaborative for REMS Education
If switching to **methadone**:  
- Reduce calculated equianalgesic dose by **75%-90%**  
- For patients on very high opioid doses (e.g., ≥1,000 mg morphine equivalents/d), be cautious converting to methadone ≥100 mg/d  
  - Consider inpatient monitoring, including serial EKG monitoring

If switching to **transdermal**:  
- **Fentanyl**, calculate dose conversion based on equianalgesic dose ratios included in the PI  
- **Buprenorphine**, follow instructions in the PI

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

Titrate new opioid dose to optimize outcomes & safety
Doses > 50-100 MED for chronic non cancer pain are not likely to be more effective in most patients than lower doses and are associated with greater risk of overdose and death

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
Guideline for Opioid Rotation: Summary

Values from EDT*

\[
\text{VALUE OF CURRENT OPIOID} \div \text{VALUE OF NEW OPIOID}
\]

Patient opioid values

\[
\text{24 HR DOSE OF CURRENT OPIOID} \div \text{X AMOUNT OF NEW OPIOID}
\]

“Solve” for X

\[
\text{EQUIALGESIC 24 HR DOSE OF NEW OPIOID}
\]

Automatically reduce dose

BY 25%-50%

Frequently assess initial response

Titrate dose of new opioid to optimize outcomes

Calculate supplemental rescue dose used for titration at 5%-15% of total daily dose‡

*If switching to transdermal fentanyl, use equianalgesic dose ratios provided in PI
†If switching to methadone, reduce dose by 75%-90%
‡If oral transmucosal fentanyl used as rescue, begin at lowest dose irrespective of baseline opioid

# 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>
<tbody>
<tr>
<td>• Disease progression or a new or unrelated pain</td>
<td>• Directed at cause of BTP or precipitating factors</td>
<td>• In chronic non cancer pain PRN IR opioids contribute to dose escalation and offer limited additive long-term benefit</td>
</tr>
<tr>
<td>• Change in psychosocial factors</td>
<td>• Nonspecific symptomatic therapies to lessen impact of BTP</td>
<td>• Nonopioid drug therapies</td>
</tr>
<tr>
<td>• Change in psychiatric condition</td>
<td></td>
<td>• Nonpharmacologic treatments</td>
</tr>
<tr>
<td>• Increased life stress</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case:

Wilma
73-Year-Old Female
Case:

Wilma

Advanced Colon Cancer

w/ peritoneal & liver metastases

Presents w/ increasing abdominal pain

Wakes frequently at night in severe pain

Regimen: oxycodone IR 5 mg q6h + 1 at bedtime

She has some considerations about opioids

Morphine means she’s about to “die” & methadone is for “addicts”

Does not like to take a lot of pills

Consider rotating to an ER/LA opioid: fewer pills & may allow her to sleep through the night

Her total current oxycodone dose is 25 mg/d

She is NOT opioid tolerant

Would require 30 mg oral oxycodone/d for a wk or longer

Morphine means she’s about to “die” & methadone is for “addicts”

Does not like to take a lot of pills

Consider rotating to an ER/LA opioid: fewer pills & may allow her to sleep through the night

Her total current oxycodone dose is 25 mg/d

She is NOT opioid tolerant

Would require 30 mg oral oxycodone/d for a wk or longer
Rotation Options for Wilma

No option for hydromorphone ER or transdermal fentanyl

Only for opioid-tolerant patients

Avoid morphine & methadone due to her resistance

Consider oxymorphone ER: calculate equianalgesic dose

20/10 = 25 mg/X
10x25 = 250 = 20X  \( X = 12.5 \text{ mg oxymorphone/d} \)

Reduce by 25% for safety = 9.4 mg oxymorphone ER/d

Wilma was on low dose of oxycodone so 25% reduction is reasonable

Start oxymorphone ER 5 mg q12h w/ oxycodone IR 5 mg PRN for BTP
Rotation Options for Wilma, cont’d

<table>
<thead>
<tr>
<th>Values from EDT</th>
<th>Patient opioid values</th>
<th>“Solve” for X</th>
<th>Automatically reduce dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALUE OF CURRENT OPIOID</td>
<td>24 HR DOSE OF CURRENT OPIOID</td>
<td>EQUINALGESIC 24 HR DOSE OF NEW OPIOID</td>
<td>BY 25% - 50%</td>
</tr>
<tr>
<td>VALUE OF NEW OPIOID</td>
<td>X AMOUNT OF NEW OPIOID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Educating Wilma to Take ER/LAs Safely

