Session V

Everything You Always Wanted to Know About ER/LA-Opioids as a Drug Class

Learning Objectives for Session V

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

- Assess the differences in opioid metabolism and how these impact appropriate ER/LA prescribing
- Identify how opioid-drug interactions influence ER/LA opioid prescribing

Opioids As A Drug Class – General Information ER/LA Opioid Analgesic Products Key Points

1. ER/LA opioid analgesic products are scheduled under Federal Controlled Substances Act
   - Can be misused and abused
   - Risk for diversion
2. Most serious adverse effect: respiratory depression
3. Most common long-term side effect: constipation
4. Drug-drug interaction profiles: Vary among products
   - Important to recognize and avoid clinically significant interactions
5. Tolerance to sedating and respiratory-depressant effects
   - Clinician and patient understanding of tolerance is fundamental for safe use
6. Adherence to ER/LA opioid dosing instructions is critical
   - Oral formulations must be taken as directed and patients instructed to not tamper with the formulation
   - For transdermal products, external heat, fever, or exertion can increase absorption
   - For buccal products, the film should not be applied if cut, damaged or changed

Neurobiology of Opioids

- Opioid receptors are ubiquitous
  - Found throughout CNS and within GI tract
  - Accounts for their numerous effects, including potent analgesia, sedation, and reduced GI motility
  - Are G-coupled receptors
  - Both endogenous and exogenous opioids exert their effect by acting as ligands on these receptors

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Schäfer M. Opioids in Pain Medicine. In: Kopf A, et al, eds. G*uide to Pain Management in Low-Resource Settings*. Washington, DC: International Association for the Study of Pain; *2010*. http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=12166. Accessed March 2, 2013.

Opioid Receptors and Analgesia

- Analgesic effects likely mediated through mu opioid receptors
  - Highly concentrated in the outer laminae of spine dorsal horn
  - Two areas of brainstem—rostral ventromedial medulla (RVM) and periaqueductal gray (PAG) area

Respiratory Depression

- Most common serious adverse effect
  - Can be immediately life-threatening
- Factors that may increase risk for respiratory depression include:
  - Sleep apnea or snoring
  - Morbid obesity
  - Older age
  - Opioid naïve
  - Concomitant use of other sedating drugs
  - Smoking

Schäfer M. Opioids in Pain Medicine. In: Kopf A, et al, eds. G*uide to Pain Management in Low-Resource Settings*. Washington, DC: International Association for the Study of Pain; *2010*. http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=12166. Accessed March 2, 2013.

Constipation

- Most common long-term side effect
  - Activation of GI peripheral opioid receptors decreases GI motility and increases fluid absorption
- Nausea and vomiting may develop as primary AE or over time as a sign of chronic constipation
- Constipation should be anticipated and managed prophylactically
  - eg, increase fiber and water intake
  - OTC agents include bulking, lubricants, stimulants
  - Prescription agents include stimulants, chloride ion (CIC-2) activators (eg, lubiprostone) and opiate antagonists (eg, methylnaltrexone, naloxegol)
  - Opioid rotation may be warranted

AE, adverse event.

Schäfer M. Opioids in Pain Medicine. In: Kopf A, et al, eds. *Guide to Pain Management in Low-Resource Settings*. Washington, DC: International Association for the Study of Pain; *2010*. http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=12166. Accessed March 2, 2013; National Comprehensive Cancer Network Guidelines Version 1.2012. Adult Cancer Pain. http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed February 27, 2013; Chou R, et al. *J Pain*. 2009;10(2):113-130.

Drug-Drug Interactions (DDI) Are Common and Vary Among Opioids

- Underlying mechanisms
  - Pharmacodynamics (pD)
    - Pharmacological effects
  - Pharmacokinetics (pK)
    - Drug absorption, metabolism and clearance
  - DDI may enhance or inhibit either pK or pD, thus altering intended and/or precipitating unintended effects

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed February 23, 2013.

