Internal Medicine Educational Conference

February Webinar
ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care

Featuring
Annette T. Carron, DO, CMD, FACOI, FAAHPM
and
Katherine E. Galluzzi, DO, CMD, FACOFP dist.

Evaluation:
http://scs.msu.edu/eval

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

Presented by CO*RE Collaboration for REMS Education
www.corerems.org

Faculty Information

Annette T. Carron, DO, CMD, FACOI, FAAHPM
Director of Geriatrics and Palliative Care
Botsford Hospital, Farmington Hills, MI
Assistant Clinical Professor, Internal Medicine
Michigan State University College of Osteopathic Medicine

DISCLOSURE:
Dr. Carron has nothing to disclose.

Faculty Information

Katherine E. Galluzzi, DO, CMD, FACOFP dist.
AOA Board-Certified Family Physician
Chairman, Department of Geriatrics
Philadelphia College of Osteopathic Medicine

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

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

www.core-rems.org

CO*RE Staff Disclosures

The following individuals disclose no relevant financial relationships:

- Debra Bisco, MD
- Professor of Family Medicine, University of California San Diego School of Medicine
- Richard Bower, MD
- Senior National Medical Director, Senior Health Services, Atrium, NC
- David Bottoms, MD
- Professor and Chair, Department of Osteopathic Medical Education, Philadelphia College of Osteopathic Medicine, Philadelphia, PA
- Alexia Burdick, MD
- Department of Neurology, University of Miami, Miller School of Medicine, Coral Gables, FL
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- Family physician and addiction medicine specialist, Permanente Medical Group, Sacramento, CA
- Harriett E. Scott, MD
- Staff, CO*RE Operations Team, Mayday TJ, Downers, CA
- Kevin Stinchcomb, DNP, APRN, FNP, FAAN
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- Amy Bowlin, DO
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- Clinical Associate Professor, University of Pennsylvania, Philadelphia, PA

Content Development/Planner/Reviewer Disclosures

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- Director, Opioid Prevention and Education, American Osteopathic Association
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- Executive Director, Interboro Postgraduate Medical Association, Malvern, PA
- Robert Reinhart, MD, MPH
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- Thomas Maracic, MD, PhD
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- Karen Reiner, MD
- President, National Postgraduate Medical Education, Denver, CO
The following individuals disclose one or more relevant financial relationships:

Charles Argoff, MD  
Professor of Neurology, Albany Medical College, Albany, NY  
Grant/research support consultant/honoraria: Nuvo Research, Covidien, Jazz Pharmaceuticals, Shinogi Pharmaceuticals, Depomed, Grunethal Pharmaceuticals, Insys Pharmaceuticals, Neurogesx, Millennium Laboratories, Quest Diagnostics, Cephalon, Amerigox, Forest Laboratories, Inflexxion Inc, Iroko Pharmaceuticals, King Pharmaceuticals, Lilly, Pfizer.

Debra Gordon, RN, DNP, FAAN  
Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA  
Consultant honorarium: American Pain Society

Brett Snodgrass, MSN, APRN, FNP-C  
Family Nurse Practitioner, Comprehensive Pain Management, Bartlett, TN  
Served as a speaker or a member of a speakers bureau for DepoMed, Inc.

Steven Stanos, DO  
Director, Corporate Pain Services, Rehabilitation Institute of Chicago; Attending Physician, Center for Pain Management; Assistant Professor, Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Chicago, IL  
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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

<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>• Butemor® 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>• Kadian® morphine sulfate ER capsules</td>
<td>• Oxycodone hydrochloride ER capsules</td>
</tr>
<tr>
<td>• Methadose™ methadone hydrochloride tablets</td>
<td>• Oxycodone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• MS Contin® morphine sulfate ER tablets</td>
<td>• Zohydro® hydrocodone bitartrate ER capsules</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>• Paladone® ER hydromorphone hydrochloride ER capsules</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>

* Not currently available due to voluntary recall (still approved); † No longer marketed (still approved)
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. For every 1 death there are: 10 treatment admissions for abuse; 32 ED visits for misuse or abuse; 83 people who abuse or are addicted; 9.6 nonmedical users.

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

Learning Objectives

- Describe appropriate patient assessment for treatment with ER/LA opioid analgesics, evaluating risks and potential benefits of ER/LA therapy, as well as possible misuse.
- Apply proper methods to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, applying best practices including accurate dosing and conversion techniques, as well as appropriate discontinuation strategies.
- Demonstrate accurate knowledge about how to manage ongoing therapy with ER/LA opioid analgesics and properly use evidence-based tools while assessing for adverse effects.
- Employ methods to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Review/assess general and product-specific drug information concerning ER/LA opioid analgesics and identifying potential adverse effects of ER/LA opioids.
Misuse, abuse, divergence and overdose of ER/LA opioids is a major public health crisis.

