FACULTY INFORMATION

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

DISCLOSURE:
This speaker has no conflicts of interest to disclose

FACULTY INFORMATION

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

DISCLOSURE:
This speaker has no conflicts of interest to disclose

ORGANIZATIONS

No CO*RE partner has any conflicts of interest to report (Appendix 2)

FACULTY ADVISORY PANEL

No CO*RE Faculty has any conflicts of interest to report (Appendix 2)
Acknowledgement

Presented by the Nurse Practitioner Healthcare Foundation, a member of the Collaborative on REMS Education (CO*RE), 11 interdisciplinary organizations working together to improve pain management and prevent adverse outcomes.

This educational activity is supported by an independent educational grant from the ER/LA Opioid Analgesic REMS Program Companies. Please see 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 & Drug Administration.

Products Covered by this REMS

**Brand Name Products**

- A Wyn™ ER morphine sulfate ER tablets
- Belbuca® buprenorphine buccal film
- Butrans® buprenorphine transdermal system
- Duragesic® fentanyl transdermal system
- Embeda® morphine sulfate/naltrexone ER capsules
- Exalgo® hydromorphone hydrochloride ER tablets
- Kadian® morphine sulfate ER capsules
- MS Contin® morphine sulfate CR tablets
- Nucynta ER™ tapentadol ER tablets
- Opana® ER oxymorphone hydrochloride ER tablets
- OxyContin® oxycodone hydrochloride CR tablets
- Targiniq ER™ oxycodone hydrochloride/naloxone hydrochloride ER tablets
- Troxyca ER™ oxycodone hydrochloride/naltrexone capsules
- Vantrela ER™ hydrocodone bitartrate ER tablets
- Xtampza ER™ oxycodone ER capsules
- Zohydro® 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
- Oxycodeone hydrochloride ER tablets

Chapter 2

Why are we here?

Overdose deaths involving opioids, U.S., 2000-2015

Prescribing patterns – we play a role

Opioid overdose deaths per 100,000 people (2015)

source: https://www.cdc.gov/drugoverdose/data/prescribing.html
Opioid Prescribing: Safe practice, Changing lives - 2017 Update

**Opioid Prescribing - The Pendulum Swings**

- **Appropriate Prescribing**
  - Complete elimination of pain
  - Emphasis on functional goals

- **Under-prescribing**
  - Pain control

- **Over-prescribing**
  - Life-threatening respiratory depression
  - Abuse by patient or household contacts
  - Interactions with other medications and substances
  - Risk of neonatal opioid withdrawal syndrome
  - Inadvertent exposure/ingestion by household contacts

**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 IRs
- Life-threatening respiratory depression
- Abuse by patient or household contacts
- Misuse, diversion, and addiction
- Physical dependence and tolerance
- Interactions with other medications and substances
- Risk of neonatal opioid withdrawal syndrome
- Inadvertent exposure/ingestion by household contacts

**Source of Most Recent Rx Opioids Among Past-Year Users 2015**

- 35% - Given by, Bought From or Taken From a Friend or Relative
- 35% - 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**

- 70.3% - Marijuana
- 12.5% - Pain Relievers
- 6.3% - Inhalants
- 5.2% - Tranquilizers
- 2.7% - Hallucinogens
- 2.6% - Stimulants
- 0.3% - Sedatives & Cocaine

**The Federal Players**

- Many agencies involved

**Rems: Risk Evaluation 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.

THE NEUROPSYCHOBIOLOGY OF PAIN

1. Perception in the brain (medial thalamus ensures)
2. Transmission along spine to brain (medial thalamus ensures)
3. Transmission along medullary tract (medial thalamus ensures)

OPPIOID SITES OF ACTION IN THE BRAIN

Pramipexol
tolbutamide
Nucleus accumbiens
Amigdala
Prefrontal cortex
Understanding Pain

- Physiologic Stimulus
  - Nociceptive
  - Neuropathic

Biopsychosocial Spiritual Context
- Physiologic
- Psychological
- Social
- Emotional
- Spiritual
- Religious
- Existential
- Meaning of illness
- Suffering
- Resilience
- Secondary gain

