CHAPTER 1
WELCOME

FACULTY INFORMATION
Teresa Keane, MSN, PMHNP-BC received her MSN and certification as a Psychiatric Mental Health NP at Oregon Health & Sciences University in 1996. Since then she has worked in pain management and psychiatry. She recently retired from the Pain Management Clinic at NW Kaiser in Portland where she had worked with chronic pain patients for more than 10 years. Currently she continues to treat patients in her private practice. Teresa represented nursing on the Oregon Pain Commission and the Prescription Drug Monitoring Advisory Committee. She is a Board Member of the Western Pain Society.

DISCLOSURE:
Ms. Keane has no disclosures or conflicts of interest related to this program.
Presented by the Nurse Practitioner Healthcare Foundation, a member of the Collaborative for Risk Evaluation and Mitigation Strategy (REMS) Education (CO*RE), eleven interdisciplinary organizations working together to improve pain management and prevent adverse outcomes.

This educational activity is supported by an independent educational grant from the Extended-Release/Long-Acting (ER/LA) Opioid Analgesic REMS Program Companies. Please see this document 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 and Drug Administration.
### PRODUCTS COVERED BY THIS REMS

<table>
<thead>
<tr>
<th>BRAND NAME PRODUCTS</th>
<th>GENERIC PRODUCTS</th>
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</thead>
<tbody>
<tr>
<td>• Arymo® morphine sulfate ER tablets</td>
<td>• Fentanyl ER transdermal systems</td>
</tr>
<tr>
<td>• Avinza® morphine sulfate ER capsules</td>
<td>• Methadone hydrochloride tablets</td>
</tr>
<tr>
<td>• Belbuca® buprenorphine buccal film</td>
<td>• Methadone hydrochloride oral concentrate</td>
</tr>
<tr>
<td>• Butrans® buprenorphine transdermal system</td>
<td>• Methadone hydrochloride oral solution</td>
</tr>
<tr>
<td>• Dolagest® fentanyl transdermal system</td>
<td>• Morphine sulfate ER tablets</td>
</tr>
<tr>
<td>• Entad® morphine sustained-release ER capsules</td>
<td>• Morphine sulfate IR tablets</td>
</tr>
<tr>
<td>• Evagrip® buprenorphine hydrochloride ER tablets</td>
<td>• Hydromorphone hydrochloride CR tablets</td>
</tr>
<tr>
<td>• Kaberlin® morphine sustained-release ER capsules</td>
<td>• Hydrocodone hydrochloride/OXycodone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• Magmalact® morphine sulfate CR tablets</td>
<td>• Hydrocodone hydrochloride/OXycodone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• MedCard® morphine sulfate CR tablets</td>
<td>• Hydrocodone hydrochloride/OXycodone hydrochloride ER tablets</td>
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<tr>
<td>• Nucynta® ER buprenorphine ER tablets</td>
<td>• Hydroxycodone hydrochloride/OXycodone hydrochloride ER tablets</td>
</tr>
<tr>
<td>• OxyStat® extended-release oxycodone CR tablets</td>
<td>• Hydroxycodone/Oxycodone ER tablets</td>
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<tr>
<td>• OxyContin® extended-release oxycodone hydrochloride CR tablets</td>
<td>• Hydroxycodone/Oxycodone IR tablets</td>
</tr>
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<td>• Tepezza® extended-release oxycodone hydrochloride/naltrexone ER tablets</td>
<td>• Hydroxycodone/Oxycodone IR capsules</td>
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<td>• Tramal® extended-release oxycodone hydrochloride ER tablets</td>
<td>• Hydroxycodone/Oxycodone extended-release IR capsules</td>
</tr>
<tr>
<td>• Tramadol® extended-release oxycodone IR capsules</td>
<td>• Hydroxycodone/Oxycodone extended-release IR capsules</td>
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<tr>
<td>• ZYDAR® Hydrocodone extended-release capsules</td>
<td>• Hydroxycodone/Oxycodone extended-release IR capsules</td>
</tr>
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</table>
PRESCRIBING PATTERNS – WE PLAY A ROLE

SOURCE: https://www.cdc.gov/drugoverdose/data/prescribing.html

OPIOID PRESCRIBING - THE PENDULUM SWINGS

PRESCRIBING BEHAVIORS
- Under-Prescribing
- Over-Prescribing
- Appropriate Prescribing

RESULTING OUTCOMES
- Unresolved Pain
- Adverse Outcomes
- Adequate Analgesia

BENEFITS VS. RISKS

BENEFITS
- Analgesia
- Adequate pain control
- Continuous, predictable (with ER/LAs)
- Improved function
- Quality of life

RISKS
- Overdose, especially as ER/LA formulations contain more opioids than Immediate Release
- Life-threatening respiratory depression
- Abuse by patient or household contacts
- Misuse, diversion, and addiction
- Physical dependence and tolerance
- Interactions with other meds and substances
- Risk of neonatal opioid withdrawal syndrome
- Inadvertent exposure/ingestion by household contacts especially children

CO*RE STATEMENT

Misuse, abuse, diversion, addiction, and overdose of opioids has created a serious public health epidemic in the U.S.

When prescribed well and used as prescribed, opioids can be valuable tools to effectively treat pain.

This course does not advocate for or against the use of Immediate Release (IR) or Extended-Release/Long-Acting (ER/LA) opioids. Our purpose is to provide proper education about safe prescribing practices along with effective patient education.

LEARNING OBJECTIVES

- Accurately assess patients with pain for consideration of an opioid trial
- Establish realistic goals for pain management and restoration of function
- Initiate opioid treatment (IR and ER/LA) safely and judiciously, maximizing efficacy while minimizing risks
- Monitor and re-evaluate treatment continuously; discontinue safely when appropriate
- Counsel patients and caregivers about use, misuse, abuse, diversion, and overdose
- Educate patients about safe storage and disposal of opioids
- Demonstrate working knowledge and ability to access general and specific information about opioids, especially those used in your practice

You and Your Team can have an immediate and positive impact on this crisis while also caring for your patients appropriately.
THE IMPACT OF PAIN

Sleep Disturbance → Chronic Pain → Substance Misuse → Functional Disabilities → Increased Stresses

Secondary Physical Problems → Anxiety Depresion → Cognitive Distortions

PAIN MANAGEMENT GOALS AND TREATMENT OPTIONS: A MULTI-MODAL APPROACH

Reduce Pain

Cognitive Behavioral Therapy
- Behavioral Modification
- Meditation
- Cognitive Restructuring

Interventional Treatments
- Nerve Blocks
- Steroid Injections
- Stimulators
- Trigger Point Injections

Self Care

Cultivate Well Being

AC Phamacotherapy
- NSAIDs
- Antidepressants
- Opioids
- Cannabinoids
- Anticonvulsants
- Topicals (e.g., lidocaine)

Exercise
- Acupuncture
- Movement Therapies
- Manual Treatments

Provider Care

Restore Function

CHAPTER 3 - PEARLS FOR PRACTICE

- Explain neurophysiology of pain processing to patients
- When patients understand, their concerns are validated
- Pain has biological, psychological, social, and spiritual components
**CHALLENGE: THE EARLY REFILL**

**RED FLAG:**
Is this misuse? Abuse?

Your patient requests an early refill for the second time in six months. Took extra medications for headache and again for toothache. Prescription is for lower back pain.