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

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

**Unit 1**

**Balance Risks Against Potential Benefits**

<table>
<thead>
<tr>
<th>Benefits Include</th>
<th>Comprehensive benefit-to-harm evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Analgesia (adequate pain control)*</td>
<td>* Overdose*</td>
</tr>
<tr>
<td>* Improved Function*</td>
<td>* Life-threatening respiratory depression*</td>
</tr>
<tr>
<td></td>
<td>* Abuse by patient or household contacts*</td>
</tr>
<tr>
<td></td>
<td>* Misuse &amp; addiction*</td>
</tr>
<tr>
<td></td>
<td>* Physical dependence &amp; tolerance*</td>
</tr>
<tr>
<td></td>
<td>* Interactions w/ other medications &amp; substances*</td>
</tr>
<tr>
<td></td>
<td>* Risk of neonatal withdrawal syndrome w/ prolonged use during pregnancy*</td>
</tr>
<tr>
<td></td>
<td>* Inadvertent exposure/ingestion by household contacts, especially children*</td>
</tr>
</tbody>
</table>
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
- Osm/Duration
- Variations / Patterns / Rhythms

What relieves the pain?

What causes or increases pain?

Effects of pain on physical, emotional, and psychosocial function

Patient’s pain & functional goals
Clinical Interview: Pain & Treatment History, cont'd

Pain Medications

<table>
<thead>
<tr>
<th>Past use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
</tr>
<tr>
<td>• Query state PDMP where available to confirm patient report</td>
</tr>
<tr>
<td>• Contact past providers &amp; obtain prior medical records</td>
</tr>
<tr>
<td>Dosage</td>
</tr>
<tr>
<td>• For opioids currently prescribed: opioid, dose, regimen, &amp; duration</td>
</tr>
<tr>
<td>• Important to determine if patient is opioid tolerant</td>
</tr>
</tbody>
</table>

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

Cutaneous or trophic findings

Neurologic exam

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

- Personal or family Hx of alcohol or drug abuse
- Younger age
- Presence of psychiatric conditions
- Assess potential risks associated w/ chronic opioid therapy
- Manage patients using ER/LA opioids based on risk assessment
- Understand limitations

Be knowledgeable about risk factors for opioid abuse
Understand & use addiction or abuse screening tools
Conduct a UDT

Risk Assessment Tools: Examples

<table>
<thead>
<tr>
<th>Tool</th>
<th># of items</th>
<th>Administered by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients considered for long-term opioid therapy:</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>Characterize misuse once opioid treatments begins:</td>
<td></td>
<td></td>
</tr>
<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>PDBQ Prescription Drug Use Questionnaire</td>
<td>40</td>
<td>clinician</td>
</tr>
<tr>
<td>Not specific to pain populations:</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>
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</table>

Opioid Risk Tool (ORT)

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family Hx of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2. Personal Hx of substance abuse</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>3. Age between 16 &amp; 45 yrs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. Hx of preadolescent sexual abuse</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5. Psychologic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADD, OCS, Bipolar, schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
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Administer
On initial visit
Prior to opioid therapy

Scoring (risk)

<table>
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<tr>
<th>Scoring Totals:</th>
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<tbody>
<tr>
<td>0-3: low</td>
</tr>
<tr>
<td>4-7: moderate</td>
</tr>
<tr>
<td>≥8: high</td>
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Screener & Opioid Assessment for Patients with Pain (SOAPP)®

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

**How is SOAPP® administered?**

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

**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>
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<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 “screening” questions</td>
<td>Add ratings for each question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score ≥12: high risk</td>
<td>Score ≥12: high risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-11: moderate risk</td>
<td>8-11: moderate risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8: low risk</td>
<td>≥8: low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥22: high risk</td>
<td>Score ≥4 increased risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-21: moderate risk</td>
<td>10-21: moderate risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤9: low risk</td>
<td>≤9: low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8 min. to complete</td>
<td>&lt;5 min. to complete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 min. to complete</td>
<td>&lt;10 min. to complete</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Questions from SOAPP V.1.0 Patients rate all questions on scale of 0-4

**SOAPP® Monitoring Recommendations.**


The SOAPP® Version 1.0 Tutorial.

https://painedu.org/soapp-tutorial_01.asp

SOAPP® Frequently Asked Questions.

https://painedu.org/soapp-development.asp

SOAPP® Version 1.0-SF

https://painedu.org

SOAPP® Version 1.0-14Q

https://painedu.org

SOAPP®-R

https://painedu.org

SOAPP® 1.0 24Q version (original) 14Q version 5Q (short-form) version 24 questions

Add ratings for 14 “screening” questions Add ratings for each question Score ≥12: high risk Score ≥4 increased risk Score ≥22: high risk ≥12: high risk 10-21: moderate risk ≤9: low risk 8-11: moderate risk ≤8: low risk 10 min. to complete <5 min. to complete <10 min. to complete

When to Consider a Trial of an Opioid

Potential benefits are likely to outweigh risks

Failed to adequately respond to nonopioid & nondrug interventions

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

Pain is chronic and severe

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

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

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

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

Selection of patients between these 2 extremes requires:
Careful assessment & characterization of patient risk
Structuring of care to match risk

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

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

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

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 AE?

