Opioid Prescribing: Safe Practice, Changing Lives

Presented by CO*RE
Collaboration for Relevant Education
www.core-rem.s.org
Faculty Information

Bio:
Alan Agins received a Masters in Pharmacology & Toxicology and a Ph.D. in Pharmaceutical Sciences from the University of Rhode Island. He has held faculty appointments at Brown University Medical School, Northeastern University School of Pharmacy and University of Virginia School of Nursing. During his tenure at Brown, Dr Agins was the recipient of the Dean’s Teaching Excellence Award for five consecutive years. Over the past twenty years, Dr. Agins has lectured nationally on all topics of pharmacology to more than 85,000 advanced practice clinicians and allied healthcare professionals. Dr Agins developed and runs his own continuing education website, Pharmacology One-on-One (pharm1on1.com) which became the blueprint for the NPHF-CORE.com website – a source for streaming video of this course with video as well as pertinent links and other information.

DISCLOSURE:
This speaker has no conflicts of interest to disclose
Faculty Information

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Jody Agins received her MSN/Family Nurse Practitioner from the University of Kansas and is board certified by the ANCC in Family Practice and Gerontology. She is the founder, Executive Director and a practicing NP for Collaborative Medical Provider Group (PLLC), a consortium of private-practice clinicians in Tucson, AZ. Jody is also the Clinical Services Director for Agape Hospice and Palliative Care and is a primary care provider for CareMore Touch. In addition, she serves as a clinical preceptor for Family and Geriatric Nurse Practitioner students for a number of universities in Arizona. Mrs. Agins is also a nationally invited speaker and is a faculty presenter for the Collaborative on REMS Education programs through the Nurse Practitioner Healthcare Foundation.

DISCLOSURE:

This speaker has no conflicts of interest 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
## Founding Partners
- American Pain Society (APS)
- American Academy of Hospice and Palliative Medicine (AAHPM)
- American Association of Nurse Practitioners (AANP)
- American Academy of Physician Assistants (AAPA)
- American Osteopathic Association (AOA)
- American Society of Addiction Medicine (ASAM)
- California Academy of Family Physicians (CAFP)
- Healthcare Performance Consulting (HPC)
- Interstate Postgraduate Medical Association (IPMA)
- Nurse Practitioner Healthcare Foundation (NPHF)

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

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<th>Position/Institution</th>
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</table>
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Presented by the Nurse Practitioner Healthcare Foundation, a member of the Collaborative on REMS Education (CO*RE), 13 interdisciplinary organizations working together to improve pain management and prevent adverse outcomes.

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

<table>
<thead>
<tr>
<th>Brand Name Products</th>
<th>Generic Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Avinza® morphine sulfate ER capsules</td>
<td>• Fentanyl ER transdermal systems</td>
</tr>
<tr>
<td>• Butrans® buprenorphine transdermal system</td>
<td>• Methadone hydrochloride tablets</td>
</tr>
<tr>
<td>• Dolophine® methadone hydrochloride tablets</td>
<td>• Methadone hydrochloride oral concentrate</td>
</tr>
<tr>
<td>• Duragesic® fentanyl transdermal system</td>
<td>• Methadone hydrochloride oral solution</td>
</tr>
<tr>
<td>• Embeda® morphine sulfate/naltrexone ER capsules</td>
<td>• Morphine sulfate ER tablets</td>
</tr>
<tr>
<td>• Exalgo® hydromorphone hydrochloride ER tablets</td>
<td>• Morphine sulfate ER capsules</td>
</tr>
<tr>
<td>• Hysingla® ER (hydrocodone bitartrate) ER tablets</td>
<td>• Oxycodone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• Kadian® morphine sulfate ER capsules</td>
<td></td>
</tr>
<tr>
<td>• Methadose™ methadone hydrochloride tablets</td>
<td></td>
</tr>
<tr>
<td>• MS Contin® morphine sulfate CR tablets</td>
<td></td>
</tr>
<tr>
<td>• Nucynta® ER tapentadol ER tablets</td>
<td></td>
</tr>
<tr>
<td>• Opana® ER oxymorphone hydrochloride ER tablets</td>
<td></td>
</tr>
<tr>
<td>• OxyContin® oxycodone hydrochloride CR tablets</td>
<td></td>
</tr>
<tr>
<td>• Targiniq™ oxycodone hydrochloride/naloxone hydrochloride ER tablets</td>
<td></td>
</tr>
<tr>
<td>• Zohydro® hydrocodone bitartrate ER capsules</td>
<td></td>
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</table>

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WHY PRESCRIBER EDUCATION IS IMPORTANT