**Action:**
Evaluate potential misuse. Confirm patient’s understanding of each medication’s dosage, time of day, and maximum daily dose. Ask him/her to repeat these instructions back to you. Avoid clinical terms such as ‘prn’. Review treatment goals and expectations. Select and document a therapy plan that is compatible with patients’ individual needs, is safe, effective and balanced. Screen for risk with Current Opioid Misuse Measure (COMM) and, if indicated, refer to addiction specialist for treatment.

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**CHAPTER 4**

**ASSESSMENT**

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**PAIN ASSESSMENT**

**DESCRIPTION OF PAIN**

<table>
<thead>
<tr>
<th>Location</th>
<th>Intensity</th>
<th>Quality</th>
<th>Onset/Duration</th>
<th>Variations/Patterns/Rhythms</th>
</tr>
</thead>
</table>

**WHAT RELIEVES THE PAIN?**

**WHAT CAUSES OR INCREASES PAIN?**

**EFFECTS OF PAIN ON PHYSICAL, EMOTIONAL, AND PSYCHOSOCIAL FUNCTION**

**PATIENT’S CURRENT PAIN AND FUNCTION**

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**SOURCE:**

TREATMENT HISTORY

NON-PHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

PHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

PAST USE

CURRENT USE

• Query state Prescription Drug Monitoring Program (PDMP) to confirm patient report.

DOSEAGE

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

GENERAL EFFECTIVENESS

PAST MEDICAL HISTORY

I N L I S S E N S R E L E V A N T T O (1) E F F E C T S O R (2) M E T A B O L I S M O F OPIOIDS

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


• Hepatitis
• HIV
• Tuberculosis
• Cellulitis
• STIs
• Trauma/Bums
• Cardiac Disease
• Pulmonary Disease


OBTAIN A COMPLETE HISTORY OF CURRENT AND PAST SUBSTANCE USE

RISK FACTORS FOR OPIOID ABUSE

• Controlled medications: prescribed or non-prescribed
• Alcohol and tobacco
• History of sexual abuse
• Family history of substance abuse and psychiatric disorders
• Age (16-45 YO)

Substance abuse history does not prohibit treatment with ER/LA opioids but may require additional monitoring and expert consultation/referral.

SOCIAL HISTORY

Employment, cultural background, social network, marital history, legal history, and other behavioral patterns.
RISK ASSESSMENT TOOLS

<table>
<thead>
<tr>
<th>TOOL</th>
<th># OF ITEMS</th>
<th>ADMINISTERED BY</th>
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<tbody>
<tr>
<td>OPIOID RISK TOOL (ORT)</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>SOAPP® Screener and Opioid Assessment for Patients with Pain</td>
<td>24, 14, &amp; 5</td>
<td>patient</td>
</tr>
<tr>
<td>DIRE Diagnosis, Intractability, Risk, and Efficacy score</td>
<td>7</td>
<td>clinician</td>
</tr>
<tr>
<td>CHARACTE RIZE MISE ONCE OPIOID TREATMENT BEGINS</td>
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<td></td>
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<tr>
<td>PMQ Pain Medication Questionnaire</td>
<td>26</td>
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<td>COMI Current Opioid Misuse Measure</td>
<td>17</td>
<td>patient</td>
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<tr>
<td>PDUG Prescription Drug Use Questionnaire</td>
<td>40</td>
<td>clinician</td>
</tr>
<tr>
<td>NOT SPECIFIC TO PAIN POPULATIONS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAGE-AD: Cut Down, Annoyed, Guilty, Eye-Opener tool, Adapted to Include Drugs</td>
<td>4</td>
<td>clinician</td>
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<tr>
<td>RAFFT Relax, Alone, Friends, Family, Trouble</td>
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<td>patient</td>
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<tr>
<td>DAST Drug Abuse Screening Test</td>
<td>28</td>
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<tr>
<td>SBIRT Screening, Brief Intervention, and Referral to Treatment</td>
<td>Varies</td>
<td>clinician</td>
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</table>

SCORING (RISK)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3: low</td>
<td></td>
</tr>
<tr>
<td>4-7: moderate</td>
<td></td>
</tr>
<tr>
<td>≥8: high</td>
<td></td>
</tr>
</tbody>
</table>

1. Mark each box that applies
2. Female
3. Male
4. For each item, mark the box that best represents the patient's history.
5. Scoring Totals

ADMINISTER

On initial visit
Prior to opioid therapy

SCREENER AND OPIOID ASSESSMENT FOR PATIENTS WITH PAIN (SOAPP®)

Identifies patients as 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 and scored SOAPP® while making opioid treatment decisions


Opioids

WHAT IS THE RISK FOR MY PATIENT?

- Risk of opioid use disorder in patients on chronic opioid therapy (COT) for chronic non-cancer pain (CNCP) is up to 30%
- Always highest with past history of substance use disorder (SUD) or psychiatric comorbidity
- Recognize that patient needs and patterns shift with age

PAIN AND ADDICTION

PAIN – 5 A’S

- Analgesia
- Activities/Function
- Aberrant Behavior
- Adverse Effects
- Affect

ADDICTION – 5 C’S

- Control, loss of
- Compulsive use
- Craving drug
- Continued use
- Chronic problem

CONSIDER A TRIAL OF AN OPIOID?

- Potential benefits are likely to outweigh risks
- Failed to adequately respond to non-opioid & nonpharmacological interventions
- Pain is moderate to severe
- Initiate trial of IR opioids

WHEN TO CONSIDER A TRIAL OF AN OPIOID

65-YR-OLD WITH CHRONIC DISABLING OA PAIN
- Non-opioid therapies not effective
- No psychiatric/medical comorbidity or personal/family drug abuse history
- High potential benefits relative to potential risks
- Could prescribe opioids to this patient in most settings with routine monitoring

30-YR-OLD WITH FIBROMYALGIA AND RECENT ALCOHOL USE DISORDER
- High potential risks relative to benefits (opioid therapy not first line for fibromyalgia)
- Requires intensive structure, monitoring, and management by clinician with expertise in both addiction & pain
- Not a good candidate for opioid therapy

INITIATING OPIOIDS: CDC GUIDELINE (2016)

- Begin with IR
- Prescribe the lowest effective dosage
- Use caution at any dosage, but particularly when:
  - Increasing dosage to ≥50 morphine milligram equivalents (MME)/day and carefully justify a decision to titrate dosage to ≥90 MME/day
- For acute pain, prescribe lowest effective dose of IRs, no more than needed
- Re-evaluate risks/benefits within 1-4 weeks of initiation or dose escalation
- Re-evaluate risks/benefits every 3 months; if benefits do not outweigh harms, optimize other therapies, work to taper and discontinue
- Link to the Guideline: https://www.cdc.gov/drugoverdose/prescribing/providers.html

Cancer pain, hospice, and palliative care patients are not covered by CDC Guideline
INFORMED CONSENT

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

- **ANALGESIC AND FUNCTIONAL GOALS OF TREATMENT**
- **EXPECTATIONS**
- **POTENTIAL RISKS**
- **ALTERNATIVES TO OPIOIDS**

**HOW TO MANAGE**
- Common Adverse Effects (AEs) (e.g., constipation, nausea, sedation)
- Risks (e.g., abuse, addiction, respiratory depression, overdose)
- AEs with long-term therapy (e.g., hyperalgesia, low testosterone, irregular menses or sexual dysfunction)