Summary of Opioid-Drug Interactions

Concomitant Use of ER/LA Opioids With:	Potential Effects
Other CNS depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants)	Increased risk of respiratory depression, hypotension, profound sedation, or coma; reduce the initial dose of 1 or both agents
Alcohol	Exposure may increase drug levels or cause dose dumping. Counsel patients not to consume alcohol when taking opioids
Monoamine oxidase inhibitors (MAOIs)	Possible increase in respiratory depression. Serotonin syndrome may occur.
Antidiuretics	Reduced efficacy of antidiuretics by inducing the release of antidiuretic hormone (ADH)
Drugs that act as inhibitors or inducers of various cytochrome P450 enzymes	Higher or lower than expected blood levels of some opioids

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

Opioids and QTc Prolongation

- Methadone and buprenorphine can prolong QTc interval in some patients
- Dose-related incidence in patients on long-term methadone maintenance
  - 9% at a dose >300 mg/d
  - 83% at a dose >600 mg/d
- Management:
  - Monitor EKG
  - Consider alternative drugs should any abnormality develop

www.fda.gov; Reddy S, et al. *J Palliat Med*. 2010;13(1):33-38.

Cytochrome P450 Enzymes

- Account for almost 50% of overall elimination of commonly used drugs, including:
  - Statins
  - SSRIs
  - Calcium channel blockers
  - Benzodiazepines
  - Beta Blockers
  - Opioids
  - Warfarin
- CYP450 drug-drug interactions often clinically relevant

SSRI, selective serotonin reuptake inhibitor.

Indiana University School of Medicine. Drug Interactions. http://medicine.iupui.edu/flockhart/table.htm. Accessed November 6, 2012; Wilkinson GR. *N Engl J Med*. 2005;352(21):2211–2221.

Opioids and CYP450 Interactions

- Pharmacokinetic drug-drug interactions can cause higher or lower blood levels of opioid than expected and result in:
  - Excess opioid effects (including fatal toxicity)
  - Loss of analgesia
  - Misinterpretation of drug tests

Overholser BR, et al. *Am J Manag Care*. 2011;17 suppl 1:S276-S287.

ER/LA Opioids and CYP450 Enzyme Interactions

- Metabolism of several commonly used opioids occurs through enzyme CYP3A4, but CYP2D6 is also important
  - 3A4 is a potent inactivation enzyme
  - 2D6 is an activating enzyme
- Inhibition
  - Can increase drug plasma levels, resulting in greater drug-related effects
- Stimulation
  - Can decrease drug plasma levels and decrease drug-related effects
- However, if an agent is a pro-drug, an inhibitor can decrease drug effects, while an inducer increases the rapidity with which the active compound enters the bloodstream
- Refer to product-specific information for specific opioid-DDIs before prescribing

Overholser BR, et al. *Am J Managed Care*. 2011;17 suppl 1:S276-S287.

Peter's Current Medication Regimen

- Returns to your office complaining of serious foot fungus.
- Current medications:
  - 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
- When considering a medication to treat the fungus, should you be concerned about possible drug-drug interactions?
- YES – many commonly used antifungals have known CYP450 interactions

Overview of Opioid Metabolism

Active Components	Metabolism (CYP450)
Morphine	Not significantly metabolized by CYP450
Oxymorphone	Not significantly metabolized by CYP450
Tapentadol	Not significantly metabolized by CYP450
Hydromorphone	Not significantly metabolized by CYP450
Oxycodone	**2D6, 3A4**
Hydrocodone	**3A4**
Hydrocodone + Acetaminophen	**2D6, 3A4**
Tramadol	**2D6, 3A4**
Codeine	**2D6**
Fentanyl	**3A4**
Methadone	**3A4, 2B6, 2D6, 2C9, 2C19**
Oxycodone + Acetaminophen	**2D6, 3A4**

www.accessdata.fda.gov.

Interactions With Other Agents and Substances

Agent	Concomitant Use With:	Potential Effect on Opioid Levels and Other Effects
Avinza (morphine sulfate ER capsule)	• Alcohol • PGP Inhibitors (quinidine)	↑ (**potentially fatal dose**) ↑
Belbuca (buprenorphine buccal film)	• CNS depressants and benzodiazepines • CYP3A4 inhibitors • CYP3A4 inducers • Class IA and III antiarrythmics, other potentially arrhythmogenic agent	Respiratory depression ↑ ↑ ↓ QTc prolongation and torsade de pointe risk ↑
Butrans (buprenorphine transdermal system)	• CYP3A4 inhibitors • CYP3A4 inducers • Benzodiazepines • Class IA and III antiarrythmics, other potentially arrhythmogenic agent	↑ ↓ Respiratory depression ↑ QTc prolongation and torsade de pointe risk ↑
Dolophine* (methadone HCl tablets)	• CYP450 inhibitors • CYP450 inducers • Anti-retroviral agents • Benzodiazepines • Potentially arrhythmogenic agents	↑ ↓ Mixed effects on levels Respiratory depression ↑ QTc prolongation and torsade de pointe risk ↑

* Pharmacokinetic drug-drug interactions with methadone are complex. Refer to package insert for additional information.