Introduction
Prescribers of ER/LA Opioids Should Balance:

The benefits of prescribing ER/LA opioids to treat pain

The risks of serious adverse outcomes

ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.
Opioid Misuse/Abuse is a Major Public Health Problem

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

This risk can be greater w/ ER/LA opioids

ER opioid dosage units contain more opioid than IR formulations

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

In 2012

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

In 2011

488,004 ED visits involved nonmedical use of opioids

- Methadone involved in 30% of prescription opioid deaths

In 2011

41,340 Americans DIED FROM DRUG POISONINGS

Nearly 17,000 deaths involved prescription opioids

In 2008

For every 1 death there are:

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


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

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

Learning Objectives

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

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

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

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

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

YOU and YOUR TEAM can have an immediate and positive impact on this crisis while also caring for your patients appropriately.
ASSESSING PATIENTS FOR TREATMENT WITH ER/LA OPIOID ANALGESIC THERAPY

Unit 1
## Balance Risks Against Potential Benefits

### Conduct thorough H&P and appropriate testing

### Comprehensive benefit-to-harm evaluation

### Benefits Include

- Analgesia (adequate pain control)
- Improved Function

### Risks Include

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

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Adequately DOCUMENT all patient interactions, assessments, test results, & treatment plans
Clinical Interview: Patient Medical History

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

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

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

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

Clinical Interview: Pain & Treatment History

Description of pain

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

What relieves the pain?

What causes or increases pain?

Effects of pain on physical, emotional, and psychosocial function

Patient’s pain & functional goals

Pain Medications

Past use

Current use

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

Dosage

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

General effectiveness

Nonpharmacologic strategies & effectiveness
Perform Thorough Evaluation & Assessment of Pain

Seek objective confirmatory data

Components of patient evaluation for pain

Order diagnostic tests (appropriate to complaint)

General: vital signs, appearance, posture, gait, & pain behaviors

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

Neurologic exam

Cutaneous or trophic findings

Assess Risk of Abuse, Including Substance Use & Psychiatric Hx

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

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

*Social history also relevant*

Employment, cultural background, social network, marital history, legal history, & other behavioral patterns
## Risk Assessment, cont'd

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

### Understand & use addiction or abuse screening tools
- Assess potential risks associated w/ chronic opioid therapy
- Manage patients using ER/LA opioids based on risk assessment

### Conduct a UDT
- Understand limitations

Conduct a UDT
## Risk Assessment Tools: Examples

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

Mark each box that applies

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Family Hx of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>☐ 1</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>☐ 4</td>
<td>☐ 4</td>
</tr>
<tr>
<td>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><strong>5. Psychologic disease</strong></td>
<td></td>
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</tr>
<tr>
<td>ADD, OCD, bipolar, schizophrenia</td>
<td>☐ 2</td>
<td>☐ 2</td>
</tr>
<tr>
<td>Depression</td>
<td>☐ 1</td>
<td>☐ 1</td>
</tr>
</tbody>
</table>

**Scoring Totals:**

- **Administer**
  - On initial visit
  - Prior to opioid therapy

**Scoring (risk)**

- 0-3: low
- 4-7: moderate
- ≥8: high

**Screener & Opioid Assessment for Patients with Pain (SOAPP)®**

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

**How is SOAPP® administered?**

<table>
<thead>
<tr>
<th>Usually self-administered in waiting room, exam room, or prior to an office visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be completed as part of an interview w/ a nurse, physician, or psychologist</td>
</tr>
<tr>
<td>Prescribers should have a completed &amp; scored SOAPP® while making opioid treatment decisions</td>
</tr>
</tbody>
</table>


*The SOAPP® Version 1.0 Tutorial: [https://painedu.org/soapp-tutorial_01.asp](https://painedu.org/soapp-tutorial_01.asp)*
When to Consider a Trial of an Opioid

Potential benefits are likely to outweigh risks

Failed to adequately respond to nonopioid & nondrug interventions

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

Pain is chronic and severe

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

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

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

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

Selection of patients between these 2 extremes requires:

- Careful assessment & characterization of patient risk
- Structuring of care to match risk

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

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

- Consider referral

Referring High-Risk Patients

Prescribers should

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

Also check your state regulations for requirements
Special Considerations: Elderly Patients

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

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

- Altered PK due to poor fat stores, muscle wasting, or altered clearance
- Monitor closely, particularly when
  - Initiating & titrating ER/LA opioids
  - Given concomitantly w/ other drugs that depress respiration
- Reduce starting dose to 1/3 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?


