Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)

Presenter:  
Affiliation:
Faculty Disclosure

FACULTY...place your disclosure information on this slide
Thank you for your participation today!

Please take the pretest now –
The pretest is part of the stapled paper handout you received
Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

Module 1
Learning Objectives

• Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits

• Assess patient’s risk of abuse, including substance use and psychiatric history

• Identify state and federal regulations on opioid prescribing

• Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain

• Manage ongoing therapy with ER/LA opioid analgesics

• Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics

• Discuss general and product-specific drug information related to ER/LA opioid analgesics
Rates of Opioid Overdose Deaths, Sales, and Treatment Admissions, United States, 1999–2010

CDC. MMWR 2011. [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60e1101a1.htm?s_cid=mm60e1101a1_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60e1101a1.htm?s_cid=mm60e1101a1_w). Updated with 2009 mortality and 2010 treatment admission data.
Widespread Abuse and Misuse of Opioids

In 2008, there were 14,800 prescription painkiller deaths

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

Drug Overdose Deaths by Major Drug Type, United States, 1999–2010

Critical Vocabulary

- **Aberrant drug-related behavior**: Conduct outside the boundaries of the agreed upon treatment plan
- **Abuse**: Any use of an illegal drug, or a medication for a nonmedical purpose
- **Addiction**: Impaired control over drug use, compulsive use, continued use despite harm, and/or craving
- **Diversion**: The intentional transfer of a controlled substance from legitimate distribution and dispensing channels
- **Misuse**: Use of a medication other than as directed or as indicated
- **Physical dependence**: A state of biologic adaptation manifested by a withdrawal syndrome produced by decreasing blood levels of the drug
- **Tolerance**: A state of physiologic adaptation in which exposure to a drug induces a diminution of one or more opioid effects over time

On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications

Updated August, 2014

### What Drugs Are Covered by This REMS?

**Brand Name Products**
- Avinza® morphine sulfate ER capsules
- Butrans® buprenorphine transdermal system
- Dolophine® methadone hydrochloride tablets
- Duragesic® fentanyl transdermal system
- Embeda® morphine sulfate/naltrexone ER capsules*
- Exalgo® hydromorphone hydrochloride ER tablets
- Kadian® morphine sulfate ER capsules
- Methadose™ methadone hydrochloride tablets
- MS Contin® morphine sulfate CR tablets
- Nucynta® ER tapentadol ER tablets
- Opana® ER oxymorphone hydrochloride ER tablets
- OxyContin® oxycodone hydrochloride CR tablets
- Palladone® hydromorphone hydrochloride ER capsules†
- Zohydro™ ER hydrocodone bitartrate ER capsules
- Targiniq® ER oxycodone HCl and naloxone HCl ER tablets

**Generics**
- 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

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

Risks of ER/LA Opioid Analgesics

• Overdose with ER/LA formulations
• Abuse by patient or household contacts
  – Especially adolescent children
• Inadvertent exposure by household contacts
• Misuse and addiction
• Physical dependence and tolerance
• Interactions with other medications and substances
  – Medication reconciliation
• Neonatal opioid withdrawal syndrome with prolonged use during pregnancy
• Financial (diverting drugs for illegal sale)
Your Patient Complains of Pain: Where to Start

- Consider source or etiology of pain
- In most circumstances, use a non-opioid pain medication first
Clinical Interview: Getting Started

• Complete history
  – Family history of substance abuse (does not preclude treatment with ER/LA opioid)
  – Family history of psychiatric disorders
  – Social history, including criminal record

• Complete physical examination

• Use a screening tool
  – ORT, SOAPP, DIRE

Clinical Interview: Description and Impact of Pain

Description of current pain complaint
- Location
- Intensity
- Quality
- Onset/Duration
- Patterns

What causes or increases pain?

Effects of pain on physical, emotional, and psychosocial function

Patient’s pain and functional goals

Clinical Interview: Pain Coping Strategies

Pain Medications

Past use

Current use
• Query state PDMP where available to confirm patient report
• Contact past providers and obtain prior medical records
• Conduct Urine Drug Test (UDT)

Dosage
• For opioid currently prescribed: opioid, dose, regimen, and duration
  – Important to determine if patient is opioid tolerant

General Effectiveness

Nonpharmacologic strategies and effectiveness

Risk Factors for Aberrant Drug-related Behaviors

Other Factors:
- History of sexual abuse
- Criminal record
- Low reliability
- Lack of social support
- Smoking

What Were They Thinking?

- Is this patient really in pain?
- Is he/she seeking opioids?
- Is he/she an abuser?
- Is he/she addicted?

- Is the doctor taking my pain seriously?
- Should I reveal my history?
- Should I reveal my home life?
### Validated Questionnaires

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORT</td>
<td>Opioid Risk Tool</td>
</tr>
<tr>
<td>SOAPP</td>
<td>Screener &amp; Opioid Assessment for Patients with Pain</td>
</tr>
<tr>
<td>DIRE</td>
<td>Diagnosis, Intractability, Risk, and Efficacy inventory</td>
</tr>
<tr>
<td>STAR</td>
<td>Screening Tool for Addiction Risk</td>
</tr>
<tr>
<td>SISAP</td>
<td>Screening Instrument for Substance Abuse Potential</td>
</tr>
<tr>
<td>PDUQ</td>
<td>Prescription Drug Use Questionnaire</td>
</tr>
</tbody>
</table>

- No “gold standard”
- Lack of rigorous testing

# Opioid Risk Tool (ORT)

Mark each box that applies

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

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
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<tbody>
<tr>
<td>5.</td>
<td>Psychologic disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADD, OCD, bipolar, schizophrenia</td>
<td>□ 2</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>□ 1</td>
</tr>
</tbody>
</table>

**Administer**

- On initial visit
- Prior to opioid therapy

**Scoring (risk)**

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

**Scoring Totals:**


Clinical Interview: Conditions Suggestive of Abuse

Abuse?

- Hepatitis
- HIV
- Cellulitis
- Trauma, burns
- Cardiac/Pulmonary disease
- STD

Rationale for Urine Drug Testing (UDT)

Prior to Therapy
- Prior drug use
- Other drug use

During Therapy
- Adherence
- Legal requirement
- Grounds for referral
- Frequency per provider
A 38-year-old divorced mother of three teenagers presents with complaints of lower back pain since an MVA 4 years ago.