**PATIENT-PRESCRIBER AGREEMENT (PPA)**

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

- Clarify treatment plan and goals of treatment with patient, patient’s family, and other clinicians involved in patient’s care
- Assist in patient education
- Discuss medication safe handling, storage, and disposal
- Document patient and prescriber responsibilities

**PATIENT PROVIDER AGREEMENT (PPA)**

Reinforce expectations for appropriate and safe opioid use

- One prescriber
- Consider one pharmacy
- Safeguard
  - Do not store in medicine cabinet
  - Keep locked (medication safe)
  - Do not share or sell
- Instructions for disposal when no longer needed
- Prescriber notification for any event resulting in a pain medication prescription
- Follow-up
- Monitoring
  - Random UDT and pill counts
  - Refills
- Identify behaviors for discontinuation
- Exit strategy
MONITOR ADHERENCE AND ABERRANT BEHAVIOR

ROUTINELY MONITOR PATIENT ADHERENCE TO TREATMENT PLAN

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

PADT = Pain Assessment and Documentation Tool

ADDRESS ABERRANT DRUG-RELATED BEHAVIOR

Behavior outside the boundaries of agreed-on treatment plan:

- Unsanctioned dose escalations or other noncompliance with therapy on 1 or 2 occasions
- Unapproved use of the drug to treat another symptom
- Openly acquiring similar drugs from other medical sources
- Multiple dose escalations or other noncompliance with therapy despite warnings
- Prescription forgery
- Obtaining prescription drugs from nonmedical sources

Any of these behaviors merit investigation. Proceed with caution

Adequately DOCUMENT all patient interactions, assessments, test results, and treatment plans.
CHAPTER 4 – PEARLS FOR PRACTICE

- Conduct a comprehensive and pain-focused history and physical
- Assess for risk of abuse and for mental health issues
- Determine if a therapeutic trial is appropriate
- Establish realistic goals for pain management and function
- Document EVERYTHING

CHALLENGE: THE DELAYED SURGERY

RED FLAG:
Patient may be stalling to continue an opioid regimen

Ms. Jones says she needs opioids to manage her pain until she can have surgery. She reports continued delays in getting to surgery. You phone the surgeon and discover that no date has been set and that she has cancelled several appointments.

Action:
Set a time limit and expectation. Offer non-pharmacologic methods and non-opioid interventions for pain management. Communicate with the surgeon and advise patient to make appointment with surgeon for discussion of treatment plan.

CHAPTER 5

MANAGEMENT
MONITORING AND DISCONTINUING
PART 1
MONITORING

OPIOID SIDE EFFECTS

- Respiratory depression – most serious
- Opioid-Induced Constipation (OIC) – most common
- Sedation, cognitive impairment
- Falls and fractures
- Sweating, miosis, urinary retention
- Hypogonadism
- Tolerance, physical dependence, hyperalgesia
- Addiction in vulnerable patients

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

OPIOID-INDUCED RESPIRATORY DEPRESSION

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

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

Instruct patients/family members to call 911
Managed with
- Close observation
- Supportive measures
- Opioid antagonists
- Depending on patient’s clinical status

FDA. Blueprint for Prescriber Education for Extended-Release and Long Acting Opioid Analgesics. 01/2017.
OPIOID-INDUCED RESPIRATORY DEPRESSION

MORE LIKELY TO OCCUR

- In elderly, cachectic, or debilitated patients
- Contraindicated in patients with respiratory depression or conditions that increase risk
- If given concomitantly with other drugs that depress respiration
- Patients who are opioid-naïve or have just had a dose increase

REDUCE RISK

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

WHEN TO MOVE FROM IR TO ER/LA OPIOIDS

PRIMARY REASONS

- Maintain stable blood levels (steady state plasma)
- Longer duration of action
- Multiple IR doses needed to achieve effective analgesia
- Poor analgesic efficacy despite dose titration
- Less sleep disruption

OTHER POTENTIAL REASONS

- Patient desire or need to try a new formulation
- Cost or insurance issues
- Adherence issues
- Change in clinical status requires an opioid with different pharmacokinetics
- Problematic drug-drug interactions

CONSIDERATIONS FOR CHANGE FROM IR TO ER/LA OPIOIDS

DRUG AND DOSE SELECTION IS CRITICAL

Some ER/LA opioids or dosage forms are only recommended for opioid-tolerant patients
- ANY strength of transdermal fentanyl or hydromorphone ER
- Certain strengths/doses of other ER/LA products (check drug prescribing information)

MONITOR PATIENTS CLOSLY FOR RESPIRATORY DEPRESSION

Especially within 24-72 hours of initiating therapy and increasing dosage

INDIVIDUALIZE DOSAGE BY TITRATION BASED ON EFFICACY, TOLERABILITY, AND PRESENCE OF AEs

Check ER/LA opioid product PI for minimum titration intervals

Supplement with IR analgesics (opioids and non-opioids) if pain is not controlled during titration
Patients considered opioid tolerant are taking at least:
- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/hour
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day

An equianalgesic dose of another opioid still requires caution when rotating a patient on an IR opioid to a different ER/LA opioid.

OPIOID ROTATION

**DEFINITION**
Change from an existing opioid regimen to another opioid with the goal of improving therapeutic outcomes or to avoid AEs attributed to the existing drug (e.g., myoclonus).

**RATIONALE**
Differences in pharmacologic or other effects make it likely that a switch will improve outcomes:
- Effectiveness and AEs of different mu opioids vary among patients
- Patients show incomplete cross-tolerance to new opioid
  - Patient tolerant to first opioid can have improved analgesia from second opioid at a dose lower than calculated from an Equianalgesic Dosing Table (EDT).

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></td>
<td>SC/IV</td>
<td>PO</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
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</tr>
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</table>

GUIDELINES FOR OPIOID ROTATION

Calculate equianalgesic dose of new opioid from EDT

REduce calculated equianalgesic dose by 25%-50%*

SELECT % REDUCTION BASED ON CLINICAL JUDGMENT

CLOSER TO 50% REDUCTION IF PATIENT IS

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

CLOSER TO 25% REDUCTION IF PATIENT

- Does not have these characteristics
- Is changing route of administration

*75%-90% reduction for methadone

GUIDELINES FOR OPIOID ROTATION (continued)

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-naive 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 (BTP)**

PATIENTS ON STABLE ATC OPIOIDS MAY EXPERIENCE BTP
- Disease progression or a new or unrelated pain
- Target cause or precipitating factors
- Dose for BTP: using an IR is 5%-15% of total daily opioid dose, administered at an appropriate interval
- Never use ER/LA for BTP

CONSIDER ADDING
- PRN IR opioid trial based on analysis of benefit versus risk
- Risk for aberrant drug-related behaviors
- High-risk: only in conjunction w/ frequent monitoring & follow-up
- Low-risk: w/ routine follow-up & monitoring
- Non-opioid drug therapies
- Non-pharmacologic treatments