Collaborative for REMS Education

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Special Considerations: Pregnant Women

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

Potential risks of opioid therapy to the newborn include:

- Low birth weight
- Premature birth
- Hypoxic-ischemic brain injury
- Neonatal death
- Prolonged QT syndrome
- Neonatal opioid withdrawal syndrome

Given these potential risks, clinicians should:

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

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

Special Considerations: Children (<18 years)

Safety & effectiveness of most ER/LA opioids unestablished

Pediatric analgesic trials pose challenges
Transdermal fentanyl approved in children aged ≥2 yrs
Oxycodone ER dosing changes for children ≥ 11 yrs (see Unit 6)

Most opioid studies focus on inpatient safety

Opioids are common sources of drug error

Opioid indications are primarily life-limiting conditions

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

When prescribing opioids to children:

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

Case:

Peter
25-Year-Old Male
Case:

Peter

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

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

Hx

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

Physical examination of knee

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

<table>
<thead>
<tr>
<th>How often:</th>
<th>Never=0</th>
<th>Seldom=1</th>
<th>Sometimes=2</th>
<th>Often=3</th>
<th>Very often=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have mood swings?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. Do you smoke a cigarette within an hr after you wake up?</td>
<td></td>
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<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>
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<tr>
<td>5. In your lifetime, have you had legal problems or been arrested?</td>
<td></td>
<td>✓</td>
<td></td>
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</table>

**Total Score: 7**

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

**After further questioning:**
- Admits smoking 1 cigarette pack/d for 10 yrs
- Claims occasional marijuana use, not for last 2 yrs
Ask for contact details of prior regular physician
• No info w/ him—can get it on Monday if you give him a prescription now

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

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

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

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

**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 THC 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
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
Collaborative for REMS Education

Federal & State Regulations

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

<table>
<thead>
<tr>
<th>Federal</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Code of Federal Regulations, Title 21 Section 1306: rules governing</td>
<td>• Database of state statutes, regulations, &amp; policies for pain</td>
</tr>
<tr>
<td>the issuance &amp; filling of prescriptions pursuant to section 309 of</td>
<td>management</td>
</tr>
<tr>
<td>the Act (21 USC 829)</td>
<td>- <a href="http://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm">www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm</a></td>
</tr>
<tr>
<td>• United States Code (USC) - Controlled Substances Act, Title 21,</td>
<td>- <a href="http://www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management">www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management</a></td>
</tr>
<tr>
<td>Section 829: prescriptions</td>
<td></td>
</tr>
</tbody>
</table>
# Initiating Treatment

*Prescribers should regard initial treatment as a therapeutic trial*

<table>
<thead>
<tr>
<th>May last from several weeks to several months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision to proceed w/ long-term treatment should be intentional &amp; based on careful consideration of outcomes during the trial</td>
</tr>
<tr>
<td>Progress toward meeting therapeutic goals</td>
</tr>
<tr>
<td>Changes in underlying pain condition</td>
</tr>
<tr>
<td>Identification of aberrant drug-related behavior, addiction, or diversion</td>
</tr>
</tbody>
</table>

ER/LA Opioid-Induced Respiratory Depression

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

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

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

ER/LA Opioid-Induced Respiratory Depression

More likely to occur

- In elderly, cachectic, or debilitated patients
  - **Contraindicated** in patients with respiratory depression or conditions that increase risk
- If given concomitantly with other drugs that depress respiration

Reduce risk

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

Drug & dose selection is critical

Monitor patients closely for respiratory depression

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

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

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

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

Check ER/LA opioid product PI for minimum titration intervals

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

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:**
Differences in pharmacologic or other effects make it likely that a switch will improve outcomes

- Effectiveness & AEs of different mu opioids vary among patients
- Patients show incomplete cross-tolerance to new opioid
  - Patient tolerant to 1st opioid can have improved analgesia from 2nd opioid at a dose lower than calculated from an EDT

Equianalgesic Doses

Opioid rotation requires calculation of an approximate equianalgesic dose

Equianalgesic dose is a construct derived from relative opioid potency estimates

• Potency refers to dose required to produce a given effect

Relative potency estimates

• Ratio of doses necessary to obtain roughly equivalent effects
• Calculate across drugs or routes of administration
• Relative analgesic potency is converted into an equianalgesic dose by applying the dose ratio to a standard
Equianalgesic Dose Tables (EDT)

Many different versions:

- Published
- Online
- Online Interactive
- Smart-phone apps

Vary in terms of:

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

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

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

<table>
<thead>
<tr>
<th>Did Not Consider</th>
<th>Chronic dosing</th>
<th>High opioid doses</th>
<th>Other routes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different pain types</td>
<td>Inter-patient variability in pharmacologic response to opioids</td>
<td>Gender, ethnicity, advanced age, or concomitant medications</td>
<td></td>
</tr>
<tr>
<td>Direction of switch from 1 opioid to another</td>
<td>Comorbidities or organ dysfunction</td>
<td>Incomplete cross-tolerance among mu opioids</td>
<td></td>
</tr>
</tbody>
</table>
Utilizing Equianalgesic Doses

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

Equianalgesic dose a starting point for opioid rotation

Intended as General Guide

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

Follow conversion instructions in individual ER/LA opioid PI, when provided
Guidelines for Opioid Rotation

Reduce calculated equianalgesic dose by 25%-50%*

Select % reduction based on clinical judgment

<table>
<thead>
<tr>
<th>Closer to 50% reduction if patient is</th>
<th>Closer to 25% reduction if patient</th>
</tr>
</thead>
</table>
| • 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**:

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

If switching to **transdermal**:

- **Fentanyl**, calculate dose conversion based on equianalgesic dose ratios included in the PI
- **Buprenorphine**, follow instructions in the PI
Guidelines for Opioid Rotation, cont'd

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

Titrate new opioid dose to optimize outcomes & safety

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

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

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

**Patients on stable ATC opioids may experience BTP**

Disease progression or a new or unrelated pain

**Therapies**

- Directed at cause of BTP or precipitating factors
- Nonspecific symptomatic therapies to lessen impact of BTP

**Consider adding**

- 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
Case:

Wilma
73-Year-Old Female
Case: Wilma

Advanced Colon Cancer
• w/ peritoneal & liver metastases
Presents w/ increasing abdominal pain
• Wakes frequently at night in severe pain
Regimen: oxycodone IR 5 mg q6h + 1 at bedtime
• She has some 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
Rotation Options for Wilma

No option for hydromorphone ER or transdermal fentanyl

- Only for opioid-tolerant patients

Avoid morphine & methadone due to her resistance

Consider oxymorphone ER: calculate equianalgesic dose

\[
\frac{20}{10} = 25 \text{ mg} / X \\
10 \times 25 = 250 = 20X \\
X = 12.5 \text{ mg oxymorphone/d}
\]

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

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

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

Values from EDT*
- Value of Current Opioid
- Value of New 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%
Educating Wilma to Take ER/LAs Safely

Advise Wilma to call

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

Caution Wilma*

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

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

#### After 1 week, pain was improved, but still moderate

- She is reluctant to take oxycodone IR for BTP
  - “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

- After 1 week, pain was improved, but still moderate
- Increase oxymorphone ER to 7.5 mg q12h w/ oxycodone IR for “emergencies”
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

- **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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taper dose to avoid withdrawal symptoms in opioid dependent patient</td>
<td></td>
</tr>
<tr>
<td>Recommend outpatient setting for patients without severe medical or psychiatric comorbidities</td>
<td></td>
</tr>
<tr>
<td>Recommend rehabilitation setting for patients unable to reduce opioid dose in less structured settings</td>
<td>• When aberrant drug-related behaviors continue, may need to enforce tapering efforts</td>
</tr>
<tr>
<td>May use a range of approaches from slow 10% dose reduction per week to more rapid 25%-50% reduction every few days</td>
<td></td>
</tr>
</tbody>
</table>
Case:

Ernesto
53-Year-Old Male
Case:

Ernesto

Workplace back injury at age 41 causes chronic back pain
• Partial diskectomy & subsequent L4-5 fusion
• He continues to work in a modified position

Presents for follow-up medication management
• Stable regimen of oxycodone ER 30 mg q12h + hydrocodone/acetaminophen IR 5 mg/500 mg q6h prn for BTP
  – 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
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

**Current opioid dose is oxycodone 60 mg/d**

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

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

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

Current dose is oxycodone 40 mg/d

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

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

Follow-up visit

• Pain well controlled & no withdrawal symptoms
• Replace scheduled oxycodone IR w/ oxycodone IR 5 mg (#30) as needed for pain if ibuprofen is not effective
• Instruct him to dispose of remaining oxycodone ER & hydrocodone IR
  - DEA National Prescription Drug Take-Back Day scheduled next Saturday

1-month follow-up visit

• Has not needed to use oxycodone IR
• Reports good function w/ no pain
• Instruct him to dispose of remaining oxycodone IR
  - No upcoming DEA National Prescription Drug Take Back Day
  - You enter his zip code at 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
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
Treat Initiation of Opioids as a Therapeutic Trial

