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Managing Chronic Pain: An Analysis of the Use of Opioids

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Behavioral Objectives

After completing this continuing education article, the pharmacist should be able to:

1. Explain the epidemiology, pathophysiology, and clinical presentation of nociceptive pain;
2. Discuss safe and appropriate equianalgesic dosing and administration of opioid analgesics in chronic pain management;
3. Assess potential adverse drug events occurring with the use of opioid analgesics;
4. Define the importance of route of administration and controlled-release delivery systems in the management of chronic pain with opioid analgesics;
5. Explain the definitions of physical dependence, addiction, pseudoaddiction, tolerance, and cross-tolerance, and discuss their significance with respect to opioid therapy in chronic pain;
6. Analyze substance abuse issues in relationship to pain management and opioids;
7. Describe the controversies and concerns regarding the use of opioids for chronic nonmalignant pain and the recommended guidelines for use;
8. Define the role of the pharmacist in chronic pain management.

See Exam on Page 97

This educational lesson will be available to pharmacists on-line at www.pharmacytimes.com.

Program Note

This continuing education article was written directly from the transcripts of the continuing education symposium, "Chronic Pain and Opioids: The Rise of Pharmaceutical Care," that was presented at the American Pharmacists Association meeting on Sunday, April 3, 2005, in Orlando, Fla. The clinical application of equianalgesic tables when rotating opioids is also reviewed. Portions of the information included in this article are

represented in the published literature, while the remainder reflects opinions of the presenting faculty, based on their clinical experience.

Background

"Pain is whatever the experiencing person says it is, existing whenever he says it does."¹ The International Association of the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."²

Objective parameters to diagnose and measure pain do not exist. Thus, pain is subjective and must be based on the individual's perception of, reaction to, and tolerance to pain.

Epidemiology

Approximately 50 million Americans—1 in 5 people—suffer from pain. Unfortunately, this number is expected to rise over the next 2 decades. The majority of chronic pain sufferers have been living with their pain for over 5 years. Annual health care costs associ-

ated with pain average \$100 billion, and pain contributes to 50 million lost work days. Chronic pain causes more disability than cancer and heart disease combined.³ A joint statement from 21 health organizations remarked, "Under-treatment of pain is a serious problem.... Effective pain management is an integral and important aspect of quality medical care, and pain should be treated aggressively."⁴

Consequences of Unrelieved Pain

Minority, female, cognitively impaired, and geriatric patients are significantly less likely to receive appropriate pain medication and, consequently, more likely to suffer from inadequate pain relief.^{5,6} Unrelieved pain affects not only the quality of life and economic security of the person with pain, but also his or her family.⁷ Table 1 summarizes the negative consequences of unrelieved pain.⁸

Characteristics of Acute and Chronic Pain

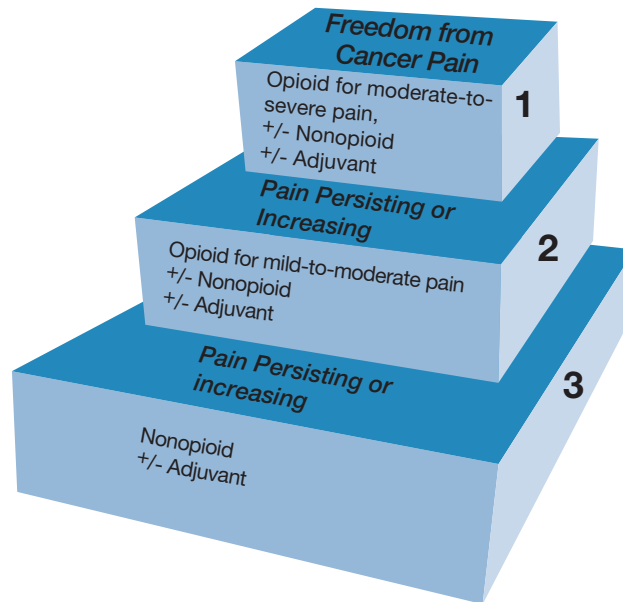
An understanding of the pathophysiology of pain is required to adequately control pain. *Nociception* refers to the process by which information about tissue damage is conveyed to the central nervous system.⁹ Tissue damage stimulates the ascending transmission of pain through the spinal cord to the brain. The brain modulates pain impulses by the release of endogenous opioids, such as endorphin, that descend to inhibit pain. These opioids bind to mu, kappa, or delta receptors to decrease transmission of the pain. Exogenous opioids work at the same mu, kappa, or delta and/or other opioid receptors. Continuous activation of *N*-methyl-*D*-aspartate (NMDA) receptors can decrease mu receptors' response to opioids.^{3,9,10}

Acute pain is a normal response after tissue injury and typically subsides once healing has occurred.¹¹ *Chronic pain* is defined as "pain that persists for longer than the expected time frame for healing or pain associated with progressive, nonmalignant disease."⁷ Table

Figure 1

World Health Organization Analgesic Ladder

WHO's Pain Relief Ladder



Adapted from: World Health Organization. WHO's pain ladder. Available at: www.who.int/cancer/palliative/painladder/en.