Experience of Pain

- Peripheral neuropathy (neuritis)
- Post herpetic neuralgia
- Sympathetic dystrophy
- Thalamic injury
- Central hypersensitization

Physical
- Tissue injury
- Mechanical abnormalities
- Inflammation
- Tissue invasion

Psychological
- Anxiety
- Catastrophizing
- Resilience
- Secondary gain

Substance Misuse
- Increased stresses
- Cognitive distortions
- Anxiety
- Depression
- Functional disabilities

Chronic Pain

Pain Management Goals and Treatment Options: A Multi-Modal Approach

- 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 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 them 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 to patient's individual needs, is safe, effective and balanced. Screen for risk with COMRA and, if indicated, refer to addiction specialist or treatment.
**Opioid Prescribing:**
Safe practice, Changing lives - 2017 Update

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### Opioid Risk Tool (ORT)

Mark each box that applies.

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
</table>
| 1. Family & of substance abuse:  
  Alcohol | 1 | 3 |
  Illicit drugs | 2 | 3 |
  Prescription drugs | 4 | 4 |
| 2. Personal & of substance abuse:  
  Alcohol | 3 | 3 |
  Illicit drugs | 4 | 4 |
  Prescription drugs | 5 | 5 |
| 3. Age between 16 & 45 yrs | 1 | 1 |
| 4. History of preadolescent sexual abuse | 2 | 2 |
| 5. Psychiatric disease:  
  ADD, OCD, bipolar, schizophrenia | 2 | 2 |
  Depression | 1 | 1 |

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

---

### Screen & Opioid Assessment for Patients with Pain (SOAPP)®

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

**How is SOAPP® administered?**
- Usually self-administered in waiting room, exam room, or prior to an office visit.
- May be completed as part of an interview w/ a nurse, physician, or psychologist.
- Prescribers should have a completed & scored SOAPP® while making opioid treatment decisions.

---

### Risk & Pain Assessment Tool Boxes

- **Pain Assessment Tool Box**
  - Pain Assessment Tools (BPI, etc)
  - Functional Assessment (SF 36, etc)
  - Pain intensity, Enjoyment of life, General activity (PEG)

- **Risk Assessment Tool Box**
  - POMP
  - UOT
  - Risk Assessment Tools (ORT or SOAPP)

**Mental Health Tools (PHQ9, GAD7, etc)**

---

### Consider a Trial of an Opioid?

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

---

**OPIOID RISK TOOL (ORT)**

Mark each box that applies.

- Female
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   - Alcohol: 1, 3  
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   - Alcohol: 3, 3  
   - Illicit drugs: 4, 4  
   - Prescription drugs: 5, 5

3. Age between 16 & 45 yrs:  
   - 1, 1

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   - 2, 2

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**Consider a Trial of an Opioid?**

- Potential benefits are likely to outweigh risks
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- Pain is moderate to severe
- Initiate trial of IR opioids
WHEN TO CONSIDER A TRIAL OF AN OPIOID

60-YR-OLD W/ CHRONIC DISABLING OA PAIN

- Non-opioid therapies not effective
- No psychiatric/medical comorbidity or personal/family drug abuse Hx
  - High potential benefits relative to potential risks
  - Could prescribe opioids to this patient in most settings with routine monitoring

30-YR-OLD W/ FIBROMYALGIA & RECENT ALCOHOL USE DISORDER

- High potential risks relative to benefits (opioid therapy not 1st line for fibromyalgia)
- Requires intensive structure, monitoring, & management by clinician with expertise in both addiction & pain
- Not a good candidate for opioid therapy

INFORMED CONSENT

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

ANALGESIC & FUNCTIONAL GOALS OF TREATMENT

EXPECTATIONS

- Common AEs
  - (e.g., constipation, nausea, sedation)
- Risk
  - (e.g., abuse, addiction, respiratory depression, overdose)
- AEs with long-term therapy
  - (e.g., hyperalgesia, testosterone, irregular menses or sexual dysfunction)

HOW TO MANAGE

PATIENT PROVIDER AGREEMENT (PPA)

- 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 Rx.