Advise Wilma to call
• Tomorrow to check in
• Any time to let you know . . .
  – If her pain worsens
  – She needs >2 doses of BTP medication/d
  – She experiences AEs

Caution Wilma*
• Store securely to prevent accidental exposure or theft
  – May result in serious harm/death (especially children) & can be abused
• Do not share w/ others
• Swallow whole: do not crush, chew, or dissolve
• Do not consume alcohol or use prescription or OTC products w/ alcohol
• Take Patient Counseling Document to any doctor visits

* Go over the Patient Counseling Document
Titrate Wilma’s Oxymorphone ER Dose

After 1 week, pain was improved, but still moderate

- She is reluctant to take oxycodone IR for BTP
- Steady-state plasma oxymorphone ER levels occur within 3 d
- Increase oxymorphone ER to 7.5 mg q12h w/ oxycodone IR for “emergencies”
- “Too many pills”
- Dosage may be adjusted every 3 to 7 d

Follow-up call the next day

- Pain was much improved
- Able to sleep through the night

Continue to re-evaluate analgesia & AEs
Wilma: Case Summary

Good candidate for rotation to an ER/LA opioid:
- Pain not well controlled
- Pain prevents her sleeping through the night
- Does not like to take a lot of pills

Choice of ER/LA opioid was limited:
- Not opioid tolerant so cannot rotate to hydromorphone ER or transdermal fentanyl
- Reluctant to take morphine or methadone

Educate:
- ER/LA opioids are harmful to people for whom they are not prescribed
- Safeguard her medications

Continue to monitor her & titrate if necessary
## Reasons for Discontinuing ER/LA Opioids

<table>
<thead>
<tr>
<th>No progress toward therapeutic goals</th>
<th>Intolerable &amp; Unmanageable AEs</th>
<th>Pain level decreases in stable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonadherence or unsafe behavior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1 or 2 episodes of increasing dose without prescriber knowledge</td>
<td>• Use of illicit drugs or unprescribed opioids</td>
<td></td>
</tr>
<tr>
<td>• Sharing medications</td>
<td>• Repeatedly obtaining opioids from multiple outside sources</td>
<td></td>
</tr>
<tr>
<td>• Unapproved opioid use to treat another symptom (e.g., insomnia)</td>
<td>• Prescription forgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Multiple episodes of prescription loss</td>
<td></td>
</tr>
</tbody>
</table>
# Taper Dose When Discontinuing

Taper dose to avoid withdrawal symptoms in opioid dependent patient

Recommend outpatient setting for patients without severe medical or psychiatric comorbidities

Recommend rehabilitation setting for patients unable to reduce opioid dose in less structured settings

- When aberrant drug-related behaviors continue, may need to enforce tapering efforts

May use a range of approaches from slow 10% dose reduction per week to more rapid 25%-50% reduction every few days

---

Taper Dose When Discontinuing, cont’d

Factors that influence the reduction rate:

- Reason for decision to discontinue the opioid
- Presence of medical & psychiatric comorbidities
- Dose
  - Initial rate more rapid at high doses (e.g., >200 mg/d morphine equivalent)
  - Slower rate at low doses (e.g., 60-80 mg/d morphine equivalent)
- Occurrence of withdrawal symptoms as taper is initiated

After taper, continue, substance use, or:

- Continue to treat pain w/ nonopioids & psychiatric disorders
- If aberrant behaviors may be due to addiction
  - Addiction treatment resources should be made available
  - Motivate patient to seek addiction treatment
Case:

Ernesto
53-Year-Old Male
Case:

Ernesto

Workplace back injury at age 41 causes chronic back pain

Partial diskectomy & subsequent L4-5 fusion

He continues to work in a modified position

Presents for follow-up medication management

Stable regimen of oxycodone ER 30 mg q12h + hydrocodone/acetaminophen IR 5 mg/500 mg q6h prn for BTP

You write prescriptions for oxycodone ER & hydrocodone IR

Ernesto states he rarely takes hydrocodone IR for BTP

Effectively controls his pain

Stress he safeguard medication in a locked medication safe

Not necessary in the last month

Has not filled a hydrocodone IR prescription for 6 months
His pain is perfectly controlled with oxycodone ER 30 mg q12h, which you continue to prescribe.