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

Interactions With Other Agents and Substances

Agent	Concomitant Use With:	Potential Effects on Opioid Levels and Other Effects
Duragesic (fentanyl transdermal system)	• CYP3A4 inhibitors • CYP3A4 inducers	↕
Embeda (morphine sulfate ER-naltrexone capsules)	• Alcohol • PGP Inhibitors (quinidine)	↑ (**potentially fatal dose**) ↑
Exalgo (hydromorphone HCl ER tablets)	None	
Hysingla ER (hydrocodone bitartrate ER tablets)	• CYP3A4 inhibitors • CYP3A4 inducers	↕
Kadian (morphine sulfate ER capsules)	• Alcohol • PGP Inhibitors (quinidine)	↑ (**potentially fatal dose**) ↑
MorphaBond (morphine sulfate ER tablets)	• PBP inhibitors (quinidine)	↑
MS Contin (morphine sulfate CR tablets)	• PGP Inhibitors (quinidine)	↑

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.

Interactions With Other Agents and Substances

Agent	Concomitant Use With:	Potential Effects on Opioid Levels and Other Effects
Nucynta ER (tapentadol HCl ER tablets)	• Alcohol • MAOIs	↑ (**potentially fatal dose**) Contraindicated in patients taking MAOIs
Opana ER (oxymorphone HCl ER tablets)	• Alcohol	↑ (**potentially fatal dose**)
OxyContin (oxycodone HCl CR tablets)	• CYP3A4 inhibitors • CYP3A4 inducers • 2D6 inhibitors • 2D6 inducer	↑ ↓ Increased effect
Targiniq ER (oxycodone HCl / naloxone HCl)	• CYP3A4 inhibitors • CYP3A4 inducers	↕
Xtampza ER (oxycodone ER capsules)	• CYP3A4 inhibitors • CYP3A4 inducers	↑ ↓
Zohydro ER (hydrocodone bitartrate ER capsules)	• CYP3A4 inhibitors • CYP3A4 inducers	↑ ↓

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

Drug Interactions Between Methadone or Buprenorphine and Select Medications

Medication	Methadone	Buprenorphine
AZT	Increase in AZT concentrations; possible AZT toxicity	No clinical significant interaction
Lopinavir/Ritonavir	Opiate withdrawal may occur	No clinically significant interaction
Rifampin	Opiate withdrawal may occur	Opiate withdrawal may occur
Fluconazole	Increased methadone plasma concentrations	
Ciprofloxacin	Increased methadone plasma concentrations	
Sertraline	No associated adverse drug interactions	No clinically significant interaction
Duloxetine	Potentially increases duloxetine exposure	
Dextromethorphan	Associated with delirium	
Aripiprazole	No clinically significant interaciton	No clinically significant interaction
Carbamazepine	Associated with opiate withdrawal	Not studied
Methylphenidate	No clinically significant interaction	No clinically significant interaction
Diphenhydramine	May have synergistic depressant effect	

Adapted from McCance-Katz EF, et al. *Am J Addict*. 2010;19(1):4-16.

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Tolerance to Sedating and Respiratory Depressant Side Effects

- Opioid-naïve patients – no prior opioid exposure
  - Especially prone to most serious adverse effects of opioids
- Tolerance to sedating and respiratory-depressant effects critical to safe use of certain opioid products, dosages, and strengths
  - Opioid-tolerant patient: at least 1 wk of tx = 60 mg morphine or equivalent/day
  - Patients must be opioid tolerant before using any strength of transdermal fentanyl or ER hydromorphone
  - With other ER/LA products, patients must be opioid tolerant before using certain strengths or certain daily doses

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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Other Important Opioid Safety Issues

- Oral formulations of ER/LA opioids must be taken as directed. Instruct patients to not tamper with the formulation:
  - Swallow tablets whole
  - Swallow capsules whole/intact
  - If necessary, pellets from some capsules can be sprinkled on applesauce and swallowed without chewing
- For transdermal products, instruct patients on proper and safe use
  - External heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose
  - Transdermal products with metal foil backings are not safe for use in MRIs
- For buccal film products, the film should not be applied if it is cut, damaged or changed in any way.
  - Use the entire film

