Opioids and Pain: Understanding ER/LA Opioids

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OPIOIDS AND PAIN: UNDERSTANDING ER/LA OPIOIDS

Goal:
The goal for this module is to train providers to have and apply a comprehensive understanding of ER/LA drug interactions.

After completing this module participants will be able to:

- Become knowledgeable about the general characteristics, toxicities, and drug interactions of ER/LA opioids
- Become knowledgeable about specific characteristics, toxicities, and drug interactions of ER/LA opioids and how to supplement treatment with other analgesics
- Become knowledgeable about factors, particularly tolerance, affecting dosage and conversion between opioids
- Provide appropriate patient education to support safe and effective treatment when prescribing ER/LA opioids

Professional Practice Gaps

Opioid misuse and abuse is a grave health concern in the U.S., and is one that continues to grow. The number of emergency department visits due to the non-medical use of prescription analgesics increased from 145,000 in 2004 to 360,000 in 2010. The number of drug poisoning deaths involving opioid analgesics increased from 4,000 in 1999 to 14,800 in 2008. By 2008, opioid analgesics were involved in 40% of all drug poisoning deaths. Also disturbing, every year starting in 2002, there have been at least 1.9 million new non-medical pain analgesic users.

Chronic pain is a very common problem encountered in clinical practice. In a study involving 111 providers (attending physicians, nurse practitioners, physician assistants, and family practice residents), a mean of 37.5% of adult patients seen in a targeted week by any of the participating providers reported having current chronic pain. Furthermore, opioids are very commonly prescribed for chronic pain. In a survey of prescribers (including physicians, physician assistants, and advanced practice nurses), 58% answered that they were “likely” to prescribe opioids for chronic pain. When comparing 2002 and 2012, MEPS estimates showed growth in the total number of outpatient prescription purchases of opioids, rising from 854.9 million to 143.9 million purchases, an increase of 67.5 percent. However, a significant amount of participants disclosed negative beliefs and attitudes about medication abuse and addiction which, they indicated, could complicate patient care and negatively impact clinical practice. In a survey of family physicians, 80% were anxious about prescribing high-dose opioids to persons with chronic nonmalignant pain, and 92.4% did not prescribe opioids to individuals with a history of substance abuse.

Professional organizations of pain specialists, based on expert consensus and review of the research literature, have created clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. The guidelines are designed to improve pain treatment outcomes and reduce the risk of prescription drug overdose and diversion. The need for prescribers to do more to prevent diversion can be inferred from studies showing that a majority of patients do not take their pain medication as prescribed and that the source for the majority of non-medically used prescription drugs is friends or...
The need for education and training in the guidelines to avoid diversion and overdose is evident in research linking "doctor shopping" to increased risk for overdose. Furthermore, research by the National Center on Addiction and Substance Abuse at Columbia University (CASA) shows that physicians do not follow key recommendations in evidence-based guidelines for avoiding diversion and overdose. CASA has concluded from their research that physicians should receive more continuing medical education related to prescribing and administering controlled substances and identifying, diagnosing, and treating substance abuse and addiction.

A survey of health care facilities regarding pain management practice standards and education revealed gaps in knowledge of pain management, and attitudes that hinder proper acute and chronic pain treatment. While some medical schools have implemented programs that have improved students’ attitudes and skills for treating patients with addiction, most medical schools have not.

From a national survey of residency programs, only 56.3% of programs required substance use disorder training, with the median number of hours ranging from 3 to 12 hours. In a survey of family physicians, the majority (60%) believed that their training in medical school did not prepare them to manage pain.

**ER/LA Opioids Practice Gaps:**

Only a few practice gaps regarding the prescribing of extended release/long acting (ER/LA) opioids have been identified in the literature, despite risks associated with their use and their frequent use. The risk of overdose and death can be greater for ER/LA opioids than other opioids and so practice gaps described above regarding these topics are especially relevant for this subclass of opioids. While ER/LA opioids were only 9% of all opioid prescriptions dispensed in 2009, they represented 22.9 million prescriptions, up from 9.3 million in 2000. In 2009, 3.8 million patients received a prescription for ER/LA opioids in an outpatient setting. Primary care providers are responsible for a large portion of the ER/LA prescriptions: General practice (GP), Family Medicine (FM), D.O.’s plus Internal Medicine, dispense around 44% of these prescriptions. Although primary care physicians may be one of the leading prescribers of opioids, they often leave out pertinent information about the safe use and storage of opioid analgesics during patient counseling, making PCPs an important target audience of our proposed program.

**INTRODUCTION**

**Overview of REMS for ER/LA Opioids**

This module will review in detail the general and specific drug information regarding extended-release/long-acting (ER/LA) opioids required by the FDA for REMS training. ER/LA opioids have certain pharmacokinetics, side effects, drug interactions, and adverse reactions in common. Specific ER/LA opioids vary, however, especially with respect to dosing information, tolerance requirements, and specific toxicity information. This module discusses these similarities and differences among ER/LA opioids.

**Warnings and Patient Education**

It is just as important that your patient be knowledgeable about their treatment. The FDA requires a black box warning, described on the next page, for all opioids; a specific version is required for ER/LA.
opioids and should be reviewed with the patient. Providing patient counseling documents, patient education materials and utilizing patient-provider agreements can help to support a safe and effective treatment environment when prescribing ER/LA opioids. We will provide you with a systematic approach to patient education as well as a checklist to help you make sure you do not omit critical information.

CAUTION TIP
Evidence-based guidelines for prescribing opioids recommend, produced by the CDC, **not using extended-release/long-acting opioids (ER/LA) in patients being started on opioid therapy**. More guidelines on a number of other limitations regarding indications for considering ER/LA opioid are presented in this module.

**TYPES OF DRUG INFORMATION TO KNOW FOR ALL OPIOIDS**

- Opioid tolerance criteria which can be found on the product's label, and products and which doses are indicated for use only in opioid tolerant patients
- Specific ER/LA opioid information including:
  - Drug Substance, Formulation, and strength
  - Dosing Interval
  - Conversion between products where available
  - Key Instructions
  - Specific Opioid Interactions
  - Use in Opioid Tolerant Patients
  - Product Specific Safety Concerns
  - Relative Potency to Oral Morphine

**Important for All Opioids**

**Patient Education Is Critical.** Tell the patient and caregiver to read the Medication Guide for the specific ER/LA opioid given to them by the pharmacy (see related resources)

**Opioids have incomplete cross tolerance with each other.** Understanding this, when converting from one opioid to another, it is essential to lower the dose. The patient may be tolerant of one opioid, but they often do not have as much tolerance to the next opioid because of different molecular structure.

CAUTION TIP
Rapid onset opioids, are approved for use in cancer patients, but have been used off label for intense non-cancer pain. They must be prescribed with extreme caution and carefully titrated up or they can result in overdose and death in a patient who is not sufficiently tolerant.

**Rapid Onset Opioids are a Different Class of Opioids**
- It is especially critical that Rapid Onset Opioids be stored in a locked container away from children.
• Transmucosal immediate release fentanyl (TIRF) is a rapid onset opioid. It has its own REMS training.

ADVERSE EFFECTS OF EXTENDED RELEASE/LONG ACTING OPIOIDS

Warning
A boxed warning is required on ER/LA opioids to warn of the safety issues of "misuse, abuse, addiction, overdose, and death"¹⁹:

• "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."
• "Because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief.

ER/LA opioids are also affected by the relatively more recent safety warnings for all opioids, including warning of risk for serotonin syndrome, adrenal insufficiency, and decreased sex hormone levels with chronic use²⁰.

Adverse Effects and Special Precautions
Before prescribing extended release (ER)/long acting (LA) opioids, it is important to be aware of the following adverse effects and the special precautions needed¹⁹. The following list is an overview of drug information and many of the special precautions to be taken with ER/LA opioids as described in the FDA blueprint for the Risk Evaluation and Mitigation Strategy (REMS) training that they require pharmaceutical companies manufacturing and marketing these medications to produce¹⁹; further detail on these topics will be provided as the module proceeds:

1. The most serious adverse effect is respiratory depression, so patients prescribed ER/LA opioids should be closely monitored:
   • Be aware of the warning signs of respiratory depression
   • Evaluate patients for tolerance to respiratory-depression effects.
2. Other adverse effects include weakness, the effect on driving, dry-itching skin, impotency, and endocrine effects with long-term use (e.g. hypogonadism, decreased libido, erectile dysfunction)⁸,²¹,²².
3. The most common side effect is constipation. Other common side effects include nausea, dizziness, and somnolence.
4. Individuals using ER/LA opioids are at a risk of developing physical dependency, tolerance, addiction, overdose, and death.⁸,²¹,²²
5. Organ toxicities are rare but can occur:
   • suppression of the hypothalamic pituitary gonadal axis²³
• >50 mg (MSO equivalents) is associated with 2 times increase risk of fracture

6. ER/LA opioids or other strong opioids (example: fentanyl patch) are for use in opioid-tolerant patients only:
   • A patient should be opioid-tolerant in order to be considered for treatment with ER/LA opioids or other strong opioids (example: fentanyl patch)
   • Treat all patients as if they are naive for a new opioid, due to the variable pharmacological properties among opioids and variations in response among patients.
   • The CDC recommends not using ER or LA opioids for acute pain.

7. Use of ER/LAs during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS - poor feeding, rapid breathing, trembling, and excessive or high-pitched crying) which can be life-threatening.

8. It is imperative that all tablets and capsules be swallowed whole. A few ER/LA opioids may be sprinkled on applesauce; see specific drug information for more detail.

9. ER/LA opioids in patch form are heat sensitive; patients should be cautioned to avoid external heat (sun, hot baths, fever, exertion etc.) while wearing the patches. Patients should rotate the location of the patch.

Contraindications
According to the CDC guidelines for prescribing opioids, ER/LA opioids should not be prescribed as initial treatment for acute or chronic pain, that is, they should not be prescribed in an opioid naive patient.

According to the FDA Blueprint for this REMS education, the following contraindications are generally true for ER/LA opioids. There may be further contraindications for specific opioids.

• Respiratory depression that is significant
• Asthma that is severe or acute, in an unmonitored setting or without equipment for resuscitation
• Paralytic ileus
• Hypersensitivity to the opioid

ER/LA OPIOIDS INTERACTIONS

Drug Interactions with ER/LA Opioids
Extended release/long acting medications increase the risk of adverse drug interactions. Opioids are contraindicated in the presence of a variety of other drugs. A thorough medical history to determination of the presence of possible adverse drug interactions is essential.

• Central nervous system (CNS) depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) may escalate respiratory depression. Reduce the initial dose of at least one agent.
• Monoamine oxidase inhibitors (MAOIs) increase risk of anxiety and respiratory depression. MAOIs and some opioids can cause serotonin syndrome.
• Opioids can reduce the efficacy of diuretics by causing the release of antidiuretic hormone (ADH)
Some opioids may interact with cytochrome P450 inhibitors resulting in higher or lower than expected opioid blood levels.

Methadone and buprenorphine may increase the QTc interval.

Partial opioid agonists (e.g., buprenorphine, pentazocine, nalbuphine, and butorphanol) may decrease the analgesia and could precipitate withdrawal; so concurrent use should be avoided.

Skeletal muscle relaxant effect may be blocked by opioids and amount of respiratory depression may be increased.

Anticholinergics combined with opioids may lead to urinary retention and severe constipation, with possible paralytic ileus

Potential Dose Dumping Effect of Alcohol

In addition to CNS depressant interactions described above, another interaction is possible between alcohol and certain formulations. Patients prescribed certain ER/LA opioids should refrain from alcohol consumption. The presence of alcohol can increase the plasma concentration of the ER/LA opioid (dose dump). Some drug levels may increase without dose dumping when exposed to alcohol. Generally, drug companies try to avoid formulations at risk for dose dumping but see individual product labeling to be certain.

KEY INSTRUCTIONS COMMON TO ER/LA OPIOIDS

The FDA describes Key Instructions common to the class of extended release and long acting opioid analgesics. The following is a concise paraphrase of their complete list.

- Titrate individually to a dose with adequate analgesia and minimal adverse reactions
- Refer to product information for titration interval; it is product specific
- Monitor continually for pain control and adverse reactions as they may change
- Monitor for continued need
- For pain increase, identify the source in addition to adjusting dose
- When discontinuing, titrate downward gradually to prevent withdrawal. Do not stop abruptly
- ER/LA opioids are not for as-needed use, mild pain, short-term pain, or acute pain
- Solid dosage instructions
  - Swallow whole. Crushing, chewing, breaking, dissolving, cutting may cause overdose.
  - See specific product information to learn which capsules can be opened and sprinkled on food
  - Some ER/LA opioids when exposed to alcohol can produce rapid release and potential overdose
- Transdermal dosage instructions
  - Avoid heat. Monitor patients with fever for increased opioid exposure
  - Rotate location of application
  - See product information for possible dose reduction for hepatic or renal impairment

RELATIVE POTENCY TO MORPHINE AND USE WITH OPIOID TOLERANCE

Overview

Morphine is often the first step III opioid prescribed to treat chronic severe pain. Other options include oxymorphone, oxycodone, and buprenorphine. While the half-life of morphine is 1.5 – 7 hours, its
effects can increase even as the blood concentrations of the drug decline\textsuperscript{29}. Morphine binds to mu receptors, and is metabolized in the liver\textsuperscript{30}.

**Relative Potency to Morphine**
- Generally speaking it is important to see the specific drug information found in current product information for each opioid when converting between opioids.
- Incomplete cross-tolerance between opioids means that conservative dosing should be used when converting between opioids. Generally, halving the calculated comparable dose and titrating the new opioid as needed is recommended\textsuperscript{19}.

**Use in Opioid Tolerance**
- Generally speaking it is important to see the specific drug information found in current product information for each opioid regarding whether it describes strengths or a total daily dose that can only be used in opioid-tolerant patients.
- Or if it is to be used only in opioid-tolerant patients, at any strength or total daily dose

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**MRS. THOMAS - PRESCRIBING ER/LA OPIOIDS**

**Patient:** Mrs. Louise Thomas

A 58 y/o female with chronic neck pain.

**Review Mrs. Thomas' Pain History:**

Mrs. Thomas seeks pain medication for chronic neck pain that bothers her daily. She says that a combination of over-the-counter medications and immediate release opioids do not provide her with enough pain relief. She has experienced the neck pain for the past 3 years. In the first year, first-line therapies, including NSAIDS and physical therapy, were tried, but the pain responded only slightly and progressed instead of improving. Two years ago, she had a cervical discectomy for a herniated disc, followed by physical therapy, and continued an opioid pain medication plus acetaminophen. Neurological symptoms resolved but treatments only yielded some pain relief. Despite extensive diagnostic testing, a specific cause for Mrs. Thomas’ pain was not identified. The surgeon refused to continue the prescription after 3 months.

Her internist prescribed immediate release oxycodone since then. The pain is now constant and severe around half the time and occurs every day. The pain is worse at night and after work, and is described as a burning ache that bothers her every day. She says she would like to take additional oxycodone when the pain is intense, even though her internist warned her about the risks; she continues to follow her internist’s recommendations.

Diagnostic imaging of her cervical and thoracic vertebrae did not reveal any structural problems. Physical exam results suggest the possibility of mild nerve impingement.

Mrs. Thomas’ doctor prescribed extended release oxycodone and recommended she return to physical therapy.
Question: Based on what you know about Mrs. Thomas’s pain so far, what indications are there for prescribing ER/LA opioids? (Choose all that apply):

Choose all that apply
- Severe pain experienced daily
  - Feedback: Severe pain is one indication for ER/LA opioids
- Severe pain is experienced over half the time.
  - Feedback: Nearly constant or constant, severe pain is one indication for ER/LA opioids
- Non-responsiveness to first-line therapies
  - Feedback: Opioids are appropriate for pain conditions for which first-line therapies have been tried and demonstrated to be unsuccessful.
- She feels she needs to take a higher dose than prescribed due to unrelieved pain.
  - Feedback: The more constant pain relief from an extended-release opioid may provide her with fewer episodes of breakthrough pain.

DRUG INFORMATION FOR SPECIFIC ER/LA OPIOIDS

Opioids may differ in specific drug information and so it is essential to consult the product information for each opioid you prescribe. For example, for some drugs, the patient should always be opioid-tolerant before starting their use: patients should be opioid-tolerant before starting use of Transdermal fentanyl or ER hydromorphone. Some opioids are more vulnerable to dose dumping when exposed to alcohol, etc.

The drug information on the following pages is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics, which was released in 2013\(^\text{19}\). However, some of the information was derived from individual drug labels, as found on the FDA website through a searchable database (see Drugs@FDA resource) and many of these documents are from earlier dates. Hyperlinks to the drug label information are provided for a more thorough understanding of each drug. But Refer to current product information before prescribing any medication.

**BUPRENORPHINE**

Drug Information for Specific ER/LA Opioids: Buprenorphine

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics\(^\text{19}\):

<table>
<thead>
<tr>
<th>Buprenorphine</th>
<th>Transdermal System (Butrans®), 5 mcg/hr, 10 mcg/hr, 20 mcg/hr</th>
</tr>
</thead>
</table>

Product information dated 2010
Dosing Interval One transdermal system every 7 days
Key Instructions Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents,
and in mild to moderate hepatic impairment - 5 mcg/hr dose.

- When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose.
- Titrate after a minimum of 72 hours prior to dose adjustment.
- Maximum dose: 20 mcg/hr due to risk of QTc prolongation.
- Application
  - Apply only to sites indicated in the 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 a minimum of 3 weeks before reapplying to the same site.
  - Do not cut.
  - Avoid exposure to heat.
  - Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
- 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.

Specific Drug Interactions

Use in Opioid-Tolerant Patients Butrans 10 mcg/hr and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only.

- QTc prolongation and torsade de pointe.

Drug-Specific Safety Concerns

- Hepatotoxicity
- Application site skin reactions

Relative Potency To Oral Morphine Equipotency to oral morphine has not been established.

**FENTANYL**

**Drug Information for Specific ER/LA Opioids: Fentanyl**
The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

**Fentanyl**
**Transdermal System (Duragesic®), 12, 25, 50, 75, and 100 mcg/hr**

**Product document dated 2009**

**Dosing Interval** Every 72 hours (3 days)
Key Instructions

• Use product specific 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

Application

• 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.
• Titrate using no less than 72 hour intervals.
• Do not cut.

• Avoid exposure to heat.
• Avoid accidental contact when holding or caring for children.
• Dispose of 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 post-operative pain, including use after out-patient or day surgery.
• Management of mild pain.

Specific Drug Interactions

• CYP3A4 inhibitors may increase fentanyl exposure.
• CYP3A4 inducers may decrease fentanyl exposure.

Use in Opioid-Tolerant Patients

All doses of Duragesic are indicated for use in opioid-tolerant patients only.

• Accidental exposure due to secondary exposure to unwashed/unclothed application site.

Product-Specific Safety Concerns

• Increased drug exposure with increased core body temperature or fever.
• Bradycardia
• Application site skin reactions

Potency Relative To Oral Morphine

See individual product information for conversion recommendations from prior opioid.

HYDROMORPHONE HYDROCHLORIDE

Drug Information for Specific ER/LA Opioids: Hydromorphone HCL

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.
(Other Label Information)
Both product documents dated 2010

Hydromorphone Hydrochloride
Extended-Release Tablets (Exalgo®), 8 mg, 12 mg, 16 mg or 32 mg

Dosing Interval
Once a day

- Use the conversion ratios in the individual product information.
- Start patients with moderate hepatic impairment on 25% 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.
- Titrate using a minimum of 3 to 4 day intervals.
- Swallow tablets whole (do not chew, crush, or dissolve).
- Do not use in patients with sulfite allergy—contains sodium metabisulfite.

Specific Drug Interactions
None

Use in Opioid-Tolerant Patients
All doses of Exalgo are indicated for opioid-tolerant patients only.

Drug-Specific Adverse Reactions
Allergic manifestations to sulfite component.

Relative Potency To Oral Morphine
Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.

METHADONE HYDROCHLORIDE

Drug Information for Specific ER/LA Opioids: Methadone HCL
The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

Methadone Hydrochloride
Tablets (Dolophine®), 5 mg and 10 mg

Dosing Interval
Every 8 to 12 hours

- Initial dose in opioid non-tolerant patients: 2.5 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.
- High inter-patient 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 (Code of Federal Regulations, Title 42, Sec 8).

Specific Drug Interactions

- Pharmacokinetic drug-drug interactions with methadone are complex.
  - CYP 450 inducers may decrease methadone levels.
  - CYP 450 inhibitors may increase methadone levels.
- Anti-retroviral 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

Use in Opioid-Tolerant Patients

Refer to full prescribing information.

- 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.

MORPHINE SULFATE

Drug Information for Specific ER/LA Opioids: Kadian Morphine Sulfate

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

<table>
<thead>
<tr>
<th>Product document dated</th>
<th>2007</th>
</tr>
</thead>
</table>

Dosing Interval

Once a day or every 12 hours

- Product information recommends not using as first opioid.
- Titrate using a minimum of 2-day intervals.
- Swallow capsules whole (do not chew, crush, or dissolve).
- May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, 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.
- PGP inhibitors (e.g. quinidine) may increase the
absorption/exposure of morphine sulfate by about two-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

Product-Specific Safety Concerns
None

Drug Information for Specific ER/LA Opioids: Morphine Sulfate
The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

Morphine Sulfate
Controlled-release Tablets (MS Contin®), 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg

Dosing Interval
Every 8 hours or every 12 hours

Key Instructions
- Product information recommends not using as first opioid.
- Titrate using a minimum of 2-day intervals.
- Swallow tablets whole (do not chew, crush, or dissolve).

Specific Drug Interactions
PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.

Use in Opioid-Tolerant Patients
MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.

Product-Specific Safety Concerns
None

Drug Information for Specific ER/LA Opioids: Morphine Sulfate
The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

Morphine Sulfate ER
Capsules (Avinza®), 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg

Dosing Interval
Once a day

Key Instructions
- Initial dose in opioid non-tolerant patients is 30 mg.
- Titrate using a minimum of 3-day intervals.
- Swallow capsule whole (do not chew, crush, or dissolve).
- May open capsule and sprinkle pellets on applesauce for patients who cannot reliably swallow without chewing; use immediately.
- Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.

Specific Drug Interactions
- Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine.
- PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.

**Use in Opioid-Tolerant Patients**

90 mg and 120 mg capsules are for use in opioid-tolerant patients only

**Product-Specific Safety Concerns**

None

### Drug Information for Specific ER/LA Opioids: Morphine Sulfate ER-Naltrexone

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

<table>
<thead>
<tr>
<th>Product document</th>
<th>Morphine Sulfate ER-Naltrexone Capsules (Embeda®), 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>dated 2009</td>
<td>Once a day or every 12 hours</td>
<td>Key Instructions</td>
</tr>
<tr>
<td></td>
<td>• Initial dose as first opioid: 20 mg/0.8 mg.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Titrate using a minimum of 3-day intervals.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Swallow capsules whole (do not chew, crush, or dissolve)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PGP inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.</td>
<td></td>
</tr>
</tbody>
</table>

**Use in Opioid-Tolerant Patients**

Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only

**Product-Specific Safety Concerns**

None

### OXYCODONE HYDROCHLORIDE

**Drug Information for Specific ER/LA Opioids: Oxycodone**

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

<table>
<thead>
<tr>
<th>Product document</th>
<th>Oxycodone Hydrochloride Controlled-release Tablets (Oxycontin®), 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>dated 2011</td>
<td>Every 12 hours</td>
<td>Key Instructions</td>
</tr>
<tr>
<td></td>
<td>• Opioid-naïve patients: initiate treatment with 10 mg every 12</td>
<td></td>
</tr>
</tbody>
</table>
hours.
- Titrate using a minimum of 1 to 2 day intervals.
- Hepatic impairment: start with one third to one half the usual dosage.
- Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage.
- Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve).
- Take one 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.

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.

Product-Specific Safety Concerns
- Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet.
- Contraindicated in patients with gastrointestinal obstruction.

Relative Potency To Oral Morphine
- Approximately 2:1 oral morphine to oxycodone oral dose ratio.

OXYMORPHONE HYDROCHLORIDE

Drug Information for Specific ER/LA Opioids: Oxymorphone HCl

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

Opana ER

Product document dated 2010

Oxymorphone Hydrochloride

ER Tablet (Opana® ER), 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

Dosing Interval

Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.

- 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 patients over 65 years of age.

Key Instructions

- Swallow tablets whole (do not chew, crush, or dissolve).
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
- Titrate using a minimum of 2-day intervals.
- Contraindicated in moderate and severe hepatic impairment.

Specific Drug Interactions

- Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
**Use in Opioid-Tolerant Patients**

No product specific considerations.

**Product-Specific Safety Concerns**

None

**Relative Potency To Oral Morphine**

Approximately 3:1 oral morphine to oxymorphone oral dose ratio

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**TAPENTADOL**

**Drug Information for Specific ER/LA Opioids: Tapentadol**

The following information is from the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics:

**Nucynta ER**

Product document dated 2011

**Tapentadol**

Extended-Release Tablets (Nucynta® ER), 50 mg, 100mg, 150 mg, 200 mg, and 250 mg

**Dosing Interval**

Every 12 hours

• Use 50 mg every 12 hours as initial dose in opioid-nontolerant patients
• Titrate by 50 mg increments using a minimum of 3-day intervals.
• Maximum total daily dose is 500 mg
• Swallow tablets whole (do not chew, crush, or dissolve).

**Key Instructions**

• Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth.
• Dose once daily in moderate hepatic impairment with 100 mg per day maximum
• Avoid use in severe hepatic and renal impairment.
• Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol.
• Contraindicated in patients taking MAOIs.

**Specific Drug Interactions**

• Risk of serotonin syndrome
• Angioedema

**Use in Opioid-Tolerant Patients**

No product-specific considerations.

**Reason for visit:** Chronic lower back pain

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**MR. PARKER - DRUG INTERACTIONS**

**Patient:** Mr. Charles Parker

**Age:** 68 years old

**Reason for visit:*** Chronic lower back pain
Scenario: Recall Mr. Parker who re-injured his back 2 years ago, with inadequate response to NSAIDs (celecoxib) and acetaminophen, so he self medicated with immediate release oxycodone obtained from a friend.

Review Mr. Parker's Pain History:

History of Present Illness:
He re-injured his back 2 years ago lifting furniture, which exacerbated his lower back pain. For 2 months immediately after the re-injury, he received physical therapy and a prescription for oxycodone that was not prescribed again. He stopped exercising after the re-injury and has not resumed it since. Prior to that, he had a 25 year history of mild left lower back pain post MVA, managed by maintaining core body strength through exercise and with OTC NSAIDs, acetaminophen, and heat as needed. The pain has gradually worsened over the past 2 years, and has gotten especially bad recently. Pain worsens with walks of over one block, going down stairs, getting up after sitting long periods, lifting more than 10 pounds, and initially lying down. Sharp constant pain in left lumbosacral region after one of these triggering events, lasting up to an hour or two, sometimes radiating down left leg. Recently, he manages daily pain with prescribed celecoxib (or naproxen when he runs out), acetaminophen, and oxycodone, obtained from a friend.

Past Medical History
Medical Illnesses: 25 year history of lower back pain post MVA
Surgeries: Open vertebroplasty of L3-L4 25 years ago
Allergies: NKDA

Family/Social History
Relatives: Mother, age 76 Hypertension; Father deceased from lung cancer age 65
Occupation: Parking Garage Attendant
Marital/Family Status: Divorced; two estranged, grown children
Alcohol/Tobacco/Recreational Drug Use: He occasionally has a "couple of beers." Smokes cigarettes: pack and a half per day, 50 pack years

Current Medications
- Celecoxib: 100 mg bid, discontinued occasionally when he cannot afford it.
- Naproxen: 500 mg bid. Taken when he runs out of celecoxib or cannot afford it.
- Acetaminophen: 500 mg bid (“2 extra strength Tylenol per day”)
- Oxycodone: 10 mg immediate release oxycontin. Not prescribed for him; obtained from a friend. 1 to 2 capsules taken intermittently as needed for pain. He takes it two to three times per day now
- Other treatments: Dry heat for occasional muscle spasms from overuse

Past Medications
- Oxycodone: 20 mg immediate release taken for two months following surgery 2 years ago. Not refilled despite requests. 6 month taper.

In module 1, because his pain is chronic and severe and had not responded to other treatments, a decision was made to consider opioids. Because his pain is chronic, severe, and constant and his
risk for abuse is low, extended release formulations are being considered, after a stable dose of immediate release opioids is established.

**Question:** Are there any drug interactions, based on this history?

**Choose all that apply**

1. Yes, acetaminophen
   - Feedback: Incorrect
   - There is no interaction between ER/LA opioids and acetaminophen.
2. Yes, smoking tobacco
   - Feedback: Incorrect
   - There is no interaction between ER/LA opioids and tobacco.
3. Yes, moderate use of alcohol
   - Feedback: Correct
   - Alcohol can increase the plasma concentration of some ER/LA opioids. Individual product labeling should be consulted to determine this effect. Additionally, additive sedative effects of opioids plus alcohol, especially when dose is newly changed is a risk when driving, operating machinery or similar types of activities requiring alertness.

**OPIOID ROTATION AND CONVERSION**

**Reasons for Rotation/Conversion**
Rotation to a new opioid may be considered for the following reasons:

- Adverse effect or allergic response to another opioid
- Lack of or insufficient response with another opioid; however, adding a co-analgesic might be sufficient, due to genetic variability there is variable response to different opioids. Also, it may be due to tolerance developing or the dose required for a particular opioid exceeding maximum dose.
- Conversion from a short-acting opioid to a long-acting opioid to provide more stable analgesia as well as the convenience of fewer doses
- Conversion from one extended-release/long-acting opioid to another may be necessary due to adverse reactions, insufficient pain relief, or tolerance.

**Conversion Between Opioids Is Complex**
A new paradigm for converting between opioids has been proposed based on a review of the literature. It responds to the problem of incomplete cross-tolerance between opioids. That is, patients who have a certain level of tolerance to one opioid, often do not have the same level of tolerance to other opioids because of different molecular structure. So they are at risk for overdose if they are given an equivalent dose of the new opioid. They found that opioids and patient response to them are dissimilar enough that the patient needs to be treated as if they are opioid naive for the new drug and the dose should be titrated up carefully. Oftentimes, the final effective dose is the same for a patient with tolerance as for a patient who is not tolerant of opioids. Careful stepwise dose titration is needed because of the patient variability as well as variable pharmacokinetic and pharmacodynamic properties. Patients should be followed closely during all periods of dose adjustments as if they are a new patient.
The new paradigm for conversion to another opioid suggests that equianalgesic tables not be used due to safety considerations and variations between the medications and patients. Other considerations include:

- Meticulous monitoring and individual dose titration are indicated with any chronic opioid therapy.
- Take precautions by limiting prescriptions, patient education, or adjunct treatments to help prevent the patient from self-dosing to a dangerously higher dose.
- Consider consultation with a specialist when opioid conversion is needed.
- Patients who are not tolerant to opioids should not be prescribed ER/LA opioids.

POLL: WHEN CONVERTING A PATIENT FROM ONE OPIOID TO ANOTHER, DO YOU CONSULT WITH A SPECIALIST?

Poll Results:

1. Yes
   - 36% (208 votes)
2. No
   - 22% (127 votes)
3. I am the specialist
   - 18% (102 votes)
4. N/A
   - 23% (134 votes)

Total votes: 571

ROTATING OPIOIDS
One paradigm for rotating opioids that has been proposed, one that aims to avoid overdose, is as follows:

1. Start by titrating the original opioid downward by decreasing the current dose by ~10-30%. At the same time start the new opioid at a dose used for opioid naive patients or the lowest dose available for that formulation.
2. Next, slowly decrease the dose of the original total daily dose by ~10-25% per week and, at the same time, increase the dose of the new daily opioid dose by ~10-20%. The switch can occur within about 3-4 weeks.
3. Make sure to provide your patient with enough IR opioid during the rotation to prevent withdrawal or treat pain if the dosing proves insufficient. It is important the patient does not try to self medicate.
SUPPLEMENTING ER/LA OPIOID THERAPY

When to supplement:
- For breakthrough/incident pain
- When rotating ER/LA Opioids

Supplementing with Immediate-Release (IR) Opioids
It is essential that the provider weighs potential risks and benefits when prescribing an as-needed, immediate-release opioid in addition to the ER/LA opioid. In addition to risk of overdose, access to these short-acting drugs may increase the patient's risk of developing aberrant behavior, particularly for those already engaging in this behavior or at a higher risk for it. Those patients with a low risk for developing aberrant behavior can be prescribed a trial dose of the immediate release opioid. It is important to have routine follow-up and monitoring when prescribing the IR-opioid supplement. The provider should occasionally reassess the relative risks and benefits of the supplemental IR-opioid.

Supplementing with Non-opioids
When to use non-opioid supplements:

Consider for all patients taking opioids
A provider should consider both nonopioid drug therapies and nonpharmacologic treatments as other options to treating breakthrough pain and for opioid sparing, especially in at-risk patients:

Multimodal therapy. If opioids are needed, they should not be used alone to treat chronic pain.

- **Combine medications.** Prescribe opioids in combination with other effective medications (adjuvant) and non-pharmacological treatments to minimize the dose and increase effectiveness.
  - nonsteroidal anti-inflammatory agents
  - other non-opioid analgesics, e.g., acetaminophen, steroids
  - adjuvant medications, such as antidepressants, anticonvulsants, and muscle relaxants.
  - topical pain killers, for example, creams containing salicylate, topical NSAIDs, capsaicin, or counter-irritants like camphor, eucalyptus oil, and menthol or patches that contain lidocaine

NON-PHARMACOLOGICAL SUPPLEMENTS

*Include non-pharmacological treatment modalities.* Patients with chronic pain should receive multiple treatment modalities, including:

- Appropriate functional restoration
- Psychotherapeutic interventions
- Adjunctive non-opioid therapies
- Other interdisciplinary treatment [Strong recommendation; moderate quality evidence]
Other non-pharmacological treatments include:

- Surgery
- Therapeutic injections
- TENS units
- Mindfulness meditation: Currently receiving a lot of research support for its effectiveness in reducing pain levels and suffering
- Exercise: An important adjunct to any pain treatment. Carefully planned exercise can have both direct, physically mediated and psychologically mediated benefits.
- Smoking cessation: Should be pursued throughout treatment to reduce high pain intensity common in many smokers
- Sleep disturbances: Should be treated as they contribute to the cycle of chronic pain.
- Depression and anxiety: Mental health issues should be treated as they contribute to the cycle of chronic pain.
- Non-medical, complementary and alternative medical supports such as acupuncture.

**MR. PARKER - CONVERSION AND SUPPLEMENTATION**

**Patient:** Mr. Charles Parker  
**Age:** 68 years old  
**Reason for visit:** Chronic lower back pain  
**Scenario:** Recall Mr. Parker who re-injured his back 2 years ago, with inadequate response to NSAIDs (celecoxib) and acetaminophen, so he self medicated with immediate release oxycodone obtained from a friend.

**Review Mr. Parker's Pain History (repeated for convenience):**

**History of Present Illness:**
He re-injured his back 2 years ago lifting furniture, which exacerbated his lower back pain. For 2 months immediately after the re-injury, he received physical therapy and a prescription for oxycodone that was not prescribed again. He stopped exercising after the re-injury and has not resumed it since.

Prior to that, he had a 25 year history of mild left lower back pain post MVA, managed by maintaining core body strength through exercise and with OTC NSAIDS, acetaminophen, and heat as needed.

The pain has gradually worsened over the past 2 years, and has gotten especially bad recently. Pain worsens with walks of over one block, going down stairs, getting up after sitting long periods, lifting more than 10 pounds, and initially lying down. Sharp constant pain in left lumbosacral region after one of these triggering events, lasting up to an hour or two, sometimes radiating down left leg.

Recently, he manages daily pain with prescribed celecoxib (or naproxen when he runs out), acetaminophen, and oxycodone, obtained from a friend.
Past Medical History

Medical Illnesses: 25 year history of lower back pain post MVA
Surgeries: Open vertebroplasty of L3-L4 25 years ago
Allergies: NKDA

Family/Social History

 Relatives: Mother, age 76 – Hypertension; Father – deceased from lung cancer age 65
Occupation: Parking Garage Attendant
Marital/Family Status: Divorced; two estranged, grown children

Alcohol/Tobacco/Recreational Drug Use: He occasionally has a "couple of beers." Smokes cigarettes: pack and a half per day, 50 pack years

Current Medications

-Celecoxib: 100 mg bid, discontinued occasionally when he cannot afford it.
-Naproxen: 500 mg bid. Taken when he runs out of celecoxib or cannot afford it.
-Acetaminophen: 500 mg bid ("2 extra strength Tylenol per day")
-Oxycodone: 10 mg immediate release oxycontin. Not prescribed for him; obtained from a friend. 1 to 2 capsules taken intermittently prn pain. He takes it two to three times per day now
-Other treatments: Dry heat for occasional muscle spasms from overuse

Past Medications

-Oxycodone: 20 mg immediate release taken for two months following surgery 2 years ago. Not refilled despite requests. 6 month taper.

In module 1, because his pain is chronic and severe and had not responded to other treatments, a decision was made to consider opioids. Because his risk for abuse is low, extended release formulations were considered.

Extended release oxycodone (Oxycontin® extended release) was chosen because his pain responded well to oxycodone. He needs to be converted from immediate release to extended release form of this medication.

Considerations in prescribing this medication:

1. It is not necessary to lower the dose when converting from the immediate-release form of the opioid to the extended-release form of the same opioid. It would, however, be correct to reduce the dose if converting to a different opioid. Conversions between opioids of a different type generally require a dose reduction and should carefully follow recommended conversion protocols for the specific medication.

2. Conversion from an immediate-release opioid to the extended-release form of the same opioid can be done by giving the patient 50% of the current total daily dose every 12 hours, according to the NIH's Daily Med website.  
   It would, however, be correct to reduce the dose if converting to a different opioid. Conversions between opioids of a different type generally require a dose reduction and should carefully follow recommended conversion protocols for the specific medication.
3. Supplementation with opioid-sparing medications, such as acetaminophen is generally indicated when possible.

**CASE VIGNETTE: MRS. BENNETT**

**Instructions:** Please review this case by reading information in all tabs. Once you have completed your review, please proceed to the next page.

**New Patient**

**Name:** Mrs. Christine Bennett  
**Age:** 40 years old  
**Reason for visit:** History of crushed foot due to dropping weights while weight lifting and now has unresolved joint pain a year later  
**History of Present Illness:** One year history of severe right foot pain and moderate pain at other times while taking prescription NSAIDs. Takes immediate release oxycodone when pain flairs up to severe levels. Previously tried tramadol, however, pain was still moderate at rest. Her ability to walk has improved since the initial injury, but she still cannot put full weight on her foot. She walks carefully to avoid use of the painful joint and experiences very severe pain after walking on it fully for more than 10 minutes. The pain then lingers at the moderate to severe level for around an hour. She is losing sleep because she waits until the pain is severe to take oxycodone and the pain often wakes her in the middle of the night. She is interested in whether "stronger" opioids might help.

<table>
<thead>
<tr>
<th><strong>Vital Signs</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Height:</strong> 5'7&quot;</td>
</tr>
</tbody>
</table>

**Past Medical History**

**Medical Illnesses:** History of transverse fracture of right first metatarsal crushed foot while weight lifting and pain never completely resolve in first metatarsal/sesimoid joint - pain is partially managed with prescription NSAIDs (etodolac) and immediate release oxycodone as needed for daily bouts of severe pain.

**Alcohol/Tobacco/Recreational Drug Use:** None

**Family/Social History**

**Relatives:** Mother, age 76 -- Hypertension and hypothyroid; Father, deceased, age 65 -- myocardial infarction

**Occupation:** 4th grade teacher

**Marital/Family Status:** married; 1 daughter age 7

**Current Medications**

-Etodolac, scheduled use, but only moderate pain relief. Pain with this medication is mild to moderate at rest, but moderate to severe after using foot

Oxycodone, immediate release - 20 mg. Used prn severe pain. Reduces pain to mild.
Ice: Used after initial injury and during flareups helps better than heat

Allergies: NKDA.

Past Medications
Tramadol - 50 mg 4 times per day - Pain was still moderate most of the time so this was discontinued
She tried acetaminophen, but says it bothered her stomach.

Labs
WNL. Drug screen negative except for expected evidence of her intermittent use of oxycodone.

Imaging
Arthrosis of right first metatarsal-sesamoid joint with osteophytes and non-uniform loss of joint space, sesamoid flattening, and subchondral sclerosis

Physical Exam
Extremities: Right foot: Hard, slight swelling at right first metatarsal-sesamoid joint.
Provocation: Severe pain elicited with full weight on joint lingers for an hour or more.

MRS. BENNETT - PATIENT PROVIDER AGREEMENT

Mrs. Bennett, who is being treated for moderate to severe pain from a severely inflamed frozen shoulder is being prescribed long-acting morphine sulfate capsules. She was assessed to have a low risk for opioid addiction or misuse.

Question: Is a written patient-provider agreement indicated?

Choose one
1. Yes, written patient-provider agreements are good risk management with all patients on chronic opioid therapy.
   - Feedback: Correct
   - Yes, written patient-provider agreements are good risk management with all patients on chronic opioid therapy. Even patients who start with low risk of addiction can develop opioid addiction. Written agreements can actually add to rapport with the patient because they demonstrate care and caution on the part of the provider.
2. No, written patient-provider agreements are not needed because she is low risk.
   - Feedback: Incorrect
   - Written patient-provider agreements are good risk management with all patients on chronic opioid therapy. Even patients who start with low risk of addiction can develop opioid addiction.
3. No, because she is just starting chronic opioid therapy. To maintain rapport with the patient, they should be added only if she demonstrates aberrant behavior.
   - Feedback: Incorrect
Written agreements can actually add to rapport with the patient because they demonstrate care and caution on the part of the provider.

MRS BENNETT - POTENTIAL TREATMENT CHOICES

Ms. Bennett
In this section you will choose treatments in order to provide Mrs. Bennett with an appropriate multi-disciplinary approach to treating her pain.

Review the following potential treatments, considering what treatments you would recommend for Mrs. Bennett at this time. (More than one might be appropriate. Some might be inappropriate at this time.)

MRS BENNETT - PHARMACOLOGICAL TREATMENT

Ms. Bennett
NSAIDs
NSAIDs are the first line of treatment for musculoskeletal pain. Ms. Bennett is already taking a prescription NSAID on a scheduled basis and it is reducing her pain to the mild to moderate level much of the time. However, she still often has pain that is moderate to severe or even severe on a daily basis so this medication alone is not enough. The benefits vs risks of side effects of NSAIDs need to be considered.

Adjunctive Pain Medications
• Acetaminophen is commonly used as an adjunctive medication in chronic pain, but Ms. Bennett has tried using this and found it induced nausea.

Chronic Opioid Therapy
Ms. Bennett is already taking oxycodone 20 mg prn severe pain. This results in her spending much of her time in moderately severe, constant pain and regularly being awakened at night with the pain. These conditions are sufficient to refer her to a pain specialist who is REMS trained in prescribing extended-release/long acting opioids to see if these might help her and be worth the risks.

MRS. BENNETT - NON-PHARMACOLOGICAL TREATMENT

Physical Therapy
Physical therapy is an excellent treatment choice, to maintain or even improve Mrs Bennett’s range of motion and strengthen supporting muscles.

Psychiatry/Counseling
It is an excellent choice to think about whether Psychiatry/Counseling is indicated. Living with this much pain for a long period of time can be depressing. A brief screening for depression is a good idea. If she does have depression, you can determine whether it is something that can be addressed in your practice or requires a referral.
Exercise
She can do exercises at home that maintain her range of motion. She can use a little heat, such as a warm shower, before doing the exercises and follow with ice afterward.

MRS. BENNETT - ER/LA OPIOIDS TITRATING TO DOSE
Mrs. Bennett
A year following her initial injury, Mrs. Bennett, was referred to a pain specialist for moderate to severe pain from foot arthrosis in a toe joint. The specialist recommended that she be prescribed long-acting morphine sulfate capsules.

Additional notes from the specialist state the following: The following disciplines might be considered for inclusion in Mrs. Bennett's treatment plan: Consultations with the following specialties might help reduce Mrs. Bennett's pain and minimize her opioid dose: Rheumatology could be consulted for best treatment of the arthrosis. She could be evaluated by a surgeon for possible joint replacement. Physical therapy treatments and prescribed exercises could help minimize/prevent secondary pain from compensating for the pain in her foot. Podiatry might help in fitting her with the most supportive shoe possible.

Mrs. Bennet had been taking a moderately low dose of immediate-release oxycodone (20 mg as needed for pain, which ended up being nearly every night and some days) when first line therapies were not effective, and now needs to be converted carefully to long-acting morphine sulfate. The risk evaluation and mitigation strategy (REMS)-trained pain specialist follows product recommendations for conversion and starts titrating to an effective dose.

Question: How long should the specialist wait between doses before moving up to the next dose?

Choose one
1. Every 12 hours
   - Feedback: Incorrect
   - Wait at least 3 days before each dose increase.
2. At least 1 day
   - Feedback: Incorrect
   - Wait at least 3 days before each dose increase.
3. At least 2 days
   - Feedback: Incorrect
   - Wait at least 3 days before each dose increase.
4. At least 3 days
   - Feedback: Correct!
   - Wait at least 3 days before each dose increase.

MRS. BENNETT: OPIOID ADVERSE EVENT
Mrs. Christine Bennett, who now has severe pain in her foot from arthrosis after a toe fracture, comes into your office saying the pain was so bad this morning after walking to work that she took an extra capsule of her extended-release morphine sulfate. When the nurse took her vitals, respiration was 12
per minute. She immediately calls you and you repeat the measure and find that her respirations are down to 10 per minute.

**Question:** Her respirations now fall to 7 per minute. What should you do immediately in response?

**CORRECT ANSWER:**
First, have staff contact Emergence Medical Services. Next, to reverse clinically significant respiratory depression, use the opioid antagonist naloxone. Follow protocol (described in Weighing Risks module) to support vital functioning and monitor.

**SUMMARY AND KEY POINTS**

- Use written and signed patient-provider agreements to facilitate safe and effective opioid treatment
- Understand and adhere to general and specific drug information, when choosing the appropriate ER/LA opioid and dosing
- Provided appropriate patient education to encourage and support safe and effective treatment
- Understand how to rotate and convert between specific opioids safely and effectively when needed
- Supplement ER/LA opioids with other medications and nonpharmacologic treatments in order to spare the dose as much as possible
- Know the signs of respiratory depression and that it is immediately life threatening and how to treat it

**RESOURCES AVAILABLE THROUGH THIS MODULE:**

- **Drugs@FDA: Searchable Database of FDA Approved Drugs**
  A searchable database from the FDA of FDA-approved drugs. This database also includes product label information.
- **ER/LA Opioid Analgesics REMS**
  Website for "The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy." Sections include Important Safety Information, Medication Guides, and U.S. Prescribing Information for each ER/LA opioid.
- **FDA announces safety labeling changes and postmarket study requirements for opioids**
  FDA News Release 8/18/2016: FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics. New boxed warning to include neonatal opioid withdrawal syndrome.
- **FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics**
  Specific Drug Information for ER/LA Opioid Analgesic Products
- **Medication Guides for ER/LA Opioids covered under REMS**
  List of all ER/LA opioids covered by REMS and their corresponding medication guide and prescribing information.
- **TIRF Opioids REMS Access**
  Educational program for Transmucosal Immediate Release Fentanyl REMS
REFERENCES USED IN THIS MODULE:


