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 13 partners has designed a core curriculum based on needs assessment, practice gaps, clinical competencies, and learner self-assessment to meet the requirements of the FDA REMS Blueprint.

www.core-rem.org
Products Covered by this REMS

**Brand Name Products**
- Exalgo
- Embeda
- Targiniq™ oxycodone hydrochloride/naloxone
- OxyContin
- Opana
- Nucynta
- MS Contin
- MorphaBond
- Kadian
- Hysingla
- Duragesic
- Butrans
- Avinza
- Hyfemorph

**Generic Products**
- Fentanyl ER transdermal systems
- Methadone hydrochloride tablets
- Methadone hydrochloride oral concentrate
- Methadone hydrochloride oral solution
- Morphine sulfate ER tablets
- Morphine sulfate ER capsules
- Oxycodone hydrochloride ER tablets
- Oxycodone hydrochloride ER capsules
- Zolpidem hydrochloride bicitarate ER capsules

Opioid Misuse/Abuse is a Major Public Health Problem

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

<table>
<thead>
<tr>
<th>2012</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 million Americans age ≥12 had used an opioid for nonmedical use some time in their life</td>
<td></td>
</tr>
<tr>
<td>488,004 ED visits involved nonmedical use of opioids</td>
<td></td>
</tr>
</tbody>
</table>

**Prescribers of ER/LA Opioids Should Balance:**

**The benefits of prescribing ER/LA opioids to treat pain**

**The risks of serious adverse outcomes**

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

Opioid education requirements issued by the US Food & Drug Administration.

**CO*RE Staff Disclosures**

The following individuals disclose no relevant financial relationships:

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer Reinard</td>
<td>Program Director, NPHF Continuing Education Program</td>
<td>National Pain and Palliative Health Foundation, Silver Spring, MD</td>
</tr>
<tr>
<td>Sharon McGill</td>
<td>Education Manager, American Pain Society</td>
<td>American Pain Society, Chicago, IL</td>
</tr>
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<td>Stephanie Townsell, MPH</td>
<td>Project Manager, Physicians’ Institute for Excellence in Medicine</td>
<td>Physicians’ Institute for Excellence in Medicine, Atlanta, GA</td>
</tr>
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<td>Nurse Practitioner Healthcare Foundation, Bellevue, WA</td>
</tr>
<tr>
<td>Susan Ziegler, MD</td>
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<td>National Pain and Palliative Health Foundation, Silver Spring, MD</td>
</tr>
<tr>
<td>Richard Fishbein, MD</td>
<td>President, Physicians’ Institute for Excellence in Medicine</td>
<td>Physicians’ Institute for Excellence in Medicine, Atlanta, GA</td>
</tr>
</tbody>
</table>

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**WHY PRESCRIBER EDUCATION IS IMPORTANT**

*Introduction*

Opioid education requirements issued by the US Food & Drug Administration.

**Acknowledgement**

Presented by the California Academy of Family Physicians, 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://co-e-l-a-opioidanalgesics.com/lwgCEU/lwgremspdfIstOfRPCCompanies.pdf](http://co-e-l-a-opioidanalgesics.com/lwgCEU/lwgremspdfIstOfRPCCompanies.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.
In 2013, 43,982 Americans died from drug poisonings. Nearly 16,235 deaths involved prescription opioids.

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>Cocaine</td>
<td>0.7</td>
</tr>
<tr>
<td>Sedatives</td>
<td>0.6</td>
</tr>
<tr>
<td>LSD</td>
<td>0.6</td>
</tr>
<tr>
<td>Hashish</td>
<td>0.4</td>
</tr>
<tr>
<td>Inhalants</td>
<td>0.2</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>0.2</td>
</tr>
<tr>
<td>PCPs</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Learning Objectives

- Describe appropriate patient assessment for treatment with ER/LA opioid analgesics, evaluating risks and potential benefits of ER/LA therapy, as well as possible misuse.
- Apply proper methods to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, applying best practices including accurate dosing and conversion techniques, as well as appropriate discontinuation strategies.
- Demonstrate accurate knowledge about how to manage ongoing therapy with ER/LA opioid analgesics and proper use of 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>Conduct thorough H&amp;P and appropriate testing</th>
<th>Comprehensive benefit-to-harm evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits Include</td>
<td>Risks Include</td>
</tr>
<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