His low back condition has improved—may be possible to control pain with a lower dose of oxycodone ER.

His low back condition has improved—may no longer need around-the-clock treatment with oxycodone ER.

To determine course of action, initiate a trial taper:

1. Closely monitor pain and withdrawal symptoms.
2. No concerns about Ernesto seeking drugs or displaying aberrant behaviors, so a slow taper is appropriate.
3. Help prevent withdrawal symptoms.

No concerns about Ernesto seeking drugs or displaying aberrant behaviors, so a slow taper is appropriate.
Ernesto: Taper Schedule – Month 1

Current opioid dose is oxycodone 60 mg/d

Prescribe oxycodone ER 20 mg q12h (#60) + oxycodone IR 5 mg (#60) w/instructions:

<table>
<thead>
<tr>
<th>Day</th>
<th>Oxycodone ER 20 mg tablet</th>
<th>Oxycodone IR 5 mg tablet</th>
<th>Total daily dose (mg)</th>
<th>Call on day:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>20 mg q12h</td>
<td>q8h</td>
<td>55 (9% decrease)</td>
<td>2: pain controlled, no withdrawal symptoms</td>
</tr>
<tr>
<td>8-14</td>
<td>20 mg q12h</td>
<td>q12h</td>
<td>50 (9% decrease)</td>
<td>9: pain controlled, no withdrawal symptoms</td>
</tr>
<tr>
<td>15-28</td>
<td>20 mg q12h</td>
<td>q12h prn</td>
<td>40 (20% decrease if prn not used)</td>
<td>16: pain controlled, no withdrawal symptoms</td>
</tr>
</tbody>
</table>

Follow-up office visit
- Pain is well controlled
- Has not needed to use IR oxycodone
- No withdrawal symptoms
# Ernesto: Taper Schedule – Month 2

**Current dose is oxycodone 40 mg/d**

<table>
<thead>
<tr>
<th>Day</th>
<th>Oxycodone ER 10 mg tablet</th>
<th>Oxycodone IR 5 mg tablet</th>
<th>Total daily dose (mg)</th>
<th>Call on day:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>10 mg q12h</td>
<td>q12h</td>
<td>30 (25% decrease)</td>
<td>2: pain controlled, no withdrawal symptoms</td>
</tr>
<tr>
<td>8-14</td>
<td>10 mg q12h</td>
<td>q12h prn</td>
<td>20 (30% decrease if PRN not used)</td>
<td>9: pain controlled, no withdrawal symptoms</td>
</tr>
<tr>
<td>15-21</td>
<td>–</td>
<td>q8h</td>
<td>15 (25% decrease)</td>
<td>16: pain controlled, no withdrawal symptoms</td>
</tr>
<tr>
<td>22-30</td>
<td>–</td>
<td>q12h</td>
<td>10 (30% decrease)</td>
<td>23: pain controlled, no withdrawal symptoms</td>
</tr>
</tbody>
</table>

Prescribe oxycodone ER 10 mg q12h (#60) + oxycodone IR 5 mg (#90) w/ instructions:
Ernesto: Follow Up

Follow-up visit

- Pain well controlled & no withdrawal symptoms
- Replace scheduled oxycodone IR w/ oxycodone IR 5 mg (#30) as needed for pain if ibuprofen is not effective
- Instruct him to dispose of remaining oxycodone ER & hydrocodone IR

1-month follow-up visit

- Has not needed to use oxycodone IR
- Reports good function w/ no pain
- Reassure him if pain recurs, you will manage it
- Instruct him to dispose of remaining oxycodone IR
  - DEA National Prescription Drug Take Back Day
  - Check zip code at http://rxdrugdropbox.org/
  - Flush down toilet
### Ernesto: Case Summary

<table>
<thead>
<tr>
<th>Not needing BTP opioid suggests pain condition may have improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine if he no longer needs oxycodone ER or if a lower dose would be effective</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slow taper is appropriate, because there is no urgency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal: minimize withdrawal symptoms while assessing effect on pain</td>
</tr>
<tr>
<td>Engage patient during taper to monitor pain &amp; withdrawal symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dispose of unneeded medications from the home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure they are not available to children, pets, &amp; household acquaintances to avoid serious risks from unintended exposure</td>
</tr>
</tbody>
</table>
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