Anticipate ER/LA Opioid-Induced Respiratory Depression

_It can be immediately life-threatening_

Be Conservative and Thoughtful In Dosing

_When initiating, titrating, and rotating opioids_

_First calculate equinalgesic dose, then reduce dose appropriately_

Discontinue ER/LA opioids slowly and safely
MANAGING THERAPY WITH ER/LA OPIOID ANALGESICS

Unit III
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

<table>
<thead>
<tr>
<th>Therapeutic risks &amp; benefits do not remain static</th>
<th>Identify patients</th>
<th>Periodically assess continued need for opioid analgesic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected by change in underlying pain condition, coexisting disease, or psychologic/ social circumstances</td>
<td>Who are benefiting from opioid therapy</td>
<td>Re-evaluate underlying medical condition if clinical presentation changes</td>
</tr>
<tr>
<td></td>
<td>Who might benefit more w/ restructuring of treatment or receiving additional services (e.g., addiction treatment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whose benefits from treatment are outweighed by risks</td>
<td></td>
</tr>
</tbody>
</table>
Monitor Patients During Opioid Therapy, cont'd

Periodically evaluate:

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

Patients requiring more frequent monitoring include:

- High-risk patients
- Patients taking high opioid doses
## Anticipate & Treat Common AEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>most common AE; does not resolve with time</td>
</tr>
<tr>
<td></td>
<td>- Initiate a bowel regimen before constipation develops</td>
</tr>
<tr>
<td></td>
<td>- Increase fluid &amp; fiber intake, stool softeners, &amp; laxatives</td>
</tr>
<tr>
<td></td>
<td>- Opioid antagonists may help prevent/treat opioid-induced bowel dysfunction</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>tend to diminish over days or weeks</td>
</tr>
<tr>
<td></td>
<td>Oral &amp; rectal antiemetic therapies as needed</td>
</tr>
<tr>
<td>Drowsiness &amp; sedation</td>
<td>tend to wane over time</td>
</tr>
<tr>
<td></td>
<td>Counsel patients about driving, work &amp; home safety as well as risks of concomitant exposure to other drugs &amp; substances w/ sedating effects</td>
</tr>
<tr>
<td>Pruritus &amp; myoclonus</td>
<td>tend to diminish over days or weeks</td>
</tr>
<tr>
<td></td>
<td>Treatment strategies for either condition largely anecdotal</td>
</tr>
</tbody>
</table>
Monitor Adherence and Aberrant Behavior

*Routinely monitor patient adherence to treatment plan*

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

**PADT** = Pain Assessment & Documentation Tool
# Address Aberrant Drug-Related Behavior

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

<table>
<thead>
<tr>
<th>Behaviors that are <strong>less</strong> indicative of aberrancy</th>
<th>Behaviors that are <strong>more</strong> indicative of aberrancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsanctioned dose escalations or other noncompliance w/ therapy on 1 or 2 occasions</td>
<td>Multiple dose escalations or other noncompliance w/ therapy despite warnings</td>
</tr>
<tr>
<td>Unapproved use of the drug to treat another symptom</td>
<td>Prescription forgery</td>
</tr>
<tr>
<td>Openly acquiring similar drugs from other medical sources</td>
<td>Obtaining prescription drugs from nonmedical sources</td>
</tr>
</tbody>
</table>
Prescription Drug Monitoring Programs (PDMPs)

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

Individual state laws determine

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

Record of a patient’s controlled substance prescriptions

- Some are available online 24/7
- Opportunity to discuss w/ patient

Provide warnings of potential misuse/abuse

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

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

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

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

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

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

*UDT frequency is based on clinical judgment*

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

Check state regulations for requirements
Main Types of UDT Methods

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

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

---

* GC/MS = gas chromatography/mass spectrometry
  IA = immunoassay
  LC/MS = liquid chromatography/mass spectrometry
## Detecting Opioids by UDT

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

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

**Positive Result**

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

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

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

---

**Negative Result**

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

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

Testing technologies & methodologies evolve

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

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

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

- Codeine → Morphine
- Morphine → 6-MAM*
- 6-MAM* → Heroin
- Hydrocodone → Hydromorphone
- Hydromorphone → Oxymorphone

*6-MAM=6-monoacetylmorphine

t₁/₂ = 25-30 min

t₁/₂ = 3-5 min
Interpretation of UDT Results

Use UDT results in conjunction w/ other clinical information

Investigate unexpected results

Discuss w/ the lab

Schedule appointment w/ patient to discuss unexpected/abnormal results

Chart results, interpretation, & action

Do not ignore the unexpected positive result

May necessitate closer monitoring &/or referral to a specialist

ER/LA Opioid Use in Pregnant Women

No adequate & well-controlled studies

Only use if potential benefit justifies the risk to the fetus

Be aware of the pregnancy status of your patients

If prolonged use is required during pregnancy:
• Advise patient of risk of neonatal withdrawal syndrome
• Ensure appropriate treatment will be available
Be Ready to Refer