<table>
<thead>
<tr>
<th>Location</th>
<th>Intensity</th>
<th>Quality</th>
<th>Onset/Dur.</th>
<th>Variations/Patters/Rhythms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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, contd

**Pain Medications**

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

**Dosage**

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

**General effectiveness**

**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 history of alcohol or drug abuse
- Younger age
- Presence of psychiatric conditions

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

Conduct a UDT
- Understand limitations

Be knowledgeable about risk factors for opioid abuse

Opioid Risk Assessment

Be knowledgeable about risk factors for opioid abuse

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

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

Conduct a UDT
- Understand limitations

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

Conduct a UDT
- Understand limitations

Opioid Risk Tool (ORT)

Mark each box that applies

1. Family history of substance abuse
   - Alcohol
   - Illegal drugs
   - Prescription drugs

2. Personal history of substance abuse
   - Alcohol
   - Illegal drugs
   - Prescription drugs

3. Age between 16 & 45 yrs
4. History of preadolescent sexual abuse
5. Psychologic disease
   - ADD, OCD, bipolar, schizophrenia
   - Depression

Scoring:
- 0-3: low
- 4-7: moderate
- ≥8: high

Administer
- On initial visit
- Prior to opioid therapy

Score Totals:

- 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

Risk Assessment Tools: Examples

<table>
<thead>
<tr>
<th>Test</th>
<th># of Items</th>
<th>% administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients considered for long-term opioid therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid Risk Tool</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>SOAPP® Screen &amp; Opioid Assessment for Patients w/ Pain</td>
<td>24, 14, 6</td>
<td>patient</td>
</tr>
<tr>
<td>DIME Diagnostic, Intratubular Risk, &amp; Efficacy Score</td>
<td>7</td>
<td>clinicians</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>37</td>
<td>patient</td>
</tr>
<tr>
<td>PDUQ Prescription Drug Use Questionnaire</td>
<td>40</td>
<td>clinicians</td>
</tr>
<tr>
<td>Not specific to pain populations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CASE-AID Cut Down, Annoyed, Guilty, Eye-Opener Tool, Adjusted to Include Drugs</td>
<td>4</td>
<td>clinicians</td>
</tr>
<tr>
<td>RAPFT Relax, Alone, Friends, Family, Troubles</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>70</td>
<td>varies</td>
</tr>
</tbody>
</table>

When to Consider a Trial of an Opioid

Potential benefits are likely to outweigh risks
- Failed to adequately respond to nonopioid & non-drug 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

SOAPP® Monitoring Recommendations
SOAPP® Version 1.0 Tutorial

Screening, Brief Intervention, & Referral to Treatment

- Scoring Totals:

  - 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

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/medicolegal comorbidities or personal/family drug abuse
- 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 first 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.

Prescribers should:

- Understand when to appropriately refer high-risk patients to pain management or addiction specialists
- Also check your state regulations for requirements

Referring High-Risk Patients

Special Considerations:

- Elderly Patients
  - 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 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
  - Oxycodeone ER dosing changes for children ≥ 11 yrs (see Unit 6)
  - Most opioid studies focus on inpatient safety
  - 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

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

Unit 1
Unit II

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

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


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

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

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

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-naive individuals

Drug & dose selection is critical

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 & nonopioids) if pain is not controlled during titration

Additional Resources:

Self-management Ladder

- Early interventions
- Nonpharmacologic therapies
- Pharmacologic therapies

Assessment of Opioid-Related Adverse Events

- Nausea & vomiting
- Constipation
- Pruritus
- Cognitive impairment
- Dysphoria & hallucinations