She describes the pain as constant, intense, and encompassing her whole lower back area. She relates that it is exacerbated by walking, bending, and lifting. The pain makes activities of daily life difficult.

She would like to have her pain reduced to a tolerable level.
Patient Work-Up

• Medical Hx
  – Prior physical therapy and medication have failed

• Social Hx
  – Remote history of marijuana use
  – Once convicted of writing bad checks

• Family Hx
  – Father abused alcohol
  – Recent break-up with an abusive boyfriend with a drug problem

• Exam
  – While describing the severity of her pain and her limitations, she does not appear to be in pain
  – Lower back demonstrates tenderness with some wincing
  – Gait is normal
What is this patient’s risk of abuse, misuse, or other aberrant behavior?

<table>
<thead>
<tr>
<th>Low</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Medium</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>High</th>
<th>7</th>
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</tbody>
</table>
Referring High-Risk Patients

Prescribers should

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

Documentation

• A risk/benefit evaluation
  – History
  – Physical exam
  – Diagnostic testing

• Patient interactions

• Previous health records, including prescriptions, MRI, CT

• Patient permission to obtain records from other providers

• Provider communication with other providers

• Treatment plan, patient/provider agreement, informed consent (module 3)

• Aberrant drug-related behavior

Module 1 Key Messages

• ER/LA opioids can be effective for pain management
• Benefit must be weighed against risk
• Medical and behavioral factors influence risk of abuse or misuse
• Patients should be regularly assessed
• Documentation of assessments, patient interactions, treatment plans, aberrant drug-related behavior, and involvement of other providers is critical
Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

Module 2
Learning Objectives

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• Manage ongoing therapy with ER/LA opioid analgesics

• Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics

• Discuss general and product-specific drug information related to ER/LA opioid analgesics
Analgesic and Functional Goals

• Decrease pain
  – Treat underlying cause where possible
  – Minimize medication use

• Restore function
  – Physical, emotional, social

• Correct secondary consequences of pain
  – Postural deficits, weakness, overuse
  – Maladaptive behavior, poor coping
Patient Prescriber Agreements
Informed Consent

Communication process between patient and provider, including:

- Potential risks and benefits
  - Side effects (both short- and long-term)
  - Tolerance and physical dependence
  - Drug interactions and over-sedation
  - Impaired motor skills
  - Misuse, dependence, addiction, and overdose
  - Evidence of benefit
- Physician’s prescribing policies and expectations
  - Number and frequency of refills
  - Policy on early refills and replacement of lost or stolen medications
- Specific reasons for changing or discontinuing opioid therapy, including violation of the treatment agreement

## Analgesic Selection

<table>
<thead>
<tr>
<th>Non-opioid approaches should be considered first</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Address underlying condition</td>
</tr>
<tr>
<td>• Non-opioid analgesia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short-acting opioids are probably safer than ER/LA for initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Shorter half-life</td>
</tr>
<tr>
<td>• May have a lower risk of inadvertent overdose</td>
</tr>
<tr>
<td>• Better for break-through pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proposed benefits of long-acting opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More consistent control of pain</td>
</tr>
<tr>
<td>• Improved adherence</td>
</tr>
<tr>
<td>• Lower risk of addiction or abuse</td>
</tr>
</tbody>
</table>

When to **Consider** a Trial of an ER/LA Opioid

- Pain is severe
- Patient failed to adequately respond to non-opioid & non-drug interventions
- Pain has an adverse impact on function or quality of life
- Potential therapeutic benefits outweigh potential harms

**Consider referral to pain or addiction specialist when risks outweigh benefits**


When to **Not Consider** a Trial of an ER/LA Opioid

Pain is acute

Condition is amenable to non-opioid or non-drug interventions

Patient is at high risk of aberrant drug-related behaviors

Presence of contraindications

Initiating & Titrating ER/LA Opioid Analgesics: Opioid-Naïve Patients

**Drug/Dose**
- For naïve?
- Drug PI

**Monitor**
- Respiratory Depression
- 24-72 hours

**Titrate**
- Efficacy
- Tolerability
- Adverse Effects
- Minimum interval → Drug PI

When Analgesia is Inadequate

<table>
<thead>
<tr>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reassess/manage underlying condition</td>
</tr>
<tr>
<td>Address behaviors that aggravate pain</td>
</tr>
<tr>
<td>Apply other non-opioid medications</td>
</tr>
<tr>
<td>Escalate opioid dose as a trial</td>
</tr>
<tr>
<td>Consider an ER/LA opioid (if using IR opioid)</td>
</tr>
<tr>
<td>Consider opioid rotation</td>
</tr>
</tbody>
</table>
Converting From Immediate Release to ER/LA Opioids

• Safety is primary

• Before conversion to a long-acting opioid, use immediate release preparations to titrate to the appropriate 24 hour dose

• Different approaches
  
  A. Use opioid equianalgesic dose table (EDT, conversion table) to switch

  B. Use cross-titration
    • Slowly decrease old opioid
    • Slowly increase new opioid
    • May take weeks to achieve proper dosing
Switching ER/LA Opioids: Rotation

Dissatisfaction

• AE
• Poor efficacy
• Drug interactions
• Route of administration
• Change in clinical status
• Financial or drug-availability

Weigh

• Age and race
• Clinical state
• Comorbidities
• Other medications

Other Drug

• Drug sensitivities
• Convenience
• Improved adherence
• Financial
• Best dose!?!?

You have decided to switch ER/LA medications. At what dose should the second ER/LA opioid be initiated?

- Equivalent dose, from the ED table
- 25–50% reduction of equivalent dose
- 75% reduction of equivalent dose
- Initiate as new treatment after wash-out period
Choosing a New Dose

Calculate equianalgesic dose of new opioid from EDT

Reduce calculated equianalgesic dose
- Generally: 25–50% reduction
- Methadone: 75–90% reduction
- Use clinical judgment

~50% reduction if patient
- Receives a high dose of current opioid
- Elderly or medically frail

~25% reduction if patient
- Is staying on current opioid but switching to a different administration route

Guidelines for Opioid Rotation

If switching to **methadone**:
- Reduce calculated equianalgesic dose by **75–90%**
- For patients on very high opioid doses, be cautious converting to methadone ≥ 100 mg/d
  - Consider inpatient monitoring, including serial EKG

If switching to **transdermal formulation**:
- **Fentanyl**: use equianalgesic dose ratios in the PI
- **Buprenorphine**: follow instructions in the PI
Guidelines for Opioid Rotation

Frequently assess:

- Analgesia
- AEs
- Withdrawal symptoms

Titrate new opioid dose

Break Through Pain

- Use a short-acting, immediate release preparation at 5–15% of total daily opioid dose
- If oral transmucosal fentanyl is used for BTP, always begin at lowest dose
- NEVER use ER/LA opioids for BTP

Opioid Rotation: Summary

Values from EDT

Patient opioid values

“Solve” for X

Always reduce dose

\[
\text{Value of current opioid} \div \text{Value of new opioid} = \text{Value of new opioid}
\]

\[
\text{24 HR dose of current opioid} \div \text{X amount of new opioid} = \text{Equianalgesic 24 HR dose of new opioid}
\]

\[
\text{By 25\% - 50\%}
\]

Frequently assess initial response

Titrate dose of new opioid to optimize outcomes

Calculate supplemental rescue dose used for titration at 5\%–15\% of total daily dose

\( ^{†} \text{If switching to methadone, reduce dose by 75–90\%} \)

\( ^{‡} \text{If oral transmucosal fentanyl used as rescue, begin at lowest dose irrespective of baseline opioid} \)

Improper Opioid Rotation Can Be Fatal

• Nearly 15,000 people die every year as a result of overdoses involving prescription painkillers
• 5 of the 15 drugs most frequently named in FDA-reported fatal outcomes were opioids
• Why?
  – Polysubstance abuse
  – Nonmedical use and misuse
  – Prescriber’s competence
  – Proliferation of inconsistent guidelines for opioid rotation
  – Use of equianalgesic tables as conversion tables
  – Limitations inherent in the equianalgesic dose tables

ER/LA Opioid-Induced Respiratory Depression

<table>
<thead>
<tr>
<th>Chief hazard of opioids</th>
<th>Reduced urge to breathe &amp; decreased respiration rate</th>
<th>Instruct patients/family</th>
</tr>
</thead>
<tbody>
<tr>
<td>May lead to respiratory arrest &amp; death</td>
<td>Shallow breathing</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Greatest risk after initiation or dose increase</td>
<td>CO₂ retention can exacerbate opioid sedating effects</td>
<td>Call 911</td>
</tr>
<tr>
<td>Alcohol, sedatives, hypnotics, etc</td>
<td></td>
<td>Dangerous polypharmacy</td>
</tr>
</tbody>
</table>

*Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.* 2012.
### Opioid Exit Strategy – Possible Paths

<table>
<thead>
<tr>
<th>Patient’s behavior consistent with drug addiction</th>
<th>Patient unable or unwilling to cooperate with outpatient taper</th>
<th>No apparent addiction problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Refer for addiction management or comanagement</td>
<td>• Provide limited and closely monitored prescriptions while referring to more intensive services</td>
<td>• Taper gradually over 1-2 months</td>
</tr>
<tr>
<td></td>
<td>• Implement non-opioid pain management (psychosocial support, CBT, PT, non-opioid analgesics)</td>
<td></td>
</tr>
</tbody>
</table>

CBT, cognitive behavioral therapy; PT, physical therapy.
Taper Dose When Discontinuing

Avoid withdrawal symptoms in opioid dependent patients

Optimal setting
• Outpatient in absence of unstable medical or psychiatric conditions or unsafe patterns of behavior
• Higher risk patients may need a more structured setting

When aberrant drug-related behaviors continue, may need
• Close monitoring and enforced tapering or
• Discontinued prescription and referral to detox or
• Agonist therapy

May use a range of approaches
• Slow...10% dose reduction/week
• Rapid...25–50% reduction every few days

Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for Management of Opioid Therapy
Taper Dose When Discontinuing

Factors that influence the reduction rate:

- Reason for discontinuation
- Medical and psychiatric comorbidities
- Initial weaning rate
  - Faster at high doses (eg, > 200 mg/d morphine equivalent)
  - Slower at low doses (eg, 60-80 mg/d morphine equivalent)
- Monitor withdrawal symptoms

After taper:

- Continue to treat pain with non-opioids
- Treat psychiatric disorders
- Assess for and treat addiction-related aberrant behaviors

Module 2 Key Messages

• Best analgesic choice depends on patient and condition
  – Non-opioid analgesia
  – Immediate-release opioid
  – ER/LA opioid

• Rotation/conversion is not an exact science but protocols give guidance

• ER/LA are not for breakthrough pain

• Respiratory depression is rare but serious

• Opioids should be discontinued by tapering
Managing Therapy with ER/LA Opioid Analgesics

Module 3
Learning Objectives

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• Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain

• Manage ongoing therapy with ER/LA opioid analgesics

• Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics

• Discuss general and product-specific drug information related to ER/LA opioid analgesics
Analgesic and Functional Goals

• **Decrease pain**
  – Treat underlying cause where possible
  – Minimize medication use

• **Restore function**
  – Physical, emotional, social

• **Correct secondary consequences of pain**
  – Postural deficits, weakness, overuse
  – Maladaptive behavior, poor coping
Pain Assessment

- **Current pain**
  - Numeric rating scale
  - Visual analog scale
  - Faces scale
- **Pain history**
- **PQRS Measure #131**

Patients sometimes assume that you don’t believe their pain complaints

They may exaggerate pain scores
Self-Reflection on Patient Management

How often do you use **quantitative scales** for pain, functional status, and adverse events?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Sometimes</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Function</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>AEs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
1. Would you say that, in general, your health is:

2. Now thinking about your **PHYSICAL HEALTH**, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

3. Now thinking about your **MENTAL HEALTH**, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

4. During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?

Side Effect Rating Scale: FIBSER
Frequency, Intensity, and Burden of Side Effects Rating

**Frequency**
- % time present
- None → always
- 0-6 scale

**Intensity**
- Severity
- None → intolerable
- 0-6 scale

**Impact**
- Degree of interference
- None → nonfunctional
- 0-6 scale

Patient Prescriber Agreements
Informed Consent

Communication process between patient and provider, including:

• Potential risks and benefits
  – Side effects (both short- and long-term)
  – Tolerance and physical dependence
  – Drug interactions and over-sedation
  – Impaired motor skills
  – Misuse, dependence, addiction, and overdose
  – Evidence of benefit

• Physician’s prescribing policies and expectations
  – Number and frequency of refills
  – Policy on early refills and replacement of lost or stolen medications

• Specific reasons for changing or discontinuing opioid therapy, including violation of the treatment agreement

Patient Prescriber Agreements
Written Opioid Treatment Agreement

Rationale for Urine Drug Testing (UDT)

Prior to Therapy
- Prior drug use
- Other drug use

During Therapy
- Adherence
- Legal requirement
- Grounds for referral
- Frequency per provider
UDT Stages

SCREENING
- Immunoassay
- Drug class
- Qualitative (+/-)
- Lab or POC

CONFIRMATION
- GC/MS or LC/MS
- Specific, definitive
- Quantitative
- Lab

## Specific Windows of Drug Detection

<table>
<thead>
<tr>
<th>Drug in Urine</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>≤ 2 d</td>
</tr>
<tr>
<td>THC</td>
<td>1-3 d; ≤ 30 d</td>
</tr>
<tr>
<td>– Single use</td>
<td></td>
</tr>
<tr>
<td>– Chronic use</td>
<td></td>
</tr>
<tr>
<td>Benzoylecgonine after cocaine use</td>
<td>2-4 d</td>
</tr>
<tr>
<td>Opiates (morphine, codeine)</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Methadone</td>
<td>≤ 3 d; ≤ 6 d</td>
</tr>
<tr>
<td>– EDDP (methadone metabolite)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines (depending on drug and dose)</td>
<td>Days to weeks</td>
</tr>
</tbody>
</table>

Interpretation of Confirmed Results

Positive Result

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

Does not diagnose
• Drug addiction, physical dependence, or impairment
• Metabolism can alter results

Can’t 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

Interpretation of UDT Results

• Use UDT results in conjunction with other clinical information
• Investigate unexpected results

Discuss with the lab

Discuss with the patient

A positive result is probably a positive result.

• Document results, interpretation, and action
• May necessitate closer monitoring and/or referral to a specialist
Screening for Substance Abuse

• Pain Assessment and Documentation Tool (PADT)
  – 17 Y/N questions
  – Plus pain and function sections

• Current Opioid Misuse Measure (COMM)
  – 17 questions
  – 5 item Likert scale

Recognizing Addiction

• DSM-5 Criteria for Substance Use Disorder\(^1\)
  – Tolerance
  – Withdrawal
  – Taken more/longer than intended
  – Desire/unsuccessful efforts to quit use
  – Great deal of time taken by activities involved in use
  – Use despite knowledge of problems associated with use
  – Important activities given up because of use
  – Recurrent use resulting in a failure to fulfill important role obligations
  – Recurrent use resulting in physically hazardous behavior (e.g., driving)
  – Continued use despite recurrent social problems associated with use
  – Craving for the substance

• Pain Medicine Questionnaire\(^2\) (PMQ, 26 self-report items)

• Screener and Opioid Assessment for Patients with Pain\(^3\) (SOAPP, 24 self-report items)

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Case

- You have started a 49-year-old married mother of 2 grown children on a short-acting opioid for failed back syndrome. She got little relief from the first dose you prescribed and little relief from 3 months of a higher dose
  - Your staff points out that she has requested early refills twice
- Her son calls about his mother’s treatment
- He reports that she is uncommunicative, spending more time in bed and on the sofa, and not leaving the house for social events and church as was her custom. This information conflicts with the patient’s reports to you that she is
  - Functioning as before
  - Having lots of pain
- A random UDT is positive for your opioid and a benzodiazepine
- At the next visit the patient reports that she is
  - Functioning as before
  - Having lots of pain
- Her physical exam is unchanged
- You decide to speak candidly with her about her care
Confidence in Patient Management

What conclusion(s) can you make on the basis of the UDT? (choose all that apply)

- She is taking the opioid as directed
- She may be abusing other drugs
- She is not taking the opioid as directed
- She may be addicted
Common Adverse Events

Nausea/Vomiting
- Tend to self-resolve
- Switch opioid
- Antiemetic

Sedation
- Tends to self-resolve
- Decrease dose

Constipation
- Laxative
- Bowel stimulant
- Switch opioid

Pruritus
- Tends to self-resolve
- Antihistamines
- Switch opioid

Many patients report being allergic to pain medication, especially opioids

Universal Precautions for Prescribing Controlled Substances

1. Make a Diagnosis with Appropriate Differential
2. Psychological Assessment Including Risk of Addictive Disorders
3. Informed Consent
4. Treatment Agreement
5. Pre- and Post-Intervention Assessment of Pain Level and Function
6. Appropriate Trial of Opioid Therapy +/- Adjunctive Medication
7. Reassessment of Pain Score and Level of Function
8. Regularly Assess the “Five A’s” of Pain Medicine
   - Analgesia
   - Adverse effects
   - Activity
   - Aberrant behavior
   - Affect
9. Periodically Review Pain Diagnosis and Comorbid Conditions, including Addictive Disorders
10. Documentation

Module 3 Key Messages

• Set specific analgesic and functional goals
• Use a PPA as a framework
• Document discussions, patient commitments, actions, results
• Refer patients for addiction and abuse treatment as needed
• Identify and manage adverse events
Learning Objectives

• Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
• Assess patient’s risk of abuse, including substance use and psychiatric history
• Identify state and federal regulations on opioid prescribing
• Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
• Manage ongoing therapy with ER/LA opioid analgesics
• Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
• Discuss general and product-specific drug information related to ER/LA opioid analgesics
Patient Counseling Document: The DOs of ER/LA Opioids

• READ the medication guide
  – Take your medicine exactly as prescribed
  – Store your medicine in a safe place away from children
  – Flush unused medicine down the toilet
  – Seek help if you do not understand something

