RESPONSIBLE OPIOID PRESCRIBING
ENGAGE EDUCATE PROTECT

ER/LA Opioid Analgesics: Applied Pharmacology in the Clinical Setting

General Drug Information for ER/LA Opioid Analgesic Products

Module V

Overall Program Learning Objectives

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

- Identify and define how to assess patients for treatment with ER/LA opioid analgesics
- Demonstrate how to initiate therapy, modify dose and discontinue use of ER/LA opioid analgesics
- Recognize how to manage ongoing therapy with ER/LA opioid analgesics
- Employ patient and caregiver counseling about the safe use of ER/LA opioid analgesics, including proper storage and disposal
- **Recall general** and product-specific **drug information concerning ER/LA opioid analgesics**

Products in ER/LA Opioid Analgesic Class

- **Avinza** (morphine sulfate ER capsules)
- **Butrans** (buprenorphine transdermal system)
- **Dolophine** (methadone HCl tablets)
- **Duragesic** (fentanyl transdermal system)
- **Embeda** (morphine sulfate ER-naltrexone capsules)
- **Exalgo** (hydromorphone HCl ER tablets)
- **Kadian** (morphine sulfate ER capsules)
- **MS Contin** (morphine sulfate CR tablets)
- **Nucynta ER** (tapentadol HCl ER tablets)
- **Opana ER** (oxymorphone HCl ER tablets)
- **OxyContin** (oxycodone HCl CR tablets)
- **Zohydro ER** (hydrocodone bitartrate ER capsules)

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Key Learning Points

- General drug information associated with the class including drug interactions, common and serious adverse events, and toxicities common to ER/LA opioids
- Key instructions for prescribing to ensure safe use and maximize pain control
- What you should know before initiating treatment related to opioid tolerance

Important Points to Remember

ER/LA opioids are scheduled under the Controlled Substance Act and can be misused or abused

Respiratory depression is the most important and serious adverse event

Constipation is the most common and long-term adverse event and should be anticipated in all cases

DEA Controlled Substance Schedules: ER/LA Opioids Are Schedule II*

Schedule	Description	Examples
I	No currently accepted medical use in the United States; 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**
III	Potential for abuse, which may lead to moderate or low physical dependence or high psychological dependence	Products containing <15 mg hydrocodone per dose, or ≤90 mg codeine per dose, **buprenorphine***, benzphetamine, phendimetrazine, ketamine, anabolic steroids
IV	Low potential for abuse	Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, triazolam
V	Low potential for abuse	Cough preparations containing ≤200 mg codeine per 100 mL or per 100 g, ezogabine

**With the exception of buprenorphine, which is Schedule III*

Drug Enforcement Administration Office of Diversion Control. *www.deadiversion.usdoj.gov/schedules/index.html.* Accessed February 26, 2013.

Respiratory Depression Is the Most Serious Complication Related to Opioids

- Occurs when initial doses are too high, opioids are titrated too rapidly, or opioids are combined with other drugs that may potentiate opioid-induced respiratory depression
- Most deaths from respiratory depression occur at night when long-acting opioids produce more adverse effects
- Concomitant medication use, obesity, and sleep apnea also increase risk

Dahan A, et al. *Pain Physician*. 2013;16(2):E85-94.

Commonly Reported Opioid-related Adverse Events

Adverse Event	Rate of Occurrence Reported
Dry mouth	42%
Constipation*	20-41%
Sweating	34%
Weight gain	29%
Somnolence	14-29%
Problems with sleep	25%
Memory deficits	24%
Loss of appetite	23%
Nausea	17-33%
Concentration Deficits	19%
Fatigue	19%
Sexual dysfunction	18%
Dizziness	12-22%
Vomiting	11-15%
Pruritus/dry skin	10%
Urinary Retention	

*Tolerance occurs with the majority of adverse events with the exception of constipation

Benjamin R, et al. *Pain Physician.* 2008;11(2 Suppl.):S105-S120.; Papaleontiou M, et al. *J. Am. Geriatr Soc*. 2010;58(7):1353-1369.; Kalso E, et al. *Pain.* 2004;112(3):372-380.; Furlan AD, et al. *CMAJ.* 2006;174(11):1589-1594.; Brown RT, et al. *J Opioid Manag*. 2006;2(3):137-146.; Moore RA, et al. *Arthritis Res Ther*. 2005;7(5):28.; Eisenberg E, et al. *JAMA.* 2005;293(24): 3043-3052.

When Does the Frequency of Opioid-related Adverse Events Increase?

- Daily opioid use (compared to intermittent)
- Higher doses
- Long-term therapy
- Polypharmacy
- Decreased renal or hepatic function

Review of Opioid Tolerance

Patient tolerant to the sedating and respiratory-depressant effects of ER/LA opioids is critical for safe use

- Patients must be opioid tolerant before using **any** strength of transdermal fentanyl or hydromorphone ER
- For other ER/LA opioids, patients must be opioid tolerant before using certain strengths or certain daily dosages

Refer to package insert for prescribing information of each ER/LA opioid

Use in Opioid Tolerant Patients

Patients that are considered opioid tolerant are taking at least one of these doses for 1 week or longer

Opioid Tolerant Doses
60 mg oral morphine per day
25 u transdermal fentanyl per hour
30 mg oral oxycodone per day
8 mg oral hydromorphone per day
25 mg oral oxymorphone per day

An equianalgesic dose of another opioid

Refer to prescribing information on ***which products and which doses*** are indicated for use ***only*** in opioid tolerant patients

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Drug-drug Interactions

Drug-Drug Interactions

- Cytochrome P450 enzymes are essential for the metabolism of many medications
- Genetic variability (polymorphism) in these enzymes may influence a patient's response to commonly prescribed drug classes, including beta blockers and antidepressants

Lynch T, Price A. *Am Fam Physician*. 2007;76(3):391-396.

The Two Most Significant Enzymes in the Metabolism of Opioids are CYP3A4 and CYP2D6

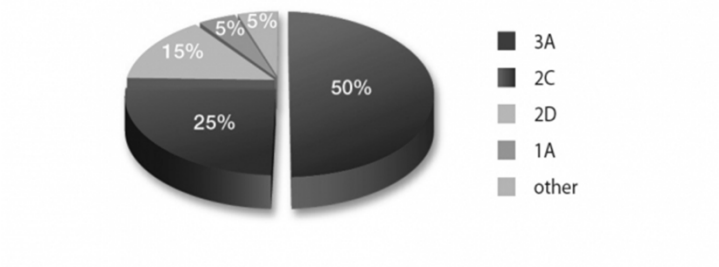

Figure 2. The approximate percentage of current drugs metabolized by each indicated CYP450 isozyme. Based on references 10,17,18.

Although the P450 Class has More than 50 Enzymes, Six of them Metabolize 90% of All Drugs

Practical Pain Management. Common Opioid-Drug Interactions: What Clinicians Need to Know *www.practicalpainmanagement.com/treatments/pharmacological/opioids/common-opioid-drug-interactions-what-clinicians-need-know?page=0,2.* Accessed March 3, 2014.; Wilkinson GR. *N Engl J Med.* 2005;352(21):2211-2221.; Williams JA, et al. *Drug Metab Dispos.* 2004;32(11):1201-1208.; Wienkers LC, et al. *Nat Rev Drug Disc.* 2005;4:825-883.

Good Pain Management Is a Complex Goal

- The overall prevalence of drug-drug interactions in patients on long-term opioids is 27%
- Good pain management practice should include knowledge of potential interactions, as well as ways to avoid and ameliorate them

Practical Pain Management. Common Opioid-Drug Interactions: What Clinicians Need to Know *www.practicalpainmanagement.com/treatments/pharmacological/opioids/common-opioid-drug-interactions-what-clinicians-need-know?page=0,2.* Accessed March 3, 2014.

Avoid Potential Opioid-induced Drug Interactions

- Provide patient counseling
- Prepare to make dosage adjustments
  - Drugs that ***induce*** the metabolism of a drug require new enzyme production so that the onset of opiate ***withdrawal*** generally occurs after about 7 days
  - Inhibitors can ***delay*** metabolism with onset of drug administration so that ***increases*** in opioid exposure can occur soon after initiating the medications
- Recognize that not all patients will develop drug interactions
- Know that occurrence is related to dose, clinical pharmacology, and individual genetics that determine CYP450 enzyme activity

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

Common Inducers and Inhibitors of the CYP450 Isozymes Involved in Opioid Metabolism