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

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

For 1 Wk Or Longer

Equianalgesic Doses

Opioid rotation requires calculation of an
approximate equianalgesic dose

Equianalgesic dose is a
construct derived from relative
opioid potency estimates

- Potency refers to dose required
to produce a given effect

Relative potency estimates

- Ratio of doses necessary
to obtain roughly
equivalent effects
- Calculate across drugs or
routes of administration
- Relative analgesic potency is converted into an
equianalgesic dose by applying the dose ratio to a standard

Equianalgesic Dose Tables (EDT)

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

Vary in terms of:

- Equianalgesic values
- Whether ranges are used

Which opioids are included:
May or may not include transdermal opioids, rapid-onset
fentanyl, ER/LA opioids, or opioid agonist-antagonists

Example of an EDT for Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Dose</th>
<th>Usual Starting Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg SC/IV PO</td>
<td>30 mg 2.5-5 mg SC/IV q3-4hr</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA 20 mg PO</td>
<td>5-10 mg q3-4 (2.5 mg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA 30 mg PO</td>
<td>1 mg q3-4 (0.25 mg)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg SC/IV PO</td>
<td>7.5 mg 0.2-0.6 mg SC/IV q3-4hr</td>
</tr>
</tbody>
</table>

Limitations of EDTs

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

Did Not Consider

- Chronic dosing
- High opioid doses
- Other routes

Different pain types
- Comorbidities or organ dysfunction
- Gender, ethnicity, advanced age, or concomitant medications

Direction of switch from 1 opioid to another
- Inter-patient variability in pharmacologic response to opioids
- Incomplete cross-tolerance among mu opioids
Utilizing Equianalgesic Doses

Incomplete cross-tolerance & inter-patient variability require use of conservative dosing when converting from one opioid to another. Equianalgesic dose a starting point for opioid rotation.

**Guidelines for Opioid Rotation**

**Reduce calculated equianalgesic dose by 25%-50%**

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

*75%-90% reduction for methadone*

**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, 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

**Breakthrough Pain in Chronic Pain Patients**

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

**Reasons for Discontinuing ER/LA Opioids**

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

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

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

Monitor Patients During Opioid Therapy

Therapeutic risks & benefits do not remain static

- 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

<table>
<thead>
<tr>
<th>Constipation</th>
<th>Nausea &amp; vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common AE does not resolve with time</td>
<td>Tend to diminish over days or weeks</td>
</tr>
<tr>
<td>Initiate a bowel regimen before complication develops</td>
<td>Oral &amp; rectal antiemetic therapies as needed</td>
</tr>
<tr>
<td>Increase fluid &amp; fiber intake, stool softeners, &amp; laxatives</td>
<td>Pruritus &amp; myoclonus</td>
</tr>
<tr>
<td>Opioid antagonists may help prevent/treat opioid-induced bowel dysfunction</td>
<td>Tend to diminish over days or weeks</td>
</tr>
<tr>
<td>Constipation</td>
<td>Treatment strategies for either condition</td>
</tr>
</tbody>
</table>

Counsel patients about driving, work & home safety as well as risks of concomitant exposure to other drugs & substances w/ sedating effects

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)

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)

- 49 states have an operational PDMP
- DC has 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

**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

**Interpretation of UDT Results**

**Positive Result**
- Demonstrates recent use
  - Most drugs in urine have detection times of 1-3d
  - Chronic use of lipid-soluble drugs: test positive for ≥1wk
- 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 patients prescribed & OTC drugs
  - Avoid to identify false-positive result
- Time taken to eliminate drugs
  - Document time of last use & quantity of drugs taken
  - Opioid metabolism may explain presence of apparently unprescribed drugs
Examples of Metabolism of Opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Metabolite</th>
<th>t½</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Morphine</td>
<td>25-30 min</td>
</tr>
<tr>
<td>6-MAM</td>
<td>Heroin</td>
<td>3-5 min</td>
</tr>
<tr>
<td>Hydrocodeine</td>
<td>Hydromorphone</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxymorphone</td>
<td></td>
</tr>
</tbody>
</table>