ATC = Around the Clock

**BE READY TO REFER**

**SUBSTANCE USE DISORDER**

**SAMHSA substance abuse treatment facility locator**
https://findtreatment.samhsa.gov/locator/ home

**SAMHSA mental health treatment facility locator**
https://findtreatment.samhsa.gov/locator/ home

HIGH-RISK/COMPLEX PATIENTS
- Refer to pain management, check state regulations for requirements

SAMHSA = Substance Abuse and Mental Health Service Administration

**RATIONALE FOR URINE DRUG TESTING (UDT)**

- Urine testing is done FOR the patient not TO the patient
- Help to identify drug misuse/addiction
- Assist in assessing and documenting adherence

UDT FREQUENCY IS BASED ON CLINICAL JUDGMENT AND STATE REGULATIONS
TYPES OF UDT METHODS

IMMUNOASSAY (IA) DRUG PANELS
- Either lab-based or point of care
- Identify substance as present or absent according to cutoff
- Many do not identify individual drugs within a class
- Subject to cross-reactivity and variability

GC/MS OR LC/MS
- Identify the presence and quantity of substance(s)
- Identify drugs not included in IA tests
- When results are contested


INTERPRETATION OF UDT RESULTS

POSTIVE RESULT
- Demonstrates recent use
  - Most drugs in urine have detection times of 1-3 days
  - Chronic use of lipid-soluble drugs: test positive for ≥1 week
- Does not diagnose
  - Drug addiction, physical dependence, or impairment
  - Excess 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
  - Binging, running out early
  - Other factors: e.g., cessation of insurance, financial difficulties

EXAMPLES OF METABOLISM OF OPIOIDS

OPIOIDS
- CODEINE
- HYDROCODONE
- OXYCODONE
- MORPHINE
- HYDROMORPHONE
- OXYMORPHONE
- 6-MAM
- T1/2=25-30 MIN
- HERON
- T1/2=3.5 MIN
CHALLENGE: THE OFFENDED PATIENT

RED FLAG:
You decide not to request routine risk assessment for fear of creating conflict

Mrs. Lane and her family have been your patients for years. She has chronic headache and back pain treatment. When you ask her to take a UDT, she becomes upset and accuses you of not trusting her. You decide against further risk assessments because you are concerned about damaging the relationship.

Action
Require all patients receiving opioids to follow a treatment plan and adhere to defined expectations. Create office policy for performing UDT for patients receiving opioids beyond two weeks. Practice universal precautions. Explain to patient that you must meet the standards of care that include evaluation of risk in all patients, use of PPAs, and other tools.

PART 2
DISCONTINUING

REASONS FOR DISCONTINUING OPIOIDS

<table>
<thead>
<tr>
<th>Pain Level Decreases in Stable Patients</th>
<th>Intolerable and Unmanageable AEs</th>
<th>No Progress Toward Therapeutic Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misuse</td>
<td>Aberrant Behaviors</td>
<td></td>
</tr>
<tr>
<td>• 1 or 2 episodes of increasing dose without prescriber knowledge</td>
<td>• Use of illicit drugs or unprescribed opioids</td>
<td></td>
</tr>
<tr>
<td>• Sharing medications</td>
<td>• Repeatedly obtaining opioids from multiple outside sources</td>
<td></td>
</tr>
<tr>
<td>• Unapproved opioid use to treat another symptom (e.g., insomnia)</td>
<td>• Prescription forgery</td>
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</tr>
<tr>
<td></td>
<td>• Multiple episodes of prescription loss</td>
<td></td>
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<tr>
<td></td>
<td>• Diversion</td>
<td></td>
</tr>
</tbody>
</table>
TAPER DOSE WHEN DISCONTINUING

- Minimize withdrawal symptoms in opioid-dependent patient, consider medications to assist with withdrawal
- May use a range of approaches from slow 10% dose reduction per week to more rapid 25%-50% reduction every few days
- If opioid use disorder or a failed taper, refer to addiction specialist or consider opioid agonist therapy
- Counseling and relaxation strategies needed

CHAPTER 5 – PEARLS FOR PRACTICE

- Establish informed consent and PPA at the beginning
- Educate the whole team: patients, families, caregivers
- Refer if necessary
- Anticipate opioid-induced respiratory depression and constipation
- Follow patients closely during times of dose adjustments
- Periodically evaluate functional outcomes
- Discontinue opioids slowly and safely

CHALLENGE: IS THIS A LAB ERROR?

RED FLAG: The questionable Urine Drug Test

Donald has been prescribed oxycodone for six months to treat back pain. His UDT at six months comes back negative in all areas. He tells you that he is taking his meds.

Action:
Do not discharge the patient as the first action. Contact the lab and discuss the test and any metabolite or specimen integrity issues. Ask: Is this the right lab test? Repeat the UDT and document everything. Discuss with the patient.
CHALLENGE: PATIENTS WHO ARE NOT WHO THEY APPEAR

RED FLAG:
Patient wants to control their pill mg dose and taper plan

Tom has back pain. He is managed by taking oxycodone (40 mg BID) but
wants to decrease his dose when he can, thus he requests only 20 mg
pills. He often brings in unused meds to show how he is trying to reduce
his dose. He resists any change.

Action:
Do not allow patient to taper on their own. Create an endpoint for the
taper. See patient once a week with a seven-day supply for the tapering
until they are off opioids. Document teaching, patient’s comments about
the plan, UDT, pill counts, non-pharmacological modalities for pain
management, and their adherence to this plan.

CHAPTER 6
SPECIAL POPULATIONS

OLDER ADULTS

RISK FOR RESPIRATORY DEPRESSION
- Age-related changes in distribution, metabolism, excretion; absorption less affected

MONITOR
- Initiation and titration
- Concomitant medications (polypharmacy)
- Falls risk, cognitive change, psychosocial status
- Reduce starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients
- Start low, go slow, but GO
- Patient and caregiver reliability/risk of diversion

ROUTINELY INITIATE A BOWEL REGIMEN
KNOW THE REPRODUCTIVE PLANS AND PREGNANCY STATUS OF YOUR PATIENTS

- 40% of women with childbearing potential are prescribed opioids
- Opioid exposure during pregnancy causes increased risk for fetus
- Most women do not know they are pregnant in first few weeks
- Therefore all women of childbearing age are at risk
- No adequate nor well-controlled studies of opioids for pain in pregnancy

THE PREGNANT PATIENT

Potential risk of opioid therapy to the newborn is neonatal opioid withdrawal syndrome

Given these potential risks, clinicians should:

- Counsel women of childbearing potential about risks and benefits of opioid therapy during pregnancy and after delivery
- Encourage minimal opioid use during pregnancy, unless potential benefits outweigh risks to fetus
- Refer to a high risk OB/Gyn who will ensure appropriate treatment for the baby
- If chronic opioid therapy is used during pregnancy, anticipate and manage risks to the patient and newborn
- If using opioids on a daily basis, consider methadone or buprenorphine

CHILDREN AND ADOLESCENTS: HANDLE WITH CARE

Judicious use of IR for brief therapy

Safety and effectiveness of most ER/LA opioids unestablished

- Pediatric analgesic trials pose challenges
- Transdermal fentanyl approved in children aged 2 yrs
- Oxycodone ER dosing changes for children ≥11 yrs

ER/LA opioid indications are primarily life-limiting conditions

When prescribing ER/LA opioids to children:

- Consult pediatric palliative care team or pediatric pain specialist or refer to a specialized multidisciplinary pain clinic
RED FLAG: Questionable family diversion

78-year-old Thelma comes into clinic, accompanied by grandson, who is in the exam room with you and Thelma. Thelma says her oxycodone 10 mg tablets q 4 hours is no longer working for her back pain. She asks for more medicine. You ask grandson to leave the exam room so you can examine her privately.