• REPORT side effects
  – Call your health care provider
  – Report to the FDA at 1-800-FDA-1088

• CALL 911 or your local emergency service right away if
  – You take too much medicine
  – You have trouble breathing or shortness of breath
  – A child has taken this medicine

• TALK to your health care provider
  – If the medication does not control your pain
  – About side effects
  – About all your medicines: Rx, OTC, vitamins, and supplements

Patient Counseling Document:
The DON’Ts of ER/LA Opioids

DON’T give your medicine to others

DON’T take medicine unless it was prescribed for you

DON’T stop taking your medicine without talking to your health care provider

DON’T break, chew, crush, dissolve, or inject your medicine
DON’T drink alcohol while taking this medicine

Reflection on Clinical Practice

How do you use the ER/LA opioid prescribing information when counseling a patient with chronic pain? (choose all that apply)

- I don’t generally refer to it
- I use it to discuss dosing
- I use it to discuss side effects and warnings
- I use to structure the patient discussion
- I give a copy to patients

Product-Specific Information

• Drug **Prescribing Information** documents include critical information
  – Indications, usage
  – Dosage forms and strengths, administration
  – Contraindications, warnings, precautions
  – Common adverse reactions, drug interactions
  – Specific populations
  – Counseling information, medication guide

• Easily available: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
One of your patients travels a lot and has an irregular lifestyle. She is scrupulously adherent; her testimony is supported by UDTs. Airline seats and lack of exercise have exacerbated her back pain and she has developed tolerance to oxycodone. What is your recommendation?

- Increase her oxycodone dose
- Convert to a transdermal formulation
- Taper her oxycodone and seek a non-opioid analgesic
FDA Labeling Supplement Boxed Warning

- TRADENAME exposes users to risks of **addiction, abuse, and misuse**, which can lead to overdose and death. Assess each patient’s risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)

- Serious, life-threatening, or fatal **respiratory depression** may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow TRADENAME (formulation) whole to avoid exposure to a potentially fatal dose of (active opioid). (5.2)

- **Accidental consumption** of TRADENAME, especially in children, can result in fatal overdose of (active opioid). (5.2)

- For patients who require opioid therapy while pregnant, be aware that infants may require treatment for **neonatal opioid withdrawal syndrome**. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome. (5.3)

*For products with an interaction with alcohol, also include the following:*

- **Instruct patients not to consume alcohol** or any products containing alcohol while taking TRADENAME because co-ingestion can result in fatal plasma (active opioid) levels. (5.4)

Special Warnings for Patients: Labeling Supplement

- Never break, chew, or crush an oral ER/LA tablet/capsule, or cut or tear patches prior to use
  - May lead to rapid release of ER/LA opioid causing overdose and death
  - Applesauce or feeding tube may be appropriate (consult PI)

- Use of other CNS depressants with ER/LA opioids can cause overdose and death
  - Sedative-hypnotics and anxiolytics
  - Alcohol
  - Illegal drugs

- Use other CNS depressants, including other opioids, under the instruction of their prescriber

- Talk to your provider about your medical history, as many functions can be impacted by ER/LA opioids

- Do not abruptly stop or reduce the ER/LA opioid dose

- After you stop taking your drug, flush any unused tablets down the toilet

Medication Guide

• Each PI contains detailed patient instructions about dosing, custody, precautions, disposal, etc
• Lay language, should be shared with patients verbally and in printed form
• Patient literacy and/or language barriers must be identified and addressed

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Medication Guide
KADIAN® (key-dee-uhn)
(morphine sulfate) extended-release capsules, CII

KADIAN is:
• A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
• A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
• Not for use to treat pain that is not around-the-clock.

Important information about KADIAN:
• Get emergency help right away if you take too much KADIAN (overdose). When you first start taking KADIAN, when your dose is changed, or if you take too much (overdose), serious or life threatening breathing problems that can lead to death may occur.
• Never give anyone else your KADIAN. They could die from taking it. Store KADIAN away from children and in a safe place to prevent stealing or abuse. Selling or giving away KADIAN is against the law.

Do not take KADIAN if you have:
• severe asthma, trouble breathing, or other lung problems.
• a bowel blockage or have narrowing of the stomach or intestines.

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Review All Medications: What Other Drugs Might Impact Treatment?

Opioids

- Alcohol
- Other Opioid Source
- PGP Inhibitors
- Anti-arrhythmics
- MAO Inhibitors
- CYP Inhibitors Inducers
- BZD
- MAO Inhibitors

Source
## Specific Drug Interactions

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<tr>
<th>Product</th>
<th>Alcohol*</th>
<th>PGP Inhibitors</th>
<th>CYP 3A4 Inhibitors/Inducers</th>
<th>CYP 450 Inhibitors/Inducers</th>
<th>Benzo-diazepines</th>
<th>MAO Inhibitors</th>
<th>Class IA + III Antiarrhythmics</th>
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</table>

*Including medications containing alcohol

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FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
Diversion in the Home

Own the Prescriptions
• Note how many pills in each prescription bottle or packet
• Take inventory of all prescription drugs in your home
• Track refills for all household members
• Keep meds in a safe place, not the bathroom cabinet

Know Their Weaknesses
• Teens: adventure
• Elderly: drug naïveté

Discard Expired or Unused Meds

Public Awareness Campaign
When to Discontinue Opioids

• Severe unmanageable adverse effects
• Serious or persistent nonadherence to the treatment plan
• Illegal or unsafe behaviors
• Misuse suggestive of addiction to prescribed medication
• Lack of effectiveness
• Patient preference
• Decreased level of pain in stable patients
• Goals of treatment are not met

Tapering Opioids: General Considerations

- Individualize; faster or slower tapering may be warranted
- Complete evaluation prior to initiation of the taper
  - Current treatment plan
  - Psychological conditions
  - Other relevant factors should be completed
- Clear written and verbal instructions should be given to patients and their families to minimize withdrawal symptoms

Tapering Opioids: Patients to Refer

- High risk to engage in aberrant behaviors (e.g., parasuicidal acts; dealing/selling medications; severe impulse control disorders)
- Complicated withdrawal symptoms
- Opioid addiction
- Refer to an addiction or pain specialist!

Tapering Opioids: Patient Considerations

• Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids.

• Consider tapering opioids in patients who have received regularly scheduled opioids at greater than the recommended starting doses for more than a few days.

• Non-daily, as-needed opioids do not usually need tapering.

• Patient-specific factors:
  – Risk of precipitating withdrawal.
  – Level of anxiety about discontinuing.
  – Duration of opioid therapy (longer use → slower taper).
  – Medical and psychological comorbidities.
  – Clinical need for rapid taper.

Tapering Opioids: Specific Considerations

• Taper by 20–50% per week for patients who are not addicted
• A patient needs 20% of the previous day’s dose to prevent withdrawal symptoms
• Consider adjuvant agents such as antidepressants to manage irritability and sleep disturbance, or antiepileptics for neuropathic pain
• Patient on fentanyl should be rotated to a different opioid, either long-acting morphine or methadone
  – Once the patient is converted, the same guidelines will apply

How should patients dispose of expired or unused opioids?

- Trash
- Mix with kitty litter and put into trash
- Flush down toilet
- Community drug collection
- Mix with kitty litter and put into trash
First Choice: Community Drug Take-Back

• National Prescription Drug Take-Back Day: “Got Drugs?”
• More than 5000 sites participate
• Check with local government for day/location

FDA Drug Disposal Guidelines

• Follow the prescription drug labeling
• Community drug take-back programs
• Container: scratch out all identifying information on the label
• Do not give your medicine to friends
• When in doubt, talk to your pharmacist

Dispose of unused ER/LA opioids by flushing down the toilet

Module 4 Key Messages

• Use a Patient Counseling Document to communicate

• Refer to drug-specific Prescribing Information
  – Includes a Medication Guide for patients
  – Proper disposal of drugs

• An exit strategy is critical
  – Know when to discontinue opioids
  – Know how to taper opioids
  – Know when to refer to a specialist
Anyone ready for a break?
Learning Objectives

• Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
• Assess patient’s risk of abuse, including substance use and psychiatric history
• Identify state and federal regulations on opioid prescribing
• Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
• Manage ongoing therapy with ER/LA opioid analgesics
• Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
• Discuss general and product-specific drug information related to ER/LA opioid analgesics
Drug Information Common to ER/LA Opioid Analgesics

Limitations of usage

- Not for as-needed analgesia
- Not for mild pain or pain not expected to persist for an extended duration
- Not for use in treating acute pain

Drug Information Common to ER/LA Opioids  

**Key Instructions**

- Reserve for use in patients for whom alternative options are ineffective, not tolerated, or inadequate.
- Titrate a dose that provides adequate analgesia and minimizes adverse reactions.
- Times required to reach steady-state plasma concentrations are product specific (Refer to PI for titration interval).
- Continually reevaluate patient to assess pain control and adverse effects.
- Consult drug PI for dosage reduction with hepatic or renal impairment.

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 08/2014  
A 32-year-old patient who suffered multiple fractures in a motor vehicle accident at age 16 has chronic pain. He is on metoprolol, NSAIDs, gabapentin, and alprazolam but needs increased pain relief. What is the best next step?

- Taper the alprazolam before ER/LA opioid initiation
- Initiate an ER/LA opioid but monitor for respiratory depression
- Begin with a medication reconciliation to avoid drug-drug interactions
- Try a different non-opioid analgesic first
ER/LA Opioids: Transdermal Dosage

• Application
  – Rotate location of application
  – Prepare skin
    ➢ Clip (don’t shave) hair; wash only with water

• Safety
  – Strenuous exertion or external heat exposure may lead to increased absorption and possible overdose
  – Monitor patients with fever for signs/symptoms of increased opioid exposure
  – Handle and dispose appropriately
    ➢ Avoid exposure of caregivers/children
  – Do not cut, damage, chew or swallow
  – Products with metal foil backings are not safe for MRIs

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
ER/LA Opioid Analgesics Drug Interactions

CNS Depressants

ER/LA Opioid Analgesics

Concurrent Use

Risk of:
• Respiratory depression
• Hypotension
• Profound sedation
• Coma

Reduce the initial dose of one or both agents

CNS Depressants

• Sedatives
• Hypnotics
• General anesthetics
• Antiemetics
• Phenothiazines
• Other tranquilizers
• Alcohol

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
Partial agonists and mixed agonist/antagonist analgesics

- Buprenorphine
- Pentazocine
- Nalbuphine
- Butorphanol

May reduce analgesic effect
Precipitate withdrawal symptoms

Avoid concurrent use
ER/LA Opioid Analgesics Drug Interactions

**Antiarrhythmic Agents**

- Methadone
- Buprenorphine

**Concurrent Use**

**Antiarrhythmic Agents such as:**
- Class IA
  - Quinidine
  - Procainamide
  - Disopyramide
- Class III
  - Sotalol
  - Amiodarone
  - Dofetilide

**May cause QTc prolongation/arrhythmia**

Avoid use of these opioids in patients with long QT Syndrome or those taking antiarrhythmic medications.

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
ER/LA Opioid Analgesics Drug Interactions

CYP Inhibitors/Inducers may impact blood levels of ER/LA opioids

!! Consult product-specific information !!

CYP Inhibitors

Opioid Levels

CYP Inducers

Opioid Levels

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
## ER/LA Opioid Analgesics Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol; medications with alcohol</td>
<td>• Some ER opioid formulations may rapidly release opioid when exposed to alcohol (&quot;<strong>dose dump</strong>&quot;)</td>
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<tr>
<td></td>
<td>• Some drug levels may increase without dose dumping when exposed to alcohol</td>
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<tr>
<td></td>
<td>• See individual PI</td>
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<tr>
<td>Monoamine oxidase inhibitors (MAOIs)</td>
<td>• Using opioids with MAOIs may increase <strong>respiratory depression</strong></td>
</tr>
<tr>
<td></td>
<td>• May cause <strong>serotonin syndrome</strong></td>
</tr>
<tr>
<td>Diuretics</td>
<td>• Opioids can reduce diuretic efficacy by inducing <strong>ADH</strong></td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>• Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and increase <strong>respiratory depression</strong></td>
</tr>
<tr>
<td>Anticholinergic medications</td>
<td>• Concurrent use increases the risk of <strong>urinary retention</strong> and <strong>severe constipation/paralytic ileus</strong></td>
</tr>
</tbody>
</table>
ER/LA Opioid Analgesics Drug Interactions

Illicit Drugs

• A retrospective study of 21,746 patients treated with opioids for chronic pain
• Urine samples analyzed to determine co-occurrence of illicit drugs
  – 13% + for THCA (tetrahydrocannabinol)
  – 4.6% + for cocaine
  – 1.1% + for methamphetamine
  – Of those using marijuana, 14% were also using cocaine or methamphetamine
• Patients using illicit drugs and prescribed opioids are at risk for reactions from the abused substances and from drug-drug interactions

ER/LA Opioid Analgesics

*Tolerance to sedating and respiratory depressant effects of opioids is critical to the safe use of certain products/strengths/doses*

- Products used **ONLY** in opioid-tolerant patients
  - Transdermal fentanyl
  - Hydromorphone HCl ER

- For other products, patients must be opioid tolerant **before** using
  - Certain strengths
  - Certain daily doses
  - Refer to individual PI

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
**ER/LA Opioid Analgesics**

*Relative Potency to Morphine*

- Intended as a *general guide*
- Follow conversion instructions in *individual PI*
- Incomplete cross-tolerance and inter-patient variability require conservative dosing when converting from 1 opioid to another
  - Halve the calculated comparable dose; titrate new opioid as needed

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FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
Prescribers should be knowledgeable about general characteristics, class adverse effects, and drug interactions for ER/LA opioid analgesic products.

- This information provides the foundation for assimilation of product-specific information and the safe/effective use of ER/LA opioid analgesics.
Specific Drug Information for ER/LA Opioid Analgesic Products

Module 6
Learning Objectives

• Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
• Assess patient’s risk of abuse, including substance use and psychiatric history
• Identify state and federal regulations on opioid prescribing
• Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
• Manage ongoing therapy with ER/LA opioid analgesics
• Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
• Discuss general and product-specific drug information related to ER/LA opioid analgesics
Informed Treatment Decisions

Consider product characteristics that align with patient needs

Drug substance
- Formulation
- Strength

Dosing interval

Key instructions
- Titration
- Limitations of usage
- Product conversion information

Specific drug interactions

Product-specific safety concerns

Use in opioid-tolerant patients

Potency relative to oral morphine

Drugs@FDA: [www.fda.gov/drugsatfda](http://www.fda.gov/drugsatfda)
A Look at Different ER/LA Opioid Analgesic Products

• Compare and contrast
  – Relative potency of ER/LA opioid agents
  – Dosing frequency
  – Use based on opioid exposure
  – Specific drug interactions

• Specific characteristics

Oral

• Morphine sulfate (4)
• Oxycodone
• Oxymorphone
• Hydromorphone
• Methadone
• Tapentadol

Transdermal

• Buprenorphine
• Fentanyl
Relative Potency to Oral Morphine

Important to consult PIs for use of opioids as first agents and for conversion/rotation procedures

Morphine
- Oxycodone: 2:1
- Oxymorphone: 3:1
- Hydromorphone: 5:1
- Transdermal Fentanyl: > 100:1

Dose Ratio (Oral Morphine to Other Agents)

Methadone
- Varies contingent on prior opioid exposure

Not Established
- Buprenorphine
- Tapentadol

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
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<th>Product</th>
<th>Every 8 or 12 hours</th>
<th>Every 12 hours</th>
<th>Once/Day or Every 12 hours</th>
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<td>Buprenorphine Transdermal (Butrans)</td>
<td><img src="Tick" alt="Tick" /></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
**Morphine Sulfate ER-Naltrexone: Embeda**

20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg Capsules

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>• Once/day or every 12 hours</th>
</tr>
</thead>
</table>
| Instructions    | • Initial dose as first opioid: 20 mg/0.8 mg  
• Titrate using a **minimum of 3-day intervals**  
• **Swallow capsules whole** (do not chew, crush, or dissolve)  
• Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms  
• May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately |
| Specific Drug Interactions | • **Alcoholic beverages** or **medications containing alcohol** may result in the rapid release and absorption of a potentially fatal dose of morphine  
• **PGP inhibitors** (eg, quinidine) may increase the absorption/exposure of morphine sulfate by about 2-fold |
| Use in Opioid Tolerant Patients | • **100 mg/4 mg capsule** is for use in **opioid-tolerant patients only** |
| Product-Specific Safety Concerns | • None |

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Morphine Sulfate ER-Naltrexone: *Embeda*

20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg Capsules

**Dosing Interval**
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**Instructions**
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- Swallow capsules whole (do not chew, crush, or dissolve)
- Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms
- May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately

**Clinical Pearls:**
- Naltrexone - deterrent for intravenous abuse
- Voluntarily recalled March 2011, may become available early 2015
- Dosage titration should only occur at 3-day intervals

**Specific Drug Interactions**
- Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine
- PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by about 2-fold

**Use in Opioid Tolerant Patients**
- 100 mg/4 mg capsule is for use in opioid-tolerant patients only

**Product-Specific Safety Concerns**
- None

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### Dosing Interval

- Every 12 hours

### Instructions

- **Opioid-naïve patients:** initiate treatment with 10 mg every 12 hours
- Titrate using a **minimum of 1 to 2 day intervals**
- **Hepatic impairment:** start with one third to one half the usual dosage
- **Renal impairment** (creatinine clearance < 60 mL/min): start with one half the usual dosage
- Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction.
- **Swallow tablets whole** (do not chew, crush, or dissolve)
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth

### Specific Drug Interactions

- **CYP3A4 inhibitors** may increase oxycodone exposure
- **CYP3A4 inducers** may decrease oxycodone exposure

### Use in Opioid Tolerant Patients

- Single dose greater than 40 mg or **total daily dose greater than 80 mg** are for use in **opioid-tolerant patients only**

### Product-Specific Safety Concerns

- Choking, gagging, regurgitation, tablets stuck in the throat, **difficulty swallowing the tablet**
- Contraindicated in patients with gastrointestinal obstruction

### Relative Potency to Oral Morphine

- ~2:1 oral morphine to oxycodone oral dose ratio

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### Oxycodone Hydrochloride CR: OxyContin

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

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 12 hours</td>
<td>- Opioid-naïve patients: initiate treatment with 10 mg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>- Titrate using a minimum of 1 to 2 day intervals</td>
</tr>
<tr>
<td></td>
<td>- Hepatic impairment: start with one third to one half the usual dosage</td>
</tr>
<tr>
<td></td>
<td>- Renal impairment (creatinine clearance &lt; 60 mL/min): start with one half the usual dosage</td>
</tr>
<tr>
<td></td>
<td>- Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction</td>
</tr>
<tr>
<td></td>
<td>- Swallow tablets whole (do not chew, crush, or dissolve)</td>
</tr>
<tr>
<td></td>
<td>- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth</td>
</tr>
</tbody>
</table>

### Clinical Pearls:
- Tablet “ghosts” may appear in stool
- Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction

### Relative Potency to Oral Morphine
- ~ 2:1 oral morphine to oxycodone oral dose ratio

---

# Methadone Hydrochloride: *Dolophine*
## 5 and 10 mg Tablets

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>• Every 8 to 12 hours</th>
</tr>
</thead>
</table>

## Instructions
- Initial dose in opioid non-tolerant patients: 2.5 to 10 mg
- **Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death.** Use low doses according to the table in the full prescribing information
- **High inter-patient variability** in absorption, metabolism, and relative analgesic potency
- Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (CFR, Title 42, Sec 8)

## Specific Drug Interactions
- Pharmacokinetic drug-drug interactions with methadone are complex
  - **CYP 450 inducers** may decrease methadone levels
  - **CYP 450 inhibitors** may increase methadone levels
  - **Anti-retroviral agents** have mixed effects on methadone levels
- **Potentially arrhythmogenic agents** may increase risk for QTc prolongation and torsade de pointes
- **Benzodiazepines** may increase respiratory depression

## Use in Opioid Tolerant Patients
- Refer to full prescribing information

## Product-Specific Safety Concerns
- QTc prolongation and torsade de pointe
- Peak respiratory depression occurs later and persists longer than analgesic effect
- Clearance may increase during pregnancy
- False positive urine drug screens possible

## Relative Potency to Oral Morphine
- Varies depending on patient’s prior opioid experience

---

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013
Methadone Hydrochloride: Dolophine

5 and 10 mg Tablets

Dosing Interval
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• Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information
• High inter-patient variability in absorption, metabolism, and relative analgesic potency
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  – CYP 450 inducers may decrease methadone levels
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  – Antiretroviral agents have mixed effects on methadone levels
• Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointes
• Benzodiazepines may increase respiratory depression

Use in Opioid Tolerant Patients
• Refer to full prescribing information

Product-Specific Safety Concerns
• QTc prolongation and torsade de pointe
• Peak respiratory depression occurs later and persists longer than analgesic effect
• Clearance may increase during pregnancy
• False positive urine drug screens possible

Relative Potency to Oral Morphine
• Varies depending on patient’s prior opioid experience

Clinical Pearls:
• Good for nociceptive/neuropathic pain
• Double-check your conversions
• There may be prolonged respiratory depression with methadone compared to other opioids at weekly intervals because of long half-life
• Titrate dose at weekly intervals depending on patient’s prior opioid experience

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics: 04/2013
# Fentanyl: *Duragesic*

12, 25, 50, 75, and 100 mcg/hr Transdermal System

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Interval</strong></td>
<td>One transdermal system every 3 days (72 hours)</td>
</tr>
<tr>
<td>Use product specific information for dose conversion from prior opioid</td>
<td>Use 50% of the dose in mild or moderate hepatic or renal impairment, <strong>avoid use in severe hepatic or renal impairment</strong></td>
</tr>
<tr>
<td>Application</td>
<td><strong>Avoid exposure to heat</strong></td>
</tr>
<tr>
<td>– Apply to intact/non-irritated/non-irradiated skin on a flat surface</td>
<td><strong>Avoid accidental contact when holding or caring for children</strong></td>
</tr>
<tr>
<td>– Skin may be prepped by clipping hair, washing site with water only</td>
<td><strong>Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet</strong></td>
</tr>
<tr>
<td>– Rotate site of application</td>
<td><strong>Specific contraindications:</strong></td>
</tr>
<tr>
<td>– Titrate using <strong>no less than 72 hour intervals</strong></td>
<td>– Patients who are not opioid-tolerant</td>
</tr>
<tr>
<td>– <strong>Do not cut</strong></td>
<td>– Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time</td>
</tr>
</tbody>
</table>

### Dosing Interval

- One transdermal system every 3 days (72 hours)

### Specific Drug Interactions

- **CYP3A4 inhibitors** may increase fentanyl exposure
- **CYP3A4 inducers** may decrease fentanyl exposure

### Use in Opioid Tolerant Patients

- All doses of fentanyl are indicated for use in **opioid-tolerant patients only**

### Product-Specific Safety Concerns

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

### Relative Potency to Oral Morphine

- See individual product information for conversion recommendations from prior opioid

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### Dosing Interval

- One transdermal system every 3 days (72 hours)

### Specific Drug Interactions

- CYP3A4 inhibitors may increase fentanyl exposure
- CYP3A4 inducers may decrease fentanyl exposure

### Use in Opioid Tolerant Patients

- All doses of fentanyl are indicated for use in opioid-tolerant patients only

### Product-Specific Safety Concerns

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

### Clinical Pearls:

- Good for late-stage pain
- Do not use in opioid naïve patients
- Residual drug in patch after use
  - Potential for abuse
  - Dispose of properly

### Relative Potency to Oral Morphine

- See individual product information for conversion recommendations from prior opioid

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**FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013**

Module 6 Key Messages

- Safe prescribing of ER/LA opioid analgesics requires knowledge of product-specific information.
- Product factors to consider when formulating individualized treatment plans:
  - Safety
  - Dosing
  - Tolerance
  - Formulation
  - Potency
  - Key Instructions
  - Drug interactions
Thank you for participating!

- Please take the posttest
- Please fill out the evaluation