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Session VI

Getting the Most Clinical Insights from Specific ER/LA Product Information Sources

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Learning Objectives for Session VI

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

- Differentiate the prescribing information among available ER/LA opioids
- Identify ER/LA opioids and dosages indicated for opioid-tolerant patients only

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Prescribers Must Be Knowledgeable

- Before prescribing an opioid, each clinician needs to be knowledgeable about specific characteristics of each available ER/LA opioid, including:
  - Drug substance
  - Formulation
  - Strength
  - Dosing interval
  - Key instructions – reserve for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain

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Prescribing Information

- For detailed information, prescribers can refer to the prescribing information available online:
  - DailyMed at www.dailymed.nlm.nih.gov
  - www.fda.gov/drugsatfda

Avinza—Morphine Sulfate ER

Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	**Once a day** Initial dose in opioid non-tolerant patients: 30 mg Maximum daily dose: 1600 mg
Key Instructions	• Initial dose in opioid non-tolerant patients: 30 mg • Titrate using minimum of 3-day intervals (4-day intervals in opioid non-tolerant patients) **Instruct patient:** - Swallow capsule whole (do not chew, crush, or dissolve) - If unable to swallow, capsule can be opened and pellets sprinkled on applesauce for patients
Specific Drug Interactions	• Avoid alcoholic beverages or medications containing alcohol; may result in "dose dump" and absorption of potentially fatal dose of morphine • PGP inhibitors (eg, quinidine) may increase absorption/exposure of morphine sulfate by approximately 2x
Use in Opioid-Tolerant Patients	Use 90 mg and 120 mg capsules in opioid-tolerant patients **ONLY**

PGP, P-glycoprotein

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Belbuca—Buprenorphine Buccal Film

Belbuca	Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Dosing Interval	**Every 12 hours (or once every 24 hrs for initiation in opioid-naïve pts and those taking <30 mg oral morphine equivalents)** • Maximum dose: 900 mcg every 12 hrs due to risk of QTc prolongation
Key Instructions	• Initiate treatment with a 75 mcg buccal film in opioid-naïve or if prior total daily dose of opioid < 30 mg oral morphine equivalents/day • Titrate in increments of 150 mcg q 12 hrs • The minimum titration interval is 4 days • In severe hepatic impairment and in oral mucositis, reduce dose by 50% • Do not use if package seal is broken or film damaged in any way
Specific Drug Interactions	• CYP3A4 inhibitors may increase buprenorphine levels • CYP3A4 inducers may decrease buprenorphine levels • Benzodiazepines may increase respirator depression • Class IA and III antiarrhythmics and other potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointes
Use in Opioid-Tolerant Patients	• 600 mcg, 750 mcg and 900 mcg are for use following titration from lower doses
Product-Specific Safety Concerns	• QTc prolongation ad torsade de pointes • Hepatotoxicity
Relative Potency to Oral Morphine	• Equipotency to oral morphine has not been established.

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Butrans—Buprenorphine

Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr
Dosing Interval	**One transdermal system every 7 days** • Initial dose: 5 mcg/hr. • Maximum dose: 20 mcg/hr due to risk of QTc prolongation
Key Instructions	• When used as first opioid analgesic initiate treatment with 5 mcg/hr • If prior total daily dose of opioid < 30 mg oral morphine equivalents per day, initiate treatment with 5 mcg/hr dose • If prior total daily dose of opioid between 30 mg to 80 mg of oral morphine equivalents, taper patient's opioid for up to 7 days to no more than 30 mg of morphine equivalents, then initiate with 10 mcg/hr dose • The minimum titration interval is 72 hours **Instruct patient** • Apply only to sites indicated in full prescribing information • Apply to intact/non-irritated skin • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application; allow a minimum of 3 weeks before reapplying to same site • Do not cut • Avoid exposure to heat • Dispose of used/unused patches by folding the adhesive side together and flushing down toilet

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Butrans—Buprenorphine (cont'd)

Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr and 20 mcg/hr
Specific Drug Interactions	• CYP3A4 inhibitors may increase buprenorphine levels • CYP3A4 inducers may decrease buprenorphine levels • Benzodiazepines may increase respiratory depression • Class IA and III antiarrythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe
Use in Opioid-Tolerant Patients	Use 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr and 20 mcg/hr transdermal systems in opioid-tolerant patients **ONLY**
Drug-Specific Safety Concerns	• QTc prolongation and torsade de pointe • Hepatotoxicity • Application site skin reactions

Torsade de pointe (TdP) –a form of polymorphic ventricular tachycardia that may result in syncope or cardiac arrest.