Action: Based on exam findings and her request for more medication:
- UDTP and PDMP check
- Discuss whether or not it is possible her grandson, or another family member, might be using her medications.
- Patient education: Do not give opioids to another person. Store in secure place—locked. Let you know if medications are not secure or if she feels any pressure about sharing medications.

FEDERAL AND STATE REGULATIONS

Comply with federal and state laws and regulations that govern the use of opioid therapy for pain

FEDERAL
- Code of Federal Regulations, Title 21 Section 1306: rules governing the issuance and filing of prescriptions pursuant to section 309 of the Act (21 USC 829)
- United States Code (USC) - Controlled Substances Act, Title 21, Section 829: prescriptions

STATE
- Database of state statutes, regulations, and policies for pain management
- www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm
- www.deadiversion.usdoj.gov/21cfr/21usc/829.htm
- www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management
PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs)

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 with the PDMP
- Whether prescribers are required to access PDMP information in certain circumstances
- Whether unsolicited PDMP reports are sent to prescribers
- Bordering states may be available
- Designated surrogates may have access

NOT ALL FEDERALLY LICENSED FACILITIES REPORT TO PDMPs

Link to state PDMP sites

PDMP BENEFITS

- Provides full accounting of prescriptions filled by patient

<table>
<thead>
<tr>
<th>RECORD OF A PATIENT’S CONTROLLED SUBSTANCE PRESCRIPTIONS</th>
<th>PROVIDE WARNINGS OF POTENTIAL MISUSE/ABUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Some are available online 24/7</td>
<td>- Existing prescriptions not reported by patient</td>
</tr>
<tr>
<td>- Opportunity to discuss with patient</td>
<td>- Multiple prescribers/pharmacies</td>
</tr>
<tr>
<td></td>
<td>- Drugs that increase overdose risk when taken together</td>
</tr>
<tr>
<td></td>
<td>- Patient pays with cash (vs insurance) for controlled meds</td>
</tr>
</tbody>
</table>

CANNABIS

- DEA Schedule 1 (“high abuse potential”) yet state laws and regulations vary
- There is evidence that cannabis or selective cannabinoids (cannabidiol) are effective for chronic pain treatment in adults
- More research is needed
- Concern for high risk groups: children, adolescents, pregnant women

CONSIDERATIONS FOR CLINICIANS

- Use available scientific evidence, advise patients
  - Inform about potential effects; AEs mostly mild and well tolerated (cough, anxiety)
  - Screen for potential misuse/abuse, diversion
- Set treatment goals, use PPA
- Encourage patients to keep notes, discuss with them
- Document everything
- Regular re-evaluation
- Consider periodic UDTs
- Discontinue if not helpful moving toward goals
- Edibles are the fastest growing delivery system
- No well controlled studies on the combined use of opioids and cannabis


CHAPTER 8
COUNSELING PATIENTS AND CAREGIVERS

USE PATIENT COUNSELING DOCUMENT

DOWNLOAD:

ORDER HARD COPIES:
www.minneapolis.cenveo.com/submitOrders.aspx

COUNSEL PATIENTS ABOUT PROPER USE

<table>
<thead>
<tr>
<th>EXPLAIN</th>
<th>INSTRUCT PATIENTS/CAREGIVERS TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Product-specific information about the IR or ER/LA opioid (especially when converting)</td>
<td></td>
</tr>
<tr>
<td>- Take opioid as prescribed</td>
<td></td>
</tr>
<tr>
<td>- Adhere to dose regimen</td>
<td></td>
</tr>
<tr>
<td>- How to handle missed doses</td>
<td></td>
</tr>
<tr>
<td>- Notify prescriber if pain not controlled</td>
<td></td>
</tr>
<tr>
<td>- Call prescriber for options on side effect management</td>
<td></td>
</tr>
<tr>
<td>- Read the ER/LA opioid Medication Guide received from pharmacy every time an ER/LA opioid is dispensed</td>
<td></td>
</tr>
</tbody>
</table>

COUNSEL PATIENTS ABOUT PROPER USE (continued)

<table>
<thead>
<tr>
<th>EXPLAIN</th>
<th>OPIOIDS CAN CAUSE DEATH EVEN WHEN TAKEN PROPERLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Inform prescriber of ALL meds being taken</td>
<td></td>
</tr>
<tr>
<td>- Warn patients not to abruptly discontinue or reduce dose</td>
<td></td>
</tr>
<tr>
<td>- Risk of falls</td>
<td></td>
</tr>
<tr>
<td>- Caution with operating heavy machinery and when driving</td>
<td></td>
</tr>
<tr>
<td>- Sharing or selling opioids can lead to others' deaths and is against the law</td>
<td></td>
</tr>
<tr>
<td>- Signs/symptoms are respiratory depression, gastrointestinal obstruction, allergic reactions</td>
<td></td>
</tr>
</tbody>
</table>

COUNSEL PATIENTS ABOUT PROPER USE (continued)

<table>
<thead>
<tr>
<th>EXPLAIN</th>
<th>OPIOIDS SHOULD BE STORED IN A SAFE AND SECURE PLACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Tell patients and caregivers, medications must be kept in a locked container</td>
<td></td>
</tr>
<tr>
<td>- Will periodically assess for benefits, side effects, and continued need for IR/ER/LA opioids</td>
<td></td>
</tr>
<tr>
<td>- Need for re-evaluation of underlying medical condition if the clinical presentation changes over time</td>
<td></td>
</tr>
<tr>
<td>- Away from children, family members, visitors, and pets</td>
<td></td>
</tr>
<tr>
<td>- Safe from theft</td>
<td></td>
</tr>
<tr>
<td>Opioids are scheduled under Controlled Substances Act and can be misused and abused</td>
<td></td>
</tr>
</tbody>
</table>
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 and death
- If unable to swallow a capsule whole, refer to PI to determine if appropriate to sprinkle contents on applesauce or administer via feeding tube

Use of CNS depressants or alcohol with ER/LA opioids can cause overdose & death
- Use with alcohol may result in rapid release and absorption of a potentially fatal opioid dose – “dose dumping”
- Other depressants include sedative-hypnotics and anxiolytics, illegal drugs

OVERDOSE POISONING, CALL 911
- Person cannot be aroused or awakened or is unable to talk
- Any trouble with breathing, heavy snoring is warning sign
- Gurgling noises coming from mouth or throat
- Body is limp, seems lifeless; face is pale, clammy
- Fingernails or lips turn blue/purple
- Slow, unusual heartbeat or stopped heartbeat

NALOXONE

Naloxone:
- An opioid antagonist administered by injection or intranasally, or iv
- Reverses acute opioid-induced respiratory depression but will also reverse analgesia

What to do:
- Discuss an ‘overdose plan’
- Involve and train family, friends, partners, and/or caregivers
- Check with pharmacy if they are prescribing
- 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 (with syringes, needles)
- Injectable
- Nasal spray