- Follow-up
  - Monitoring
    - Random UDT & pill counts
  - Refills
  - Identify behaviors for discontinuation
  - Exit strategy

CLARIFY TREATMENT PLAN & GOALS OF TREATMENT W/ PATIENT, PATIENT’S FAMILY, & OTHER CLINICIANS INVOLVED IN PATIENT’S CARE

ASSESS IN PATIENT EDUCATION

DISCUSS MEDICATION SAFE HANDLING, STORAGE, AND DISPOSAL

DOCUMENT PATIENT & PRESCRIBER RESPONSIBILITIES

PATIENT-PRESCRIBER AGREEMENT (PPA)

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

MONITOR ADHERENCE AND ABERRANT BEHAVIOR

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

PADT=Pain Assessment & Documentation Tool

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

ADDRESS ABERRANT DRUG-RELATED BEHAVIOR

Behavior outside the boundaries of agreed-on treatment plan:

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

Any of these behaviors merit investigation. Proceed with caution.

CHAPTER 4 – PEARLS FOR PRACTICE

- Conduct a comprehensive and pain-focused H&P
- 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.
**OPIOID SIDE EFFECTS**

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

**OPIOID-INDUCED RESPIRATORY DEPRESSION**

Chief hazard of opioid analgesics, including ER/LA opioids,
- **Do not overestimate** dose when converting dosage from another opioid product
- Can result in fatal overdose w/ first dose

**MORE LIKELY TO OCCUR**

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

**REDUCE RISK**

- Proper dosing & titration are essential
- Instruct patients to swallow tablets/capsules whole

**CONSIDERATIONS FOR CHANGE FROM IR TO ER/LA OPIOIDS**

**DRUG & 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 PI)

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

- Check ER/LA opioid product PI for minimum titration intervals
- Supplement w/ IR analogs as opioids are not controlled during titration

**WHEN TO MOVE FROM IR TO ER / LA OPIOIDS**

**PRIMARY REASONS**

- Maintain stable blood levels
- 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 w/ different PK
- Problematic drug-drug interactions

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**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 & 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 EDT

**EXAMPLE OF AN EDT FOR ADULTS**

<table>
<thead>
<tr>
<th>Equlianalgesic Dose</th>
<th>Usual Starting Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td>**SC/IV</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

**GUIDELINES FOR OPIOID ROTATION**

Calculate equianalgesic dose of new opioid from 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.

**MU OPIOID RECEPTORS & 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

**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

<table>
<thead>
<tr>
<th>Value of Current Opioid</th>
<th>Value of New Opioid</th>
<th>24 Hr dose of Current Opioid</th>
<th>Amount of New Opioid</th>
<th>Solving for X</th>
<th>Automatically Reduce Dose</th>
</tr>
</thead>
</table>

- Frequently assess initial response
- Titrate dose of new opioid to optimize outcomes
- Calculate supplemental rescue dose used for irritation at 15%-25% of total daily dose.

BREAKTHROUGH PAIN (BTP)

- Patients on stable ATC opioids may experience BTP
- Disease progression or a new or unrelated pain
- Dose for BTP: using an IR a 5%-15% of total daily opioid dose, administered at an appropriate interval
- Never use ER/LA for BTP

Therapies
- Target cause or precipitating factors
- Non-specific symptomatic therapies to lessen impact of BTP

Consider Adding
- Pain IR opioid trial based on analysis of benefit versus risk
- Risk for aberrant drug-related behaviors
- High-risk, only in conjunction with frequent monitoring & follow up
- Low-risk, w/ routine follow-up & monitoring
- Nonopioid drug therapies
- Nonpharmacologic treatments

STANDARDIZE OPIOID THERAPIES TO
- Add treatments based on risk
- Improve pain therapy

RATIONAL 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’re testing and not testing
- 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