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

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
Case:

Peter
25-Year-Old Male

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 therapeutic 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=9</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

After further questioning:
• Admits smoking 1 cigarette pack/d for 10 yrs
• Claims occasional marijuana use, not for last 2 yrs
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
- Examine 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

- **POC test positive for THC & negative for other substances**

- **Second 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 cocaine 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

Challenge: The Friday Afternoon Patient

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

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

Challenge: The Delayed Surgery

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.
Unit 1

Pearls for Practice

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

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

Unit II

Federal & State Regulations

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

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

State
- Database of state statutes, regulations, & policies for pain management
  www.medscape.com/resource/pain/opioid-policies
  www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management
**Initiating Treatment**

*Prescribers should regard initial treatment as a therapeutic trial*

- May last from several weeks to several months
- Decision to proceed w/ long-term treatment should be intentional & based on careful consideration of outcomes during the trial
- Progress toward meeting therapeutic goals
- Presence of opioid-related AEs
- Changes in underlying pain condition
- Changes in psychiatric or medical comorbidities
- Identification of aberrant drug-related behavior, addiction, or diversion

---

**ER/LA Opioid-Induced Respiratory Depression**

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

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

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

---

**ER/LA Opioid-Induced Respiratory Depression**

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

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

- **Drug & dose selection is critical**
  - Some ER/LA opioids or dosage forms are only recommended for opioid-tolerant patients
    - WHO strengths of transdermal fentanyl or hydromorphone ER
    - Certain strengths/formulations of other ER/LA products (check drug PI)

- **Monitor patients closely for respiratory depression**
  - Especially within 24-72 h of initiating therapy & increasing dosage

- **Individualize dosage by titration based on efficacy, tolerability, & presence of AEs**
  - Check ER/LA opioid product PI for minimum titration intervals
  - Supplement w/ IR analgesics (opioids & nonopioid) if pain is not controlled during titration

---

**Initiating: Opioid-Tolerant Patients**

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

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

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

---

**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:**

- 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

---

**Rationale:**

- 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

- **Cross-tolerance if tolerant to drug:**
  - **A** - Partial Partial Yes
  - **B** - Partial No Yes
  - **C** - Yes No - Yes
  - **D** - Partial Partial Partial -

---

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 w/ different PK
  - Problematic drug-drug interactions
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, DUA 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></td>
<td>SC/IV</td>
<td>PO</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>NA</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
</tr>
</tbody>
</table>
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
- Direction of switch from 1 opioid to another
- Inter-patient variability in pharmacologic response to opioids
- Incomplete cross-tolerance among mu opioids

Utilizing Equianalgesic Doses

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

Equianalgesic dose a starting point for opioid rotation

Intended as General Guide

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

Closely follow patients during periods of dose adjustments

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

Guidelines for Opioid Rotation

Reduce calculated equianalgesic dose by 25%-50% *

Select % reduction based on clinical judgment

- Receiving a relatively high dose of current opioid regimen
- Elderly or medically frail
- Does not have these characteristics
- Is switching to a different administration route of same drug

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

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

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

Guideline for Opioid Rotation Summary

- **Values from EDT**: Value of Current Opioid
- **Patient opioid values**: 24 Hr dose of Current Opioid, X Amount of New Opioid
- **“Solve” for X**: Equianalgesic 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**
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></td>
<td></td>
</tr>
<tr>
<td>• Directed at cause of BTP or precipitating factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nonspecific symptomatic therapies to lessen impact of BTP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• 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

Consider adding

Breakthrough Pain in Chronic Pain Patients

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 resistance to 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
No option for hydromorphone ER or transdermal fentanyl

Avoid morphine & methadone due to her resistance

Consider oxymorphone ER: calculate equianalgesic dose

\[
\begin{align*}
20/10 & = 25 \text{ mg} / X \\
10x25 & = 250 \text{ mg oxymorphone/d} \\
x & = 12.5 \\
\end{align*}
\]

W ilma 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

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

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

Values from EDT*

<table>
<thead>
<tr>
<th>Patient opioid values</th>
<th>&quot;Solve&quot; for X</th>
<th>Automatically reduce dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of Current Opioid</td>
<td>Value of New Opioid</td>
<td></td>
</tr>
<tr>
<td>24 Hr dose of Current Opioid</td>
<td>X Amount of New Opioid</td>
<td></td>
</tr>
<tr>
<td>Equianalgesic 24 Hr Dose of New Opioid</td>
<td>By 25% – 50%</td>
<td></td>
</tr>
</tbody>
</table>

