Chapter 7: Risk Evaluation Mitigation Strategy (REMS)
Extended-Release Long-Acting (ER/LA) Opioid Analgesics

3 CE Hours

By: Elite Staff

Learning objectives

Upon completion of this course, the participant will be able to:
- Explain the reasons this risk evaluation mitigation strategy (REMS) was developed.
- Compare characteristics and risks of immediate-release (IR) versus extended-release (ER) opioids.
- Evaluate the benefits and risks of ER/Long-acting (LA) opioid therapy according to US Food and Drug Administration (FDA)-approved criteria.
- Identify characteristics that suggest a patient is a good or poor candidate for opioid treatment.
- Assess the nature and underlying cause of the patient’s pain according to REMS-compliant standards.
- Describe three complications associated with dental patients who are chronic opioid users.
- List written agreements between the prescriber and patient that should precede opioid treatment.
- Explain the need for ongoing monitoring and re-evaluation of all patients treated with opioids.
- Inform patients and caregivers how to take prescriptions safely and the risks associated with their use.
- Explain the function of a Patient Prescriber Agreement (PPA).
- Recognize signs of opioid diversion, nonmedical use, abuse, and addiction.
- Safely modify dosage and discontinue use of ER/LA opioid.
- Explain the significance of “Elements to Assure Safe Use” (ETASU) for prescription opioid abuse.
- Inform patients about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Locate and refer to accurate up-to-date product specific drug information for prescribed ER/LA opioids.
- List the primary objectives for REM-compliant prescriber training.
- Describe mandatory training, patient education, and clinical practice elements of the class-wide REMS for prescribers.

Introduction

Under new safety guidelines, long-acting and extended-release opioids are subject to a formal class-wide Risk Evaluation and Mitigation Strategy (REMS). This course provides training in REMS-compliant use of these drugs, collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics, or ER/LA opioid, and including the following branded and generic drug products:

- Extended release, oral dosage forms containing:
  - Hydromorphone.
  - Morphine.
  - Oxycodone.
  - Oxymorphone.
  - Tapentadol.
- Fentanyl- and buprenorphine containing transdermal delivery systems.
- Methadone tablets and solutions that are indicated for use as analgesics.

Extended-release and long-acting (ER/LA) opioid analgesics are highly addictive, potent pain medications primarily indicated in the treatment of chronic conditions with moderate-to severe persistent pain. While these medications provide very effective pain management, prescription opioid abuse has emerged as a major public health problem, posing serious risks associated with their potential for diversion and misuse. Many ER/LA prescriptions opioids find their way to individuals without prescriptions who use them in a way that increases the potential for adverse effects, including addiction and overdose. As the number of opioid prescriptions has increased, so has the illegal supply of prescription opioids to people without prescriptions. Individuals who use opioids illegally are at higher risk of adverse effects and lethal overdose than individuals who use the drug as prescribed. When prescription drugs appear to pose a disproportionately high risk-to-benefit ratio, the Food and Drug Administration (FDA) studies the drug or class of drugs to assess if the medication requires additional safety measures in the form of a Risk Evaluation and Mitigation Strategy (REMS). REMS is a formalized risk management plan that provides additional drug prescribing information to identify and manage risk factors associated with a drug’s use, with the intention of reducing their potential for adverse effects, injury, and death.

REMS-compliant training

In 2012, after a comprehensive review of the data, the FDA approved a class-wide REMS for ER/LA opioids. The main objective of the REMS is reducing the potential for serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while ensuring that patients with legitimate need for these drugs continue to have access to them. Its main component is mandatory prescriber training to facilitate appropriate ER/LA opioid-prescribing practices, reducing potential risks of use and increasing patient safety.

Under the new class-wide guidelines, all ER/LA opioids require a REMS, and all DEA-registered prescribers of Schedule II and III controlled substances (which include the class of ER/LA opioids addressed in this REMS) must complete REMS-compliant training to maintain licensing. This continuing education activity was developed according to standards established by the FDA and specified in the REMS Blueprint for Prescriber Training, and in compliance with state and federal professional continuing education requirements for...
dentistry. It fulfills three credits of coursework in ER/LA Opioid Risk Evaluation and Mitigation Strategies. [1]

Approximately 320,000 healthcare professionals prescribe ER/LA opioid analgesics in the United States. Of these prescribers, dentists may be particularly well suited to educating patients about opioid risks and potential for abuse and recognizing characteristics of drug abuse or addiction in patients. [2] Dentists are in a key position to communicate opioid risks to patients and intervene if abuse is suspected, not only because they see patients relatively frequently compared to other healthcare providers, but also because many patients have their first experience with an opioid painkiller at the dentist—typically for post-surgical pain—at a relatively young age. An American Dental Association study found that 18- to 20-year-old patients reported the pain medication prescribed to them after wisdom tooth removal was their first time taking an opioid. [3] Dentists can use this opportunity as a teaching moment, to discuss risk mitigation strategies, including correct disposal of unused medication.

Dentists can play an important role in reducing the illegal supply of drugs simply by adjusting their own prescribing practices, and explaining the risks of sharing or selling excess prescription medication for nonprescription use. The ER/LA opioid REMS provides information and tools to assist the prescriber in:

- Clarifying the potential benefits and risks of opioid therapy.
- Specifying safe, responsible prescribing practices.
- Learning to recognize signs of opioid diversion, abuse, and addiction.
- Anticipating and addressing potential adverse effects.

The REMS information in this course was accurate at the time of writing, but, like all medical guidelines and policies, the content is subject to revision according to new evidence-based research findings. Please refer to the links and references provided to ensure the information is up-to-date.

### Prescription opioids

Opioids are pain relievers derived naturally from the opium poppy, or synthetically from substances that mimic its effects. They are the source material for many narcotics (drugs that produce sedating effects) including codeine and morphine. All prescription opioids are extremely effective at relieving pain, and have sedating effects due to their depression of central nervous system (CNS) function. They are highly habit-forming, particularly if used over long periods, and are more commonly abused than any other prescription substances. Some of the most commonly prescribed opioids are codeine, hydrocodone (e.g., Vicodin®), oxycodone (e.g., OxyContin®, Napp Pharmaceutical Holdings Limited; Percocet®, Endo Pharmaceuticals, Inc.), and morphine (e.g., Kadian®, Actavis Elizabeth L.L.C; Avinza®, King Pharmaceuticals R&D Inc.).

While opioids (codeine and morphine) and nonopioids [acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs)], are both classified as pain relievers, opioids are narcotic analgesics. Narcotic analgesics are much stronger than non-narcotic analgesics. Opioids are able to provide a much greater degree of pain relief than nonopioids because they directly attach to pain receptors throughout the nervous system, in the brain and spinal cord, as well as the gastrointestinal tract and other organs. Once attached to receptors, opioids trigger a range of effects, including reduced pain, increased drowsiness, mental confusion, nausea, and constipation. Fatality most commonly results when excessive amounts of the drug are consumed, causing shallow respiration, and eventual death.

### Increased risk of ER/LA opioids

Prescription opioids are available in pills, liquids, and skin patches, as either immediate-release (IR) or ER (extended release) products. Examples of opioid analgesics formulated as IR and ER products include hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. (Note: some long-acting opioid analgesics (e.g., methadone), have a longer period of action because of the inherent characteristics of the drug substance, which stays longer in the body, and not because of special design features of the product formulation.)

Improper use of any opioid can result in addiction, overdose, and death. This risk is magnified with ER/LA opioid medications. The amount of opioid analgesic contained in an ER tablet can be much greater than the amount in an IR tablet, due to the larger amount of active ingredient contained an ER dose, which is designed to release the drug in a sustained manner over an extended period.

Immediate-release (IR) opioids release the medication more rapidly, and must be taken more frequently to maintain analgesic effects.

### Scope of nonmedical use and abuse

While opioids provide very effective pain management, prescription opioid abuse has emerged as a major public health problem, posing serious risks due to the potential for drug diversion and misuse. Based on 2009 and 2010 national survey data:

- Up to 23% of prescribed opioid doses are used nonmedically, or about 1 out of every 25 prescriptions written. [4]
- More than 35 million Americans age 12 years and older used an opioid analgesic for nonmedical use some time in their life—an increase from about 30 million in 2002. [5]
- Almost 2 million people in the United States meet the criteria for prescription opioid abuse or dependence. [6]

The number of opioid prescriptions has risen sharply in recent years, primarily due to their increased use in chronic pain management. Between 1991 and 2010, opioid prescriptions grew in number from about 75 million to 209 million. [7] The risks associated with more widespread nonmedical use are reflected in rising numbers of postmarket reports of nonmedical opioid-related adverse events and death due to accidental overdose. Although rates of overdose have increased for other drugs, including cocaine and heroin, the most dramatic increase has been observed with prescription opioid medications. [8]

### Sources of misused prescription opioids

A large-scale study of prescription opioid abusers (those who use opioids without a valid prescription) identified the following sources for nonmedical drug use: [9]

- 18% of all prescription opioid abusers obtained the medication legally from a single prescriber.
- More than 17% of opioid abusers used medication of their own kept from a previous prescription for a valid medical complaint.
- 55% of all prescription opioid abusers obtained the medication free from a friend or family member.
- 5% of opioid abusers took the drug from a friend or family member without that individual’s knowledge or permission. [9]
- Almost 10% of abusers purchased the drug from a family member or friend who had a supply remaining from an old prescription. [9]
- Prescription opioids provided by friends or relatives were obtained from a single prescriber more than 80% of the time. [10]
- Almost 5% purchased the opioid from a dealer who was known to the purchaser in some cases, but in other cases was a stranger. [9]
Responsible prescribing practices

Current prescribing practices fuel a black market of surplus prescription opioids, with increasing numbers of people engaging in nonmedical drug use or diversion. Overprescribing occurs when prescriptions are written for quantities greater than needed to treat the patient’s pain, or in a stronger dosage than required. Over-prescribers may choose an ER/LA opioid when an IR opioid will do.

A 2008 study showed that 72% of respondents who were prescribed an opioid by their dentist had leftover medication, and 71% of patients with leftover medications did not dispose of them. Given these statistics, it is easy to see how such a vast number of prescription drugs find their way into public use.

Research findings recommend clinicians prescribe no more than the number of doses recommended by the ADA. In most cases, this would translate to a prescription for no more than a few days of medication.

REMS training

REMS-compliant training for prescribers stresses risk reduction through well-designed assessment and implementation tools, careful monitoring, periodic evaluation, better-educated prescribers, and more informed patients. The training component of the ER/LA opioid REMS defines the prescriber’s professional responsibilities and obligations to the patient regarding patient assessment and management, and prescriber-patient communication (also referred to as counseling).

Patient assessment

Patients require a thorough dental examination and appropriate diagnostic testing to identify and evaluate their current state of health and underlying pain condition. Prescribers should document detailed information regarding the nature and intensity of the pain, current and past treatments for pain, underlying or coexisting diseases or conditions, and the effect of the pain on physical and psychological function.

Any prescriber evaluating a patient for opioid treatment must assess the patient’s risk of substance misuse, abuse, or addiction based on a detailed patient history, including history of substance abuse, disclosure of psychosocial risk factors, and relevant family history. If no information is available, the prescriber should collect this information using intake forms and further discuss them with the patient to establish documentation of the current condition to serve as a basis for treatment. All information used for assessment purposes should be documented in the dental record.

Dentists have a responsibility to identify patients with substance abuse issues due to the increased risk they pose for adverse events due to drug interaction or overdose. A patient’s self-reported medical history is unlikely to provide information indicating excessive drug use; nonetheless, intake forms should include a section with relevant questions, and dentists should raise the issue with patients in the context of protecting their welfare and ensuring their safety in dental treatment.

All patients should be asked what pain relievers they have used in the past; how effective they were; and what side effects, if any, occurred. Even if a patient is not truthful about drug use on the medical history, it is a good starting point for a discussion about pain medication.

Certain patient characteristics are correlated with abuse, including a history of substance use or certain psychological conditions. Individuals at increased risk for opioid abuse include patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Brief clinical assessment instruments (e.g., the Opioid Risk Tool (ORT) or Screener and Opioid Assessment for Patients with Pain (SOAPP®-R)) can be used to classify patients according to risk of potential for opioid abuse or addiction prior to being prescribed opioids.

Evaluating treatment options

Prescribers need to evaluate the benefits and potential risks of ER/LA opioid analgesic treatment, to provide the appropriate, effective pain relief without unnecessary drug-related risks.

Risks include:
- Mild to severe adverse effects.
- Death due to lethal overdose or other opioid-related complications.
- Diversion for nonprescription use.
- Physical tolerance, dependence, and addiction.
- Drug-drug interaction.

ER/LA opioids are not appropriate for many types of pain. Dentists should prescribe the form of medication best indicated by patient symptoms. ER/LA opioids are:
- Not intended for acute pain, pain that is mild or not expected to persist for extended periods, or for use on an as-needed basis.
- Only indicated in the management of moderate to severe pain, when a continuous administration (24 hours a day) of opioid analgesic is needed over extended periods.

Due to ER/LA opioid risks, alternative treatments, including IR opioid formulations or nonopioids, should always be the first option for addressing pain. These alternatives are only preferred, however, if they are able to relieve the patient’s discomfort. If opioids must be avoided, a long-acting anesthetic (e.g., bupivacaine) can be used to address localized pain for a longer period.

Nonopioid pain relievers, including NSAIDs, do not produce tolerance or physical dependence and are not associated with abuse or addiction. However, the nonopioid pain relievers have an upper threshold (ceiling effect) where additional medication will not produce additional analgesic effects. This ceiling effect makes nonopioids inappropriate for severe pain. NSAID analogesics can be very effective, however, in post-operative or prophylactic use for moderate pain. Studies comparing patients using NSAIDs and opioids following dental implant surgery reported some patients found ibuprofen and naproxen, taken for an average period of 4 to 6 days, as effective as opioid analogesics in addressing postoperative symptoms of sensitivity or pain.

Patients who have moderate-to-severe pain that affects functioning or quality of life, and present with a favorable risk-benefit balance are the most likely candidates for opioid therapy. All patients receiving opioids must be monitored for signs of misuse, abuse, and addiction. A history of substance abuse does not prohibit treatment with ER/LA opioid.
If the patient and pain assessment support the use of opioid therapy, the dental records must document the presence of one or more recognized dental indications for use of an opioid or other controlled substance.

**PATIENT MANAGEMENT**

Before initiating treatment, the prescriber and patient must establish formal treatment parameters in writing, signed by both parties to signify agreement to the Treatment Plan and provide Informed Consent. While this is standard practice with any patient, prescribers using ER/LA opioids or IR opioid treatment for an extended period must establish well-defined analgesic and functional goals for therapy, periodically evaluating pain control, functional outcomes, the frequency and intensity of side effects, and health-related quality of life.

### Establishing a treatment plan

A formal written Treatment Plan should state criteria and objectives for determining treatment success (e.g., targeted pain relief and improved oral-facial, physical, and psychosocial function), and indicate if any further diagnostic evaluation or other treatments are planned.

After treatment begins, the prescriber should assess and adjust drug therapy according to the patient’s needs. Other treatment modalities or a rehabilitation program may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

### Informed consent

The practitioner should discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient, or with the patient’s surrogate or guardian if the patient is incompetent or a minor. Ideally, the patient should receive prescriptions from no more than one dental care practitioner and one pharmacy. If the patient has a history of substance abuse, the Informed Consent must address the possibility that opioid treatment could trigger a relapse.

### Patient prescriber agreements

Prescribers may require a Patient Prescriber Agreement (PPA) for patients posing an elevated risk of diversion or misuse. PPAs are agreements signed by the prescriber and patient before treatment begins. They document that patients and caregivers understand the goals and risks of treatment, and provide written acknowledgment that the patient understands how to use the medication safely and correctly, and agrees to take the prescription only as directed.

Prescribers treating current opioid users or patients with a history of substance abuse, may require the PPA spell out additional patient obligations, including commitments to return for follow-up visits, safeguard medication, comply with monitoring mechanisms, and the circumstances under which drug therapy may be discontinued, including violation of the Agreement.

### Documentation

The dental office must maintain accurate and complete documentation throughout treatment. Patient records must include:

- Medical history and physical examination.
- Diagnostic, radiographic, therapeutic, and laboratory results.
- Evaluations and consultations.
- Treatments and treatment objectives.
- Discussion of risks and benefits.
- Medications (including date, type, dosage, and quantity prescribed).
- Instructions and agreements.
- Periodic reviews.

Documentation must be current, readily accessible for review, and maintained in a recognized SOAP (Subjective, Objective, Assessment, Plan) format.

### Ongoing assessment and reevaluation

Once a patient begins treatment with prescribed ER/LA opioids, ongoing evaluation of treatment benefits and risk should include patient assessment of the following factors:

- Quality of pain relief.
- Nature and severity of side effects.
- Changes in patient tolerance to dosage.
- Changes in patient symptoms.
- Abuse-related behaviors.

If the patient exhibits aberrant behaviors (e.g., lost prescriptions, unsanctioned dose escalations) predictive of abuse, the prescriber should review the treatment plan and consider modifying the dosage, consider patient co-management or referral to a specialist, and/or consider the option of discontinuing opioid therapy. Even in the absence of risk-related behaviors, prescribers must reevaluate the continued need for opioid analgesic treatment for all patients at reasonable intervals, reviewing and adjusting treatment according to changes in the patient’s underlying medical condition and clinical presentation over time.

The practitioner’s evaluation of progress toward stated treatment objectives is the determining factor in continuation or modification of therapy. Objectives used as evaluation criteria include decreased pain intensity, improved physical and/or psychosocial function, a reduced need for healthcare resources, and ability to resume normal daily activities. If a patient is not meeting anticipated benchmarks or progressing toward treatment goals, the prescriber should investigate possible causes, and incorporate the findings into a revised Treatment Plan.

### Complications

Prescribers should be able to anticipate and manage common treatment complications, including drug interactions, associated with their use. To do so, they must be familiar with contraindications and adverse effects associated with ER/LA opioids. REMS-compliant clinical class-wide and drug-specific ER/LA opioid reference guides containing detailed information regarding potential risks of use, and strategies to address those risks, can be found in the tables at the end of the course.
Contraindications
ER/LA opioid analgesics are contraindicated in patients:
- With a known hypersensitivity to any of the components of ER/LA opioid drugs.
- With significant respiratory depression.
- With acute or severe bronchial asthma.
- Who have or are suspected of having paralytic ileus.
Some ER/LA opioids are contraindicated for use in patients who are nonopioid tolerant.

Drug interactions
Drug-drug interaction profiles vary among different ER/LA opioid products. Ensuring patient safety requires that the prescriber to have a working knowledge of the potentially harmful opioid-drug interactions listed below, and their underlying pharmacokinetic and pharmacodynamic mechanisms:
- Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
- When combined with alcohol, some ER opioid formulations rapidly release the drug (dose dump), causing blood opioid levels to increase quickly.
- Using opioids with monoamine oxidase inhibitors (MAOIs) may result in:
  - Respiratory depression.
- With a known hypersensitivity to any of the components of ER/LA opioid drugs.
- With significant respiratory depression.
- With acute or severe bronchial asthma.
- Who have or are suspected of having paralytic ileus.

Adverse effects
The most serious adverse effects of ER/LA opioids are associated with CNS depression, which causes sedating effects that can slow respiration to a life-threatening degree in seconds. This effect is magnified when opioids and alcohol are combined. Other potentially fatal adverse effects include apnea, circulatory depression, and hypotension.

Common ER/LA opioid side effects include constipation, gastrointestinal distress, nausea, vomiting, somnolence (sleepiness), dizziness, confusion, vomiting, pruritus (itching), headache, dry mouth, asthenia (weakness), and sweating. One of the most common effects of opioid ingestion is slowed gut motility, making constipation an almost guaranteed side effect of chronic opioid use. Prescribers can anticipate and address this potential problem by providing patients the option of a stool softener, or other laxative measures, along with the prescription.

Excessive opioid use can cause severe constipation, hemorrhoids and rectal pain, and bowel obstruction or rupture, among other serious and fatal adverse effects. Spinal administration may reduce the risk of constipation, as spinal opioid receptors do not appear to inhibit intestinal motility to the same degree as other administration sites.

Other less commonly reported adverse effects include:
- Erythema (redness) and rash at application sites for transdermal buprenorphine and fentanyl products.
- Hyperalgesia, or increased pain sensitivity, associated with long-term, high-dose opioid use, and characterized by lack of relief or an increase in degree of acute pain, despite the administration of higher opioid doses.
- Liver and kidney damage from high dosage use.
- Death, especially in children, due to accidental exposure.
- Torsades de pointes, a severe arrhythmia (irregular heartbeat) in patients treated for pain with large multiple daily doses of methadone, or maintenance treatment for opioid addiction.

Mandatory adverse event reporting
All members of the office, organization, or clinic are required to report any suspected adverse effects in patients using ER/LA opioids to the FDA.

Healthcare facilities should establish and implement policies for reporting adverse events in a nonpunitive environment.

Prescribers should emphasize to patients the importance of reporting any adverse effects or side effects they experience while taking the medication to the prescriber.

Prescribers and patients can report adverse events related to a prescribed ER/LA opioid to FDA's MedWatch Reporting System by calling 1-800-FDA-1088 (1-800-332-1088), or online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

DOSAGE AND ADMINISTRATION
ER/LA opioid formulations have product-specific dosage and administration instructions. Prescribers should instruct patients in how to measure doses correctly (e.g., using a measuring teaspoon, rather than a dining teaspoon, because it holds a standardized volume of liquid that is consistent for all measuring teaspoons, rather than a dining teaspoons vary significantly in size), and refer to the full product-specific prescribing information regarding specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole. This formulation must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms causes the rapid release and absorption of a potentially fatal amount of the drug. Patients who have difficulty swallowing their medication whole can refer to product-specific instructions for ways to consume oral products safely in another manner.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated due to a risk of choking or lethal overdose. Patients should avoid direct external heat sources to transdermal application site and surrounding area, as any external heat, as well as fever or exertion, can increase absorption of the opioid to toxic levels. Transdermal products with metal foil backings are not safe for use during MRI (magnetic resonance imaging).
Opioid tolerance

It can be very difficult to manage pain in chronic opioid users, whether they are patients with prescriptions using the drugs legally in doses known to the dentist, or users without prescriptions who hide the information. Individuals who take regular, daily, around-the-clock opioids (e.g., prescription patients with chronic pain or heavy nonprescription users) are likely to be opioid-tolerant after taking the drug for an extended period, meaning they require larger doses of the opioid to experience the same degree of pain relief. Given enough time, increased tolerance to an opioid’s analgesic effects is inevitable.

Knowledge of the patient’s history of and current use of opioids are critical to patient safety, as many types of ER opioids, such as hydromorphone and transdermal fentanyl, are only appropriate for opioid-tolerant patients. The amount of fentanyl in a dose of Fentora® (Cima Labs, Inc), for example, is large enough to cause lethal respiratory depression in a nonopioid-tolerant person. Prescribers must understand opioid tolerance criteria, as defined in the product-specific labeling, and be aware what products and doses are indicated for use with opioid-tolerant patients only.

Prescribers are responsible for knowing drug and dose indications for use in opioid-tolerant patients. Formal guidelines for defining opioid tolerance vary by particular drug and dosage. The following list shows criteria for opioid tolerance with these specific opioid formulations, or any equianalgesic opioid dose (one that provides equivalent pain relief). All drugs are taken for at least 1 week:

- 60 mg/day oral morphine, or the equivalent for at least 1 week.
- 25 mcg transdermal fentanyl/hour.
- 8 mg oral hydromorphone/day.
- 25 mg oral oxymorphone/day.

Prescribers are responsible for implementing REMS-compliant drug-specific measures to safely modify dosage, when necessary. Prescribers should be aware that:

- Dose selection is critical, particularly when initiating therapy in opioid nontolerant patients.
- Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients.

Dependence and addiction

Physical dependence is a virtually certain consequence of chronic opioid use. Many users progress to addiction, defined by a psychological/emotional dependence on the drug, as well as a physical need. According to the 2010 National Survey on Drug Use and Health, many opioid addicts are chronic users obtaining the medication through valid prescriptions. Among chronic pain patients receiving long-term opioid therapy, findings showed: [19]

- Addiction rates 4 × higher than the general population.
- 80% of patients reported at least one lifetime aberrant drug behavior (e.g., request for early refills, unauthorized dose escalation, purposely self-over-sedating, using opioids for nonpain-related reasons, or feeling intoxicated from opioid administration). These individuals were far more likely to be opioid addicts than chronic pain patients who did not engage in these behaviors.

Abuse

Opioid abuse poses unique challenges for pain management. Dental professionals must ensure that the analgesic effects of the drug are sufficient, without exposing the patient to any unnecessary risks. Risks and treatment concerns are an issue for patients in recovery as well as current drug users. Patients with a history of substance abuse, as well as patients who currently abuse substances, were former abusers, are in drug-free recovery or rehabilitation, or are in treatment programs that administer methadone or buprenorphine to recovering addicts, may be at increased risk of adverse effects. [20] If the patient is in recovery for opioid abuse, administering or prescribing an opioid containing analgesic can potentially cause relapse. [21]

Patients experiencing increased tolerance to a drug, or who want more potency for the same amount of money may snort or inject the drug to intensify its effects. Ingesting an oral form of medication (e.g., OxyContin®) formulated to treat moderate to severe pain through a slow, steady release of the opioid, in an unprescribed manner, increases the risk for serious medical complications, including overdose. Greater potency or dosage causes increased risk of undesirable side effects including dysphoria (feelings of discomfort, unhappiness, or restlessness), and symptoms of gastrointestinal distress, including nausea and vomiting. The increased risk also includes serious adverse events and potential for severe respiratory distress. [22]

Taken in ways other than prescribed, prescription opioids have effects similar to heroin. A number of recent studies suggest that prescription opioids are a frequent precursor to heroin abuse. Almost one-half of IV heroin users who participated in surveys about their drug use reported abusing prescription opioids (typically by crushing, snorting, or injecting the drugs) before trying heroin. Many reported switching to heroin because it was cheaper and easier to obtain than prescription opioids. [23]
The management of pain in patients with a history of substance abuse or with a comorbid psychiatric disorder requires close attention. Some patients will also require additional appointments and consultations, more frequent monitoring or testing, and referral to an expert if the patient poses a risk to himself or others.

### Drug-seeking behavior

Given the strong hold of prescription opioid addiction, all dental personnel and staff should be aware that substance abusers might target healthcare providers when they need a new source of prescription drugs. Because opioid abusers fit no reliable profile, but come from every age group, socioeconomic status, and ethnicity, dentists and staff members should familiarize themselves with common drug-seeking behaviors and practices, including doctor shopping, in which a patient visits multiple medical professionals to obtain as many prescriptions for a controlled substance as possible.

There is little data to suggest how many prescriptions a year are obtained through fraudulent means. A survey of dentists in West Virginia found 58% of respondents believed they were the victims of fraud or theft of prescriptions. Dentists reported patients using the following strategies to obtain drugs: 43% pretended to be in pain; 28% claimed their prescriptions were stolen; 14% forged prescriptions; and another 14% found a way to increase the number of pills in their prescription. [24]

### Elements to assure safe use (ETASU)

The patient’s welfare is best served when prescribers are able to identify current and former drug users and assess their state of recovery. In most cases, however, patients using medications without a prescription are unlikely to disclose accurate information about their illegal drug use. REM-compliant Elements to Assure Safe Use (ETASU) address the risks associated with hidden prescription drug use through use of state and national databases that monitor and track prescription activity to expose diversion and abuse.

Dentists should not prescribe drugs without first examining the patient in person and documenting the patient’s condition in his or her dental record. [25] Requesting a photo ID (e.g., a driver’s license) can identify patients who have traveled a significant distance to the dental office, rather than choosing one closer to their home. [26]

Dentists are encouraged to use the automated prescription systems to monitor and report suspected diversions. Many states have their own prescription-monitoring programs (PMPs) that track prescriptions, providing accurate, up-to-date information about patient prescriptions. Dental professionals can consult these statewide electronic databases to check what controlled substances the patient is currently prescribed, or were prescribed in the past. Using this technology, local pharmacies and dental clinicians can identify the doctor prescribing a medication, the pharmacy dispensing it, and a patient’s prescription history. [27]

ETASU implementation measures include:

- **Patient monitoring and registry enrollment**
  - Each patient using the drug is enrolled in the registry to facilitate ongoing assessment and mitigate risk through patient tracking and contact. Patients in the registry are subject to monitoring and collection of clinical data for assessment of long-term safety or root cause analysis. These mechanisms include blood tests or other forms of monitoring at periodic intervals. Questionnaires are administered at points throughout the treatment, as well as after the patient discontinues the drug.

- **Documentation of safe-use**
  - Drugs are only dispensed to patients who show evidence of safe-use conditions. Examples include documentation of:
    - Registry enrollment.
    - Laboratory tests (e.g., female patients of childbearing age receive the drug only after a documented negative pregnancy test).
    - Patient consent after prescriber instruction and counseling regarding the risks of the drug, the importance of follow-up appointments, and monitoring requirements.

- **Use of support systems and appropriate referrals**
  - Prescribers encourage patients to seek support and professional care in treatment programs before and after dental procedures, especially those involving pain, and cooperate with patients’ family members or support networks to ensure safe prescription use. This is crucial if a family member or other trusted individual is required to dispense the controlled medication to the patient. Prescribers should be able to make appropriate referrals or interventions to achieve treatment goals. Prescribers should know when it is appropriate to refer a patient to pain management specialists for additional evaluation, substance abuse counseling, or treatment for addiction.

Prescribers can protect patients by incorporating these basic risk-minimization strategies into their practice:

- Learning the signs and symptoms of substance abuse.
- Incorporating standard safeguards for prescribing opioids.
- Educating patients about proper disposal of unused opioids.
- Incorporating substance abuse screening into routine practice.
- Testing a specific patient, when necessary, to confirm drug use.
- Using prescription drug monitoring programs, where practical, to uncover illegal activity and abuse.
- Developing a referral network for the treatment of substance abuse disorders.

### Communication (counseling) plan

Prescribers have a responsibility to instruct the patient how to take the prescription safely, and communicate essential information about a prescription’s risks. Because prescribers have to communicate a good deal of important information in a limited amount of time, the communication and counseling component of this REM contains written information and strategies to facilitate communication between the prescriber and patient. These REM-compliant materials include:

- Revised labeling.
- Patient Counseling (Communication) Document (PCD).
- Medication Guide.

### Revised labeling

New labeling requirements for extended-release and long-acting opioid pain relievers are intended to help prescribers and patients weigh a medication’s benefits and costs. Labels were redesigned according to evidence-based research finding to clarify instructions and minimize ambiguity.

Previously, ER/LA opioid labels indicated these medications were for “the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.” The revised indications emphasize that other, less potentially addictive, treatment options should be considered first. Labeling states the drugs are “indicated for the management of pain severe enough to require..."
Patient decision-making should include information about any adverse effects that may occur with certain prescribed drugs and biological products when the Agency determines that:
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] 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.

This new labeling language emphasizes that patients in pain should be assessed not only by their rating on a pain intensity scale, but also based on a more thoughtful determination that their pain—however it may be defined—is severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate.

The “limitations of use” portion of the new labeling retains language indicating that the drugs are not intended for use as an “as-needed” pain reliever. Furthermore, the new labeling adds:
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] 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.

Patient counseling document (PCD)

The Patient Counseling Document (PCD) on ER/LA opioids was developed under the REMS to assist the prescriber in discussing safe use, serious risks, proper storage, and disposal. The PCD should be given to the patient and caregiver by the prescriber when the prescription is written, providing an opportunity to discuss these points with the patient, and answer any questions about its use, every time you prescribe these medications. This communication can help the prescriber assess the patient or caregiver’s level of understanding regarding the prescription or treatment plan, among other issues.

The PCD can take different forms, but should contain all the information provided in the sample below. Prescribers may add other relevant information, if desired, or include space where the prescriber and patient can make additional notes for clarification or as a reminder.

PATIENT COMMUNICATION/COUNSELING DOCUMENT (PCD) EXTENDED-RELEASE/LONG-ACTING (ER/LA) OPIOID ANALGESICS

Patient Name:
Patient Specific Information
- Take this card with you every time you see your healthcare provider.
- Take your opioid pain medicine exactly as prescribed by your healthcare provider.
- Tell him or her:
  - Your complete medical and family history, including any history of substance abuse or mental illness.
  - The cause, severity, and nature of your pain.
  - Your treatment goals.
- All the medicines you take, including over-the-counter (nonprescription) medicines, vitamins, and dietary supplements.
- Any side effects you may be having.
- Call 911 or your local emergency service right away if:
  - You take too much medicine.
  - You have trouble breathing, or shortness of breath.
  - A child has taken this medicine.
- Talk to your healthcare provider:
  - If the dose you are taking does not control your pain.
  - About any side effects you may be having.

DO:
- Read the Medication Guide.
- Take your medicine exactly as prescribed.
- Store your medicine in a safe place, away from children.
- Dispose of medicine in a legal, environmentally sound manner. Do not flush unused medication down the sink or toilet.
- Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

DO NOT
- Do not give your medicine to others, even if you share similar symptoms.
- Do not take medicine that was not prescribed for you.
- Do not stop taking your medicine without talking to your healthcare provider.
- Do not break, chew, crush, dissolve, inhale, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider about other options.
- Do not drink alcohol while taking this medicine.

Medication guide

Medication Guides are the paper handouts that accompany prescription medicines. They address issues specific to particular drugs and drug classes, and contain FDA-approved information to help patients avoid serious adverse events.

The FDA requires the distribution of a drug-specific Medication Guide with certain prescribed drugs and biological products when the Agency determines that:
- Certain information is necessary to prevent serious adverse effects.
- Patient decision-making should include information about any known serious side effect associated with a product.

An accurate, up-to-date Medication Guide is an indispensable REMS component that facilitates adherence to directions and communication with the patient. Like previous ER/LA opioid medication guides, the REMS-compliant Medication Guide outlines drug-specific information regarding the symptoms of overdose, the risks associated with physically manipulating or tampering with the product (e.g., breaking, chewing, or crushing the tablet), and the risk of sharing medications with others.
Patients are instructed to report adverse events, and warned of the risks of concomitant use of other CNS depressants, alcohol, or illegal drugs.

The revised REMS-compliant medication guide for ER/LA opioids includes:

- A more extensive description of drug-related symptoms and risks.
- More detailed instructions for safe use and the necessity of adhering to the prescribed dosing regimen.
- Specific information on safe and effective use of the particular opioid, as well as information relevant to all products in the class.
- Instructions advising patients to consult their healthcare professional before changing doses.
- Methods for safe storage, to minimize the risk of accidental exposure or theft.
- Instructions for properly disposing of the any unused prescription medication.
- Signs of potential overdose.
- Emergency contact instructions.

The prescriber is professionally responsible for ensuring this vital information is conveyed to, and understood by, the patient, and the Medication Guide can communicate that information effectively—but only if it is reviewed and understood. Most patients receive the Medication Guide when they fill their ER/LA opioid prescription (as required by the REMS). While prescribers can stress that patients review the information in the Medication Guide when they pick up their prescription, there is no way of knowing if the patient looked at it or not.

To ensure the safe and effective use of the prescribed opioid, the prescriber should have a copy of the Medication Guide on hand, and take the time to review it with the patient in person, when he or she is still at the office.

The prescriber can briefly review the document with the patient, point-by-point, asking questions throughout the process to assess the patient’s level of understanding and risk of abuse.

REMS-compliant Medication Guides for ER/LA opioids are available through the ER/LA Opioid Analgesic REMS website (www.ER-LA-REMS.com). For a current list of medication guides, see www.fda.gov/Drugs/DrugSafety/ucm085729.htm.

REM-compliant Medication Guides take the form of the sample below. TRADENAME is:

| Medication Guide TRADENAME ® <Include phonetic spelling>  
| (chemical name) Tablets, CII |
| TRADENAME is:  
| A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain. |
| Important information about TRADENAME:  
| Get emergency help right away if you take too much TRADENAME (overdose). TRADENAME overdose can cause life threatening breathing problems that can lead to death.  
| Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law. |

Do not take TRADENAME if you have:
- Severe asthma, trouble breathing, or other lung problems.
- A bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:
- Head injury or seizures.
- Liver, kidney, or thyroid problems.
- Problems urinating.
- Pancreas or gallbladder problems.
- Abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
- Pregnant or planning to become pregnant. TRADENAME may harm your unborn baby.
- Breastfeeding. TRADENAME passes into breast milk and may harm your baby.
- Taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

When taking TRADENAME:
- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take X dose at the same time every day. Do not take more than X dose in XX hours. If you miss a dose, do not take TRADENAME. Take your next dose at your usual time the next day.
- Swallow TRADENAME whole. Do not cut, break, chew, crush, dissolve, or inject TRADENAME.
- Call your healthcare provider if the dose you are taking does not control your pain.
- Do not stop taking TRADENAME without talking to your healthcare provider.
- After you stop taking TRADENAME, dispose of any extra medication in an environmentally friendly way. Do not flush medication down the sink or toilet. Water treatment plants are not equipped to filter it out, and this practice has introduced countless controlled substances into drinking water.

While taking TRADENAME Do Not:
- Do not drive or operate heavy machinery until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or light-headed.
- Do not drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of TRADENAME are:
- Constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:
- Trouble breathing, shortness of breath, rapid heartbeat, chest pain, swelling of the face, tongue or throat, extreme drowsiness, or are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov

This Medication Guide has been approved by the U.S. FDA Issue: DATE

Proper medication disposal

While current FDA and Office of National Drug Control Policy informational materials and guidelines still direct patients to flush unused prescription opioids down a sink or a toilet, the Environmental Protection Agency (EPA) and DEA strongly disagree and condemn this manner of disposal for any type of medication, even if the instructions or label specifically direct the patient to do so. Prescribers should be aware of the misinformation in opioid-specific instructions and ensure that their written materials do not recommend disposing of medication in this environmentally damaging way.
Sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.

Patients must receive all written materials, and review them, preferably with the prescriber, who should make him/herself available to answer questions or discuss any of the issues raised by the information. Under the ER/LA Opioid REMS, prescribers are responsible for conveying certain essential information to the patient, and ensuring it is understood, even if the patient is receiving the same information in written form. This means the prescriber needs to do more than simply hand out forms. He or she is responsible for reviewing and discussing the following subject areas with the patient, all of which are essential to patient safety.

Say it, read it, repeat it

Written REMS-compliant materials provide some of the same information on each of the forms; the Medication Guide (which must be dispensed with each filled ER/LA opioid analgesic prescription); the PCD (which must be given to the patient and discussed with him by the prescriber); and the revised labeling (viewed or read by those who see the bottle of medication or other form of prescribed opioid). This duplication is a deliberate risk reduction strategy, intended to increase patient safety through repetition and reinforcement of critical ER/LA opioid prescription information, in written and spoken (prescriber-patient) REM-compliant communication tools.

REMS Checklist- communication responsibilities for prescribers of ER/LA opioid analgesics

Has the prescriber instructed the patient to:
- Tell doctors all the medications they are taking.
- Store their ER/LA opioids in a safe and secure place away from children, family members, household visitors, and pets.
- Dispose of any ER/LA opioid analgesics when no longer needed according to environmentally sound product-specific disposal information.

Has the prescriber instructed the patient and caregivers to:
- Identify and respond to potential side effects.
- Read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- Identify the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.

Has the prescriber explained:
- Product-specific information about the prescribed ER/LA opioid analgesic.
- How to take the ER/LA opioid analgesic as prescribed.
- The importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- Sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.

Has the prescriber cautioned the patient about:
- Serious side effects of ER/LA opioids that can be lethal.
- The increased risk of overdose and death when other CNS depressants, including sedative-hypnotics and anxiolytics, alcohol, other opioids, or illegal drugs, are used at the same time as ER/LA opioids.

Has the prescriber warned the patient:
- An oral ER/LA opioid analgesic should never be broken, chewed or crushed, and patches should never be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
- Not to abruptly discontinue or reduce their ER/LA opioid analgesic, and the need to safely taper the dose as directed by the prescriber to avoid adverse effects.
- About the most common side effects of ER/LA opioid analgesics, including respiratory depression, an increased risk of falls, and the need to avoid driving and working with heavy machinery.
- ER/LA opioid analgesics should be protected from theft.

Proper disposal of medicines:
- Prevents poisoning of children and pets.
- Reduces the possibility of illegal use.
- Avoids health problems from accidentally taking the wrong medicine, too much of a medicine, or a medicine that is too old to work well.
- Keeps medicines from entering streams and rivers when poured down the drain or flushed down the toilet.

Written materials should explain that these drugs flow into the nation’s water supply. Water treatment plants are unable to filter the medication out, so the world’s water supply has become increasingly polluted with medication due to this common practice. In homes that use septic tanks, these prescription and over-the-counter drugs leach into the ground and seep into ground water. In cities and towns where residences connect to wastewater treatment plants, the drugs pass through filtering systems, entering rivers and lakes, and flowing downstream, where they contaminate community drinking water supplies sourced from those areas.

If possible, prescribers should provide information regarding community resources for safe disposal of prescription and nonprescription medication. Many household trash and recycling services, or authorized community organizations, have established drug take-back or return programs, where patients can safely donate unused medication. Some counties hold household hazardous waste collection days, where prescription and over-the-counter drugs are accepted at a central location for safe disposal.[28]
Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The following tables can be used as general guides for much of this information. For more detail, prescribers can refer to online information available via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

### Drug Information Common to the Class of Extended-release and Long-acting Opioid Analgesics (ER/LA opioid analgesics)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avinza</td>
<td>(morphine sulfate ER capsules)</td>
</tr>
<tr>
<td>Butrans</td>
<td>(buprenorphine transdermal system)</td>
</tr>
<tr>
<td>Dolophine</td>
<td>(methadone HCl tablets)</td>
</tr>
<tr>
<td>Duragesic</td>
<td>(fentanyl transdermal system)</td>
</tr>
<tr>
<td>Embeda</td>
<td>(morphine sulfate ER-naltrexone capsules)</td>
</tr>
<tr>
<td>Exalgo</td>
<td>(hydromorphone HCl ER tablets)</td>
</tr>
<tr>
<td>Kadian</td>
<td>(morphine sulfate ER capsules)</td>
</tr>
<tr>
<td>MS Contin</td>
<td>(morphine sulfate CR tablets)</td>
</tr>
<tr>
<td>Nucynta ER</td>
<td>(tapentadol HCl ER tablets)</td>
</tr>
<tr>
<td>Opana ER</td>
<td>(oxymorphone HCl ER tablets)</td>
</tr>
<tr>
<td>OxyContin</td>
<td>(oxycodone HCl CR tablets)</td>
</tr>
</tbody>
</table>

#### Dosing Interval
- Refer to individual product information.

#### Key Instructions
- Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions.
- The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval.
- Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions.
  - During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids.
- If pain increases, attempt to identify the source, while adjusting the dose.
- When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products.
- Limitations of usage:
  - 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.
- Solid oral dosage forms:
  - Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid.
  - Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information.
  - 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.
- Transdermal dosage forms:
  - Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure.
  - Location of application must be rotated.
  - Prepare skin by clipping, not shaving hair, and washing area only with water.
- See individual product information for the following:
  - Dosage reduction for hepatic or renal impairment.

#### Drug Interactions Common to the Class
- Concurrent use with other central nervous system depressants sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents.
- Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use.
- Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
### Use in Opioid-Tolerant Patients
- See individual product information for which products:
  - Have strengths or total daily doses only for use in opioid-tolerant patients.
  - Are only for use in opioid-tolerant patients at all strengths.

### Contraindications
- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis)

See individual product information for additional contraindications.

### Relative Potency To Oral Morphine
- These are intended as general guides.
  - Follow conversion instructions in individual product information.
  - Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

### Specific Drug Information for Extended-release and Long-acting Opioid Analgesics (ER/LA opioid analgesics)

#### Avinza
- Morphine Sulfate ER
- Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg

**Dosing Interval**
- Once a day

**Key Instructions**
- Initial dose in opioid nontolerant 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 can 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

#### Butrans
- Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr

**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.

**Specific Drug Interactions**
- CYP3A4 Inhibitors may increase buprenorphine levels.
- CYP3A4 Inducers may decrease buprenorphine levels.
- Benzodiazepines may increase respiratory depression.
- Class 1A and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.

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

**Drug-Specific Safety Concerns**
- QTc prolongation and torsade de pointe.
- Hepatotoxicity.
- Application site skin reactions.

**Relative Potency To Oral Morphine**
- Equipotency to oral morphine has not been established.
| Dolophine Methadone Hydrochloride Tablets, 5 mg and 10 mg |
|---|---|
| **Dosing Interval** | Every 8 to 12 hours |
| **Key Instructions** | ● 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. |
| **Product-Specific Safety Concerns** | ● QTc prolongation and torsade de pointe.  
● Peak respiratory depression occurs later and persists longer than analgesic effect.  
● Clearance may increase during pregnancy.  
● False positive urine drug screens possible. |
| **Relative Potency To Oral Morphine** | Varies depending on patient’s prior opioid experience. |

| Duragesic Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr |
|---|---|
| **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 postoperative pain, including use after outpatient 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. |
| **Product-Specific Safety Concerns** | ● Accidental exposure due to secondary exposure to unwashed/unclothed application site.  
● Increased drug exposure with increased core body temperature or fever.  
● Bradycardia.  
● Application site skin reactions. |
| **Relative Potency To Oral Morphine** | See individual product information for conversion recommendations from prior opioid |

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

<table>
<thead>
<tr>
<th>Use in Opioid-tolerant Patients</th>
<th>Product-Specific Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.</td>
<td>None</td>
</tr>
</tbody>
</table>

**Exalgo**

**Hydromorphone Hydrochloride**

**Extended-Release Tablets, 8 mg, 12 mg, 16 mg or 32 mg**

**Dosing Interval** Once a day

**Key Instructions**

- 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**

- 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**

All doses of Exalgo are indicated for opioid-tolerant patients only.

**Product-Specific Safety Concerns**

- 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.

**Kadian**

**Morphine Sulfate**

**Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg**

**Dosing Interval** Once a day or every 12 hours

**Key Instructions**

- 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).
- Product information recommends not using as first opioid.
- Titrate using a minimum of 2-day intervals.

**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

**MS Contin**

**Morphine Sulfate**

**Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg**

**Dosing Interval** Every 8 hours or every 12 hours

**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

**Nucynta ER**

**Tapentadol**

**Extended-release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg**

**Dosing Interval** Every 12 hours
### Key Instructions
- 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).
- 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.

### Specific Drug Interactions
- 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.

### Use in Opioid-tolerant Patients
- No product-specific considerations.

### Product-specific Safety Concerns
- Risk of serotonin syndrome
- Angioedema

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

#### Opana ER
**Oxymorphone Hydrochloride**
**ER Tablets, 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.

**Key Instructions**
- Use 5 mg every 12 hours as initial dose in opioid nontolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients older than 65 years of age.
- 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

#### OxyContin
**Oxycodone Hydrochloride**
**Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg**

**Dosing Interval**
Every 12 hours

**Key Instructions**
- Opioid-naïve patients: initiate treatment with 10 mg every 12 hours.
- Titrate using a minimum of 1 to 2 day intervals.
- Hepatic impairment: start with one third to one half 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.
References

31. Up to 23% of prescribed opioid doses are used nonmedically.
   - True
   - False

32. Medication obtained free from a friend or family member is identified as the most common prescription opioid source for abusers in a large-scale study of prescription opioid abuse.
   - True
   - False

33. Treatment plan documentation is used with patients posing an elevated risk of diversion or misuse to spell out additional patient obligations, including commitments to return for follow-up visits, and safeguard medication, comply with monitoring mechanisms, and the circumstances under which drug therapy may be discontinued.
   - True
   - False

34. Tapentadol is associated with erythema (redness) and rash.
   - True
   - False

35. 30 mg/day oral morphine taken for at least one week does not satisfy the criteria for opioid-tolerance.
   - True
   - False