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Dolophine—Methadone Hydrochloride

Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	**Every 8 to 12 hours** Initial dose in opioid non-tolerant patients: 2.5 mg to 10 mg slowly titrated to effect
Key Instructions	• Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death; use low doses according to table in full prescribing information (PI) • High interpatient variability in absorption, metabolism, and relative analgesic potency • Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program
Specific Drug Interactions	• Complex pharmacokinetic drug-drug interactions with methadone • CYP450 inducers may increase methadone levels • CYP450 inhibitors may decrease methadone levels • Antiretroviral agents have mixed effects on methadone levels • Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe • Benzodiazepines may increase respiratory depression

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Dolophine—Methadone Hydrochloride (cont'd)

Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Use in Opioid-Tolerant Patients	Refer to full prescribing information
Product-Specific Safety Concerns	• QTc prolongation and torsade de pointe • Peak respiratory depression occurs later and persists longer than analgesic effect • Clearance may increase during pregnancy • False-positive urine drug screens possible
Relative Potency to Oral Morphine	Varies depending on patient's prior opioid experience

Duragesic—Fentanyl Transdermal System

Duragesic	Fentanyl Transdermal System, 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (*these strengths available only in generic form)
Dosing Interval	Every 72 hours (3 days)
Key Instructions	• Use product-specific information in the full prescribing information for dose conversion from prior opioid • Use 50% of the dose in mild or moderate hepatic or renal impairment; avoid use in severe hepatic or renal impairment • Titrate generally using no less than 72-hour intervals; some patients may require 48 hour titration if adequate analgesia not achieved at 72 hour dose **Instruct patient:** - Apply to intact/non-irritated/non-irradiated skin on a flat surface - Skin may be prepped by clipping hair, washing site with water only - Rotate site of application - Do not cut - Avoid exposure to heat - Avoid accidental contact when holding or caring for children - Dispose used/unused patches by folding the adhesive side together and flushing down the toilet **Specific contraindications:** • Patients who are not opioid-tolerant • Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time • Management of postoperative pain, including use after outpatient or day surgery • Management of mild pain

Duragesic—Fentanyl Transdermal System (cont'd)

Duragesic	Fentanyl Transdermal System, 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (*these strengths available only in generic form)
Specific Drug Interactions	• CYP3A4 inhibitors may increase fentanyl drug levels and exposure • CYP3A4 inducers may decrease fentanyl drug levels and exposure • Discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in fentanyl plasma concentration
Use in Opioid-Tolerant Patients	Indicated for use in opioid-tolerant patients **ONLY**
Product-Specific Safety Concerns	• Accidental exposure due to secondary exposure to unwashed/unclothed application site • Increased drug exposure with increased core body temperature or fever • Bradycardia • Application site skin reactions
Relative Potency to Oral Morphine	See full prescribing information for conversion recommendations from prior opioid

Embeda—Morphine Sulfate ER-Naltrexone

Embeda	Morphine Sulfate ER-Naltrexone 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, and 100 mg/4 mg
Dosing Interval	**Once a day or every 12 hours** Initial dose as first opioid: 20 mg/0.8 mg Titrate using 1-2 day intervals
Key Instructions	• **Swallow capsules whole (do not chew, crush, or dissolve)** • **Instruct patient:** - Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms - If unable to swallow capsule whole, **can open capsule and sprinkle pellets on applesauce; use immediately**
Specific Drug Interactions	• Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine • GP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Use 100 mg/4mg capsule in opioid-tolerant patients **ONLY**

Exalgo—Hydromorphone Hydrochloride

Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg, and 32 mg
Dosing Interval	**Once a day** Titrate using a minimum of 3- to 4-day intervals
Key Instructions	• Use conversion ratios in the full prescribing information • Start patients with moderate hepatic impairment on 25% of the dose that would be prescribed for a patient with normal hepatic function • Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function • Do not use in patients with sulfa allergy • **Instruct patient to swallow tablets whole** - **DO NOT chew, crush, or dissolve**
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	Use in opioid-tolerant patients **ONLY**
Drug-Specific Adverse Reactions	Allergic manifestations to sulfa component
Relative Potency to Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the full prescribing information