Interpretation of UDT Results

- Use UDT results in conjunction with other clinical information
- Investigate unexpected results
  - Discuss with the lab
  - Schedule appointment with patient to discuss unexpected/abnormal results
- Chart results, interpretation, & action
- Do not ignore the unexpected positive result
  - May necessitate closer monitoring & 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 with referral sources for abuse or addiction that may arise from use of ER/LA opioids
  - SAMHSA substance abuse treatment facility locator
  - SAMHSA mental health treatment facility locator

Unit 3

Pearls for Practice

- Anticipate and treat common adverse effects
- Use informed consent and patient provider agreements
- Use UDT and PDMP as valuable sources of data about your patient
  - However, know their limitations
- Monitor patient adherence, side effects, aberrant behaviors, and clinical outcomes
- Refer appropriately if necessary

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

Unit IV
Use Patient Counseling Document to help counsel patients


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


Counsel Patients About Proper Use

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 apple sauce 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, contd

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
- NARCAN nasal spray
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

Abuse Deterrent/Tamper Resistant Opioids

- Response to growing nonmedical use problem
- An ER/LA opioid with physical barrier to deter extraction
- Less likely to be crushed, injected, or snorted
- Consider these formulations as one part of an overall REMS strategy
- There is mixed evidence on the impact of ADF/TR on misuse
- Remember overdose is still possible if taken orally in excessive amounts

Protecting the Community

Caution Patients

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

Educate Parents: Not in My House

- 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

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

- Free: friend/relative
- 1 doctor
- Bought/took: friend/relative
- Other
- Drug dealer/stranger
- >1 doctor
- Bought on Internet

Rx Opioid Disposal

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

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

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

Mail-back packages
Obtained from authorized collectors

Voluntarily maintained by:
- Law enforcement
- Authorized collection, including:
  - Manufacturer
  - Distributor
  - Reverse distributor
  - Retail or hospital/clinic pharmacy
- Including long-term care facilities

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

DEA National Prescription Drug Take-Back Day on April 30, 2016
Other Methods of Opioid Disposal

- Take drugs out of original containers
- Mix with undesirable substance, e.g., used coffee grounds or kitty litter
- Place in sealable bag, can, or other container
- 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
- 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

Unit 4

Pears 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!

Unit V

GENERAL DRUG INFORMATION FOR ER/LA OPIOID ANALGESIC PRODUCTS

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
- Slight drug levels may increase without dose dumping
- 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 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

Refer to product information for titration interval

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

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
- 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

Relative potency to oral morphine
- See individual drug PI

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 agonist* or mixed agonist/antagonists* with full opioid agonist
- May reduce analgesic effect &/or precipitate withdrawal

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

Transdermal Dosage Forms

Do not cut, damage, chew, or swallow

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

Drug Interactions Common to this Class

- Concurrent use w/ other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma
- Reduce initial dose of one or both agents
- May enhance neuromuscular blocking action of skeletal muscle relaxants & increase respiratory depression

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

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

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

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

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

---

**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>
</tbody>
</table>

**Specific drug interactions**

**Morphine Sulfate ER Capsules (Avinza)**

<table>
<thead>
<tr>
<th>Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing interval</strong></td>
</tr>
<tr>
<td><strong>Key instructions</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
</tr>
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<td></td>
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<tr>
<td><strong>Opioid-tolerant</strong></td>
</tr>
<tr>
<td><strong>Product-specific safety concerns</strong></td>
</tr>
</tbody>
</table>

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

**Buprenorphine Buccal Film (Belbuca)**

<table>
<thead>
<tr>
<th>75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg</th>
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</thead>
<tbody>
<tr>
<td><strong>Dosing interval</strong></td>
</tr>
<tr>
<td><strong>Key instructions</strong></td>
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**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.
### Buprenorphine Buccal Film (Belbuca) cont'd

**Key instructions**
- Maximum dose: 100 mcg every 12 h due to the potential for QTc prolongation
  - Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function
  - Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis
  - Do not use if the package seal is broken or the film is cut, damaged, or changed in any way

**Specific Drug Interactions**
- CYP2D6 inhibitors may increase buprenorphine levels
- CYP2D6 inducers may decrease buprenorphine levels
- Benzodiazepines may increase respiratory depression
- Class IA & III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes

**Use in Opioid-Tolerant Patients**
- Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses of Belbuca

**Product-Specific Safety Concerns**
- QTc prolongation and torsade de pointes
- Hepatotoxicity

**Relative Potency: Oral Morphine**
- Equipotency to oral morphine has not been established.

### Methadone Hydrochloride Tablets (Dolophine) cont'd

**Opioid-tolerant**
- Relative potency: oral morphine not established

**Product-specific safety concerns**
- QTc prolongation & torsade de pointes
- Hepatotoxicity
- Application site skin reactions

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

### Methadone Hydrochloride Tablets (Dolophine) (CFR, Title 42, Sec 8)

- Anti-retroviral agents have mixed effects on methadone levels
- CYP3A4 inhibitors may increase methadone levels
- CYP3A4 inducers may decrease methadone levels
- Benzodiazepines may increase respiratory depression
- Benzodiazepines may increase risk for QTc prolongation & torsade de pointe

### Fentanyl Transdermal System (Duragesic)

- Refer to full PI

**Opioid-tolerant**
- QTc prolongation & torsade de pointes
- 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

### Methadone Hydrochloride Tablets (Dolophine)

**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 site skin reactions
  - Apply to intact/non-irritated skin
  - Rotate site of application
  - Avoid accidental contact when holding or caring for children
  - Dispose of used/unused patches: fold adhesive side together & flush down toilet

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

### Fentanyl Transdermal System (Duragesic)

**Key instructions**
- 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

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

### Buprenorphine Transdermal System (Butrans)

**Key instructions**
- Apply only to sites indicated in PI
- Apply to intact/non-irritated skin
- Avoid accidental contact when holding or caring for children
- Avoid exposure to heat
- Dispose of patches: fold adhesive side together & flush down toilet

**Dosing interval**
- Every 7 d

### Methadone Hydrochloride Tablets (Dolophine)

**Key instructions**
- Do not cut
- Avoid accidental contact when holding or caring for children
- Dispose of used/unused patches: fold adhesive side together & flush down toilet

**Dosing interval**
- Every 12 h

### Buprenorphine Transdermal System (Butrans)

**Key instructions**
- Maximum dose: 20 mcg/h due to risk of QTc prolongation
- Do not cut
- Avoid exposure to heat
- Dispose of patches: fold adhesive side together & flush down toilet

**Dosing interval**
- Every 7 d
### Fentanyl Transdermal System (Duragesic), cont’d

<table>
<thead>
<tr>
<th>Key instructions</th>
<th>Product-specific safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid-tolerant</td>
<td>All doses indicated for opioid-tolerant patients only</td>
</tr>
</tbody>
</table>

### Hydromorphone Hydrochloride (Exalgo)

<table>
<thead>
<tr>
<th>ER Tablets</th>
<th>8 mg, 12 mg, 16 mg, 32 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing interval</td>
<td>Once a day</td>
</tr>
<tr>
<td>Key instructions</td>
<td>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 renal impairment on 50% &amp; patients w/ severe on 25% dose prescribed for patient w/ normal function. Titrate in increments of 0.5 to 2 mg using a minimum of 3 to 4 d intervals. Swallow tablets whole (do not chew, crush, or dissolve). Do not use in patients w/ sulfa allergy (contains sodium metabisulfite).</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>None</td>
</tr>
<tr>
<td>Relative potency: oral morphine</td>
<td>See individual PI for conversion recommendations from prior opioid</td>
</tr>
</tbody>
</table>

### Hydrocodone Bitartrate (Hysingla ER)

<table>
<thead>
<tr>
<th>Capsules</th>
<th>20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg, 3.2 mg, 100 mg/4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing interval</td>
<td>Once a day or every 12 h</td>
</tr>
<tr>
<td>Key instructions</td>
<td>Initial dose is 10 mg for opioid tolerant patients only</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP3A4 inhibitors may increase hydrocodone exposure. CYP3A4 inducers may decrease hydrocodone exposure. Concomitant use of Hysingla ER with strong CYP3A4 inhibitors (e.g., unafide) that rapidly lower CYP3A4 activity may increase hydrocodone absorption and exposure. The use of MAO inhibitors or tri cyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER. Use conversion ratios in individual PI.</td>
</tr>
<tr>
<td>Relative potency: oral morphine</td>
<td>See individual PI for conversion recommendations from prior opioid</td>
</tr>
</tbody>
</table>

### Morphine Sulfate ER-Naltrexone (Embeda)

<table>
<thead>
<tr>
<th>Capsules</th>
<th>20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing interval</td>
<td>Once a day</td>
</tr>
<tr>
<td>Key instructions</td>
<td>Initial dose is 10 mg for opioid tolerant patients only</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Morphine interacts with Naltrexone. Alcoholic beverages or medications w/ alcohol may result in rapid release &amp; absorption of potentially fatal dose. The use of CYP3A4 inhibitors may increase absorption/exposure of morphine by ~2 fold. Naltrexone, possibly resulting in naloxone-like symptoms. May open capsule &amp; sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.</td>
</tr>
<tr>
<td>Relative potency: oral morphine</td>
<td>None</td>
</tr>
</tbody>
</table>

### Hydrocodone Sulfate (Kadian)

<table>
<thead>
<tr>
<th>Capsules</th>
<th>10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130mg, 150 mg, 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing interval</td>
<td>Once a day</td>
</tr>
<tr>
<td>Key instructions</td>
<td>PI recommends not using as first opioid. Titrate using minimum of 2-3 d intervals. Swallow capsules whole (do not chew, crush, or dissolve). Swallow tablets whole (do not chew, crush, or dissolve). Avoid use in patients with concomitant CYP3A4 inhibitors. Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation. Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation. 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.</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Morphine interacts with Naltrexone. Alcoholic beverages or medications w/ alcohol may result in rapid release &amp; absorption of potentially fatal dose. May open capsule &amp; sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.</td>
</tr>
<tr>
<td>Relative potency: oral morphine</td>
<td>None</td>
</tr>
</tbody>
</table>
**Oxycodone Hydrochloride (OxyContin)**

**ER Tablets:** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg

**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 dose intervals.
- Swallow tablets whole (do not chew, crush, or dissolve).

**Specific Drug interactions:**
- P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~5-fold.

**Opioid-tolerant:**
- Morphine 100 mg tablets are for use in opioid-tolerant patients only.

**Product-specific safety concerns:**
- None

**New Dosing info:**
- Initial dose in opioid-naive and non-tolerant patients: 10 mg every 12 h.
- Titrate using a minimum of 1-2 dose intervals.
- Use 5 mg every 12 h as initial dose in opioid non-tolerant patients.
- Do not exceed 40 mg total daily dose.
- Use 5 mg every 12 h as initial dose in opioid non-tolerant patients.
- For adults: Single dose greater than 40 mg is not recommended.
- For pediatric patients (age 11 and older): Single dose greater than 60 mg is not recommended.
- For opioid-naive and non-tolerant patients: Start with 10 mg every 12 h.
- For adults: Single dose greater than 40 mg is not recommended.
- For pediatric patients (age 11 and older): Single dose greater than 60 mg is not recommended.
- For opioid-naive and non-tolerant patients: Start with 10 mg every 12 h.
- For adults: Single dose greater than 40 mg is not recommended.
- For pediatric patients (age 11 and older): Single dose greater than 60 mg is not recommended.
- For opioid-naive and non-tolerant patients: Start with 10 mg every 12 h.

**Relative potency:**
- Approximately 1:1 relative potency to oxymorphone oral dose ratio

**Morphine Sulfate (MS Contin)**

**ER Tablets:** 15 mg, 30 mg, 60 mg, 100 mg, 200 mg

**Dosing interval:** Every 6 h or every 12 h

**Key instructions:**
- Product information recommends not using as first opioid.
- Titrate using a minimum of 1-2 dose 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.
- P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold.
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- 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 (Nucynta ER)**

**ER Tablets:** 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

**Dosing interval:** Every 12 h

**Key instructions:**
- Product information recommends not using as first opioid.
- Titrate by 50 mg increments, using minimum of 3-6 dose intervals.
- Swallow tablets whole (do not chew, crush, or dissolve).

