Opioid Pharmacology and Considerations in Pain Management

Release Date: May 2007
Expiration Date: May 31, 2009

FACULTY:
Anne Zichterman, PharmD, BCPS
Assistant Professor, Department of Pharmacy
University of Tennessee College of Pharmacy

FACULTY DISCLOSURE STATEMENTS:
Dr. Zichterman has nothing to disclose.

U.S. Pharmacist does not view the existence of relationships as an implication of bias or that the value of the activity was planned to be balanced, objective, and scientifically rigorous. Occasionally, authors may express opinions that reflect a viewpoint. Conclusions drawn by participants should be derived from objective analysis of scientific data.

ACCREDITATION STATEMENTS:
Pharmacists
Postgraduate Healthcare Education, LLC is accredited by the Accreditation Council for Pharmacy Education.
Program No.: 430-000-07-012-H01
Credits: 2.0 hours (.20 ceu)

Published: May 2007
Expires: May 31, 2009

Exam processing inquiries and booklet orders to:
CE Customer Service Manager (800) 825-4696

Direct educational content inquiries to:
TARGET AUDIENCE:
This accredited program is targeted to pharmacists and pharmacist technicians.

DISCLAIMER:
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of other authorities.

GOAL:
To educate pharmacists about the variations in opioid pharmacology and effective clinical strategies for pain management.

LEARNING OBJECTIVES:
After completing this article, the pharmacist will be able to:

1. Compare and contrast the differences between opioids and their pharmacologic profiles that may lead to variations in patient outcomes.
2. Assess the advantages and disadvantages of available routes of administration.
3. Implement effective pain management using as-needed and scheduled regimens, dosage titration, and opioid conversion.
4. Develop management strategies for adverse effects, and distinguish the difference between tolerance, physical dependence, and addiction.

Throughout the past century, the availability of opioids has expanded to include semisynthetic opiate derivatives (e.g., hydrocodone, oxycodone, and oxymorphone) and synthetic opioid analogs (e.g., tramadol, fentanyl, meperidine, methadone, propoxyphene). These drugs bind to three types of opioid receptors: mu, delta, and kappa. When selecting an opioid analgesic, consideration should be given to potency and efficacy, speed of onset, duration of effect, route of administration, and adverse effect profile. Knowledge in this area may aid the practitioner in tailoring therapy for effective and safe pain management.

Opioids for Mild-to-Moderate Pain

**Codeine:** Codeine, like morphine, is a naturally occurring opiate. It is a weak analgesic and should be used for severe pain is extremely limited due to its lack of potency; a 60-mg dose produces less analgesia than two 325-mg doses of aspirin. Some researchers have proposed that codeine is a pro-drug with analgesic activity dependent on its conversion to morphine by the CYP2D6 enzyme. If a patient is taking a drug that inhibits the CYP2D6 enzyme (e.g., a phenothiazine, haloperidol, fluoxetine, paroxetine), codeine’s efficacy may be reduced. Additionally, up to 10% of the population lack the CYP2D6 enzyme and may experience adverse effects with codeine-containing products.

Codeine is not recommended for patients with impaired renal function; serious adverse effects have been reported in this setting.

**Hydrocodone:** Hydrocodone is only available in combination with non-opioids. Compared with codeine, it provides a longer duration of action. Hydrocodone is a prodrug metabolized by CYP2D6, with analgesic effects dependent on the conversion to oxycodone. Consequently, drug interactions with CYP2D6 inhibitors and genetic enzyme deficiencies may affect the analgesic response.

Dose titrations are limited by the non-opioid content, which makes using this agent for severe or escalating pain difficult.
combination products contain at least 500 mg of acetaminophen; at these dosages, the maximum 4-g dose of acetaminophen is risk of ingestion of eight tablets. If taken as commonly prescribed (one or two tablets every four to six hours), patients may exceed the maximum dose of acetaminophen. According to one study, 42% of acute liver failure cases in the United States resulted from intentional use of acetaminophen and check ingredients of OTC pain relievers and cold remedies who unintentionally overdosed, 63% used opioid-containing compounds, most commonly hydrocodone. Propoxyphene: Propoxyphene is usually used alone (Darvon) or in combination with acetaminophen (Darvocet). It is structurally similar to codeine and hydrocodone and more closely resembles the phenylheptylamine opioid methadone. Propoxyphene may cause adverse effects, such as dizziness and euphoria. Propoxyphene is metabolized to norpropoxyphene, which may cause irreversible cardiac toxicity and arrhythmias. Thus, propoxyphene is not recommended for the treatment of chronic pain or for patients with renal insufficiency.

Tramadol: Tramadol is a weak opioid analgesic that may be useful for chronic pain. It comes in three formulations and is available in immediate- and sustained-release products. Its unique properties include weak binding to mu receptors and inhibition of norepinephrine and serotonin reuptake. The non-opioid mechanism may contribute to the usefulness of tramadol for neuropathic pain. Due to a high incidence of nausea and vomiting, dosages must be increased slowly over several weeks, thereby limiting its effectiveness for acute pain.

Since seizures have been described with tramadol administration, concurrent use of monoamine oxidase inhibitors (SSRIs), and tricyclic antidepressants should be avoided. To lower the risk of adverse events, dosages should be reduced for patients or for patients with renal or hepatic dysfunction. Tramadol is not a controlled substance and is less likely to produce significant tolerance, physical dependence, or abuse. Opioids for Moderate-to-Severe Pain

Morphine: Morphine is the prototype pure mu-receptor agonist. It is extensively used and is available in immediate- and sustained-release products. Morphine has two biologically active metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G does not bind to mu receptors but acts as a neuroexcitatory agent, contributing to adverse effects such as hyperalgesia, myoclonus, and confusion. M6G has weak receptor activity; it is at least two to four times more potent than morphine and may significantly contribute to analgesia. M6G is renally eliminated; accumulation of M6G may lead to oversedation and respiratory depression in patients with advanced renal disease. Morphine is known to induce histamine release, which may lead to hypotension and pruritus. As a hydrophilic opioid, morphine has significantly longer duration compared with more lipophilic opioids (e.g., fentanyl, meperidine). Like most opioids, a small amount of orally administered drug that reaches the circulation, giving a parenteral-to-oral dose ratio of 1:3

Hydromorphone: Hydromorphone is five to seven times more potent than morphine but is not more likely to produce significant adverse effects. Hydromorphone has an improved side effect profile over morphine, with less histamine release and less pruritus, making it a preferable option to morphine for patients with renal insufficiency.
The use of hydromorphone for chronic pain has been limited by the lack of a sustained-release product. It was suspended and recalled by the FDA due to an interaction with alcohol that caused destruction of the timed release mechanism. The intravenous and oral forms of hydromorphone also undergo first-pass metabolism; the parenteral-to-oral dose ratio is 1:5.

Oxycodone: Oxycodone is more potent and causes fewer severe adverse effects (e.g., histamine release) than other opioids. It is available as an injection and as oral formulations: immediate-release (Opana) and sustained-release (Opana ER). Because it has a longer half-life than morphine, hydromorphone, and oxycodone, the immediate-release product may be dosed at longer intervals (up to every 3 to 6 hours).

Oxymorphone: Oxymorphone is approximately twice as potent as oxycodone. It is more lipophilic than morphine, allowing for a faster onset of action. It is available as an injection and as oral formulations: immediate-release (Opana) and sustained-release (Opana ER). Because it acts selectively at the mu receptor, leading to an improved side effect profile with negligible histamine release, it is extremely lipophilic, with an almost immediate onset when administered intravenously. In addition, its duration is relatively short, usually lasting only 30 to 60 minutes. Analgesic effects may be prolonged after continuous infusion due to redistribution of the drug into fat stores; in these cases, the elimination half-life may be extended to 13 to 24 hours. Fentanyl has no pharmacologically active metabolite, making it the safest option for patients with renal impairment.

Fentanyl: Fentanyl is 100 times more potent than morphine when administered intravenously and is dosed intermittently as-needed (prn) or continuously. It acts selectively at the mu receptor, leading to an improved side effect profile with negligible histamine release, less sedation, and negligible weight loss. Its extremely lipophilic, with an almost immediate onset when administered intravenously. In addition, its duration is relatively short, usually lasting only 30 to 60 minutes. Analgesic effects may be prolonged after continuous infusion due to redistribution of the drug into fat stores; in these cases, the elimination half-life may be extended to 13 to 24 hours. Fentanyl has no pharmacologically active metabolite, making it the safest option for patients with renal impairment.

Meperidine: Despite its continued use, meperidine is not recommended as a first-line opioid analgesic. It has a rapid onset and shorter duration of analgesia (usually 2-3 hours) than other short-acting opioids. This is commonly prescribed four- to six-hour dosing interval, resulting in uncontrolled pain before the next dose is due. Meperidine causes withdrawal symptoms which may be related to its lipophilicity and rapid transport into the central nervous system (CNS). It has a shorter elimination half-life, which is five to 10 times longer than the parent drug. Because it is eliminated renally, adverse effects are higher in patients with renal insufficiency.
Two of the most commonly used routes of administration—oral and intramuscular—are problematic. Significant first-pass metabolism of normeperidine that is considerably higher when the drug is given orally. However, oral bioavailability is low, and higher doses are required when using this route. The American Pain Society (APS) recommends avoiding oral meperidine use, as absorption of meperidine is erratic and can vary by 50% or more (even when administered by injection).

Meperidine inhibits the reuptake of norepinephrine and serotonin, and is contraindicated for coadministration with MAOIs. The risk of serotonin syndrome is increased with concurrent use of serotonin-receptor agonists and SSRIs. Meperidine is not recommended for PCA administration due to the high doses needed for acceptable analgesia, which can result in unacceptable adverse effects. Although intermittent intravenous dosing of meperidine may be required in patients who are allergic to other opioids such as morphine or hydromorphone, its use for PCA may be obsolete given the availability of structurally similar opioids. Meperidine is often used for pain associated with pancreatitis, because it is thought to cause less spasm at the sphincter of Oddi. However, recent studies indicate that at equianalgesic dosages, all opioids cause an increase in bile pressure and that there is no evidence for any benefit with meperidine use. The most recent practice guideline for acute pancreatitis treatment guidelines have listed meperidine as the opioid of choice, even as recently as the year 2000. Studies that supported the use of meperidine used animals or small sample sizes and did not use comparative dosages. The most recent practice guideline for acute pancreatitis does not recommend the use of any particular opioid. Due to the risk of toxicity, meperidine should not be used for chronic pain, elderly patients, or patients with renal or hepatic disease or seizure disorders. The maximum recommended daily dosage is 600 mg per day, for less than 48 hours.

Because of its unique toxicity profile, meperidine is not an appropriate choice for chronic pain, elderly patients, or patients who have allergic reactions to other opioids such as morphine or hydromorphone; for the treatment of induced rigors; or for treatment of postanesthesia shivering. Methadone: Methadone’s pharmacology is unique; unlike other opioids, methadone is a racemic mixture (d)-isomers. The l-isomer gives methadone its opioid activity, while the d-isomer is a N-methyl-D-aspartate norepinephrine and serotonin reuptake inhibitor. As the NMDA receptor has been demonstrated to play a role in the development of tolerance, it is likely that the d-isomer of methadone is at least partially responsible for its increased potency in patients already receiving opioids. Changing to methadone may benefit patients who require high doses of opioids but also experience adverse effects. Methadone’s unique mechanism and low cost have contributed to a renewed interest in its use. However, predispose patients to developing serious adverse effects. Methadone has the longest and most variable half-life of any of the opioids—12 to 190 hours (the usual half-life is approximately 24 hours). The duration of analgesia is much shorter than every four to eight hours at the beginning of treatment and every six to 12 hours at steady state. As life-threatening sedation and respiratory depression within three to five days after starting methadone therapy or increasing the dosage may be worsened by drug interactions with CYP3A4 inhibitors or other QTc interval-prolonging agents. Methadone is highly lipophilic and redistributes to fat stores; significant weight loss may necessitate dosage adjustment. Methadone is metabolized by CYP3A4, with minor activity at CYP2D6. High doses may cause QTc interval prolongation and may be worsened by drug interactions with CYP3A4 inhibitors or other QTc interval-prolonging agents. Caution should be used whenever initiating or adjusting a methadone regimen, especially in patients with renal or hepatic disease or are taking additional medications that may prolong the QTc interval.
Methadone's low cost and long half-life may provide an advantage for patients who cannot tolerate or afford sustained-release opioid regimens for pain are scheduled every six to eight hours, as opposed to the once-daily regimens used to prevent withdrawal. Methadone may be highly effective when used by practitioners who are familiar with its dosing and adverse effects. Indiscriminate use may be hazardous if its safety profile is not appreciated and toxicity carefully managed. The Drug Abuse Warning Network indicated that in five of six states, methadone outnumbered oxycodone or hydrocodone in opiate-related deaths. Health and Human Services has attributed the rise in deaths to increased use of methadone as an analgesic closely followed by a knowledgeable physician and receive thorough instruction on how to take methadone.

**Levorphanol:** Levorphanol is considered a second-line opioid for patients with moderate-to-severe chronic pain who cannot tolerate or afford sustained-release opioids. Like methadone, levorphanol has a long half-life (usually 12-15 hours), and accumulation may result in delayed respiratory depression. Duration of analgesia is usually four to six hours, with typical dosages scheduled at six-hour intervals. Levorphanol exhibits NMDA receptor antagonism and may provide benefit for the treatment of neuropathic pain.

Levorphanol is available for administration. The oral formulation is available only as a 2-mg tablet, which makes titration difficult.

**Agonist-Antagonist Derivatives:** Pentazocine, nalbuphine, and butorphanol are kappa receptor agonists and mu receptor antagonists. Buprenorphine exhibits partial activity at the mu receptor and antagonism at the kappa receptor; it is often used in these agents cause less respiratory depression than pure mu-agonist opioids, the ceiling effect for analgesia limits the ability to titrate for severe pain. Administration may cause opioid withdrawal in patients who are already receiving pure mu-agonists. These agents exhibit psychomimetic effects such as confusion and hallucinations; these may be particularly severe with use of pentazocine in elderly patients with renal impairment. These agents are not recommended for the treatment of moderate-to-severe pain. Formulations of buprenorphine (Subutex, Suboxone) have been approved only for the maintenance of opioid dependence and may be administered via several routes. Altho intraspinal (including intrathecal and epidural) administration and PCA are additional methods of delivery.

**Route of Administration**

Patients may require different routes of administration, especially if they are unable to ingest or tolerate oral opioids. Immediate-release opioids are available in a variety of formulations and may be administered via several routes. Administration may be crushed for ease of administration. Liquid formulations of morphine, hydromorphone, oxycodone, and hydrocodone may be administered via several routes. Subcutaneous administration may be an alternative if intravenous access cannot be obtained. Opioids may be given continuously or intermittently. Subcutaneous boluses have a slower onset and lower peak effect than intravenous administration. For this reason, hydromorphone may be preferred over morphine, as it is available as a more concentrated injectable formulation.

**Intravenous:** The intravenous route provides the most rapid onset but also a shorter duration than oral or intramuscular administration. The time-to-peak effect depends on the lipophilicity of the opioid (ranging from five minutes for fentanyl to 15-30 minutes for morphine). Subcutaneous boluses have a slower onset and lower peak effect than intravenous administration. For this reason, hydromorphone may be preferred over morphine, as it is available as a more concentrated injectable formulation.

**Intramuscular:** Intramuscular injections are painful, may exhibit wide fluctuations in absorption, and can cause severe pain. For this reason, hydromorphone may be preferred over morphine, as it is available as a more concentrated injectable formulation.

**Rectal:** Several immediate-release opioids may be administered via this route, including morphine, hydromorphone, and oxycodone. Absorption of opioids is variable and highly dependent on suppository placement; if inserted past the rectal

---

**Notes:**

- Methadone: low cost and long half-life may provide an advantage for patients who cannot tolerate or afford sustained-release opioids.
- Indiscriminate use of methadone may be hazardous if its safety profile is not appreciated and toxicity carefully managed.
- Levorphanol: considered a second-line opioid for moderate-to-severe chronic pain.
- Agonist-Antagonist Derivatives: pentazocine, nalbuphine, butorphanol, and buprenorphine.
- Route of Administration: oral, intravenous, subcutaneous, intramuscular, and rectal routes.
- Intravenous administration is preferred due to efficacy and convenience.
- Subcutaneous administration may be an alternative if intravenous access cannot be obtained.
- Intramuscular injections are painful and may exhibit wide fluctuations in absorption.
- Rectal administration of opioids is variable and highly dependent on suppository placement.

---

**Source:** USPharmacist.com > Continuing Education > http://www.uspharmacist.com/continuing_education/ceviewtest/less...
may be avoided. Sustained-release morphine tablets may be administered rectally every 12 hours using however, some patients may require slight dosage reductions. This technique has often been used in the p

**Transdermal:** Transdermal administration of fentanyl may be useful for patients with chronic pain who can patch (Duragesic) is designed to provide analgesia for 72 hours, although some patients may experience t 48 hours. This formulation is unique and carries a number of warnings not shared by other sustained-release large amount of medication, and starting an opioid-naive patient on a fentanyl patch could result in overmedication depression. As such, the fentanyl patch should be used only for opioid-tolerant patients (defined as a daily other opioid equivalent, every day for at least a week). Patients with acute pain or those who have not con-candidates for treatment with the transdermal fentanyl patch. Transdermal fentanyl does not work immediately upon placement of the patch. There is a delay of 12 to 16 hours for blood levels to drop by half once the patch is removed. The lag time for effect and prolonged titration is considered when selecting a sustained-release opioid for a terminally ill patient whose analgesic requirements remain high. Heat can increase absorption of fentanyl, resulting in a potentially lethal overdose. Fever over 104°F third, necessitating an increase in monitoring for toxicity. Patients should be cautioned not to apply a heat or blanket directly to the patch.6

**Oral Transmucosal and Buccal:** The fentanyl oral transmucosal lozenges (Actiq) and fentanyl buccal tab management of breakthrough cancer pain in patients who are tolerant to opioid therapy. Both are contrainc patients who are opioid naive. These formulations allow for an extremely fast onset of action within five over oral short-acting opioids, which take longer to work.

There is no strict dose conversion ratio from other immediate-release opioids to the fentanyl lozenges and the lowest dosage of each (Actiq 200 mcg lozenge or Fentora 100 mcg buccal tablet). Doses of the lozenge are interchangeable; the Fentora buccal tablets have faster and higher absorption than the Actiq lozenges, but proportionally.

**As-Needed Versus Scheduled Dosing**

The disadvantage of administering analgesics on a prn basis is that pain must be a problem before it can t result in high peaks and low troughs, causing alternating periods of uncontrolled breakthrough pain and to up with the pain. If pain is present for most of the day, then sustained-release or long-acting opioids adrr preferable to maintain consistent plasma levels. Sustained-release and long-acting products may limit episodes of breakthrough pain, improve compliance, Several products are available (TABLE 1). If cost is a concern, or if other methods are not successful, met since their long duration of action is independent of dosage formulation. The dose of the sustained-release previous 24-hour opioid requirement. The APS recommends treating patients for 48 hours with an immedi thirds of the estimated daily requirement to the sustained-release regimen.

When sustained-release opioids are used, an immediate-release opioid should be provided for prn rescue equal 10% to 15% of the total daily requirement. If four to six rescue doses are required in a 24-hour peri increased. A sustained-release opioid should never be used as a prn medication, since the delivery mech immediately.
Titration
There is no ceiling effect for pure opioids. Dosage requirements vary widely among patients, and opioids should be titrated to analgesia or until side effects occur. Dosage increases of 10% to 20% during the first few days, or 30% to 50% after five days of treatment, are appropriate. Elderly patients or those with comorbidities, such as pulmonary or CNS diseases, may require a lower starting dosage.

The duration of action and time to steady state must be considered when titrating an opioid dosage. The onset of oral immediate-release opioids typically within 45 minutes, with maximum effect occurring at one to two hours. If a patient has not achieved an acceptable level of analgesia within this time, a second dose of an immediate-release opioid may be administered. Because transdermal fentanyl release may take 48 hours to reach steady state, the first dosage adjustment may be made after three days, with subsequent increases every six days.

Table 1

<table>
<thead>
<tr>
<th>Sustained-Release and Long-Acting Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Levorphanol</td>
</tr>
</tbody>
</table>

* The maximum dosage of Avinza is 1,600 mg/day due to fumaric acid content, which may cause renal toxicity.

Dosage Conversion
When switching to another opioid, the dosage may be determined by using an equianalgesic chart. Incomplete, and calculated dose equivalents should be reduced by 30% to 50% (see PATIENT CASE for an example conversion). A dose reduction is not necessary when changing between routes with the same opioid. Equianalgesic dose variation may occur. Clinicians should remain attentive to the patient during the first few days after changing analgesia or adverse effects.
Conversion to methadone does not involve the use of a single equianalgesic dose ratio. Methadone increases in relative potency when other opioids are used. Due to this effect, some practitioners recommend an empiric 75% to 90% decrease in the calculated equianalgesic methadone. An alternative method that determines methadone dosing ratios based on the daily requirement of oral morphine has been described. Several dose equivalency ratios have been described for converting oral opioids to transdermal fentanyl. The APS equates each 25 mcg per hour increment to 45 mg per day of oral morphine.

Table 2

<table>
<thead>
<tr>
<th>Equianalgesic Oral</th>
<th>Dose (mg) Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>200</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
</tr>
<tr>
<td>Morphine</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4 (acute)</td>
</tr>
<tr>
<td></td>
<td>1 (chronic)</td>
</tr>
</tbody>
</table>

Note: For repeated dosing, IV and IM dose ratios are assumed to be equivalent. For single dosing, the IV dose may be lowered to half the IM dose to achieve the same peak effect.

Source: References 6, 10.
### Conversion Ratio of Oral Morphine to Oral Methadone

<table>
<thead>
<tr>
<th>Daily oral morphine dose (mg)</th>
<th>Conversion ratio, oral morphine to oral methadone (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>3:1</td>
</tr>
<tr>
<td>101-300</td>
<td>5:1</td>
</tr>
<tr>
<td>301-600</td>
<td>10:1</td>
</tr>
<tr>
<td>601-800</td>
<td>12:1</td>
</tr>
<tr>
<td>801-1000</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1001</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Note: Reduce calculated dose by 30% to 50% to account for incomplete cross-tolerance. Dose ratios do not apply to conversions from methadone to another opioid.

Source: Reference 43.

### Patient Case: Opioid Conversion

A patient is receiving a hydromorphone IV infusion of 1.2 mg/h, and the physician wishes to convert to a regimen of sustained-release oral oxycodone.

1. **Determine the total daily dose of hydromorphone for the previous 24 h.**

   Hydromorphone IV 1.2 mg/h x 24 h = hydromorphone IV 28.8 mg

2. **Determine the equivalent dose of oxycodone for the daily requirement.**

   Hydromorphone IV 28.8 mg ◊ 1.5 (equivalency dose for hydromorphone IV) = 19.2 mg equianalgesic dose units
19.2 mg equianalgesic dose units x 20 (equivalency dose for oxycodone po) = oxycodone 384 mg

3. Reduce the oxycodone dose for incomplete cross-tolerance.

Oxycodone 384 mg x 70% (i.e., 30% reduction) = oxycodone 269 mg

The new regimen of oxycodone may be Oxycontin 120 mg twice daily (total daily dose, 240 mg), which closely approximates the calculated total daily dose of 269 mg.

Management of Adverse Effects
Opioids share a common side effect profile, including sedation, constipation, nausea, vomiting, pruritus, myoclonus, and respiratory effects. Tolerance develops to most opioid adverse effects within a few days. Patients taking opioid therapy should be routinely assessed for side effects.

If opioids cause unwanted side effects, clinicians can change the dosage, schedule, or route. If analgesia suffers as a result of side effects, the time interval may be decreased. Alternatively, sustained-release formulations may decrease peak effects and resulting toxicity, thus altering the side effect profile. Patients with liver cirrhosis may have reduced metabolism and require extended dosing intervals of opioids.

Opioid rotation, or changing to another opioid, may reduce side effects and/or improve efficacy if a patient does not tolerate some opioids well. Most opioids share adverse effects at equianalgesic dosages, some opioids have slight advantages over others with decreased incidence of constipation and histamine release. Occasionally, patients may tolerate certain opioids better than others, possibly due to differences in opioid receptor subtypes. Opioid rotation may also decrease adverse effects caused by accumulation of toxic metabolites. Patients with renal insufficiency should be changed to an opioid that lacks active metabolites (Table 4). Nonoral routes of administration may decrease the incidence of nausea and vomiting or myoclonus.

Patients with liver cirrhosis may have reduced metabolism and require extended dosing intervals of opioids. Opioids to a nonoral route of administration may decrease the incidence of nausea and vomiting or myoclonus.

Opioid rotation, or changing to another opioid, may reduce side effects and/or improve efficacy if a patient does not tolerate some opioids well. Most opioids share adverse effects at equianalgesic dosages, some opioids have slight advantages over others with decreased incidence of constipation and histamine release. Occasionally, patients may tolerate certain opioids better than others, possibly due to differences in opioid receptor subtypes. Opioid rotation may also decrease adverse effects caused by accumulation of toxic metabolites. Patients with renal insufficiency should be changed to an opioid that lacks active metabolites (Table 4). Nonoral routes of administration may decrease the incidence of nausea and vomiting or myoclonus.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid Selection in Renal Failure</strong></td>
</tr>
<tr>
<td>Not Recommended for Use</td>
</tr>
<tr>
<td>Meperidine</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
</tbody>
</table>

Patients with liver cirrhosis may have reduced metabolism and require extended dosing intervals of opioids. Opioids to a nonoral route of administration may decrease the incidence of nausea and vomiting or myoclonus.
Multimodal therapy with the addition of nonpharmacologic treatments (e.g., heat, cold, relaxation technique) non-opioid analgesics (e.g., nonsteroidal anti-inflammatory drugs or other adjuvant drugs) may improve pain control and allow for dosage. Combination pharmacotherapy relies on multiple mechanisms of action and is often more effective.

If the previous methods fail, adjuvant medications may be used for symptomatic treatment of adverse effects.

**Sedation:** Sedation and cognitive impairment are more likely to occur when opioid therapy is initiated or during despite opioid rotation and dosage reductions, therapy with psychostimulants may be considered. Caffeine and modafinil have all been used for this purpose.\(^\text{10}\)

**Constipation:** Tolerance does not develop to this adverse effect. Patients on chronic opioid therapy should be placed on a stimulant laxative (e.g., senna or bisacodyl) to increase bowel motility. Stool softeners such as docusate may be added as monotherapy. Other classes of laxatives can be expensive and may not be effective.\(^\text{6,10}\) Bulk-forming laxatives should be avoided, since concurrent therapy with opioids may result in impaction.\(^\text{6}\) Constipation may be avoided by using a lower incidence of this adverse effect than oral sustained-release opioids such as morphine.

**Nausea/Vomiting:** Nausea and vomiting may be avoided by using a nonoral route of administration for the first few days until the tolerance to this side effect. However, nausea and vomiting may occasionally persist. Chronic nausea is often morphine for chronic cancer pain. If changing the opioid or route of administration is not helpful, antiemetics may be used. There are no studies to indicate the superiority of one antiemetic over another. Recommended agents include metoclopramide, haloperidol, phenothiazines, transdermal scopolamine, ondansetron (or another 5-HT3 antagonist), and dexamethasone.

**Pruritus:** Morphine and codeine have a high incidence of histamine release and pruritus. Changing to fentanyl or oxymorphone, which has negligible histamine release, may avert this problem.\(^\text{10}\) Antihistamines are commonly recommended to treat pruritus, but there is evidence for success with paroxetine.\(^\text{37}\)

**Myoclonus:** Myoclonus is uncontrolled twitching or jerking, usually of the arms or legs, that may be caused by adverse effect may occur with high-dose opioid therapy.\(^\text{6,37}\) Oral morphine causes a threefold higher incidence of myoclonus than morphine, implicating the role of higher M3G concentrations resulting from first-pass metabolism. Opioid rotation may eliminate this problem.\(^\text{6}\) Myoclonus persists, adjuvants such as baclofen, diazepam, clonazepam, midazolam, valproic acid, and de

**Respiratory Depression:** Opioids exert a depressant effect on the respiratory center, which can slow breathing and lead to cyanosis. Pain is a powerful stimulus to counter this effect.\(^\text{5}\) Respiratory depression is rare in patients receiving opioid therapy. It can usually be avoided by careful titration but may occur in opioid naive patients who require high doses. If a patient has succumbed to respiratory depression while awake, the opioid antagonist naloxone may reverse the effect. The duration of naloxone is minutes), and repeated doses are often needed. Patients should be monitored closely for at least three hours past the time of administration to ensure effective analgesic blood concentrations.\(^\text{11}\) Prolonged naloxone opioid antagonism has been reported in patients with opioid allergy.
True opioid allergies are rare. Patients frequently confuse common side effects, such as nausea or pruritus, with drug allergies to describe their reaction may help to clarify whether the reported allergy involves anaphylaxis or a side effect.

There are three classes of opioids: phenanthrenes, phenylpiperidines, and phenylheptylamines (TABLE 5). A reaction to a natural phenanthrene like codeine or morphine may not exhibit the same reaction to a semisynthetic oxycodone could be tried in this case. However, if the reaction is severe or if the patient describes an anaphylactic reaction such as breathing, switching to an opioid from another chemical class (such as fentanyl or methadone) may be indicated. The incidence of cross-allergy in these instances is unknown.

<table>
<thead>
<tr>
<th>Chemical Classes of Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
</tbody>
</table>

Source: References 2, 40.

**Tolerance, Physical Dependence, and Addiction**

Tolerance occurs when a constant opioid dosage produces a decreasing effect. With the exception of constipation, tolerance develops for induced side effects (e.g., respiratory depression, sedation, nausea). Tolerance to analgesic effects may occur within the first week and is usually characterized by a decrease in the duration of analgesia. After this time, however, tolerance patient has been stabilized on an opioid regimen and a dosage escalation is required, the development of new pathology is the most likely explanation. Cross-tolerance among opioids is not complete, for either analgesic effects or toxicity.

Physical dependence is a predictable pharmacologic effect that is manifested by the development of a withdrawal syndrome after discontinuation of therapy. It is often confused with addiction; however, physical dependence is unrelated to addiction and occurs of drugs, including steroids and antihypertensive agents. Physical dependence may be anticipated in patients...
opioid for more than two weeks. A withdrawal syndrome may be avoided by tapering doses by 10% to 20% per day.

Addiction is a psychological dependence, rather than dependence related to a property of the drug. The APS defines addiction as compulsive drug use characterized by a continued craving for an opioid and the need to use the opioid for effects other than pain. Patients with addiction disorders may focus of their life and exhibit aberrant drug-seeking behaviors.  

The incidence of addiction in patients treated with opioids is widely debated and often overestimated. A frequently reported incidence of 0.01% is not likely representative of the true incidence in the population, as it was based on a retrospective chart review that excluded patients with a prior history of substance abuse from the final analysis. Subsequent studies have corroborated that the risk of addiction in patients with active or prior history of substance abuse disorders is low, and most experts agree that fear of opioid addiction should not be a primary concern. The prevalence of addiction among patients treated with opioids in chronic pain centers has been estimated to be between 3.2% and 18.9%.  

_Pseudoaddiction_ is a term used to describe aberrant behavior by patients who are not truly addicted to opioids. Patients who use deception or illicit methods to obtain medication due to the fear of uncontrolled pain. Demanding behavior, clockwatching, and use of analgesics are not always predictive of addiction and may instead result from a desire for pain relief. Pseudoaddiction in that once patients are effectively treated, aberrant or drug-seeking behaviors cease.  

Conclusion  
Opioids have been considered the mainstay of cancer pain management, and they are increasingly used for noncancer pain. As understanding of the pharmacology of this class of drugs becomes more sophisticated, clinicians may anticipate adverse effects and variations in individual response. Pharmacists can use this knowledge as part of a multidisciplinary team to select the appropriate opioid therapy, identify correct dosages and schedules, and monitor for adverse effects. Counseling patients will aid in ensuring overall treatment success.

REFERENCES  
12. Wittwer E, Kern SE. Role of morphine's metabolites in analgesia: concepts and controversies. AA
13. FDA asks Purdue Pharma to withdraw Palladone for safety reasons [press release]. U.S. Food and
15. McPherson ML. Exploring the pharmacist's role in the management of chronic pain: focus on opio
2005;suppl:1-10.
postoperative analgesia: a multicenter study of opioid-induced adverse reactions. Hosp Pharm. 200
17. Clinical Practice Guideline: Acute Pain Management: Operations or Medical Procedures and Traum
and Human Services, Agency for Health Care Policy and Research; 1992. AHCPR Publication 92-0
Health Care Policy and Research; 1994. AHCPR Publication 94-0592.
21. Seifert CF, Kennedy S. Meperidine is alive and well in the new millennium: evaluation of meperidine
22. Munoz A, Katerndahl DA. Diagnosis and management of acute pancreatitis. Am Fam Physician. 20
23. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therape
24. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterol
27. Goodman F, Jones WN, Glassman P. Methadone dosing recommendations for treatment of chronic
30. U.S. Department of Health and Human Services, Office of Applied Studies, Substance Abuse and M
(SAMHSA). Drug Abuse Warning Network. The DAWN Report. Opiate-related drug misuse deaths i
31. Centers for Disease Control and Prevention. Increase in poisoning deaths caused by non-illicit drug
33. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Tre:
35. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl t
38. Cherny N, Ripamonti C, Pereira J. Strategies to manage the adverse effects of oral morphine: an ev
2001;19:2542-2554.