Consider offering a naloxone prescription to all patients prescribed IR and ER/LA opioids
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

Look for local take-back events
- Conducted by Federal, State, tribal, or local law enforcement
- Partnering with community groups

Watched over by:
- Law enforcement
- Authorized collectors, including:
  - Manufacturer
  - Distributor
  - Reverse distributor
  - Retail or hospital/clinic pharmacy
  - Including long-term care facilities


OTHER METHODS OF OPIOID DISPOSAL

IF COLLECTION RECEPTACLE, MAIL-BACK PROGRAM, OR TAKE-BACK EVENT UNAVAILABLE, THROW OUT IN HOUSEHOLD TRASH

- Take drugs out of original containers
- Mix with undesirable substance
- Place in sealable bag, can, or other container
- Remove identifying info on label

FDA: PRESCRIPTION DRUG DISPOSAL

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 (3 days) 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
  - Butrans (buprenorphine transdermal system)
    exception: can seal in Patch-Disposal Unit provided and dispose of in the trash
CHAPTER 8 – PEARLS FOR PRACTICE

• Use formal tools (PPAs, counseling documents) to educate patients and caregivers
• Emphasize safe storage and disposal to patients and caregivers
• Consider co-prescribing naloxone

CHAPTER 9
DRUG CLASS CONSIDERATIONS

FOR SAFER USE: KNOW DRUG INTERACTIONS, PK, AND PD

CNS depressants can potentiate sedation and respiratory depression

Use with MAOIs may increase respiratory depression
Certain opioids with MAOIs can cause serotonin syndrome

Methadone and buprenorphine can prolong QTc interval

Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol
Some drug levels may increase without dose dumping

Can reduce efficacy of diuretics
Inducing release of antidiuretic hormone

Drugs that inhibit or induce CYP enzymes can increase or lower blood levels of some opioids.
**TRANSDERMAL/TRANSMUCOSAL 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 with water.
- For buccal film products the film should not be applied if it is cut, damaged, or changed in anyway – use entire film.

**DRUG INTERACTIONS COMMON TO OPIOIDS**

- Concurrent use with 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 and increase respiratory depression.
- Avoid concurrent use of partial agonists* or mixed agonist/antagonists† with full opioid agonist.
- May reduce analgesic effect and/or precipitate withdrawal.
- Concurrent use with anticholinergic medication increases risk of urinary retention and severe constipation.
- May lead to paralytic ileus.
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- Reduce i
Our session stops here, but your review continues...

Refer to Appendix 1 for specific drug information on ER/LA opioid analgesic products.

For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.druginfo.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda

YOUR PARTICIPATION IS IMPORTANT

Thank you for completing the post-activity assessment for this CO*RE session.

Your participation in this assessment allows CO*RE to report de-identified numbers to the FDA.

A strong show of engagement will demonstrate that clinicians have voluntarily taken this important education and are committed to patient safety and improved outcomes.

THANK YOU!
Appendix 1. Drug Specific Slides

Morphine Sulfate ER Tablets (Arymo ER)
Capsules 15 mg, 30 mg, 60 mg

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Every 8 or 12 hours</th>
</tr>
</thead>
</table>
| Key instructions | • Initial dose in opioid-naïve and opioid non-tolerant patients is 15 mg every 8 or 12 hours  
|                  | • Dosage adjustment may be done every 1 to 2 days  
|                  | • Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth |
| Drug interactions | • P-gp inhibitors (e.g. quinidine) can increase the exposure of morphine by about two-fold and increase risk of respiratory depression |
| Opioid-tolerant | • A single dose of ARYMO ER greater than 60 mg, or total daily dose greater than 120 mg, is for use in opioid-tolerant patients only |
| Product-specific safety concerns | • Do not attempt to chew, crush, or dissolve. Swallow whole.  
|                  | • Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen |

Morphine Sulfate ER Capsules (Avinza)
Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg

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

* MDD = maximum daily dose; P-gp = P-glycoprotein
## Buprenorphine Buccal Film (Belbuca)

**Dosing interval**
- Every 12 h (or once every 24 h for initiation in opioid naïve patients & patients taking less than 30 mg oral morphine sulfate eq)

**Key instructions**
- Opioid-naive pts or pts taking <30 mg oral morphine sulfate eq:
  - Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 h
  - Titrate to 150 mcg every 12 h no earlier than 4 d after initiation
  - Individual titration to a dose that provides adequate analgesia and minimizes adverse reaction should proceed in increments of 150 mcg every 12 h, no more frequently than every 4 d
- When converting from another opioid, first taper the current opioid to no more than 30 mg oral morphine sulfate eq/day prior to initiating Belbuca
  - If prior daily dose before taper was 30 mg to 89 mg oral morphine sulfate eq, initiate with 150 mcg dose every 12 h
  - If prior daily dose before taper was 90 mg to 160 mg oral morphine sulfate eq, initiate with 300 mcg dose every 12 h
  - Titration of the dose should proceed in increments of 150 mcg every 12 h, no more frequently than every 4 d
- Maximum dose: 900 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
- CYP3A4 inhibitors may increase buprenorphine levels
- CYP3A4 inducers may decrease buprenorphine levels
- Benzodiazepines may increase respiratory depression
- Class IA and 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.

## Buprenorphine Transdermal System (Butrans)

**Dosing interval**
- One transdermal system every 7 d

**Key instructions**
- Initial dose in opioid non-tolerant patients on <30 mg morphine equivalents & in mild-moderate hepatic impairment: 5 mcg/h
- When converting from 30 mg-80 mg morphine equivalents, first taper to 30 mg morphine equivalent, then initiate w/10 mcg/h
- Titrate in 5 or 10 mcg/h increments by using no more than 2 patches of the 5 or 10 mcg/h system(s) w/ minimum of 72 h prior between dose adjustments. Total dose from all patches should be ≤20 mcg/h
- Maximum dose: 20 mcg/h due to risk of QTc prolongation
- Application:
  - Apply only to sites indicated in PI
  - Apply to intact/non-irritated skin
  - Prep site by clipping hair, wash site w/ water only
  - Rotate application site (min weekly between patch changes)
  - Do not cut
  - Avoid exposure to heat
  - Dispose of patches: fold adhesive side together & flush down toilet
Buprenorphine Transdermal System (Butrans) continued

Drug Interactions
- CYP3A4 inhibitors may increase buprenorphine levels
- CYP3A4 inducers may decrease buprenorphine levels
- Benzodiazepines may increase respiratory depression
- Class IA & III antiarythmics, other potentially arrhythmogenic agents, may increase risk of QTc prolongation & torsade de pointe

Opioid Tolerant
- 7.5 mcg/h, 10 mcg/h, 15 mcg/h, & 20 mcg/h for use in opioid-tolerant patients only

Product-Specific Safety Concerns
- QTc prolongation & torsade de pointe
- Application site skin reactions

Relative Potency: Oral Morphine
- Equipotency to oral morphine not established

Methadone Hydrochloride Tablets (Dolophine)