* Go over the Patient Counseling Document

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
Collaborative for REMS Education

**Titrate Wilma’s Oxymorphone ER Dose**

**After 1 week, pain was improved, but still moderate**
- She is reluctant to take oxycodone IR for BTP – “too many pills”
- Steady-state plasma oxymorphone ER levels occur within 3 d
  - Dosage may be adjusted every 3 to 7 d
- Increase oxymorphone ER to 7.5 mg q12h w/ oxycodone IR for “emergencies”

**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**

**STOP**

**No progress toward therapeutic goals**

**Intolerable & Unmanageable AEs**

**Pain level decreases in stable patients**

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

**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
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

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 analgesics.
- Continue to treat 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
Ernesto

Case:

Workplace back injury at age 41 causes chronic back pain
- Partial disectomy & 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
  - Effectively controls his pain
- You write prescriptions for oxycodone ER & hydrocodone IR
  - Stress he safeguard medication in a locked medication safe
- Ernesto states he rarely takes hydrocodone IR for BTP
  - Not necessary in the last month
  - Has not filled a hydrocodone IR prescription for 6 months

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- Ernesto states he rarely takes hydrocodone IR for BTP
  - Not necessary in the last month
  - Has not filled a hydrocodone IR prescription for 6 months

Ernesto: What Now?

1. His pain is perfectly controlled w/ oxycodone ER 30 mg q12h, which you continue to prescribe
2. His low back condition has improved—may be possible to control pain w/ a lower dose of oxycodone ER
3. His low back condition has improved—may no longer need around-the-clock treatment w/ oxycodone ER

To determine course of action, initiate a trial taper:

- Closely monitor pain & withdrawal symptoms
- No concerns about Ernesto seeking drugs or displaying aberrant behaviors, so a slow taper is appropriate
- Help prevent withdrawal symptoms

Ernesto: Taper Schedule – Month 1

<table>
<thead>
<tr>
<th>Current opioid dose is oxycodone 60 mg/d</th>
<th>Prescribe oxycodone ER 20 mg q12h (+50) + oxycodone IR 5 mg (+40) w/ instructions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Oxycodone IR 20 mg tablet</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>1-7</td>
<td>20 mg q12h</td>
</tr>
<tr>
<td>8-14</td>
<td>20 mg q12h</td>
</tr>
<tr>
<td>15-28</td>
<td>20 mg q12h</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**

<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 pm</td>
<td>20 (20% 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>

**Ernesto: Follow Up**

- 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
- DEA National Prescription Drug Take Back Day
  - You enter his zip code at [http://rxdrugdropbox.org/](http://rxdrugdropbox.org/)
  - A prescription drug drop box is located in police department of the town in which he works
- Reassure him if pain recurs, you will manage it
- 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
- DEA National Prescription Drug Take-Back Day scheduled next Saturday

**Ernesto: Case Summary**

- Not needing BTP opioid suggests pain condition may have improved
- Determine if he no longer needs oxycodone ER or if a lower dose would be effective
- Slow taper is appropriate, because there is no urgency
- Goal: minimize withdrawal symptoms while assessing effect on pain
- Engage patient during taper to monitor pain & withdrawal symptoms
- Dispose of unneeded medications from the home
- Ensure they are not available to children, pets, & household acquaintances to avoid serious risks from unintended exposure
**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.

**Unit 2 Pearls for Practice**

- 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 equianalgesic dose, then reduce dose appropriately
- Discontinue ER/LA opioids slowly and safely
Informed Consent

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

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

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

Patient-Prescriber Agreement (PPA)

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

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

Reinforce expectations for appropriate & safe opioid use

- Obtain opioids from a single prescriber
- Fill opioid prescriptions at a designated pharmacy
- Safeguard opioids
  - Do not store in medicine cabinet
  - Keep locked (e.g., use a medication safe)
  - Do not share or sell medication
- Instructions for disposal when no longer needed
- Commitments to return for follow-up visits
- Comply w/ appropriate monitoring
  - E.g., random UDT & pill counts
- Frequency of prescriptions
- Enumerate behaviors that may lead to opioid discontinuation
- An exit strategy

Monitor Patients During Opioid Therapy

- Therapeutic risks & benefits do not remain static
- Affected by change in underlying pain condition, coexisting disease, or psychologic/social circumstances
- Identify patients
  - Who are benefiting from opioid therapy
  - Who might benefit more w/ restructuring of treatment or receiving additional services (e.g., addiction treatment)
  - Whose benefits from treatment are outweighed by risks
- Periodically assess continued need for opioid analgesic
- Re-evaluate underlying medical condition if clinical presentation changes

Monitor Patients During Opioid Therapy, contd

- 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

**Constipation**
- Most common AE; does not resolve with time
  - Initiate a bowel regimen before constipation develops
  - Increase fluid & fiber intake, stool softeners, & lubricants
  - Opioid antagonists may help prevent/treat opioid-induced bowel dysfunction

**Drowsiness & sedation**
- Tend to wane over time
  - Counsel patients about driving, work & home safety as well as risks of concomitant exposure to other drugs & substances w/ sedating effects

**Nausea & vomiting**
- Tend to diminish over days or weeks
  - Oral & rectal antemetic therapies as needed

**Pruritus & myoclonus**
- Tend to diminish over days or weeks
  - Treatment strategies for either condition largely anecdotal

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Monitor Adherence and Aberrant Behavior

**Routine 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)

Address Aberrant Drug-Related Behavior

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

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

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

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

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

Status of State PDMPs

PDMPs: Substances Monitored
This report may contain another person’s controlled substance information. Review the “Patients that Match Search Criteria” section below to ensure all prescriptions belong to the requested individual.

Search Criteria: (Last Name Begins ‘smith’ AND First Name Contains ‘john’) AND (D.O.B = ‘12/09/1965’ AND State = ‘CT’) AND Request Period = ‘08/11/2011’ to ‘02/18/2012’

Patients that match search criteria

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>JOHN SMITH</td>
<td>56 West First Street CT 06417</td>
<td>12/09/1965</td>
</tr>
<tr>
<td>JOHN SMITH</td>
<td>21 Hill Road Wallingford CT 06492</td>
<td>12/09/1965</td>
</tr>
<tr>
<td>JOHN SMITH</td>
<td>92 Pecan Dr Jurynia CT 06442</td>
<td>12/09/1965</td>
</tr>
<tr>
<td>JOHN SMITH</td>
<td>16 Forest St Haddam CT 06438</td>
<td>12/09/1965</td>
</tr>
</tbody>
</table>

Prescribers for prescriptions listed

<table>
<thead>
<tr>
<th>Prescriber</th>
<th>Address</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAV R169 RICHARD DAVIS Jones Family Practice 19 Peach St Durham CT 06422</td>
<td>10/14/11</td>
<td>632XX N CDXXX 04</td>
</tr>
<tr>
<td>NEU SH62 SHAUL NEUTON NP 12 Crescent Ave Derby CT 06418</td>
<td>12/20/11</td>
<td>221XX N ABXXX 04</td>
</tr>
</tbody>
</table>

Pharmacies that dispensed prescriptions listed

<table>
<thead>
<tr>
<th>Pharmacy</th>
<th>Address</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBA: CVS/PHARMACY #1100; 12 Swan St New Britain CT 06053</td>
<td>12/20/11</td>
<td>221XX N ABXXX 04</td>
</tr>
</tbody>
</table>

---

PDMP Unsolicited Patient Threshold Reports

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

E-mailed to prescribers to whom prescriptions were attributed

Prescribers review records to confirm it is your patient & you wrote the prescription(s) attributed to you

If inaccurate, contact PDMP

If you wrote the prescription(s), patient safety may dictate need to discuss the patient w/ other prescribers listed on report

• Decide who will continue to prescribe for the patient & who might address drug abuse concerns.
Rationale for Urine Drug Testing (UDT)

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

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

UDT frequency is based on clinical judgment

Depending on patient’s display of aberrant behavior and whether it is sufficient to document adherence to treatment plan

Check state regulations for requirements

Main Types of UDT Methods

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

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

Detecting Opioids by UDT

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

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

How long a person excretes drug &/or metabolite(s) at a concentration above a cutoff

Detection time of drugs in urine

<table>
<thead>
<tr>
<th>Drug in urine</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>≤3 d</td>
</tr>
<tr>
<td>THC (depending on grade &amp; frequency of use)</td>
<td>1-3 d, ≤30 d</td>
</tr>
<tr>
<td>– Single use</td>
<td></td>
</tr>
<tr>
<td>– Chronic use</td>
<td></td>
</tr>
<tr>
<td>Benzoylecgonine after cocaine use</td>
<td>2-4 d</td>
</tr>
<tr>
<td>Opiates (morphine, codeine)</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Methadone</td>
<td>≤3 d, ≤6 d</td>
</tr>
<tr>
<td>– EDDP (methadone metabolite)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines (depending on drug &amp; dose)</td>
<td>Days to wks</td>
</tr>
<tr>
<td>EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics of Urine: Assessing Specimen

<table>
<thead>
<tr>
<th>Specimen color related to concentration</th>
<th>Concentrated samples more reliable than dilute samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp within 4 min of voiding is 90-100°F</td>
<td></td>
</tr>
<tr>
<td>pH fluctuates within range of 4.5-8.0</td>
<td></td>
</tr>
<tr>
<td>Creatinine varies w/ hydration</td>
<td></td>
</tr>
<tr>
<td>Normal urine: 20 mg/dL. Dilute creatinine: 20 mg/dL &amp; specific gravity ≤1.000</td>
<td></td>
</tr>
<tr>
<td>Creatinine ≤2 mg/dL not consistent w/ human urine</td>
<td></td>
</tr>
</tbody>
</table>
**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

**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

---

**Interpretation of UDT Results, cont'd**

**Be aware**

**Testing technologies & methodologies evolve**
- Cross-reactivity patterns
- Maintain list of all patient's prescribed & OTC drugs
- Cutoff levels

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

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

**Differences exist between IA test menu panels vary**
- Morphine 3 to 10 µg/mL

**Be aware**

**Examples of Metabolism of Opioids**

- **Codeine** → **Morphine** → **6-MAM** → **Heroin**
  - 6-MAM = 6-monoacetylmorphine
  - t₁/₂ = 25-30 min
  - t₁/₂ = 3-5 min
- **Hydromorphone**
- **Hydrocodone**
- **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/TreatmentFacilitiesSearch.aspx

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.”

**Red Flag:** Patient refuses to consider non-opioid treatment options

**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.

**Pearls for Practice**

Anticipate and Treat Common Adverse Effects
Use Informed Consent and Patient Provider Agreements
Use UDT and PDMP as Valuable Sources of Data About your Patient

*However, know their limitations*

Monitor Patient Adherence, Side Effects, Aberrant Behaviors, and Clinical Outcomes
Refer Appropriately if Necessary
Use Patient Counseling Document to help counsel patients

Download:

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


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

Prescribers should report serious AEs to the FDA:
www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf or 1-800-FDA-1088

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

Explain
- Importance of adherence to dosing regimen, handling missed doses, & contacting their prescriber if pain cannot be controlled

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Warn Patients

Never break, chew, or crush 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

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

• Discuss how to safely taper the dose when discontinuing

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

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WARN!!

A person who at first only seems to be overmedicated may get much worse. They should be kept awake & watched closely.

If a child or pet ever swallows an opioid that was not prescribed for them, it is always an emergency. Call 911 immediately.

Overdose Poisoning - Call Emergency Services

1-800-222-1222

1-800-Safety-2585 (1-800-728-3735)

Optional Slide

Signs to Watch For - Overmedication (or Oversedation) (Share this slide with your caregiver)

• Irritated behavior - confusion, slurred speech, stumbling
• Feeling dizzy or faint
• Feeling or acting very drowsy, grumpy, or having off to sleep
• Unusual restlessness, pacing, or moving during sleep
• Difficulty waking up then sleep and becoming alert or staying awake

Overmedication Warning - Call Healthcare Provider

1-800-Safety-2585 (1-800-728-3735)

• Person cannot be aroused or awakened, or is unable to talk if awakened
• Any trouble with breathing, such as shortness of breath, slow or fast breathing, or stopped breathing
• Grunting noises coming from mouth or throat
• Body is limp, seems relaxed, face is pale, clammy
• Fingernails or toe nails turn blue/purple
• Skin or unusual heartbeat or stopped heartbeat

1-800-Safety-2585 (1-800-728-3735)

WARNING!

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Overdose Poisoning - Call Emergency Services

1-800-222-1222

1-800-Safety-2585 (1-800-728-3735)
Consider Prescribing Naloxone

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

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

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

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

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

Protecting the Community

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

Source of Most Recent Rx Opioids Among Past-Year Users (2011-2012)

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

- **Rx medicines should only be taken when prescribed to you by a provider**
  - Taking a pill prescribed for someone else is drug abuse and illegal, "even just once".
- **Misusing Rx drugs can be as dangerous as illegal "street" drugs**
- **Mixing Rx opioids w/ alcohol or w/ sedatives / hypnotics is potentially fatal**

**Parents Should Set Good Examples & Educate Teens**

**Parent Survey**

- 45% of parents have taken pain medications w/o a prescription at some point
- 14% have given their children pain medications w/o a prescription

**Teen Survey**

- Teens continue to report that their parents do not talk to them about the risks of prescription drugs at the same levels of other abused substances

**Substances Parents Have Discussed With Teens**

- Beer/alcohol: 81%
- Marijuana: 77%
- Cocaine: 50%
- Rx pain reliever w/o doctor’s Rx: 23%
- Any Rx drug used w/o doctor’s Rx: 23%
- Heroin: 22%
- Ecstasy: 21%
- Methamphetamine: 21%
- Non-Rx cold/cough medicine to get high: 18%
- Steroids w/o doctor’s Rx: 15%
- Inhalants: 54%

As reported by teens.
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

**Step Two: Secure**
- Do not store prescription meds in the medicine cabinet
- Keep meds in a safe place (e.g., locked cabinet)
- Tell relatives, especially grandparents, to lock meds or keep in a safe place
- Encourage parents of your teen's friends to secure meds

**Step Three: Dispose**
- Take inventory of all prescription drugs in your home
- Discard expired or unused meds

---

**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 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
    - Distributor
    - Reverse distributor
    - Retail or hospital/clinic pharmacy
      - Including long-term care facilities

Last DEA National Prescription Drug Take-Back Day on September 27, 2014
Other Methods of Opioid Disposal

- Take drugs out of original containers
- Mix with 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

Prescription Drug Disposal

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

Case:

Anne
47-Year-Old Female
Case:

Anne

Anne has ovarian cancer

- Stable disease based on recent imaging
- Stable pain management for 1 yr w/hydromorphone ER 12 mg q24h
- Last 2 months she asked for a renewal prescription 5-7 days early
- "None considered did not feel she was responding rapidly"
- She reports no change in her pain control
- Current regimen is still effective
- Last 2 months she asked for a renewal prescription 5-7 days early
- When questioned did not realize she was requesting refills early

Query your state PDMP: she has not been doctor shopping

Collect urine sample: send to lab for pain management panel that includes hydromorphone, opiates, & drugs of abuse

Anne: What Would You Do Next?

1. Refuse to give her a refill until the "correct" time
2. Make her next prescription for only 2 weeks & have her bring in her pill bottles for a count at next visit
3. Ask where she keeps her medications & how she secures them

Answer 3 is correct

Anne: Interview

Anne reports that she keeps her medications in her purse on top of the refrigerator

Further questioning reveals that her niece & nephews have recently visited her home more often than usual
Anne: What Now? Should You:

1. Only prescribe 2 wks of hydromorphone ER at a time & request she brings in her prescription bottles for pill counts at each visit
2. Stress to her the safety concerns when ER/LA opioids are taken by someone for whom they are not prescribed; request she brings her prescription bottles for pill count next visit
3. Call the police

Answer 2 is correct

Anne: Case Summary

Explain to Anne:
- ER/LA opioids are extremely harmful—can be fatal w/ just 1 dose—if taken by someone other than the patient
- She is responsible for storing medication in a safe & secure place away from children, family members, & visitors
- If she cannot safeguard her medications, you will consider an alternative therapy

You will not provide early renewal of prescription again

At the next visit:
- UDT positive for hydromorphone (negative other drugs)
- Anne reports she:
  - Purchased a medication safe that same day
  - Counts her medication daily
  - Spoke to her sister regarding concerns about her niece/nephew

Challenge: The Offended Patient

Red Flag:
You decide not to request routine risk assessment for fear of creating conflict

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.

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**Unit 4**

**Pearls for Practice**

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!

---

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

**Unit V**
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
- **Constipation** is the most common long-term AE
- Can be immediately life-threatening
- Should be anticipated

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

- CNS depressants can potentiate sedation & respiratory depression
- Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol
- Use w/ MAOIs may increase respiratory depression
- Certain opioids w/ MAOIs can cause serotonin syndrome
- Methadone & buprenorphine can prolong QTc interval
- 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 equivalent 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.

Continually re-evaluate to assess maintenance of pain control & emergence of AEs.

Do not abruptly discontinue.

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.

Common Drug Information for This Class

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

Dosage reduction for hepatic or renal impairment:
See individual drug PI.

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

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- Intended as general guide.
- Follow conversion instructions in individual PI.
- Incomplete cross-tolerance & inter-patient variability require conservative dosing when converting from 1 opioid to another.
- Have calculated comparable dose & titrate new opioid as needed.
Transdermal Dosage Forms
Do not cut, damage, chew, or swallow

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

Exertion or exposure to external heat can lead to fatal overdose.

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 & precipitate withdrawal.

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

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><strong>Key instructions</strong></td>
<td><strong>Use in opioid-tolerant patients</strong></td>
<td><strong>Product-specific safety concerns</strong></td>
<td><strong>Relative potency to morphine</strong></td>
</tr>
<tr>
<td><strong>Specific information about product conversions, if available</strong></td>
<td><strong>Specific drug interactions</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For detailed information, refer to online PI: DailyMed at [www.dailymed.nlm.nih.gov](http://www.dailymed.nlm.nih.gov) Drugs@FDA at [www.fda.gov/drugs@fda](http://www.fda.gov/drugs@fda)

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### 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

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### 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 site 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 antiarythmics, 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**
- Equi potency 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 to 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 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

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**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)

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

### 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

### Product-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)

### 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
- 7-hi infections (e.g., spina bifida) may increase absorption/exposure of morphine by ~2-fold

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

### Product-specific safety concerns
- None
Hydromorphone Hydrochloride ER Tablets (Exalgo)

**Dosing Interval**: Once a day

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

**Drug Interactions**: None

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

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

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

Morphine Sulfate ER Capsules (Kadian)

**Dosing Interval**: Once a day or every 12 h

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

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

**Opioid-tolerant**: 100 mg & 200 mg capsules for use in opioid-tolerant patients only

**Product-specific safety concerns**: None

Morphine Sulfate CR Tablets (MS Contin)

**Dosing Interval**: Every 8 h or every 12 h

**Key Instructions**
- Product information recommends not using as first opioid
- Titrate using a minimum of 1-2 d intervals
- Swallow tablets whole (do not chew, crush, or dissolve)

**Drug Interactions**
- P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold

**Opioid-tolerant**: 100 mg & 200 mg tablet strengths for use in opioid-tolerant patients only

**Product-specific safety concerns**: None
Tapentadol ER Tablets (Nucynta ER)

Dosing interval
- Every 12 h

Key instructions
- 50 mg every 12 h is initial dose in opioid non-tolerant patients
- Titrate by 50 mg increments using minimum of 5-d intervals
- MDD: 500 mg
- Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time; sufficient water to ensure complete swallowing immediately after placing in mouth
- Dose ceased in moderate hepatic impairment (100 mg/d max)
- Avoid use in severe hepatic & renal impairment

Drug interactions
- Alcohol or medications with alcohol may result in rapid release & absorption of a potentially fatal dose of tapentadol
- Contraindicated in patients taking MAOIs

Opioid-tolerant
- No product-specific considerations

Product-specific safety concerns
- Risk of serotonin syndrome
- Angio-edema

Relative potency: oral morphine
- Equipotency to oral morphine has not been established

Oxymorphone Hydrochloride ER Tablets (Opana ER)

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

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

Drug interactions
- Alcohol or medications with alcohol may result in absorption of a potentially fatal dose of oxymorphone

Opioid-tolerant
- No product-specific considerations

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

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

Oxycodone Hydrochloride CR Tablets (OxyContin)

Dosing interval
- Every 12 h

Key instructions
- Initial dose in opioid non-tolerant patients: 10 mg every 12 h
- Titrate using a minimum of 1-2 d intervals
- Hepatic impairment: start w/ ½ usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage
- Consider other analgesics in patients w/ difficulty swallowing or underlying GI disorders that predispose to obstruction: Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time; sufficient 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 = 80 mg or total daily dose = 320 mg for use in opioid-tolerant patients only

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

Relative potency: oral morphine
- Approximately 2:1 oral morphine to oxycodone oral dose ratio
### Oxycodeone Hydrochloride/Naloxone Hydrochloride ER Tablets (Targiniq 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>- Opioid-naive patients: initiate treatment w/ 10mg/5mg every 12 h.</td>
</tr>
<tr>
<td></td>
<td>- Titrate using min of 1-2 d intervals</td>
</tr>
<tr>
<td></td>
<td>- Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h)</td>
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<tr>
<td></td>
<td>- May be taken w/ or without food</td>
</tr>
<tr>
<td></td>
<td>- Swallow whole. Do not chew, crush, split, or dissolve; this will release oxycodone (possible fatal overdose) &amp; naloxone (possible withdrawal)</td>
</tr>
<tr>
<td></td>
<td>- Hepatic impairment: contraindicated in moderate-severe impairment. In patients w/ mild impairment, start w/ 1/3-1/2 usual dosage</td>
</tr>
<tr>
<td></td>
<td>- Renal impairment (creatinine clearance &lt;60 mL/min): start w/ 1/2 usual dosage</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>- CYP3A4 inhibitors may increase oxycodone exposure</td>
</tr>
<tr>
<td></td>
<td>- CYP3A4 inducers may decrease oxycodone exposure</td>
</tr>
<tr>
<td><strong>Opioid-tolerant</strong></td>
<td>Single dose &gt;40 mg/20 mg or total daily dose of 80 mg/40 mg for opioid-tolerant patients only</td>
</tr>
<tr>
<td><strong>Product-specific safety concerns</strong></td>
<td>- Contraindicated in patients w/ moderate-severe hepatic impairment</td>
</tr>
<tr>
<td><strong>Relative potency to oral morphine</strong></td>
<td>See individual PI for conversion recommendations from prior opioids</td>
</tr>
</tbody>
</table>

### 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>- Alcohol 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 to oral morphine</strong></td>
<td>Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio</td>
</tr>
</tbody>
</table>

### 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
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

Evaluation:
http://scs.msu.edu/eval