2 summarizes similarities and differences between acute and chronic non-cancer-related pain characteristics.⁷ Chronic nonmalignant pain will be the focus of this continuing education article.

Pain is subjective; therefore, a comprehensive assessment of the pain—ie, the patient's perception of pain, emotional state and somatic preoccupation, functional status at home and at work, and use of analgesic medications—is vital.¹² The goals of chronic pain therapy are to decrease pain, increase function, and improve overall quality of life.

Treatment of Chronic Pain

Both nonpharmacologic and pharmacologic treatment strategies are effective in achieving adequate pain relief when used appropriately. Nonpharmacologic treatment options include exercise, acupuncture, massage, transcutaneous electrical nerve stimulation, hydrothera-

py, manipulation, guided feedback, hypnotherapy, biofeedback, and treatment of concomitant mood disorders. Certain patients may require the addition of pharmacologic treatment to achieve adequate pain relief.

Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs)—including cyclooxygenase type 2 (COX-2) selective agents—muscle relaxants, anticonvulsants, antidepressants, stimulants, sleeping pills, sleep medications, anxiolytics, glucocorticoids, anesthetics, topical analgesics, and opioids may help in adequately controlling chronic pain.

Opioid Analgesics

The World Health Organization's (WHO) 3-Step Analgesic Ladder (Figure 1) supports opioids as the cornerstone of analgesic therapy for patients with moderate-to-severe cancer pain.^{13,14} In clinical practice, the WHO Ladder is

Table 1

Harmful Effects of Unrelieved Pain	
• Cardiovascular	• Immune
• Respiratory	• Developmental
• Genitourinary	• Endocrine
• Gastrointestinal	• Metabolic
• Musculoskeletal	• Quality of life
• Cognitive	• Catabolism

Adapted from Page GG. The medical necessity of adequate pain management. *Pain Forum*. 1996;5(4):227-233.

Table 2

Characteristics of Acute and Chronic Non-Cancer-Related Pain		
	Acute Pain	Chronic Pain
Duration	Hours to days	Months to years
Associated pathology	Present	Commonly none
Prognosis	Predictable	Unpredictable
Associated problems	Uncommon	Depression, anxiety, secondary gain issues
Nerve conduction	Rapid	Slow
Autonomic-nervous-system involvement	Present	Generally absent
Biological value	High	Low or absent
Social effects	Few	Profound
Treatment	Primary analgesics	Multimodal, largely behavioral, drugs may have moderate role

Adapted from Ashburn MA, Staats PS. Management of chronic pain. *Lancet*. 1999;353:1865-1869.

Table 3

Common Opioid Adverse Drug Events, Tolerance, and Treatment ²¹⁻²⁴		
Adverse Drug Event	Development of Tolerance	Treatment
Respiratory depression*	Yes	Gradual dose titration, naloxone [†]
Constipation	No	Stool softener AND stimulant laxative [‡]
Sedation and cognitive impairment	Yes	Lower dose, discontinue concomitant central nervous system depressants, add stimulant, change opioid
Nausea/vomiting	Yes	Antiemetic
Itching	Yes	Antihistamine, change opioid
Urinary retention	Yes	Lower dose

* Respiratory depression rarely occurs in patients receiving opioid therapy >5 days.⁵ Factors predisposing to respiratory depression include overweight, sleep apnea, and asthma.

[†] Naloxone should be reserved for select patients, administered cautiously, and by a slow intravenous infusion.^{5,25-29}

[‡] The first-line regimen for prevention of opioid-induced constipation is docusate sodium 50-300 mg orally daily and senna 1-2 tablets (8.6 mg sennosides per tablet) orally bid to qid. A soft bowel movement every 1-2 days is the goal of therapy.^{23,30-32}

commonly extrapolated for patients with non-cancer-related pain.

Numerous barriers to effective pain management with opioid analgesics have been identified. Failure to routinely assess pain and pain relief is the most common reason for unrelieved pain. The Joint Commission on Accreditation of Healthcare Organizations recognizes pain as the fifth vital sign and encourages routine assessment.¹⁵ Health-provider barriers include misunderstanding of the pathophysiology of pain, lack of knowledge of opioid analgesic pharmacotherapy, lack of accountability of pain control among health care providers, insufficient supplies of opioids in pharmacies, and legal and regulatory issues governing opioid use and abuse. Patients often underreport pain for fear of addiction, fear of disappointing or annoying friends and family, and to avoid adverse drug events (ADEs).^{3,4,16-20}

Common Opioid ADEs

Recall that exogenous opioids bind to certain opiate receptors in the brain and spinal cord to inhibit the transmission of pain. Activation of these receptors also causes the common ADEs associated with opioid analgesics (Table 3).²¹⁻³²

It is believed by many that common ADEs of opioids are allergic reactions. A true opioid allergy is rare (<1%), however, and is a reaction in which the body's immune system responds in an overstated way (skin rash, facial swelling, or asthma) to a foreign substance. In the case of a true opioid allergy, the offending opioid should be discontinued and replaced with another opioid from a different analogue class. The theory is to change the chemical structure enough to avoid antibody recognition. Cross-reactivity to another analogue class is rare (Table 4).³³⁻³⁷

Advantages of Long-Acting Opioids

Patients with continuous or frequent pain should be given a fixed scheduled dose of a long-acting opioid to prevent the pain from recurring and to provide continuous relief.²²

Long-acting opioids may be more favorable than short-acting opioids for the following reasons^{38,39}:

- More stable pain relief
- Long duration of pain relief
- Less euphoria
- Less abuse potential
- Less frequent dosing required
- Improved sleep patterns

Choice of long-acting opioid may be limited by renal and hepatic function, however. Metabolites or active drug may accumulate in the presence of renal dysfunction (Table 5) and hepatic dysfunction (Table 6).

Route of Administration

Long-acting agents are available in a variety of delivery systems (Table 7).⁴⁰ Oral administration is the most common and preferred route by patients. Most oral formulations last less than 24 hours and require multiple daily dosing. If the oral route is not feasible, noninvasive routes such as transdermal or rectal are alternatives. Transdermal delivery allows for enhanced compliance (application usually every 72 hours for fentanyl, although every-48-hour changes are acceptable if required). Rectal administration is not acceptable to many patients. Invasive parenteral routes are reserved for later use. Intramuscular administration of pain medications is not recommended, as this route of administration is painful, yields wide fluctuation in absorption, has up to a 60-minute lag time for analgesic effect, has a rapid falloff, and may cause sterile abscesses and fibrosis of muscle and soft tissue.^{5,41}

Morphine

Morphine is the gold standard to which all other opioids are compared. Several oral extended-release formulations are available. Controlled-release (CR) morphine sulfate may be administered every 8 to 12 hours.⁴² Sustained-release (SR) morphine sulfate may be administered every 12 to 24 hours.^{43,44} CR or SR morphine formulations should not be crushed, as the inherent release property is obliterated, and the

Table 4

Opioid Analgesics and Related Cross-Sensitivity ³³⁻³⁷		
Opioid Analgesic	Analogue Class*	Source of Chemical†
Morphine	Phenanthrene (hydroxylated)‡	Natural
Codeine	Phenanthrene (hydroxylated)‡	Natural
Hydromorphone	Phenanthrene (dehydroxylated)	Semisynthetic
Oxycodone	Phenanthrene (dehydroxylated)	Semisynthetic
Hydrocodone	Phenanthrene (dehydroxylated)	Semisynthetic
Meperidine	Phenylpiperidine	Synthetic
Fentanyl	Phenylpiperidine	Synthetic
Methadone	Diphenylheptane	Synthetic
Propoxyphene	Diphenylheptane	Synthetic

*Allergic cross-reactivity is more likely to happen within each class and less likely with a drug from another analogue class.
 †Naturally occurring and semisynthetic compounds are the most potent histamine releasers.
 ‡Presence of a 6-hydroxyl group may cause erythema and fever.

Table 5

Opioids in Renal Dysfunction			
Opioid Analgesic	Metabolite	Warning	Renal Dosing
Meperidine*	Normeperidine	Altered mental status, CNS excitation, tremors, seizures	Avoid
Morphine†	Morphine-6-glucuronide (M6G)	CNS and respiratory depression	Caution
Propoxyphene‡	Norpropoxyphene	CNS excitation, seizures	Caution

*Meperidine is not recommended for the treatment of chronic pain due to its short duration and accumulation of the normeperidine metabolite, which may cause seizures.^{10,23}
 †Morphine's active metabolite, M6G, is more potent than morphine. Risk of accumulation increases with around-the-clock administration; however, with careful titration, morphine may be used in renal dysfunction.²⁴
 ‡Propoxyphene is not recommended for routine use due to long half-life and increased risk of metabolite accumulation.²³
 CNS = central nervous system.

Table 6

Opioids in Hepatic Dysfunction
Best AVOIDED in Hepatic Dysfunction:
Combination Products with Acetaminophen (APAP)*
hydrocodone/APAP
oxycodone/APAP
Controlled-Release (CR) or Sustained-Release (SR) Opioids†
morphine sulfate CR and SR
oxycodone CR

*Not to exceed 4 g daily of acetaminophen in most patients.
 †May accumulate and increase the risk of respiratory depression.

Table 7

Comparison of Long-Acting Opioid Delivery Systems

Route	Advantages	Disadvantages
Oral	<ul style="list-style-type: none"> • Noninvasive, most preferred route • Generally cost-effective 	<ul style="list-style-type: none"> • Subject to first-pass metabolism and reduced bioavailability
Transdermal	<ul style="list-style-type: none"> • Convenient, several dosage strengths • Long duration of action • May improve patient compliance by lessening the need to take a medication by mouth on a regular basis 	<ul style="list-style-type: none"> • Unsuitable for rapid dose titration • Slower onset of action • Less useful in patients with edema
Rectal	<ul style="list-style-type: none"> • Useful when oral route is unavailable • Rapid absorption and onset of action • Alternative to injections in patients with bleeding disorders or edema 	<ul style="list-style-type: none"> • Risk of infection • Cannot be used in patients with diarrhea, a colostomy, hemorrhoids, anal fissures, or neutropenia • Appropriate dose varies widely among individuals, requiring careful individual titration
Parenteral (IV, SubQ)	<ul style="list-style-type: none"> • Provides the most rapid onset of analgesia • IV route can be used for intermittent or continuous drug delivery 	<ul style="list-style-type: none"> • Risk of infection, bleeding • Puts a burden on the family in terms of equipment, learning how to administer medication, and associated costs

IV = intravenous; SubQ = subcutaneous.
Adapted from Brookoff D. Abuse potential of various opioid medications. *J Gen Intern Med.* 1993;8(12):688-690.

patient receives the equivalent of an immediate-acting morphine dose. A sprinkle-dose formulation of morphine sulfate once daily is now available.⁴⁵ The capsules can be opened and sprinkled on soft food in patients who have difficulty swallowing or who require administration via nasogastric, percutaneous esophageal gastric, or jejunal tubes. Morphine extended-release products are not approved for use in children. Due to morphine's histamine-releasing activity, it may cause more nausea and pruritus than other opioids.

Oxycodone

Oxycodone may cause less nausea and pruritus than morphine. It is also more potent than morphine. To prevent overdose especially in opioid-naïve patients, oxycodone CR should not be crushed.⁴⁶ Oxycodone CR is not FDA-approved for use in children.

Hydromorphone

Hydromorphone is approximately 5 to 10 times more potent than morphine. Hydromorphone CR tablets are now available and should not be crushed.⁴⁷ Hydromorphone CR is not FDA-approved for use in children.

Methadone⁴⁸⁻⁵²

Recall that NMDA receptors can decrease mu receptors' response to opioids. Methadone is an mu-receptor agonist and a NMDA-receptor antagonist. Therefore, it may be especially useful during opioid rotation. The concept of opioid rotation is discussed below. Methadone tablets may be crushed, because methadone exhibits long-acting properties due to its long half-life (not drug formulation). An oral solution is also available. Methadone is an alternative in patients with true morphine allergy; it is inexpensive; it does not require renal dose adjustment; it is

relatively safe in stable, chronic liver disease; and it may be given once or twice daily. Methadone's unique properties include high oral bioavailability; long, highly variable half-life (up to 190 hours); and high lipophilicity (creates a depot effect by slowing releasing of drug from the tissue into the bloodstream). These unique properties increase the risk of delayed toxicity such as sedation, respiratory depression, and (rarely) coma. Paradoxically, when converting to methadone, higher doses of the chronically taken opioid will result in a relatively more potent methadone response. Equianalgesic tables fail to consider these unique properties of methadone, and dose conversions based on these ratios may result in drastic overdose. When converting to methadone, some references recommend reducing the calculated equianalgesic dose of methadone by 75% to 90% to achieve a well-tolerated and efficacious conversion (Table 8).⁴¹ Other sources recommend more accurately dosing in a triphasic fashion such that the conversion ratio changes as the total daily dose of morphine (or its equivalent) increases. For example, when doses of morphine are low (<90 mg/day), the ratio is approximately 4:1 (morphine:methadone). When doses of morphine are high (>300 mg/day), the ratio of oral morphine to oral methadone approaches 12:1. For doses in the middle, a ratio of 8:1 has been studied.⁵² Methadone may be used in children.

Fentanyl Transdermal System

A fentanyl transdermal system (FTS) is comprised of a protective liner (removed prior to application) and 4 functional layers⁵³:

- 1) contact adhesive
- 2) rate-controlling membrane
- 3) drug reservoir of fentanyl and alcohol
- 4) backing

Cutting this patch renders the system unusable. Generic FTS has a protective liner (removed prior to application) and 2 functional layers⁵⁴:

Table 8

Equianalgesic Doses for Opioid Analgesics Used for the Treatment of Chronic Pain

Drug	Dose (mg) Equianalgesic to Morphine 10 mg IM*		Half-Life (hr)	Duration (hr)	Comment
	PO	IM			
Morphine	20-30	10	2-3	2-4	Standard for comparison
Morphine CR	20-30	10	2-3	8-12	Various formulations are not bioequivalent
Morphine SR	20-30	10	2-3	24	
Oxycodone	20		2-3	3-4	
Oxycodone CR	20		2-3	8-12	
Hydromorphone	7.5	1.5	2-3	2-4	Potency may be greater, ie, IV hydromorphone:IV morphine = 3:1, rather than 6.7:1 during prolonged use
Methadone	20	10	12-190	4-12	Although a 1:1 ratio with morphine was used in a single-dose study, there is a change with repeated administration, and a large dose reduction (75%-90%) is needed when switching to methadone
Oxymorphone	10 (rectal)	1	2-3	2-4	Available in rectal and injectable formulations
Levorphanol	4	2	12-15	4-6	
Fentanyl			7-12		Can be administered as a continuous IV or SubQ infusion; based on clinical experience, 100 mcg/hr is roughly equianalgesic to morphine 4 mg/hr
Fentanyl TS			16-24	48-72	Based on clinical experience, 100 mcg/hr is roughly equianalgesic to morphine 4 mg/hr. A recent study indicates a ratio of oral morphine: transdermal fentanyl of 70:1 (the recommended converting ratio was 100:1)

*Studies to determine equianalgesic doses of opioids have used morphine by the IM route. The IM and IV routes are considered to be equivalent, and IV is the most common route used in clinical practice.

†Although the PO:IM morphine ratio was 6:1 in a single-dose study, other observations indicate a ratio of 2-3:1 with repeated administration.

CR = controlled-release; IM = intramuscular; IV = intravenous; PO = oral; SubQ = subcutaneous; SR = sustained-release; TS = transdermal system.

Adapted from Derby S, Chin J, Portenoy RK. Systemic opioid therapy for chronic cancer pain: practical guidelines for converting drugs and routes of administration. *CNS Drugs*. 1998;9(2): 99-109.

- 1) fentanyl-containing adhesive
- 2) backing

Some generic transdermal fentanyl patches do not have a rate-controlling membrane. These patches are a matrix-type system, unlike the compartmental delivery system seen with the Duragesic Transdermal System and similar mechanically and generically equivalent alternatives. In the case of the matrix system, drug absorption is likely more dependent on patient specific characteristics (skin thickness). Cutting this patch may lead to misuse. Both FTSs should be disposed of properly. An FTS may be used in children older than 2 years of age.

An FTS should be reserved for those patients with chronic, stable pain and analgesic needs whose pain cannot be

maintained on oral opioids, because the patient is unable to swallow, has a dysfunctional gastrointestinal tract, or is intolerant of other opioids due to allergy or ADEs.^{53,54} Consideration of dosage, initiation, dose adjustments, and discontinuation of an FTS requires knowledge of the drug delivery system.

Dose Calculation and Conversion to Transdermal Fentanyl^{53,54}

1. Calculate total opioid use in the past 24 hours.
2. Convert to oral or intravenous equivalents of morphine using the information in Table 8.
3. Use Table 9 to determine the approximate equivalent topical dose to be given every 72 hours

(some patients may require every-48-hour dosing).

4. After application of the patch, it takes 12 to 16 hours to see a substantial therapeutic effect and 48 hours to achieve steady-state blood concentrations.

If no SR opioid prior to conversion:

Apply the patch. To manage breakthrough pain, the patient may use short-acting opioids.

If receiving SR opioid prior to conversion:

With the application of the first patch, the patient receives the last tablet of SR morphine preparation, allowing sufficient opioid serum levels until fentanyl concentration begins to increase.⁵⁵

Table 9

Conversion Table for Fentanyl Transdermal System⁵³⁻⁵⁵

Fentanyl Transdermal System (25, 50, 75, or 100 mcg/hr patch)			
Oral 24-hour morphine (mg/day) 6:1 ratio*	Oral 24-hour morphine (mg/day) 3:1 ratio†	IV 24-hour morphine (mg/day)	Fentanyl Transdermal System (mcg/hr)
45–134	24–66	8–22	25
135–224	67–101	23–37	50
225–314	102–156	38–52	75
315–404	157–201	53–67	100
405–494	202–226	68–82	125
495–584	227–291	83–97	150
585–674	292–336	98–112	175
675–764	337–381	113–127	200
765–854	382–426	128–142	225
855–944	427–471	143–157	250
945–1034	472–516	158–172	275
1035–1124	517–561	173–187	300

*The package insert suggests that 60 mg PO morphine = 10 mg IM morphine (6:1 ratio) [acute pain study]. This ratio would imply oral morphine/transdermal fentanyl ratio of 150:1. The package insert states that with the 6:1 ratio, 50% of patients will require upward dose titration (the dose is likely too low for 50% of the patients).

†Clinical experience in patients with chronic pain suggests that 30 mg PO morphine = 10 mg IM morphine (3:1 ratio). The literature shows an oral morphine/transdermal fentanyl ratio of 100:1 (consistent with the 3:1 ratio).

PO = by mouth; IM = intramuscular; IV = intravenous.

5. Do not use for breakthrough pain.
6. Do not cut patches.

Dose Adjustments^{53,54}

1. The initial dosage may be increased after 3 days based on the supplemental dose of the rescue short-acting opioid (25 mcg/hr increase in fentanyl patch = 90 mg oral morphine per 24 hours).
2. Subsequent dose adjustments should not occur more frequently than every 6 days, because this amount of time is required for the patient to reach a new steady state.

Discontinuation of Transdermal Fentanyl^{53,54}

1. Calculate the equianalgesic dose of the opioid using Tables 8 and 9.
2. Remove the fentanyl patch, and initiate treatment with half of the equianalgesic SR dose 12 to 18 hours later. It takes >17 hours for fentanyl serum concentration to fall by 50% after patch removal.

In summary, long-acting opioids may increase vitality, social functioning, and mental health by providing extended periods of pain relief and fewer ADEs, compared with short-act-

ing opioids.³⁹ Dosing and product selection must be patient-specific. No single medication is perfect for every patient, and some patients may require the use of 2 long-acting opioids.⁵⁶ Evaluation of treatment outcomes associated with opioid analgesics in chronic pain may be summarized by the 4 As: analgesia, activities of daily living, ADEs, and aberrant drug-related behaviors.⁵⁷

Terminology

Inconsistent use of terms related to pain often results in misunderstandings between regulators, health care providers, patients, and the general public regarding the use of opioids for the treatment of pain.⁵⁸ The establishment of uniform definitions promotes enhanced patient care in patients receiving opioid therapy. It is vital to recognize that *physical dependence*, *tolerance*, *cross-tolerance*, *addiction*, and *pseudoaddiction* are all distinct terms.

Physical Dependence

Physical dependence is defined as “a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drugs, and/or administration of an antagonist.”⁵⁸ Withdrawal symptoms include irritability, chills, nausea, vomiting, diarrhea, abdominal pain, sweating, runny nose, and insomnia. Withdrawal symptoms are not evidence of addiction—they also occur with many nonnarcotic medications (antihypertensives and antidepressants). These symptoms do not occur if the patient

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continues to take the opioid (avoids abstinence). Physical dependence is a pharmacologic property of the opioid and is common in patients receiving opioid therapy >5 days.⁵

Tolerance

“Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of 1 or more of the drug’s effects over time.”⁵⁸ Patients with tolerance to opioid therapy require higher than normal doses to achieve the same level of analgesic effect. Tolerance to pain relief is uncommon. Rapid increases in pain or in opioid dose may represent disease progression and not tolerance. Tolerance can also develop to common opioid ADEs. When tolerance develops to a particular opioid, cross-tolerance to other opioids concomitantly develops, although such tolerance may be incomplete.

Cross-Tolerance

Cross-tolerance may be thought of as the ability of one drug to suppress the manifestations of physical withdrawal produced by another drug and to maintain the physically dependent state. Caution must be used when switching to an alternative opioid drug; this is also termed *opioid rotation* or *sequential opioid trials*.^{41,59} When rotating opioids, “the degree of tolerance to opioid effects, both analgesic and nonanalgesic, does not fully transfer to the new drug, leading to a greater potency of the new drug than expected.”⁴¹ Equianalgesic tables do not take into consideration cross-tolerance (Table 8). Thus, it is commonly recommended to decrease the dose of the new opioid by 30% to 50% when initiating a *different* opioid.⁴¹ When keeping the same opioid, but converting to a different route, adjustments for cross-tolerance do not have to be made.

Addiction

Although physical dependence is common, addiction is rare in patients treated with prolonged opioid therapy.^{57,60} *Addiction* is defined as “a mal-

Table 10

Aberrant Drug-Related Behaviors ^{56,57}	
<p>More Predictive of Addiction</p> <ul style="list-style-type: none"> • Selling prescription drugs • Forging prescriptions • Stealing or “borrowing” drugs • Frequent prescription “loss” • Obtaining prescription drugs from nonmedical sources • Injecting oral/topical formulations • Concurrent abuse of illicit drugs • Multiple dose escalations • Repeated episodes of gross impairment 	<p>Less Predictive of Addiction</p> <ul style="list-style-type: none"> • Aggressive demand for more drug • Drug hoarding during periods of reduced symptoms • Requesting specific drugs • Acquisition of drugs from other medical sources • Unsanctioned dose escalation once or twice • Unapproved use of drug to treat another symptom • Reporting psychic effects not intended by the clinician • Occasional impairment

Table 11

Percentage Change in Use and Abuse of Opioids (1990-1996) ⁶⁴		
Product	Medical Use	Abuse
Morphine	↑ 59%	↑ 3%
Oxycodone	↑ 23%	↓ 29%
Hydromorphone	↑ 19%	↓ 15%
Fentanyl	↑ 1168%	↓ 59%

adaptive pattern of substance use leading to clinically significant impairment or distress.”⁶¹ Addiction is a psychological property of the patient. Addictive behaviors are psychological in nature and include a dysfunctional and compulsive pattern of use in which craving, obtaining, and using a drug constitute the principal focus of the user’s life; in addition, use is continued despite harm. Addiction is diagnosed by the observation of aberrant drug-related behavior (Table 10).^{56,57}

Clinicians can recognize addiction by noting the following behaviors^{56,57}:

- Demands end-of-office-hour appointments or arrives just after close (running late)
- Needs immediate action
- Refuses physical examination or tests
- Prohibits release of medical records
- Cannot or will not provide past providers
- Uses excuses of visiting from out of town and lost or stolen prescriptions

- No medical basis for allergies to nonopioids
- Unusual knowledge of controlled substances

History of previous substance abuse by the patient and/or family are strong indicators of the likelihood of continued abuse.^{56,57} Appropriate medical use of opioids is not generally thought to be associated with addiction.

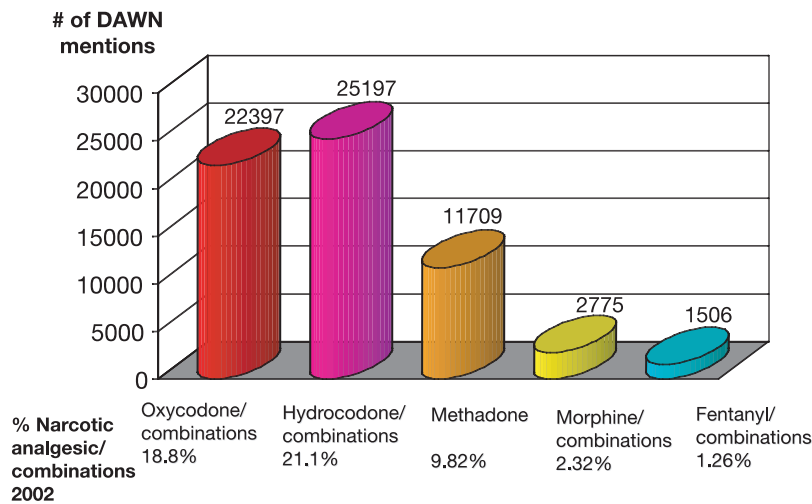
Pseudoaddiction

Pseudoaddiction is commonly seen in patients with severe, unrelieved pain. Patients become preoccupied with finding opioids. Their underlying focus, however, is on finding relief for their pain. Pseudoaddiction may be differentiated from true addiction because drug-seeking behaviors typically resolve when pain is adequately controlled.^{58,62}

Opioids and Drug Abuse

The US Department of Health and Human Services sponsors the Drug Abuse Warning Network (DAWN).⁶³

Figure 2

DAWN Mentions⁶⁶

Adapted from Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Emergency department trends from the Drug Abuse Warning Network, Final Estimates 1995-2002, DAWN Series: D-24, DHHS Publication No. (SMA) 03-3780; Rockville, MD; 2003.

DAWN reports the frequency of emergency department (ED) drug abuse-related visits and the total drug mentions for nonmedical purposes. Information was gathered from a representative sample of 21 metropolitan EDs (437 hospitals participated in 2002). In 2002, there were approximately 670,000 visits to the ED that were related to drug abuse.⁵⁷ The visits were categorized, and 7 categories accounted for more than 80% of all drug mentions: alcohol in combination, cocaine, heroin, marijuana, benzodiazepines, antidepressants, and analgesics. About 10% (119,185) of drug mentions involved narcotic analgesics. Trends in opioid abuse have changed over time (Table 11).⁶⁴ Figure 2 shows the likelihood of drug abuse between short-acting and long-acting opioid analgesics.⁶³

Opioid Use in Clinical Practice

In 1998, the Federation of State Medical Boards created model guidelines for the use of controlled substances for the treatment of pain.⁶⁵ In May 2004, these were adopted as policy.⁶⁶ As opioids are the standard of care for chronic pain, clinicians should perform thorough patient evaluations, obtain informed consent for an appropriate opioid treatment plan, periodically assess for opioid efficacy and ADEs, and maintain adequate documentation. Clinicians may follow several practical pointers to differentiate between drug-seeking behavior and medical necessity of opioid use. Maintenance of archived, complete medical records is vital. In addition, an agreement between the clinician and patient may curtail

drug-seeking behavior; such a document might include an agreement to seek services only from 1 doctor and 1 pharmacy, reasonable treatment goals, no early refills or changes in therapy without an office visit, no illicit drug use, and as-needed urine drug screens or serum monitoring.^{17,56} Knowledge of federal and state regulations restricting opioid use is also fundamental. A lawful prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his or her professional practice and must be documented in the medical records. Federal law does not preclude the use of opioids as analgesics for legitimate medical purposes, including treating chronic pain and treating pain in addicts. However, federal law does prohibit the use of opioids to maintain an addicted state without special registration.

Pharmacist's Role in Chronic Pain Management

Pharmacists are key members of the interdisciplinary approach to the management of chronic pain.⁷ Because of their knowledge of opioid medications, pharmacists can provide valuable information on the most appropriate opioid for pain management and perform a comprehensive review of past and current pharmacologic interventions.^{7,67} To alleviate concerns about addiction,⁷ pharmacists can educate patients about the principles of tolerance, dependence, addiction, and pseudoaddiction. Pharmacists play a vital role in the safe delivery of pain medications by providing pain medication education and "clinical pearls"; maintaining updated and easily acces-



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sible equianalgesic conversion tables; assisting in the conversion between changes in medications and routes of opioid therapy; and assisting in the monitoring of opioid therapy for safety and efficacy.^{67,68}

Conclusion

Long-acting opioids are safe and

effective when used appropriately for the management of chronic pain and may be rotated to gain better pain control by using equianalgesic tables. Treatment-induced addiction are rare. Documentation and knowledge of regulations regarding opioid use are essential. The best analgesic results are obtained when a therapeutic alliance

between the patient and health care professional is formed. **R**

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: astahl@ascendmedia.com.

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CE REVIEW QUESTIONS

Managing Chronic Pain An Analysis of the Use of Opioids:

This educational lesson will be available to pharmacists on-line at www.pharmacytimes.com.

(Based on the article starting on page 101) Choose the 1 most correct answer.

1. The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience:
 - a. Associated with actual tissue damage.
 - b. Associated with potential tissue damage.
 - c. Associated with either actual or potential tissue damage.
 - d. That has no relationship to tissue damage.
2. Unrelieved pain affects the patient's quality of life and also may affect:
 - a. The cardiovascular system.
 - b. The gastrointestinal system.
 - c. The immune system.
 - d. All of the above.
3. Barriers to effective pain management include all of the following *except*:
 - a. Insufficient supplies of opioids in pharmacies.
 - b. Patients reporting pain.
 - c. Legal and regulatory issues governing opioid use and abuse.
 - d. Inadequate knowledge of opioid analgesic pharmacotherapy.
4. Patients with chronic pain receiving opioids develop tolerance to all of the following opioid-induced adverse drug events *except*:
 - a. Respiratory depression.
 - b. Constipation.
 - c. Nausea and vomiting.
 - d. Sedation.
5. A cancer patient reports an allergy to morphine (throat swollen shut). The most appropriate alternative opioid in this patient is:
 - a. Codeine.
 - b. Hydromorphone.
 - c. Fentanyl.
 - d. Oxycodone.
6. Advantages of long-acting opioids include:
 - a. More stable pain relief.
 - b. Long duration of pain relief.
 - c. Less abuse potential.
 - d. All of the above.
7. Which of the following opioids is most appropriate for acute pain management in a 73-year-old woman with seizure disorder and end-stage renal disease on dialysis?
 - a. Meperidine
 - b. Propoxyphene
 - c. Morphine controlled release
 - d. Hydromorphone
8. Which of the following opioids is most appropriate for chronic pain management in a 55-year-old man with chronic, stable end-stage alcoholic liver disease?
 - a. Meperidine
 - b. Oxycodone/acetaminophen
 - c. Oxycodone immediate release, without acetaminophen
 - d. Methadone

9. Recommended routes of administration for chronic opioid use include all of the following *except*:

- Oral.
- Intravenous.
- Intramuscular.
- Transdermal.

10. A patient is to have all medications crushed and administered through the nasogastric tube. The patient reports an allergy to fentanyl transdermal patches (erythematous rash with blisters). The most appropriate long-acting opioid is:

- Methadone tablets.
- Morphine sulfate controlled-release.
- Oxycodone controlled-release.
- Fentanyl transdermal system.

11. All of the following are unique properties of or considerations regarding methadone *except*:

- Long, highly variable half-life.
- Lipophilic.
- Does not require renal or hepatic dose adjustment.
- Reduce the calculated equianalgesic dose by at least 30% to 50% when changing to methadone.

12. All of the following are indications for the fentanyl transdermal system *except*:

- Chronic, stable pain and analgesic needs.
- Tolerating oral opioids and responding well without intolerable side effects.
- Being unable to swallow.
- Having a dysfunctional gastrointestinal tract.

13. How do the potencies of morphine and fentanyl compare?

- Fentanyl is 100 times more potent than morphine.
- Morphine is 100 times more potent than fentanyl.
- Fentanyl is 10 times more potent than morphine.
- Morphine and fentanyl are approximately equivalent.

14. Which of the following statements is *incorrect* regarding physical dependence?

- Abrupt cessation of the chronic opioid may cause withdrawal symptoms.
- It is common during chronic opioid use.
- It is a physical property of the drug.
- It is a psychological property of the person.

15. Which of the following statements is *incorrect* regarding addiction?

- Addictive behaviors include drug-seeking behavior.
- It is rare during chronic opioid use.
- It is a physical property of the drug.
- It is a psychological property of the person.

16. Equianalgesic tables do not take into consideration cross-tolerance.

When changing from oral morphine to oral hydromorphone, it is most appropriate to:

- Reduce the calculated equianalgesic dose by at least 30% to 50%.
- Increase the calculated equianalgesic dose by at least 30% to 50%.
- Reduce the calculated equianalgesic dose by at least 75%.
- Initiate the calculated equianalgesic dose without a dose reduction.

17. Drug-related behaviors predictive of addiction include:

- Prohibiting release of medical records.
- Frequent prescription "losing."
- Demanding end-of-office-hour appointments.
- All of the above.

18. Which of the following should be used in the management of patients when they are receiving a narcotic for chronic pain?

- The patient agrees that only one medical practice will prescribe for them.
- Only one pharmacy refills prescriptions for the patient.
- There are no refills after hours or on weekends.
- All of the above.

19. Because of federal and state laws governing the prescribing and dispensing of Schedule II narcotics, clinicians should:

- Never prescribe opioids.
- Prescribe opioid narcotics for legitimate medical purposes.
- Avoid maintaining up-to-date medical records.
- Encourage patients to see numerous doctors.

20. Which of the following roles may a pharmacist play in chronic pain management?

- Pharmacists may provide valuable information on the most appropriate opioid.
- To alleviate concerns of addiction, the pharmacist can educate the patient on the differences between addiction and dependence.
- Pharmacists can maintain updated and easily accessible equianalgesic tables.
- All of the above.

**JULY 2005
PROGRAM 290-000-050-010-H01**

MANAGING CHRONIC PAIN: AN ANALYSIS OF THE USE OF OPIOIDS

**(TEST VALID THROUGH JULY 31, 2008.
NO CREDIT WILL BE GIVEN AFTER THIS DATE.)**

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1.	a	b	c	d	8.	a	b	c	d	15.	a	b	c	d
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3.	a	b	c	d	10.	a	b	c	d	17.	a	b	c	d
4.	a	b	c	d	11.	a	b	c	d	18.	a	b	c	d
5.	a	b	c	d	12.	a	b	c	d	19.	a	b	c	d
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