Dosing Interval
- Every 8 to 12 h

Key Instructions
- Initial dose in opioid non-tolerant patients: 2.5 – 10 mg
- Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose & death. Use low doses according to table in full PI
- Titrate slowly with dose increases no more frequent than every 3–5 d. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 d)
- High inter-patient variability in absorption, metabolism, & relative analgesic potency
- Opioid detoxification or maintenance treatment only provided in a federally certified opioid (addiction) treatment program (CFR, Title 42, Sec 8)

Drug Interactions
- Pharmacokinetic drug-drug interactions w/ methadone are complex
  - CYP 450 inhibitors may decrease methadone levels
  - CYP 450 inducers may increase methadone levels
  - Anti-retroviral agents have mixed effects on methadone levels
  - Potentially arrhythmogenic agents may increase risk for QTc prolongation & torsade de pointe
  - Benzodiazepines may increase respiratory depression

Opioid Tolerant
- Refer to full PI

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

Relative Potency: Oral Morphine
- Varies depending on patient's prior opioid experience
**Fentanyl Transdermal System (Duragesic)**

12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr

("These strengths are available only in generic form)

### Dosing Interval
- Every 72 h (3 d)

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

### Specific Contraindications:
- Patients who are not opioid-tolerant
- Management of:
  - Acute or intermittent pain, or patients who require opioid analgesia for a short time
  - Non-operative pain, post-op patient, or day surgery
  - Mild pain

### Drug Interactions:
- CYP3A4 inhibitors may increase fentanyl exposure
- CYP3A4 inducers may decrease fentanyl exposure
- Discontinuation of concurrent CYP P450 3A4 inducer may increase fentanyl plasma concentration

### Opioid-tolerant
- All doses indicated for opioid-tolerant patients only

### Product-specific Safety Concerns
- Accidental exposure due to secondary exposure to unwashed/unclothed application site
- Increased drug exposure with increased core body temp or fever
- Bradycardia
- Application site skin reactions

### Relative Potency:
- See individual PI for conversion recommendations from prior opioid

---

**Morphine Sulfate ER-Naltrexone (Embeda)**
Capsules 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

### Dosing Interval
- Once a day or every 12 h

### Key Instructions
- Initial dose as first opioid: 20 mg/0.8 mg
- Titrate using a minimum of 1-2 d intervals
- Swallow capsules whole (do not chew, crush, or dissolve)
- Crushing or chewing will release morphine, possibly resulting in fatal overdose, & naltrexone, possibly resulting in withdrawal symptoms
- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately

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

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

### Product-specific Safety Concerns
- None
Hydromorphone Hydrochloride (Exalgo)

**ER Tablets 8 mg, 12 mg, 16 mg, 32 mg**

**Dosing Interval**
- Once a day

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

**Drug Interactions**
- None

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

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

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

Hydrocodone Bitartrate (Hysingla ER)

**ER Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120mg**

**Dosing interval**
- Once a day

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

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

**Opioid-tolerant**
- A single dose ≥ 80 mg is only for use in opioid tolerant patients.

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

**Relative potency: oral morphine**
- See individual PI for conversion recommendations from prior opioid.
### Morphine Sulfate (Kadian)

**ER Capsules 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, 200 mg**

<table>
<thead>
<tr>
<th>Dosing Interval</th>
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</thead>
</table>
| Key instructions | • PI recommends not using as first opioid  
|                 | • Titrate using minimum of 2 d intervals  
|                 | • Swallow capsules whole (do not chew, crush, or dissolve)  
|                 | • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately |
| Drug interactions | • Alcohol/medication containing alcohol may result in rapid release & absorption of potentially fatal dose of morphine  
|                 | • P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |
| Opioid-tolerant | 100 mg, 130 mg, 150 mg, 200 mg capsules for use in opioid-tolerant patients only |
| Product-specific safety concerns | • None |

### Morphine Sulfate (MorphaBond)

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

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<thead>
<tr>
<th>Dosing Interval</th>
<th>• Every 8 h or every 12 h</th>
</tr>
</thead>
</table>
| Key instructions | • Product information recommends not using as first opioid  
|                 | • Titrate using a minimum of 1 – 2 d intervals  
|                 | • Swallow tablets whole (do not chew, crush, or dissolve) |
| Specific Drug interactions | • P-gp inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold |
| Opioid-tolerant | MorphaBond 100 mg tablets are for use in opioid-tolerant patients only |
| Product-specific safety concerns | • None |

### Morphine Sulfate (MS Contin)

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

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>• Every 8 h or every 12 h</th>
</tr>
</thead>
</table>
| Key instructions | • Product information recommends not using as first opioid  
|                 | • Titrate using a minimum of 1-2 d intervals  
|                 | • Swallow tablets whole (do not chew, crush, or dissolve) |
| Drug interactions | • P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold |
| Opioid-tolerant | 100 mg & 200 mg tablet strengths for use in opioid-tolerant patients only |
| Product-specific safety concerns | • None |
### Tapentadol (Nucynta ER)
**ER Tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg**

**Dosing interval**
- Every 12 h

**Key instructions**
- 50 mg every 12 h is initial dose in opioid non-tolerant patients
- Titrate by 50 mg increments using minimum of 3 d intervals
- MDD: 100 mg
- Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time w/ enough water to ensure complete swallowing immediately after placing in mouth
- Avoid use in severe hepatic & renal impairment

**Drug interactions**
- Alcohol: may result in rapid release & absorption of a potentially fatal dose of tapentadol
- Contraindicated in patients taking MAOIs

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

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

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

### Oxymorphone Hydrochloride (Opana ER)
**ER Tablets 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg**

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

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

**Drug interactions**
- Alcohol: may result in absorption of a potentially fatal dose of oxymorphone

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

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

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

### Oxycodone Hydrochloride (OxyContin)
**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: 5 mg q12h in opioid naïve and non-tolerant patients. 10 mg every 12 h
- Titrate using a minimum of 1-2 d intervals
- Hepatic impairment: start w/ 1/4-1/2 usual dosage
- Renal impairment (creatinine clearance <30 mL/min): start w/ 1/2 usual dosage
- Consider other analgesics in patients w/ difficulty swallowing or underlying GI disorders that predispose to obstruction (e.g. small gastrointestinal lumen)
- Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth

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

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

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

**Relative potency to oral morphine**
- Approximately 2:1 oral morphine to oxycodone oral dose ratio
Oxycodone Hydrochloride (OxyContin) continued

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

Key Instructions

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

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

IMPORTANT:
- Opioids are rarely indicated or used to treat pediatric patients with chronic pain.
- The recent FDA approval for this oxycodone formulation was NOT intended to increase prescribing or use of this drug in pediatric pain treatment. Review the product information and adhere to best practices in the literature.

Oxycodone Hydrochloride/Naloxone Hydrochloride (Targiniq ER)

ER Tablets 10 mg/5mg, 20 mg/10mg, 40 mg/20mg

Dosing Interval: Every 12h

Key Instructions

- Opioid-naïve patients initiate treatment w/ 10/5mg every 12h.
- Titrate using min of 1-2 d intervals.
- Do not exceed 80 mg/40 mg daily total dose (40 mg/20 mg q12h).
- May be taken w/ or without food.
- Seawolf white. 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:
- CYP2D6 inhibitors may increase oxycodone exposure.
- CYP2D6 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:
- See individual PI for conversion recommendations from prior opioids.