**Drug interactions:**
- Alcoholics beverages or medications w/ alcohol may result in rapid release & absorption of a potentially fatal dose of tapentadol.
- Contraindicated in patients taking MAOIs.

**Opioid-tolerant:**
- No product-specific considerations.

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

**Morphine Sulfate (MorpheaBond)**

**ER Tablets:** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg

**Dosing interval:** Every 6 h or every 12 h

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

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

**Opioid-tolerant:**
- Morphine 100 mg tablets are for use in opioid-tolerant patients only.

**Product-specific safety concerns:**
- None

**Oxymorphone Hydrochloride (Opana ER)**

**ER Tablets:** 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg

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

**Key instructions:**
- Use with caution in patients who have difficulty swallowing or underlying GI disorders that may predispose to obstruction.

**Product-specific safety concerns:**
- None

**Relative potency:**
- Approximately 3.5 oral morphine to oxymorphone oral dose ratio

**Oxycodone Hydrochloride (OxyContin) New Dosing Info**

**ER Tablets:** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg

**Dosing interval:** Every 12 h

**Key instructions:**
- Initial dose in opioid-naive and non-tolerant patients: 10 mg every 12 h.
- Titrate using a minimum of 1-2 dose intervals.
- Use 5 mg every 12 h as initial dose in opioid non-tolerant patients.
- For adults: Single dose greater than 40 mg is not recommended.
- For pediatric patients (age 11 and older): Single dose greater than 60 mg is not recommended.
- For opioid-naive and non-tolerant patients: Start with 10 mg every 12 h.
- For adults: Single dose greater than 40 mg is not recommended.
- For pediatric patients (age 11 and older): Single dose greater than 60 mg is not recommended.
- For opioid-naive and non-tolerant patients: Start with 10 mg every 12 h.

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

**Oxycodone Hydrochloride (OxyContin) Con’t**

**ER Tablets:** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg

**Key instructions:**
- Opioids are rarely indicated or used to treat pediatric patients with chronic pain.
- All patients with chronic pain should be evaluated for opioid treatment.
- 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 (Targiniq ER)**

**Dosing interval**
- Every 12 h

**Key instructions**
- Opioid-naïve patients: initiate treatment w/ 10 mg/5 mg 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 to oral morphine**
- See individual PI for conversion recommendations from prior opioids

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**Hydrocodone Bitartrate (Zohydro ER)**

**Dosing interval**
- Every 12 h

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

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

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

**Product-specific safety concerns**
- None

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

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**Naloxone (Narcan)**

**Dosing interval**
- IM or SQ: onset 2-5 minutes, duration >45 min
- IV: onset 1-2 min, duration 45 minutes
- IN: onset 2-3 min, duration ~ 2 hours

**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 w/i 2 min – 2 hrs
- Vomiting, restlessness, abdominal cramps, increased respiratory rate
- Severity depends on naloxone dose, opioid involved & degree of dependence

**Product-specific safety concerns**
- Ventricular arrhythmia, hypertension, hypotension, nausea & vomiting
- As naloxone plasma levels decrease, sedation from opioid overdose may increase

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**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
- Be familiar w/ general & product-specific drug information concerning ER/LA opioids
- Know how to counsel patients & caregivers about the safe use of ER/LA opioids, including proper storage & disposal

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**IMPORANT!**

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!**
ER/LA Opioids REMS Knowledge Test

1. Among the risk factors contained in screening tools for predicting aberrant drug-related behavior in patients, modeling opioids for chronic pain are family and personal history of substance abuse, legal problems, history of previoudon sexual abuse, psychological problems, and
A. Age (35-55 years)
B. Age (16-45 years)
C. Age (45-75 years)
D. Age (75+)
E. Risk is even across age

2. Which of the following is most important to consider when determining a starting dosage of an extended-release/long-acting opioid?
A. Calculation of epinephrine dosage
B. Presence of clostridium
C. Potential for adverse effects
D. Assessment of individual needs
E. Starting dosage listed in the package insert

3. A 55-year-old man who is being treated for chronic lower back pain after undergoing lumbar spine surgery for follow-up evaluation. A trial of oxycodone ER therapy is planned. Completion of which of the following is the most appropriate step before initiation of therapy?
A. Oswestry Disability Index
B. Roland Morris Disability Questionnaire
C. Patient-Physician Agreement
D. MRI of the lumbar spine
E. Routine blood tests

4. A 63-year-old man with a history of spinal stenosis and peripheral neuropathy secondary to breast cancer treatment comes for evaluation because of increasingly severe neck pain. She reports that the pain started two weeks ago after doing yard work. She underwent chemotherapy 12 years ago. Medications include an opioid. Which of the following is the most appropriate next step?
A. Assume the patient had an injured sensitivity to pain is to be expected
B. Remind the underlying medical condition
C. Refer the patient to physical therapy and administer a short-acting opioid as necessary
D. Increase extended-release/long-acting opioid therapy dosage for up to one month
E. Consider adding an adjuvant analgesic for neuropathic pain

5. Use of ER/LA opioids in pediatric patients <18 years of age deserves special consideration because
A. Safety & effectiveness of most ER/LA opioids has not been established in this population
B. Many children experience chronic pain conditions with indications for ER/LA opioids
C. Starting doses of opioids are reduced by one-third to one-half that in adults
D. Assessment of individual needs
E. Starting dosage listed in the package insert

6. A 20-year-old woman is brought to the emergency department because of the sudden onset of anxiety and confusional state taking her taking
A. Hydromorphone ER
B. Oxycodone CR
C. Methadone
D. Fentanyl transdermal patch
E. Tapentadol ER

7. An inappropriate method to dispose of unused opioid medications in:
A. Return the medication to a pharmacy
B. ER/LA drug take-back event
C. Mix into cat litter before putting in the regular trash
D. Dispose of medication in the regular trash
E. Flush down the toilet

8. The most important reason a patient should be counseled to never break, cut, chew, or crush a ER/LA opioid tablet or cut or tear patches is because:
A. The medicine will expire
B. It is against the law
C. The dose will be less than prescribed
D. The patient may die
E. The medicine will not work

9. To avoid inadvertent overdose and death a patient should be counseled to avoid co-administration of an extended-release/opioid with which of the following?
A. Alcohol
B. Diphenhydramine
C. St John's wort
D. Aspirin
E. Methamphetamine

10. Which of the following extended-release/long-acting opioids is most likely to induce a peak respiratory depression that occurs later and persists longer than the analgesic effect?
A. Fentanyl transdermal patch
B. Hydromorphone ER
C. Methadone
D. Opioid CR
E. Tapentadol ER

11. When using an equianalgesic table to rotate opioids (other than methadone) on an important step to account for incomplete cross-tolerance among mu opioids includes:
A. Initiate the new opioid at the calculated equianalgesic dose
B. Increase the calculated maximum dose by 30-50%
C. Reduce calculated equianalgesic dose by 25-30%
D. Convert and total all opioids to oral morphine equivalents
E. Refer to the packaging insert for appropriate supplemental rescue dose

12. Which of the following most accurately reflects the potency of certain oral opioid analogues?
A. Hydromorphone ER > oxycodone
B. Morphine > oxycodone
C. Methadone > hydromorphone
D. Oxycodone ER > hydromorphone
E. Oxymorphone ER > hydromorphone

13. A 35-year-old man with chronic back pain is beginning a trial therapy with oxycodone extended-release tablets. Which of the following is the minimum interval for dose titration?
A. One day
B. Three days
C. Five days
D. Seven days
E. Nine days

14. A positive result of hydromorphone of a urine drug toxicology test for a patient on
A. Use of heroin in past month
B. Presence of semisynthetic opioids
C. Presence of the oxycodone metabolite
D. Presence of the morphine metabolite
E. Use of methadone in past month