Opioid Prescribing: Safe practice, Changing lives – Update 2018

CHAPTER 1
WELCOME

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-on-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 (PLLC), 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 a 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.

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

No CO*RE Partner has any conflicts of interest to report (Appendix 3).
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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

<table>
<thead>
<tr>
<th>BRAND NAME PRODUCTS</th>
<th>GENERIC PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Anyone ER morphine sulfate ER tablets</td>
<td>- Fentanyl ER transdermal systems</td>
</tr>
<tr>
<td>- Belbuca® buprenorphine buccal film</td>
<td>- Methadone hydrochloride tablets</td>
</tr>
<tr>
<td>- Butrans® buprenorphine transdermal system</td>
<td>- Methadone hydrochloride oral concentrate</td>
</tr>
<tr>
<td>- Duragesic® fentanyl transdermal system</td>
<td>- Methadone hydrochloride oral solution</td>
</tr>
<tr>
<td>- Embeda® morphine sulfate ER capsules</td>
<td>- Morphine sulfate ER tablets</td>
</tr>
<tr>
<td>- Exalgo® hydromorphone hydrochloride ER tablets</td>
<td>- Morphine sulfate ER tablets</td>
</tr>
<tr>
<td>- Hysingla® ER (hydrocodone bitartrate) ER tablets</td>
<td>- OxyContin® oxycodone hydrochloride CR tablets</td>
</tr>
<tr>
<td>- Kadian® morphine sulfate ER capsules</td>
<td>- Opana® ER oxymorphone hydrochloride ER tablets</td>
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<tr>
<td>- MS Contin® morphine sulfate CR tablets</td>
<td>- OxyContin® oxycodone ER tablets</td>
</tr>
<tr>
<td>- Morphine Bond® morphine sulfate ER tablets</td>
<td>- OxyContin® oxycodone ER tablets</td>
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<tr>
<td>- MS Contin® morphine sulfate CR tablets</td>
<td>- Targiniq® oxycodone hydrochloride/naloxone hydrochloride ER tablets</td>
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<tr>
<td>- Nucynta® ER tapentadol ER tablets</td>
<td>- Troxyca® ER oxycodone HCl-naltrexone capsules</td>
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<tr>
<td>- OxyContin® oxycodone hydrochloride ER tablets</td>
<td>- Zohydro® hydrocodone bitartrate ER capsules</td>
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<td>- OxyContin® oxycodone hydrochloride ER tablets</td>
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<tr>
<td>- OxyContin® oxycodone hydrochloride ER tablets</td>
<td>- Zohydro® ER oxycodone ER capsules</td>
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</table>

WHY ARE WE HERE?

CHAPTER 2


PRESCRIBING PATTERNS – WE PLAY A ROLE

SOURCE: MMWR, January 1, 2016/64(50);1378-82
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm

SOURCE: https://www.cdc.gov/drugoverdose/data/prescribing.html
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**OPIOID PRESCRIBING - THE PENDULUM SWINGS**

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

- **Under-prescribing**
  - 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 meds and substances
  - Risk of neonatal opioid withdrawal syndrome
  - Inadvertent exposure/ingestion by household contacts especially children

- **Over-prescribing**
  - Improved Function
  - Quality of Life

**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 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 USERS 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**

- 70.3% - Marijuana
- 12.5% - Pain Relievers
- 6.3% - Inhalants
- 5.2% - Tranquilizers
- 2.7% - Stimulants
- 2.6% - Hallucinogens
- 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 (XR) and long-acting (LA) opioid medications.
- First time FDA has ever used accredited CE/CME as part of a REMS
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

Opioid Sites of Action in the Brain

Peripherally

Nucleus accumbens

Prefrontal cortex

Amygdala

Percutaneous

Injury

Transmission along spinal up to brain (medullary structures)

Transmission along spin to brain (medullary structures)
**Understanding Pain**

- Physiologic Stimulus
  - Nociceptive → Neuropathic

- Biopsychosocial
  - Spirituality
  - Context
  - Physical
  - Psychological

- Experience of Pain

**The Impact of Pain**

- Sleep Disturbance
- Substance Misuse
- Secondary Physical Problems
- Chronic Pain
- Functional Disabilities
- Anxiety Depression
- Cognitive Distortions
- Increased Stresses

**Pain Management Goals and Treatment Options: A Multi-modal Approach**

- Cognitive Behavioral Therapy
  - Behavioral Modification
  - Mindfulness
  - Cognitive Restructuring

- Physical
  - Exercise
  - Aquatic Therapy
  - Movement Therapy
  - Manual Therapies

- Interventional Treatments
  - Nerve Blocks
  - Epidural
  - Trigger Point Injections

- Pharmacotherapy
  - NSAIDs
  - Acetaminophen
  - Opioids
  - Anti-inflammatory
  - Antidepressants
  - Anticonvulsants

**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 patients’ individual needs, is safe, effective and balanced. Screen for risk with COMM and, if indicated, refer to addiction specialist or treatment.
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 & PSYCHOSOCIAL FUNCTION

PATIENT’S CURRENT PAIN & FUNCTION

PHYSICAL EXAM & ASSESSMENT

Seek objective confirmatory data

Components of patient evaluation for pain

Order diagnostic tests (appropriate to complaint)

GENERAL: vital signs, appearance, & pain behaviors

Musculoskeletal Exam
- Inspection
- Gate & posture
- Range of motion
- Palpation
- Perfusion
- Assimilation

Neurologic Exam
- Cutaneous or trophic findings

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

OBTAIN A COMPLETE HISTORY OF CURRENT & PAST SUBSTANCE USE

RISK FACTORS FOR OPIOID ABUSE
- Prescription drugs, controlled medications (Benzodiazepine)
- Alcohol & tobacco
  - Substance abuse He does not prohibit treatment w/ ER/LA opioids but may require additional monitoring & expert consultation/referral
- History of sexual abuse
- Family Hx of substance abuse & psychiatric disorders
- Age (14-45 YO)

SOCIAL HISTORY

- Employment, cultural background, social network, marital history, legal history & other behavioral patterns

TREATMENT HISTORY

NONPHARMACOLOGIC STRATEGIES & EFFECTIVENESS

PHARMACOLOGIC STRATEGIES & EFFECTIVENESS

PAST USE

CURRENT USE
- Query state PDMP to confirm patient report
- Contact past providers & obtain prior medical records

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

GENERAL EFFECTIVENESS

OBTAIN A COMPLETE HISTORY OF CURRENT & PAST SUBSTANCE USE

RISK ASSESSMENT TOOLS

Risk Assessment Tools

<table>
<thead>
<tr>
<th>TOOL</th>
<th>TOP INDEX</th>
<th>RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIRT Opioid Risk Tool</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td>SCAPP® Screener &amp; Opioid Assessment for Patients w/ Pain</td>
<td>24, 44 &amp; 5</td>
<td>patient</td>
</tr>
<tr>
<td>DRE Diagnosis, Intoxication, Risk, &amp; Efficacy Score</td>
<td>0</td>
<td>clinician</td>
</tr>
</tbody>
</table>

CHARACTERIZE MISUSE ONCE OPIOID TREATMENTS BEGINS

- PMQ Pain Medication Questionnaire
- COMM Current Opioid Medication Measure
- PDOP Prescription Drug Use Questionnaire
- DASS-21 Depression, Anxiety, & Stress Score

NOTE: SPECIFIC TO PAIN POPULATIONS

- CAGE-20 Cut Down, Annoyed, Guilty, Eye Opener Tool
- CRAFFT Relate, Alone, Friends, Family, Trouble
- DAST Drug Abuse Screening Test
- SBIRT Screening, Brief Intervention, & Referral to Treatment

RISK ASSESSMENT TOOLS

PATIENTS CONSIDERED FOR LONG-TERM OPIOID THERAPY

- Opioid Tolerant

NOTE: SPECIFIC TO PAIN POPULATIONS

- Opioid Risk Tool
- Adjusted to Include Drugs

PATIENTS CONSIDERED FOR SHORT-TERM OPIOID THERAPY

- PATIENTS CONSIDERED FOR LONG-TERM OPIOID THERAPY
- Opioid Tolerant

NOTE: SPECIFIC TO PAIN POPULATIONS

- Opioid Risk Tool
- Adjusted to Include Drugs

- PATIENTS CONSIDERED FOR SHORT-TERM OPIOID THERAPY

PATIENTS CONSIDERED FOR SHORT-TERM OPIOID THERAPY

- Opioid Tolerant

NOTE: SPECIFIC TO PAIN POPULATIONS

- Opioid Risk Tool
- Adjusted to Include Drugs

- PATIENTS CONSIDERED FOR LONG-TERM OPIOID THERAPY
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**OPIOID RISK TOOL (ORT)**

Mark each box that applies.

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

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

3. Age between 16 & 45 yrs

4. Hx of preadolescent sexual abuse

5. Psychologic disease
   - ADD, OCD, bipolar, schizophrenia
   - Depression

**ADMINISTER**

On initial visit
Prior to opioid therapy

**SCORING (RISK)**

0-3: low
4-7: moderate
≥8: high

**Scoring Totals:**


**SCREENER & 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

**WHAT IS THE RISK FOR MY PATIENT?**

- Risk of opioid use disorder in patients on COT for Chronic Non-Cancer Pain (CNCP) is up to 30%
- Always highest with past history of SUD or psychiatric comorbidity
- Recognize that patient needs and patterns shift with age

**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**
- POMA
- UOT
- Risk Assessment Tools (ORT or SOAPP)

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

**CONSIDER A TRIAL OF AN OPIOID?**

**POTENTIAL BENEFITS ARE LIKELY TO OUTWEIGHT RISKS**

**FAILED TO ADEQUATELY RESPOND TO NONOPIOID & NONDRUG INTERVENTIONS**

**PAIN IS MODERATE TO SEVERE**

**INITIATE TRIAL OF IR OPIOIDS**


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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

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

Analgesic & Functional Goals of Treatment

Expectations

Potential Risks

Alternatives to Opioids

How to Manage

- 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)

Patient-Provider Agreement (PPA)

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

Reinforce expectations for appropriate & safe opioid use

- One prescriber
- Consider one pharmacy
- Safeguard
  - Do not store in medicine cabinet
  - Keep locked (medication safe)
  - Do not share or sell
- Instructions for disposal when no longer needed
- Prescriber notification for any event resulting in a pain medication Rx.

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

Follow-up

- 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, PAMQ, or PDUQ
  - Medication reconciliation (e.g., pill counts)

Monitor adherence and aberrant behavior

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

Informed Consent

Patient-Provider Agreement (PPA)

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

Clarify treatment plan & goals of treatment w/ patient, patient's family, & other clinicians involved in patient's care

Assist in patient education

Discuss medication safe handling, storage, and disposal

Document patient & prescriber responsibilities

Patient-adherence and aberrant behavior

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.

Adequately DOCUMENT all patient interactions, assessments, test results, & treatment plans.

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.

CHAPTER 5

MANAGEMENT MONITORING AND DISCONTINUING

PART 1

MONITORING
**OPIOID SIDE EFFECTS**

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

Prescribers should report serious AEs to the FDA:

www.fda.gov

Prescribers should report serious AEs to the FDA:


**OPIOID-INDUCED RESPIRATORY DEPRESSION**

**MORE LIKELY TO OCCUR**

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

**REDUCE RISK**

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

**INDUCED RESPIRATORY DEPRESSION**

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

**WITHDRAWAL**

Managed w/ close observation, supportive measures, & opioid agonists, depending on patient’s clinical status

**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
- Problems with drug-drug interactions

**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

- Any strength of transdermal fentanyl or hydromorphone ER
- Certain strengths/doses of other ER/LA products (check drug PI)

**MONITOR PATIENTS Closely FOR RESPIRATORY DEPRESSION**

Especially within 24-72 h of initiating therapy & increasing dosage

**INDIVIDUALIZE DOSAGE IN TITRATION BASED ON Efficacy, Toxicity, & Presence of AEs**

Check ER/LA opioid product PI for minimum titration intervals

Supplement w/ IR analgesics opioids & non-opioids: if pain is not controlled during titration

**OPIOID TOLERANCE**

If opioid tolerant — no restrictions on which products can be used

Patients considered opioid tolerant are taking at least

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/hr
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day
- An equipotent dose of another opioid

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

**EQUIANALGESIC DOSE TABLES (EDT)**

Many different versions:
- PUBLISHED
- ONLINE
- ONLINE INTERACTIVE
- SMART-PHONE APPS

Vary in terms of:
- EQUIANALGESIC VALUES
- WHETHER RANGES ARE USED

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

**EXAMPLE OF AN EDT FOR ADULTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>SC/IV</th>
<th>PO</th>
<th>Parenteral</th>
<th>PO</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
<td>2.5-5 mg SC/IV</td>
<td>5-15 mg q3-4hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.25-2.5 mg</td>
<td>(IR or oral solution)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.5-7.5 mg)</td>
<td></td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>NA</td>
<td>20 mg</td>
<td>NA</td>
<td>5-10 mg q3-4</td>
</tr>
<tr>
<td>Hydrocodeone</td>
<td>NA</td>
<td>30 mg</td>
<td>NA</td>
<td>5 mg q3-4h</td>
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<tr>
<td>Hydromorphone</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
<td>0.2-0.6 mg SC/IV</td>
<td>1-2 mg q3-4hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>q2-3hr (0.2mg)</td>
<td>(0.5-1 mg)</td>
</tr>
</tbody>
</table>

**MU OPIOIDS & 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**

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

Closer to 25% reduction if patient:
- Does not have these characteristics
- Is changing route of administration

*75%-90% reduction for methadone

**GUIDELINES FOR OPIOID ROTATION (continued)**

If switching to methadone:
- Standard EDTs are less helpful in opioid rotation to methadone
- In opioid tolerant patients, methadone doses should not exceed 30-40 mg/day upon rotation
  - Consider inpatient monitoring, including serial EKG monitoring
- In opioid-naive patients, methadone should not be given as an initial drug

If switching to transdermal:
- Fentanyl, calculate dose conversion based on equianalgesic dose ratios included in the PI
- Buprenorphine, follow instructions in the PI
GUIDELINE FOR OPIOID ROTATION: SUMMARY

<table>
<thead>
<tr>
<th>VALUES FROM IOA</th>
<th>PATIENT OPIOID VALUES</th>
<th>SOLVE FOR X</th>
<th>AUTOMATICALLY REDUCE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of Current Opioid</td>
<td>24 Hr dose of Current Opioid</td>
<td>Equivalency: 24 Hr Dose of New Opioid</td>
<td>By 25% – 50%</td>
</tr>
<tr>
<td>Value of New Opioid</td>
<td>6 Amount of New Opioid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Frequently assess initial response
- Titrate dose of new opioid to optimize outcomes
- Calculate supplemental rescue dose used for variation at 15%–30% of total daily dose

BREAKTHROUGH PAIN (BTP)

Patients on stable ATC who 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
- Nonopioid specific 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

UDT FREQUENCY IS BASED ON CLINICAL JUDGMENT AND STATE REGULATIONS

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

| SPECIFIC WINDOWS OF DRUG DETECTION (continued) |
|-----------------|-----------------|-----------------|-----------------|
| Drug            | How soon after taking drug will there be a positive drug test? | How long after taking drug will there continue to be a positive drug test? |
| Marijuana/Herb | 1-3 hours        | 1-7 days        |
| Crack (Cocaine) | 2-6 hours        | 2-3 days        |
| Heroin (Opiates)| 2-6 hours        | 1-3 days        |
| Speed/Euph (Amphetamine, methamphetamine) | 4-6 hours | 2-3 days |
| Angel Dust/PFC | 4-8 hours        | 2-14 days       |
| Ecstasy         | 2-7 hours        | 2-4 days        |
| Benzo/PCP       | 2-7 hours        | 1-4 days        |
| Barbiturates    | 2-4 hours        | 1-3 weeks       |
| Methadone       | 3-8 hours        | 1-3 days        |
| Tricyclic Antidepressants | 8-12 hours | 2-7 days |
| Oxycodone       | 1-3 hours        | 1-2 days        |

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
  - May 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

Be READY TO REFER

SUBSTANCE USE DISORDER

<table>
<thead>
<tr>
<th>SAMHSA substance abuse treatment facility locator</th>
<th>SAMHSA mental health treatment facility locator</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="https://findtreatment.samhsa.gov/">https://findtreatment.samhsa.gov/</a></td>
<td></td>
</tr>
</tbody>
</table>

High-Risk/Complex Patients

- Refer to pain management, check state regulations for requirements
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
- 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: eg, cessation of insurance, financial difficulties

**NEGATIVE RESULT**
- Does not diagnose recent use

EXAMPLES OF METABOLISM OF OPIOIDS

- **CODEINE**
- **MORPHINE**
- **6-MAM**
- **HEROIN**
- **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.

REASONS FOR DISCONTINUING OPIOIDS

- **PAIN LEVEL DECREASES IN STABLE PATIENTS**
- **INTOLERABLE & UNMANAGEABLE AES**
- **NO PROGRESS TOWARD THERAPEUTIC GOALS**
- **MISUSE**
- **ABERRANT BEHAVIORS**
  - 1 or 2 episodes of increasing dose without prescriber knowledge
  - Sharing medications
  - Unapproved opioid use to treat another symptom (e.g., insomnia)
  - 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.

CHAPTER 6

SPECIAL POPULATIONS

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


• 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
Opioid Prescribing: Safe practice, Changing lives – Update 2018

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 ensure appropriate treatment for the baby
• If they are using opioids on a daily basis, consider Methadone or Buprenorphine
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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.medscape.com/resource/pain/opioid
  www.painpolicy.wisc.edu/database

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

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 (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 while managing pain. This history does not mean you should discharge or avoid treating the patient’s pain.

CHAPTER 8
COUNSELING PATIENTS & CAREGIVERS

COUNSEL PATIENTS ABOUT PROPER USE

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

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

OPIOIDS 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

OPIOIDS SHOULD BE STORED IN A SAFE & SECURE PLACE

- Away from children, family members, visitors and pets
- Safe from theft
- 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 ‘in-dose 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 (syringes, needle)
- 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
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 med 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

TALK WITH YOUR PATIENTS WHO ARE PARENTS

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

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
- Buprenorphines exception: can seal in Patch-Disposal Unit provided & dispose of in the trash

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

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
- 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
- Metal foil backings are not safe for use in MRIs
- Monitor patients w/ fever for signs or symptoms of increased opioid exposure
- 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

DRUG INFORMATION COMMON TO OPIOIDS

Know for opioid products you prescribe:

- Use in opioid-tolerant patients
- 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 information about product conversions, if available
- Specific drug interactions

SPECIFIC CHARACTERISTICS

- Drug substance
- Formulation
- Strength
- Dosing interval
- Key instructions
- Use in opioid-tolerant patients
- Product-specific safety concerns
- Relative potency to morphine

For detailed information, refer to online PI:
- Drugs@FDA at www.fda.gov/drugsatfda
Opioid Prescribing: Safe practice, Changing lives – Update 2018

SUMMARY

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

- Assess patients for treatment w/ IR and ER/LA opioids
- Initiate therapy, modify dose & discontinue use of opioids
- Monitor ongoing therapy w/ IR and ER/LA opioids
- Counsel patients & caregivers about the safe use of opioids, including proper storage & disposal
- Be familiar w/ 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.

YOUR PARTICIPATION IS IMPORTANT

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

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

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

THANK YOU!

Appendix 1. 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

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Key instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 8 or 12 hours</td>
<td>Initial dose in opioid-naive and opioid non-tolerant patients is 15 mg every 8 or 12 hours</td>
</tr>
<tr>
<td></td>
<td>Dosage adjustment may be done every 1 to 2 days.</td>
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<tr>
<td></td>
<td>Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Drug interactions</th>
<th>Opioid-tolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp inhibitors (e.g., quinidine) can increase the exposure of morphine by about two-fold and increase risk of respiratory depression</td>
<td></td>
</tr>
<tr>
<td>A single dose of ARYMO ER greater than 60 mg, or total daily dose greater than 220 mg, is for use in opioid-tolerant patients only.</td>
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<table>
<thead>
<tr>
<th>Product-specific safety concerns</th>
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<tbody>
<tr>
<td>Do not attempt to chew, crush, or dissolve. Swallow whole.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
Buprenorphine Transdermal System (Butrans)

- **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)

Morphine Sulfate ER Capsules (Avinza)

- **Dosing interval:** Once a day
- **Specific safety concerns:**
  - **MDD:**
    - 30 mg: 600 mcg, 750 mcg, and 900 mcg for use in opioid naïve patients
    - 60 mg: 1200 mcg, 1500 mcg, and 1800 mcg for use in opioid tolerant patients

Buprenorphine Buccal Film (Belbuca)

- **Dosing interval:** Every 12 h (or 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 belbuca film, once daily, or if tolerated, every 12 h
  - Titrate to 350 mcg every 12 h no earlier than 4 h 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 h
  - 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 89 mg oral morphine sulfate eq, initiate with 130 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 h

Buprenorphine Transdermal System (Butrans) continued

- **Drug interactions:**
  - CYP3A4 inhibitors may increase buprenorphine levels
  - CYP3A4 inducers may decrease buprenorphine levels
  - Benzodiazepines may increase respiratory depression
  - Class IA & IB 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

Buprenorphine Transdermal System (Butrans)

- **Dosing interval:** Every 12 h
- **Key instructions:**
  - Initial dose in opioid non-tolerant patients on <30 mg morphine equivalents & in mild-moderate hepatic impairment: 5 mg/eq
  - When converting from 30 mg-60 mg morphine equivalents, first taper to 30 mg morphine equivalent, then initiate w/ 10 mcg/eq
  - Titrate in 5 or 10 mcg/eq increments by using no more than 2 patches of the 5 or 20 mcg/eq system(s) w/ minimum of 72 h prior between dose adjustments. Total dose from all patches should be ≤20 mcg/eq
  - Maximum dose: 20 mcg/eq due to risk of QTc prolongation
  - Application
    - Apply only to sites indicated in PI
    - Apply to intact, unbroken skin
    - Prep skin by clipping hair; wash site w/ water only
    - Rotate application site (min 3 wks before reapply to same site)
  - Do not cut
  - Avoid exposure to heat
  - Dispose of patches: fold adhesive side together & flush down toilet

Methadone Hydrochloride Tablets (Dolophine)

- **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 (CFR, Title 42, Sec 8)

- **Drug interactions:**
  - Pharmacokinetic drug-drug interactions w/ methadone are complex
    - CYP 450 inhibitors may decrease methadone levels
    - CYP 450 inducers may increase methadone levels
  - Anti-retroviral agents have mixed effects on methadone levels
  - Potentially arrhythmogenic agents may increase risk for QTc prolongation & torsade de pointe
  - Benzodiazepines may increase respiratory depression
Fentanyl Transdermal System (Duragesic), continued

- Refer to full PI

- Use product-specific information for dose conversion from prior opioid

- QTC prolongation & torsade de pointe

- Peak respiratory depression occurs later & persists longer than analgesic effect

- Clearance may increase during pregnancy

- False-positive UDT possible

- Varies depending on patient’s prior opioid experience

### 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 site 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

### Drug interactions

- CYP3A4 inhibitors may increase fentanyl exposure

- CYP3A4 inducers may decrease fentanyl exposure

- Discontinuation of concomitant CYP3A4 inducer may increase fentanyl plasma concentration

### Opioid-specific safety concerns

- Allergic manifestations to sulfite component

- Do not use in patients w/ sulfite allergy (contains sodium sulfite)

- Swallow tablets whole (do not chew, crush, or dissolve)

- Titrate in increments of 10 mg to 20 mg every 3 to 5 days

- Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose to obstruction

- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth

- Use 1:1 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

### Precautions

- False positive UDT possible

- Clearances may increase during pregnancy

- Analgesic effect may decline for up to 8 h after patch removal

- QTc prolongation & torsade de pointe

- May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately

- Do not open capsules or reconstitute

- Accidental exposure due to secondary exposure to unwashed/unclothed application site

- May increase absorption of potentially fatal dose

- Gastrointestinal disorders that may predispose to obstruction

- Be aware of patients who are prone to accidental exposure

- May increase absorption/exposure of morphine by ~2-fold

- 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 patient, or day surgery

    - IV/IM use

  - Q6H (3 d)

  - Varies depending on patient’s prior opioid experience

### Dosing interval

- Every 72 h (3 d)

### 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

- Once a day or every 12 h

### Key instructions

- Initial dose at first opioid: 30 mg/1.8 mg

- Titrate using a minimum of 72 h intervals between dose adjustments

- 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

### 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

- 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 patient, or day surgery

    - IV/IM use

  - Q6H (3 d)

  - Varies depending on patient’s prior opioid experience

### Dosing interval

- Once a day or every 12 h

### Key instructions

- Titrate using a minimum of 72 h intervals between dose adjustments

- 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

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- 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

- 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 patient, or day surgery

    - IV/IM use

  - Q6H (3 d)

  - Varies depending on patient’s prior opioid experience

### Dosing interval

- Once a day or every 12 h

### Key instructions
### Hydrocodone Bitartrate (Hysingla ER) continued

<table>
<thead>
<tr>
<th>Drug interactions</th>
<th>Opioid-tolerant</th>
<th>Product-specific safety concerns</th>
<th>Relative potency: oral morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inhibitors may increase hydrocodone exposure.</td>
<td>A single dose &gt; 80 mg is only for use in opioid-tolerant patients.</td>
<td>Morphabond 100 mg tablets are for use in opioid-tolerant patients only.</td>
<td>See individual PI for conversion recommendations from prior opioid.</td>
</tr>
<tr>
<td>CYP3A4 inducers may decrease hydrocodone exposure.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentrated 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.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In nursing mothers, discontinue nursing or discontinue drug. QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid use in patients with congenital long QRS syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmia, electrolyte abnormalities, or who are taking medications that are known to prolong the QRS interval.</td>
<td></td>
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</tr>
<tr>
<td>In patients who develop QTc prolongation, consider reducing the dose.</td>
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</tr>
</tbody>
</table>

### Relative potency:

- Oral morphine

### Opioid-specific safety concerns

- None

### Morphine Sulfate (Morphabond) ER Tablets 15 mg, 30 mg, 60 mg, 100 mg

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Key instructions</th>
<th>Specific Drug interactions</th>
<th>Opioid-tolerant</th>
<th>Product-specific safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 h or every 12 h</td>
<td>Product information recommends not using as first opioid</td>
<td>P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold</td>
<td>Morphabond 100 mg tablets are for use in opioid-tolerant patients only.</td>
<td>None</td>
</tr>
</tbody>
</table>

### Morphine Sulfate (MS Contin) ER Tablets 15 mg, 30 mg, 60 mg, 100 mg, 200 mg

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Key instructions</th>
<th>Specific Drug interactions</th>
<th>Opioid-tolerant</th>
<th>Product-specific safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 6 h or every 12 h</td>
<td>Product information recommends not using as first opioid</td>
<td>P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold</td>
<td>Morphine 100 mg &amp; 200 mg tablet strengths for use in opioid-tolerant patients only.</td>
<td>None</td>
</tr>
</tbody>
</table>

### Tapentadol (Nucynta ER) ER Tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Key instructions</th>
<th>Specific Drug interactions</th>
<th>Opioid-tolerant</th>
<th>Product-specific safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 12 h</td>
<td>50 mg every 12 h is initial dose in opioid non-tolerant patients</td>
<td>Alcoholic beverages or medications w/ alcohol may result in rapid absorption of potentially fatal dose of tapentadol.</td>
<td>No product-specific considerations</td>
<td>Risk of serotonin syndrome Angio-edema Equipotency to oral morphine has not been established</td>
</tr>
<tr>
<td></td>
<td>Titrate by 50 mg increments using minimum of 2-3 d intervals MDD: 300 mg</td>
<td>Contraindicated in patients taking MAOIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid use in severe hepatic &amp; renal impairment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>Key instructions</th>
<th>Specific Drug interactions</th>
<th>Opioid-tolerant</th>
<th>Product-specific safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 12 h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.</td>
<td>Use 5 mg every 12 h as initial dose in opioid non-tolerant patients &amp; patients w/ mild hepatic impairment. &amp; renal impairment (creatinine clearance &lt;50 ml/min) &amp; patients &gt; 65 yrs.</td>
<td>Alcoholic beverages or medications w/ alcohol may result in absorption of a potentially fatal dose of oxymorphone</td>
<td>No product-specific considerations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Titrate in increments of 5-10 mg using a minimum of 2-3 d intervals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated in moderate &amp; severe hepatic impairment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Relative potency:

- Oral morphine
Oxydcode Hydrochloride (OxyContin) ER Tablets 10mg/5mg, 15mg/7.5mg, 20mg/10mg, 40mg/20mg, 60mg/30mg, 80mg/40mg

**DOSE INDICATIONS**

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

**PRODUCT SPECIFIC SAFETY CONCERNS**

- **Durability:** Abrasion will result in immediate release.

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Opioid-inducing agents:** CYP3A4 inhibitors may increase hydrocodone exposure.

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**DOSE INDICATIONS**

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

**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

**DOSE INDICATIONS**

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

**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

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- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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**PRODUCT SPECIFIC SAFETY CONCERNS**

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**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

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- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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

**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.

**KEY INSTRUCTIONS**

- **Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h).**

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**PRODUCT SPECIFIC SAFETY CONCERNS**

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

**RELATIVE POTENCY ORAL MORPHINE**

- **Approximately 21 oral morphine to oxycodone oral dose ratio**

**PRODUCT INFORMATION & ADHERENCE**

- See individual product information for conversion recommendations from prior opioids.
### 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/ min ~2 hrs
- Vomiting, restlessness, abdominal cramps, increased IR temperature
  - Ventricular arrhythmias, hypertension, hypotension, nausea & vomiting
  - As naloxone plasma levels decrease, sedation from opioid overdose may increase

**Product-specific safety concerns**
- CNS depression
- Hypertension
- Hypotension
- Bradycardia
- Seizures
- Epilepsy
- Respiratory depression
- Tachycardia
- Arrhythmia
- Headache
- Neuraxial block

---

### 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**
- Use only in opioid-tolerant patient
- Titrating in increments of 10 mg using a min of 3-7 d intervals
  - Swallow capsules whole (do not chew, crush, or dissolve)

**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**
- None

**Relative potency: oral morphine**
- Approximately 1.5 times the hydrocodone oral dose ratio

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

**The following individuals disclose no relevant financial relationships:**

<table>
<thead>
<tr>
<th>Staff Person</th>
<th>Partner Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chris McKeithen</td>
<td>California Academy of Family Physicians</td>
</tr>
<tr>
<td>Tom Larrison</td>
<td>California Academy of Family Physicians</td>
</tr>
<tr>
<td>Nancy McKeon</td>
<td>California Academy of Family Physicians</td>
</tr>
<tr>
<td>Phyllis Zimmer</td>
<td>California Academy of Family Physicians</td>
</tr>
<tr>
<td>Sarah Williams</td>
<td>California Academy of Family Physicians</td>
</tr>
<tr>
<td>Cyndi Grimes</td>
<td>California Academy of Family Physicians</td>
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<tr>
<td>Kate Nisbet</td>
<td>California Academy of Family Physicians</td>
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<td>Jerri Davis</td>
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<td>Brianna Townsell</td>
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<td>Catherine Underwood</td>
<td>California Academy of Family Physicians</td>
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<tr>
<td>Molly Piyali Muzuk</td>
<td>California Academy of Family Physicians</td>
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<tr>
<td>Penny Mills</td>
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<tr>
<td>Arlene Stephanie McKeithen</td>
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<tr>
<td>Stephanie McKeithen</td>
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<tr>
<td>Julie Bruno</td>
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<tr>
<td>Anne Norman</td>
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<tr>
<td>Michele McKay</td>
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<thead>
<tr>
<th>CO*RE Partner Staff COI</th>
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<tbody>
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</table>

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### Faculty Advisory Panel & Reviewer COI

<table>
<thead>
<tr>
<th>Faculty Advisory Panel</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Price, MD</td>
<td>Division of Pain Medicine, University of California at San Diego, School of Medicine</td>
</tr>
<tr>
<td>Ron Grover, MD</td>
<td>Vice President, Medical Affairs and Chief Medical Officer at St. Joseph’s Health Care, Los Angeles, CA</td>
</tr>
<tr>
<td>Saul E. Gruchy, MD, PhD</td>
<td>Professor and Chair, Department of Anesthesiology, University of California, San Francisco</td>
</tr>
<tr>
<td>Carla Harms, MD</td>
<td>Director of Physician Education and Development, Kaiser Permanente Northern California</td>
</tr>
<tr>
<td>Rachel Mayer-Mills, PhD, MBA, MA, PMHNP-BC, PMHNP</td>
<td>Professor and Director, Doctor of Nursing Practice Program, Pepperdine University</td>
</tr>
<tr>
<td>Catherine R. Young, MD, MPH, MS</td>
<td>Senior Physician Executive, Portland Health and Hospital Systems, Oregon Health &amp; Science University, Portland, OR</td>
</tr>
<tr>
<td>Sarah S. White, MD, MPH, MS, MIP</td>
<td>Assistant Professor, University of Maryland School of Medicine, Baltimore, MD</td>
</tr>
<tr>
<td>Victoria K. N. Naidu, MD, MPH</td>
<td>Assistant Professor, Division of Palliative Care and Supportive Medicine, University of California, San Francisco</td>
</tr>
<tr>
<td>Teddlie R. Savage, MD</td>
<td>Assistant Professor, Division of Palliative Care and Supportive Medicine, University of California, San Francisco</td>
</tr>
<tr>
<td>Elizabeth Caudill, MD, MS</td>
<td>Assistant Professor, Division of Palliative Care and Supportive Medicine, University of California, San Francisco</td>
</tr>
</tbody>
</table>

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### The following individuals disclose no relevant financial relationships:

<table>
<thead>
<tr>
<th>CO*RE Operations Organizations</th>
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