Chapter 2: Best Practices for Prescribing Opioids in Chronic Non-Cancer Pain

3 Contact Hours

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Learning objectives

- Describe how to assess patients for the appropriateness of treatment with opioid analgesics.
- Explain how to start opiate therapy, change dosages, and discontinue treatment with opioid analgesics.
- Recognize the types of written agreements that can be used to initiate and monitor therapy with opioid analgesics.
- Describe how to monitor patients on opiate therapy, including high-risk patients and those showing signs of abuse.

- Explain the side effects associated with opiate treatment, including management of side effects.
- Discuss switching between opiates and variables that may influence opioid rotation.
- Describe the important points that must be conveyed to the patient during patient consultation.
- Explain general and product-specific information related to the prescribing of extended-release/long-acting opiates.
- Emergency-room visits related to non-medical use of opioids rose 111% between 2004 and 2008 [7].
- Between 1998 and 2008, the rate of opioid misuse increased 400% [8].
- Drug overdose is now the second-leading cause of accidental death in America, exceeded only by car crashes [9].

Introduction

Opioid analgesics are widely accepted for the treatment of severe acute pain and chronic pain related to active cancer or at the end of life [1]. The widespread use of opioids for other types of moderate-to-severe chronic pain, however, has been evolving in the past two decades and continues to generate controversy. Prior to the 1990s, clinicians often viewed opioid pain medications with skepticism and avoided prescribing them, even when risks were thought to be low [2]. This perspective gave way to the recognition that many patients were being undertreated for their pain, leading to increased interest in the clinical value of opioids and a dramatic rise in rates of opioid prescribing for analgesia. Prescriptions for opioids escalated from around 40 million in 1991 to roughly 257 million in 2009 [3]. In 2011, hydrocodone-acetaminophen was the single most-prescribed drug in the United States, with a little more than 4 million prescriptions dispensed [4].

Unfortunately, escalating opioid prescribing rates have been mirrored by similar escalations in drug diversion and nonmedical uses of opioids. The opioid medications associated with these problems include immediate- and extended-release products, as well as methadone. Many people directly affected by the crisis have been previously healthy and have had no history of substance misuse [5]. The scope of the problem can be seen in these statistics:

- In 2009, the latest year for which data are available, an estimated 7 million Americans were abusing prescription drugs – more than the number abusing cocaine, heroin, hallucinogens, and inhalants, combined [6].
patient education to promote the safe use of long-acting opiates. This program offers pharmacists a solid foundation for responsible and vigilant opioid use.

Definitions
The International Association for the Study of Pain defines chronic pain as “pain that persists beyond normal tissue healing time, which is assumed to be three months” [12]. Numerous diseases and syndromes can result in chronic pain. For the purposes of this monograph, all chronic pain disorders outside of cancer pain or pain at end of life are collectively labeled “chronic non-cancer pain” (CNCP).

Many treatment modalities exist for CNCP – opioid pain medications are only one of many tools in the pain management armamentarium.

The challenge of pharmacovigilance
In their daily practice, clinicians who treat patients with chronic non-cancer pain face must balance pain relief with the risks associated with opioid analgesics. The term “pharmacovigilance” refers to the range of procedures and processes used to achieve this balance. Such procedures need not be burdensome and are not unlike the kinds of balancing acts required in the prescription of a great many other therapeutic agents. What makes opioids of particular concern is that, not only are they potentially dangerous for patients, they are also highly sought after by recreational drug users and criminals.

In their efforts to find the appropriate, effective middle ground between relieving pain and preventing diversion and misuse of prescription opioids, clinicians must bear in mind that the problem of unrelieved pain remains as urgent as ever. In a 2011 study, chronic pain was estimated to affect approximately 100 million Americans and to cost roughly $635 billion annually in treatment and lost productivity [13]. In fact, the incidence of chronic pain in the United States is greater than that of diabetes, heart disease, and cancer combined [14] [15].

At the same time, opioids are subject to abuse and also have a wide range of potential adverse effects that can predispose a patient to serious morbidity and mortality. Risk is increased among older adults; those with impaired renal or hepatic function; individuals with obesity, cardiopulmonary disorders, sleep apnea, or mental illness; and in patients who combine opioids with other respiratory depressants such as alcohol, sedative-hypnotics, benzodiazepines, or barbiturates.

In 2010, the Centers for Disease Control and Prevention (CDC) issued recommendations aimed at helping clinicians find a balance between responsible opioid prescribing and minimizing the risks of abuse, addiction, and drug diversion. However, the recommendations were based on promising interventions and expert opinion, not rigorous evidence-based research [9]. The recommendations include:

- Use opioid medications for acute or chronic pain only after determining that alternative therapies do not deliver adequate pain relief. The lowest effective dose of opioids should be used.
- In addition to behavioral screening and use of patient contracts, consider random, periodic, urine-testing for opioids and other drugs for any patient under 65 years old with non-cancer pain who is being treated with opioids for more than 6 weeks.
- Do not prescribe ER/LA opioids for acute pain.
- If your state has a prescription drug monitoring program (PDMP) periodically request a report on the history of opioid prescriptions to your patients by other providers.

The rest of this monograph details how to implement these general guidelines in ways that are consistent with the time and budgetary constraints often found in modern practice settings.

Case study: Initial presentation
Matt Davidson, 69, is a retired high school physical education teacher. He has come to his primary care physician for his annual physical. He has a history of hypertension, osteoarthritis, and prostate cancer, for which he was treated 2 years ago with a combination of external beam radiation and chemotherapy. His prostate-specific antigen (PSA) level is now near zero and he has no signs of disease, although he continues to be troubled by mild urinary incontinence and erectile dysfunction. On this visit, Mr. Davidson complains of joint pain, as well as a burning, tingling pain in his hands and feet and asks if anything can be done for it. He says he has been taking between 800 and 1200 mg ibuprofen daily for the pain, which he rates as 7 to 8 on a 10-point scale, but has also been having heartburn as a result.

A full evaluation of the patient’s pain leads to a dual diagnosis of osteoarthritis and peripheral neuropathy secondary to chemotherapy.

As part of the evaluation, the patient is asked how his pain is affecting his life and whether it is preventing him from engaging in any activities. He reports disturbed sleep, which he says makes him more irritable during the day. He also says he no longer plays tennis, walking has begun to hurt, and it is becoming difficult to use the computer keyboard.

This information is used to create a treatment plan with the functional goals of reducing nighttime awakenings to no more than one per night; walking daily at least 1 mile without pain; and using the computer without pain. A return to tennis is a possible goal if less strenuous goals are achieved first. An extended-release oxycodone product is prescribed, as well as a prophylactic laxative. The patient is given printed information about the safe use, storage, and disposal of opioid medications.

Assessing patients for opioid therapy
Determining if an opioid medication is appropriate for a patient with chronic non-cancer pain involves assessing both the condition itself and the patient’s potential for misuse or abuse of the medications. The FDA has recommended that providers contemplating prescribing an opioid pain medication complete a “comprehensive history and physical examination, including assessment of psychosocial factors and family history of substance misuse, as well as special considerations for the elderly, women, children, and cultural/ethnic groups” [16]. Regulators expect to see at least a basic physical examination as part of the evaluation that leads to treatment with controlled substances [17]. The exact components of the examination, however, are left to the medical judgment of the clinician, who is expected to have performed an examination proportionate to the diagnosis that justifies a treatment.
Any basic pain assessment includes the familiar elements of: chief complaint; history of present illness; past medical, surgical, and psychosocial history; family history; physical examination; and examination of imaging and other diagnostic studies or tests. As when assessing any patient, clinicians should take the time to look beyond the specific complaint or body part/system and evaluate holistically the broader mental, cultural, and socioeconomic contexts within which the chief complaint is embedded [17].

**History and physical exam**

Physical exams conducted as part of an assessment of pain should include an evaluation of the patient’s nervous system, with focus on sensory function. Clinicians should assess for allodynia (pain from stimulation that would not normally evoke pain, such as light touch), hyperalgesia (amplified pain response to stimulation that would normally evoke only mild pain), or pain insensitivity. A sensory examination could include response to light touch, light pressure, pinprick, cold, or vibration [18].

**Figure 1: Numeric Pain Scale**

<table>
<thead>
<tr>
<th>No Pain</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moderate pain</td>
</tr>
<tr>
<td>2</td>
<td>Worst pain possible</td>
</tr>
</tbody>
</table>

It is important for clinicians to avoid the mistake of assuming that if an organic pathology cannot be found, the patient’s pain is “all in their head.” As Goodwin and Bajwa (2004) note, “Pain is what the patient says it is” [19]. Psychological factors may be important in a patient’s experience of pain, and the importance of such factors should be taken seriously and incorporated into the overall treatment plan [19].

A comprehensive evaluation of a patient in pain usually requires moving beyond the typical list of questions asked during a general history. It may be possible to gather this information before an in-person visit by using paper or online questionnaires. In most cases where pain is the chief complaint, it is appropriate to begin by asking about the pain, and then to review the broader context and impact of that pain [17]. Here are some points that may be useful to cover in an initial evaluation [17] [18]:

- Location of pain.
- Character of pain (i.e., shooting or stinging, continuous or intermittent, worse at night or in the morning).
- Lowest and highest pain on a 10-point scale in a typical day.
- Usual pain on a 10-point scale on a typical day (augmented by verbal descriptors).

**Psychosocial evaluation**

Pain affects every aspect of a patient’s life. Therefore, it is vital to evaluate how pain impacts, or may be affected by, psychosocial elements of a patient’s life [1]. Clinicians must be alert for signs of depression or anxiety, which are very common. They must also be particularly alert for suicidal thoughts since the risk of suicide is roughly double for patients with chronic pain [20]. Some freely accessible instruments for gathering a psychiatric history are available [see, for example, the Depression Anxiety & Positive Outlook Scale (ww.dapos.org) or the Patient Health Questionnaire (PHQ Screeners www.phqscreeners.com)]. Referral to a mental-health professional is warranted if the clinician’s judgment suggests the patient has active psychological issues beyond the clinician’s expertise.

Clinicians should also probe for ways in which pain may be affecting the patient’s family, work, or social activities. Pain can seriously erode psychological issues beyond the clinician’s expertise.

During an initial evaluation, clinicians should be alert for signs that a patient is minimizing his or her pain. This may result from a variety of psychological or emotional factors. For example, some patients may worry that they will be labeled a complainer if they mention pain, or that their health care provider will suspect they are addicted if they ask about opioid pain medications. Other patients may underreport pain because they fear pain medications will dull their cognitive abilities, lead to addiction, or produce undesirable side effects. Clinicians should be empathic, supportive and honest, neither promising too much nor removing all hope, when evaluating a patient in chronic pain [18].

**Evaluating patients for risk of opioid dependence or abuse**

Whenever a clinician considers treating pain with a controlled substance, risk of misuse or diversion is always a possibility, no matter how remote, and must be assessed. To date, no convincing data exist to support the strategy of focusing on any one specific population or setting – which means that prescribers must be vigilant with all patients [17]. The concept of “universal precautions” has been applied to this approach, which means that any patient in pain could have a drug misuse problem – just as any patient requiring a blood draw for a simple lab test could have HIV [21]. Treating everyone with the same screens, diagnostic tests, and administrative procedures can help remove bias and level the playing field so everyone is treated equally and screened thoroughly.

Nonetheless, it is also true that some patient characteristics are predictive of a potential for drug abuse, misuse, or other aberrant behaviors. The most predictive factor is a personal or family history of alcohol or drug abuse [1]. Some studies have also shown that younger age and the presence of psychiatric conditions are also associated with aberrant drug-related behaviors [1].
In evaluating patients with chronic pain for risk of addiction or signs that they may be abusing a controlled substance, it may be helpful to consider the sets of characteristics listed in Table 1.

<table>
<thead>
<tr>
<th>Chronic-pain patient</th>
<th>Addicted patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication use is not out of control.</td>
<td>Medication use is out of control.</td>
</tr>
<tr>
<td>Medication use improves quality of life.</td>
<td>Medication use impairs quality of life.</td>
</tr>
<tr>
<td>Wants to decrease medication if adverse effects develop.</td>
<td>Medication use continues or increases despite adverse effects.</td>
</tr>
<tr>
<td>Is concerned about the physical problem being treated with the drug.</td>
<td>Unaware of or in denial about any problems that develop as a result of drug treatment.</td>
</tr>
<tr>
<td>Follows the practitioner-patient agreement for use of the opioid.</td>
<td>Does not follow opioid agreement.</td>
</tr>
<tr>
<td>May have leftover medication.</td>
<td>Does not have leftover medication.</td>
</tr>
<tr>
<td></td>
<td>Loses prescriptions.</td>
</tr>
<tr>
<td></td>
<td>Always has a story about why more drug is needed.</td>
</tr>
</tbody>
</table>

Adapted from: Webster LR, Dove B. Avoiding Opioid Abuse While Managing Pain. Sunrise River Press, North Branch, MN. 2007.

Many tools have been developed for the formal assessment of a patient’s risk of having a substance misuse problem, some of which are appropriate for routine clinical use because they are relatively brief and easily implemented. Table 2 lists some tools for patient risk assessment, although to date, no single tool has been widely endorsed or thoroughly validated [1].

Regardless of the tool used, it is important for health care professionals to thoroughly assess a patient’s risk of abuse of controlled substances. Patients who are determined to be at a high risk of opiate abuse should be referred to a pain management specialist to ensure thorough follow-up and monitoring of the patient's pain status and opiate use.

<table>
<thead>
<tr>
<th>Tool</th>
<th>Use</th>
<th>Who Administers?</th>
<th>Length</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid Risk Tool (ORT).</td>
<td>Screen for risk of opioid addiction.</td>
<td>Clinician or patient self-report.</td>
<td>5 yes/no questions.</td>
<td><a href="http://www.opioidrisk.com/node/887">www.opioidrisk.com/node/887</a></td>
</tr>
</tbody>
</table>

Written agreements

Written documentation of all aspects of a patient’s care, including assessments, informed consent, treatment plans, and provider/patient agreements, are a vital part of opioid prescription best practices. Such documentation provides a transparent and enduring record of a clinician’s rationale for a particular treatment and provides a basis for ongoing monitoring and, if needed, modifications of a treatment plan [17].

Many computerized systems are now available for the acquisition, storage, integration, and presentation of medical information. Most offer advantages that will benefit both patients and prescribers, such as maintaining up-to-date records, and providing instant availability of information relevant to prescribing or treatment. Although automation can help, clear documentation is not dependent on electronic record-keeping; it merely requires a commitment to creating clear and enduring communication in a systematic fashion. Good documentation can be achieved with the most elaborate electronic medical record systems, with paper and pen, or with dictated notes. Clinicians must decide for themselves how thoroughly, and how frequently, their documentation of a patient’s treatment should be.

Informed consent

Informed consent is a fundamental part of planning for any treatment, but it is critically important in long-term opioid therapy, given the potential risks of such therapy. At its best, consent also fortifies the clinician/patient relationship. Prescribers must be able to answer with confidence four key questions when obtaining informed consent in the context of treatment with opioids [22]:

1. Does the patient understand the various options for treatment?
2. Has the patient been reasonably informed of the potential benefits and risks associated with each of those options?
3. Is the patient free to choose among those options, free from coercion by the health care professional, family, or others?
4. Does the patient have the capacity to communicate his or her preferences – verbally or in other ways (e.g., if the patient is deaf or mute)?
in a pain score (i.e., roughly two points on the standard 10-point pain functional improvements as pain rating declines [27]. A 20% reduction in anxiety, insomnia, and even suicide. Clinicians should know that interpersonal relationships, and sleep. This can, in turn, degrade functionality.

Although evidence is lacking about the most effective methods to convey the information included in most patient-provider agreements, such agreements have been widely used and are recommended by regulators and many experts on treatment guidelines for long-term opioid therapy [1]. Recently, the U.S. Department of Veterans Affairs and the U.S. Department of Defense chartered an expert panel to undertake a systematic review of existing medical literature on this subject. In the clinical practice guidelines resulting from that work, the panel concluded that opioid treatment agreements are a standard of care when prescribing long-term opioid therapy [23]. [Samples of several commonly used agreements, including a low-literacy version, are available at: opioid911.org/media/doc/Opi911-OpioidRxAgreements.doc].

Provider/patient agreements have many potential advantages, including [17]:

- Allowing treatment to start on a note of mutual respect and partnership.
- Enhancing transparency.
- Engaging patients in a collaborative education and decision-making process.
- Helping to set functional goals and clarify the clinician’s and patient’s roles and responsibilities to attain these goals.
- Documenting acceptance of treatment risks and benefits.
- Documenting informed consent.
- Helping avoid misunderstandings that may occur over long treatment time periods.
- Providing a foundation for subsequent decisions about changes in medications or termination of treatment.

Patient-provider agreements

A written agreement between a clinician and a patient about the specifics of their pain treatment with opioids can help clarify the plan with the patient, the patient’s family, and other clinicians who may become involved in the patient’s care [1]. Such agreements can also reinforce expectations about the appropriate and safe use of opioids [1]. Caution must be exercised, however, to ensure that patient/provider agreements are not used in a coercive way to unethically place patients in the position of having to agree to its terms or else lose an important component of their treatment (or even lose all treatment) [22].

Although a patient’s subjective pain and suffering are obviously measured and used to create objective treatment goals. This impact takes many forms, but typically, chronic pain erodes foundations of daily life, such as physical activity, concentration, emotional stability, interpersonal relationships, and sleep. This can, in turn, degrade functioning at work or in the home, which can lead to depression, anxiety, insomnia, and even suicide. Clinicians should know that even relatively modest reductions in pain can translate into significant functional improvements as pain rating declines [27]. A 20% reduction in a pain score (i.e., roughly two points on the standard 10-point pain scale) may be acceptable if it produces significant functional benefits for a patient.

Clinicians should strive to craft agreements that serve their patients’ best interests and avoid coercive or punitive language. Thus, agreements should avoid [17]:

- Putting all burden on the patient rather than sharing it between patient and clinician.
- Framing the agreement in terms of punishments for possible future crimes or difficulties.
- Using language that is stigmatizing, dominating, or pejorative.
- Using coercion in any way.
- Imposing limitations for the clinician’s convenience without clear and substantial benefit for the patient.
- Insisting on behaviors unrelated to actual use of medications.
- Using the term “fired” to describe termination of treatment.
- Threatening abandonment or suggesting that patients will not have continued access to non-opioid pain relieving treatments if opioids are terminated.

To be effective, written agreements must be clearly understood by the patient. This may require the provision of agreements in multiple languages and translators may be needed for speakers of other languages to ensure understanding and effective informed consent. All agreements should be written at the sixth- to seventh-grade level or even lower [24] [25]. A patient who does not fully understand the potential risks and benefits of a treatment cannot be truly “informed” as required by the legal and ethical guidelines for medical practice. Time must be allowed for patients to ask questions, and for prescribers to ensure patients understand what they are being told. Some, or all, of these tasks may be handled by trained personnel (or staff members) rather than clinicians.

Although the term “agreement” is generally perceived as being more patient-friendly than the word “contract,” clinicians should understand that, from a legal standpoint, any written or oral agreement between a prescriber and a patient may be considered a binding contract [26]. Clinicians should ensure the terms in any agreement are understood by the patient, and are acceptable, attainable, and consistent with high-quality practice [26].

Creating function-based opioid treatment plans

Once a patient has been assessed and accepted as a candidate for treatment with an opioid pain medication, and after informed consent has been obtained for such treatment, a written plan for implementing the treatment should be drafted. Such plans typically include a statement of the goals of therapy. These goals should be written carefully in light of the inherent subjectivity of pain. Since pain itself cannot be measured objectively, framing treatment goals solely in terms of pain relief means that such goals cannot be objectively confirmed.

Although a patient’s subjective pain and suffering are obviously important factors, only the functional impact of the pain can be measured and used to create objective treatment goals. This impact takes many forms, but typically, chronic pain erodes foundations of daily life, such as physical activity, concentration, emotional stability, interpersonal relationships, and sleep. This can, in turn, degrade functioning at work or in the home, which can lead to depression, anxiety, insomnia, and even suicide. Clinicians should know that even relatively modest reductions in pain can translate into significant functional improvements as pain rating declines [27]. A 20% reduction in a pain score (i.e., roughly two points on the standard 10-point pain
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experiencing the burning/tingling pain in his hands and feet. He has
his arthritis pain has gotten only slightly better, but that he is still
Mr. Davidson returns for a follow-up after 2 weeks. He reports that
Case study: Treatment hits a roadblock

Components of an effective treatment plan

The creation of an effective function-based treatment plan must be a
collaboration between patient and clinician. A patient’s pain score will be just one of many variables to be considered in framing goals. These
goals should be realistic, meaningful to the patient, and verifiable.
The details of a function-based treatment plan are necessarily specific
to the patient, but one way to initiate the process is to begin with the
question: “What do you hope to do as a result of treatment that you
cannot do now?”

The treatment plan can include a discussion of, and the setting of
expectations about, periodic reassessment of goals. Patients may stabilize at a certain level, and the clinician and patient together must
decide if this is acceptable or whether changes are needed.

As is the case in drafting other types of patient/provider documents,
patients should be reminded of the benefits and risks of a chosen
therapy. With opioids, these include the realities of tolerance and
physical dependence and the potential need to taper the medication
slowly to avoid withdrawal. Patients must also be educated about the
possibility that opioids may be either ineffective or have intolerable adverse
effects, and that there is also the possibility of psychological
dependence, which could lead to misuse or, less commonly, addiction.

Another critical component of any treatment plan is a description
of how treatment with an opioid medication might be terminated.

Table 3: Evidence for functional goals

| Functional goal                     | Evidence                                            |
|-------------------------------------|                                                    |
| Begin physical therapy.             | Letter from physical therapist.                    |
| Sleeping in bed as opposed to lounge chair. | Report by family member or friend (either in person or in writing).* |
| Participation in pain-support group. | Letter from group leader.                          |
| Increased activities of daily living. | Report by family member or friend.                 |
| Walk around the block.              | Pedometer recordings or written log of activity.   |
| Increased social activities.        | Report by family member or friend.                 |
| Resumed sexual relations.           | Report by partner.                                 |
| Returned to work.                   | Pay stubs from employer or letter confirming the patient is off of disability leave. |
| Daily exercise.                     | Gym attendance records or report from family member or friend. |

* Involving other persons requires explicit permission from the patient, and this permission should be documented, preferably in writing.


Limiting side effects, or untreated affective disorders. Sometimes impaired functioning is the result of addiction or misuse, and these objective results may shed valuable light on an otherwise confusing presentation of a patient’s pain symptoms.

Functional treatment goals should be realistic. Progress in restoring function is usually slow and gains are typically incremental. Chronic non-cancer pain is often marked by long-standing physical and psychological deconditioning, and recovery may require reconditioning that may take weeks, months, or years. It is much better to set goals that are slightly too low than slightly too high. Raising goals after a patient has “succeeded” in achieving them is far more motivational and encouraging than lowering goals after a patient has “failed.”

Table 3 illustrates some simple functional goals and ways they might be verified.

The responsibility for obtaining evidence of success in meeting a functional goal lies with the patient and should be made explicit in the prescribing agreement. If a patient is unable to document or achieve the progress outlined in a treatment plan, this may suggest a need for goal readjustment.

The experience of intolerable side effects, and that there is also the possibility of psychological deconditioning, and recovery may require reconditioning that may take weeks, months, or years. It is much better to set goals that are slightly too low than slightly too high. Raising goals after a patient has “succeeded” in achieving them is far more motivational and encouraging than lowering goals after a patient has “failed.”

Case study: Treatment hits a roadblock

Mr. Davidson returns for a follow-up after 2 weeks. He reports that his arthritis pain has gotten only slightly better, but that he is still experiencing the burning/tingling pain in his hands and feet. He has not achieved any of his functional goals. Upon questioning, he reveals that he has not been taking the opioid medication as frequently as prescribed because he “doesn’t want to become an addict.”

This common patient fear is allayed with careful, compassionate education that explains the differences between addiction and tolerance and that communicates the key idea that proper use of an opioid may improve functioning and quality of life. The prescription for the ER-LA opioid is continued, and a prescription for 10 mg ER gabapentin is added.

Stopping opioid therapy in cases of chronic non-cancer pain is often more difficult than starting it, and doses should always be tapered slowly, not abruptly discontinued. Being clear about the conditions under which opioid therapy will end is important because opioids are not curative, have no standard duration of treatment, and may be associated with substantial risks [17].

Termination may be required for many reasons, including:

- Healing or resolution of a specific pathology underlying the pain.
- The experience of intolerable side effects.
- Lack of adequate response to a medication in terms of either pain relief or functional improvement.
- Evidence of non-medical or inappropriate use of the medication(s).

If inappropriate use of a prescription medication is discovered, treatment must usually be suspended, although provisions should be in place for continuation of some kind of pain treatment or referral to other professionals or members of a pain management team. Some clinicians may be willing and able to continue a regimen of opioid therapy even after the discovery of aberrant behavior if done with intensified monitoring, patient counseling, and careful documentation of all directives. This level of vigilance and risk management, however, may exceed the abilities and resources of the average prescriber. In such cases, referral to a provider with specialized skill or experience in dealing with high-risk patients may be prudent.
Initiating treatment with opioids

Prior to an initial prescription of an opioid pain medication, clinicians should be certain that: 1) all other potentially effective treatments that offer a more optimal benefit-to-risk profile have been considered or tried, 2) a complete evaluation has been performed and fully documented, 3) the patient’s level of opioid tolerance has been determined, and 4) informed consent and agreement to treat have been obtained [17]. At the outset, both the clinician and the patient should view a new opioid prescription as a short-term trial of therapy [1]. The goal of the trial is to provide data to guide decisions on the continued appropriateness of opioid medications and on the specific dose and formulation of medication used. Such a trial might be as brief as a few days or as long as several months.

Opioid selection, initial dosing, and titration must be individualized to the patient’s health status, previous exposure to opioids, and treatment plan [1]. Although still not widely used, it is also becoming increasingly possible to use commercially available genetic screening tools to assess for genetic variations in drug metabolism that could affect the way a patient responds to opioids [28]. Caution should be exercised when using opioids in patients with conditions that may be complicated by adverse effects from opioids, including chronic obstructive pulmonary disease (COPD), congestive heart failure, sleep apnea, current or past alcohol or substance misuse, mental illness, advanced age, or patients with a history of renal or hepatic dysfunction [29]. In addition, opioids should not be combined with other respiratory depressants, such as sedative-hypnotics (benzodiazepines or barbiturates) unless there is a specific medical or psychiatric indication for such a combination [30]. In such cases, much more intensive monitoring is required.

A decision to continue opioid therapy after an appropriate trial should be based on careful review of the trial outcomes. Outcomes to consider include [17]:
- Progress toward meeting therapeutic goals.
- Changes in functional status.
- Presence and nature of opioid-related adverse effects.
- Changes in the underlying pain condition.
- Changes in medical or psychiatric comorbidities.
- Degree of opioid tolerance in the patient.
- Identification of altered or aberrant behaviors, misuse, or diversion.

Dose titration

Patients who are opioid-naïve (i.e., not tolerant) or have modest previous opioid exposure should be started at a low dose of a short-acting opioid and titrated slowly upward to decrease the risk of opioid-related adverse effects [1]. If it is unclear whether a patient has recently been using opioids (either prescribed or non-prescribed), the clinician should assume that the patient is opioid-naïve and proceed as described. Short-acting opioids are usually safer for initial therapy since they have a shorter half-life and may be associated with a lower risk of overdose from drug accumulation [1].

Tolerance to the sedating and respiratory depressant effects of opiates should be established before prescribing an ER/LA opioid due to the increased risks associated with longer-acting formulations [17]. The selection of a starting dose and manner of titration are clinical decisions that must be made on a case-by-case basis because of the many variables involved, but health care providers should carefully weigh the benefits vs. the risks before starting ER/LA opioid treatment. These risks include overdose, misuse, abuse, and addiction by the patient or other members of the patient’s household and tolerance, physical dependence, drug interactions, and accidental use by other household members, especially children.

Further studies are needed to confirm more consistent control of pain and improved adherence to prescribed therapy with use of ER/LA opioids [1]. Although low-dose, short-acting opioids may offer the greatest safety for initiating opioid therapy, clinicians must recognize that short-acting opioids are not intrinsically safer than other formulations, and stress to their patients the importance of strict adherence to prescribed doses/administration [1].

Considerations in opioid selection

Opioids, as a class, comprise many specific agents available in a wide range of formulations. A given patient might be appropriate for ER/LA therapy only, short-acting only, or a combination of an ER/LA opioid with a short-acting opioid for breakthrough pain.

Short-acting, orally administered opioids typically have rapid onset of action (10 to 60 min) and relatively short duration of action (2 to 4 hours) [31]. They are used for acute or intermittent pain, or breakthrough pain that occurs against a background of a persistent level of pain [31]. Transmucosal immediate-release fentanyl is a special class of short-acting opioid that is only approved for breakthrough pain in cancer, and there is a separate FDA REMS devoted to this topic [32].

Combination products join an opioid with a non-opioid analgesic, usually for use in patients with moderate pain. Using a combination product when dose escalation is required risks increasing adverse effects from the non-opioid co-analgesic, even if an increase of the opioid dose is appropriate [17]. In such cases, using a pure opioid may be preferable.

Unfortunately, at this time, no pharmaceutically manufactured single-agent option for hydrocodone is available, although clinical trials are underway as part of an effort to secure FDA approval for such an agent. Single-agent formulations are available for other types of opioids, such as codeine, morphine, oxycodone, oxymorphone, and hydromorphone. In 2011, the FDA announced new rules effective January 1, 2014, that will limit the amount of acetaminophen allowed in opioid combination products to 325 mg in an attempt to limit liver damage and other ill effects from the use of these products with over-the-counter (OTC) analgesics [33].

ER/LA opioids usually have a relatively slow onset of action (typically between 30 and 90 min) and a relatively long duration of action (4 to 72 hrs) and are typically used for patients with constant background pain [31]. These agents achieve their extended activity in various ways. Methadone and levorphanol have intrinsic pharmacokinetic properties that make their effects more enduring than many short-acting opioids [34]. ER/LA agents such as controlled-release morphine, oxycodone, or transdermal fentanyl achieve their prolonged time course via a delivery system that is modified to slow absorption or to slow the release of the active ingredient [31]. Clinicians should warn patients that unless specifically instructed otherwise, oral ER/LA opioids should not be broken, chewed, or crushed, and patches should not be cut or torn prior to use, since this may lead to rapid release of the opioid and could cause overdose or death.

Prescribers should educate themselves about the general characteristics, toxicities, and drug interactions for ER/LA opioid products. [For detailed information on current ER/LA opioid analogies, see the FDA Blueprint for Prescriber Education, available at: http://www.er-la-opioidrems.com]. Respiratory depression is the
most serious adverse effect of opioids as it can be immediately life-threatening. The risk of respiratory depression or respiratory arrest is higher in patients with an upper respiratory infection, asthma, or other respiratory problem – if these conditions arise, the opioid dose needs to be reduced. Constipation is the most common long-term side effect, but can often be managed. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.

Central nervous system depressants (sedatives, hypnotics, tranquilizers, tricyclic antidepressants and alcohol) can have a potentiating effect on the sedation and respiratory depression due to opioids [30]. Alcohol consumption should be avoided entirely with some oral products (e.g., morphine, hydromorphone, oxymorphone) because ethanol increases the plasma concentration of the opioid [30].

Opioids may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in confusion, anxiety, and respiratory depression [30]. Opioids can reduce the efficacy of some diuretics by inducing the release of antidiuretic hormone (ADH) [30]. In addition, some opioids interact with various cytochrome P450 enzyme inhibitors and inducers and thus, may result in higher or lower than expected blood levels of the drug.

Methadone can be an effective opioid, but it must be prescribed carefully and with full knowledge of its highly variable pharmacokinetics and pharmacodynamics.

**Abuse-deterrent formulations**

As concern has risen about opioid misuse and abuse, efforts have been made to create abuse-deterrent and tamper-resistant opioid formulations. One class of deterrent formulation incorporates an opioid antagonist into a separate compartment deep within a single capsule; crushing the capsule releases the antagonist and neutralizes the opioid effect [31]. The central opioid antagonist compartment is eliminated from the body unchanged if the capsule is consumed normally without tampering. Another strategy is to modify the physical structure of tablets or incorporate compounds that make it difficult or impossible to liquefy, concentrate, or otherwise transform the tablets [31].

Transdermal opioid formulations have been thought to be less vulnerable to misuse, but such formulations can be abused. For example, a transdermal, 7-day duration formulation of buprenorphine has been reported to be an increasingly abused opioid, particularly in prison populations [35]. As a partial opioid agonist, buprenorphine was thought to be a lower-risk agent than full agonist opioids; however, it is clear that this medication can also be susceptible to abuse.

Abuse-deterrent opioid formulations, of course, do not prevent users from simply consuming too much of a medication. These formulations may help reduce the public health burden of prescription opioid abuse, but the evidence to date is inadequate to project whether this potential will actually be achieved [31].

**Case study: Progress**

At the next scheduled follow-up visit, Mr. Davidson reports reduced pain and improved functioning. He says his pain is now 3-4 on a 10-point scale. He can now walk his dog twice daily, and is using the computer without pain. He says his sleep has improved as well. Mr. Davidson asks for a higher dose of the opioid “to see if I can get the pain down to zero.” Although seemingly reasonable, it is explained to Mr. Davidson that, in fact, “zero pain” is an unrealistic goal for anyone, and that increasing the dose to achieve that goal would likely incur a range of side effects that would erode his overall quality of life.

**Periodic review and monitoring**

If a trial of an opioid medication is deemed successful and opioid therapy is continued, periodic review and monitoring of pain management, as well as the patient’s underlying condition, should be performed for the duration of treatment. The tests performed, questions asked, and evaluations made should be tailored to the patient as guided by the physician’s clinical judgment. For example, a physical examination may or may not be required at each follow-up visit. Clinicians must evaluate progress against agreed-upon treatment goals and assess for a wide range of potential adverse effects, ranging from mood changes, signs of drug craving or seeking, or impaired function in various domains of daily living [17]. As part of routine practice, clinicians who prescribe opioids should perform medication reconciliation at each patient visit [36]. The American Medical Association defines “medication reconciliation” as “...making sense of a patient’s medications and resolving conflicts between different sources of information to minimize harm and maximize therapeutic effects” [36].

The intensity and frequency of monitoring is dependent on an assessment of the patient’s risk for abuse, diversion, or addiction. Tools and techniques similar or identical to those used during an initial assessment of a patient’s risk can be used to reassess or monitor risk on an on-going basis [2].
Reviewing functional goals

A key part of periodic monitoring is a careful review of previously agreed-upon functional goals. Patients should come to appointments ready to provide the evidence upon which an evaluation of progress can be made. This evidence should span as many domains of a person’s life as possible: personal and social relationships, employment, physical activities, health, hobbies, and spiritual activities. Functional goals that are not attained require investigation, possible adjustment, and encouragement that future progress is possible. If the goals have been attained, clinicians should be supportive and positive, while setting new goals to motivate further progress.

Managing breakthrough pain

Patients with chronic pain receiving a steady dose of an opioid medication may experience episodes of pain that break through the analgesic effects of the steady-state drug (regardless of the route of administration) [1]. Close monitoring of breakthrough episodes is key to helping patients reduce pain and facilitate functioning. Providing patients either paper or electronic pain diaries can help them track breakthrough episodes and spot correlations between the episodes and variables in his or her life. If specific triggers are identified, this may provide opportunities for changes that will reduce the prevalence of breakthrough episodes without recourse to increased reliance on medication [17].

Non-opioid methods of dealing with breakthrough pain (e.g., cold or warmth, massage, yoga, acupuncture, meditation, electrical stimulation) might be considered prior to any increases in opioid medication; although research evidence regarding many complementary and alternative medicine (CAM) approaches is inconclusive. If a short-acting opioid preparation is prescribed for breakthrough pain, clinicians should remind patients about the potentials problems of diversion and misuse of these agents. As with the management of the underlying chronic pain condition, clinicians should use an agreed-upon set of functional goals as a way to monitor and, if necessary, adjust the use of as-needed opioid medications for breakthrough pain.

Monitoring adherence

Drug testing should be approached in a consensual manner as part of an agreed-upon treatment plan and with the idea that such testing benefits both the patient and the provider [2]. The potential benefits of clinical drug testing include [2]:

- Serving as a deterrent to inappropriate use.
- Providing objective evidence of abstinence from drugs of abuse.
- Assisting with a diagnosis.
- Helping patients allay concerns by family members, employers, or law enforcement.
- Demonstrating to regulatory authorities a clinician’s dedication to monitoring best practices.

In the context of family practice settings, unobserved urine collection is usually an acceptable procedure for drug testing. Prescribers, however, should be aware of the many ways in which urine specimens can be adulterated. Specimens should be shaken to determine if soap products have been added, for example. The urine color should be noted on any documentation that accompanies the specimen for evaluation, since unusually colored urine could indicate adulteration. If possible, urine temperature and pH should be measured immediately after collection [2].

One way to reduce the risk of urine test false-positives or false-negatives is to develop a relationship with a single laboratory, become familiar with its testing tools and threshold values, and use the same screening and confirmatory tests regularly to build familiarity with the range of normal results [17].

Prescribers should be familiar with the metabolites associated with each opioid that may be detected in urine, since the appearance of a metabolite can be misleading [2]. A patient who is prescribed codeine, for example, may test positive for morphine because morphine is a metabolite of codeine. Similar misunderstandings may occur for patients prescribed hydrocodone who appear positive for hydromorphone or oxycodone and oxymorphone (see Table 4).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Urinary analytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Morphine</td>
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<tr>
<td></td>
<td>Hydromorphone</td>
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<td></td>
<td>Codeine</td>
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<td>Morphine</td>
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<td>Hydrocodone</td>
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<td>6-Hydromocol</td>
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<td>Oxycodone</td>
<td>Oxycodone</td>
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<tr>
<td></td>
<td>Oxymorphine</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
</tr>
</tbody>
</table>


Case study: A caution light

After 3 weeks, the physician is given a message that a young woman has called requesting an early refill of Mr. Davidson’s opioid “because he’s suffering.” This raises the physician’s suspicions. He accesses his state PDMP to see if Mr. Davidson might be getting prescriptions from another provider. He is not, and nothing appears unusual. The physician calls Mr. Davidson directly and Mr. Davidson confirms that he did ask his granddaughter to call for the prescription because he was having increased pain after playing tennis for an hour. Mr. Davidson is advised to temporarily use an OTC NSAID (not more than 600 mg) and is asked to return for an in-person visit within a week. At that visit, a range of non-pharmacological strategies are reviewed to provide additional pain relief (i.e., post-exercise cold/warm treatments; exercises to improve flexibility; massage; and the use of an elbow brace to be used for tennis).
COMMON ISSUES RELATED TO OPIOID PAIN MEDICATIONS

Preventing and managing opioid-related side effects

Many patients treated with an opioid will experience side effects, the most common of which is constipation. Other possible effects include [31]:

- Respiratory depression.
- Sedation.
- Urinary hesitancy or retention.
- Dry mouth.
- Nausea/vomiting.
- Itching.
- Sweating.
- Hypogonadism.
- Myoclonus.

Some side effects, such as sedation, may lessen over time after treatment initiation. Others, such as constipation, rarely become less problematic. Constipation is so common, in fact, that when patients use opioids and do not have constipation, clinicians should consider possible reasons ranging from rapid bowel transit time to diversion. Constipation requires proactive treatment, with stimulating laxatives prescribed at the time of initiating opioids, and frequent reevaluation. With the exception of constipation, uncomfortable or unpleasant side effects may potentially be reduced by switching to another opioid or route of administration (such side effects may also be alleviated with adjunctive medications).

Opioids and pregnancy

Some data suggest an association between the use of long-term opioid therapy during pregnancy and adverse outcomes in newborns, including low birth weight and premature birth, though co-related maternal factors may play a role in these associations and causality is not certain [1]. Higher doses of antenatal methadone in tolerant mothers do not seem to increase complication rates [1]. Importantly, opioid withdrawal can be expected in up to half of newborns of opioid-dependent mothers [1]. If a mother is receiving long-term opioid therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be available [1].

Nonetheless, given the potential risks of opioids during pregnancy, current American Pain Society-American Academy of Pain Medicine (APS-AAPM) guidelines suggest that clinicians should encourage minimal or no use of opioids during pregnancy unless the potential benefits outweigh risks [1]. If opioid medications are prescribed, clinicians should thoroughly counsel pregnant women about the potential risks and benefits, and clinicians should be prepared to anticipate and manage risks to the patient and newborn.

Driving and work safety

Driving while using opioid medications remains a controversial issue. Particularly at the initiation of therapy, opioid medications may cause sleepiness, clouded thinking, decreased concentration, slowed reflexes, or incoordination, all of which may pose a danger to the patient and others when driving or operating machinery [1]. On the other hand, a number of epidemiologic studies failed to show an association between long-term opioid use and motor vehicle accidents, fatalities, or citations for impaired driving [1]. Since at least some of the cognitive and motor-impairing effects of opioids resolve with steady use and a consistent dose, some activities or driving may be allowable at the discretion of the clinician and in the absence of signs of impairment.

Current APS-AAPM guidelines recommend that all patients who are initially prescribed opioid medications, or those who have their dose increased, be advised not to drive or engage in potentially dangerous work or other activities [1]. There is no consensus on exactly how long they should abstain from driving. Patients should be educated about the increased risk of impairment when starting opioid therapy, when increasing doses, and when taking other drugs or substances (such as, alcohol, benzodiazepines, or even some cold remedies) that may exacerbate cognitive and motor impairment. Clinicians should be aware that certain professions (i.e., school bus drivers and pilots) may be subject to restrictions in the use of opioid medications [1]. Clinicians should check with their state medical society or the Federation of State Medical Boards to obtain up-to-date information in this regard.

Screening for endocrine function

Both male and female patients on long-term opioid therapy are at risk for hypogonadism, thus the endocrine function of all patients should be assessed at the start of long-term opioid therapy and at least annually thereafter. The symptoms of hypogonadism in both genders may include fatigue, mood changes, decreased libido, loss of muscle mass, and osteoporosis. Although there are insufficient data to recommend routine endocrine screening of asymptomatic patients, current guidelines do recommend such testing for patients exhibiting any of the aforementioned signs and symptoms [1].
Opioid rotation

“Opioid rotation” means switching from one opioid to another to better balance analgesia and side effects. Rotation may be needed because of a lack of efficacy (often related to tolerance), bothersome or unacceptable side effects, increased dosing that exceeds the recommended limits of the current opioid (e.g., dose limitations of co-compounded acetaminophen), or inability to absorb the medication in its present form (i.e., there is a change in the patient’s ability to swallow, switch to a formulation that can be absorbed by a different route such as transdermal) [31]. Because of the large number of variables involved in how any given opioid will affect any given patient, opioid rotation must be approached cautiously, particularly when converting from an immediate-release formulation to an ER/LA product [31]. An equianalgesic chart should be used when changing from one opioid to another or from one route of administration to another. Such charts must be used carefully, however. A high degree of variation has been found across the various charts and online calculator tools, and may account for some overdoses and fatalities [39]. The optimal dose for a specific patient must be determined by careful titration and appropriate monitoring, and clinicians must be mindful that patients may exhibit incomplete cross-tolerance to different types of opioids because of differences in the receptors or receptor sub-types to which different opioids bind [31].

In some cases, because of the risk of potential harm during the time of rotating from one chronic opioid regimen to another, it may be wise to initially use lower doses of an ER/LA opioid than might be suggested by equianalgesic charts, while temporarily liberalizing, as needed, the use of a short-acting opioid. This would then be followed by gradual titration of the LA opioid to the point where the as-needed short-acting opioid is incrementally reduced, until no longer necessary.

Managing non-adherent patients

Patients who begin to exhibit aberrant drug-related behaviors or non-adherence to a prescription should be monitored more strictly than compliant patients. Suspicion that a patient is non-adherent should prompt a thorough investigation of the situation, including an honest evaluation of the patient/provider relationship. The way clinicians interact with patients can affect the relationship (for better or worse) and influence treatment outcomes [17]. A clinician’s negative reactions to non-adherence might include anger at the patient, disappointment and sadness at the apparent betrayal of trust, or fear that the patient’s behavior could expose the provider to legal jeopardy [17]. Before accusing a patient of not adhering to a prescribed regimen, clinicians should assess the situation fully and document objective evidence of non-adherence, as well as their concerns about the patient. Possible reasons for non-adherence include:

- Inadequate pain relief.
- Misunderstanding of the specifics of the prescription.

Case study: Stable improvement

After a slight dose adjustment of the gabapentin, Mr. Davidson reports continued functional progress and acceptable levels of pain. He has increased his level of physical activity and reports that his mood and general health is better as a result. He says he would like to try to taper down his use of the opioid, and he is given clear and specific instructions for how to do so.

Treatment termination

Reasons for discontinuation of an opioid analgesic can include the healing of or recovery from an injury, medical procedure, or condition; intolerable side effects; lack of response; or discovery of misuse of medications. Regardless of the reason, termination should be accomplished so as to minimize unpleasant or dangerous withdrawal symptoms by tapering the opioid medication slowly, or by carefully changing to a new formulation. Approaches to weaning range from a slow 10% reduction per week to a more aggressive 25% to 50% reduction every few days [1]. In general, a slower taper will produce fewer unpleasant symptoms of withdrawal.

In general, opioid therapy must be discontinued or reevaluated whenever the risk of therapy is deemed to outweigh the benefits being provided. A clinician may choose to continue opioid treatment with intensified monitoring, counseling, and careful documentation if it is deemed in the best interest of the patient. This requires, careful consideration and a well-documented risk management plan that addresses the greater resources necessary for opioid continuation following evidence of misuse.

If termination of the provider/patient relationship is deemed necessary, clinicians must ensure that the patient is transferred to the care of another provider and that the patient has adequate medications to avoid unnecessary risk, such as from uncontrolled or potentially dangerous withdrawal [17]. Practitioners can be held accountable for patient abandonment if medical care is discontinued without justification or adequate provision for subsequent care.

Methadone

Methadone has recently received growing attention and concern because it is frequently involved in unintentional overdose deaths [40]. These deaths have escalated as methadone has increasingly been used as an analgesic drug for chronic pain [41]. At one time, methadone had been used almost exclusively in opioid maintenance therapy programs to treat addiction. Its relatively long plasma elimination half-life compared with its relatively short analgesic half-life makes it optimal for maintenance, allowing for once-daily dosing. But methadone only exerts potent analgesic effects in the early phase of its elimination half-life, and this, along with the fact that it is among the least expensive opioids, has led to a dramatic increase in its use for alleviating chronic non-cancer pain [1].
Methadone has unique pharmacokinetic and pharmacodynamic characteristics that add substantial risk to its use. Although its chemical structure is different from classic opioids such as morphine, methadone acts on the same set of opioid receptors, though with different affinities for the various opioid receptor subtypes [34]. In addition, methadone has non-opioid receptor effects that may explain some of its potential special efficacy. These varied effects across opioid receptors, along with its non-opioid properties, have garnered methadone the reputation of being a broad-spectrum opioid [34]. For a number of reasons, however, methadone must be titrated very carefully to avoid overdose. These reasons include [34]:

- An analgesic half-life much shorter than its elimination half-life (leading to accumulation).
- Metabolism by a group of liver enzymes that differ from those associated with most other opioids, hence leading to unexpected drug-drug interactions.
- Significant genetic variations in the liver enzymes that metabolize methadone, which contribute to the unpredictability of methadone’s effects and side effects.
- Metabolism may be affected by smoking (which accelerates elimination) and alcohol (which can augment methadone toxicity acutely and accelerate metabolism with chronic use).

The APS/AAPM guidelines recommend a starting dose in most opioid-naïve patients of 2.5 mg every 8 hours, with dose increases occurring no more frequently than weekly [1]. The lowest possible dose titration should be followed, even in opioid-tolerant patients, because methadone appears to be more potent in patients who have been using higher doses of the pre-switch opioid. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 30 to 40 mg/d regardless of prior exposure [42]. In older patients or those with renal or hepatic comorbidities, lower starting doses, less frequent dosing, and more cautious dose titration are recommended. Because of its long half-life and variable pharmacokinetics, methadone is not recommended to treat breakthrough pain or as an as-needed medication.

When rotating from another opioid to methadone, extreme caution must be used when referring to equianalgesic conversion tables. The consensus recommendations from an expert panel suggest a 75% to 90% decrement in the equianalgesic dose from conventional conversion tables when a switch is made from another opioid to methadone [43].

Because the risk of overdose is particularly acute with methadone, patients should be educated about these risks and counseled to use methadone exactly as prescribed. They should also be warned about the dangers of mixing unauthorized substances with their medication. Benzodiazepines, in particular, pose a threat. Death investigations often find that benzodiazepines have been used in combination with methadone and other opioids [40]. Other respiratory depressants, including alcohol, pose similar risks. Dosing should, therefore, be conservative and cautious until patients demonstrate the ability to tolerate and use the drug safely.

In 2006, the FDA issued a public health advisory warning that methadone can cause serious cardiac conduction disturbances, including QT interval prolongation and Torsades de pointes, a potentially fatal ventricular arrhythmia [44]. It appears that methadone-related corrected QT (QTc) interval prolongation and cardiac arrhythmias can occur at any dose but are more likely at higher doses or with concomitant use of drugs that interact with methadone or that themselves prolong QTc. Although uncommon, the cardiac arrhythmias that can be induced by methadone can be lethal if not detected. The cardiac health of patients who are candidates for methadone should be assessed, with particular attention paid to any history of heart disease or arrhythmias [45]. An initial ECG may be advisable prior to starting methadone, particularly if a patient has a specific cardiac disease or cardiac risk factors or is taking agents that may interact with methadone [45].

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**Required patient education**

Thorough patient education about the safe use, storage, and disposal of opioid medications is an essential part of best practices opioid prescribing. This education can be partially integrated into standard patient/provider agreements or informed consent documents. As with other patient-directed materials, education must be provided in a language and at a reading level (typically 6th to 7th grade) appropriate for a clinician’s patient population. Examples of effective patient education can be found online, such as http://www.er-la-opioidrems.com/lwgUI/remis/pdf/patient_counseling_document.pdf.

Safe use of opioid medications means that patients carefully follow their prescribed instructions, including special directions about timing of doses and whether to administer the medication with or without food. Clinicians should be mindful of any physical limitations (i.e., poor eyesight) that a patient might have that could interfere with accurate and timely administration of prescribed opioids. Adherence to the prescribed directions is critical to adequate pain management, and patients should contact their prescriber if doses are missed or pain is not properly controlled. Product-specific information should be discussed with the patient, and reinforced by encouraging the patient to read the medication guide they receive from the pharmacy.

Here are some key ideas to convey to patients about proper use [46]:

- Never abruptly stop pain medications without consultation with the prescriber.
- Do not take a pain medicine with alcohol or other prescription or illegal sedatives, as this can result in overdose or death.
- Do not take a pain medicine to promote sleep.
- Never break, chew, or crush medicines, particularly ER/LA opioid medications.
- For transdermal products, external heat, fever, and exertion can increase absorption, leading to a potentially fatal overdose.
- Transdermal products with metal foil backings are not safe for use in MRI scanners.
- Do not use transdermal products if they are broken or torn.

Patients should be thoroughly counseled on the potential adverse effects of opiates – including signs, symptoms, and risk factors for overdose, respiratory depression, constipation, and potential allergic reactions. Risk for falls, especially in the elderly, should also be discussed with patients and caregivers, as well as limitations to activities including driving and operating machinery. Patients and caregivers should be instructed to consult with their health care provider if side effects occur, in order to properly manage adverse reactions and maximize pain management therapy. Providers should report adverse events to the FDA by calling 1-800-FDA-1088 or online at http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf [16].
Safe storage

Patients need to be reminded that even children or close relatives can be tempted to use pain medications they have not been prescribed. Opioids are often obtained by teens, for example, from unsecured medicine cabinets of family and friends.

If possible, opioid pain medications should be stored in a locked cabinet or other secure storage unit to protect from theft. Storage areas should be cool, dry, and out of direct sunlight. Remind patients not to store medications in their car, to keep medications in the original containers, and to avoid storing medications in the refrigerator or freezer unless specifically directed to do so by a health care provider or pharmacist.

Proper disposal

The Office of National Drug Control Policy currently recommends that unused opioid pain medications be flushed down a toilet [47]. However, some states may have different or more stringent guidelines. California, for example, instructs consumers not to flush any medicines down the toilet or drain, to avoid introduction of medications into the water supply. If flushing medicines is not allowed in your state, instruct patients to follow the instructions of a pharmacist for disposal or to mix the medicines with an undesirable substance, such as used coffee grounds, put the mixture into a disposable container with a lid or a sealable bag, and place it in the trash.

Take-home naloxone

It may become more common to provide patients and their caregivers with the intranasal preparation of the opioid antagonist medication naloxone as a way to reverse the complications associated with accidental overdose. Although naloxone was FDA-approved in 1971 and has been used for decades by emergency medical services personnel, intranasal administration of naloxone is not currently approved by the FDA for at-home use as an antidote for opioid overdose so, as of this writing, this represents an off-label use of this medication. Numerous studies and community initiatives have attested to the safety, convenience, and effectiveness of providing intranasal naloxone to patients who may be at risk of overmedication or overdose [48]. This includes patients who:

- Receive prescriptions of more than 50 mg of morphine equivalent/day.
- Are being rotated from one opioid to another when there may be incomplete cross-tolerance.
- Are opioid naïve and who have been prescribed methadone or who are rotated from another opioid to methadone.
- Are released after emergency medical care involving opioid intoxication or poisoning.
- Have a suspected history of substance abuse, dependence, or nonmedical opioid use.
- Have known or suspected concurrent heavy alcohol use.
- Have a respiratory infection or illness.
- May have difficulty accessing emergency medical services.

Efforts are underway in several states to make intranasal naloxone more widely available to the public and to train health care and emergency service providers in its use [48].

Dealing with opioid overdose

Because respiratory depression is the most serious potential harm from opioids, it is incumbent on clinicians to fully inform patients of this and educate them (and their home caregivers, if possible) on recommended steps to take in an emergency. Respiratory depression might occur because a patient takes more than the prescribed amount, either intentionally or unintentionally, or because the patient was mistakenly given too much medication by a caregiver. Respiratory depression typically takes time to develop, hence there will be early warning signs of overdose including:

- Intoxicated behavior – confusion, slurred speech, stumbling.
- Feeling dizzy or faint.
- Acting very drowsy or groggy.
- Unusual snoring, gasping, or snorting during sleep.
- Difficulty waking up from sleep or staying awake.

Patients and their caregivers should be counseled to immediately call 911 or an emergency service if they observe any of these warning signs. If naloxone has been provided for the patient, it should be administered immediately, which will reverse respiratory depression and should allow the patient to begin breathing more normally. If a person has stopped breathing, artificial respiration cardiopulmonary resuscitation (CPR, including rescue breathing) should be begun immediately until emergency help arrives.

Conclusions

This monograph has summarized best practices for the responsible prescribing of opioid pain medications for chronic non-cancer pain. More detailed information on many of these topics is available from the resources listed. The treatment of pain is a dynamic and evolving field, and clinicians should periodically refresh their knowledge through reading, attending seminars or other events, or by taking additional CME courses.

Clinicians face the competing demands of relieving pain while minimizing potential harm to both patients and society. The steps and procedures described in this monograph provide a roadmap and structure by which clinicians can achieve these twin goals without incurring undue burdens of time or energy. Pharmacovigilance simply means that prescribers apply basic principles of prudent medicine to the needs of patients in pain. And because the evidence base for current guidelines remains suboptimal, clinicians retain a great deal of latitude in deciding how that vigilance is best deployed on a day-to-day basis.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Dosing interval</th>
<th>Key instructions</th>
<th>Specific drug interactions</th>
<th>Use in opioid-tolerant patients</th>
<th>Drug-specific safety concerns</th>
<th>Relative potency to oral morphine</th>
</tr>
</thead>
</table>
| Avinza       | Morphone Sulfate ER - Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg | Once a day               | Initial dose in opioid non-tolerant patients is 30 mg.  
Titrating using a minimum of 3-day intervals.  
Swallow capsule whole (do not chew, crush, or dissolve).  
May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately.  
Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.                                                                      | Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine.  
PGP inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about twofold.                                                                 | 90 mg and 120 mg capsules are for use in opioid-tolerant patients only.                                                                                          | None.                          | Equiepotency to oral morphine has not been established. |
| Butrans      | Buprenorphine - Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr.          | One transdermal system every 7 days. | 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.  
Titrating after a minimum of 72 hours prior to dose adjustment.  
Maximum dose: 20 mcg/hr due to risk of QTc prolongation.  
Application  
○ Apply only to sites indicated in the Full Prescribing Information.  
○ Apply to intact/non-irritated skin.  
○ Skin may be prepped by clipping hair, washing site with water only.  
○ Rotate site of application a minimum of 3 weeks before reapplying to the same site.  
○ Do not cut.  
Avoid exposure to heat.  
Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.                                                                 | CYP3A4 Inhibitors may increase buprenorphine levels.  
CYP3A4 Inducers may decrease buprenorphine levels.  
Benzodiazepines may increase respiratory depression.  
Class IA and III antiarrythmic agents, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and Torsade de pointes. | Butrans 10 mcg/hr and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only. | QTc prolongation and Torsade de pointes.  
Hepatotoxicity.  
Application site skin reactions.                                   |                                                        |
| Dolophine    | Methadone Hydrochloride - Tablets, 5 mg and 10 mg                           | Every 8 to 12 hours.     | Initial dose in opioid non-tolerant patients: 2.5 to 10 mg.  
Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information.  
High inter-patient variability in absorption, metabolism, and relative analgesic potency.  
Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8). | Pharmacokinetic pharmacodynamics interactions with methadone complex.  
○ CYP 450 inducers increase methadone levels.  
○ CYP 450 inhibitors decrease methadone levels.  
○ Anti-retroviral agents have mixed effects on methadone levels.  
○ Potentially arrhythmogenic agents increase risk for QTc prolongation and Torsade de pointes.  
Benzodiazepines may increase respiratory depression. | Refer to full prescribing information.                                                                                                                          | QTc prolongation and Torsade de pointes.  
Peak respiratory depression occurs later and persists longer than analgesic effect.  
Clearance may increase during pregnancy.  
False-positive urine drug screens possible.                                                                                                                    | Varies depending on patient's prior opioid experience.                                                             |
### Table 5 (continued): Specific drug information for extended-release and long-acting opioid analgesics (ER/LA opioid analgesics)

<table>
<thead>
<tr>
<th><strong>Duragesic</strong></th>
<th><strong>Fentanyl</strong> - Transdermal System, 12, 25, 50, 75, and 100 mcg/hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing interval</strong></td>
<td>Every 72 hours (3 days).</td>
</tr>
</tbody>
</table>
| **Key instructions** | - Use product specific information for dose conversion from prior opioid.  
  - Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment.  
  - Application:  
    ○ Apply to intact/non-irritated/non-irradiated skin on a flat surface.  
    ○ Skin may be prepped by clipping hair, washing site with water only.  
    ○ Rotate site of application.  
    ○ Titrate using no less than 72 hour intervals.  
    ○ Do not cut.  
  - Avoid exposure to heat.  
  - Avoid accidental contact when holding or caring for children.  
  - Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.  
  - **Specific contraindications:**  
    ○ Patients who are not opioid-tolerant.  
    ○ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time.  
    ○ Management of postoperative pain, including use after out-patient or day surgery.  
    ○ Management of mild pain. |
| **Specific drug interactions** | - CYP3A4 inhibitors may increase fentanyl exposure.  
  - CYP3A4 inducers may decrease fentanyl exposure. |
| **Use in opioid-tolerant patients** | All doses of Duragesic are indicated for use in opioid-tolerant patients only. |
| **Product-specific safety concerns** | - Accidental exposure due to secondary exposure to unwashed/unclothed application site.  
  - Increased drug exposure with increased core body temperature or fever.  
  - Bradycardia.  
  - Application site skin reactions. |
| **Relative potency to oral morphine** | See individual product information for conversion recommendations from prior opioid. |
| **Embeda** | Morphine Sulfate ER-Naltrexone - Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg. |
| **Dosing interval** | Once a day or every 12 hours. |
| **Key instructions** | - Initial dose as first opioid: 20 mg/0.8 mg.  
  - Titrate using a minimum of 3-day intervals.  
  - Swallow capsules whole (do not chew, crush, or dissolve).  
  - Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.  
  - May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately. |
| **Specific drug interactions** | - Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine.  
  - PGP inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about twofold. |
| **Use in opioid-tolerant patients** | Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only. |
| **Product-specific safety concerns** | None. |
| **Exalgo** | Hydromorphone Hydrochloride - Extended-Release Tablets, 8 mg, 12 mg, or 16 mg. |
| **Dosing interval** | Once a day. |
| **Key instructions** | - Use the conversion ratios in the individual product information.  
  - Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function.  
  - Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function.  
  - Titrate using a minimum of 3 to 4 day intervals.  
  - Swallow tablets whole (do not chew, crush, or dissolve).  
  - Do not use in patients with sulfa allergy – contains sodium metabisulfite. |
<p>| <strong>Specific drug interactions</strong> | None. |
| <strong>Use in opioid-tolerant patients</strong> | All doses of Exalgo are indicated for opioid-tolerant patients only. |
| <strong>Drug-specific adverse reactions</strong> | Allergic manifestations to sulfa component. |
| <strong>Relative potency to oral morphine</strong> | Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information. |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Product Information</th>
<th>Dosing Interval</th>
<th>Key Instructions</th>
<th>Specific Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kadian</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Once a day, or every 12 hours.</td>
<td>● Product information recommends not using as first opioid.</td>
<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></td>
<td></td>
<td></td>
<td>● Titrate using a minimum of 2-day intervals.</td>
<td>● PGP inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about twofold.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Swallow capsules whole (do not chew, crush, or dissolve).</td>
<td></td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

**Use in opioid-tolerant patients**
Kadian 100 mg and 200 mg capsules are for use in opioid-tolerant patients.

**Product-specific safety concerns**
None.

<table>
<thead>
<tr>
<th><strong>MS Contin</strong></th>
<th>Product Information</th>
<th>Dosing Interval</th>
<th>Key Instructions</th>
<th>Specific Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphine Sulfate - Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg.</td>
<td>Every 8 hours or every 12 hours.</td>
<td>● Product information recommends not using as first opioid.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Titrate using a minimum of 2-day intervals.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>● Swallow tablets whole (do not chew, crush, or dissolve).</td>
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</table>

**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.

<table>
<thead>
<tr>
<th><strong>Nucynta ER</strong></th>
<th>Product Information</th>
<th>Dosing Interval</th>
<th>Key Instructions</th>
<th>Specific Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tapentadol - Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg.</td>
<td>Every 12 hours.</td>
<td>● Use 50 mg every 12 hours as initial dose in opioid non-tolerant patients.</td>
<td>● Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Titrate by 50 mg increments using a minimum of 3-day intervals.</td>
<td>● Contraindicated in patients taking MAOIs.</td>
</tr>
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<td></td>
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<td>● Maximum total daily dose is 500 mg.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>● Swallow tablets whole (do not chew, crush, or dissolve).</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>● Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth.</td>
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<tr>
<td></td>
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<td></td>
<td>● Dose once daily in moderate hepatic impairment with 100 mg per day maximum.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>● Avoid use in severe hepatic and renal impairment.</td>
<td></td>
</tr>
</tbody>
</table>

**Use in opioid-tolerant patients**
No product-specific considerations.

**Product-specific safety concerns**
None.

**Relative potency to oral morphine**
Equiopotency to oral morphine has not been established.

<table>
<thead>
<tr>
<th><strong>Opana ER</strong></th>
<th>Product Information</th>
<th>Dosing Interval</th>
<th>Key Instructions</th>
<th>Specific Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxymorphone Hydrochloride - ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.</td>
<td>Every 12 h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.</td>
<td>● 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 &lt; 50 mL/min) and patients over 65 years of age.</td>
<td>● Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Swallow tablets whole (do not chew, crush, or dissolve).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Titrate using a minimum of 2-day intervals.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Contraindicated in moderate and severe hepatic impairment.</td>
<td></td>
</tr>
</tbody>
</table>

**Use in opioid-tolerant patients**
No product specific considerations.

**Product-specific safety concerns**
None.

**Relative potency to oral morphine**
Approximately 3:1 oral morphine to oxymorphone oral dose ratio.
Table 5 (continued): Specific drug information for extended-release and long-acting opioid analgesics (ER/LA opioid analgesics)

<table>
<thead>
<tr>
<th>OxyContin</th>
<th>Oxycodone Hydrochloride - Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing interval</td>
<td>Every 12 hours.</td>
</tr>
</tbody>
</table>

**Key instructions**

- Opioid-naive patients: Initiate treatment with 10 mg every 12 hours.
- Titrate using a minimum of 1 to 2 day intervals.
- Hepatic impairment: start with one third to one half the usual dosage.
- Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage.
- Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve).
- Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

**Specific drug interactions**

- CYP3A4 inhibitors may increase oxycodone exposure.
- CYP3A4 inducers may decrease oxycodone exposure.

**Use in opioid-tolerant patients**

- Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.

**Product-specific safety concerns**

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

**Relative potency to oral morphine**

Approximately 2:1 oral morphine to oxycodone oral dose ratio.

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.

**Source:** FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 7/9/2012.

**Resources**

American Academy of Pain Medicine  
www.painmed.org

American College of Physicians  
www.doctorsforadults.com

American Chronic Pain Association  
www.theacpa.org

Drug Enforcement Administration Diversion Control Program  
www.DEAdvision.usadoj.gov

Federation of State Medical Boards  
www.fsmb.org

The National Association of State Controlled Substances Authorities  
www.nascua.org

National Association of Drug Diversion Investigators  
www.naddi.org

Pain Treatment Topics  
www.pain-topics.org

University of Wisconsin Pain & Policy Studies Group  
www.painpolicy.wisc.edu

**References**


BEST PRACTICES FOR PRESCRIBING OPIOIDS IN CHRONIC NON-CANCER PAIN

Final Examination Questions
Choose the best answer for questions 1 through 5 and mark your answers online at Pharmacy.EliteCME.com

1. Long-acting (LA) and extended-release (ER) formulations of opioids should not be used to treat which of the following types of pain?
   b. Acute pain.
   c. End-of-life pain.
   d. Chronic non-cancer pain.

2. Which of the following questions does not need to be considered by health care professionals when obtaining informed consent from patients considering opiate treatment?
   a. Does the patient understand the various options for treatment?
   b. Has the patient been reasonably informed of the potential benefits and risks associated with each of those options?
   c. Is the patient free to choose among those options, free from coercion by the health care professional, the patient’s family, or others?
   d. Does the prescriber understand the various options for treatment?

3. It is unsafe to combine opioids with which of the following types of medicines?
   a. Stimulant medications.
   b. SSRI antidepressants.
   c. Benzodiazepines or barbiturates.
   d. Anti-hypertensive medications.

4. Which of the following metabolites does not commonly arise on a urinalysis of a patient taking codeine?
   a. Codeine.
   b. Oxycodone.
   c. Morphine.
   d. Hydrocodone.

5. Which of the following is not an early warning sign of opiate overdose that patients should be counseled about?
   a. Intoxicated behavior – confusion, slurred speech, stumbling.
   b. Unusual snoring, gasping, or snorting during sleep.
   c. Difficulty waking up from sleep or staying awake.
   d. Difficulty getting to sleep or staying asleep.