Hysingla ER—Hydrocodone Bitartrate

Hysingla ER	Hydrocodone Bitartrate Extended-Release Tablets, 20, 30, 40, 60, 80, 100 mg
Dosing Interval	**Once a day (every 24 hours)** Titrate in increments of 10 mg to 20 mg every 3-5 days
Key Instructions	• In patients who are not opioid tolerant, initiate therapy with 20 mg • QTc prolongation has been observed with daily doses of 160 mg • Hepatic impairment: use half the initial dose • Renal impairment: use half the initial dose • Instruct patients to swallow tablets whole • Consider alternative analgesic in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction
Specific Drug Interactions	• CYP3A4 inhibitors may increase hydrocodone exposure • CYP3A4 inducers may decrease hydrocodone exposure • Concomitant use with strong laxatives may decrease hydrocodone absorption • Concomitant use of MAOIs or TCAs may increase the effect of either drug
Use in Opioid-Tolerant Patients	Doses equal to or greater than 80 mg are for use in opioid tolerant patients only
Abuse Deterrence	This product is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

Hysingla ER—Hydrocodone Bitartrate (cont'd)

Hysingla ER	Hydrocodone Bitartrate Extended-Release Tablets, 20, 30, 40, 60, 80, 100 mg
Product-Specific Safety Concerns	• Use with caution in patients with difficulty swallowing or with underlying GI disorders that may predispose them to obstruction • Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER • In nursing mothers, discontinue nursing or discontinue drug • QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with CHF, bradyarrhythmias, electrolyte abnormalities, or if taking medications known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.
Relative Potency to Oral Morphine	See individual product information for conversion recommendations from prior opioid.

Kadian—Morphine Sulfate

Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	**Once a day or every 12 hours** Titrate using a minimum of 2-day intervals
Key Instructions	• Do not use as first/initial opioid (see PI) • **Instruct patient:** - Swallow capsules whole • **DO NOT** chew, crush, or dissolve - If unable to swallow capsule whole, can open capsule and sprinkle pellets on applesauce; use immediately
Specific Drug Interactions	• Do not use with alcoholic beverages or medications containing alcohol as may result in the rapid release and absorption of a potentially fatal dose of morphine • PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Kadian 100-mg, 130 mg, 150 mg and 200-mg capsules are for use in opioid-tolerant patients **ONLY**

MorphaBond—Morphine Sulfate

MorphaBond	Morphine Sulfate Extended-Release Tablets, 15 mg, 30 mg, 60 mg, 100 mg
Dosing Interval	**Every 8 hours or every 12 hours** Titrate using a minimum of 1 to 2-day intervals
Key Instructions	• Do not use as first/initial opioid (see PI) • Instruct patient to swallow tablets whole - **Do NOT** chew, crush, or dissolve
Specific Drug Interactions	PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Use MorphaBond 100 mg tablet strengts in opioid-tolerant patients **ONLY**

MS Contin—Morphine Sulfate

MS Contin	Morphine Sulfate Controlled-Release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	**Every 8 hours or every 12 hours** Titrate using a minimum of 2-day intervals
Key Instructions	• Do not use as first/initial opioid (see PI) • Instruct patient to swallow tablets whole - **Do NOT** chew, crush, or dissolve
Specific Drug Interactions	PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Use MS Contin 100-mg and 200-mg tablet strengths in opioid-tolerant patients **ONLY**

Nucynta ER—Tapentadol

Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	**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
Key Instructions	• Dose once daily in moderate hepatic impairment with 100 mg per day maximum • **Avoid use in severe hepatic and renal impairment** • **Instruct patient :** - **Swallow tablets whole** • **Do not chew, crush, or dissolve** - Take 1 tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	• Do not use with alcoholic beverages or medications containing alcohol as may result in the rapid release and absorption of a potentially fatal dose of tapentadol • Contraindicated in patients taking MAOIs

Nucynta ER—Tapentadol (cont'd)

Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg
Use in Opioid-Tolerant Patients	No product-specific considerations
Product-Specific Safety Concerns	• Risk of serotonin syndrome • Angioedema
Relative Potency to Other Oral Opioids	• Equipotency to oral morphine not established • Studies leading to its FDA approval use a dose ratio of 5:1 of Tapentadol ER to Oxycodone CR