CYP	Inducers
1A2	Barbiturates (ie, phenobarbital), carbamazepine, omeprazole, phenytoin, rifampin, tobacco smoke)
2B6	Artemisinin, barbiturates, carbamazepine, efavirenz, nevirapine, phenytoin, rifampin
2C9	Barbiturates, phenytoin, rifampin, St. John's wort
2C19	Barbiturates, carbamazepine, lopinavir/ritonavir, phenytoin, rifampin, St. John's wort
2E1	Ethanol, isoniazid
3A4	Barbiturates, carbamazepine, corticosteroids (dexamethasone), efavirenz, modafinil, nevirapine, oxcarbazepine, phenytoin, rifabutin, rifampin, St. John's wort, troglitazone
CYP	**Inhibitors**
1A2	Cimetidine, fluoroquinolones, fluvoxamine, grapefruit juice, isoniazid
2B6	Clopidogrel, thiotepa, ticlopidine, voriconazole
2C9	Amiodarone, chloramphenicol, cimetidine, azole antifungals, isoniazid, metronidazole, SSRIs, probenecid, zafirlukast
2C19	Cimetidine, indomethacin, fluconazole, fluvoxamine, ketoconazole, lansoprazole, omeprazole, modafinil, probenecid, SSRIs, topiramate
2D6	Amiodarone, chloramphenicol, cimetidine, cinacalcet, diphenhydramine, haloperidol, methadone, mibefradil, quinidine, fluoroquinolones, SSRIs, terbinafine, thioridazine
3A4	Amiodarone, azole antifungals, cimetidine, clarithromycin, diltiazem, erythromycin, fluoroquinolones, grapefruit juice, HIV protease inhibitors, quinine SSRIs

CYP=cytochrome P450; HIV=human immunodeficiency virus; SSRIs=selective serotonin reuptake inhibitors

Drug Interactions Common to this Class

Reduce initial dose of one or both agents

Concurrent use w/ other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma

Avoid using partial agonists and mixed agonist/antagonist analgesics† together, may reduce analgesic effect or precipitate withdrawal

May enhance neuromuscular blocking action of skeletal muscle relaxants and increase respiratory depression

Concurrent use w/ anticholinergic medication increases risk of urinary retention and severe constipation

May lead to paralytic ileus

†Buprenorphine, pentazocine, nalbuphine, butorphanol

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf*. Accessed March 3, 2014.

For Safer Use: Know Drug Interactions PK and PD – CNS Depressants

- Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids
  - Caution against concomitant use of alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.

For Safer Use: Know Drug Interactions PK and PD – MAOIs and Diuretics

- Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression
- Using certain opioids with MAOIs may cause serotonin syndrome
- Can reduce efficacy of diuretics by inducing the release of antidiuretic hormone (ADH)

Serotonin syndrome is a potentially life-threatening drug reaction that may occur following inadvertent reactions between drugs

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.

For Safer Use: Know Drug Interactions PK and PD – Alcohol (Dose Dumping)

- Some ER formulations may rapidly release opioid (dose dump) when exposed to alcohol
- Some drug levels may increase without dose dumping when exposed to alcohol

Always check individual package insert

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.

For Safer Use: Know Drug Interactions PK and PD – Methadone and Buprenorphine

- Methadone and buprenorphine can prolong the QTc interval

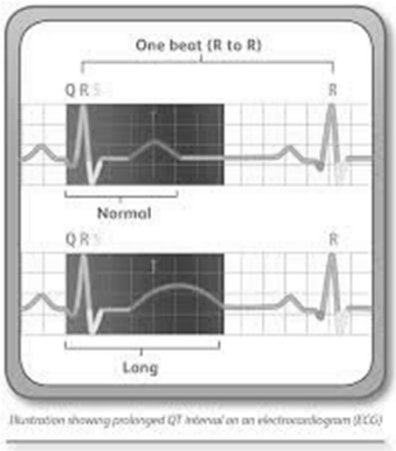

Illustration showing prolonged QT interval on an electrocardiogram (ECG)

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.