Oxycodone Hydrochloride/Naltrexone Hydrochloride (Travixa ER)

ER Capsules 10/1.2mg, 20/2.4mg, 30/3.6mg, 40/4.8mg, 60/7.2mg, 80/9.6mg

Dosing Interval: Every 12h

Key Instructions

- Opioid-naïve & non-tolerant patient is 10/1.2mg, every 12h.
- Total daily dose may be adjusted by 20/2.4 mg every 2-3 d.
- Seawolf capsules whole do not chew, crush, or dissolve; possible fatal overdose, and naltrexone (possible withdrawal).
- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
- Do not administer through NG or G tube.

Drug Interactions:
- CYP3A4 inhibitors may increase hydrocodone exposure.
- CYP3A4 inducers may decrease hydrocodone exposure.

Opioid-tolerant:
- Single dose >40/4.8mg or total daily dose >80/9.6mg for use in opioid-tolerant patients only.

Product-specific safety concerns:
- None.

Relative potency:
- See individual product information for conversion recommendations from prior opioid.
Hydrocodone Bitartrate (Vantrela ER)
ER Tablets 15 mg, 30 mg, 45 mg, 60 mg, 90 mg

Dosing interval
- Every 12 h

Key instructions
- Initial dose in opioid naive and non-tolerant patient is 15 mg every 12 h. Dose can be increased to next higher dose every 3-7 d
- Swallow capsules whole (do not chew, crush, or dissolve)
- Mild or moderate hepatic and moderate to severe renal impairment: initiate therapy with ½ recommended initial dose. If a dose <15 mg needed, use alternative options

Drug interactions
- CYP3A4 inhibitors may increase hydrocodone exposure
- CYP3A4 inducers may decrease hydrocodone exposure

Opioid-tolerant
- A 90 mg tablet, a single dose greater than 60 mg, or a total daily dose >120 mg are for use in opioid-tolerant patients only

Product-specific safety concerns
- None

Relative potency
- See individual product information for conversion recommendations from prior opioid

Oxycodone (Xtampza ER)
ER Capsules 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg

Dosing interval
- Every 12 h

Key instructions
- Opioid naive and non-tolerant, initiate with 9 mg every 12 h
- Titrate using a minimum of 2-3 intervals
- Take with same amount of food to ensure consistent plasma levels
- Maximum daily dose: 288 mg (8 x 36 mg), safety of excipients not established for higher doses
- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
- May also be administered through a NG or G feeding tube
- Hepatic impairment: initiate therapy at 1/3 to ½ usual dose
- Renal impairment: creatinine clearance <60 mL/min, follow conservative approach

Drug interactions
- CYP3A4 inhibitors may increase hydrocodone exposure
- CYP3A4 inducers may decrease hydrocodone exposure

Opioid-tolerant
- A single dose >36 mg or a total daily dose >72 mg for opioid-tolerant patients only

Product-specific safety concerns
- None

Relative potency
- There are no established conversion ratios for Xtampza ER, defined by clinical trials

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 2-4 hours after expected peak of blood concentrations
- Note that reversal of analgesia will occur

Drug interactions
- Larger doses required to reverse effects of butorphanol, nalbuphine, or pentazocine

Opioid-tolerant
- Assess signs and symptoms of opioid withdrawal, may occur within 2 min–2 hrs
- Vomiting, restlessness, abdominal cramps, increased BP, temperature
- Severity depends on naloxone dose, opioid involved & degree of dependence
- Ventricular arrhythmias, hypertension, hypotension, nausea & vomiting

Product-specific safety concerns
- As naloxone plasma levels decrease, sedation from opioid overdose may increase
Hydrocodone Bitartrate (Zohydro ER)
ER Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg

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:
- Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio

Appendix 2. Detailed Disclosure
Information for CO*RE Staff and Faculty

The following individuals disclose no relevant financial relationships:
Faculty Advisory Panel & Reviewer COI

<table>
<thead>
<tr>
<th>Faculty Advisory Panel</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Bazzo, MD</td>
<td>Clinical Professor of Family Medicine, University of California San Diego, School of Medicine</td>
</tr>
<tr>
<td>Ron Crossno, MD</td>
<td>Vice President, Medical Affairs and Chief Medical Officer at Kindred at Home</td>
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<tr>
<td>Katherine Galluzzi, DO</td>
<td>Professor and Chair, Department of Geriatrics, Philadelphia College of Osteopathic Medicine</td>
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<td>Director of Physician Education and Development, Kaiser Permanente, Northern California</td>
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<td>Randall Steven Hudspeth PhD, MBA, MS, APRN-CNP, FRE, FAANP</td>
<td>Practice and Regulation Consultant in Advanced Practice Pain Management and Palliative Care</td>
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<td>Senior Physician Assistant, Parkland Health and Hospital Systems</td>
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<tr>
<td>Barbara St. Marie, PhD, ANP-GNP</td>
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<td>Edwin A. Salsitz, MD, DFASAM</td>
<td>Mount Sinai Beth Israel Medical Center, Division of Chemical Dependency; Assistant Professor, Icahn School of Medicine at Mount Sinai</td>
</tr>
<tr>
<td>Seddon R. Savage, MD</td>
<td>Associate Professor, Geisel School of Medicine, Dartmouth College, Director Dartmouth Center on Addiction Recovery and Education</td>
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<tr>
<th>External / Consulting Reviewers</th>
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<tbody>
<tr>
<td>Roberto Cardarelli, DO, MPH</td>
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<tr>
<td>Marcia Jackson, PhD</td>
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© CO*RE Education 2017
ER Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg

Collaborative for REMS Education
### CO*RE Partner Staff COI

<table>
<thead>
<tr>
<th>Staff Person</th>
<th>Partner Affiliation</th>
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<tbody>
<tr>
<td>Julie Bruno</td>
<td>American Academy of Hospice and Palliative Medicine</td>
</tr>
<tr>
<td>Michael McCoy</td>
<td>American Academy of Nurse Practitioners</td>
</tr>
<tr>
<td>Sarah Norwegian</td>
<td>American Academy of Physician Assistants</td>
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<tr>
<td>Stephanie Townsend</td>
<td>American Osteopathic Association</td>
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<tr>
<td>Marie Leger</td>
<td>American Society of Radiation Oncology</td>
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<tr>
<td>Eric Peterson</td>
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<td>Stephanie Townsell</td>
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<td>Conner Bellis</td>
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<td>Molly Muzuk</td>
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<td>Catherine Underwood</td>
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<tr>
<td>Brianna Wixted</td>
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<td>Robin Heyden</td>
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<td>Neil Heyden</td>
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<tr>
<td>Tom McKeithen</td>
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<tr>
<td>Chris Larrison</td>
<td>American Academy of Physician Assistants</td>
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The following individuals disclose no relevant financial relationships:

### CO*RE Operations Organizations

<table>
<thead>
<tr>
<th>Staff Person</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cynthia Kear</td>
<td>Cynitha Kear, LLC</td>
</tr>
<tr>
<td>Katie Detzler</td>
<td>Forefront Collaboration</td>
</tr>
<tr>
<td>Kathy Dugan</td>
<td>Healthcare Performance Consulting</td>
</tr>
<tr>
<td>Molly Muzuk</td>
<td>Healthcare Performance Consulting</td>
</tr>
</tbody>
</table>

The following individuals disclose no relevant financial relationships: