FACULTY INFORMATION

BIO:
Barbara St. Marie is a certified Adult, Gerontology, Primary Care Nurse Practitioner, Pain Management Certified through ANCC. She has a PhD from the University of Wisconsin, Milwaukee, Wisconsin. She has been editor of the first and second edition of the Core Curriculum for Pain Management Nursing. She is on the Faculty Advisory Board for CORE REMS and Board of Directors of the American Pain Society. She is Principal Investigator on a study entitled, "Decision Support for Responsible Pain Management" funded through the National Institute on Drug Abuse. She is an Assistant Professor at the College of Nursing, University of Iowa where she teaches pathophysiology in the DNP program.

DISCLOSURE:
No disclosures.
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

#### Brand Name Products
- Arymo ER morphine sulfate ER tablets
- Avinza® morphine sulfate ER capsules
- Belbuca® buprenorphine buccal film
- Butrans® buprenorphine transdermal system
- Dolophine® methadone hydrochloride tablets
- Duragesic® fentanyl transdermal system
- Embeda® morphine sulfate/naltrexone ER capsules
- Exalgo® hydromorphone hydrochloride ER tablets
- Hysingla ERY hydrocodone ER tablets
- Hygeia® morphine sulfate ER capsules
- Kadian® morphine sulfate ER capsules
- Methadone® morphine sulfate ER capsules
- MS Contin® morphine sulfate CR tablets
- Nucynta ER extended-release tablets
- Opana® ER oxymorphone hydrochloride ER tablets
- OxyContin® ER oxycodone hydrochloride CR tablets
- Tapentadol® ER tapentadol extended-release ER tablets
- Troxyca ER oxycodone hydrochloride/naltrexone ER tablets
- Zohydro ER hydrocodone bitartrate ER capsules

#### Generic Products
- Fentanyl ER transdermal systems
- Methadone hydrochloride tablets
- Methadone hydrochloride oral concentrate
- Methadone hydrochloride oral solution
- Morphine sulfate ER tablets
- Morphine sulfate ER capsules
- Hydromorphone hydrochloride ER tablets
- Hydrocodone hydrochloride ER tablets
- Hydromorphone hydrochloride ER tablets

### Chapter 2

**Why Are We Here?**
OPIOID DEATHS, TREATMENT ADMISSIONS AND PRESCRIBING

Treatment Admissions / 10,000
Opioid Pain Relievers Deaths / 100,000
Opioid Pain Relievers Sales kg / 10,000

YEAR


Any Opioid
Narcotics

PRESCRIBING PATTERNS – WE PLAY A ROLE

Number of opioid prescriptions per 100 people
52-71
72-90.1
90.2-95
96-149

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

**SOURCE OF MOST RECENT RX OPIOIDS AMONG PAST-YEAR MISUSERS 2015**

Source where pain relievers were obtained for most recent misuse among 12.5 million people aged 12 or older who misused prescription pain relievers in the past year: percentages, 2015

- 54% - Given by, bought from, or taken from a friend or relative
- 36% - Through a prescription or stolen from healthcare provider
- 5% - Bought from a dealer or stranger
- 5% - Some other way
FIRST SPECIFIC DRUG ASSOCIATED WITH INITIATION OF ILLICIT DRUG USE 2013

2.8 million initiates of illicit drugs
- 70.3% - Marijuana
- 12.5% - Pain Relievers
- 6.3% - Inhalants
- 5.2% - Tranquilizers
- 2.7% - Stimulants
- 2.6% - Hallucinogens
- 0.3% - Sedatives and Cocaine

SOURCE: SAMHSA Annual National Survey on Drug Use and Health, June 2015
https://www.drugabuse.gov/publications/drugfacts/nationwide-trends

THE FEDERAL PLAYERS

Many agencies involved

WE ARE HERE BECAUSE OF...

REMS: RISK EVALUATION AND MITIGATION STRATEGY

- On July 9, 2012, the Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications
- First time FDA has ever used accredited CE/CME as part of a REMS
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.
CHAPTER 3
PAIN

THE NEUROPSYCHOBIOLOGY OF PAIN

1. Perception in the tissue (modulation occurs)
2. Transmission along nerve to spinal cord (modulation occurs)
3. Transmission along spinal cord to brain (modulation occurs)

OPIOID SITES OF ACTION IN THE BRAIN

Prefrontal cortex
Nucleus accumbens
Amygdala
Periaqueductal gray area

Optional Slide
UNDERSTANDING PAIN

Biopsychosocial Spiritual Context
- Acute
- Post-traumatic
- Post-surgical
- Chronic
- Complex regional pain syndrome
- Gangrene
- Pheochromocytoma
- Acute
- Post-traumatic
- Post-surgical
- Chronic
- Complex regional pain syndrome
- Gangrene
- Pheochromocytoma

Experience of Pain

THE IMPACT OF PAIN

SLEEP DISTURBANCE
- CHRONIC PAIN
- SUBSTANCE MISUSE
- SECONDARY PHYSICAL PROBLEMS
- FUNCTIONAL DISABILITIES
- ANXIETY DEPRESSION
- COGNITIVE DISTORTIONS
- INCREASED STRESSES

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

COGNITIVE BEHAVIORAL THERAPY
- Behavioral Modification
- Meditation
- Cognitive Restructuring

INTERVENTIONAL TREATMENTS
- Nerve Blocks
- Steroid Injections
- Stimulators
- Trigger Point Injections

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

PHYSICAL
- Exercise
- Acupuncture
- Movement Therapies
- Manual Treatments

Quality of Life
- Cultivate Well Being
• Explain neurophysiology of pain processing to patients
• When patients understand, their concerns are validated
• Pain has biological, psychological, social, and spiritual components

**CHAPTER 3 - PEARLS FOR PRACTICE**

**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.

**CHAPTER 4 - ASSESSMENT**
PAIN ASSESSMENT

DESCRIPTION OF PAIN

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

WHAT RELIEVES THE PAIN?
WHAT CAUSES OR INCREASES PAIN?
EFFECTS OF PAIN ON PHYSICAL, EMOTIONAL, AND PSYCHOSOCIAL FUNCTION
PATIENT'S CURRENT PAIN AND FUNCTION

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

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

- GENERAL EFFECTIVENESS

PAST MEDICAL HISTORY

ILLNESS RELEVANT TO (1) EFFECTS OR (2) METABOLISM OF OPIOIDS
1. Pulmonary disease, constipation, nausea, cognitive impairment
2. Hepatic, renal disease

ILLNESS POSSIBLY LINKED TO SUBSTANCE USE DISORDER (SUD):
- Hepatitis
- HIV
- Tuberculosis
- Cellulitis
- STIs

OBTAINT 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

PHYSICAL EXAM AND ASSESSMENT

Seek objective confirmatory data

Components of patient evaluation for pain

Order diagnostic tests (appropriate to complaint)

General: vital signs, appearance, and pain behaviors

Musculoskeletal exam
  - Inspection
  - Gait and posture
  - Range of motion
  - Palpation
  - Percussion
  - Auscultation
  - Provocative maneuvers

Neurologic exam

Cutaneous or trophic findings


RISK ASSESSMENT TOOLS

<table>
<thead>
<tr>
<th>TOOL</th>
<th># OF ITEMS</th>
<th>ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENTS CONSIDERED FOR LONG-TERM OPIOID THERAPY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT Opioid Risk Tool</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>DREI Diagnosis, Variability, Risk, and Efficacy score</td>
<td>7</td>
<td>clinician</td>
</tr>
<tr>
<td>CHARACTE:RIZE MISUSE ONCE OPIOID TREATMENT BEGINS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMQ Pain Medication Questionnaire</td>
<td>26</td>
<td>patient</td>
</tr>
<tr>
<td>COMM Current Opioid Misuse Measure</td>
<td>17</td>
<td>patient</td>
</tr>
<tr>
<td>PDUQ 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>CAGEAD Cut Down, Annoyed, Guilty, Eye-Opener test, Adapted to Include Drugs</td>
<td>4</td>
<td>clinician</td>
</tr>
<tr>
<td>RAFTT Rates, Alone, Friends, Family, Trouble</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>DART Drug Abuse Screening Test</td>
<td>28</td>
<td>patient</td>
</tr>
<tr>
<td>SERTT Screening, Brief Intervention, and Referral to Treatment</td>
<td>Varies</td>
<td>clinician</td>
</tr>
</tbody>
</table>
**OPIOID RISK TOOL (ORT)**

Mark each box that applies

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of substance abuse</td>
<td>☐ 1</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Stated drugs</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>☐ 4</td>
<td>☐ 4</td>
</tr>
</tbody>
</table>

**ADMINISTER**

On initial visit or prior to opioid therapy

**SCORING (RISK)**

0-2: low risk
4-7: moderate risk
≥8: high risk

**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

**SOAPP®: 4 FORMATS AVAILABLE TO ASSESS MISUSE RISK**

<table>
<thead>
<tr>
<th>SOAPP® V.1 24Q VERSION (ORIGINAL)</th>
<th>14Q VERSION</th>
<th>5Q (SHORT-FORM) VERSION</th>
<th>SOAPP® R 24Q VERSION (REVISED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 questions (14 used to score tool)</td>
<td>14 questions*</td>
<td>5 questions*</td>
<td>24 questions</td>
</tr>
<tr>
<td>Add ratings for 14 &quot;screening&quot; questions</td>
<td>Add ratings for each question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 min. to complete 10 &quot;unscored&quot; questions provide background</td>
<td>&lt;5 min. to complete</td>
<td>&lt;10 min. to complete</td>
<td></td>
</tr>
</tbody>
</table>

*Questions from SOAPP® V.1 - Patients ask all questions in order of 1-14
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.

WHAT IS THE RISK FOR MY PATIENT?

PAIN AND ADDICTION

<table>
<thead>
<tr>
<th>PAIN – 5 A’S</th>
<th>ADDICTION – 5 C’S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Control, loss of</td>
</tr>
<tr>
<td>Activities/Function</td>
<td>Compulsive use</td>
</tr>
<tr>
<td>Aberrant Behavior</td>
<td>Craving drug</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Continued use</td>
</tr>
<tr>
<td>Affect</td>
<td>Chronic problem</td>
</tr>
</tbody>
</table>
RISK AND PAIN ASSESSMENT TOOL BOXES

PAIN ASSESSMENT TOOL BOX
- Pain Assessment Tools (BPI, etc.)
- Functional Assessment (SF 36, PPS, geriatric assessment, etc.)
- Pain intensity, Enjoyment of life, General activity (PEO)

Risk Assessment Tools (ORT or SOAPP®)
Mental Health Tools (PHQ9, GAD7, etc.)

PAIN ASSESSMENT TOOL BOX
- PDMP
- UDT
- Risk Assessment Tools (ORT or SOAPP®)

CONSIDER A TRIAL OF AN OPIOID?

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

When to consider a trial of an opioid

60-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](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:

<table>
<thead>
<tr>
<th>ANALGESIC AND FUNCTIONAL GOALS OF TREATMENT</th>
<th>HOW TO MANAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPECTATIONS</td>
<td>- Common Adverse Effects (AEs) (e.g., constipation, nausea, sedation)</td>
</tr>
<tr>
<td>POTENTIAL RISKS</td>
<td>- Risks (e.g., abuse, addiction, respiratory depression, overdose)</td>
</tr>
<tr>
<td>ALTERNATIVES TO OPIOIDS</td>
<td>- AEs with long-term therapy (e.g., hyperalgesia, low testosterone, irregular menses or sexual dysfunction)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>REINFORCE EXPECTATIONS FOR APPROPRIATE AND SAFE OPIOID USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• One prescriber</td>
</tr>
<tr>
<td>• Consider one pharmacy</td>
</tr>
<tr>
<td>• Safeguard</td>
</tr>
<tr>
<td>- Do not store in medicine cabinet</td>
</tr>
<tr>
<td>- Keep locked (medication safe)</td>
</tr>
<tr>
<td>- Do not share or sell</td>
</tr>
<tr>
<td>• Instructions for disposal when no longer needed</td>
</tr>
<tr>
<td>• Prescriber notification for any event resulting in a pain medication prescription</td>
</tr>
<tr>
<td>• Follow-up</td>
</tr>
<tr>
<td>• Monitoring</td>
</tr>
<tr>
<td>- Random UDT and pill counts</td>
</tr>
<tr>
<td>• Refills</td>
</tr>
<tr>
<td>• Identify behaviors for discontinuation</td>
</tr>
<tr>
<td>• Exit strategy</td>
</tr>
</tbody>
</table>

### MONITOR ADHERENCE AND ABBERRANT BEHAVIOR

<table>
<thead>
<tr>
<th>ROUTINELY MONITOR PATIENT ADHERENCE TO TREATMENT PLAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recognize and document aberrant drug-related behavior</td>
</tr>
<tr>
<td>- In addition to patient self-report also use:</td>
</tr>
<tr>
<td>• State PDMPs</td>
</tr>
<tr>
<td>• UDT</td>
</tr>
<tr>
<td>- Positive for non-prescribed drugs</td>
</tr>
<tr>
<td>- Positive for illicit substance</td>
</tr>
<tr>
<td>- Negative for prescribed opioid</td>
</tr>
<tr>
<td>• Family member or caregiver interviews</td>
</tr>
<tr>
<td>• Monitoring tools such as the COMM, PADT, PMQ, or PDUQ</td>
</tr>
<tr>
<td>• Medication reconciliation (e.g., pill counts)</td>
</tr>
</tbody>
</table>

PADT = Pain Assessment and Documentation Tool

### ADDRESS ABBERRANT DRUG-RELATED BEHAVIOR

Behavior outside the boundaries of agreed-on treatment plan:

<table>
<thead>
<tr>
<th>Unsanctioned dose escalations or other noncompliance with therapy on 1 or 2 occasions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unapproved use of the drug to treat another symptom</td>
</tr>
<tr>
<td>Openly acquiring similar drugs from other medical sources</td>
</tr>
<tr>
<td>Multiple dose escalations or other noncompliance with therapy despite warnings</td>
</tr>
<tr>
<td>Prescription forgery</td>
</tr>
<tr>
<td>Obtaining prescription drugs from nonmedical sources</td>
</tr>
</tbody>
</table>

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.
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/UCM183919.pdf
or 1-800-FDA-1088
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 increase

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

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

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

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

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

WHEN TO MOVE FROM IR TO ER/LA OPIOIDS
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)

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-opioid) if pain is not controlled during titration

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Supplement with IR analgesics (opioids and non-opioid) if pain is not controlled during titration

OPIOID TOLERANCE
If opioid tolerant caution should still be used at higher doses

Patients considered opioid tolerant are taking at least
- 60 mg oral morphine/day
- 25 mg oral oxycodone/day
- 8 mg oral oxymorphone/day
- 25 mg oral oxymorphone/day
An equianalgesic dose of another opioid
Still requires caution when rotating a patient on an IR opioid to a different ER/LA opioid

FOR 1 WEEK OR LONGER

OPIOID TOLERANCE
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- 25 mg oral oxymorphone/day
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Still requires caution when rotating a patient on an IR opioid to a different ER/LA opioid

FOR 1 WEEK OR LONGER

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
- Smartphone Apps

Vary in terms of:

- Equianalgesic Values
- Whether ranges are used

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

EXAMPLE OF AN EDT FOR ADULTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>SC/IV</th>
<th>PO</th>
<th>Parenteral PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
<td>2.5-5 mg SC/IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(q3-4h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.25-2.5 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-15 mg q3-4h (IR or oral solution)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.5-7.5 mg)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20 mg NA</td>
<td>5-10 mg q3-4h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.5 mg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30 mg NA</td>
<td>5 mg q3-4h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.5 mg)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
<td>0.2-0.6 mg SC/IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(q3-4h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.5-1 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2 mg q3-4h (IR or oral solution)</td>
</tr>
</tbody>
</table>

MU OPIOID RECEPTORS AND INCOMPLETE CROSS-TOLERANCE

Mu opioids bind to mu receptors

Many mu receptor subtypes:

- Mu opioids produce subtly different pharmacologic response based on distinct activation profiles of mu receptor subtypes

May help explain:

- Inter-patient variability in response to mu opioids
- Incomplete cross-tolerance among mu opioids
INCOMPLETE CROSS-TOLERANCE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Partial</th>
<th>Partial</th>
<th>Full</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1+3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>2+3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1+2+3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CROSS-TOLERANCE IF TOLERANT TO DRUG:

<table>
<thead>
<tr>
<th>Challenge</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Partial</td>
<td>Partial</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>Partial</td>
<td>Partial</td>
<td>Partial</td>
<td>-</td>
</tr>
</tbody>
</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 IS
- Does not have these characteristics
- Is changing route of administration

*25%-50% 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-naïve patients, methadone should not be given as an initial drug

IF SWITCHING TO TRANSDERMAL:
- Fentanyl, calculate dose conversion based on equianalgesic dose ratios included in the PI
- Buprenorphine, follow instructions in the PI
GUIDELINE FOR OPIOID ROTATION: SUMMARY

VALUES FROM

Patient Opioid

Values

"Solve" for x

Automatically Reduce Dose

Value of Current Opioid

24 Hour Dose of Current Opioid

Equianalgesic: 24 Hour Dose of New Opioid

By 25%-50%\(^1\)

\(x\) Amount of New Opioid

Frequently assess initial response

Titrated dose of new opioid to optimize outcomes

Calculate supplemental rescue dose used for titration at 5%-15% of total daily dose\(^2\)

---

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/

SAMHSA mental health treatment facility locator

https://findtreatment.samhsa.gov/locator/

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

Be aware of what you are testing and not testing

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

GC/MS=gas chromatography/mass spectrometry
LC/MS=liquid chromatography/mass spectrometry


SPECIFIC WINDOWS OF DRUG DETECTION

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

DETECTION TIME OF DRUGS IN URINE

Governed by various factors, e.g., dose, route of administration, metabolism, fat solubility, urine volume and pH

For most drugs it is 1-3 days

Chronic use of lipid-soluble drugs increases detection time, e.g., marijuana, diazepam, ketamine
**SPECIFIC WINDOWS OF DRUG DETECTION** (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>How soon after taking drug will there be a positive drug test?</th>
<th>How long after taking drug will there continue to be a positive drug test?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana/Pot</td>
<td>1-3 hours</td>
<td>1-7 days</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>2-6 hours</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Heroin/Opiates</td>
<td>2-6 hours</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Speed/Uppers (Amphetamines, methamphetamine)</td>
<td>4-6 hours</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Angel Dust/PCP</td>
<td>4-6 hours</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>2-7 hours</td>
<td>2-4 days</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>2-7 hours</td>
<td>1-4 days</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>2-4 hours</td>
<td>1-3 weeks</td>
</tr>
<tr>
<td>Methadone</td>
<td>3-8 hours</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>8-12 hours</td>
<td>2-7 days</td>
</tr>
<tr>
<td>Opiates</td>
<td>1-3 hours</td>
<td>1-2 days</td>
</tr>
</tbody>
</table>

Source: [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/DrugsofAbuseTests/ucm125722.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/DrugsofAbuseTests/ucm125722.htm)

**URINE SPECIMEN INTEGRITY**

**SPECIMEN COLOR RELATED TO CONCENTRATION**

- Concentrated samples more reliable than dilute samples

**TEMP WITHIN 4 MINUTES OF VOIDING IS 90-100ºF**

**PH FLUCTUATES WITHIN RANGE OF 4.5-8.0**

**CREATININE VARIES WITH HYDRATION**

- Normal urine: >20 mg/dL
- Dilute: creatinine <20 mg/dL, and specific gravity <1.003
- Creatinine <2 mg/dL not consistent with human urine

**INTERPRETATION OF UDT RESULTS**

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

- CODEINE → MORPHINE → 6-MAMP → HERON
  - T₁/₂ = 25-30 MIN
- HYDROCODONE → HYDROMORPHONE
- OXYCODONE → OXYMORPHONE

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**

**Pain Level Decreases in Stable Patients**

**Intolerable and Unmanageable AEs**

**No Progress Toward Therapeutic Goal**

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

**Aberrant Behaviors**
- Use of illicit drugs or unprescribed opioids
- Repeatedly obtaining opioids from multiple outside sources
- Prescription forgery
- Multiple episodes of prescription loss
- Diversion

**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**

### WOMEN WITH CHILDBEARING POTENTIAL

**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/no 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, antepartum 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 dosage change 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

CHALLENGE: VULNERABILITY IN CO-DEPENDENT OLDER ADULTS

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:
- UDT 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.

CHAPTER 7

KNOW YOUR FEDERAL AND STATE LAWS
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 filling of prescriptions pursuant to section 309 of the Act (21 USC 829)
  - www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm
- United States Code (USC) - Controlled Substances Act, Title 21, Section 829: prescriptions
  - www.deadiversion.usdoj.gov/21cfr/21usc/829.htm

**STATE**
- Database of state statutes, regulations, and policies for pain management
  - www.medscape.com/resource/pain/opioid
- Database of state statutes, regulations, and policies for pain management
  - www.painpolicy.wisc.edu/database

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>
# Content Outline

<table>
<thead>
<tr>
<th>Overdose deaths</th>
<th>309 (2015)</th>
</tr>
</thead>
</table>

- Prescription Drug Monitoring Program (PDMP)
- Prescriber Status and Education Requirements
- Naloxone Regulation
- Medical and Recreational Marijuana Status
- Patient Prescriber Agreement & Treatment Programs

## PDMP: Prescription Drug Monitoring Program

### General
- **Iowa Prescription Monitoring Program**
  - https://pharmacy.iowa.gov/prescription-monitoring-program
- Administered by the Board of Pharmacy
- Schedule II IV are monitored
- Dispensers are required to register and input data
- Before prescribing, there is no obligation to review under certain circumstances

### Access
- Prescribers, dispensers, law enforcement and judicial/prosecutorial, licensing/regulatory boards, patient, health care agent
- Prescribers can authorize a registered delegate

### Reporting
- Must be entered into PDMP 7 days after dispensing
- Unsolicited reports/alerts are not sent
- Iowa does share data with other states’ PDMP
- Out-of-state pharmacies are required to report to the patient’s home state
- Patient will not be notified if their record has been accessed

http://www.namsdl.org/prescription-drug-monitoring-programs-maps.htm  June 2017
Prescriber Status & Education Requirements

<table>
<thead>
<tr>
<th>Physician</th>
<th>Physician Assistant</th>
<th>Advanced Practice Nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensed</td>
<td>II-V</td>
<td>Schedule II-V</td>
</tr>
</tbody>
</table>

Education Requirements:
- 2 hrs./5 yrs.
- None
- None

Initial prescribing limits for acute pain: None

Naloxone Regulation
- Effective date: April 2016
- Immunity: Criminal
  - Prescribers: No
  - Dispensers: No
  - Lay People: No
- Prescribing Permitted
  - 3rd Party Status: Yes
  - Standing Order: Yes
- Available without a prescription: Yes
- Who carries it:
  - First responders

Medical and Recreational Marijuana Status
- It is not legal to prescribe
- It is not legal for recreational use

Patient Prescriber Agreement and Treatment Programs
- A Patient Prescriber Agreement (PPA) is recommended or required
- For a list of treatment programs in this state:
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

CHALLENGE: THE HIGH RISK PATIENT

RED FLAG:
Proceed with caution, but treat the high risk patient

18-year-old with a recurrent wound in the antecubital fossa secondary to intravenous injection. This is her third wound debridement and she is in more pain than before. She tells you if she cannot get relief from you, she will go to the street for meds.

Action:
With a drug abuse history, proceed with caution and use extra safety measures. Patient may require admission to either hospital or treatment facility while managing pain. This history does not mean you should discharge or avoid treating the patient’s pain.
CHAPTER 8
COUNSELING PATIENTS AND CAREGIVERS

USE PATIENT COUNSELING DOCUMENT

DOWNLOAD:

ORDER HARD COPIES:
www.minneapolis.cenveo.com/pcd/SubmitOrders.aspx

SOURCE: FDA. Extended-release (Er) And Long-acting (La) Opioid Analgesics Risk Evaluation And Mitigation Strategy (Rems). Modified 06/2015

COUNSEL PATIENTS ABOUT PROPER USE

EXPLAIN

• Product-specific information about the IR or ER/LA opioid (especially when converting)
• Take opioid as prescribed
• Adhere to dose regimen
• How to handle missed doses
• Notify prescriber if pain not controlled
• Call prescriber for options on side effect management

INSTRUCT PATIENTS/ CAREGIVERS TO

• Read the ER/LA opioid Medication Guide received from pharmacy every time an ER/LA opioid is dispensed
COUNSEL PATIENTS ABOUT PROPER USE (continued)

EXPLAIN

• Inform prescriber of ALL meds being taken
• Warn patients not to abruptly discontinue or reduce dose
• Risk of falls
• Caution with operating heavy machinery and when driving
• Sharing or selling opioids can lead to others’ deaths and is against the law

OPIOIDS CAN CAUSE DEATH EVEN WHEN TAKEN PROPERLY

• Signs/symptoms are respiratory depression, gastrointestinal obstruction, allergic reactions

EXPLAIN

• Tell patients and caregivers, medications must be kept in a locked container
• Will periodically assess for benefits, side effects, and continued need for IR/ER/LA opioids
• Need for re-evaluation of underlying medical condition if the clinical presentation changes over time

OPIOIDS SHOULD BE STORED IN A SAFE AND SECURE PLACE

• Away from children, family members, visitors, and pets
• Safe from theft

Opioids are scheduled under Controlled Substances Act and can be misused and abused

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

**Available as:**
- Naloxone kit (with syringes, needles)
- Injectable
- Nasal spray

**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

ABUSE-DETERRENT FORMULATION/TAMPER RESISTANT (ADF/TR) OPIOIDS

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

**TLAK WITH YOUR PATIENTS WHO ARE PARENTS**

- Consider the behavior you are modeling
- 45% of parents have taken pain medications without a prescription at some point
- 14% have given their children pain medications without a prescription
- Teens report that their parents do not talk with them about prescription drug risks
  - Evidence suggests that pre-college parental conversation helps reduce high-risk substance abuse among college students

**SUBSTANCES PARENTS HAVE DISCUSSED WITH TEENS**

<table>
<thead>
<tr>
<th>Substance</th>
<th>% of teens whose parents have discussed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer/alcohol</td>
<td>61%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>77%</td>
</tr>
<tr>
<td>Caffeine/energy drink</td>
<td>30%</td>
</tr>
<tr>
<td>Rx pain relief w/o doctor’s Rx</td>
<td>23%</td>
</tr>
<tr>
<td>Any Rx drug used w/o doctor’s Rx</td>
<td>22%</td>
</tr>
<tr>
<td>Heroin</td>
<td>21%</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>21%</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>21%</td>
</tr>
<tr>
<td>Non-Rx cough/cold/medication to get high</td>
<td>15%</td>
</tr>
<tr>
<td>Sedatives w/o doctor’s Rx</td>
<td>15%</td>
</tr>
<tr>
<td>Inhalants</td>
<td>14%</td>
</tr>
</tbody>
</table>

*As reported by teens

**REMEMBER...**

**STEP 1: MONITOR**
- Note how many pills in each prescription
- Keep track of dosage and refills
- Make sure everyone in the home knows

**STEP 2: SECURE**
- Keep meds in a safe place (locked cabinet)
- Encourage parents of your teen's friends to secure their prescriptions

**STEP 3: DISPOSE**
- Discard expired or unused meds
- Consult PI for best disposal
RX OPIOID DISPOSAL

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

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

DEA. Disposal Act: General Public Fact Sheet.

DECREASES AMOUNT OF OPIOIDS INTRODUCED INTO THE ENVIRONMENT, PARTICULARLY INTO WATER

OTHER METHODS OF OPIOID DISPOSAL

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

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

FDA: PRESCRIPTION DRUG DISPOSAL

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

CHALLENGE: THE DAUGHTER’S PARTY

RED FLAG:
 Patients do not safeguard their opioid medications correctly

Your patient’s daughter stole her father’s opioids from his bedside drawer to take to a “fishbowl party.” Her best friend consumed a mix of opioids and alcohol and died of an overdose.

Action:
Always counsel patients about safe drug storage; warn patients about the serious consequences of theft, misuse, and overdose. Tell patients that taking another person’s medication, even once, is against the law.
FOR SAFER USE: KNOW DRUG INTERACTIONS, PK, AND PD

- CNS depressants can potentiate sedation and respiratory depression
- Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol
- Some drug levels may increase without dose dumping
- Use with MAOIs may increase respiratory depression
- Certain opioids with MAOIs can cause serotonin syndrome
- Methadone and buprenorphine can prolong QTc interval
- 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
- Monitor patients with fever for signs or symptoms of increased opioid exposure
- Metal foil backings are not safe for use in MRIs
- For buccal film products the film should not be applied if it is cut, damaged, or changed in any way — 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

*Butorphanol, nalbuphine, pentazocine
†Buprenorphine
DRUG INFORMATION COMMON TO OPIOIDS

USE IN OPIOID-TOLERANT PATIENTS
- See individual PI for products which:
  - Have strengths or total daily doses only for use in opioid-tolerant patients
  - Are only for use in opioid-tolerant patients at all strengths

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

SPECIFIC CHARACTERISTICS

Know for opioid products you prescribe:

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>Formulation</th>
<th>Strength</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key instructions</td>
<td>Use in opioid-tolerant patients</td>
<td>Product-specific safety concerns</td>
<td>Relative potency to morphine</td>
</tr>
<tr>
<td>Specific information about product conversions, if available</td>
<td>Specific drug interactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SUMMARY

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

- Assess patients for treatment with IR and ER/LA opioids
- Initiate therapy, modify dose, and discontinue use of opioids
- Monitor ongoing therapy with IR and ER/LA opioids
- Counsel patients and caregivers about the safe use of opioids, including proper storage and disposal
- Be familiar with general and product-specific drug information concerning opioids
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.dailymed.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!

THANK YOU!
WWW.CORE-REMS.ORG
### Appendix 1. Drug Specific Slides

#### Morphine Sulfate ER Tablets (Arymo ER)

**Capsules 15 mg, 30 mg, 60 mg**

| Dosing Interval | • Initial dose in opioid-naïve and opioid non-tolerant patients is 15 mg every 8 or 12 hours  
|                 | • Dose 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. |

| Key Instructions | • P-gp inhibitors (e.g. quinidine) can increase the exposure of morphine by about two-fold and increase risk of respiratory depression. |

| Drug Interactions | • 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. |

| Opioid-tolerant | • 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**

| Dosing Interval | • Once a day |

| Key Instructions | • Initial dose in opioid non-tolerant patients is 30 mg  
|                 | • Titrate in increments of not greater than 30 mg using a minimum of 3-4 d intervals  
|                 | • Swallow capsule whole (do not chew, crush, or dissolve)  
|                 | • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately  
|                 | • MDD* 1600 mg (renal toxicity of excipient, fumaric acid). |

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

| Opioid-tolerant | • 90 mg & 120 mg capsules for use in opioid-tolerant patients only. |

| Product-specific safety concerns | • None |

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

75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg

**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-naïve 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)

**Drug Interactions**
- CYP3A4 inhibitors may increase buprenorphine levels
- CYP3A4 inducers may decrease buprenorphine levels
- Benzodiazepines may increase respiratory depression
- Class Ia & Ii antiarrhythmics, 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
- Hepatotoxicity
- Application site skin reactions

**Relative potency: oral morphine**
- Equipotency to oral morphine not established

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### Methadone Hydrochloride Tablets (Dolophine)

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

**Key instructions**
- Initial dose in opioid non-tolerant patients: 2.5 – 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 (21CFR, Title 42, Sec 8)
- 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 & 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) (text)

**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 w/ water only
  - Rotate site of application
  - Titrate using a minimum of 72 h intervals between dose adjustments
  - Do not cut
- Avoid exposure to heat
- Avoid accidental contact when holding or caring for children
- Dispose of used/unused patches: fold adhesive side together & flush down toilet

**Relative potency: oral morphine**
- See individual PI for conversion recommendations from prior opioid

---

### Fentanyl Transdermal System (Duragesic), continued (text)

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

**Drug interactions**
- CYP3A4 inhibitors may increase fentanyl exposure
- CYP3A4 inducers may decrease fentanyl exposure
- Discontinuation of 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 w/ increased core body temp or fever
- Bradycardia
- Application site skin reactions

---

### Morphine Sulfate ER-Naltrexone (Embeda) (text)

**Capsules 20 mg, 30 mg, 42 mg, 50 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 interaction
- None

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

Product-specific adverse reactions
- Allergic manifestations to sulfite component

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

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

Opioid-tolerant
- 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.
- Swallow tablets whole (do not chew, crush, or dissolve).
- Discontinue nursing or discontinue drug OD; prolongation has been observed with Hysingla ER following daily doses of 100 mg.
- Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congregate heart failure, bradycardia, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval.
- In patients who develop QTc prolongation, consider reducing the dose.

Relative potency
- See individual PI for conversion recommendations from prior opioid.
Morphine Sulfate (Kadian)

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

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

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

**Opioid-tolerant**
- 100 mg, 130 mg, 150 mg, 200 mg capsules for use in opioid-tolerant patients only

**Product-specific safety concerns**
- None

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Morphine Sulfate (MorphaBond)

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

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

**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)

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

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

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

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

**Product-specific safety concerns**
- None
**Tapentadol (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: 500 mg
- Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time, enough water to ensure complete swallowing immediately after placing in mouth
- Avoid use in severe hepatic & renal impairment
- Titrate in increments of 5-10 mg using a minimum of 3-7 d intervals
- Contraindicated in moderate & severe hepatic impairment

**Drug interactions**
- Alcoholic beverages or medications w/ alcohol may result in 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
- Angioedema

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

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**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, enough water to ensure complete swallowing immediately after placing in mouth
- Titrate in increments of 5-10 mg using a minimum of 3-7 d intervals
- Contraindicated in moderate & severe hepatic impairment

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

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

**Product-specific safety concerns**
- Use with caution in patients who have difficulty swallowing or underlying GI disorders that may predispose to obstruction. Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time, enough water to ensure complete swallowing immediately after placing in mouth

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

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**Oxycodone Hydrochloride (OxyContin)**

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

**NEW DOSING INFO**

**Dosing interval**
- Every 12 h

**Key instructions**
- Initial dose 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/ ½-¼ usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage
- Consider other analgesics in patients w/ difficulty swallowing or underlying GI disorders that predispose to obstruction. Swallow tablets whole (do not chew, crush, or dissolve)
- Take 1 tablet at a time, 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
- For AADs: Single dose >40 mg or total daily dose >80 mg for use in opioid tolerant patients only

**Opioid-tolerant**
- Contraindicated in patients w/ GI obstruction

**Product-specific safety concerns**
- Choking, gagging, regurgitation, tablets stuck in throat, difficulty swallowing tablet

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

**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.
### Hydrocodone Bitartrate (Vantrela ER)

**ER Tablets 15 mg, 30 mg, 45 mg, 60 mg, 90 mg**

<table>
<thead>
<tr>
<th><strong>Dosing interval</strong></th>
<th>Every 12 h</th>
</tr>
</thead>
</table>
| **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 days.  
- 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 oral morphine** | - 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**

<table>
<thead>
<tr>
<th><strong>Dosing interval</strong></th>
<th>Every 12 h</th>
</tr>
</thead>
</table>
| **Key instructions** | - Opioid naive and non-tolerant, initiate with 9 mg every 12 h.  
- Titrate using a minimum of 2-3 day intervals.  
- Take with same amount of food in order 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 oral morphine** | - 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 45-60 minutes  
- IN: onset 2-3 min, duration ~2 hours |
|---------------------|--------------------------------------------------|
| **Key instructions** | - Monitor respiratory rate.  
- Monitor level of consciousness for 3-4 hours after expected peak of blood concentrations.  
- Note that reversal of analgesia will occur. |
| **Drug interactions** | - Larger doses required to reverse effects of buprenorphine, butorphanol, nalbuphine, or pentazocine. |
| **Opioid-tolerant** | - Assess signs and symptoms of opioid withdrawal, may occur w/ 2 min – 2 hrs.  
- Vomiting, restlessness, abdominal cramps, increased BP. |
| **Product-specific safety concerns** | - Ludwig arrhythmias, hypotension, hypertension, nausea & vomiting.  
- 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>
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<th>Faculty Name</th>
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<tbody>
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<td>David Neumark, MD</td>
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<td>Julie Bruno</td>
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