Action Plan to Mitigate Risks of Drug-Drug Interactions

1. Be aware of which medications/ substances are metabolized via the CYP450 enzyme
2. Initiate any CYP450-affected opioid analgesic at low dose and only increase the opioid dose gradually after carefully assessing patient's response
3. Keep the dose of any co-prescribed CYP450 inhibitor as low as possible
4. Consider co-prescribing drugs that are metabolized via other pathways
5. Do not assume that potential opioid-drug interactions will be detected by the pharmacist/patient

At each visit:

1. Review every medication being taken (Rx, OTC and illicit)
2. Advise patients that they must tell you if they themselves or any health care providers have made any additions or changes to their medication
3. Educate patients about potential adverse/lethal effects of prescribed medications, street medications or alcohol and document that patients have been advised

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Key Practice Reminders for ER/LA Opioids

Key Practice Reminders for ER/LA Opioids

- **Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions**
- **Continually re-evaluate to assess maintenance of pain control and emergence of AEs**
- **Refer to product information for titration interval**
- **Times required to reach steady-state plasma concentrations are product-specific**

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.

Key Practice Reminders for ER/LA Opioids

During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids

If pain increases, attempt to identify source, while adjusting dose

When an ER/LA opioid is no longer required, gradually titrate dose downward to prevent signs and symptoms of withdrawal in physically dependent patients

Do not abruptly discontinue

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.

Common Drug Information for this Class

Limitations of usage	Dosage reduction for hepatic or renal impairment	Relative potency to oral morphine
• Not for use as an as-needed analgesic • Not for mild pain or pain not expected to persist for an extended duration • Not for use in treating acute pain	See individual drug PI	• Intended as general guide • Follow conversion instructions in individual PI • Incomplete cross-tolerance and inter-patient variability require conservative dosing when converting from one opioid to another – Halve calculated comparable dose and titrate new opioid as needed

www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed March 3, 2014.

ER/LA Opioid Analgesics: Contraindications

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

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Dosage Formulations: Special Considerations

ARS QUESTION

ER/LA opioid analgesic *tablets* and *capsules* must always be swallowed whole

A. True
B. False

Solid Oral Dosage Forms

- ER/LA opioid analgesic ***tablets*** and ***capsules*** must be swallowed whole
  - Crushing, chewing, breaking, cutting, or dissolving may result in rapid release and absorption of a potentially fatal opioid dose
  - Some capsules* can be opened and pellets sprinkled on applesauce, swallowed without chewing and used immediately

*Please see package insert for listing of capsules which may be opened and sprinkled on applesauce. Always refer to Prescribing Information

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.; The ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy. Selected Important Safety Information. Abuse potential and risk of life-threatening respiratory depression. *www.er-la-opioidrems.com/lwgUI/rems/pdf/important_safety_information.pdf.* Accessed March 3, 2014.

Solid Oral Dosage Forms

- Crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of potentially fatal opioid dose
- Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid
- Dispose of unused product by flushing down the toilet

*Always refer to Prescribing Information

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 8-28-2012.; *www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.* Accessed March 3, 2014.; The ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy. Selected Important Safety Information. Abuse potential and risk of life-threatening respiratory depression. *www.er-la-opioidrems.com/lwgUI/rems/pdf/important_safety_information.pdf.* Accessed March 3, 2014.

Transdermal Dosage Forms

- Do not cut, damage, chew, or swallow
- External heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose
- Patients with fever must be monitored for signs or symptoms of increased opioid exposure
- ***Transdermal products with metal foil backings are not safe for use in MRIs***

Transdermal Dosage Forms

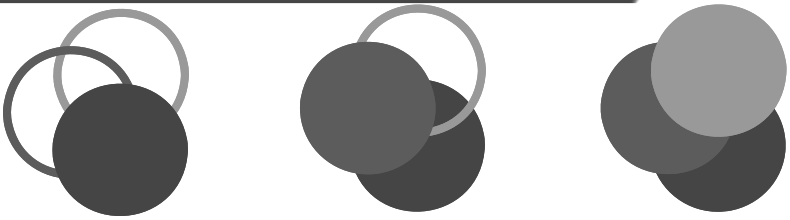
Application

- Rotate site of application
- Prepare skin by clipping, not shaving hair, and washing area only with water

Disposal

- Drug take-back events
  - If not available, flush down toilet
  - Butrans (buprenorphine): seal in patch-disposal unit and dispose of in trash

Summary



Engage

Ensure patients provide information on all concomitant medications

Educate patients on particular risks of their prescribed medications

Educate

Know the risks of drug-drug interactions

What to know before initiating treatment related to opioid tolerance

Review of key instructions for prescribing to ensure safe use and maximize pain control

Protect

Employ active risk mitigation principles to minimize risks of drug interactions

Thank you for completing Module 5.

You must answer the post-test questions at the end of this module before moving on to Module 6

You must complete all six modules in order to print your CE certificate