Opana ER—Oxymorphone Hydrochloride

Opana ER	Oxymorphone Hydrochloride Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every-12-hours dosing; some benefit from asymmetric (different dose given in AM than PM) dosing
Key Instructions	• Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance <50 mL/min) and in patients over 65 years of age • Titrate using 3-7-day intervals • Contraindicated in moderate and severe hepatic impairment **Instruct patient:** • **Swallow tablets whole (do not chew, crush, or dissolve)** • Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth • Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction
Specific Drug Interactions	Do not use with alcoholic beverages or medications containing alcohol as may result in absorption of a potentially fatal dose of oxymorphone
Use in Opioid-Tolerant Patients	No product specific considerations
Relative Potency to Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio

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OxyContin—Oxycodone Hydrochloride

OxyContin	Oxycodone Hydrochloride Controlled-Release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	**Every 12 hours**
Key Instructions	• **Opioid-naïve patients: initiate treatment with 10 mg every 12 hours** • 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 • **Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction** • **Instruct patient:** - **Swallow tablets whole** • **DO NOT chew, crush, or dissolve** - Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	• CYP3A4 inhibitors may increase oxycodone exposure • CYP3A4 inducers may decrease oxycodone exposure

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OxyContin—Oxycodone Hydrochloride (cont'd)

OxyContin	Oxycodone Hydrochloride Controlled-Release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Use in Opioid-Tolerant Patients	Single dose greater than 40 mg or total daily dose greater than 80 mg is for use in opioid-tolerant patients **ONLY**
Product-Specific Safety Concerns	• Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet • Contraindicated in patients with GI obstruction
Relative Potency to Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio
New as of 4/16/2013	This product has abuse-deterrent properties. The tablet is more difficult to crush, break, or dissolve. It forms a viscous hydrogel and cannot be easily prepared for injection.
New as of 8/13/2015	Indicated for opioid-tolerant pediatric patients 11 years and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent

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Targiniq ER—Oxycodone HCl / Naloxone HCl

Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-Release Tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Dosing Interval	**Every 12 hours**
Key Instructions	• **Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours** • Titrate using a minimum of 1- to 2-day intervals • Do not exceed 80 mg/40 mg total daily dose • Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In mild hepatic impairment, start with one-third to one-half usual dosage • Renal impairment (creatinine clearance <60 mL/min): start with one-half usual dosage • **Instruct patient:** - **Swallow tablets whole** • DO NOT chew, crush, split or dissolve as this will release oxycodone possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms - Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	• CYP3A4 inhibitors may increase oxycodone exposure • CYP3A4 inducers may decrease oxycodone exposure

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Targiniq ER—Oxycodone HCl / Naloxone HCl

Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-Release Tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Use in opioid-tolerant patients	Singe dose greater than 40 mg/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients only
Product-specific safety concerns	• Contraindicated in moderate and severe hepatic impairment.
Relative potency to oral morphine	• See individual product information for conversion recommendations from prior opioid

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Xtampza ER—Oxycodone HCl

Xtampza ER	Oxycodone Extended-Release Capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg
Dosing Interval	**Every 12 hours**
Key Instructions	• **Opioid-naïve patients: initiate treatment with 9 mg every 12 hours** • 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): follow a conservative approach and adjust according to clinical situation • **Maximum daily dose: 288 mg** • For patients that have difficulty swallowing, Xtampza ER can be opened and sprinkled on soft foods or into a cup and immediately swallowed • Xtampza ER can be administered through a feeding tube • Patient instructions: take with the same amount of food to ensure consistent plasma level are achieved
Specific Drug Interactions	• CYP3A4 inhibitors may increase oxycodone exposure • CYP3A4 inducers may decrease oxycodone exposure
Use in opioid-tolerant patients	• A single dose >36 mg or total daily dose >72 mg
Relative potency to oral morphine	• There are no established conversion ratios

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Zohydro ER—Hydrocodone Bitartrate

Zohydro ER	Hydrocodone Bitartrate Extended-release capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg and 50 mg
Dosing Interval	**Every 12 hours**
Key Instructions	• **Opioid-naïve patients: initiate treatment with 10 mg every 12 hours** • Titrate using 3- to 7-day intervals • Renal impairment (creatinine clearance <60 mL/min): start with a low dose • **Instruct patient:** - **Swallow capsules whole** • **DO NOT chew, crush, or dissolve**
Specific Drug Interactions	• CYP3A4 inhibitors may increase hydrocodone exposure • CYP3A4 inducers may decrease hydrocodone exposure
Use in Opioid-Tolerant patients	• Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only
Relative Potency to Oral Morphine	• Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio