Educational Grants in Support of this CME Activity

This educational activity is supported by an independent educational grant from the Extended-Release/Long-Acting Opioid Analgesic REMS Program Companies. Please see http://ce.er-la-opioidrems.com/IwgCEUI/rems/pdf/List_of_RPC_Companies.pdf for a listing of REMS Program Companies. This activity is intended to be fully compliant with the Extended-Release/Long-Acting Opioid Analgesics REMS education requirements issued by the US Food & Drug Administration.

Overall Program Learning Objectives Sessions I–VI

Upon completion of this initiative, the participants will be better able to:

- Implement patient assessment strategies, including tools to assess risk of abuse, misuse, or addiction when prescribing extended-release (ER/LA) opioids
- Employ approaches to safely initiate therapy, modify dose, and discontinue ER/LA opioids
- Monitor patients by evaluating treatment goals and implementing periodic urine drug testing (UDT)
- Employ patient education strategies about the safe use of ER/LA opioids
- Identify similarities and differences among ER/LA opioids

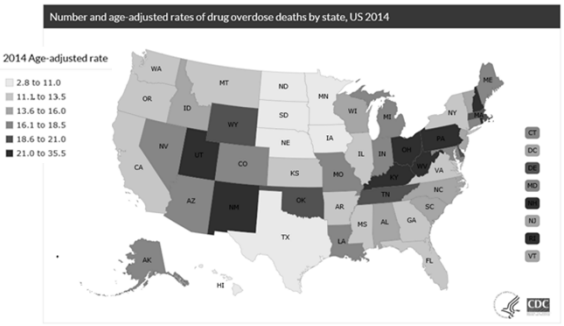
Background: Painkiller Overdoses = Public Health Epidemic

- In 2014, 4.3 million people ≥12 years old reported current (past month) nonmedical opioid use
- Overdose deaths from opioid analgesics
  - 18,893 in 2014; >4x # in 2000
  - Of opioid-analgesic deaths: Benzodiazepines involved in 31%; alcohol in 19%
  - Highest prescription painkiller overdose rates in middle-aged adults
  - Highest rates in rural counties
  - Highest rates in Whites and American Indians or Alaska Natives
  - Many more Rx opioid overdose deaths in men than women
- In 2011, nearly 420,000 ED/ER visits involving nonmedical use of opioids
- Direct health care costs of nonmedical prescription painkiller use: $72.5 billion annually
- In 2016, the CDC issued an Opioid Prescribing Guideline for primary care

While improper use of any opioid can result in serious side effects, including overdose and death, risks may be greater with Rx ER/LA Opioids

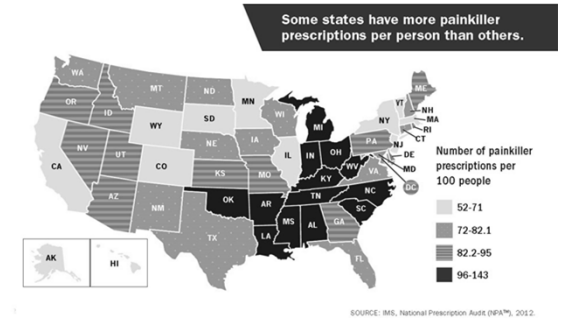
SAMHSA 2015; Rudd RA et al. MMWR Morb Mortal Wkly Rep. 2016 Jan 1;64(50-51):1378-82. Chen LH, et al. NCHS Data Brief, No. 166, September 2014; Opioids drive continued increase in drug overdose deaths. The DAWN Report 2013.

Drug Overdose Rates by State – 2014



www.cdc.gov.

Amount of All Prescription Opioids Sold by State – 2012



www.cdc.gov.

The Prevalence of Chronic Pain in the United States Is High

- Approximately 100 million US adults experience chronic pain (33%)
- Numerous studies indicate undertreated pain: eg, cancer, older adults, children, minorities
- Goal: define most appropriate analgesic regimen for each person in pain, which may include the use of ER/LA opioids

Ensure availability of opioids for patients with pain **AND** Establish systems of control to prevent abuse

IOM (Institute of Medicine). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. 2011; www.painpolicy.wisc.edu.

Goals of Risk Evaluation and Mitigation Strategy (REMS) CME on ER/LA Opioid Analgesics

- In 2012, the US Food and Drug Administration (FDA) directed all ER/LA opioid companies to provide independent CME grants to educate prescribers and to provide information for patients to:
  - **Ensure that the benefits of ER/LA opioids outweigh the risks**
  - Help to reduce risk for ER/LA opioid analgesics misuse, abuse, and overdose while ensuring access to pain medication
  - Follow FDA "Blueprint" on ER/LA opioids CME to engage and educate prescribers and be in compliance with standards for continuing education for physicians and other health care professionals, including Accreditation Council for Continuing Medical Education (ACCME)

This 6-Session Activity Is FDA REMS-Compliant CME

CME, continuing medical education.

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed Jan 4, 2016.

