A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

Overview

Chronic pain is a prevalent medical condition that has a significant clinical and societal impact. However, despite scientific advances in the diagnosis of chronic pain, large numbers of individuals remain inadequately treated. A comprehensive pain assessment can help determine the feasibility and appropriateness of analgesic therapy, which may include the use of opioid analgesics. Although opioids can provide effective pain relief for many patients, their use for chronic pain relief remains controversial due to insufficient data regarding long-term efficacy and adverse events and drug misuse, abuse, and addiction. Therefore, the challenge for clinicians is to balance the patient’s need for adequate pain relief with these adverse effects. This activity is part of the FDA Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh their risks. It will discuss the epidemiology and prevalence of chronic pain and opioid abuse, followed by a discussion of the clinical pharmacology of opioid analgesia and drug abuse and addiction. The rest of the discussion will focus on comprehensive pain assessment, determination if a patient is a candidate for opioids, initiation of opioid therapy, ongoing management of therapy with ER/LA opioid analgesics, and counseling of patients and their families on the safe use of ER/LA analgesics. It will conclude with a presentation of general and specific drug information about ER/LA opioids. This information is based on a series of presentations being given at regional pain management conferences throughout the U.S. in 2016.
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Audience

This education is intended for primary care providers and other clinicians involved in pain management, and is designed to help them recognize and balance optimal pain reduction to improve function and productivity with minimization of adverse events (e.g. abuse, addiction, and risk of workplace accidents). Additional challenges to optimal pain management include keeping up to date with the increasing volume of information on pain management, implementing changes recommended by evolving guidelines, and recognizing changes to practice needed to combat the growing rate of opioid abuse.

Educational Objectives

This program is designed to address the following IOM competencies: provide patient-centered care and employ evidence-based practice.

At the conclusion of this activity, participants should be able to demonstrate the ability to:

- Describe how to counsel patients and caregivers on safe use of ER/LA opioid analgesics, including proper storage and disposal
- Review how to safely initiate therapy, modify dose, and discontinue use
- Explain general and product-specific drug information
- Identify patients who are candidates for treatment with ER/LA opioid analgesics
- Describe how to minimize risks of opioid abuse, addiction, diversion while managing patients who are receiving ongoing therapy

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Faculty
Lynn Webster, MD
Reported Financial Relationship
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Jeffrey Gudin, MD
Consultant/Independent Contractor: Daiichi, Depomed, Insys, KemPharm, Quest Diagnostics, Scilex, Shionogi; Grant/Research: KemPharm, Sentanyl; Speakers’ Bureau: AstraZeneca, Iroko, Purdue, Teva, Xenoporo

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Name of Planner or Manager
Kristen Delisi, NP
Andrea Funk
Laura Gilsdorf, MS
Amanda Glazar, PhD
Matthew Horn, MD
Jay M. Katz, MA, CHCP
Ashley Marostica, RN, MSN
Blair St. Amand

Reported Financial Relationship
Nothing to disclose
Nothing to disclose
Nothing to disclose
Nothing to disclose
Nothing to disclose
Nothing to disclose
Nothing to disclose
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Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.

This course is not intended to advocate for the use of Extended-Release/Long-Acting (ER/LA) Opioids, but to ensure the proper education about safe prescribing practices should a medical provider determine that ER/LA Opioids are the best course of treatment.

System Requirements

In order to view this supplement online and/or complete the post-test and evaluation, your computer must have the Adobe Flash Player. The Adobe Flash Player can be downloaded from: https://get.adobe.com/flashplayer/.

Privacy Policy

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This activity is jointly provided by Global Education Group and Rockpointe Corporation.

This educational activity is supported by an independent educational grant from the ER/LA Opioid Analgesic REMS Program Companies.

Please see: http://ce.er-la-opioidrems.com/lwgCEUI/remst/pdf/List_of_RPC_Companies.pdf for a listing of the member companies. This activity is intended to be fully compliant with the ER/LA Opioid Analgesics REMS education requirements issued by the US Food & Drug Administration.

This program was planned in accordance with AANP CE Standards and Policies and the AANP Commercial Support Standard.
Faculty

Lynn Webster, MD has dedicated more than three decades to becoming an expert in the field of pain management. He is the Vice President of Scientific Affairs for PRA Health Sciences and is the Past President of the American Academy of Pain Medicine. A leading voice in trying to help physicians safely treat pain patients, Dr. Webster actively works within the industry to develop safer and more effective therapies for chronic pain and addiction. He is board-certified in anesthesiology and pain medicine, and is also certified in addiction medicine. Dr. Webster lectures extensively on the subject of preventing opioid abuse and criminal diversion in chronic pain patients and has authored more than 300 scientific abstracts, manuscripts, and journal articles, many of which are the basis for training physicians who are studying pain, along with the book, *Avoiding Opioid Abuse While Managing Pain: A Guide for Practitioners*.

Dr. Webster has played an instrumental role in his industry as a strong advocate for safe and effective pain-resolution methods. The Opioid Risk Tool (ORT), which he developed, is currently used and is the standard in multiple countries and thousands of clinics worldwide. He spends most of his time developing safer and more-effective therapies for chronic pain and campaigning for safer use of medications.

He received his doctorate of medicine from the University of Nebraska and later completed his residency at the University of Utah Medical Center’s Department of Anesthesiology. Dr. Webster has been quoted by multiple media sources, including the *Los Angeles Times* and the *Wall Street Journal*, and has given more than 250 presentations across the United States and internationally. He is the author of *The Painful Truth: What Chronic Pain Is Really Like and Why It Matters to Each of Us* (Webster Media LLC) and Co-producer of the documentary, “The Painful Truth,” to be released this winter.

Jeffrey Gudin, MD completed his residency in anesthesiology at the Yale University School of Medicine and his fellowship in Pain Management at the Yale Center. While in New Haven, Dr. Gudin also trained in addiction medicine and directed a substance abuse treatment center. For the last 15 years, Dr. Gudin has been the Director of Pain Management and Palliative Care at Englewood Hospital and Medical Center, a Mt. Sinai University School of Medicine teaching affiliate in New Jersey. He remains active in teaching and research, and has lectured internationally on a variety of topics in pain management, palliative care, and addiction medicine.

Dr. Gudin has dedicated his career to promoting education in pain management. He attends and has presented at the American Pain Society, American Academy of Pain Management (AAPM), American Academy of Physical Medicine and Rehabilitation, as well as many other national venues. Dr. Gudin serves as a consultant to state medical boards on challenging cases, as well as to industry on novel analgesic products and risk management associated with opioids. He has presented annually at the AAPM Safe Opioid Prescribing Course.
Protection from and relief of pain and suffering are a fundamental feature of the human contract we make as parents, partners, children, family, friends, and community members, as well as a cardinal underpinning of the art and science of healing. Pain is part of the human condition; at some point, for short or long periods of time, we all experience pain and suffer its consequences. While pain can serve as a warning to protect us from further harm, it also can contribute to severe and even relentless suffering, surpassing its underlying cause to become a disease in its own domains and dimensions. We all may share common accountings of pain, but in reality, our experiences with pain are deeply personal…Through the ages, pain and suffering have been the substrates for great works of fiction, but the reality of the experience, especially when persistent, has little redeeming or romantic quality. The personal story of pain can be transformative or can blunt the human values of joy, happiness, and even human connectedness.


Introduction: Dueling crises: Balancing the management of chronic pain and opioid addiction

Nociceptive pain is a warning system, an adaptive mechanism with a protective function that allows an individual to detect harmful stimuli and respond appropriately for survival and to prevent further injury.\(^1\) It is a physiologic event that involves the entire nervous system, and can be classified as either acute or chronic.\(^1,2\) Acute pain occurs as a result of trauma, diminishes with healing, and disappears when healing is complete. Chronic pain has little or no protective purpose; persists despite healing after injury or disease, sometimes for months or longer; and can interfere with normal activity.\(^3\) It may occur from an initial injury such as a muscle sprain, an illness that persists, or there may be no clear cause.\(^3\) The risk of chronic pain is universal.\(^2\) National epidemiologic studies on chronic pain, although limited in number, indicate that the prevalence of chronic pain is high and its impact is substantial and wide ranging. According to the Institute of Medicine of the National Academies, common chronic pain conditions affect at least 116 million U.S. adults.\(^2,4\) It costs about $560-$635 billion dollars annually, an amount equivalent to about $2,000 for every person in the United States.\(^2\)

“From 1990 to 2010 the number of people in the United States dying annually from opioid analgesic-related overdoses quadrupled…Patients’ predisposition to overdose could not have changed substantially in that time; what has changed substantially is their exposure to opioids. During this same time, the amount of opioids prescribed also quadrupled.”

**Dowell D, Kunins HV, Farley TA. Opioid analgesics—risks drugs, not risky patients. JAMA. 2013;309(21):2219-2220.**

“Imagine a jumbo jet full of people crashing every 10 days. That would represent the number of people who are dying in opioid-related causes annually. Imagine if that were occurring to our congress, to our public, imagine the outrage that would cause.”

**Lynn Webster, MD. Vice President of Scientific Affairs, PRA Health Sciences, Salt Lake City, UT**
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Treating chronic pain is difficult and often requires long-acting opioids, which are the most potent drugs for pain management. However, the prescription of opioid analgesics for chronic pain conditions continues to be controversial and contentious. As with chronic pain, opioid abuse is widespread and exacts a heavy toll on patients, physicians, and society. The United States and Canada have the highest consumption of prescription opioids in the world. In 2012, 259 million opioid prescriptions were written, which equates to one bottle of pills for every adult American. Also in 2012, nearly 2 million people aged 12 or older either abused or were dependent on pain relievers. Longtime opioid use can lead to analgesic tolerance and a loss of pain relief. To overcome tolerance, patients are often prescribed higher or more frequent doses of opioids, or switched to more potent opioid agonists. However, tolerance may return over time, leaving the patient without adequate pain control while at the same time escalating the risk of severe side-effects such as respiratory depression.

Federal watchdog agencies estimate that deaths resulting from the nonmedical use of opioids increased by almost 500% between 1999 and 2014, from 4,030 deaths to 18,893 (about 52 deaths per day); the deaths per 100,000 population increased from 0.7 to 3.4 during this time.

“I’m a little worried about our country. We landed on the moon. We ended a world war. We are a nation of inventors. Yet we can’t solve two problems at a time. There is NO POINT tackling addiction and not tackling pain.”

Lynn Webster, MD. Vice President of Scientific Affairs, PRA Health Sciences, Salt Lake City, UT

It is difficult to balance the dueling crises of chronic pain and addiction. Dr. Webster stated that “after 20 years of expanded opioid prescribing we have either learned something fundamental about the clinical use of opioids, or something fundamental about the problems of our healthcare system. I think we’re going to underscore the latter. Opioids can be problematic, but our healthcare system has made it worse.” For example, interdisciplinary care for chronic pain patients has been shown to be very effective in terms of cost, functional restoration, and relief of psychological symptoms. These programs combine biological, psychological, and social care. Unfortunately, insurers limit their coverage for these types of programs, and the number of such programs in the United States has decreased from about 1000 in 1990 to about 90 today (excluding the Veterans Administration).

Clinical pharmacology of opioid analgesia

To help in understanding opioid analgesia and its many adverse effects, it is useful to review the clinical pharmacology of opioids. Endogenous opioid compounds and their receptors exist throughout the central and peripheral nervous systems. These systems are involved in a diverse number of homeostatic functions, including pain modulation and antinociception; addiction; the regulation of membrane ionic homeostasis; cell proliferation; emotional response; epileptic seizures; immune function; feeding; obesity; respiratory and cardiovascular control; and some neurodegenerative disorders.

Pain transmission in the spinal cord is regulated by the balance of facilitatory and inhibitory influences operating on the neural circuits of the somatosensory system. Opioids produce analgesic effects by activating receptors that comprise part of an endogenous opioid system that modulates sensory input by noxious stimuli. The three families of endogenous opioids are the endorphins, enkephalins, and dynorphins. These endogenous opioids are neurotransmitters that have analgesic activity through their interactions with one of three primary opioid receptor subtypes, µ, κ, and δ receptors. Opioid drugs mimic and amplify the effects of these endogenous modulators.

Opioids are classified as pure agonists, agonist-antagonists, or pure antagonists. The opioid analgesics routinely used for chronic pain selectively bind to µ receptors and are called pure µ-agonists. Pure µ-agonists do not exhibit a ceiling to their effects; that is, their efficacy increases with dose. Dosage may be increased until adequate analgesia is achieved or side effects limit any further increases. Agonist-antagonists can be either partial agonists that have lower intrinsic efficacy than do pure agonists or they can be mixed agonist-antagonists that act as agonists at one opioid receptor and as antagonists at another. Agents of this class exhibit a ceiling to analgesic effects and are more likely to be associated with psychotomimetic effects than are pure agonists. Pure antagonists compete with other opioids at µ receptors, blocking activity of either endogenous or exogenous opioids. Pure antagonists may be used to prevent or reverse opioid effects.
The primary analgesic effect of opioids is not only an increase in the threshold of pain, but also a lessening of the subjective evaluation of pain. For example, patients treated with morphine for excruciating pain can feel the pain, but do not associate the pain as a problem. Thus, they have a conscious response to pain that is modified at higher brain levels. In addition to their modulation of nociception, opioid receptors are involved in a number of diverse functions. Activation of these receptors leads to the large number of adverse effects of opioid use, including constipation, nausea or vomiting, sedation or clouded mentation, hypogonadism, pruritus, and myoclonus. Neurological impairments in addiction are considered to reflect drug-induced dysfunction. The mechanisms underlying this dysfunction are not well understood, but an important role in the neurochemical mechanisms of opioid reward, dependence, and vulnerability to addiction has been ascribed to the activation of endogenous opioid peptides. Opioid abuse also leads to tolerance and adaptation, which occur through complex mechanisms of receptor regulation that include desensitization and internalization. Opioids depress ventilation through a direct action on the respiratory-generating structures in the brain. Endogenous opioid peptides are present in the heart, including endorphins, enkephalins, and dynorphins. During ischemia, these peptides are elevated. In animal models, it has been found that the opioid system can modulate hemodynamic and cardiovascular activity. They may also lead to opportunistic infections through suppression of the immune function.

**Pain assessment and determination of appropriate therapy**

Dr. Webster commented that the major reasons for opioid-associated deaths in patients can be attributed primarily to three sources: physicians, patients, and unanticipated comorbidities. Physicians often start opioid doses too high, escalate dosage too rapidly, rely too much on conversion tables, and do not assess patient risk adequately. For patients, pain is a strong motivator. They are often guilty of nonadherence to drug regimens as they try to control pain, coping with their chronic disease by self-medicating. Drug-related causes include QT elongation, pharmacogenetics issues, and respiratory depression. Therefore, responsible opioid prescribing must take all three sources into account when beginning an opioid trial.

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**Steps in Responsible Opioid Prescribing**

- Patient evaluation, including risk assessment
- Treatment plans that incorporate functional goals
- Informed consent and prescribing agreements
- Periodic review and monitoring of patients
- Referral and patient management
- Documentation
- Compliance with state and federal law


When considering chronic opioid therapy, patient selection is critical, and should include a benefit-to-harm evaluation that weighs the potential positive effects of opioids on pain and function against patient risk for addiction and other adverse effects. A chronic opioid therapy trial should only be considered when potential benefits are likely to outweigh risks. Before initiating a trial of chronic opioid therapy, healthcare providers should conduct a thorough history, physical examination, and appropriate testing, including an assessment of risk for aberrant behavior related to opioid therapy. Will opioid therapy be short- or long-term? Chronic opioid therapy can be considered in well-selected patients with a history of substance abuse, psychiatric issues, or serious aberrant drug-related behaviors only if highly structured conditions are in place, such as more frequent or intense monitoring strategies, authorization of limited prescription quantities, and consultation or co-management with professionals who have expertise in addiction or mental health issues.

Evaluation of the underlying pain condition can help determine whether the patient may be treated more effectively with nonopioid therapy rather than with opioids. Pain intensity, onset, location, duration and quality should all be assessed. Is the pain acute or chronic? The origin of the pain and patterns of radiation should be discussed as well as the severity, quality, and factors that worsen or relieve the pain. Most pain is classified as nociceptive (pain that results from identifiable tissue damage) or neuropathic (pain that results from neurologic dysfunction). Patients may describe nociceptive pain originating in somatic structures as sharp, aching, throbbing, or pressure-like. Nociceptive visceral pain may be described as gnawing or cramping. Neuropathic
pain results from disorders of the central or peripheral nervous systems, which control pain perception. Typically, most neuropathic pain is resistant to over-the-counter analgesics, and may be aggravated by touch (alldynia). It may be characterized by the patient as abnormal, unusual, strange, or unfamiliar compared with pain experienced previously. Even though both neuropathic and non-neuropathic pain conditions appear to respond similarly to opioid therapy, there is little evidence that opioids are uniformly efficacious for conditions with strong psychosocial contributors, such as some types of chronic low back pain, daily headache, and fibromyalgia.

The impact of chronic pain on quality of life also is an important part of pain assessment. Evaluation of baseline levels of patient function and quality of life can be useful in the initial characterization of pain and in the ongoing assessment of response to treatment. Pain-related disabilities and other comorbidities should be taken into account. The history and exam should include assessment of any psychosocial factors and family history to aid in risk stratification. Prior opioid treatment failure may be a contraindication for opioid therapy. Therefore, pain assessment should involve a review of prior pharmacologic and nonpharmacologic treatments, especially adherence, adverse effects, and outcomes with prior opioid use. Other considerations include current medications and allergies; medical, psychiatric, and social history; substance abuse history; and an evaluation of the risk level for aberrant behavior, including the possibility of abuse by family members. These factors and screening tools are described in more detail below.

Dr. Webster stated that “anyone with a history of substance abuse is seven times more likely to have a second substance abuse problem in their lifetime. Also, one of four-to-five people have a mental health problem. Opioids tend to ameliorate mental health symptoms temporarily. This may foster dependency with opioids. We need to remember that 10%–18% of the population is genetically vulnerable to developing a substance abuse problem. Finally, you have to inform the patient of all of the risks and potential harms, including adverse effects and possible life-threatening respiratory depression. That comes with a treatment agreement but also with an opioid consent.” Therefore, a management plan/care agreement should also be discussed prior to initiation of opioid therapy. The management plan should include the goals of therapy; how opioids should be prescribed and taken; expectations for follow-up and monitoring; alternatives to opioid therapy; expectations regarding use of concomitant therapies; and potential indications for tapering or discontinuing opioid therapy. The patient should be informed of the risks (including side effects, physical dependence, and addiction), benefits, and alternatives to opioid therapy; and a patient care agreement should be initiated emphasizing the need to adhere to treatment and monitoring. This education should be extended to family members and caregivers.

**Initiating opioid therapy, modifying dosing, and discontinuing the use of ER/LA analgesic therapy**

Before initiating opioid therapy, opioid prescribers need to be aware of federal and state regulations on opioid prescribing. There are at least six to eight national regulations regarding opioid prescriptions, and many states have their own guidelines. REMS will not replace these existing federal and state policies regarding opioid prescribing. Dr. Webster stated that the American Pain Society and the American Academy of Pain Medicine (APS/AAPM) guidelines, developed in 2009, remain the standard as the best guidelines available today. However, clinicians need to check with their local medical boards for any new developments that may rapidly evolve. Sometimes the state laws may be the most restrictive, and clinicians need to be aware of these. And sometimes state medical boards are going to have policies that will be more restrictive than some of the other guidelines. The implementation of REMS principles into current practice is intended to advance the responsible use of opioid therapy. These principles are designed to ensure the safe use of opioids, to improve patient outcomes, minimize adverse events, and to keep access to opioid therapy available to people in pain.

A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria:

1. Moderate to severe pain that has failed to adequately respond to indicated non-opioid and non-drug therapeutic interventions
2. The potential benefits of opioid therapy are likely to outweigh the risks (i.e., no absolute contraindications)
3. The patient is fully informed and consents to the therapy
4. Clear and measurable treatment goals are established
**Understanding Patient Selection**

Which of the following patients could benefit from a trial with chronic opioid therapy?

**Case 1:** RH is a 76-year-old male with right hip OA and severe coronary artery disease (not a surgical candidate). No personal history of addiction. Family history of alcoholism. Had been using hydrocodone/APAP for last year. Still has daily intermittent pain. Concerned about continued use and the risk of addiction.

**Case 2:** KT is a 42-year-old female with complex regional pain syndrome (CRPS) with compound ankle fracture post motor vehicle accident. She is on hydrocodone/APAP and is requesting oxycodone/APAP. Stressed, depressed, and using alcohol and marijuana. Sexually abused as a preadolescent.

**Case 3:** BD is a 46-year-old male with failed back syndrome. Used street drugs when in college and treated for alcoholism. Sober for the last 15 years; attends AA regularly. Smokes ½ pack of cigarettes per day (reduced from 2 packs a day more than a year ago). Working full time and providing for a family of 3 children. No family history of addiction; no other psychiatric illness.

The correct answer is ALL OF THEM!

A chronic opioid therapy trial should only be considered when potential benefits are likely to outweigh risks. A comprehensive history and physical examination, including an assessment of psychosocial factors, is always necessary. Risk assessment should be conducted even if the patient is already receiving opioid therapy. Opioid therapy can be considered in well-selected patients with history of substance abuse, psychiatric issues, or serious aberrant drug-related behaviors only if highly structured conditions are in place, e.g. more frequent or intense monitoring strategies, authorization of limited prescription quantities, and consultation or co-management with professionals who have expertise in addiction or mental health issues.

Always rely on your clinical judgment when deciding whether a patient should or should not receive opioid therapy—risk assessment tools should be used as a guide:

In addition to the ORT and SOAPP, other risk assessment tools include:

- Current Opioid Misuse Measure (COMM™)
- Pain Assessment and Documentation Tool (PADT™)
- Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument.

Implement opioid therapy as a component of a multimodal, interdisciplinary treatment plan that may include psychological and functional restoration interventions.

In patients such as in these cases, it is important to manage the conversion from short-acting to long-acting opioid therapy. During intervals between doses, patients treated with short-acting opioids may experience intermittent withdrawal symptoms, which may be misinterpreted as pain, or which may act to increase pain. Moreover a switch from short-acting opioids to long-acting opioids may reduce the pain-reinforcing properties of opioids, as a regularly scheduled opioid administration does not facilitate a behavior in which pain is rewarded with the administration of an opioid. All of these disadvantages may be exacerbated in patients whose pain is chronic and intractable.
An initial course of treatment with opioids for chronic, non-cancer pain (CNCP) should be considered a short-term, therapeutic trial that lasts between several weeks and several months. In most cases, the opioid dose should be effectively titrated through incremental dose escalations until adequate pain relief is achieved, as long as no serious harms are present. For patients who have had no previous opioid exposure, or only modest opioid exposure, opioids should be started at a low dose and titrated slowly in order to decrease the risk of opioid-related adverse effects. Dose titration is generally complete after the first several weeks, although dose adjustments may be needed periodically thereafter. Improved function is a primary goal of therapy, but partial analgesia may be a reasonable goal. However, because patients will respond differently to different opioids, opioid rotation (conversion) may be used in cases where adverse effects are dose limiting. The patient’s need for analgesia should be balanced against his or her age and cardiopulmonary, renal, and hepatic function to determine the starting dose and the rate at which the dose of the new agent is increased. Brief hospitalization should be considered for elderly or frail patients or those in extreme pain. Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse effects or inadequate pain relief despite dose increases.

Dr. Jeffrey Gudin stated that at reasonable intervals, depending on specific circumstances of a given patient, the healthcare professional should review the course of treatment and any new information about the etiology of the pain. Continuation or modification of therapy should depend on the healthcare professional’s evaluation of progress toward the stated treatment goals, such as a reduction in a patient’s pain scores and/or improved physical and/or psychosocial function including the ability to work, utilization of healthcare resources, activities of daily living, and overall quality of life.

An opioid treatment trial should be discontinued if the goals are not ultimately met, and opioid treatment should be discontinued at any point if adverse effects outweigh benefits or if dangerous or illegal behaviors are demonstrated. The clinician may decide to discontinue opioid therapy for one of the following reasons:

1. Severe unmanageable adverse effects
2. Serious non-adherence to the treatment plan or unsafe behaviors
3. Misuse suggestive of addiction to prescribed medication
4. Lack of effectiveness of therapy or a desire on the part of the patient to discontinue therapy

Lack of therapeutic benefit can result when the painful condition is resolved, intolerable side effects occur at the minimum analgesic dose, or if there is inadequate pain control at any tolerated dose. However, Dr. Gudin continued, it is important to distinguish between abandoning opioid therapy and abandoning the patient. In the case that opioids need to be tapered, specialty assistance should be considered.

The decision to discontinue opioid treatment should ideally be made jointly with the patient and, if appropriate, the family/caregiver, and needs to include careful consideration of the outcomes. Discontinuing opioids for patients who choose to stop therapy for elective reasons, such as adverse effects or lack of efficacy, can readily be achieved on an outpatient basis with minimal withdrawal symptoms. However, if withdrawal symptoms occur, pain may temporarily increase. If therapy is being discontinued due to non-adherence, additional support and counseling may be needed.

After discontinuation, follow-up care should include monitoring and consideration for consultation or referral to help maintain patient safety and comfort during the initial phase of opioid abstinence. The symptoms of opioid withdrawal can be very unpleasant, but are generally not life threatening. According to the APS/AAPM guidelines, approaches to weaning range from a slow 10% dose reduction per week to a more rapid 25% to 50% reduction every few days. There is insufficient evidence to provide specific recommendations on the rate of reduction, but a slower rate may help reduce the unpleasant symptoms of opioid withdrawal. Factors that may influence the rate of reduction include the reason driving the decision to discontinue chronic opioid therapy, presence of medical and psychiatric comorbidities, the starting dose, and the occurrence of withdrawal symptoms as the process is initiated.

**Eight opioid prescribing principles for Providers**

Dr. Webster outlined his eight prescribing principles for providers, which are designed to help minimize the harm of prescribing opioids and other psychotherapeutics:

1. **Assess patients for risk of abuse before starting opioid therapy and manage accordingly**
Considering vulnerability to addiction, 50% of the risk of developing an opioid addiction is genetically-based and fifty percent is environmental. Most will never develop an addiction regardless of dose or duration of therapy. Some are never prescribed an opioid because they never experience a need for one to be prescribed. Others, with a genetic vulnerability, could be triggered with the very first exposure. That does not mean that these individuals will go on to develop an addiction, but they could. A priori, there is no way to know, with certainty, who will develop an addiction.

Fifty percent of the risk of developing an opioid addiction is genetic-based, the other 50% is environmental. Whereas most patients will not develop an opioid addiction (See Figure 1, page 12), a substantial number of patients are vulnerable to addiction. Therefore, it is necessary to assess all patients before beginning a trial of opioid therapy. Providers may use one of several available tools before prescribing for opioids to assess patients for their risk of developing problematic drug-taking behaviors (Table 1, page 12). These tools are based on biological, social, and psychiatric risk factors associated with misusing opioids prescribed for pain. These screening tools ask the questions that are most informative and useful for stratifying patients by risk of addiction (Table 2, page 13). The tools include an assessment of pain severity, past and present history of substance abuse by the patient and family members, psychopathology, results of urine drug testing, and results of prescription monitoring programs. After risk stratification, clinicians should implement a plan according to risk level. For example, for high-risk patients, refer for psychiatric evaluation or co-manage with a chemical dependency expert prior to opioid trial. After a patient is started on opioids, different tools should be used to continually monitor patients (Table 3, page 13).

Dr. Webster commented that when he was seeing his patients and had to make a decision as to whether or not to prescribe an opioid, he gave a physical exam, recorded the patient’s history, and did his risk assessment.

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### Table 1 Screening Tools to Assess Patient Risk before Prescribing Opioids

<table>
<thead>
<tr>
<th>Tool</th>
<th># of items</th>
<th>Administered by</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORT</strong> Opioid Risk Tool</td>
<td>5</td>
<td>patient</td>
</tr>
<tr>
<td><strong>SOAPP</strong> Screener &amp; Opioid Assessment for Patients with Pain</td>
<td>24, 14, or 5</td>
<td>patient</td>
</tr>
<tr>
<td><strong>DIRE</strong> Diagnosis, Intractability, Risk, &amp; Efficacy Score</td>
<td>7</td>
<td>clinician</td>
</tr>
</tbody>
</table>

Several tools have been developed to assess for the risk of aberrant drug use prior to the initiation of opioid analgesia, including those listed here.
If he thought that an opioid might be appropriate, he would sit back and consider the patient and consider the patient’s level of stress. He stated that “the greatest environmental stimulus is prolonged, high-intensity pain. Stress becomes a reason why some people will self-medicate, not necessarily becoming an addict, but certainly dangerously self-medicating and as a result they could overdose.”

2. Watch for and treat comorbid mental disease if present

Co-occurrence of mental health disorders with chronic pain place a patient at high risk for opioid misuse, drug-drug interactions, and overdose.20 This higher risk develops because the patient may be self-medicating. That is, they may be taking some other drug for their mental health problem, which in turn can affect the blood level of the opioid and lead to an overdose. Dr. Webster stated that in his practice, about 70%–80% of patients with chronic pain have some level of mental health problems. In addition, as many as 6 in 10 people who have an illicit drug use disorder also suffer from mental illnesses.26 However, Dr. Webster again commented that he thinks this is an underestimate, as in his practice almost all patients who had an opioid or alcohol addiction had a mental illness. Therefore it is essential to assess for mental health disease before initiating a trial with chronic opioid therapy.

Dr. Webster stated that managing these patients is “an Olympian challenge” because clinicians are dealing with a “trio diagnosis”: pain disorder, addiction disorder, and psychiatric disorder. In addition, primary care clinicians are managing cardiovascular disease, diabetes, and
cancer. All of these problems combined can lead to an increase in suicide risk for these patients. As shown in Figure 2 (page 14), between 2004 and 2011, there was an 87% increase in suicide attempts by users of opioid analgesics, compared with a 41% increase by users of all drugs, as measured in emergency rooms. Dr. Webster stated that it is often difficult to distinguish a suicide attempt from an accidental drug overdose, with the patient taking more drugs to escape their pain.

3. **Conventional conversion tables can cause harm and should be used cautiously when rotating (switching) from one opioid to another**

When rotating from one opioid to another, equianalgesic tables provide insufficient guidance to determine the equivalent dose of different opioids. Individual consideration is necessary for each patient. Dr. Webster stated that when a patient is started on a new ER/LA opioid, the patient should be considered opioid naïve. They should not discontinue the old drug abruptly, but the dosage should be decreased incrementally, about 25% per week, while slowly increasing the dose of the new opioid. In most cases, the switch can be completed in 3-4 weeks. During this time, the patient should be seen on a weekly basis so that their tolerance for the rotation can be evaluated (e.g. not switching too fast or too slow). Another consideration is to provide some immediate release opioids for breakthrough pain. Dr. Webster recommended that if you are not experienced with opioid rotation, you should seek expert help.

The equianalgesic tables provide insufficient guidance to determine the equivalent doses of different opioids. Dr. Webster commented that there is no scientific basis for the equianalgesic tables in people who are on chronic opioid therapy. These tables were developed for a 24-hour post-op equivalence in the hospital for hysterectomies. He stated that reliance on these tables for patients on chronic opioid therapy can be lethal for patients.

4. **Avoid combining benzodiazepines with opioids, especially during sleep hours**

According to Dr. Webster, about a third of all unintentional opioid overdose deaths were associated with benzodiazepines because benzodiazepines enhance the respiratory-depressant effects of opioids. They are frequently co-prescribed with opioids in up to 50% of patients, and the co-prescription is more common in chronic pain patients with substance abuse disorders. Whenever possible, find a substitute for benzodiazepines.
5. **Start methadone at a very low dose and titrate slowly regardless of whether your patient is opioid tolerant or not**

The use of methadone for CNCP has increased dramatically, even though few trials have evaluated benefits and harms of methadone for CNCP.\(^1\) In addition, a number of epidemiologic studies suggest an increased rate of methadone-associated deaths in the United States, with six times as many people dying of a methadone overdose in 2009 than in 1999.\(^2\) Methadone represents only about 2% of the opioids prescribed, but it contributed to almost one in three prescription opioid deaths in 2009; and 5,000 people die every year from an overdose related to methadone.\(^2\) As shown in Figure 3 (page 15), the death rate from overdose caused by a single prescription painkiller was almost 3 times higher for methadone than for any other prescription painkiller.\(^2\)

Methadone has a very long and highly variable half-life, which necessitates careful titration to avoid delayed adverse events, such as overdose. Although the half-life of methadone is usually estimated at 15 to 60 hours, in some reports the half-life is as high as 120 hours.\(^1\) The effect on respiratory depression is variable. Tolerance to the respiratory depressant properties of methadone develops slowly and accumulates over 7-14 days with each dose escalation. In a patient for whom the methadone half-life is 60 hours, it would take almost 12 days on a stable dose of methadone to approach a steady state (5 half-lives).\(^1\) In a legal review of opioid deaths,\(^2\) Dr. Webster found that starting doses ranged from 20–140 mg/day, although most were started on ≤ 30 mg/day. He stated that the reason why one patient was started on 140 mg/day was because the prescriber used the equianalgesic conversion chart to determine the starting dose, and the patient died within 24 hours.

About 90% of the patients were opioid tolerant, and about 80% died within 4 days of first starting methadone.\(^2\) Snoring was common for these patients, a sign of sleep disorder. Occasional upper respiratory infection or flu onset preceded death.\(^2\) Dr. Webster stated that patient families should be alerted to watch for snoring or respiratory distress in these patients. Methadone should be started at low doses and titrated slowly.\(^1,2\) Consider starting patients, whether or not they are opioid naive, on ≤ 15 mg/day in divided doses (qh8). Increase the total daily dose by no more than 25%–50%, and no more frequently than weekly. Finally, if you are not experienced prescribing methadone, consult with an experienced clinician.
6. Assess for sleep apnea in patients on high daily doses of methadone or other opioids and in patients with a predisposition

Research has shown a high prevalence of sleep apnea in patients on chronic opioid therapy. The data suggest a dose relation, and the sleep apnea can be life threatening on moderate-to-high doses of opioids. In one study of 149 chronic pain patients on opioid therapy, the apnea–hypopnea index was abnormal (≥ 5 per hour) in 75% of patients (39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea); 25% had no sleep apnea. Dr. Webster stated that he and his colleagues were able to demonstrate a near linear relationship in dose of opioid and central sleep apnea. At a dose of about 150 mg equivalent, about 50%–60% of the population is going to have central sleep apnea. Dr. Webster suggested that clinicians need to think about ordering sleep studies whenever possible on people who are on methadone above 50 mg/day or on 150 mg of morphine equivalent for the other opioids. If the insurance company does not approve the study, then oximetry should be performed to record any desaturations. However, continuous positive airway pressure (CPAP) is often not a successful strategy. Consultation with a sleep specialist may be necessary to find the appropriate therapy.

7. Tell patients on long-term opioid therapy to reduce opioid dose during upper respiratory infections or asthmatic episodes

Advise patients to reduce their daily opioid doses by 30% or more during events with acute respiratory tract compromise because of a decreased margin of safety. These events include the flu, pneumonia, upper respiratory infections, and asthmatic episodes.

8. Avoid using long-acting opioid formulations for acute, post-operative, or trauma-related pain

Reserve ER/LA opioids for patients who have developed a tolerance to opioids. That is, who take regular, daily, around-the-clock opioids. They should not be used for acute, postoperative, or trauma-related pain. Dr. Webster stated that opioid naïve patients have not developed a tolerance for the respiratory-depressive effects of the drug. If they self-medicate, take more drugs, then with the ER/LA opioids, the dose builds up and they may cause serious respiratory depression.

In summary, when initiating and modifying opioid dosing, the regular assessment of pain is the cornerstone of effective pain management because it guides the clinician in the selection and titration of pain treatments for balancing against potential risks. Finally, when opioid therapy is no longer needed, the opioid dose should be tapered in order to safely discontinue treatment.

Managing therapy with ER/LA opioid analgesics

The goal of pain management is for the patient to live as full and meaningful a life as is possible with their chronic pain.

Steven Passik, PhD

Dr. Steven Passik stated that the goal of pain management is for the patient to live as full and meaningful a life as is possible with their chronic pain. The goal, therefore, is not 100% pain reduction, but rather to improve functioning. He said that he continuously sees about 57% relief in his group’s studies, and that we should want patients to adapt to this level of relief and overcome the rest of their pain in order to return to their lives. This goal is sometimes codified in the 4 As (Analgesia, Activities of daily living, Adverse effects, Aberrant drug taking). Dr. Passik stated that the 4 As can be used to engage patients in the process of assessing their own outcomes and recognizing how their clinicians understand success or failure in opioid therapy. Patient engagement is fundamental to achieving these goals. Because the population of patients with persistent pain is tremendously diverse, subgroups require a variety of strategies to allow them to realize the benefits of opioids and/or other interventions. Pain occurs in not only diverse but complex human beings, and is often complicated by depression and the negative life consequences it brings. Many patients require comprehensive management that goes beyond the relief that opioids and other strictly medical interventions can bring to encompass extensive lifestyle change. Having drug therapy be the sole focus can lead to overuse and a range of compliance problems as people seek to get more from their medications than they can bring and ignore the need for other interventions.

Dr. Passik said that he likes to teach the patient about these 4 As, and that they should understand that he only considers pain relief as one of several domains that are important for a desirable outcome. These domains...
include increased functioning as a quality of life issue. This means improved sleep, mood, and the ability for patients to fulfill their daily roles. The patient should have increased comfort, which can be measured with pain scales, being careful to distinguish between usual pain and flares. When discussing these goals with the patient, the role of medications should be decentralized. That is, it should be stressed to the patient that whereas medications are important, they are not the only way to recover and live their lives with chronic pain. Finally, patient satisfaction with therapy is crucial to avoid aberrant behavior. Monitoring for compliant drug-taking and appropriate attention to substance abuse and recovery activities is a necessary aspect of this approach.

**Opioid treatment agreements and monitoring patient adherence**

### Characteristics of an Opioid Agreement
- Goals of therapy
- Discussion of risks and benefits
- Expectations about prescribing and taking opioids
- Considered a trial
- Use of one prescriber and one pharmacy
- Avoiding abruptly stopping opioids
- No early refills
- No replacement of lost, stolen, or destroyed medication
- Patients must inform providers of all medications being taken
- Avoidance of alcohol and illicit substances while on opioids
- Prohibition of sharing, selling, or providing others access to opioids
- Follow-up and monitoring parameters
- Office visits
- Urine drug screening
- Prescription drug monitoring programs
- Pill counts
- Reasons for continuing or discontinuing opioids
- Secure storage of medications


Informed consent and patient prescriber agreements (PPA) are valuable tools that facilitate discussion, education, and structuring of care between the clinician and patient. Informed consent is conceptually separate from an opioid treatment agreement, and the documents serve separate but overlapping and reinforcing purposes. However, they may be combined.

### DEFINITIONS

**Addiction:** A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

**Physical dependence:** A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

**Tolerance:** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.


According to Dr. Webster, the informed consent form should discuss the potential adverse effects of opioids, including but not limited to sleepiness, constipation, nausea, itching, respiratory depression, inadequate pain relief, and risk of addiction. The definitions and descriptions of tolerance, physical dependence, and addiction should be included (see Box above). Alternative treatments should be discussed or tried. It should include a discussion of the risks for low testosterone in men and risks and discussion of pregnancy-related concerns of opioid therapy in women who may become pregnant. A description of counseling regarding operating heavy machinery, driving, etc., while taking opioids, particularly during initiation and dose changes, should also be included. And finally, the document should be signed and dated by the prescribing clinician and the patient.
According to the APS/AAPM guidelines the PPA should be discussed with patients prior to initiation of opioid therapy. Although a PPA is widely used, it is not evidence based. It should include:

- **A reminder that opioids are just one modality in a multifaceted approach to achieving goals of therapy**

There are a number of treatment strategies that can be incorporated in the treatment of chronic pain. As explained above, a complete history of your patient’s pain, including treatment, should be addressed. For example, pharmacotherapy may be combined with physical rehabilitation to facilitate functional improvement. Simple lifestyle changes such as weight loss may be incorporated into a multidisciplinary treatment plan. Spiritual and psychological support may be crucial to patients who suffer from depression because of their chronic pain conditions. Complementary or alternative approaches may also be incorporated. Because pharmacotherapy may be an integral component of your treatment regimen for a patient with chronic pain, it is important to understand the role of different classes of medications across increasing degrees of symptomatic severity.

- **It should list prohibited behaviors, and the grounds for tapering or discontinuation if these behaviors persist.**

Prohibited behaviors could include Concurrent abuse of alcohol or illicit drugs; injecting oral formulations; nonadherence with therapy despite warnings; obtaining prescription drugs from nonmedical sources; prescription forgery; repeatedly seeking prescriptions from other physicians or emergency departments without informing prescriber; selling prescription drugs; and/or stealing or borrowing drugs from others.

- **It should let the patient know that they should obtain opioids from only one prescriber, and fill prescriptions at only one pharmacy.**

- **The limitations on prescriptions (e.g. weekly or bimonthly instead of monthly amounts) should be delineated.**

- **It should include statements on the need for urine drug testing; and the schedule for office visits as well as the procedure for emergency issues (see above).**

- **Refill and dose-adjustment procedures should be explained and the need to maintain adherence.**

- **It should include instructions on the safe storage and disposal of opioids; and procedures to account for missed or missing doses.**

Tell the patient that prescriptions should be secured the same way as other valuables in the home, like jewelry or cash. Take prescription medications out of the medicine cabinet and hide them in a place only you know about. Some safe storage options are: an existing fire safe or gun safe; in a cut-proof bag designed for travel safety; in a “LOCKMED” Medicine Storage Lock Box; a “Vacation Vault”; locking medicine box or cabinet.

Teach your patients how to safely dispose of remaining drugs. They should be instructed to not flush prescription drugs down the toilet or drain unless the label or accompanying patient information specifically instructs them to. Prescription drugs not labeled to be flushed may be able to be disposed of at community drug take-back programs. If a drug take-back or collection program is not available, take the prescription drugs out of their original containers and either: 1) Mix drugs with an undesirable substance (e.g., cat litter or used coffee grounds), 2) Put the mixture into a disposable container with a lid or a sealable bag. Place the sealed container with the mixture and the empty drug containers in the trash after concealing or removing any personal information, including Rx number, from the empty drug container by covering it with black permanent marker or duct tape, or by scratching it off.

- **Patients should always be in a position to know if any pills are missing**

Dr. Gudin stated that the patient should be instructed to take note of how many pills are in each prescription bottle or pill packet. They should keep track of refills for their own medication, as well as for other members of the household. They should make sure friends and relatives are aware of the risks and regularly monitor their own medicines.

- **It should also describe an exit strategy for when opioids are no longer needed or when the aberrant behavior negates their use.**

- **Should be signed by both the prescriber and the patient.**

After signing the agreements, prescribers should continue to monitor patient adherence to the agreements. Pill counts, urine drug screening, family member or caregiver interviews, and use of prescription monitoring program data can be useful supplements to the PPA because patient self-reports may be unreliable.
for determining amount of opioid use, functionality, or aberrant drug-related behaviors. If necessary, referral for substance abuse treatment should be considered.

**Managing adverse events**

Adverse effects are a common and predictable consequence of opioid therapy. The degree of analgesia achieved, opioid-related side effects, physical and psychosocial status of the patient, and the possibility of aberrant drug-related behaviors should be assessed and documented at every visit. Anticipation of potential adverse effects facilitates timely treatment should a problem arise. Most of the side effects of opioid use are not life-threatening, and tolerance to these effects is typical. A meta-analysis of trials using opioid treatment for chronic pain showed that constipation, nausea, dizziness, somnolence, vomiting, and dry skin, itching, or pruritus were reported significantly more often in patients treated with opioids than in those treated with placebo. Constipation is the most common side effect of chronic opioid use and can be minimized with adequate hydration and treatment with a bowel regimen. Nausea and vomiting often occur early in the course of treatment and can usually be controlled with an antiemetic. Somnolence may occur at the start of treatment. The risk of this effect can be reduced by using a low starting dose and gradually increasing doses until analgesia is reached.

Respiratory depression is often considered the most serious adverse event associated with opioid treatment. However, tolerance to respiratory effects develops rapidly and therefore is not a common problem if dosing guidelines are followed for titration. On the other hand, a study evaluating 98 consecutive patients on chronic opioid therapy for sleep disordered breathing found that 36% of patients had obstructive sleep apnea, 24% had central sleep apnea, and 21% had mixed disorder. Another study compared 50 methadone maintenance treatment (MMT) patients to 20 matched normal subjects. Thirty percent of the MMT patients had central sleep apnea while all of the control subjects were normal (see also discussion above).

Finally, managing chronic noncancer pain in pregnant women can be challenging. COT in this setting affects at least two patients. Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Pregnant women should be encouraged to use minimal or no opioid therapy during their pregnancy, unless the potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn.

**Counseling patients and caregivers about the safe use of ER/LA opioid analgesics**

Given the complexities and risks of chronic opioid therapy, patients and their caregivers need education and counseling about the safe use of ER/LA opioid analgesics. As discussed above, this counseling starts when it is decided to initiate a trial of ER/LA opioids for chronic pain. The informed consent and PPA documents will contain much of the basic, general information about how opioids should be prescribed and taken, expectations for follow-up and monitoring, alternatives to opioid therapy, expectations regarding use of concomitant therapies, and potential indications for tapering or discontinuing opioid therapy. In addition, the FDA states that Prescribers should counsel patients to:

- Give product-specific information about the prescribed opioid. (This information is covered below.)
- Explain how to take the opioid as prescribed.
- Explain adherence to dosing regimen and how to handle missed doses.
- Warn that under no circumstances should an oral ER/LA opioid be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid causing overdose and death.
- Caution that the use of other CNS depressants, alcohol, or illegal drugs with ER/LA opioids can cause overdose and death. Patients should only use other CNS depressants under the instruction of their prescriber.
- Discuss that withdrawal symptoms can occur if an ER/LA opioid is discontinued suddenly. Patients should discuss plans to stop the ER/LA opioid with their prescriber. Patients should discuss a tapering regimen with their prescriber.
- Explain that sharing ER/LA opioids with others may cause serious side effects including death, and that selling or giving away ER/LA opioids is against the law.
- Counsel patients to store their ER/LA opioid in a safe and secure place away from children and pets and to read the product-specific disposal information included with the ER/LA opioid product.
A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

A table lists the FDA-approved ER/LA opioid analgesic products, including:
- **Avinza** (morphine sulfate ER capsules), **Belbuca** (buprenorphine buccal film), **Butrans** (buprenorphine transdermal system), **Dolophine** (methadone HCl tablets), **Duragesic** (fentanyl transdermal system), **Embeda** (morphine sulfate ER-naltrexone capsules), **Exalgo** (hydromorphone HCl ER tablets), **Hysingla ER** (hydrocodone bitartrate ER tablets), **Kadian** (morphine sulfate ER capsules), **MorphaBond** (morphine sulfate ER tablets), **MS Contin** (morphine sulfate CR tablets), **Nucynta** ER (tapentadol HCl ER tablets), **Opana ER** (oxymorphone HCl ER tablets), **OxyContin** (oxycodone HCl CR tablets), **Targiniq ER** (oxycodone HCL/naloxone HCL ER tablets), **Xtampza ER** (oxycodone), and **Zohydro ER** (hydrocodone bitartrate ER capsules).

There are currently 17 FDA approved ER/LA opioid analgesic products.

Prescriptions should be secured the same way as other valuables in the home, like jewelry or cash. They should be taken out of the medicine cabinet and hidden in a place only the patient knows about. They should also encourage their relatives and friends to secure their medications. If possible, all medicines should be stored in a safe place, such as an existing fire safe or gun safe, a cut-proof bag designed for travel safety, or in a locking medicine box or cabinet.

- Caution patients that ER/LA opioids can cause serious side effects that can lead to death. Patients should call their prescriber or get emergency medical help if they have symptoms of overdose or respiratory depression; symptoms of stomach or intestinal blockage; or allergic reactions. Patients should also be counseled on the most common side effects of ER/LA opioids and be cautioned about the risk of falls, working with heavy machinery, and driving.

In addition, patients should be counseled to call their prescriber for advice about side effects. Prescribers or patients are encouraged to report side effects to the FDA at 1-800-FDA 1088.

**General drug information for ER/LA opioid analgesic products**

Opioids are the kind of pain medicine that can treat nerve or neuropathic pain, visceral pain, nociceptive pain, musculoskeletal pain, even some forms of psychological pain. Patients get that little dopamine kick and they feel better. They improve function for many of our patients, relieve pain, improve quality of life, and clearly, play an important role in pain management and palliative care. On the other side of the balance, opioids can certainly be abused and misused.

**Dr. Jeffrey Gudin**

According to Knotkova et al., opioid dose escalation can yield intolerable and unmanageable side effects, such as somnolence or mental clouding. In addition, severe pain, often with emerging side effects, may continue despite repeated dose escalations. Dr. Gudin stated that under these circumstances, patients may benefit from opioid rotation. Opioid rotation refers to a switch from one opioid to another in an effort to improve therapeutic response or reduce undesirable effects. Although the specific mechanisms by which opioid rotation can improve the overall response to therapy are not known, the theoretical basis relates broadly to the large individual variation in responses to different µ-agonist opioids, and more specifically, to the

**Complexities of opioid therapy**

**Maximizing pain relief and minimizing adverse effects:**

Dr. Gudin stated that healthcare professionals who prescribe ER/LA opioids are in a key position to balance the benefits of pain relief against the risks of adverse events and serious adverse outcomes (Table 4, page 21). Healthcare providers should anticipate, identify, and treat common adverse effects associated with opioid therapy. Patients should also be closely monitored for any signs of tolerance, dependence, addiction, or withdrawal.

Dr. Gudin also commented that one of the major challenges with opioid therapy is that for most patients, the best we can provide is partial efficacy. Pain is never fully relieved. He stated that years ago he had been taught that there was no ceiling dose to a pure µ opioid, the prescriber could just keep going up on the dose until pain was controlled. However, he continued, he later found that in clinical practice, pain is almost never controlled. Therefore, he prescribes limiting doses of opioids for the safety reasons. He emphasized that he still uses opioids in most of his appropriate patients, but at more limited doses than in the past.
phenomenon of incomplete cross-tolerance to both analgesic and nonanalgesic opioid effects.\textsuperscript{41} Due to individual differences in opioid receptor subtypes, changing the opioid administered may improve pain relief or decrease intolerable side effects. For example, there are demonstrated gender differences in receptors and in opioid response.\textsuperscript{42,43} Therefore, any change from one opioid to another may yield a different set of effects, sometimes more favorable and sometimes less favorable. In addition, the impact of incomplete cross-tolerance may bias this change toward relative improvement.\textsuperscript{41} Dr. Gudin commented that “You could be a morphine responder, another might be a fentanyl responder, while I might be a hydromorphone responder. Let’s say it takes two or three or four rotations until you find the right drug for the right patient. Believe it or not, that’s true of NSAIDs as well. NSAIDs have different chemical classes and you could rotate NSAIDs and get an analgesic or an anti-inflammatory response with one class that you weren’t getting with another class, so we have to remember about this whole concept of receptor subtypes.” If cross-tolerance to the analgesic response produced by the first opioid is less complete than cross-tolerance to treatment-limiting side effects of the second opioid, the switch will yield a more favorable overall response to therapy.\textsuperscript{41} The phenomena of individual variation and cross-tolerance are poorly understood. There also may be benefit in switching to a different route of administration (e.g., transdermal rather than oral), or drug formulation (e.g., a formulation with once-daily dosing).\textsuperscript{41} Also, a change in the clinical status of the patient may suggest the need for an opioid with different pharmacokinetic properties, for example, a drug without active metabolites in a patient with progressive renal insufficiency.\textsuperscript{41} As discussed above, when implementing an opioid rotation, a clinician must calculate an approximate equianalgesic dose between the old and new opioids.\textsuperscript{41} The calculated starting dose of the new opioid must be safe, i.e. neither high enough to cause opioid toxicity nor low enough to cause withdrawal.\textsuperscript{41} The dose should also be sufficient to produce no worsening of the pain. The optimal dose of the new opioid usually must be titrated from this starting dose, and should ideally yield an improved balance between analgesia and side effects.\textsuperscript{41} The calculation of an approximate equianalgesic dose is necessary because the analgesic potency of the various opioid drugs varies greatly. Among the various opioids available for clinical use, potency varies by orders of magnitude (i.e., from micrograms to milligrams).\textsuperscript{41} For example, an opioid naïve patient is likely to experience comparable analgesic effects from parenteral administration of a single 100 mg dose of fentanyl (FE) and a single 10


**Table 5  Industry’s approach to abuse-deterrent opioids**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agonist/Antagonist Combos</strong></td>
<td>May curb euphoria when formulation compromised</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Antagonist may be formulated to be clinically active only when tampered with</td>
</tr>
<tr>
<td><strong>Aversion</strong></td>
<td>Substances may be added to create unpleasant effects when tampered with or taken at higher doses</td>
</tr>
<tr>
<td><strong>Delivery System</strong></td>
<td>Drug-release designs or method of drug delivery can offer resistance to abuse</td>
</tr>
<tr>
<td><strong>New Molecular Entities and Prodrugs</strong></td>
<td>May require enzymatic activation, different receptor binding profiles, slower CNS penetration, or other novel effects</td>
</tr>
<tr>
<td><strong>Physical/Chemical Barriers</strong></td>
<td>May prevent chewing, crushing, cutting, grating, or grinding</td>
</tr>
<tr>
<td></td>
<td>May resist extraction by solvents</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>Use of 2 or more technologies in 1 product to deter abuse</td>
</tr>
<tr>
<td><strong>Novel Approaches</strong></td>
<td>Use of technologies not captured by any of the above</td>
</tr>
</tbody>
</table>

The instruction for conversion in the Dosage and Administration section (2.1) in the Prescribing Information of each product should be followed when converting patients from one opioid to another.44

Misuse and abuse of opioids

Abuse-deterrent opioids: Dr. Gudin explained that there are two categories of patients who misuse or abuse prescription opioids: medical users who just want more pain relief or who have emotional issues, and nonmedical users who are recreational abusers or patients with addiction. As discussed above, opioid analgesics are among the most commonly misused or abused pharmaceuticals. Dr. Gudin stated that because the potency of prescription drugs will be consistent with each use, it makes them preferable to street drugs. He continued, saying “there is no single approach to


A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

treating prescription drug abuse in this country that will work. We need a collaborative approach between health care providers, patients, the federal and state governments, and the pharmaceutical industry. The REMS national effort is a good start to educate those on the front lines.”

Industry is involved in this effort by developing abuse-deterrent formulations of drugs. These are designed to counter the most common methods of abuse, including administration of drugs orally, by inhaling (snorting), through parenteral means (IV, IM, SC), and smoking. The primary forms of opioid manipulation include crushing or grinding into small particles or powder, dissolving in a solvent (e.g. alcohol or acetone), and extraction by exposure to hot or cold temperatures. The FDA has identified seven categories of abuse-deterrent technologies (Table 5, page 22). Current abuse-deterrent formulations include Oxycontin, Targiniq ER, Hysingla ER, Embeda, Oxaydo, Suboxone, Zohydro ER, and Xtampza ER. Other formulations are in development. However, it is important to remember that abuse-deterrent drug formulations do not replace a comprehensive assessment.

**Adverse effects**

The incidence and severity of side effects can have a significant impact on the outcome of chronic opioid therapy. Typical opioid adverse effects include constipation, nausea, vomiting, somnolence, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, sedation, osteoporosis, sexual dysfunction, and endocrine dysfunction. It has been reported in one study that testosterone levels were subnormal in 74% of the opioid-treated patients in the study. The same group found significant inhibition of ovarian sex hormone and adrenal androgen production among women chronically consuming sustained-action opioids. Patients often discontinue opioid use due to these side effects. To minimize adverse effects, opioids should be titrated so that an acceptable level of pain relief is balanced against an acceptable tolerance of side effects. Adverse effects due to opioids often subside over time as the patient may develop a tolerance for them. Therefore, only temporary symptomatic management may be needed. However, adverse events that usually do not diminish are constipation, endocrine dysfunction, and sleep-disordered breathing. Therefore, regular reassessments and monitoring may be required.

Other less common adverse effects, such as sweating, peripheral edema, urinary retention, myoclonus, and dyspepsia, may be treated by dose reduction or opioid rotation. Slower titration may minimize adverse effects.

The Veterans Affairs and Department of Defense (VA/DOD) suggests the following approaches to managing these side effects:

1. **Overall:** Recommend modifying the dose or rotating the opioid agent to minimize adverse effects.

2. **For constipation:** Initial bowel regimens should generally include a stimulant laxative and a stool softener.

3. **For nausea and vomiting:** Consider prophylactic antiemetic therapy. Add or increase non-opioid adjuvants. If analgesia is satisfactory, decrease opioid dose by 25%.

4. **For sedation:** Determine whether sedation is due to the opioid; eliminate nonessential CNS depressants. If analgesia is satisfactory, reduce opioid dose by 10%–15%. Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced. Add stimulant drug during the day such as caffeine. Change opioid.

5. **For itching:** Consider treatment with antihistamines; Change opioid.

6. **For hallucination/dysphoria:** Evaluate underlying cause. Eliminate nonessential CNS-acting medications (e.g. steroids).

7. **For delirium:** Delirium should be managed by first ruling out or eliminating other causes (metabolic disturbances, hypoxia, and dehydration), offending antipsychotic agent (phenothiazines or tricyclic antidepressants) and reducing doses of or discontinuing nonessential, centrally acting medications, if pain is under control. Opioid switch rather than opioid reduction is a reasonable option if pain is not well controlled. Reduction in the dose of opioid, and the addition, if needed, of an adjuvant analgesic may resolve symptoms. If pharmacologic treatment is deemed necessary, haloperidol may be considered for patients who have agitated delirium, because of its efficacy and low incidence of cardiovascular and anticholinergic side effects.

8. **For opioid induced endocrinopathy:** Evidence indicates that a significant percentage of patients treated with opioid therapy develop opioid-induced endocrinopathy. This side effect is responsive to therapy if it is appropriately recognized and diagnosed. Symptoms of opioid-induced endocrinopathy include decreased libido, erectile dysfunction (men), infertility, depression and anxiety, decreased muscle mass and strength, tiredness or fatigue, hot flashes and night sweats, amenorrhea,
irregular menses, galactorrhea (women), osteoporosis and fractures. Testosterone patch therapy was beneficial in treating men with low testosterone. In a study with 23 men, androgen deficiency symptoms, sexual function, mood, depression and hematocrit levels showed improvement during treatment. Testosterone patch therapy was beneficial in treating men with low testosterone. In a study with 23 men, androgen deficiency symptoms, sexual function, mood, depression and hematocrit levels showed improvement during treatment. 18,47,48 Testosterone patch therapy was beneficial in treating men with low testosterone. In a study with 23 men, androgen deficiency symptoms, sexual function, mood, depression and hematocrit levels showed improvement during treatment. 18,47,48

Respiratory depression is a serious adverse effect of opioids. Opioids produce a concentration-dependent shift in the carbon dioxide response curve. Patients can usually compensate for the shift at clinically appropriate opioid doses. 12 However, if some other cardiopulmonary insult occurs, the patient may be at risk. 12 Also, if the patient is taking another central nervous system depressant, the patient may be at risk. An analysis of the root causes of opioid-related deaths found that likely contributors to many opioid-related deaths were the presence of additional central nervous system depressant drugs, such as alcohol, benzodiazepines, and antidepressants, as well as sleep-disordered breathing. 50

Other considerations in choosing an opioid

Drug-drug interactions. Drug-drug interactions are another potential source of adverse effects in patients with chronic pain. Most opioids undergo hepatic metabolism using cytochrome P-450 (CYP) CYP2D6 and CYP3A4 enzymes. This metabolic route is shared with a wide variety of other drugs. Moreover, genetic variability in metabolic capacity may influence opioid efficacy. Because comorbidity is common in the chronic pain population, potential interactions should be considered before prescribing opioids. 12

Elderly patients. Although the principles of prescribing opioids for older patients are the same as those for younger patients, it is important to recognize that the elderly may be more sensitive to both analgesic and adverse effects of these medications. 12 Evidence suggests that the rate of administration rather than the absolute dose may need to be adjusted to optimize analgesia and reduce the risks of adverse effects such as respiratory depression. 15

Specific drug information for ER/LA opioid analgesic products

As mentioned above, there are currently 17 available ER/LA drugs that are included in this program. Prescribers need to understand specific characteristics of the ER/LA opioid analgesic products they prescribe. Appendix 2 (page 29) lists a summary of the most recent information regarding these ER/LA agents. Most of the ER/LA opioids are available as pill or capsule formulations, except for Butrans (buprenorphine) and Duragesic (fentanyl) which are available as transdermal patches; and Belbuca (buprenorphine), which is available as a buccal film (see Appendix 2, page 29). In addition, most opioids are metabolized through the liver microsomal cytochrome P-450 system. Therefore, if patients are taking drugs which either inhibit or induce these enzymes, or if the patient has either genetic factors which affect these enzyme levels, or has severe liver disease, it is important to consider if these drug interactions or pathological conditions can have clinically relevant effects on the patient. Opioid classes which can have specific interactions with cytochrome P-450 enzymes include buprenorphine, fentanyl, hydrocodone, methadone, and oxycodone (see Appendix 2). Opioid classes without specific interactions with the cytochrome P-450 enzymes include hydromorphone, morphine, oxymorphone, and tapentadol (see Appendix 2). For more detailed information, refer to prescribing information available at www.dailymed.nlm.nih.gov or at www.fda.gov/drugsatfda.

Summary

The goal of treatment for chronic pain is to achieve adequate pain relief while limiting the risk of aberrant medication-related behaviors and other adverse effects. However, before undertaking management of patients requiring opioids for chronic pain, clinicians need to have an adequate understanding of the benefits and risks of ER/LA opioid analgesia. Clinicians should assess their skills and the capacity of their practice to monitor patients and to recognize complications as soon as they arise, including adverse events and opioid misuse and abuse. In addition, a clear understanding of the specific characteristics of the drugs prescribed is necessary. Strategies to minimize the risk of adverse effects, including aberrant behavior, require initial screening and ongoing assessment of patients. Providing adequate pain relief and minimizing adverse effects will require dose titration and possible opioid rotation. Risk of aberrant behaviors can be reduced by educating the patient, the patient’s family, and caregivers about the need to carefully follow the prescribed treatment. Prescription oversight by a single physician who is familiar with the patient combined with close monitoring can provide further risk reduction. In cases of abuse or misuse of prescription opioids, rotation to opioids with lower abuse potential, along with tighter controls of prescriptions and increased monitoring, may allow for continued therapy. In other cases, discontinuation of opioid therapy may be necessary.
References


26. NIDA. Comorbid drug abuse and mental illness: A research update from the National Institute on Drug Abuse. 2007.


Appendix 1  Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

| Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics) |
|---|---|
| Avinza (morphine sulfate ER capsules) | MorphaBond (morphine sulfate ER tablets) |
| Belbuca (buprenorphine buccal film) | MS Contin (morphine sulfate ER tablets) |
| Butrans (buprenorphine transdermal system) | Nucynta ER (tapentadol HCl ER tablets) |
| Dolophine (methadone HCl tablets) | Opana ER (oxymorphone HCl ER tablets) |
| Duragesic (fentanyl transdermal system) | OxyContin (oxycodeone HCl ER tablets) |
| Embeda (morphine sulfate ER-naltrexone capsules) | Tarjecty ER (oxycodone HCl/naloxone HCl ER tablets) |
| Exalgo (hydromorphone HCl ER tablets) | Xtampza ER (oxycodone ER capsules) |
| HySTING LA (hydrocodone bitartrate ER tablets) | Zohydro ER (hydrocodone bitartrate ER capsules) |

Dosing Interval

- Refer to individual product information.

Key Instructions

- Limitations of usage:
  - Reserve 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.
  - 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.

- 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.

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.

Buccal film dosage form:
- Do not use if the package seal is broken or the film is cut, damaged, or changed in any way.
- See individual product information for the following:
  - Dosage reduction for hepatic or renal impairment.
A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics

<table>
<thead>
<tr>
<th>Drug Interactions Common to the Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• Avoid concurrent use of mixed opioid agonist/antagonists (i.e., pentazocine, nalbuphine, and butorphanol) or partial opioid agonists (buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist. In these patients, mixed opioid agonist/antagonists and partial opioid agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms.</td>
</tr>
<tr>
<td>• Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.</td>
</tr>
<tr>
<td>• Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use in Opioid-Tolerant Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adult patients considered opioid-tolerant are those receiving, for one week or longer:</td>
</tr>
<tr>
<td>• at least 60 mg oral morphine/day</td>
</tr>
<tr>
<td>• 25 mcg transdermal fentanyl/hour</td>
</tr>
<tr>
<td>• 30 mg oral oxycodone/day</td>
</tr>
<tr>
<td>• 8 mg oral hydromorphone/day</td>
</tr>
<tr>
<td>• 25 mg oral oxymorphone/day</td>
</tr>
<tr>
<td>• Pediatric patients (11 years and older) considered opioid-tolerant are those who are already receiving and tolerating a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (applicable to OxyContin’s pediatric indication only).</td>
</tr>
<tr>
<td>• See individual product information for which products:</td>
</tr>
<tr>
<td>• Have strengths or total daily doses only for use in opioid-tolerant patients</td>
</tr>
<tr>
<td>• Are only for use in opioid-tolerant patients at all strengths.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significant respiratory depression</td>
</tr>
<tr>
<td>• Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment</td>
</tr>
<tr>
<td>• Known or suspected paralytic ileus</td>
</tr>
<tr>
<td>• Hypersensitivity (e.g., anaphylaxis)</td>
</tr>
<tr>
<td>• See individual product information for additional contraindications.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Potency To Oral Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• These are intended as general guides.</td>
</tr>
<tr>
<td>• Follow conversion instructions in individual product information.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
</tbody>
</table>
Appendix 2. Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)\(^4\)

<table>
<thead>
<tr>
<th>Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avinza</strong></td>
</tr>
<tr>
<td>Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg</td>
</tr>
<tr>
<td><strong>Dosing Interval</strong></td>
</tr>
<tr>
<td>Once a day</td>
</tr>
<tr>
<td><strong>Key Instructions</strong></td>
</tr>
<tr>
<td>• Initial dose in opioid non-tolerant patients is 30 mg.</td>
</tr>
<tr>
<td>• Titrate in increments of not greater than 30 mg using a minimum of 3 to 4 day intervals.</td>
</tr>
<tr>
<td>• Swallow capsule whole (do not chew, crush, or dissolve).</td>
</tr>
<tr>
<td>• May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately.</td>
</tr>
<tr>
<td>• Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excit mental, tauric acid.</td>
</tr>
<tr>
<td><strong>Specific Drug Interactions</strong></td>
</tr>
<tr>
<td>• Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine.</td>
</tr>
<tr>
<td>• P-gp inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.</td>
</tr>
<tr>
<td><strong>Use in Opioid-Tolerant Patients</strong></td>
</tr>
<tr>
<td>90 mg and 120 mg capsules are for use in opioid-tolerant patients only.</td>
</tr>
<tr>
<td><strong>Product-Specific Safety Concerns</strong></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td><strong>Belbuca</strong></td>
</tr>
<tr>
<td>Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg</td>
</tr>
<tr>
<td><strong>Dosing Interval</strong></td>
</tr>
<tr>
<td>Every 12 hours (or once every 24 hours for initiation in opioid naïve patients and patients taking less than 30 mg oral morphine sulfate equivalents)</td>
</tr>
<tr>
<td><strong>Key Instructions</strong></td>
</tr>
<tr>
<td>• Opioid-naïve patients or patients taking less than 30 mg oral morphine sulfate equivalents: Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 hours.</td>
</tr>
<tr>
<td>• Titrate to 150 mcg every 12 hours no earlier than 4 days after initiation.</td>
</tr>
<tr>
<td>• Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days.</td>
</tr>
<tr>
<td>• When converting from another opioid, first taper the current opioid to no more than 30 mcg oral morphine sulfate equivalents per day prior to initiating Belbuca.</td>
</tr>
<tr>
<td>• If prior daily dose before taper was 30 mg to 89 mg oral morphine sulfate equivalents, initiate with 150 mcg dose every 12 hours.</td>
</tr>
<tr>
<td>• If prior daily dose before taper was 90 mg to 160 mg oral morphine sulfate equivalents, initiate with 300 mcg dose every 12 hours.</td>
</tr>
<tr>
<td>• Titration of the dose should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days.</td>
</tr>
<tr>
<td>• Maximum dose: 900 mcg every 12 hours due to the potential for QTc prolongation.</td>
</tr>
<tr>
<td>• Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function.</td>
</tr>
<tr>
<td>• Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis.</td>
</tr>
<tr>
<td>• Do not use if the package seal is broken or the film is cut, damaged, or changed in any way.</td>
</tr>
</tbody>
</table>
### Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

#### Specific Drug Interactions
- CYP3A4 inhibitors may increase buprenorphine levels.
- CYP3A4 inducers may decrease buprenorphine levels.
- Benzodiazepines may increase respiratory depression.
- Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes.

#### Use in Opioid-Tolerant Patients
- Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses of Belbuca.

#### Product-Specific Safety Concerns
- QTc prolongation and torsade de pointes
- Hepatotoxicity

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

#### Butrans
- Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 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 in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20 mcg/hour
- 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 IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes.

#### Use in Opioid-Tolerant Patients
- Butrans 7.5 mcg/hr, 10 mcg/hr, 15 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 pointes.
- Hepatotoxicity
- Application site skin reactions

#### Relative Potency To Oral Morphine
- Equipotency to oral morphine has not been established.
### Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolophine</td>
<td>Methadone Hydrochloride Tablets, 5 mg and 10 mg</td>
</tr>
<tr>
<td>Dosing Interval</td>
<td>Every 8 to 12 hours</td>
</tr>
</tbody>
</table>

#### 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.
- Titrate slowly, with dose increases no more frequent than every 3 to 5 days. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days).
- 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, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (*These strengths are available only in generic form)
- 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 a minimum of 72 hour intervals between dose adjustments.
  - 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.
## FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

**04/2016**

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

<table>
<thead>
<tr>
<th>Specific Drug Interactions</th>
<th>Use in Opioid-Tolerant Patients</th>
<th>Product-Specific Safety Concerns</th>
<th>Relative Potency To Oral Morphine</th>
<th>Embeda</th>
<th>Dosing Interval</th>
<th>Key Instructions</th>
<th>Specific Drug Interactions</th>
<th>Use in Opioid-Tolerant Patients</th>
<th>Drug-Specific Adverse Reactions</th>
<th>Relative Potency To Oral Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CYP3A4 inhibitors may increase fentanyl exposure.</td>
<td>All doses of Duragesic are indicated for use in opioid-tolerant patients only.</td>
<td>• Accidental exposure due to secondary exposure to unwashed/unclothed application site.</td>
<td>See individual product information for conversion recommendations from prior opioid.</td>
<td>Morphine Sulfate ER-Naltrexone</td>
<td>Once a day or every 12 hours</td>
<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 and absorption of a potentially fatal dose of morphine.</td>
<td>Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.</td>
<td>Allergic manifestations to sulfite component.</td>
<td>Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.</td>
</tr>
<tr>
<td>• CYP3A4 inducers may decrease fentanyl exposure.</td>
<td></td>
<td>• Increased drug exposure with increased core body temperature or fever.</td>
<td></td>
<td>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.</td>
<td></td>
<td>• Swallow capsules whole (do not chew, crush, or dissolve).</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>• Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.</td>
<td></td>
<td>• Bradycardia</td>
<td></td>
<td></td>
<td></td>
<td>• Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• Application site skin reactions</td>
<td></td>
<td></td>
<td></td>
<td>• May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics

#### Hysingla ER
- Hydrocodone bitartrate
- Extended-Release Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg

#### Dosing Interval
- Every 24 hours (once-daily)

#### Key Instructions
- Opioid-naïve patients: initiate treatment with 20 mg orally once daily. During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved.
- Swallow tablets whole (do not chew, crush, or dissolve).
- Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction.
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
- Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.

#### Specific Drug Interactions
- CYP3A4 inhibitors may increase hydrocodone exposure.
- CYP3A4 inducers may decrease hydrocodone exposure.
- Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels.
- The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.

#### Use in Opioid-Tolerant Patients
- A single dose of Hysingla ER greater than or equal to 80 mg is only for use in opioid tolerant patients.

#### Product-Specific Safety Concerns
- Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction.
- Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER.
- In nursing mothers, discontinue nursing or discontinue drug.
- QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

#### Relative Potency To Oral Morphine
- See individual product information for conversion recommendations from prior opioid.

#### Key Instructions
- Product information recommends not using as first opioid.
- Titrater 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.
A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

<table>
<thead>
<tr>
<th>Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)</th>
</tr>
</thead>
</table>
| **Specific Drug Interactions**                                      | • Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine.  
  • P-gp 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 |
| **MorphaBond**                                                     | Morphine Sulfate  
  Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 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 1 to 2-day intervals.  
  • Swallow tablets whole (do not chew, crush, or dissolve). |
| **Specific Drug Interactions**                                      | P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold. |
| **Use in Opioid-Tolerant Patients**                                | MorphaBond 100 mg tablets are for use in opioid-tolerant patients only. |
| **Product-Specific Safety Concerns**                              | None |
| **MS Contin**                                                      | Morphine Sulfate  
  Extended-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 1 to 2-day intervals.  
  • Swallow tablets whole (do not chew, crush, or dissolve). |
| **Specific Drug Interactions**                                      | P-gp 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. |
### Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

<table>
<thead>
<tr>
<th>Use in Opioid-Tolerant Patients</th>
<th>No product-specific considerations.</th>
</tr>
</thead>
</table>
| 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 non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 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.  
• Titrated in increments of 5 to 10 mg using a minimum of 3 to 7-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 | • Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen. |
| Relative Potency To Oral Morphine | Approximately 3:1 oral morphine to oxymorphone oral dose ratio |
| **OxyContin** | **Oxycodone Hydrochloride**  
Extended-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg |
| Dosing Interval | • Every 12 hours |
| Key Instructions | • For Adults:  
• Initial dose in opioid-naive and opioid non-tolerant patients is 10 mg every 12 hours.  
• If needed, adult dosage may be adjusted in 1 to 2 day intervals.  
• When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose.  

• For Pediatric patients (11 years and older): Use only in opioid-tolerant patients (see below, Use in Opioid-Tolerant Patients for dosing information).  

• For all patients:  
• 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.  

• CYP3A4 inhibitors may increase oxycodone exposure.  
• CYP3A4 inducers may decrease oxycodone exposure. |
### Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

<table>
<thead>
<tr>
<th>Use in Opioid-Tolerant Patients</th>
<th>For Adults:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in adult patients in whom tolerance to an opioid of comparable potency has been established.</td>
</tr>
<tr>
<td></td>
<td>• For Pediatric patients (11 years and older):</td>
</tr>
<tr>
<td></td>
<td>• For use only in opioid-tolerant pediatric patients already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OxyContin.</td>
</tr>
<tr>
<td></td>
<td>• If needed, pediatric dosage may be adjusted in 1 to 2 day intervals.</td>
</tr>
<tr>
<td></td>
<td>• When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% of the current total daily dose.</td>
</tr>
</tbody>
</table>

| 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. |

<table>
<thead>
<tr>
<th>Tarrimon ER</th>
<th>Oxycodone Hydrochloride / Naloxone Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extended-release tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg</td>
</tr>
</tbody>
</table>

| Dosing Interval | Every 12 hours |

| Key Instructions | Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours. |
|                  | Titrate using a minimum of 1 to 2 day intervals. |
|                  | Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12) of Tarrimon ER. |
|                  | May be taken with or without food. |
|                  | Swallow tablets whole. Do not chew, crush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms. |
|                  | Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In patients with mild 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. |

| 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/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients only. |

| Product-Specific Safety Concerns | Contraindicated in patients with moderate to severe hepatic impairment. |

| Relative Potency To Oral Morphine | See individual product information for conversion recommendations from prior opioid. |

<table>
<thead>
<tr>
<th>Xttampza ER</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extended-Release Capsules, 9 mg 13.5 mg, 18 mg, 27 mg, and 36 mg (strengths equivalent to 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxycodone hydrochloride, respectively)</td>
</tr>
</tbody>
</table>

| Dosing Interval | Every 12 hours |
A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

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<tr>
<th>Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)</th>
</tr>
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<tbody>
<tr>
<td><strong>Key Instructions</strong></td>
</tr>
<tr>
<td>- Opioid naive and opioid non-tolerant patients: Initiate with 9 mg every 12 hours.</td>
</tr>
<tr>
<td>- Titrate using a minimum of 1 to 2 day intervals.</td>
</tr>
<tr>
<td>- Take Xtampza ER capsules with the same amount of food in order to ensure consistent plasma levels are achieved.</td>
</tr>
<tr>
<td>- Maximum daily dose: 288 mg (8 x 36 mg capsules) because the safety of excipients has not been established for higher doses.</td>
</tr>
<tr>
<td>- For patients that have difficulty swallowing, Xtampza ER can also be taken by sprinkling the capsule contents on soft foods or into a cup and then administering directly into the mouth and swallowing immediately. Xtampza ER may also be administered through a gastrostomy or nasogastric feeding tube.</td>
</tr>
<tr>
<td>- Hepatic impairment: Initiate therapy at 1/3 to 1/2 the usual dosage</td>
</tr>
<tr>
<td>- Renal impairment: (creatinine clearance &lt;80 mL/min): Follow a conservative approach to dose initiation and adjust according to the clinical situation.</td>
</tr>
</tbody>
</table>

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<tr>
<th>Specific Drug Interactions</th>
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<td>- CYP3A4 inhibitors may increase oxycodone exposure</td>
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<td>- CYP3A4 inducers may decrease oxycodone exposure</td>
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<tr>
<th>Use in Opioid-Tolerant Patients</th>
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<tbody>
<tr>
<td>A single dose greater than 36 mg or a total daily dose greater than 72 mg is for use in opioid-tolerant patients only.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Product-Specific Safety Concerns</th>
</tr>
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<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Potency To Oral Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no established conversion ratios for conversion from other opioids to Xtampza ER defined by clinical trials.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zohydro ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing Interval</th>
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<tbody>
<tr>
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<table>
<thead>
<tr>
<th>Key Instructions</th>
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</thead>
<tbody>
<tr>
<td>Initial dose in opioid non-tolerant patient is 10 mg.</td>
</tr>
<tr>
<td>Titrate in increments of 10 mg using a minimum of 3 to 7 day intervals.</td>
</tr>
</tbody>
</table>

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<tr>
<th>Specific Drug Interactions</th>
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<tr>
<td>- Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone.</td>
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<tr>
<td>- CYP3A4 inhibitors may increase hydrocodone exposure.</td>
</tr>
<tr>
<td>- CYP3A4 inducers may decrease hydrocodone exposure.</td>
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<th>Use in Opioid-Tolerant Patients</th>
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<td>Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.</td>
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<th>Product-Specific Safety Concerns</th>
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<tbody>
<tr>
<td>None</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Potency To Oral Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.</td>
</tr>
</tbody>
</table>

For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.
Post-test

In order to receive credit, please complete the online CME/CE post-test and evaluation form at www.rockpointe.com/REMS. The post-test questions are listed below for your reference and convenience, and are identical to the post-test you will find online. However, to receive credit you must complete the online form at: www.rockpointe.com/REMS. If you are experiencing problems or have any questions, please email contact@rockpointe-pcme.com.

1. Opioid risk assessment should include:
   a) Genetic testing for 2D6 mutations
   b) Liver function tests and cholesterol levels
   c) Prior pharmacologic and nonpharmacologic treatments
   d) Pulmonary function testing

2. ER/LA drugs can be used in any of the following cases except:
   a) Intractable back pain
   b) Neuropathic pain
   c) Postsurgical recovery
   d) Postherpetic neuralgia

3. If highly structured conditions are in place (i.e. more frequent or intense monitoring strategies, authorization of limited prescription quantities, and consultation or co-management with professionals who have expertise in addiction or mental health issues), which of the following patients could be considered for opioid therapy? Patients with:
   a) Past or current psychopathology
   b) Past history of substance abuse disorders
   c) Aberrant drug-related behaviors
   d) All of the above

4. In converting patients from one extended release opioid to another extended release opioid:
   a) Start the new ER opioid at a lower dose or dose as if the patient is opioid naïve
   b) Use conversion tables to determine the exact starting dose of the new opioid
   c) Adjust dose of new opioid every 24 hours
   d) Never use immediate release opioids during an opioid rotation

5. For patients who have had no previous opioid exposure, which of the following statements is correct?
   a) Opioids should be started at a low dose and titrated slowly
   b) Only short-acting opioids should be considered until the patient shows he/she will not become addicted
   c) Patients should only be prescribed opioids if they agree to counseling
   d) They should be referred to a pain specialist

6. Which of the following screening tools is useful in identifying opioid misuse once therapy has begun?
   a) ORT
   b) SOAPP
   c) DIRE
   d) COMM

7. Monitoring patients on opioids should include:
   a) Monthly urine drug test
   b) Prescription monitoring database review with every prescription
   c) Police arrest record review annually
   d) Adverse effects, pain level, and change in activity

8. In converting patients from one extended release opioid to another extended release opioid:
   a) Start the new ER opioid at a lower dose or dose as if the patient is opioid naïve
   b) Use conversion tables to determine the exact starting dose of the new opioid
   c) Adjust dose of new opioid every 24 hours
   d) Never use immediate release opioids during an opioid rotation
9. Which of the following is the correct definition of TOLERANCE?
   a) A state of adaptation characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving
   b) A state of adaptation that imitates a drug class-specific withdrawal syndrome
   c) A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time
   d) A state of adaptation at which the patient is able to abide their chronic pain without opioids

10. When counseling regarding Extended Release opioids, patients should be informed that these agents:
   a) Can be chewed if the patient is having trouble swallowing them
   b) Must be taken with food
   c) Should not be stopped abruptly
   d) Should be kept in the medicine cabinet

11. When counseling patients regarding safety, patients should be informed that all of the following are common AEs of opioid analgesics except?
   1. Pupillary dilation
   2. Constipation
   3. Pruritus
   4. Respiratory depression

12. Patients should be counseled that if they have any pills remaining after chronic opioid therapy ends:
   a) They should save the opioids in case their pain becomes too severe later
   b) They should take the pills back to the pharmacy and have them dispose of the pills
   c) They should crush the pills and wash down the sink
   d) They should follow the proper and legal method to dispose of the pills under manufacturer instruction and state law

13. Examples of opioids that have been formulated to deter abuse include all of the following except:
    1. Oxycodone
    2. Hydrocodone
    3. Hydromorphone
    4. Methadone

14. Which of the following dosage levels being taken for one week or longer would NOT be considered indicative of an opioid-tolerant patient?
    a) Receiving at least 12 mcg fentanyl/hour
    b) Receiving at least 8 mg oral hydromorphone/day
    c) Receiving at least 25 mg oral oxymorphone/day
    d) Receiving at least 30 mg oral oxycodone/day

15. Which of the following adverse effects of opioids do NOT diminish over time?
    a) Nausea
    b) Constipation
    c) Itching
    d) Pruritus

16. Which of the following opioids is available as a transdermal patch?
    a) Morphine
    b) Tapentadol
    c) Buprenorphine
    d) Hydromorphone

17. It can be exceedingly dangerous to combine opioids with which of the following medications?
    a) Statins
    b) SSRI antidepressants
    c) Anti-hypertensive medications
    d) Benzodiazepines

18. Cytochrome P-450 inhibitors and inducers may affect the levels of which of the following classes of opioids?
    a) Morphine
    b) Oxycodone
    c) Tapentadol
    d) Oxymorphone