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Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

BARRY D. WEISS, MD, FAAFP

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Learning Objectives

After reading this *CME Bulletin*, learners should be able to:

- Review/assess general and product-specific drug information concerning ER/LA opioid analgesics and identifying potential adverse effects of ER/LA opioids.

Toxicities and Drug Interactions

Sedation and Respiratory Depression

Most clinicians who prescribe opioid analgesics are aware that sedation occurs commonly with opioid use and that respiratory depression is the most serious adverse effect of opioid analgesics. Indeed, respiratory depression due to overdose was the likely cause in most of the approximately 16,000 opioid-related mortalities that occurred in the United States in 2010, the most recent year for which data are available. The number of opioid-related overdose mortalities has nearly quadrupled since 1999.[1]

With continued use of opioid analgesics, individuals develop tolerance to the sedative and respiratory depressive effects. However, concomitant use of drugs that act on the central nervous system–including alcohol, sedative-hypnotics, tricyclic antidepressants and, in particular, benzodiazepines[2]–can potentiate the sedative and respiratory depressive effects even in individuals who might otherwise be considered opioid tolerant. A similar effect can be seen occasionally when opioid analgesics are used concomitantly with, or within 2 weeks of discontinuing, monoamine oxidase inhibitors.[3] Avoiding these substances while taking opioid analgesics will minimize the risk of opioid-induced sedation and respiratory depression.

Constipation

Most clinicians are also aware that constipation is an adverse effect experienced by individuals using short- or long-acting opioid analgesics. The reported incidence of problems related to constipation in users of chronic opioid analgesics is shown to be as high as 29% in large population-based studies.[4] Among the extended-release and long-acting (ER/LA) opioid analgesics, one older study found that the rate of constipation is higher with sustained-release morphine than with transdermal fentanyl.[5] A more recent study that did not include morphine found the constipation rate (defined as no stools for more than 72 hours) was similar with transdermal fentanyl (22%)[5] and transdermal buprenorphine (21%), but substantially lower, at 2%, with extended-release hydromorphone (Exalgo).[6]

Opioid-induced constipation is typically managed by increasing intake of fluids and dietary fiber, plus use of both stool softeners and stimulant laxatives; stool softeners alone are often insufficient.[7] Increasingly, however, the emphasis is on prevention of constipation rather than management, with institution of stool softeners and stimulant laxatives when opioid therapy is started, rather than after constipation develops.[8]

Decreased Effectiveness of Diuretics

Opioid analgesics induce release of antidiuretic hormone (ADH), which counteracts the effect of diuretic drugs. Although not often considered by clinicians, this effect may be important for patients with medical conditions that require diuretic therapy, such as heart failure.[9]

QT-Interval Prolongation

Methadone and high doses of transdermal buprenorphine (greater than 20 mcg/hr) are known to prolong the electrocardiographic QT interval, which in turn poses an increased risk of torsades de pointes, or torsades, ventricular tachycardia. Although either of these ER/LA drugs has the potential to induce torsades on its own, particularly at higher doses, the risk of torsades may be even greater when these opioid

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

Avinza (morphine sulfate ER capsules)
Butrans (buprenorphine transdermal system)
Dolophine (methadone HCl tablets)
Duragesic (fentanyl transdermal system)
Embeda (morphine sulfate ER-naltrexone capsules)
Exalgo (hydromorphone HCl ER tablets)
Kadian (morphine sulfate ER capsules)
MS Contin (morphine sulfate CR tablets)
Nucynta ER (tapentadol HCl ER tablets)
Opana ER (oxymorphone HCl ER tablets)
OxyContin (oxycodone HCl CR tablets)

Dosing interval	**Refer to individual product information.**
Key instructions	■ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ■ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ■ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ■ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ■ If pain increases, attempt to identify the source, while adjusting the dose. ■ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. **Do not abruptly discontinue these products.** ■ Limitations of usage: ■ Not for use as an as-needed analgesic. ■ Not for mild pain or pain not expected to persist for an extended duration. ■ Not for use in treating acute pain. ■ Solid oral dosage forms: ■ Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. ■ Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. ■ Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. ■ Dispose of unused product by flushing down the toilet. ■ Transdermal dosage forms: ■ Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. ■ Location of application must be rotated. ■ Prepare skin by clipping, not shaving hair, and washing area only with water. ■ See individual product information for the following: ■ Dosage reduction for hepatic or renal impairment.
Drug interactions common to the class	■ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ■ Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use. ■ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ■ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in opioid-tolerant patients	■ See individual product information for which products: ■ Have strengths or total daily doses only for use in opioid-tolerant patients. ■ Are only for use in opioid-tolerant patients at all strengths.
Contraindications	■ Significant respiratory depression ■ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ■ Known or suspected paralytic ileus ■ Hypersensitivity (e.g., anaphylaxis) ■ See individual product information for additional contraindications.
Relative potency to oral morphine	■ **These are intended as general guides.** ■ Follow conversion instructions in individual product information. ■ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another – halve the calculated comparable dose and titrate the new opioid as needed.

analgesics are taken in combination with other drugs that prolong the QT interval. Commonly prescribed drugs that prolong the QT interval and that have the strongest evidence for inducing torsades include azithromycin, clarithromycin, citalopram, and escitalopram.[10] Clinicians can quickly identify drugs known to cause QT prolongation at http://www.crediblemeds.org.

Changes in Opioid Levels with Cytochrome Enzyme Inhibitors

Several ER/LA opioid analgesics are metabolized in the liver by cytochrome enzyme systems. The levels of these opioid analgesics can increase when they are taken simultaneously with drugs that inhibit those cytochrome enzymes.

In particular, methadone levels can increase when taken simultaneously with drugs that inhibit cytochrome P450 enzyme systems. Although many drugs inhibit cytochrome P450, some of the more commonly prescribed drugs with this effect include antidepressants (including bupropion, fluoxetine, and paroxetine), cimetidine, acyclovir, duloxetine (Cymbalta), fluoroquinolone antibiotics, ketoconazole, several protease inhibitors (indinavir [Crixivan], nelfinavir [Viracept], ritonavir [Norvir]), proton pump inhibitors, verapamil, and diltiazem.[11] Buprenorphine, fentanyl, and oxycodone levels can increase when taken simultaneously with drugs that inhibit cytochrome P3A4 (a subtype of the P450 system). Commonly prescribed drugs that inhibit P3A4 inhibitors include cimetidine, diltiazem, protease inhibitors, fluconazole, ketoconazole, and verapamil. Grapefruit juice is also a P3A4 inhibitor.[11]

Conversely, the levels of several opioid analgesics can decrease when they are taken with drugs that stimulate cytochrome enzymes involved in opioid metabolism, both cytochrome P450 and subtype P3A4. Levels of buprenorphine, fentanyl, methadone, and oxycodone may decrease when patients simultaneously use cytochrome inducers that include carbamazepine, isoniazid, tobacco, rifampin, and St. John's wort (*Hypericum perforatum*).[11]

Prescribing Considerations for Specific Extended-Release/Long-Acting Opioid Analgesics

Tolerance

Because the sedative and respiratory depressive effects of ER/LA opioid analgesics are so potent, some ER/LA formulations should not be used by individuals who are intolerant to these effects. Tolerance typically develops after taking an opioid for 1 week or more at a morphine-equivalent dose of 60 mg/day.

Other ER/LA agents can be used in patients who are intolerant, but only at low doses. Still others should not be used, regardless of dose, in patients who have never received opioid analgesics.

Transdermal fentanyl and extended-release hydromorphone are the two ER/LA opioid analgesics that should not be used by patients who are intolerant. These drugs, regardless of the dose, are specifically contraindicated in such patients.[3] For other ER/LA opioid analgesics, although not specifically contraindicated in patients who are intolerant, there are limits to the strength of individual doses and total daily doses. Notably, those strengths and doses can vary with different brands and formulations of the same drug. For example, when prescribing extended-release morphine under the brand names of MS Contin and Kadian, the patient must be opioid tolerant to receive doses of 100 mg or more.[3] For the brand name Avinza extended-release morphine, the corresponding dose is 90 mg.[3] Clinicians should check the dosing and tolerance requirements for the various ER/LA opioid analgesics before prescribing (see *Table 2*).

Finally, two oral ER/LA agents should not be used as a first opioid (ie, by patients who have never taken opioid analgesics), regardless of the dose. These two agents are extended-release morphine under the brand names of Kadian and MS Contin.[3]

Concerns with Oral Administration

Oral ER/LA opioid analgesics must be swallowed whole. Breaking, crushing, or chewing these pills is dangerous because doing so can cause a rapid release of the opioid into the circulation, resulting in respiratory depression and death.

There is, however, an exception for patients who are unable to swallow ER/LA opioid pills. For these patients, there are three ER/LA formulations available in capsule formulation that can be opened and the contents either administered through a feeding tube or sprinkled onto food (applesauce is recommended). If taken with applesauce, it is important to swallow without chewing to avoid breaking the sprinkled pellets, and the mouth should be rinsed with water after ingesting the applesauce to assure that all contents have been swallowed.[12] The three ER/LA opioid analgesics that can be administered in this way are morphine sulfate under the brand names of Avinza, Embeda, and Kadian.[3]

Concerns with Transdermal Administration

Fentanyl and buprenorphine are available in transdermal formulations. When these transdermal ER/LA opioid analgesics are prescribed, patients should be made aware of several important safety concerns.

First, patches should never be cut or torn before use. Doing so could lead to rapid release of opioid through the skin into the circulation with resultant overdose.

Second, exposure to heat can increase release and absorption of opioid analgesics from transdermal formulations, resulting in inadvertent overdose. Heat exposure can involve external heat, such as occurs in saunas, hot tubs, or hot baths; with use of heat lamps, electric blankets, or heating pads; or even with prolonged sun exposure. Heat exposure with increased opioid absorption also can occur during strenuous exercise or with a fever. Febrile patients using transdermal opioid analgesics should be monitored for signs and symptoms of increased opioid effect.[13-16]

Third, caution should be exercised in caring for the application site. For adults, the patch should be applied on the chest, side of the waist, or upper arm, ideally in a place without hair. If hair is unavoidable, it should be clipped as close to the skin as possible but not shaved because shaving-induced trauma to the skin can result in increased drug absorption. The application site should be kept clean by washing with water only; no other substances should be used, including soaps, lotions, oils, or alcohol. The site of application should be rotated. That is, the same site should not be used for two consecutive applications,

and the used patch should always be removed before, not after, applying a new one.[16]

Concerns about Pharmacokinetics and Pharmacodynamics

Finally, the basic pharmacokinetics and pharmacodynamics of opioid analgesics are important considerations. Indeed, it is often the failure to consider these factors that can result in unintentional overdose. For example, because opioids undergo biotransformation in the liver, impaired hepatic function may result in slow clearance and increased opioid levels, particularly with long-acting agents. Some opioid analgesics, such as morphine and hydromorphone, undergo renal clearance so impaired kidney function, even the common age-associated decline in kidney function, might result in accumulation of these drugs. Older adults may be particularly sensitive to opioid effects, such as experiencing increased sedation even when taking opioid analgesics at recommended doses. Thus, when prescribing opioid analgesics, clinicians should be familiar with the specific modes of metabolism and excretion for the drug being considered, and consider the needs and comorbidities of individual patients.

Table 2. Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA Opioid Analgesics)

Avinza	**Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg**
Dosing interval	Once a day
Key instructions	▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific drug interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in opioid-tolerant patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-specific safety concerns	None
Butrans	**Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr**
Dosing interval	One transdermal system every 7 days
Key instructions	▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents – first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. Application: ▪ Apply only to sites indicated in the Full Prescribing Information. ▪ Apply to intact/non-irritated skin. ▪ Skin may be prepped by clipping hair, washing site with water only ▪ Rotate site of application a minimum of 3 weeks before reapplying to the same site. ▪ Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific drug interactions	▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in opioid-tolerant patients	Butrans 10 mcg/hr and 20 mcg/hr transdermal systems are for use in opioid- tolerant patients only.
Drug-specific safety concerns	▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative potency to oral morphine	Equipotency to oral morphine has not been established.

continued

Table 2. Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA Opioid Analgesics) continued

Dolophine	**Methadone Hydrochloride Tablets, 5 mg and 10 mg**
Dosing interval	Every 8 to 12 hours
Key instructions	▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the Full Prescribing Information. ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific drug interactions	▪ Pharmacokinetic drug-drug interactions with methadone are complex. ▪ CYP 450 inducers may decrease methadone levels. ▪ CYP 450 inhibitors may increase methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in opioid-tolerant patients	Refer to full prescribing information.
Product-specific safety concerns	▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative potency to oral morphine	Varies depending on patient's prior opioid experience.
Duragesic	**Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr**
Dosing interval	Every 72 hours (3 days)
Key instructions	▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment Application: ▪ Apply to intact/non-irritated/non-irradiated skin on a flat surface. ▪ Skin may be prepped by clipping hair, washing site with water only ▪ Rotate site of application. ▪ Titrate using no less than 72 hour intervals. ▪ Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. **Specific contraindications:** ▪ Patients who are not opioid-tolerant. ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific drug interactions	▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure.
Use in opioid-tolerant patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
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

continued

Table 2. Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA Opioid Analgesics) continued

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 two-fold.
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, 16 mg or 32 mg**
Dosing interval	Once a day
Key instructions	■ Use the conversion ratios in the individual product information. ■ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ■ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ■ Titrate using a minimum of 3 to 4 day intervals. ■ Swallow tablets whole (do not chew, crush, or dissolve). ■ Do not use in patients with sulfite allergy—contains sodium metabisulfite.
Specific drug interactions	None
Use in opioid-tolerant patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-specific adverse reactions	Allergic manifestations to sulfite component.
Relative potency to oral morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Kadian	**Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg**
Dosing interval	Once a day or every 12 hours
Key instructions	■ Product information recommends not using as first opioid. ■ Titrate using a minimum of 2-day intervals. ■ Swallow capsules whole (do not chew, crush, or dissolve). ■ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific drug interactions	■ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ■ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in opioid-tolerant patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant patients only.
Product-specific safety concerns	None
MS Contin	**Morphine Sulfate Controlled-Release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg**
Dosing interval	Every 8 hours or every 12 hours
Key instructions	■ Product information recommends not using as first opioid. ■ Titrate using a minimum of 2-day intervals. ■ Swallow tablets whole (do not chew, crush, or dissolve).
Specific drug interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in opioid-tolerant patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-specific safety concerns	None

continued

Table 2. Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA Opioid Analgesics) continued

Nucynta ER	**Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg**
Dosing interval	Every 12 hours
Key instructions	▪ Use 50 mg every 12 hours as initial dose in opioid nontolerant patients ▪ Titrate by 50 mg increments using a minimum of 3-day intervals. ▪ Maximum total daily dose is 500 mg ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Dose once daily in moderate hepatic impairment with 100 mg per day maximum ▪ Avoid use in severe hepatic and renal impairment.
Specific drug interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. ▪ Contraindicated in patients taking MAOIs.
Use in opioid-tolerant patients	No product-specific considerations.
Product-specific safety concerns	▪ Risk of serotonin syndrome ▪ Angioedema
Relative potency to oral morphine	Equipotency to oral morphine has not been established.
Opana ER	**Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg**
Dosing interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key instructions	▪ Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Titrate using a minimum of 2-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific drug interactions	Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in opioid-tolerant patients	No product specific considerations.
Product-specific safety concerns	None
Relative potency to oral morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	**Oxycodone Hydrochloride Controlled-Release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg**
Dosing interval	Every 12 hours
Key instructions	▪ Opioid-naïve patients: initiate treatment with 10 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Hepatic impairment: start with one third to one half the usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. ▪ Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific drug interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in opioid-tolerant patients	▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-specific safety concerns	▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.
Relative potency to oral morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.

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.

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Author Information

Barry D. Weiss, MD, FAAFP, is a professor of family and community medicine at the University of Arizona College of Medicine, Tucson. He is the medical editor for *FP Essentials* and associate editor for *American Family Physician*. He is the author of nearly 150 journal articles and several medical textbooks.

Medical Editor Information

S. Hughes Melton, MD, FAAFP, is co-founder and president of C-Health, PC, in Russell County, Virginia, a family medicine practice focused on improving citizen health in an underserved region. He is co-director of REMOTE, or the Rural Enhanced Model for Opioid Treatment Expansion, a project that promotes substance abuse treatment. Dr Melton is the 2011 recipient of the AAFP Physician of the Year Award.

Self-Assessment Quiz

1. Which of the following agents can increase the chance of respiratory depression when taken by the patient who is also taking an extended-release/long-acting opioid analgesic?
   A. Isoniazid
   B. Rifampin
   C. St John's wort (*Hypericum perforatum*)
   D. Tricyclic antidepressants

2. Which of the following extended-release/long-acting opioid analgesics is known to increase the electrocardiographic QT interval and thus should be avoided in patients taking other drugs that prolong the QT interval?
   A. Controlled-release oxycodone
   B. Extended-release morphine
   C. Methadone
   D. Transdermal fentanyl

3. Which statement best describes the approach to prescribing extended-release/long-acting opioid analgesics for patients who are not opioid tolerant?
   A. A test dose should be administered in the office to observe for adverse effects.
   B. All extended-release/long-acting opioid analgesics are contraindicated in patients who are not opioid tolerant.
   C. The dose of a particular opioid analgesic that can be given safely to patients who lack tolerance varies, even among different brands and formulations of the same drug.
   D. Until tolerance develops, only transdermal preparations should be prescribed.

4. Your patient has been using extended-release morphine for several months. She has now had a stroke and is having difficulty swallowing. You would like to maintain her on the same morphine regimen because it has been successful in managing the pain and there have been no important side effects. You check the prescribing information in *Table 1, Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics*, and find that the morphine she is using is a capsule that can be opened and the contents (pellets) sprinkled on food. What instructions should you give this patient about proper administration of the pellets with food?
   A. Ice cream is the recommended food.
   B. She should rinse her mouth with water after eating the pellet-containing food.
   C. The pellet-containing food should be chewed thoroughly prior to swallowing.
   D. The pellets should be crushed prior to sprinkling them on the food.

5. You are prescribing a transdermal long-acting opioid analgesic to a patient for management of pain caused by bone metastases due to prostate cancer. Which of the following should be part of the instructions you give to this patient about proper use of the transdermal drug?
   A. Apply the patch over the most painful areas.
   B. Apply the patch to the upper thigh, alternating legs each time a new patch is applied.
   C. Do not shave hair at the site of patch application.
   D. Wash the application site with soap and water prior to applying the patch.

Answers: 1) D, 2) C, 3) C, 4) B, 5) C

AAFP Members: To complete the quiz, see instructions at right.

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Elaine Kierl Gangel, Manager, CME Subscriptions & Bulletins Department, Continuing Medical Education

Andrea Harden, Senior Associate Editor

Sam Carlson, Editorial Assistant

Bryan Colley, Graphic Associate

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