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Goals of This REMS-Compliant Education for ER/LA Opioid Analgesics

- As clinicians, WE are best positioned to balance treatment of pain against risks of serious adverse outcomes, including addiction, unintentional overdose, and death
- In this 6-session curriculum, we will review many best-practice aspects of managing ER/LA opioid analgesic therapy
  - Patient assessment
  - Therapy initiation, dose modification, and discontinuation
  - Therapy management
  - Counseling of patients and caregivers
  - General drug information
  - Product-specific drug information

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed Jan 4, 2016

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Session I

Evaluation is Essential for Safe and Effective Pain Management Using ER/LA Opioids

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Learning Objectives for Session I

Upon completion of this module, the participants will be better able to:

- Identify risk factors for opioid-related aberrant behavior
- Differentiate among tolerance, physical dependence, and addiction

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Opioid Therapy in Chronic Pain Management

- Opioids ARE commonly prescribed for chronic pain
  - Efficacious for many types of pain, though not necessarily for all people who experience a certain type of pain
  - Appropriate use is KEY to safety and success
- Goals of chronic opioid therapy:
  - Improve and/or stabilize pain intensity
  - Improve function
  - Improve quality of life (QOL)
- However, significant gaps exist between guideline recommendations for safe prescribing practices of ER/LA opioids and how they are being used in practice
  - Highlights need for further education

McCarberg BH. *Postgrad Med.* 2011;123(2):119-130.

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Opioid Therapy – Good Pain Management Principles

- Evidence-based
- Multidimensional
- Based on appropriate assessment
- A dynamic process

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But There Are Also Risks

- Opioid analgesics are among the most commonly misused or abused pharmaceuticals
  - Over- or under-concern by physicians, patients, and/or caregivers is disruptive to physician-patient relationship as well as to effective care
  - Other drugs also commonly abused, eg, stimulants, benzodiazepines
- Misuse:
  - Using a medication other than as directed or indicated, whether intentional or not, and whether harm results or not
    - eg, taking more than recommended dose of an opioid analgesic because pain is poorly controlled
    - eg, offering opioid analgesics to another person who is in pain
- Abuse:
  - Intentionally taking a medication for a nonmedical purpose
    - eg, taking an opioid to get high
- Both misuse and abuse are of concern
  - Can lead to an overdose
  - Common misconception that because opioid is a prescription drug it is safe

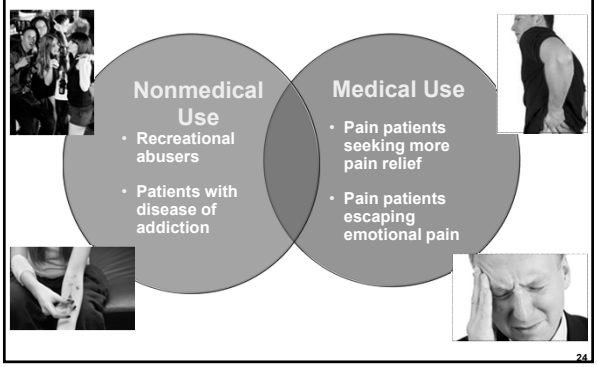
Chou R, et al. *J Pain*. 2009;10(2):113-130.

Risks Associated With ER/LA Opioids

- Overdose with ER/LA formulations
- Life-threatening respiratory depression
- Abuse by patient or household contacts
- Misuse and addiction
- Physical dependence and tolerance
- Interactions with other medications and substances
- Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy
- Inadvertent exposure by household contacts, especially children

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed Jan 4, 2016

Who Misuses/Abuses Opioids and Why?



Key Concepts

Term	Definition
Tolerance	**State of adaptation.** Exposure to a drug induces changes that result in a diminution of 1 or more of the drug's effects over time. Indicated by a need for increasing doses to achieve the same effect. Commonly occurs with opioids. **Tolerance is not indicative of addiction.**
Physical Dependence	**State of adaptation manifested by drug class-specific withdrawal syndrome** that can occur with abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. **Physical dependence occurs in all patients using opioids for a period of time. Physical dependence is not indicative of addiction.**
Addiction	A **primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental components**. Characteristic behaviors include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, craving.

Savage SR, et al. *J Pain Symptom Manage*. 2003;26(1):655-667; Jamison RN, et al. *Clin Neuropsychol*. 2013;27(1):60-80.

Tolerance, Dependence, and Addiction — Critical Differences

What a patient who has developed tolerance to the analgesic effect of the prescribed opioid would say to you:

"The fentanyl patch that you prescribed used to work really well, and now it doesn't seem to be easing as much of the pain as before. I am worried."

What a patient who has become opioid-dependent will typically say to you:

"I went up to the lake this weekend and forgot to take along my long-acting morphine. I was without it for 2 days. I got so sick that I went to the ER."

Tolerance, Dependence and Addiction — Critical Differences

Behavior that the addicted patient may display:

" My husband used his entire month's supply of that extended-release opioid you gave him in 1 week. He seems like a totally different person. I am very concerned."

The *FDA* Definition of Opioid Tolerance

- Opioid naïve vs opioid tolerant
- Patients are considered opioid tolerant if they are taking, **for 1 week or longer**, at least:
  - Oral morphine – 60 mg daily
  - Transdermal fentanyl – 25 mcg/h
  - Oral oxycodone – 30 mg daily
  - Oral hydromorphone – 8 mg daily
  - Oral oxymorphone – 25 mg daily
  - Equianalgesic daily dose of another opioid

www.fda.gov.

Key Concepts

Term	Definition
Abuse	Any use of an illegal drug, or the intentional self-administration of a medication for a **nonmedical purpose**, such as altering one's state of consciousness—for example, getting high
Misuse	Use of a medication (for a medical purpose) **other than as directed or as indicated,** whether willful or unintentional, and whether harm results or not
Aberrant Drug-Related Behavior	A behavior outside the boundaries of the agreed-on treatment plan

Chou R, et al. *J Pain*. 2009;10(2):113-130.

Examples of Misuse and Abuse

What patients will typically say to you:

"Sometimes in the morning I need to take extra pills just to get going…"

"My friend was visiting this weekend and had terrible back pain. I gave her one of my oxycodone pills. It really helped her. That's OK, right?"

"That hydrocodone you gave my wife—well, it seems to make her feel a little too good sometimes. I think she's taking more than you've prescribed and I'm worried about it…"

Prescribers Can Play an Active Role in Reducing the Risks Associated With Opioids

- Establish diagnosis
  - History and physical
  - Relevant diagnostic tests
- When opioids are being considered as part of acute or chronic pain treatment plan, complete an appropriate risk assessment
  - This is an active and ongoing process

McCarberg BH. *Postgrad Med*. 2011;123(2):119-130; Brennan MJ, et al. *PM R*. 2010;2(6):544-558.

Risk Factors for Opioid-Related Aberrant Behaviors

- Family history of substance abuse
  - Alcohol, illegal drugs, prescription drugs
    - Prescription drug abuse history carries greater risk
- Personal history of substance abuse
  - Alcohol, illegal drugs, prescription drugs
    - Prescription drug abuse history carries greater risk
- Age 16 to 45 years
- History of preadolescent sexual abuse
  - Increases risk for women
- Psychological disease
  - Attention deficit disorder (ADD) or depression
    - ADD carries higher risk

Use of Risk Stratification Tools and Ongoing Monitoring KEY to Safe and Effective Opioid Use

Webster LR, et al. *Pain Med*. 2005;6(6):432-442.

Risk Stratification and Monitoring Tools

Risk Stratification Tool (used before opioids are prescribed)	Available
Screener and Opioid Assessment for Patients with Pain (SOAPP)	www.painEDU.org
Opioid Risk Tool (ORT)	www.partnersagainstpain.com

Opioid Risk Tool (ORT)

Category	Risk Factor	Score if Female	Score if Male
Family History of Substance Abuse	Alcohol Illegal Drugs Prescription Drugs	1 2 4	3 3 4
Personal History of Substance Abuse	Alcohol Illegal Drugs Prescription Drugs	3 4 5	3 4 5
Age	Age 16-45 years	1	1
History of Preadolescent Sexual Abuse		3	0
Psychological Disease	ADD, OCD, Bipolar Disorder, Schizophrenia Depression	2 1	2 1
Total Risk Score			

Total Score Risk Category

Low Risk 0–3 **Moderate Risk 4–7** **High Risk ≥8**

OCD, obsessive compulsive disorder.

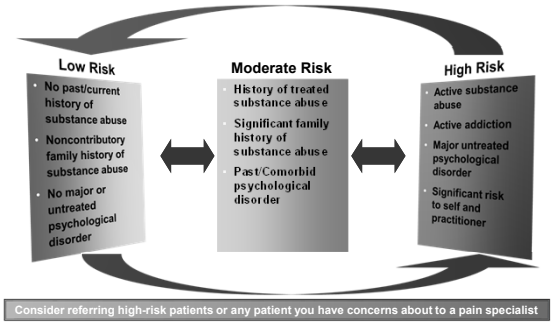
Webster LR, et al. *Pain Med*. 2005;6(6):432-442.
Opioid Risk Tool. www.partnersagainstpain.com/printouts/Opioid_Risk_Tool.pdf. Accessed January 8, 2013. Reprinted with permission: Lynn Webster, MD.

SOAPP — Sample Questions

Please answer the questions below, using the following scale:
0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

1. How often do you have mood swings? 0 1 2 3 4
2. How often do you smoke a cigarette within an hour after you wake up? 0 1 2 3 4
3. How often have you taken medication other than the way that it was prescribed? 0 1 2 3 4
4. How often have you used illegal drugs (for example, marijuana, cocaine, etc) in the past five years? 0 1 2 3 4
5. How often, in your lifetime, have you had legal problems or been arrested? 0 1 2 3 4

Stratify Risk



Consider referring high-risk patients or any patient you have concerns about to a pain specialist

Webster LR, et al. *Pain Med.* 2005;6(6):432-442.