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

SAMHSA substance abuse treatment facility locator

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

SAMHSA mental health treatment facility locator

Anticipate and Treat Common Adverse Effects

Use Informed Consent and Patient Provider Agreements

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

*However, know their limitations*

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

Refer Appropriately if Necessary
COUNSELING PATIENTS & CAREGIVERS ABOUT THE SAFE USE OF ER/LA OPIOID ANALGESICS

Unit IV
Use Patient Counseling Document to help counsel patients

Download:

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

Counsel Patients About Proper Use

**Explain**

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

**Instruct patients/caregivers to**

- Read the ER/LA opioid Medication Guide received from pharmacy every time an ER/LA opioid is dispensed
- At every medical appointment explain all medications they take
Counsel Patients About Proper Use, cont’d

Counsel patients/caregivers:

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

Prescribers should report serious AEs to the FDA:

www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf

or 1-800-FDA-1088
Warn Patients

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

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

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

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

Misuse of ER/LA opioids can lead to death

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

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

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

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

Naloxone:

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

What to do:

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

Available as:

- Naloxone kit (w/ syringes, needles)
- EVZIO™ (naloxone HCl) auto-injector
When to Consider Co-Prescribing Naloxone:

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

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

Caution Patients

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

Know Your Poison Center’s Number.

1-800-222-1222
You could save a life.
Source of Most Recent Rx Opioids Among Past-Year Users (2011-2012)

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

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

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

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

Mail-back packages
Obtained from authorized collectors

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

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

Last DEA National Prescription Drug Take-Back Day on September 26, 2015

Other Methods of Opioid Disposal

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

- Take drugs out of original containers
- Mix w/ undesirable substance, e.g., used coffee grounds or kitty litter
  - Less appealing to children/pets, & unrecognizable to people who intentionally go through your trash
- Place in sealable bag, can, or other container
  - Prevent leaking or breaking out of garbage bag
- Before throwing out a medicine container
  - Scratch out identifying info on label
FDA lists especially harmful medicines – in some cases fatal w/ just 1 dose – if taken by someone other than the patient
• Instruct patients to check medication guide

Flush down sink/toilet if no collection receptacle, mail-back program, or take-back event available
• As soon as they are no longer needed
  – So cannot be accidentally taken by children, pets, or others
• Includes transdermal adhesive skin patches
  – Used patch worn for 3d still contains enough opioid to harm/kill a child
  – Dispose of used patches immediately after removing from skin
• Fold patch in half so sticky sides meet, then flush down toilet
• Do NOT place used or unneeded patches in household trash
  – Exception is Butrans: can seal in Patch-Disposal Unit provided & dispose of in the trash
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. Can be immediately life-threatening.
- **Constipation** is the most common long-term AE. Should be anticipated.
For Safer Use: Know Drug Interactions, PK, & PD

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

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

Patients must be opioid tolerant before using

- Any strength of transdermal fentanyl or hydromorphone ER
- Certain strengths or daily doses of other ER products

Opioid-tolerant patients are those taking at least

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

FOR 1 WK OR LONGER
Key Instructions: ER/LA Opioids

- Individually titrate to a dose that provides adequate analgesia & minimizes adverse reactions
- Times required to reach steady-state plasma concentrations are product-specific
- Refer to product information for titration interval
- Continually re-evaluate to assess maintenance of pain control & emergence of AEs
Key Instructions: ER/LA Opioids, cont’d

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

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

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

Do not abruptly discontinue
Common Drug Information for This Class

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

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

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

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

Do not cut, damage, chew, or swallow

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

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

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

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

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

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

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

**Contraindications**
- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis)
- See individual PI for additional contraindications
Patients MUST be opioid-tolerant in order to safely take most ER/LA opioid products.

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

Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
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>Key instructions</td>
<td>Use in opioid-tolerant patients</td>
<td>Product-specific safety concerns</td>
<td>Relative potency to morphine</td>
</tr>
<tr>
<td>Specific information about product conversions, if available</td>
<td>Specific drug interactions</td>
<td>For detailed information, refer to online PI: DailyMed at <a href="http://www.dailymed.nlm.nih.gov">www.dailymed.nlm.nih.gov</a> Drugs@FDA at <a href="http://www.fda.gov/drugsatfda">www.fda.gov/drugsatfda</a></td>
<td></td>
</tr>
</tbody>
</table>
# Morphine Sulfate ER Capsules (Avinza)

| Dosing interval | • Once a day |
| Key instructions | • Initial dose in opioid non-tolerant patients is 30 mg  
• Titrate in increments of not greater than 30 mg using a minimum of 3-4 d intervals  
• Swallow capsule whole (do not chew, crush, or dissolve)  
• May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately  
• MDD:* 1600 mg (renal toxicity of excipient, fumaric acid) |
| Drug interactions | • Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose  
• P-gp* inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |
| Opioid-tolerant | • 90 mg & 120 mg capsules for use in opioid-tolerant patients only |
| Product-specific safety concerns | • None |