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 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 (Amphetamine, 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>1-4 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>Oxycodone</td>
<td>1-3 hours</td>
<td>1-2 days</td>
</tr>
</tbody>
</table>
INTERPRETATION OF UDT RESULTS

**POSITIVE RESULT**
- Demonstrates recent use
  - Most drugs in urine have detection times of 1-3 d
  - Chronic use of lipid-soluble drugs: test positive for ≥1 wk
- Does not diagnose
  - Drug addiction, physical dependence, or impairment
- Does not provide enough information to determine
  - Exposure time, dose, or frequency of use

**NEGATIVE RESULT**
- Does not diagnose diversion
  - More complex than presence or absence of a drug in urine
  - May be due to maladaptive drug-taking behavior
    - Bingeing, running out early
    - Other factors: eg, cessation of insurance, financial difficulties

EXAMPLES OF METABOLISM OF OPIOIDS

- **CODINE**
- **MORPHINE**
- **6-MAM**
- **HEROIN**

    \[ T_{1/2} = 25-30 \text{ MIN} \]
    \[ T_{1/2} = 3-5 \text{ MIN} \]

- **HYDROCODONE**
- **HYDROMORPHONE**
- **OXYCODONE**
- **OXYMORPHONE**

CHALLENGE: THE OFFENDED PATIENT

**RED FLAG:**
You decide to request 1st urine sample for testing from your patient who already is taking opioids

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 on all 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 & UNMANAGEABLE AES**
- **NO PROGRESS TOWARD THERAPEUTIC GOALS**

- **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 & 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 and 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 [40mg BID] but wants to decrease his dose when he can, thus he requests only 20mg 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.

OLDER ADULTS

RISK FOR RESPIRATORY DEPRESSION

- Age-related changes in distribution, metabolism, excretion; absorption less affected

MONITOR
- Initiation & 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 & 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 don’t know they’re 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 & benefits of opioid therapy during pregnancy & after delivery
• Encourage minimal/no opioid use during pregnancy, unless potential benefits outweigh risks to fetus
• Refer to a high risk OBGyn who will insure appropriate treatment for the baby
• If they are using opioids on a daily basis, consider Methadone or Buprenorphine
• If chronic opioid therapy is used during pregnancy, anticipate & manage risks to the patient and newborns
• If they are using opioids on a daily basis, consider Methadone or Buprenorphine

CHILDREN & ADOLESCENTS: HANDLE WITH CARE

JUDICIOUS USE OF IR FOR BRIEF THERAPY

SAFETY & EFFECTIVENESS OF MOST ER/LA OPIOIDS UNESTABLISHED

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

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

FEDERAL & STATE REGULATIONS

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

FEDERAL

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

STATE

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

PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs)

INDIVIDUAL STATE LAWS DETERMINE

• Who has access to POMP information
• Which drug schedules are monitored
• Which agency administers the POMP
• Whether prescribers are required to register w/ the POMP
• Whether prescribers are required to access POMP information in certain circumstances
• Whether unsolicited POMP reports are sent to prescribers
• Bordering states may be available
• Designated surrogates may have access

NOT ALL FEDERALLY LICENSED FACILITIES REPORT TO PDMPs

PDMP BENEFITS

Provides full accounting of prescriptions filled by patient

RECORD OF A PATIENT’S CONTROLLED SUBSTANCE PRESCRIPTIONS

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

PROVIDE WARNINGS OF POTENTIAL MISUSE/ABUSE

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

- DEA Schedule 1 ("high abuse potential") yet state regulations vary
- There is good evidence that cannabis or selective cannabinoids (cannabinoids) 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 UDIs
- 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 while managing pain. This history does not mean you should discharge or avoid treating the patient’s pain.

COUNSEL PATIENTS ABOUT PROPER USE

EXPLAIN
- Product-specific information about the prescribed IR or ER/LA opioid
- Take opioid as prescribed
- Adhere to dose regimen
- How to handle missed doses
- Notify prescriber if pain not controlled
- Call prescriber for info on handling side effects

INSTRUCT PATIENTS/CAREGIVERS TO
- Read the ER/LA opioid Medication Guide received from pharmacy every time an ER/LA opioid is dispensed

USE PATIENT COUNSELING DOCUMENT

DOWNLOAD:

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

SOURCE: FDA. Extended-release (Er) And Long-acting (La) Opioid Analgesics Risk Evaluation And Mitigation Strategy (Rems). Modified 08/2014
COUNSEL PATIENTS ABOUT PROPER USE (continued)

EXPLAIN

**OPSIODS CAN CAUSE DEATH EVEN WHEN TAKEN PROPERLY**

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

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

COUNSEL PATIENTS ABOUT PROPER USE (continued)

EXPLAIN

**OPSIODS SHOULD BE STORED IN A SAFE & SECURE PLACE**

- Away from children, family members, visitors and pets
- Opioids are scheduled under Controlled Substances Act and can be misused & 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 & 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 w/ ER/LA opioids can cause overdose & death

- Use with alcohol may result in rapid release & absorption of a potentially fatal opioid dose – “dose dumping”
- Other depressants include sedative-hypnotics & anxiolytics, illegal drugs

OVERDOSE POISONING, CALL 911

- Person can not 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 (in syringes, needles)
- Injectable
- Nasal spray

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

ABUSE DETERRENT/TAMPER RESISTANT OPIOIDS

- Response to growing nonmedical use problem
- An ER/LA opioid with physical barrier to deter extraction
- Less likely to be crushed, injected, or snorted
- Consider 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
Opioid Prescribing:
Safe practice, Changing lives - 2017 Update

TALK WITH YOUR PATIENTS WHO ARE PARENTS

- Consider the behavior you are modeling
- 45% of parents have taken pain medications w/o a prescription at some point
- 14% have given their children pain medications w/o 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

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 OSA 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 w/ community groups

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

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

OTHER METHODS OF OPIOID DISPOSAL

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

- Take drugs out of original containers
- Mix w/ undesirable substance
- 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 exception: can seal in Patch-Disposal Unit provided & dispose of in the trash

CHAPTER 8 – PEARLS FOR PRACTICE

- Use formal tools (PPAs, counseling documents) to educate patients and caregivers
- Emphasize patients and caregivers safe storage and disposal
- Consider co-prescribing Naloxone
CHAPTER 9
DRUG CLASS CONSIDERATIONS

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

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

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 w/ water
- Monitor patients w/ 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 anyway. Use entire film.

DRUG INTERACTIONS COMMON TO OPIOIDS

- Concurrent use w/ other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma
- Reduce initial dose of one or both agents
- May enhance neuromuscular blocking action of skeletal muscle relaxants & increase respiratory depression
- Concurrent use w/ anticholinergic medication increases risk of urinary retention & severe constipation
- May lead to paralytic ileus

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 & 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 & discontinue use of opioids
- Monitor ongoing therapy with IR and ER/LA opioids
- Counsel patients & caregivers about the safe use of opioids, including proper storage & disposal
- Be familiar with general & product-specific drug information concerning opioids

To Our Learners

Our Session Stops here, but your review continues...

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

Appendix 1. Specific Drug Information for ER/LA Opioid Analgesic Products

For the ER/LA opioids you frequently use, know:
- Formulation availability
- Dosing intervals
- Key instructions
- Drug interactions
- Opioid-tolerant information
- Product specific adverse reactions
- Relative potency: morphine

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

Dosing Interval
- Every 8 or 12 hours

Key Instructions
- Initial dose in opioid-naive 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

Dosing interval: Once a day

Key instructions:
- Initial dose in opioid non-tolerant patients is 30 mg
- Titrated 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 apple sauce for patients who can reliably swallow without chewing. Use immediately
- MDD*: 1600 mg (renal toxicity of excipient, fumaric acid)

Drug interactions:
- Alcoholics beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose
- Pgp* 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

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

---

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-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 300 mcg every 12 h or 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 10 mg to 80 mg oral morphine sulfate eq, initiate with 130 mcg dose every 12 h
- If prior daily dose before taper was 80 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

Specific Drug Interactions:
- CYP3A4 inhibitors may increase buprenorphine levels
- CYP3A4 inducers may decrease buprenorphine levels
- Benzodiazepines may increase respiratory depression
- Class 1A & III antiarrythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation & torsade de pointe

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 & torsade de pointe
- Hepatotoxicity

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

---

Buprenorphine Transdermal System (Butrans)

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

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 mcg-80 mcg 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 20 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

Drug Interactions:
- Application
- Apply only to sites indicated in PI
- Avoid contact with intact skin
- Prepare skin by clipping hair; wash site w/ water only
- Remove application site (min. 3.4 hrs before reapply to same site)
- Do not cut
- Avoid exposure to heat
- Dispose of patches: fold adhesive side together & flush down toilet

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.

---

Methadone Hydrochloride Tablets (Dolophine)

75 mcg, 100 mcg, 150 mcg, 200 mcg, 300 mcg, and 400 mcg

Dosing interval:
- Every 8 to 12 h

Key instructions:
- Initial dose in opioid non-tolerant patients: 25 – 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 (OAT, Title X, Sec 8)

Drug Interactions:
- Pharmacokinetic drug-drug interactions w/ methadone are complex
- CYP 450 inducers may decrease methadone levels
- CYP 450 inhibitors may increase methadone levels
- Ant-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

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Safe practice, Changing lives - 2017 Update
Methadone Hydrochloride Tablets (Dolophine) continued

- Refer to full PI
- Opioid-Tolerant
  - QT prolongation & torsade de pointe
  - Peak respiratory depression occurs later & persists longer than
    analgesic effect
  - Clearance may increase during pregnancy
  - False-positive UDT possible
- Product-specific safety concerns
  - Varies depending on patient’s prior opioid experience

Hydromorphone Hydrochloride (Exalgo)

Key instructions
- Use conversion ratios in individual PI
- Renal impairment: start patients w/ moderate renal impairment 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
- Avoid use in patients w/ sulfa allergy (contains sodium
  metabisulfite)
- Do not use in patients w/ sulfa allergy

Dosing interval
- Once a day

Drug interactions
- None
- Opioid-Tolerant
  - All doses are indicated for opioid-tolerant patients only
- Product-specific safety concerns
  - Allergic manifestations to sulfonamide
  - Relative potency: morphine
  - ~5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in individual product information

Fentanyl Transdermal System (Duragesic), continued

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, post-dental pain, or only staff
- CYP3A4 inhibitors may increase fentanyl exposure
- CYP3A4 inducers may decrease fentanyl exposure
- Discontinuation of concurrent CYP3A4 inducers may increase plasma fentanyl concentration
- All doses indicated for opioid-tolerant patients only
- Opioid-Tolerant
  - 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

Product-specific safety concerns
- None
- See individual PI for conversion recommendations from prior opioid

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 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

Methadone Hydrochloride Tablets (Dolophine) continued

Dosing interval
- Once a day or every 12 h

Key instructions
- Initial dose w/ first opioid: 30 mg/1.8 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, & withdrawal symptoms
  - May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
  - Alcohol 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

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 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/ sulfa allergy (contains sodium
  metabisulfite)

Drug interactions
- None
- Opioid-Tolerant
  - All doses are indicated for opioid-tolerant patients only
- Product-specific safety concerns
  - Allergic manifestations to sulfonamide
  - Relative potency: 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, 120 mg

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 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.

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 w/ first opioid: 30 mg/1.8 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, & withdrawal symptoms
  - May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
  - Alcohol 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

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 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/ sulfa allergy (contains sodium
  metabisulfite)

Drug interactions
- None
- Opioid-Tolerant
  - All doses are indicated for opioid-tolerant patients only
- Product-specific safety concerns
  - Allergic manifestations to sulfonamide
  - Relative potency: 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, 120 mg

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 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.

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 w/ first opioid: 30 mg/1.8 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, & withdrawal symptoms
  - May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
  - Alcohol 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

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 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/ sulfa allergy (contains sodium
  metabisulfite)
Hydrocodone Bitartrate (Hysingla ER) continued

Drug interactions
- CYP3A4 inhibitors may increase hydrocodone exposure.
- CYP3A4 inducers may decrease hydrocodone exposure.
- Concurrent use of hydrocodone ER with strong CYP3A4 inhibitors (e.g., LaCidole) that rapidly increase CYP3A4 activity 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 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 aspiration.
- Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER.
- In nursing mothers, discontinue nursing or discontinue drug. QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg.
- Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, 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)
ER Tablets 15 mg, 30 mg, 60 mg, 100 mg

Dosing interval
- Every 8 h or every 12 h

Key instructions
- Product information recommends not using as first opioid.
- Titrate using a minimum of 1-2 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

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 5-7 d intervals
- MAD: 500 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 using in severe hepatic & renal 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:
- Equi potency 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 >10 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 or medications w/ alcohol may result in absorption of a potentially fatal dose of oxymorphone

Opioid-tolerant
- No product-specific considerations

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

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

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Safe practice, Changing lives - 2017 Update

Opioid Prescribing:
Cooperative for REMS Education
Safe practice, Changing lives - 2017 Update
# Opioid Prescribing: Safe practice, Changing lives - 2017 Update

## Oxycodone Hydrochloride (OxyContin)

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

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Every 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key instructions</strong></td>
<td></td>
</tr>
<tr>
<td>- Initial dose in opioid naïve and non-tolerant patients: 10 mg every 12 h</td>
<td></td>
</tr>
<tr>
<td>- Titrate using a minimum of 1-2 mg intervals</td>
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<tr>
<td>- Hepatic impairment: start w/ 1/2 usual dosage</td>
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<tr>
<td>- Renal impairment (creatinine clearance &lt;60 mL/min): start w/ 1/2 usual dosage</td>
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</tr>
<tr>
<td>- Consider other analgesics in patients w/ difficulty swallowing or undergoing GI disorders that predispose to obstruction. Swallow tablets whole (do not chew, crush, or dissolve)</td>
<td></td>
</tr>
<tr>
<td>- Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth.</td>
<td></td>
</tr>
</tbody>
</table>

| Drug interactions | CYP3A4 inhibitors may increase 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 |
| Relative potency vs oral morphine | Approximately 2 oral morphine to oxycodone oral dose ratio |

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

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

- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
- Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h)

- Titrate using min of 1 mg increase per dose or interval

### For Pediatric Patients (11 years and older):

- Single dose >36 mg or a total daily dose >72 mg for opioid naïve and non tolerant patients only

### CYP3A4 inducers may decrease oxycodone exposure

### Renal impairment: start w/ ½ usual dosage

### 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 your practice.

## Oxycodone Hydrochloride/Naloxone Hydrochloride (Targiniq ER)

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

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Every 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key instructions</strong></td>
<td></td>
</tr>
<tr>
<td>- Initial dose in opioid naïve and non-tolerant patient: 10/5 mg every 12 h</td>
<td></td>
</tr>
<tr>
<td>- Titrate using min of 1-2 mg intervals</td>
<td></td>
</tr>
<tr>
<td>- Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q24h)</td>
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</tr>
<tr>
<td>- May be taken w/ or without food</td>
<td></td>
</tr>
<tr>
<td>- Swallow whole. Do not chew, crush, split, or dissolve; this will release oxycodone (possible fatal overdose) &amp; naloxone (possible withdrawal)</td>
<td></td>
</tr>
<tr>
<td>- Hepatic impairment: contraindicated in moderate-severe impairment. In patients w/ mild to moderate impairment, start w/ 1/2 usual dosage</td>
<td></td>
</tr>
<tr>
<td>- Renal impairment (creatinine clearance &lt;60 mL/min): start w/ 1/2 usual dosage</td>
<td></td>
</tr>
</tbody>
</table>

| Drug interactions | CYP3A4 inhibitors may increase oxycodone exposure |
| Opioid-tolerant | For Adults: Single dose >40 mg/20 mg or total daily dose >80 mg/40 mg for opioid-tolerant patients only |
| Product-specific safety concerns | - Contraindicated in patients w/ moderate-severe hepatic impairment |
| Relative potency vs oral morphine | See individual PI for conversion recommendations from prior opioids |

## Oxycodone Hydrochloride/Naltrexone Hydrochloride (Troxyca ER)

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

<table>
<thead>
<tr>
<th>Dosing interval</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Key instructions</strong></td>
<td></td>
</tr>
<tr>
<td>- Initial dose in opioid naïve and non-tolerant patient: 10/1.2 mg every 12 h</td>
<td></td>
</tr>
<tr>
<td>- Total daily dose may be adjusted by 20/2.4 mg every 2-3 days</td>
<td></td>
</tr>
<tr>
<td>- Swallow capsules whole (do not chew, crush, or dissolve); possible fatal overdose, and naloxone (possible withdrawal)</td>
<td></td>
</tr>
<tr>
<td>- May open capsule &amp; sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately</td>
<td></td>
</tr>
<tr>
<td>- Do not administer through NG or G tube</td>
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</tbody>
</table>

| Drug interactions | CYP3A4 inhibitors may increase hydrocodone exposure |
| Opioid-tolerant | Single dose >40 mg/4.8 mg or total daily dose >80 mg/9.6 mg for use in opioid tolerant patients only |
| Product-specific safety concerns | None |
| Relative potency vs oral morphine | 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

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Key instructions</strong></td>
<td></td>
</tr>
<tr>
<td>- Initial dose in opioid naïve and non-tolerant patient: 15 mg every 12 h</td>
<td></td>
</tr>
<tr>
<td>- Dose can be increased to next higher dose every 3-7 days</td>
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</tr>
<tr>
<td>- Mild or moderate hepatic and moderate to severe renal impairment: initiate therapy w/ 1/2 recommended initial dose. If a dose &lt;15 mg needed, use alternative options</td>
<td></td>
</tr>
</tbody>
</table>

| Drug interactions | CYP3A4 inhibitors may increase 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 vs 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>
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<tbody>
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<td><strong>Key instructions</strong></td>
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</tr>
<tr>
<td>- Initial dose in opioid naïve and non-tolerant patient: 9 mg every 12 h</td>
<td></td>
</tr>
<tr>
<td>- Titrate using a minimum of 1-2 mg intervals</td>
<td></td>
</tr>
<tr>
<td>- Take with same amount of food to ensure consistent plasma levels</td>
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<tr>
<td>- Maximum daily dose: 288 mg (8 x 36 mg), safety of excipients not established for higher doses</td>
<td></td>
</tr>
<tr>
<td>- May open capsule &amp; sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately</td>
<td></td>
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<tr>
<td>- May also be administered through NG or G feeding tube</td>
<td></td>
</tr>
<tr>
<td>- Hepatic impairment: initiate therapy at 1/2 to 1/3 usual dose</td>
<td></td>
</tr>
<tr>
<td>- Renal impairment: creatinine clearance &lt;60 mL/min, follow conservative approach</td>
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</tbody>
</table>

| Drug interactions | CYP3A4 inhibitors may increase 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 vs 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 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 IR temperature
- Severity depends on naloxone dose, opioid involved & degree of dependence
- Ventricular arrhythmias, hypertension, hypotension, nausea & vomiting
- As naloxone plasma levels decrease, sedation from opioid overdose may increase

Product-specific safety concerns:
- As nausea levels decrease, sedation from opioid overdose may increase

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

The following individuals disclose no relevant financial relationships:

CO*RE Partner Staff COI

<table>
<thead>
<tr>
<th>Staff Person</th>
<th>Partner Affiliation</th>
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<tbody>
<tr>
<td>Amber Boex</td>
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<tr>
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<td>American Osteopathic Association</td>
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<tr>
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</tr>
</tbody>
</table>

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
- No oral use in opioid-dependent patients only

Drug interactions:
- 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:
- Approximately 1.5 x oral morphine to hydrocodone oral dose ratio

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