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)

Jeffrey Gudin, MD
Director
Pain Management and Palliative Care
Englewood Hospital and Medical Center
Englewood, New Jersey
Responsible Opioid Prescribing

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

Module V

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*

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No currently accepted medical use in the United States; high potential for abuse</td>
<td>Heroin, LSD, marijuana, peyote, methaqualone, Ecstasy</td>
</tr>
<tr>
<td>II</td>
<td>High potential for abuse, which may lead to severe psychological or physical dependence</td>
<td>Hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, and codeine, amphetamine, methamphetamine, methylphenidate</td>
</tr>
<tr>
<td>III</td>
<td>Potential for abuse, which may lead to moderate or low physical dependence or high psychological dependence</td>
<td>Products containing &lt;15 mg hydrocodone per dose, or ≤90 mg codeine per dose, buprenorphine*, benzphetamine, phendimetrazine, ketamine, anabolic steroids</td>
</tr>
<tr>
<td>IV</td>
<td>Low potential for abuse</td>
<td>Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, triazolam</td>
</tr>
<tr>
<td>V</td>
<td>Low potential for abuse</td>
<td>Cough preparations containing ≤200 mg codeine per 100 mL or per 100 g, ezogabine</td>
</tr>
</tbody>
</table>

*With the exception of buprenorphine, which is Schedule III

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

Commonly Reported Opioid-related Adverse Events

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

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


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

- 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 ug 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
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

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

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

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
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


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

<table>
<thead>
<tr>
<th>CYP</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Barbiturates (ie, phenobarbital), carbamazepine, omeprazole, phenytoin, rifampin, tobacco smoke)</td>
<td>Cimetidine, fluoroquinolones, fluvoxamine, grapefruit juice, isoniazid</td>
</tr>
<tr>
<td>2B6</td>
<td>Artemisinin, barbiturates, carbamazepine, efavirenz, nevirapine, phenytoin, rifampin</td>
<td>Clopidogrel, thiotepa, ticlopidine, voriconazole</td>
</tr>
<tr>
<td>2C9</td>
<td>Barbiturates, phenytoin, rifampin, St. John's wort</td>
<td>Amiodarone, chloramphenicol, cimetidine, azole antifungals, isoniazid, metronidazole, SSRIs, probenecid, azithromycin</td>
</tr>
<tr>
<td>2C19</td>
<td>Barbiturates, carbamazepine, lopinavir/ritonavir, phenytoin, rifampin, St. John's wort</td>
<td>Cimetidine, indomethacin, fluoroquinolones, fluvoxamine, ketoconazole, lansoprazole, omeprazole, modafinil, probenecid, SSRIs, topiramate</td>
</tr>
<tr>
<td>2E1</td>
<td>Ethanol, isoniazid</td>
<td>Amiodarone, chloramphenicol, cimetidine, cinacalcet, diphenhydramine, haloperidol, methadone, mibebradil, quinidine, fluoroquinolones, SSRIs, terbinafine, thioridazine</td>
</tr>
<tr>
<td>2D6</td>
<td>Amiodarone, chloramphenicol, cimetidine, cinacalcet, diphenhydramine, haloperidol, methadone, mibebradil, quinidine, fluoroquinolones, SSRIs, terbinafine, thioridazine</td>
<td>Amiodarone, azole antifungals, cimetidine, clarithromycin, diltiazem, erythromycin, fluoroquinolones, grapefruit juice, HIV protease inhibitors, quinine SSRIs</td>
</tr>
</tbody>
</table>

CYP=cytochrome P450; HIV=human immunodeficiency virus; SSRIs=selective serotonin reuptake inhibitors
Drug Interactions Common to this Class

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

Reduce initial dose of one or both agents
May lead to paralytic ileus

1Buprenorphine, pentazocine, nalbuphine, butorphanol

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

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


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

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

- Methadone and buprenorphine can prolong the QTc interval


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
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

Responsible Opioid Prescribing
ER/LA Opioid Analgesics: Applied Pharmacology in the Clinical Setting
Module V

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.;

Common Drug Information for this Class

<table>
<thead>
<tr>
<th>Limitations of usage</th>
<th>Dosage reduction for hepatic or renal impairment</th>
<th>Relative potency to oral morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Not for use as an as-needed analgesic</td>
<td>See individual drug PI</td>
<td>• Intended as general guide</td>
</tr>
<tr>
<td>- Not for mild pain or pain not expected to persist for an extended duration</td>
<td></td>
<td>• Follow conversion instructions in individual PI</td>
</tr>
<tr>
<td>- Not for use in treating acute pain</td>
<td></td>
<td>• Incomplete cross-tolerance and inter-patient variability require conservative dosing when converting from one opioid to another</td>
</tr>
</tbody>
</table>

- Halve calculated comparable dose and titrate new opioid as needed

### 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

### 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

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


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