Meet Peter

- 45-year-old white male, railroad worker for line maintenance and reconstruction
- S/p lumbar fusion with chronic back and leg pain
- Hx of back pain prior to injury that led to surgery, otherwise healthy
- Still experiencing pain despite multiple treatments described below

History

- Injured at work; pain on lower right side, radiating down right leg to outside of foot
  - Pain described as aching and throbbing
  - Pain severity 6/10 at rest and 7-9/10 when bending, coughing, or straining with a bowel movement
- NSAIDs, muscle relaxant, and light work duty attempted
- Patient struggled on job; complaints of severe pain

NSAID, nonsteroidal anti-inflammatory drug.

Peter

History (cont)

- Physical therapy (PT), Xray, MRI (L5-S1 disc w impingement of S1 nerve root)
- Failed steroid taper, hydrocodone, epidural steroid, more PT
- Sleep deprived, anxious, withdrawn, financially stressed
- Surgery and rehabilitation – no improvement
- Pain specialist prescribed:
  - Oxycodone CR tablets 40 mg every 12 hours
  - Hydrocodone/acetaminophen 5/300 8/day for breakthrough pain
  - Gabapentin 300 mg/ 2 tablets TID
  - Zolpidem 10 mg/HS

- Returns to your office for ongoing pain management

CR, controlled-release; MRI, magnetic resonance imaging.

Next Steps: Make No Assumptions

- Even though the prescriber of the CR oxycodone and hydrocodone/acetaminophen has evaluated Peter's risk for opioid misuse before initiating these drugs, should you re-assess his level of risk now that the patient is back in your care?

Yes, because the risk level can change and you want to document you have performed a risk assessment

CR, controlled-release

Peter's Score on ORT

Category	Risk Factor	Score if Female	Score if Male
Family History of Substance Abuse	Alcohol Illegal Drugs Prescription Drugs	1 2 4	(3) 3 4
Personal History of Substance Abuse	Alcohol Illegal Drugs Prescription Drugs	3 4 5	3 4 5
Age	Age 16-45 years	1	(1)
History of Preadolescent Sexual Abuse		3	0
Psychological Disease	ADD, OCD, Bipolar Disorder, Schizophrenia Depression	2 1	2 1
Total Risk Score			4

Total Score Risk Category

Low Risk 0–3 Moderate Risk 4–7 High Risk ≥8

Webster LR, et al. *Pain Med*. 2005;6(6):432-442.
Opioid Risk Tool. www.partnersagainstpain.com/printouts/Opioid_Risk_Tool.pdf.
Accessed January 8, 2013. Reprinted with permission: Lynn Webster, MD.

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Peter – Next Steps: Make No Assumptions

- Complete history and physical
- Ask Peter about his goals for treatment:
  - Explain that complete pain relief is rarely achieved
  - Focus on functional goals, eg, return to work, work part-time, able to play golf on weekends, able to walk the dog daily
- Risk for aberrant drug behavior – Moderate (4 on ORT)
- Evaluate mental health status
- Peter's Rx: oxycodone CR, hydrocodone/APAP, gabapentin, zolpidem – any other Rx? OTC? Drug-drug interactions?
- Re-establish care with new treatment agreement and UDT
- Peter's household – What is the possibility of inadvertent exposure to the opioids you are prescribing by household contacts, especially children? Have you discussed safe storage?

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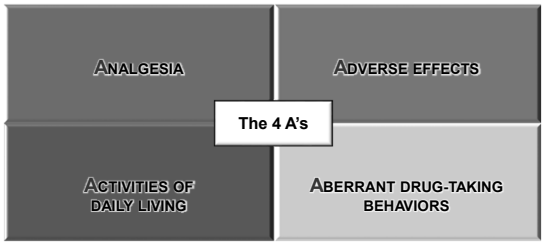
Opioid Therapy – Ongoing Monitoring



Important to remember two other "A's": **A**ssessment and **A**ction (treatment plan)

Passik SD, et al. *Adv Ther*. 2000;17(2):70-83.

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Additional Tools for Ongoing Monitoring

Current Opioid Misuse Measure (COMM) – Sample Questions
In the past 30 days, how often have you taken your medications differently than how they are prescribed?
In the past 30 days, how much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc)?
In the past 30 days, how often have you had to visit the Emergency Room?
Available at www.painEDU.org

Pain Assessment and Documentation Tool (PADT) – Sample Questions
Is the patient's functioning with the current pain reliever(s) better, the same, or worse since last assessment?
Is patient experiencing any side effects from current pain reliever(s)?
Check-list of potential aberrant drug-related behavior
Available at www.ucdenver.edu

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Session II

Best Practices for How to Start Therapy with ER/LA Opioids, How to Stop, and What to Do in Between

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Learning Objectives for Session II

Upon completion of this module, the participants will be better able to:

- Convert patients from immediate-release to ER/LA opioids as well as from one ER/LA opioid to another
- Identify predisposing risk factors for significant respiratory depression

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Key Principles of Safe Prescribing

- Know how to:
  - Identify the ER/LA opioid and dosage to use in the appropriate patient
  - Supplement pain management with immediate-release opioids and non-opioids
  - Convert patients from immediate-release to ER/LA opioids and from one ER/LA opioid to another
  - Identify the warning signs and symptoms AND PREDISPOSING RISK FACTORS for significant respiratory depression
  - Safely taper an opioid dose when therapy is no longer needed
- Keep current with regulations for opioid prescribing, both federal and those in your own state

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed August 10, 2016.

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Benefits and Limitations of ER/LA Opioids

Potential Benefits

- Provide more consistent plasma concentrations of drug compared with short-acting agents
  - This minimizes serum level fluctuations that could contribute to end-of-dose breakthrough pain
- More consistent nighttime pain control
- Less clock-watching by patients
- Possible improved compliance/ adherence due to a lower pill volume

Not for

- Not for as needed or "prn" use
- Not for mild pain
- Not for pain that is not expected to persist for an extended duration
- Not for acute pain
- Not for routine use in headache disorders or post-operative pain

ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Nicholson B. *Pain Pract.* 2009;9(1):71-81; www.fda.gov.

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ER/LA Opioids – Contraindications

- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity

See individual product information for additional contraindications

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed February 1, 2016.

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Opioid-Naïve vs. Opioid-Tolerant

- Tolerance is a function of both time and dose
  - Patients who have not taken an opioid recently are considered opioid naïve
  - THESE patients are at greater risk for respiratory depression and sedation

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Know The Risk Factors for Respiratory Depression

- Generally preceded by sedation and decreased respiratory rate
- Risk factors for respiratory depression include:

Sleep apnea or a sleep disorder diagnosis	Morbid obesity with a high risk of sleep apnea	Snoring
Risk increases with age (>60)	No recent opioid use	Post-surgery (particularly upper abdominal or thoracic)
Use of other sedating drugs (CNS depressants)	Preexisting pulmonary or cardiac disease or dysfunction or major organ failure	Smoking

The Joint Commission. Sentinel Event Alert. August 8, 2012;49. www.jointcommission.org. Accessed February 22, 2013.

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The ***FDA*** Definition of Opioid Tolerance

- Opioid naïve vs opioid tolerant
- Patients are considered opioid tolerant if they are taking, **for 1 week or longer**, at least:
  - Oral morphine – 60 mg daily
  - Transdermal fentanyl – 25 mcg/h
  - Oral oxycodone – 30 mg daily
  - Oral hydromorphone – 8 mg daily
  - Oral oxymorphone – 25 mg daily
  - Equianalgesic daily dose of another opioid

www.fda.gov.

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Be Aware

- Certain ER/LA-opioid medications should ONLY be initiated in patients who have become opioid tolerant as a result of ongoing therapy

www.fda.gov.

Be Aware

- Some agents should never be prescribed unless a patient is opioid tolerant:
  - **Duragesic (fentanyl transdermal system) – all doses**
  - **Exalgo (hydromorphone hydrochloride ER) – all doses**
  - **Oxycontin (oxycodone hydrochloride ER) for pediatric patients (11 years and older)**
- Some agents can be prescribed to opioid-naïve patients, but not at higher doses -- some ER/LA opioid doses can ONLY be used in opioid-tolerant patients

Opioid Tolerance—Agents and Dosing

(Refer to full prescribing information)

Agent	Selected Doses for Use in Opioid-Naïve Patients	Selected Doses for Use in Opioid-Tolerant Patients ONLY
Avinza (morphine sulfate ER capsules)	Initial dose is 30 mg	**90 mg** and **120 mg** capsules
Embeda (morphine sulfate ER-Naltrexone capsules)	Initial dose as first opioid is 20 mg/0.8 mg	**100 mg/4 mg** capsule
Hysingla (hydrocodone bitartrate ER tablets)	Initiate treatment with 20 mg every 24 hrs	Daily dose **≥80 mg**
Kadian (morphine sulfate ER capsules)	Product information recommends not using as first opioid	**100 mg** and **200 mg** capsules
MorphaBond (morphine sulfate ER tablets)	Product information recommends not using as first opioid	**100 mg** tablets or a total daily dose **>120 mg**
MS Contin (morphine sulfate CR tablets)	Product information recommends not using as first opioid	**100 mg** and **200 mg** tablets
OxyContin (oxycodone hydrochloride CR tablets)	Initial dose in adults is 10 mg every 12 hrs	Single dose **>40 mg** or **total daily dose >80 mg** All doses in pediatric patients.
Targiniq ER (oxycodone HCl/ naloxone HCl)	Initiate treatment with 10 mg/5 mg every 12 hrs	Single dose **>40 mg/20 mg** or **total daily dose >80 mg/40 mg**

www.fda.gov.

Opioid Tolerance—Agents and Dosing

(Refer to full prescribing information)

Agent (Oral)	Selected Doses for Use in Opioid-Naïve Patients	Selected Doses for Use in Opioid-Tolerant Patients ONLY
Belbuca (buprenorphine buccal film)	Initiate treatment with 75 mcg buccal film	**600 mcg, 750 mcg, 900 mcg**
Butrans (buprenorphine transdermal system)	Initial dose 5 mcg/hr	**7.5 mcg/hr, 10 mcg/hr, 20 mcg/hr**
Dolophine (methadone hydrochloride)	Initial dose 2.5 to 10 mg	Refer to full prescribing information
Nucynta ER (tapentadol)	Initial dose 50 mg every 12 hrs	No product-specific considerations
Opana ER (oxymorphone hydrochloride)	Initial dose 5 mg every 12 hrs	No product-specific considerations
Xtampza ER (oxycodone ER)	Initiate with 9 mg every 12 hrs	Single dose **>36 mg** or **total daily dose >72 mg**
Zohydro ER (hydrocodone bitartrate)	Initiate with 10 mg every 12 hrs	Single dose **>40 mg** or **total daily dose >80 mg**

www.fda.gov.

Initiating Therapy:
Dose Selection and Titration

Individually titrate all opioids to a dosage that provides adequate analgesia and minimizes adverse reactions

Drug	Initial Dosing
Avinza (morphine sulfate ER capsules)	• Once daily • Initial dose as first analgesic (opioid-naive patients) is 30 mg once daily • Titrate using a minimum of 3-day intervals (4-day intervals for opioid-naïve patients) • **Maximum daily dose 1600 mg** (due to risk of renal toxicity)
Butrans (buprenorphine transdermal system)	• One transdermal system applied every 7 days • Initial dose as first analgesic (opioid-naïve patients) is 5 mcg/hour • Initial dose if prior total daily dose <30 mg oral morphine equivalents/day – 5 mcg/hour • When converting from 30-mg to 80-mg morphine equivalents – first taper to 30-mg morphine equivalent, then initiate with 10 mcg/hour dose • The minimum Butrans titration interval is 72 hours • **Maximum daily dose: 20 mcg/hour** (due to risk of QTc interval prolongation)

www.fda.gov.

Initiating Therapy:
Dose Selection and Titration

Drug	Initial Dosing
Dolophine (methadone HCl tablets)	• Every 8 to 12 hours • Initial dose as first opioid analgesic (opioid-naïve patients) is 2.5 mg to 10 mg • Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information • **Special considerations: Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously by clinicians familiar with its use and risks (Refer to Module VI)**
Duragesic (fentanyl transdermal system)	• Every 72 hours (3 days) • Duragesic is contraindicated in opioid non-tolerant patients • Use product-specific information for dose conversion from prior opioid • Use 50% usual dosage in mild or moderate hepatic or renal impairment • Titrate using no less than 72-hour intervals
Embeda (morphine sulfate and naltrexone HCl) ER	• Once a day or every 12 hours • Initial dose as first opioid is 20 mg/0.8mg • Dosage adjustments may be done every 1 to 2 days

www.fda.gov.

Initiating Therapy:
Dose Selection and Titration

Drug	Initial Dosing
Exalgo (hydromorphone HCl ER tablets)	• Once a day • Not for use in opioid non-tolerant patients. Do not begin any patient on Exalgo as the first opioid • Use the conversion tables in the full prescribing information • Start patients with moderate hepatic impairment on 25% usual dosage • Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% usual dosage • Titrate using a minimum of 3- to 4-day intervals
Belbuca (buprenorphine buccal film)	• Every 12 hours • For opioid-naïve patients and those taking less than 30 mg oral morphine sulfate equivalents, initiate treatment with a 75 mcg buccal film once daily, or if tolerated, every 12 hours • Titrate to 150 mcg every 12 hrs no earlier than 4 days after initiation • Titrate using a minimum of 4 day intervals and increments of 150 mcg • Start patients with severe hepatic impairment on 50% initial dose
Hysingla ER (hydrocodone bitartrate ER tablets)	• Once a day • For opioid-naïve patients, initiate with 20 mg tablets • Dose titration may occur every 3 to 5 days in increments of 10 mg to 20 mg • Daily doses greater than or equal to 80 mg are for opioid tolerant patients only • Start patients with severe hepatic or renal impairment on 50% initial dose

www.fda.gov.

Initiating Therapy:
Dose Selection and Titration

Drug	Initial Dosing
Nucynta ER (tapentadol HCl ER tablets)	• Every 12 hours • Use 50 mg every 12 hours as initial dose in opioid non-tolerant patients • Titrate by 50 mg increments using a minimum of 3-day intervals • **Maximum total daily dose is 500 mg**
Kadian (morphine sulfate ER capsules)	• Once a day or every 12 hours • Not recommended as a first opioid • Titrate using a minimum of 2-day intervals
MorphaBond (morphine sulfate ER tablets)	• Every 8 hours or every 12 hours • Not recommended as first opioid • Titrate using a minimum of 1 to 2-day intervals
MS Contin (morphine sulfate CR tablets)	• Every 8 hours or every 12 hours • Not recommended as a first opioid • Titrate using a minimum of 2-day intervals
Opana ER (oxymorphone HCl ER tablets)	• Every 12 hrs; some may benefit from asymmetric dosing (higher in the AM than PM) • Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients • Titrate dose at increments of 5-10 mg every 12 hours, at 3-7 day intervals • Start with lowest dose in patients with mild hepatic impairment and renal impairment (creatinine clearance <50 mL/min) and in patients older than 65 years of age

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Initiating Therapy:
Dose Selection and Titration

Drug	Initial Dosing
OxyContin (oxycodone HCl CR tablets)	• Every 12 hours • Initiate treatment with 10 mg every 12 hours in opioid non-tolerant patients • Titrate using a minimum of 1- to 2-day intervals • Hepatic impairment: start with one-third to one-half usual dosage • Renal impairment (creatinine clearance <60 mL/min): start with one-half usual dosage
Xtampza ER (oxycodone ER capsules)	• Every 12 hours • Initiate treatment with 9 mg every 12 hours in opioid non-tolerant patients • Titrate using a minimum of 1 to 2 day intervals • Hepatic impairment: initiate therapy at 1/3 to ½ the usual dose • Renal impairment: follow a conservative approach
Targiniq ER (oxycodone hydrocloride / naloxone hydrochloride tablets)	• Every 12 hours • For opioid-naïve patients, initiate with 10 mg/5 mg tablet every 12 hours • Titrate using a minimum of 1 to 2 day intervals • Contraindicated in moderate and severe hepatic impairment. Start with one-third to one-half dose in mild hepatic impairment. Start with one-half dose in renal impairment
Zohydro ER (hydrocodone bitartrate ER capsules)	• Every 12 hours • For opioid-naïve patients, initiate with 10 mg capsule every 12 hours • Titrate dose at increments of 10 mg every 12 hours, at 3-7 day intervals • Start with low initial dose in patients with renal impairment and severe hepatic impairment

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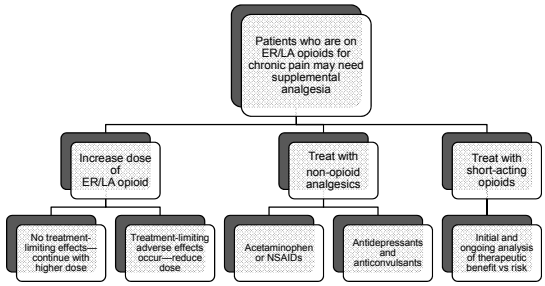
Supplementing ER/LA Opioids



Zeppetella G. ***Curr Opin Support Palliat Care*****. 2009;3:1-6; Prommer E, et al.** ***Patient Prefer Adherence*****. 2012;6:465-475; Chou R, et al.** ***J Pain*****. 2009;10(2):113-130; Burton AW. Medscape. June 15, 2005. www.medscape.org/viewarticle/506124. Accessed September 7, 2012; Rhiner MI, et al.** ***J Support Oncol*****. 2010;8:232-238.**

Peter

- S/p lumbar fusion with chronic back and leg pain
- Returns to your primary care office for ongoing pain management
- Current medications:
  - Oxycodone CR tablets 40 mg every 12 hours
  - Hydrocodone/acetaminophen 5/300; 8/day for breakthrough pain
  - Gabapentin 300 mg/2 tabs TID
  - Zolpidem 10 mg/HS
- Goals of therapy:
  - Work a full day
  - Sleep through the night
  - Improve daytime somnolence
- Opioid rotation may be considered if goals of therapy are not met, adverse effects are intolerable, or to lower opioid dose

Rationale for Opioid Rotation

- Opioid rotation is switching from one opioid to another
- Rationale for opioid rotation
  - Adverse effects or toxicity of initial opioid
  - Lack of efficacy of initial opioid
  - Lowering the dose
- Rotation may work because of:
  - Incomplete cross-tolerance among opioids
  - Inter-patient variability of response based on opioid receptor genetic polymorphisms

Note: Conservative dose-conversion ratios are advised

Fine PG, et al. ***J Pain Symptom Manage*****. 2009 Se;38(3):418-25; Chou R, et al.** ***J Pain*****. 2009;10(2):113-130.**

Equianalgesic Dose Table – An Example

Opioid	Equianalgesic (mg) Dose Oral	Equianalgesic (mg) Dose Other
Morphine	60 PO	10 IM/IV/SQ
Hydromorphone	7.5 PO	1.5 IM/IV/SQ
Oxycodone	20-30 PO	No information available
Oxymorphone	15 PO	1 IM/IV/SQ; 10 PR
Levorphanol	4 PO	2 IM/IV/SQ
Methadone	20 PO	10 IM/IV/SQ
Fentanyl		50-100 mcg IV/SQ

- Hydrocodone potency ranges 1:1 to 1:2 with morphine, but safest approach is 1:1
- Be aware that individual responses may vary
- Refer to individual full prescribing information (PI) for complete information
- Follow patients closely during all periods of dose adjustments

Knotkova H, et al. *J Pain Symptom Manage*. 2009;38(3):426-439.

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Another Example: Duragesic (fentanyl transdermal system)

- Recommended Initial Duragesic Dose Based Upon Daily Oral Morphine Dose

Oral 24-hour Morphine (mg/day)	DURAGESIC Dose (mcg/hour)
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

Duragesic Full Prescribing Information. Available at www.fda.gov.

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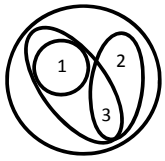
Incomplete Cross-Tolerance

- Pharmacologic phenomenon whereby tolerance developed to the effects of one drug translates into tolerance to other drugs from the same class
  - Incomplete cross-tolerance: Failure to develop complete cross-tolerance, increasing the likelihood of therapeutic effects as well as adverse effects
- It is known to occur among opioids
  - Mechanism behind opioid rotation
  - Also reason for caution in converting from one opioid to another



Chou R, et al. *J Pain*. 2009;10(2):113-130.

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Converting Patients From Immediate-Release to ER/LA Opioids or to Another ER/LA Agent

- Guidelines for select agents
  - Belbuca (buprenorphine buccal film)
    - Equipotency to oral morphine not established
  - Butrans (buprenorphine transdermal system)
    - Converting from 30-mg to 80-mg morphine equivalents:
      - First taper to 30-mg morphine equivalent per day
      - Then initiate with 10-mcg/hr dose
  - Dolophine (methadone HCl tablets)
    - ***Converting opioid-tolerant patients using equianalgesic tables can result in overdose and death.***
    - To minimize risk, use low doses according to table in full PI
    - Note: Relative potency to oral morphine varies, depending on patient's prior opioid experience
  - Duragesic (fentanyl transdermal system)
    - For relative potency to oral morphine, see individual product-specific PI for conversion recommendations from prior opioid

Always refer to full prescribing information (PI)

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Converting Patients From Immediate-Release to ER/LA Opioids or to Another ER/LA Agent

- Exalgo (hydromorphone HCl ER tablets)
  - Use conversion ratios in individual product-specific PI
  - Relative potency to oral morphine approximately 5:1 oral morphine to hydromorphone oral dose ratio
- Hysingla ER (hydrocodone bitartrate)
  - See individual product-specific PI for conversion recommendations from prior opioid
- Nucynta ER (tapentadol HCl ER tablets)
  - Equipotency to oral morphine not established
- Opana ER (oxymorphone HCl ER tablets)
  - Relative potency to oral morphine approximately 3:1 oral morphine to oxymorphone oral dose ratio
- OxyContin (oxycodone HCl CR tablets)
  - Relative potency to oral morphine approximately 2:1 oral morphine to oxycodone oral dose ratio
- Targiniq ER (oxycodone HCl/naloxone HCl tablets)
  - See individual product-specific PI for conversion recommendations from prior opioid
- Zohydro ER (hydrocodone bitartrate)
  - Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio

Always refer to full prescribing information (PI)

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Tapering and Discontinuing ER/LA Opioid Analgesics

- When ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically dependent patient
- **Do not abruptly discontinue these products**
  - Decrease original dose by 10% per week
- Abrupt discontinuation of chronic opioids may cause withdrawal characterized by:
  - Stomach cramps, diarrhea, rhinorrhea, sweating, elevated heart rate, increased blood pressure, irritability, dysphoria, hyperalgesia, and insomnia

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed February 1, 2016; Manchikanti L et al. *Pain Phys*. 2012;15(3 suppl):S67-S116; Morgan MM, et al. *Br J Pharmacol*. 2011;164(4):1322-1334.

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Federal DEA Controlled Substance Schedules: ER/LA-Opioids are Schedule II

Sch	Description	Examples
I	No currently accepted medical use in the U.S.; high potential for abuse	Heroin, LSD, marijuana, peyote, methaqualone, Ecstasy
II	**High potential for abuse, which may lead to severe psychological or physical dependence**	**Hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, and codeine, amphetamine, methamphetamine, methylphenidate, hydrocodone combination products**
III	Potential for abuse, which may lead to moderate or low physical dependence or high psychological dependence	Products containing ≤ 90 mg codeine per dose, buprenorphine, benzphetamine, phendimetrazine, ketamine, anabolic steroids
IV	Low potential for abuse	Alprazolam, carisoprodol, clonazepm, clorazepate, diazepam, lorazepam, midazolam, temazepam, tramadol (as of 2014), triazolam
V	Low potential for abuse	Cough preparations containing ≤ 200 mg codeine per 100 ml or per 100 g, ezogabine

State Laws/Regulations Vary. KNOW YOUR OWN STATE Rx REQUIREMENTS

DEA Diversion Control. Available at www.deadiversion.usdoj.gov/schedules/index.htm. Accessed Jan, 2016