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

<table>
<thead>
<tr>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>• One transdermal system every 7 d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initial dose in opioid non-tolerant patients on &lt;30 mg morphine equivalents &amp; in mild-moderate hepatic impairment: 5 mcg/h</td>
</tr>
<tr>
<td>• When converting from 30 mg-80 mg morphine equivalents, first taper to 30 mg morphine equivalent, then initiate w/ 10 mcg/h</td>
</tr>
<tr>
<td>• 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</td>
</tr>
<tr>
<td>• Maximum dose: 20 mcg/h due to risk of QTc prolongation</td>
</tr>
<tr>
<td>• Application</td>
</tr>
<tr>
<td>• Apply only to sites indicated in PI</td>
</tr>
<tr>
<td>• Apply to intact/non-irritated skin</td>
</tr>
<tr>
<td>• Prep skin by clipping hair; wash site w/ water only</td>
</tr>
<tr>
<td>• Rotate application site (min 3 wks before reapply to same site)</td>
</tr>
<tr>
<td>• Do not cut</td>
</tr>
<tr>
<td>• Avoid exposure to heat</td>
</tr>
<tr>
<td>• Dispose of patches: fold adhesive side together &amp; flush down toilet</td>
</tr>
</tbody>
</table>
Buprenorphine Transdermal System (Butrans) cont’d

| Drug interactions | • CYP3A4 inhibitors may increase buprenorphine levels  
|                   | • CYP3A4 inducers may decrease buprenorphine levels  
|                   | • Benzodiazepines may increase respiratory depression  
|                   | • Class IA & III antiarrythmics, other potentially arrhythmogenic agents, may increase risk of QTc prolongation & torsade de pointe |
| Opioid-tolerant   | • 7.5 mcg/h, 10 mcg/h, 15 mcg/h, & 20 mcg/h for use in opioid-tolerant patients only |
| Drug-specific safety concerns | • QTc prolongation & torsade de pointe  
|                   | • Hepatotoxicity  
|                   | • Application site skin reactions |
| Relative potency: oral morphine | • Equipotency to oral morphine not established |
# Methadone Hydrochloride Tablets (Dolophine)

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>• Every 8 to 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key instructions</td>
<td>• Initial dose in opioid non-tolerant patients: 2.5 – 10 mg</td>
</tr>
<tr>
<td></td>
<td>• Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose &amp; death. Use low doses according to table in full PI</td>
</tr>
<tr>
<td></td>
<td>• Dosage adjustments using a minimum of 1-2 d intervals</td>
</tr>
<tr>
<td></td>
<td>• High inter-patient variability in absorption, metabolism, &amp; relative analgesic potency</td>
</tr>
<tr>
<td></td>
<td>• Opioid detoxification or maintenance treatment only provided in a federally certified opioid (addiction) treatment program (CFR, Title 42, Sec 8)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>• Pharmacokinetic drug-drug interactions w/ methadone are complex</td>
</tr>
<tr>
<td></td>
<td>– CYP 450 inducers may decrease methadone levels</td>
</tr>
<tr>
<td></td>
<td>– CYP 450 inhibitors may increase methadone levels</td>
</tr>
<tr>
<td></td>
<td>– Anti-retroviral agents have mixed effects on methadone levels</td>
</tr>
<tr>
<td></td>
<td>• Potentially arrhythmogenic agents may increase risk for QTc prolongation &amp; torsade de pointe</td>
</tr>
<tr>
<td></td>
<td>• Benzodiazepines may increase respiratory depression</td>
</tr>
</tbody>
</table>

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

**NOTE:**

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Methadone Hydrochloride Tablets (Dolophine) cont’d

<table>
<thead>
<tr>
<th>Opioid-tolerant</th>
<th>Drug-specific safety concerns</th>
<th>Relative potency: oral morphine</th>
</tr>
</thead>
</table>
| • Refer to full PI | • QTc prolongation & torsade de pointe  
• Peak respiratory depression occurs later & persists longer than analgesic effect  
• Clearance may increase during pregnancy  
• False-positive UDT possible | • Varies depending on patient’s prior opioid experience |
# Fentanyl Transdermal System (Duragesic)

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

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

## Key instructions

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

## Key instructions

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

## Drug interactions

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

## Opioid-tolerant

- All doses indicated for opioid-tolerant patients only

## Drug-specific safety concerns

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

## Relative potency: oral morphine

- See individual PI for conversion recommendations from prior opioid
Morphine Sulfate ER-Naltrexone Tablets (Embeda)*

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>• Once a day or every 12 h</th>
</tr>
</thead>
</table>
| Key instructions| • Initial dose as first opioid: 20 mg/0.8 mg  
• Titrating using a minimum of 1-2 d intervals  
• Swallow capsules whole (do not chew, crush, or dissolve)  
• Crushing or chewing will release morphine, possibly resulting in fatal overdose, & naltrexone, possibly resulting in withdrawal symptoms  
• May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately |
| Drug interactions| • Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose  
• P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |
| Opioid-tolerant | • 100 mg/4 mg capsule for use in opioid-tolerant patients only |
| Product-specific safety concerns | • None |

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

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>• Once a day</th>
</tr>
</thead>
</table>

| 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) |

<table>
<thead>
<tr>
<th>Drug interactions</th>
<th>• None</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Opioid-tolerant</th>
<th>• All doses are indicated for opioid-tolerant patients only</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Product-specific adverse reactions</th>
<th>• Allergic manifestations to sulfite component</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Relative potency: oral morphine</th>
<th>• ~5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in individual product information</th>
</tr>
</thead>
</table>
Hydrocodone Bitartrate (Hysingla ER)

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

Dosing interval

- Once a day

Key instructions

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

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

### Opioid-tolerant

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

### Drug-specific safety concerns

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

### Relative potency: oral morphine

- See individual PI for conversion recommendations from prior opioid

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**Hydrocodone Bitartrate (Hysingla ER), cont’d**

Collaborative for REMS Education
# Morphine Sulfate ER Capsules (Kadian)

<table>
<thead>
<tr>
<th><strong>Dosing interval</strong></th>
<th>• Once a day or every 12 h</th>
</tr>
</thead>
</table>
| **Key instructions** | • PI recommends not using as first opioid  
• Titrate using minimum of 2-d intervals  
• Swallow capsules whole (do not chew, crush, or dissolve)  
• May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately |
| **Drug interactions** | • Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose of morphine  
• P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |
| **Opioid-tolerant** | • 100 mg & 200 mg capsules for use in opioid-tolerant patients only |
| **Product-specific safety concerns** | • None |
## Morphine Sulfate CR Tablets (MS Contin)

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

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

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

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

### Drug interactions
- Alcoholic beverages or medications w/ alcohol may result in absorption of a potentially fatal dose of oxymorphone

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

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

### Relative potency: oral morphine
- Approximately 3:1 oral morphine to oxymorphone oral dose ratio
**Oxycodone Hydrochloride CR Tablets**  
(OxyContin) Extended Release Tablets  
10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80 mg

### 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/ ⅓-½ 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, w/ enough water to ensure complete swallowing immediately after placing in mouth

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

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

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

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

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

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

IMPORTANT:
• Opioids are rarely indicated or used to treat pediatric patients with chronic pain.
• The recent FDA approval for this oxycodone formulation was NOT intended to increase prescribing or use of this drug in pediatric pain treatment. Review the product information and adhere to best practices in the literature.
## Oxycodone Hydrochloride/Naloxone Hydrochloride ER Tablets (Targiniq ER)

### Dosing interval
- Every 12 h

### Key instructions
- Opioid-naïve patients: initiate treatment w/ 10mg/5mg every 12 h
- Titrate using min of 1-2 d intervals
- Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h)
- May be taken w/ or without food
- Swallow whole. Do not chew, crush, split, or dissolve: this will release oxycodone (possible fatal overdose) & naloxone (possible withdrawal)
- Hepatic impairment: contraindicated in moderate-severe impairment. In patients w/ mild impairment, start w/ ⅓-½ usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage

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

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

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

### Relative potency: oral morphine
- See individual PI for conversion recommendations from prior opioids
# Hydrocodone Bitartrate ER Capsules (Zohydro ER)

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

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

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

- Understand how to assess patients for treatment w/ ER/LA opioids
- Be familiar w/ how to initiate therapy, modify dose, & discontinue use of ER/LA opioids
- Know how to manage ongoing therapy w/ ER/LA opioids
- Know how to counsel patients & caregivers about the safe use of ER/LA opioids, including proper storage & disposal
- Be familiar w/ general & product-specific drug information concerning ER/LA opioids
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-remms.org