SPECIAL FEATURE

The opioid abuse and misuse epidemic: Implications for pharmacists in hospitals and health systems

DANIEL J. COBAUGH, CARL GAINOR, CYNTHIA L. GASTON, TAI C. KWONG, BARBARAJEAN MAGNANI, MARY LYNN MCPHERSON, JACOB T. PAINTER, AND EDWARD P. KRENZELOK

isuse and abuse of prescription opioids in the United States constitute a public health crisis that has grown to epidemic proportions over the last decade. The Centers for Disease Control and Prevention (CDC) has identified prescription drug abuse and overdose as one of the top five health threats for 2014.¹ It is imperative that pharmacists across the health system have a complete understanding of this epidemic. This article reviews the role of opioids in pain management, the epidemiology of opioid misuse and abuse, the clinical toxicology of these medications, and the role of laboratory analyses in monitoring opioid therapy, as well as legal issues surrounding opioid distribution and therapy, the use of prescription drug monitoring programs to combat opioid abuse and misuse, and implications for medication-use policy in hospitals and health systems.

Purpose. The current epidemic of prescription opioid abuse and misuse in the United States is discussed, with an emphasis on the pharmacist's role in ensuring safe and effective opioid use.

Summary. U.S. sales of prescription opioids increased fourfold from 1999 to 2010, with an alarming rise in deaths and emergency department visits associated with the use of fentanyl, hydrocodone, oxycodone, and other opioid medications. Signs and symptoms of opioid toxicity may include altered mental status, hypoventilation, decreased bowel motility, central nervous system and respiratory depression, peripheral vasodilation, pulmonary edema, hypotension, bradycardia, and seizures. In patients receiving long-term opioid therapy for chronic pain, urine drug testing is an important tool for monitoring and assessment of therapy; knowledge of opioid metabolic pathways and assay limitations is essential for appropriate use and interpretation of screening and confirmatory tests. In recent years, there has been an increase in federal enforcement actions against pharmacies and prescription drug wholesalers involved in improper opioid distribution, as well as increased reliance on state-level prescription drug monitoring programs to track patterns of opioid use and improper sales. Pharmacies are urged to implement or promote appropriate guidelines on opioid therapy, including the use of pain management agreement plans; policies to ensure adequate oversight of opioid prescribing, dispensing, and waste disposal; and educational initiatives targeting patients as well as hospital and pharmacy staff.

Conclusion. Pharmacists in hospitals and health systems can play a key role in recognizing the various forms of opioid toxicity and in preventing inappropriate prescribing and diversion of opioids.

Am J Health-Syst Pharm. 2014; 71:e82-97

Opioid use in pain management

The term *opium* refers to a mixture of alkaloids from the poppy seed, and the term *opiates* refers to naturally occurring alkaloids (e.g., morphine, codeine). The term *opioid* refers to all compounds that bind to opioid receptors.² Opioids have been used for thousands of years for the treatment of moderate-to-severe acute and chronic pain. In 1806,

DANIEL J. COBAUGH, PHARM.D., DABAT, FAACT, is Vice President, ASHP Research and Education Foundation, Bethesda, MD. CARL GAINOR, J.D., PH.D., is Clinical Assistant Professor of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA. CYNTHIA L. GASTON, PHARM.D., BCPS, is Medication Use Policy Analyst, UW Health, Madison, WI. TAI C. KWONG, PH.D., is Professor of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry, and Director, Hematology and Chemistry Labs, Strong Memorial Hospital, University of Rochester ter Medical Center, Rochester, NY. BARBARAJEAN MAGNANI, PH.D., M.D., is Chair and Pathologist-in-Chief, Department of Pathology and Laboratory Medicine, Tufts Medical Center, and Professor and Chair, Department of Anatomic and Clinical Pathology, Tufts University School of Medicine, Boston, MA. MARY LYNN MCPHERSON, PHARM.D., BCPS, CPE, is Professor and Vice Chair, Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore. JACOB T. PAINTER, PHARM.D., M.B.A., PH.D., is Assistant Professor of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences, Little Rock. EDWARD P. KRENZELOK, PHARM.D., FAACT, FEAPCCT, DABAT, is Professor Emeritus, School of Pharmacy, University of Pittsburgh.

Address correspondence to Dr. Cobaugh (dcobaugh@ashp.org). The authors have declared no potential conflicts of interest. This article will appear in the September 15, 2014, issue of *AJHP*.

Copyright © 2014, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/14/0000-0e82\$06.00. DOI 10.2146/ajhp140157 Sertürner isolated morphine from opium; beginning in the 1850s, injectable morphine was used to treat both acute and chronic pain.

Opioids provide their pharmacologic effects by binding to opioid receptors located both within and outside of the central nervous system.² Depending on which receptors they bind to and their level of intrinsic activity, opioids are classified as full or partial agonists, mixed agonistantagonists, or opioid antagonists. The primary opioid receptor is the μ receptor. The μ receptor is responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility, pruritus, anorexia, sedation, and physical dependence. The κ receptor, another opioid receptor, is responsible for spinal analgesia, dyspnea, opioid dependence, sedation, respiratory depression, and dysphoria. The σ receptor is responsible for dysphoria, psychotomimetic effects, and stress-induced depression. The role of the δ -opioid receptor has not been well studied.²

Opioids are used routinely to treat both acute and chronic cancer pain and noncancer pain. Numerous clinical guidelines have been published over the past 20 years to guide practitioners in the appropriate use of opioids to treat moderate-to-severe pain.³⁻⁷ The management of acute and chronic pain is generally best accomplished through a multimodal approach that includes nonpharmacologic interventions, as well as nonopioid analgesics (e.g., acetaminophen, nonsteroidal antiinflammatory drugs [NSAIDs]), opioids, and coanalgesics (e.g., anticonvulsants, antidepressants, skeletal muscle relaxants, topical or oral anesthetics).6 Appendix A lists the American Pain Society recommendations for considerations when selecting analgesics to treat acute or chronic pain.

Opioid therapy for acute pain

One potential strategy to reduce

postoperative pain is the use of preemptive analgesics. However, there is limited evidence that demonstrates major clinical benefits (e.g., consistent immediate postoperative pain relief, reduced need for supplemental analgesia) after the use of preemptive analgesics.⁸⁻¹² Despite these findings, it is clear that optimal postoperative pain management begins preoperatively, continues through the perioperative period, and is sustained through the postoperative period as indicated clinically. One useful strategy is the use of a multimodal approach.^{13,14}

Opioids are used to treat acute pain when the pain cannot be managed with nonopioid therapy alone. For example, the acute pain after a dental procedure may be primarily controlled with the use of nonopioids such as an NSAID, possibly supplemented with an oral opioid as needed. Alternatively, a patient who has had major surgery will likely require parenteral opioid therapy for several days, potentially supplemented with nonopioid analgesics or coanalgesics. While morphine, hydromorphone, and fentanyl are the most frequently used parenteral opioids for acute pain, the selection of a specific opioid for a given patient must be individualized. It is imperative that the clinician obtain a pain medication history that captures previous opioid therapy and adverse reactions. For example, a patient may report that morphine causes significant itching whereas hydromorphone does not. Genetic polymorphisms may explain the interpatient variability often seen with opioid dosing. In 2013 the Food and Drug Administration (FDA) added a boxed warning to the drug label of codeine-containing products regarding overdose deaths experienced by children after tonsillectomy or adenoidectomy.15,16 Children from certain ethnic groups are ultrarapid metabolizers of codeine, which can lead to higher-than-expected serum concentrations of morphine and a risk of death.

When opioids are part of the acute pain management regimen, they may be administered by the oral, parenteral, and neuraxial routes. Research dating back almost 50 years demonstrated that small i.v. doses of morphine administered on an as-needed basis for acute pain are superior to scheduled dosing.17,18 The use of patient-controlled analgesia is a standard intervention used in contemporary pain management for the treatment of acute pain. Increasingly, neuraxial opioid administration is part of an effective multimodal acute pain management plan.¹⁹

When determining the dose of an opioid for acute pain, it is critically important for clinicians to take into account whether the patient is opioid naive or opioid tolerant. Opioidtolerant patients are those who have been taking regularly scheduled prescribed opioids or have a history of substance abuse related to illicit use of prescription opioids, illicit drug use, or participation in an opioid maintenance program. To avoid underdosing the patient with acute pain and possibly precipitating opioid withdrawal, this opioid tolerance must be taken into consideration. One possible strategy is to continue a previously used opioid while treating the acute pain separately; another involves calculating a larger opioid dose to treat the acute pain that incorporates an equianalgesic dose of the previous opioid.20,21

Another important skill for practitioners is the ability to safely and accurately calculate equianalgesic opioid doses when converting a patient from one opioid to another or from one route of administration or dosage formulation to another.²² A commonly seen error occurs when postoperative patients are switched from an effective dosage of parenteral hydromorphone (e.g., 1 mg i.v. every four hours) to a nonequivalent and ineffective oral opioid (e.g., oral oxycodone 5 mg every four hours). This could result in pain relief failure SPECIAL FEATURE Opioid abuse and misuse

as well as a loss of trust in the health care team by the patient and assumptions by providers that the patient is exhibiting drug-seeking behavior when the patient is actually demonstrating appropriate pain relief– seeking behavior.

Opioids to treat chronic pain

Chronic pain management strategies are often viewed differently by practitioners depending on whether it is chronic cancer pain or noncancer pain, although the same analgesics are used to treat both. Both nonpharmacologic and pharmacologic strategies are used to treat chronic cancer pain and noncancer pain in a multimodal strategy. The prevalence of pain in cancer patients and persistent pain in cancer survivors is high, and opioids are frequently part of the treatment strategy. Researchers who conducted a recent systematic review of observational studies on the effectiveness of opioid therapy for cancer pain assigned a strong recommendation to the use of these agents to treat cancer-related pain.23

The use of opioids in the management of acute pain and chronic cancer pain is more widely accepted than their use in treating chronic noncancer pain. There are many reasons to explain this finding. The available evidence that opioids conclusively reduce pain severity and increase function (e.g., activities of daily living) in patients with chronic noncancer pain is not convincing. A review by Trescot and colleagues²⁴ concluded that there was weak evidence of the long-term (i.e., six months or longer) effectiveness of morphine and transdermal fentanyl in reducing pain and improving function. This review found no evidence of effectiveness of other opioids. Long-term opioid therapy may be associated with tolerance, opioidinduced hyperalgesia, physical and psychological dependence, persistent adverse effects, a lower quality of life, higher rates of depression, and increased healthcare utilization.25

Role of the urine drug test

Published practice guidelines for opioid therapy for noncancer pain from governmental agencies and professional organizations (Appendix B) recommend using urine drug testing as part of the initial patient evaluation, the treatment plan agreement, and monitoring and assessment of therapy.^{26,27} The urine drug test supplements tools such as patient self-reporting and behavioral monitoring, identifies noncompliance with the prescribed medications, and detects the use of alcohol, undisclosed medications, and illicit drugs.

The advantage of urine drug tests is that there are well-established analytical methods and extensive experience in result interpretation²⁸; the disadvantages include specimen collection and the potential for tampering and adulteration. Oral fluid testing, or saliva testing, is gaining in popularity and has an advantage over urinalysis in that it entails a simple and noninvasive specimen collection process. Oral fluid testing, however, faces technical challenges with regard to both screening and confirmation methodologies.²⁹

The urine drug test menu, whether performed inhouse or by a reference laboratory, should test for commonly prescribed opioids and the typical illicit drug groups (Table 1). The urine drug test is performed in most clinical settings by immunoassays, which, if positive, may lead to confirmation testing.

Proper utilization of immunoassaybased urine drug testing and correct interpretation of results must take into consideration the limitations of immunoassays.

Most immunoassays, such as those for the amphetamines, benzodiazepines, and opioids, are class assays; they detect not one target drug but a family of related compounds.^{28,30} For example, the opiates immunoassays detect morphine (the target analyte) and codeine and also the related opioids with a phenanthrene ring, such as hydromorphone, hydrocodone, dihydrocodeine, and oxycodone, with varying sensitivities; these opioids, when present singly or in combination, can also produce a positive immunoassay result. Thus, an immunoassay cannot be used to monitor a patient using a prescribed opioid for possible abuse of another (i.e., nonprescribed) opioid.

Immunoreactivity assays for a drug determine the assay sensitivity for that drug.²⁸ For example, the opiates assay is less reactive to hydromorphone than to morphine and thus requires that a comparatively higher hydromorphone concentration be present for a positive result. Therefore, a patient may test negative for the prescribed opioid due to lower assay sensitivity, especially if the drug is taken in low doses, which can result in urine drug concentrations that fall below the assay cutoff; this is a "clinical" false-negative result and does not necessarily indicate nonadherence.^{30,31} In this case, an alternative (and more sensitive and specific) assay should be able to detect the specific opioid. For example, oxycodone is poorly detected by the opiates assay, and the nonopiate opioids buprenorphine, fentanyl, and methadone are not detected by the opiates assay at all. Detection of these drugs requires analyte-specific (i.e., drug-specific) immunoassays.

Most clinical laboratories perform confirmation testing using mass spectrometry (MS) assays such as liquid chromatography–mass spectrometry (LC/MS). The MS assays offer specific identification of drugs and metabolites and quantitative measurement at low concentrations, thus allowing interpretation of cases involving the presence of minor opioid metabolites or pharmaceutical impurities.³⁰ MS, however, is costly and technologically challenging, and its deployment is limited to large laboratories.

Correct interpretation of urine drug test results requires knowledge of the limitations of the assay methodology. Moreover, there should not be unrealistic expectations of what information can be obtained from the urine drug test. For example, the urine drug concentration cannot be extrapolated reliably to gauge the serum drug concentration, nor can it be used to infer patient adherence with the prescribed dosage regimen.

When interpreting an unexpected negative urine drug test, nonadherence may not be the only explanation. Besides the reasons mentioned previously, other possible explanations include dilution or substitution of the urine sample; genetic polymorphism in enzymes and transporters involved in opioid metabolism and transport (e.g., cytochrome P-450 enzymes, uridyl glucuronide transferase, P-glycoprotein), which can result in lower drug concentrations; and altered pharmacokinetics due to disorders involving reduced gastrointestinal absorption (e.g., diarrhea, short-gut syndrome), concurrent medications, or diet.³²

An unexpected positive result suggests the patient may have taken undisclosed medications or illicit drugs. Other explanations, however, must also be considered. For example, the unexpected opioid may be present as a minor metabolite of the prescribed opioid and not as a result of abuse of the unexpected (nonprescribed) opioid. For example, hydromorphone is a prescription opioid but also a minor

Table 1.

Recommended Urine Drug Test Menu for Patients Receiving Opioids for Noncancer Paina

Immunoassays			
Drug/Class ^b	Target Analyte(s) ^b	Cutoff Values (ng/mL) ^b	Typical Confirmation Assay Targets ^b
Amphetamines	d-Methamphetamine	500, 1000	Amphetamines
			Methamphetamine
			Methylenedioxymethamphetamine
			(MDMA)
			Methylenedioxyamphetamine (MDA)
Barbiturates	Secobarbital	200, 300	Amobarbital
			Butalbital
			Pentobarbital
			Phenobarbital
			Secobarbital
Benzodiazepines	Nordiazepam	200, 300	Diazepam
			Nordiazepam
			Oxazepam
			Temazepam
			Clonazepam, 7-aminoclonazepam
			Alprazolam, α -hydroxyalprazolam
			Flunitrazepam, 7-aminoflunitrazepam
			Lorazepam
Buprenorphine	Buprenorphine	5	Buprenorphine, norbuprenorphine
	Norbuprenorphine	10	Buprenorphine, norbuprenorphine
Cocaine	Benzoylecgonine	150, 300	Benzoylecgonine, cocaine, cocaethylene
Fentanyl	Fentanyl	2	Fentanyl, norfentanyl
Marijuana	$\Delta 9$ -Tetrahydrocannabinolcarboxylic	20, 50	Δ 9-Tetrahydrocannabinolcarboxylic acid
	acid		
Methadone	Methadone	300	Methadone, methadone metabolite ^c
	Methadone metabolite ^c	300	Methadone, methadone metabolite ^c
Opiates	Morphine	300, 2000	Morphine
			Codeine
			Oxycodone
			Oxymorphone
			Hydrocodone
			Hydromorphone
Oxycodone	Oxycodone	100	Oxycodone, noroxycodone, oxymorphone

^aReproduced, with permission, from reference 31.

^bConsult laboratory for specifics of assays in use.

^c2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).

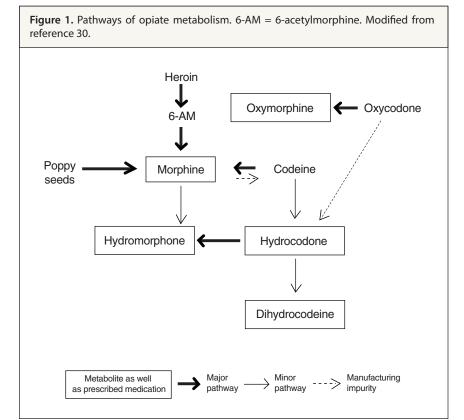
metabolite of morphine³³ (Figure 1). Knowing the metabolic pathway and the relative concentrations of both morphine and hydromorphone may help to distinguish between the two scenarios.³³

An alternative explanation for an unexpected positive urine test result is that high-sensitivity MS assays can detect opioids at very low concentrations, and some opioids are impurities created during pharmaceutical manufacturing processes; specifically, hydrocodone and codeine are impurities in pharmaceutical preparations of oxycodone and morphine, respectively.34,35 A very low ratio (<1%) of the unexpected opioid (e.g., hydrocodone) to the prescribed opiate (e.g., oxycodone) suggests that the unexpected opioid is present as a manufacturing impurity.³⁴

The urine drug test is a useful laboratory test for the management of patients on chronic opioid therapy. Consultation with a clinical laboratory professional can help to maximize the clinical efficacy of the urine drug test.

Epidemiology of opioid misuse and abuse

Reports from CDC, the Drug Abuse Warning Network (DAWN), and the National Poison Data System have demonstrated an alarming increase in opioid misuse and abuse over the last two decades.^{1,36-41} Poisoning deaths in the United States nearly doubled from 1999 to 2006, from 20,000 to 37,000. This was due largely to deaths from prescription opioid analgesics, with methadone, oxycodone, and hydrocodone most frequently implicated. This increase in deaths coincided with a nearly fourfold increase in the use of prescription opioids nationally.36 A review of data on individuals with adverse drug events who were treated in emergency departments from January 1, 2004, through December 31, 2005, found that central nervous system agents constituted the most frequently implicated therapeutic



category (21.4% of cases); within that category, opioid-containing analgesics were the most frequently implicated medication class, accounting for an estimated 1,167 (24.8%) of the evaluated cases.37 Sales of prescription opioids in 2010 were four times those in 1999. Overdose deaths involving opioid medications now exceed deaths involving heroin and cocaine combined. In 2010 alone, 16,500 people died from analgesic-related overdoses, the majority of which involved opioids.³⁸ Deaths from opioid analgesics have been reported across the United States, in all age groups, and specific opioids such as hydrocodone, methadone, morphine, and oxycodone have been implicated. In 2008, overdose death rates ranged from 5.5 per 100,000 population in Nebraska to 27.0 per 100,000 in New Mexico.³⁹ The prevalence of nonmedical use of opioids in 2008–09 ranged from 3.6% in Nebraska to 8.1% in Oklahoma. Rates of prescription opioid sales in 2008 ranged from 3.7 kg per 10,000 population in Illinois to 12.6 kg per 10,000 in Florida, with the highest sales rates reported in the Southeast and the Northwest.

In a review of 295 unintentional pharmaceutical overdose deaths in West Virginia, opioids were implicated in 93% of cases.40 However, 44% of the decedents had not been prescribed an opioid. Ninety percent of the decedents were men ranging in age from 18 to 70 years, with a mean age of 39 years. Sixtythree percent of the deaths were associated with pharmaceutical diversion, and 21% involved evidence of doctor shopping. The 35- to 44-years age range was associated with a notably higher rate of doctor shopping. Substance abuse indicators were identified in 95% of the decedents, and having prescriptions for five or more controlled substances was more common in women (30.9%) than in men (16.7%).40

DAWN also collects important data that provide insights into recent national trends in drug-related morbidity and mortality. A 2010 report from DAWN on emergency department visits for the misuse and abuse of all drugs estimated an increase from 1.6 million cases in 2004 to 2 million cases in 2008.41 The number of visits related to opioid analgesics increased by 111% (from 144,600 to 305,900 visits) in the same time period. Visit rates increased across the five years for fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxycodone; for oxycodone, estimated annual emergency department visits increased from 41,700 to 105,200.38

In Florida, from 2003 through 2009, the death rate due to prescription drugs increased by 84.2%, from 7.3 to 13.4 per 100,000 people.⁴¹ The greatest increases in rates were observed with oxycodone (264.6%), alprazolam (233.8%), and methadone (79.2%). Figure 2 compares Florida overdose trends for opioids as a group and for hydrocodone, methadone, morphine, and oxycodone specifically.

Clinical toxicology

While all opioids have some degree of affinity for the μ -, δ -, and κ -opioid receptors, the μ -opioid receptor is responsible for the majority of the adverse effects associated with opioid misuse, abuse, and overdose.43 The classical elements of the opioid toxidrome include altered mental status, hypoventilation, decreased bowel motility, and miosis. Contrary to conventional wisdom, miosis is not a universal finding in opioidtoxic patients and neither its presence nor absence is pathognomonic of opioid toxicity or the lack thereof. For example, hypoxic patients and those who coingest anticholinergic agents may exhibit mydriasis. Other findings may include peripheral vasodilation, pulmonary edema, hypotension, bradycardia, chest wall rigidity, and myoclonus (with fentanyl) and seizures (with meperidine).42-44 Opioids induce a delay in gastric emptying and may increase the risk

of vomiting and pulmonary aspiration that can complicate respiratory depression.45 Respiratory depression, modulated by the effects of opioids on medullary chemoreceptors' ability to detect hypercapnia, and the consequential reduced respiratory rate are diagnostic of opioid toxicity; a respiratory rate of less than 12 breaths per minute is characteristic.46 Each opioid has unique pharmacokinetic and pharmacodynamic properties that determine the extent and duration of toxicity and affect treatment decisions, and these differences must be considered when evaluating the patient with opioid toxicity. While not yet applicable clinically, human genomics is linked to the magnitude of toxicity for some drugs, and, as mentioned previously, at least one opioid receptor polymorphism has been identified and may have diagnostic and treatment implications in the future.47

Characteristics of selected opioids

Buprenorphine. Buprenorphine is a potent semisynthetic opioid with partial agonist activity at the µ receptor. Its primary indication is treatment of opioid addiction since it has an extraordinarily high affinity for the μ receptor and the ability to prevent binding of other opioids. Buprenorphine formulations for opioid maintenance therapy are sublingual tablets and a sublingual film that are coformulated with naloxone, which serves as a deterrent to the i.v. abuse of buprenorphine. Unlike methadone, whose use requires the individual to obtain a daily dose at a methadone clinic, buprenorphine is dispensed through licensed officebased practices, and multiple doses can be dispensed.48,49 Consequently, unintentional exposures to buprenorphine are now commonplace in the pediatric population and may be associated with significant morbidity.48-51 Due to the long halflife of buprenorphine, children who may have been exposed to a single dose should be hospitalized for 24 hours and even longer if the use of naloxone was necessary to reverse the associated central nervous system and respiratory depression.⁵⁰ The high affinity of buprenorphine for the μ receptor may necessitate doses of naloxone that exceed customary doses in both children and adults or the use of a naloxone infusion.⁵² Buprenorphine has minimal bioavailability, and since most pediatric exposures involve the sublingual route, the use of activated charcoal is unnecessary unless there are coingestants that dictate its use.

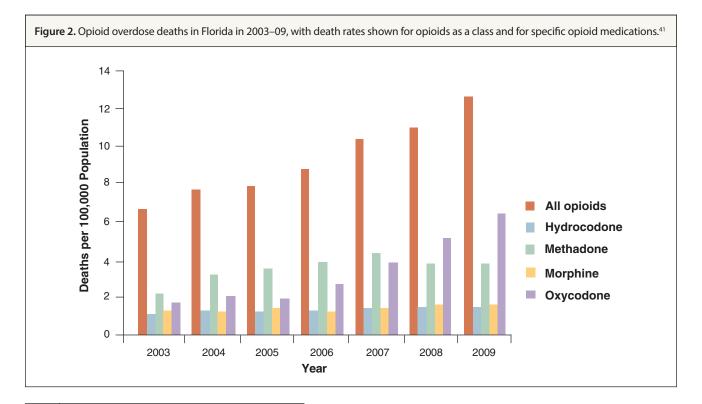
Fentanyl. Fentanyl is a pure synthetic opioid agonist of high potency (80–100 times that of morphine) with a short duration of action.53 It is a µ-opioid receptor agonist indicated for the treatment of chronic pain, with delivery achieved via transdermal patches, nasal spray, and transmucosal products. Intravenous fentanyl is used in the perioperative setting, postoperatively for pain management, and as a sedative in the emergency department and critical care settings, and it is associated with notable morbidity and mortality when abused or when prescribed inappropriately to opioid-naive individuals. Fentanyl patch ingestion for abuse purposes is common; unused or spent patches contain fentanyl in a matrix or reservoir that becomes bioavailable when ingested.54-58 Additionally, the inappropriate use of fentanyl patches on compromised skin (e.g., sunburned skin) or with external heat sources such as heating pads and blankets, saunas, and hot tubs increases transdermal absorption and may result in fentanyl toxicity.59 Fentanyl toxicity is characterized by the classical opioid toxidrome along with sustained central nervous system and respiratory depression. Unlike the parenteral therapeutic use of fentanyl, the ingestion of patches is associated with an extremely long duration of action that may necessitate the prolonged use of naloxone.

Hydrocodone. The fixed combination of hydrocodone and acet-

aminophen is the most commonly prescribed generic medication in the United States.60 Given the prominent presence of hydrocodone-containing products in U.S. homes, children are at a pronounced risk of being exposed to hydrocodone. Hydrocodone has considerable abuse potential and is associated with substantial morbidity and mortality.61 As with other opioids, hydrocodone has considerable affinity for μ receptors and its toxic effects are consistent with the classical opioid toxidrome. Hydrocodone has been approved for manufacture in a single-entity extended-release form as a Schedule II product, but currently it is always combined with acetaminophen as an oral analgesic product.62 Therefore, overdoses of hydrocodone-containing analgesics are also complicated by the presence of acetaminophen and are one of the leading causes of acetaminophen-related fatalities due to hepatic necrosis.^{63,64} Consequently, when an exposure to a hydrocodonecontaining product is suspected, serum acetaminophen and salicylate

concentrations should be obtained. Hydrocodone is also available with ibuprofen as a combination product. The treatment of an overdose may include the use of activated charcoal to prevent drug absorption, naloxone to reverse the effects of hydrocodone, and acetylcysteine to treat acetaminophen toxicity. If the patient develops salicylate toxicity from a combination hydrocodone-aspirin product, appropriate supportive care (e.g., airway protection and ventilatory support, sodium bicarbonate to reverse acidemia, sedatives, anticonvulsants) and interventions (e.g., hemodialysis) must be initiated to prevent possibly lifethreatening salicylate toxicity.

Methadone. The use of methadone, a synthetic μ agonist, has evolved beyond its traditional role in helping to prevent opioid withdrawal in patients enrolled in methadone maintenance programs. Methadone is now also used in the management of severe pain in patients with cancer or non-cancer-related chronic pain. Methadone's long half-life of approximately 24 hours (range, 8–59 hours) makes it suitable for once-daily dosing and ideal for the prevention of opioid withdrawal65; that characteristic is also one of its major toxicological drawbacks, since methadone toxicity, especially a decreased level of consciousness and respiratory depression, may be prolonged considerably. Therefore, a naloxone infusion is often necessary to prevent the recurrence of respiratory depression.66 Opioid-addicted individuals who rely on or abuse methadone often use multiple pharmaceuticals that produce synergistic toxicity and increased morbidity and mortality.67-69 This is especially true when methadone users take benzodiazepines concurrently.68-70 Methadone, like all opioids, may cause airway musculature relaxation and resultant airway obstruction and sleep apnea. Benzodiazepines contribute to death by exacerbating the adverse effects of methadone. Researchers who evaluated 1193 opioid overdoses that occurred in one Australian state over a 10-year period reported that nearly



63.7% of methadone-related fatalities (n = 193) were complicated by the concurrent presence (and likely the abuse) of benzodiazepines.⁶⁸ Another often overlooked adverse event that is associated with both methadone maintenance use and overdose is Q-T interval prolongation, which increases the risk of developing ventricular dysrhythmias, including torsades de pointes.⁷⁰⁻⁷³

Oxycodone. Oxycodone is a potent semisynthetic opioid and, like other potent opioids, has a high affinity for the μ receptors. It has been used commonly in combination with both aspirin and acetaminophen. However, when oxycodone was introduced in 1995 as a single-entity sustained-release preparation, its use became widespread and its abuse became epidemic.74 Abusers ingested, injected, and nasally insufflated the product, since crushing and snorting the drug resulted in its rapid release and high blood concentrations. The sustained-release product has been reformulated to reduce the abuse potential.75 Similar to methadone, oxycodone is often abused concurrently with benzodiazepines such as alprazolam and other psychoactive drugs that enhance toxicity.76,77 Especially in overdose, oxycodone is associated with an increased risk of Q-T interval prolongation.78,79

Diagnosis and treatment

Respiratory depression is the result of opioid toxicity, and supportive care to restore ventilation and oxygenation is the cornerstone of patient management. The conventional management of respiratory depression in most poisoned patients is to perform endotracheal intubation and provide ventilatory support. In contrast, respiratory depression in the patient with opioid toxicity can be treated with the competitive µ-opioid receptor antagonist naloxone.42 Unless the patient has a traumatic brain injury, has prolonged hypoxia, or has used an additional substance or substances that produce

central nervous system or respiratory depression, naloxone will reverse the adverse effects of opioids. Therefore, intubation is unnecessary in most patients experiencing opioid intoxication. Naloxone is generally administered intravenously. Opioid-dependent individuals who abuse substances intravenously may have inadequate vascular access; naloxone is effective via any parenteral route (intramuscular, subcutaneous, or sublingual), through an endotracheal tube, intranasally, or by nebulization.^{42,80-84}

While naloxone can rapidly reverse the symptoms of opioid toxicity, its administration can precipitate acute opioid withdrawal. Opioid withdrawal is unlikely to be lifethreatening. However, it is extremely uncomfortable for the patient, who may become agitated and combative. In the emergency department setting, naloxone should be administered intravenously at the smallest effective dose and then adjusted accordingly to reverse respiratory depression. The initial adult i.v. dose is 0.04 mg and can be followed (if necessary) by progressively larger doses every 2-3 minutes until opioid toxicity is reversed^{42,85}; some clinicians advocate adjusting the dose by 0.04-mg increments to prevent withdrawal.85 The half-life of naloxone is approximately 30 minutes, whereas the half-life of most opioids exceeds that notably, necessitating the continued administration of naloxone to prevent recurrent respiratory depression; this is often accomplished through the use of a naloxone infusion. Patients who receive naloxone must not be discharged until several hours have passed since the last naloxone dose in order to ensure that opioid toxicity is no longer a risk. In the prehospital setting, it may be difficult for emergency medical providers and companions of opioid users to administer naloxone parenterally. The administration of intranasal naloxone has been determined to be as effective as parenteral

administration, and this intervention has been implemented in many cities worldwide.81-84 Additionally, in early 2014 FDA approved a naloxone delivery system that enables subcutaneous or intramuscular naloxone administration by individuals who are not health professionals.⁸⁶ The apparatus is technically similar to the automatic defibrillators that are located in public venues. When activated, it provides the person who is administering the naloxone with verbal instructions on the use of the drug. The device delivers 0.4 mg of naloxone per dose.

Opioids may be taken by any route (e.g., orally, intravenously, via nasal insufflation); therefore, gastrointestinal decontamination may not be indicated or effective. If the opioid was ingested, the only gastrointestinal decontamination that may be effective is the administration of an aqueous slurry of activated charcoal within two hours of the ingestion87; gastric lavage, emesis, and cathartics have no role in these cases. The clinician must recognize that coingestants (e.g., acetaminophen) or illicit drugs (e.g., cocaine) may have been used and that the patient may require additional treatment to prevent or reverse the effects of these agents.

With some overdoses, such as those involving acetaminophen, laboratory testing is diagnostic and determines the appropriate therapeutic interventions (e.g., acetylcysteine administration). However, laboratory testing has limited value in the treatment of the patient with opioid toxicity.88 Most initial laboratory toxicology screens focus on analyzing a urine specimen, which provides only qualitative evidence of exposure to opioids with a phenanthrene ring (e.g., morphine). The semisynthetic (e.g., hydrocodone) and synthetic (e.g., fentanyl) opioids may be detected only at higher concentrations (as with hydrocodone) or not at all (as with fentanyl) with the conventional assays that are utilized by most hospitals.88 In a patient with

respiratory depression, waiting for the results of a laboratory test delays the use of appropriate therapy. The patient history and the clinical presentation are the best indicators that the patient is experiencing opioid toxicity and requires treatment.

Legal implications

As a result of the increases in opioid-related deaths, over the last two years the Drug Enforcement Administration (DEA) has become much more aggressive in its enforcement of the Controlled Substances Act (CSA) with respect to prescription drug wholesalers, physicians, pharmacists, and pharmacies that distribute, prescribe, and dispense controlled substances. Historically, DEA focused its enforcement actions on independent community pharmacies more than retail chain or hospital pharmacies, but in 2012 that focus expanded to include legal actions against large chain pharmacies, long-term care pharmacies, and prescription drug wholesalers.

A brief review of some of the prosecutions undertaken by DEA and a state government in 2012 and 2013, as well as the resulting court actions (summarized in news releases available from the U.S. Department of Justice website [www.justice.gov/dea/ pr/news.shtml]), is illustrative of the current practice environment:

- 1. DEA issued an immediate suspension order on a wholesaler's distribution facility. DEA alleged that the wholesaler endangered the public health by selling excessive quantities of oxycodone to certain pharmacies in Florida. This was one of the first times DEA argued that a drug wholesaler had a responsibility for the actions of its customers. This action was settled with the wholesaler agreeing to not sell any controlled substances from its Florida facility until May 2014, establish a customer monitoring program, and report suspicious orders to DEA.
- 2. DEA suspended the controlled substance registrations of two retail

chain pharmacies in central Florida, alleging that the pharmacies had improperly sold massive quantities of oxycodone. Although the parent corporation argued that the pharmacies had adopted new policies to verify the legitimacy of prescriptions for such drugs, DEA revoked the registrations in October 2012.

- 3. A national long-term care pharmacy agreed to pay \$50 million to resolve claims that its facilities dispensed controlled substances improperly. Two of the allegations against the longterm care pharmacy were that some prescriptions did not contain all the items required by CSA regulations (21 C.F.R. 1306.14 and 1306.24) and that the pharmacy had not properly documented partially filled prescriptions. The DEA administrator was quoted as saying, "This case highlights the responsibilities of pharmacists, doctors and others when prescribing and dispensing controlled substances."
- 4. The attorney general of West Virginia filed legal actions against over a dozen drug wholesalers, alleging that the distributors failed to properly assure that orders for controlled substances were for legitimate quantities, thereby contributing to the drug abuse problems in West Virginia.
- 5. DEA took separate actions against at least six Florida chain pharmacies and issued an immediate suspension of registration against the chain's wholesale distribution center. The agency alleged that the pharmacies did not keep adequate records and filled prescriptions that were not issued for a legitimate medical use. These cases and others pending in additional states were resolved when the pharmacy chain agreed to pay \$80 million-the largest settlement in DEA history-and to the suspension of dispensing privileges in some stores until 2015.

Health-system pharmacists are subject to the same level of DEA scrutiny as retail pharmacists and have similar responsibilities in relation to controlled substances. Numerous health systems operate outpatient and retail pharmacies, and hospitals have risks associated with employee theft, loss or destruction of controlled substances, recordkeeping issues, and documentation of a legitimate medical need for the use of opioids.

The diversion of opioids and other controlled substances from hospital pharmacies may result from improper actions by employees.89 Hospitals, like many other employers, are subject to the risk that some employees will steal merchandise. In addition, hospital pharmacies are at risk for diversion related to the use of prefilled syringes or single-use vials of controlled substances when the prescriber orders a dose that is less than the total contents of the syringe or vial. If the syringe or vial contains 100 mg of an opioid but the prescribed dose is 75 mg, the disposal of the remaining 25 mg can become a diversion risk. As an example, a nurse could carry an empty sterile vial in a pocket and, instead of destroying the excess drug, inject it into the vial; this pattern could be repeated several times throughout the shift, and by the time the nurse left the hospital at the end of the day, he could have diverted a substantial quantity of a controlled substance that was extremely difficult to trace. In this case, the hospital could not identify or demonstrate a shortage from the patient records. A director of pharmacy must be vigilant to these risks and establish and consistently apply policies and procedures that will minimize the risk of employee theft or diversion of controlled substances.

The final area for legal consideration is the actual use of controlled substances in the health-system environment for inpatients and outpatients. Health-system pharmacists must be familiar with DEA regulations controlling the use of opioids in the inpatient setting. Hospitals have the same legal duty as retail pharmacies to ensure that controlled substances are ordered for a legitimate medical purpose. The definition of legitimacy is subject to change, however, as evidenced by the September 2013 change in the FDA labeling standards for long-acting and extended-release opioid analgesics.⁹⁰ The new labeling indicates that these drugs should only be used for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate.

This issue of appropriate opioid therapy may appear to be less of a problem in the hospital environment than in the retail sector, but healthsystem pharmacists must remain vigilant for questionable orders or prescriptions. As individuals who abuse drugs find it more difficult to obtain opioids from retail pharmacies, they may turn to emergency departments and outpatient pharmacies to obtain these medications. Further, health-system pharmacists must also remember that all orders, prescriptions, and prescription labels must be complete and accurate, as mandated by DEA regulations. Policies should be in place to ensure that these record-keeping requirements are met.

In addition to ensuring that opioids are being ordered for a legitimate medical purpose and that proper record-keeping and labeling procedures are followed, healthsystem pharmacists must understand the restrictions on using opioids for maintenance or detoxification of patients who are drug addicted. The basic rule is that only an opioid treatment program registered with DEA is permitted to use an opioid drug to maintain or detoxify an opioid-addicted individual; the one exception is if a buprenorphine product is ordered by a specially certified prescriber. However, there is a critical exception in the DEA regulations pertaining to hospitalized patients: Provisions of 21 C.F.R., section 1306.07(c), stipulate that the hospital staff is permitted to provide opioid maintenance or detoxification

therapy to a patient as an incidental adjunct to medical or surgical treatment of conditions other than addiction, thereby allowing a hospitalized addicted person to avoid the risk of withdrawal while being treated for some other condition. It is even possible to withdraw the patient from the opioid addiction if the withdrawal is accomplished during legitimate treatment for some other medical or surgical condition. The other important exception found in section 1306.07(c) is that hospital staff may administer or dispense opioids to an addicted patient with intractable pain for whom no relief or cure is possible or none has been found after reasonable efforts. As an example, this provision protects health-system pharmacists treating a patient with cancer (as either an inpatient or an outpatient) who has become addicted to opioids.

Prescription drug monitoring programs

Prescription drug monitoring programs (PDMPs) are electronic databases created and overseen at the state level to collect data on opioids and other controlled substances as well as noncontrolled drugs with potential for abuse. PDMPs are currently active in 47 states.⁹¹ New Hampshire and Maryland are in the process of implementing systems, and the District of Columbia has pending legislation. Missouri is the only state without a PDMP and no pending legislation. The goals of individual PDMPs vary from state to state, but in general these programs are designed to (1) monitor prescribing and dispensing to individual patients, thereby providing treatment history information to the health professionals responsible for a patient's care, (2) provide information to parties, including law enforcement, for the identification and deterrence of prescription drug abuse and diversion, (3) provide information to practitioners and third parties for the identification of individuals at risk for addiction to a controlled substance, and (4) provide information to researchers and public health officials for identification of druguse trends and public health needs.⁹²

Because PDMP laws flow from state legislatures and the rules and regulations are determined by the executive body identified in each state's statutes, each state has determined its own laws, regulations, rules for implementation, and program structure. There is state-to-state variation in terms of which agency houses the program (e.g., department of public health, office of attorney general, board of pharmacy), which controlled substances are monitored (e.g., Schedule II only, Schedules II-V, other drugs), how often pharmacy reporting is required (e.g., weekly, biweekly, monthly), and who can query the database (e.g., prescribers, pharmacists, law enforcement).93 Another key factor differing among states is whether the system is proactive or reactive. In proactive systems, information is delivered to prescribers or dispensers when certain prescribing or dispensing thresholds are met by a patient under their care. Reactive systems query available information, but the system is utilized only at the discretion of the prescriber or dispenser.93 Finally, states differ in requirements for prescribers or pharmacists to utilize the PDMP. Currently, 16 states require mandatory PDMP use when various conditions are met before certain controlled substances can be prescribed.93

The effectiveness of PDMPs in accomplishing the goals listed above has not been investigated thoroughly. Research that has been conducted in this field has generally examined either the effect programs have on opioid-related outcomes (e.g., hospital admissions, mortality) or the ability of the program to influence behaviors associated with abuse and misuse of opioids.

There are conflicting findings regarding the ability of PDMPs to

reduce mortality related to opioid abuse. A 2011 study of opioid overdose deaths in 19 states found that PDMP status was not associated with decreased drug overdose or opioidrelated mortality.94 However, new data from the RADARS (Researched Abuse, Diversion and Addiction-Related Surveillance) System's Poison Center Program and Opioid Treatment Program surveillance databases show an association between the presence of a PDMP and a decrease in the number of poison center interventions as well as a decrease in admissions for opioid overdose.95 One weakness in this area of research thus far has been the treatment of PDMP presence as a dichotomous variable. Because of the varying structures of these programs, their effectiveness is likely to vary from state to state; this is especially true when comparing reactive and proactive programs.

While the effectiveness of PDMPs at reducing poor outcomes associated with opioids has not been shown definitively, the ability of these programs to influence the behavior of prescribers, pharmacists, and patients is well established. Studies using survey methods have shown that providers who utilize PDMP reports are likely to change their prescribing practices in response to the new information. These studies have taken place in a variety of settings (e.g., primary care,⁹⁶ emergency department,⁹⁷ substance abuse treatment programs98) and in several distinct geographic locations.⁹⁹⁻¹⁰¹ While studies of pharmacists are more limited, pharmacists' attitudes toward PDMPs have been positive, with their primary use of the programs being to help reduce doctor shopping.¹⁰² One of the most straightforward uses of PDMPs is altering this aberrant patient behavior by providing a coordinated and convenient source of controlled substance use information to prescribers, pharmacists, and law enforcement. One study showed that PDMP implementation reduced the time necessary to conduct investigations into possible doctor shopping from 156 to 16 days.¹⁰¹

CDC and the Office of National Drug Control Policy have identified PDMPs as important strategies in the response to the opioid abuse and misuse epidemic.¹⁰³ The continued expansion of PDMPs to cover all 50 states and the District of Columbia is a good first step in implementing this strategy; however, looking beyond this, the National Alliance for Model State Drug Laws and the National Safety Council have recommended PDMP best practices for states to consider.¹⁰⁴ Interstate data sharing, the expansion of authorized users (including allowing delegate access), and the determination of compulsory-use requirements by professional licensing boards are key components of these recommendations.¹⁰⁴ As the expansion of PDMPs across the nation continues, utilization of the growing body of evidence relating to these programs to identify and implement program improvements will be important. Implementing evidence-based policy changes to increase PDMP effectiveness at achieving the various program goals described above will ensure greater utility for all stakeholders in the future.

Implications for medication-use policy in health systems

Opioids are included on the Institute for Safe Medication Practices list of high-alert medications (i.e., agents associated with a high risk of patient harm when used inappropriately) and require heightened oversight in hospitals and health systems.¹⁰⁵ Institutional policies, beyond federal and state legal requirements, further direct appropriate use and monitoring of opioids and promote standardized practices to prevent and identify diversion. Clinical policies can address appropriate treatment of severe pain with opioid medications, which requires ongoing assessment and reassessment of analgesia, activities of daily living, adverse effects, and aberrant behavior along with appropriate documentation. Operational policies outline procedures to ensure proper control and accountability and prevent diversion.

Consistent practice for appropriate screening, assessment, and prescribing for pain can be directed through computerized prescriber order entry (CPOE), clinical decision support (CDS), pharmacy and therapeutics committee-approved guidelines, and formulary restrictions. Printed or computerized order sets should include best practices and standardize prescribing of appropriate doses, patient-controlled analgesia, epidural opioid infusions, procedure-specific dosing protocols, and monitoring. Discharge and ambulatory care order sets or protocols can be utilized to ensure consistent discharge analgesia regimens and minimize the amount of opioid dispensed after routine outpatient procedures or minor surgeries. If the prescriber concludes that opioids are required, a standard minimal number of doses for each procedure can be designated (e.g., 5-10 doses) instead of an ample supply to cover any and all pain. By minimizing the amounts of opioids that are prescribed routinely but are not used by patients, the amounts of opioids available in the community for misuse and abuse can be reduced.

Prescribers can receive additional direction through best-practice alerts or red flags built into CPOE and CDS systems regarding dose limits and the risks of respiratory depression or misuse. Safe prescribing through formulary restrictions and guidelines further minimizes risk and liability from high-harm opioids such as meperidine and codeine. Due to the risk of neurotoxicity, meperidine is not recommended for pain treatment and should be removed from the formulary or restricted to treatment of rigors.^{106,107} Codeine use should also be limited due to the drug's unpredictable analgesia arising from a genetic polymorphism and a recent FDA boxed warning on its use

in children after tonsillectomy or adenoidectomy.^{108,109}

Some emergency departments restrict the prescribing of opioids by limiting quantities to a small amount for the short-term treatment of acute pain and restricting treatment of patients with chronic pain.110,111 In some emergency departments, patients with chronic pain are treated with nonopioid analgesics and then referred for follow-up care. In conjunction with these policies, emergency physicians do not replace lost or stolen opioids, and signage in the emergency department delineates the policy clearly. These policies and practices are most effective if coordinated within a geographic area.

Management of opioid-dependent chronic pain can be challenging due to common comorbidities of depression, anxiety, and addiction.^{112,113} Development of institutional guidelines or protocols can provide a consistent and safe method of initiating and monitoring therapy for these patients.^{114,115} Along with a thorough history and physical examination, chronic pain management plans should include universal screening for illicit drug use and addictive disorders prior to initiation of treatment. One exception is the patient with limited life expectancy. Screening may include the urine drug screen, review of public records for prior convictions, and evaluation of state PDMPs. Similarly, as discussed in Appendix B, a pain management agreement plan (PMAP), or "opioid contract," should be constructed for most patients. The intent of the PMAP is to provide full disclosure of the risks and benefits of opioid therapy and institutional policies with regard to ongoing regular pain assessment, random urine drug screening, and the use of a single opioid prescriber group and pharmacy. In addition, the PMAP addresses consequences of missed appointments, aberrancies in urine drug tests, and illegal actions related to substance abuse. Violation of a PMAP may require

the placement of limits on a patient's opioid supply, more frequent clinic appointments and urine drug screening, selection of therapy with a lower street value, or referral to a substance abuse specialist. In addition to these measures, some facilities require more frequent monitoring and documentation of therapeutic benefit for patients receiving opioid doses over a target threshold (e.g., greater than 120 mg of oral morphine equivalents per day) to identify potentially inappropriate use and minimize harmful consequences associated with high opioid doses.¹¹⁶

The pharmacist's role in opioid therapy and developing guidelines, policies, and patient education to promote safe practices is paramount in both the inpatient and ambulatory care settings.117 In addition to their important legal responsibilities to ensure appropriate prescribing and dispensing, ambulatory care pharmacists should further define organizational practices for consistent dispensing of opioids. For example, pharmacies could require a check of the state PDMP prior to the dispensing of opioids to new or unfamiliar patients, especially those residing a long distance from the pharmacy, along with a government-issued identification for picking up opioid prescriptions. Other standards might include criteria for contacting prescribers and law enforcement officials regarding potentially forged or altered prescriptions, frequent requests for early prescription refills, and unusual patient behavior. A standard documentation process for the steps required for prescription validation should be implemented as well. Despite their best efforts to identify inappropriate prescriptions, pharmacists may face the challenge of opioid prescriptions written by valid prescribers for large quantities of opioids with questionable indications (sometimes referred to as "pill-mill" operations) but with insufficient information to validate a patient-prescriber relationship. One pharmacy chain limited the dispensing of inappropriate prescriptions by identifying prescribers writing for larger quantities of high-risk medications more frequently than others within the same specialty and geographic area.¹¹⁸ Pharmacists from these facilities stopped filling prescriptions if the prescribers were unable or unwilling to justify their practice of prescribing high volumes of high-risk medications. As discussed above, the absence of these types of measures can place healthsystem pharmacies and pharmacists in legal jeopardy.

Education of healthcare staff, as well as patients, on appropriate treatment of pain, including nondrug and nonopioid therapy, and the risk of opioid diversion is recommended to minimize opioid abuse.^{116,117} Pharmacists can be instrumental in developing educational content for their institution, patients, and the public. Medication counseling during dispensing provides the perfect opportunity to counsel patients to lock up opioids, never share medications with others, and appropriately dispose of unused medications.

Prevention of opioid diversion within the healthcare system occurs through implementation of comprehensive policies accounting for opioids from the point of ordering to administration to the patient.¹¹⁹

The numbers of personnel responsible for ordering, receiving, and taking inventory of controlled substances should be limited, and those responsibilities should be rotated. Preemployment criminal background checks and urine drug screening should be considered for employees with these direct responsibilities. Technology and automated dispensing devices further facilitate tracking and documentation of opioids and generate utilization reports. One vulnerable step in the process is opioid waste disposal.¹²⁰ A "second-witness" policy (i.e., a requirement that not just one but two coworkers be present during the disposal of drug waste), with appropriate documentation,

should be required for all instances of waste disposal at the point of patient care as well as in the pharmacy. Also, pharmacy policy must reinforce actual witnessing, as opposed to "virtual witnessing," which occurs when a coworker attests to but does not actually visualize the disposal of waste. Reconciliation of the number of opioid medication doses administered in the operating room with the amount disposed as waste is one method of oversight to prevent the diversion of anesthesia agents. Routine surveillance along with timely and thorough investigation of diversion reports is also required. Random audits by independent personnel not responsible for opioid tracking or documenting opioid use should be conducted to help ensure appropriate ordering, stocking, dispensing, disposal, and returns of controlled substances. All staff can conduct informal surveillance if educated on the risk of diversion and provided a means of anonymous reporting.¹²⁰ Any report on questionable behavior or discrepancies must be investigated fully. Some institutions utilize a formal controlled substance diversion team consisting of experts from multiple disciplines to further investigate aberrancies.120

Despite the web of policy for prescribing, dispensing, and tracking opioids throughout a facility, addicts and those diverting opioids for financial profit are innovative and willing to take risks. Policies, procedures, and guidelines require ongoing review and updating. Healthcare practitioners must be vigilant and collaborate to ensure appropriate treatment of pain while minimizing misuse and abuse.

Opioid misuse and abuse have reached epidemic proportions in the United States, and there has been an increase in associated morbidity and mortality. Pharmacists in hospitals and health systems must play a key leadership role in preventing diversion and inappropriate prescribing and dispensing of opioids. In order to most effectively develop health system-based medication-use policies that aim at reducing the misuse and abuse of opioids, it is imperative that health-system pharmacists understand the appropriate role of opioids in the treatment of pain, the epidemiology of the opioid abuse epidemic and the clinical toxicology of these agents, legal implications for individual pharmacists and departments of pharmacy, and state-level monitoring programs that can be incorporated into prescribing, dispensing, and monitoring processes.

Conclusion

Pharmacists in hospitals and health systems can play a key role in recognizing the various forms of opioid toxicity and in preventing inappropriate prescribing and diversion of opioids.

References

- Centers for Disease Control and Prevention. CDC's top ten: 5 health achievements in 2013 and 5 health threats in 2014 (December 17, 2013). http://blogs. cdc.gov/cdcworksforyou24-7/2013/12/ cdc%e2%80%99s-top-ten-5-healthachievements-in-2013-and-5-healththreats-in-2014/ (accessed 2014 Feb 10).
- Trescot A, Glaser SE, Hansen H et al. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician*. 2008; 11:S181-200.
- Carr DB, Jacox AK, Chapman DR et al. Acute pain management: operative or medical procedures and trauma. Clinical practice guideline no. 1. Rockville, MD: Agency for Health Care Policy and Research; 1992 Feb. AHCPR publication no. 92-0032.
- Jacox A, Carr DB, Payne R et al. Management of cancer pain. Clinical practice guideline no. 9. Rockville, MD: Agency for Health Care Policy and Research; 1994 Mar. AHCPR publication no. 94-0592.
- Miaskowski Č, Cleary J, Burney R et al. Guideline for the management of cancer pain in adults and children. APS clinical practice guidelines series, no. 3. Glenview, IL: American Pain Society; 2005.
- American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. 6th ed. Glenview, IL: American Pain Society; 2008:2.
- Chou R, Fanciullo GJ, Fine PG et al., for the American Pain Society–American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy

in chronic noncancer pain (February 2009). www.jpain.org/article/S1526-5900(08)00831-6/abstract (accessed 2013 Oct 18).

- Bromley L. Pre-emptive analgesia and protective premedication. What is the difference? *Biomed Pharmacother*. 2006; 60:336-40.
- 9. Dahl JB, Møiniche S. Pre-emptive analgesia. *Br Med Bull*. 2004; 71:13-27.
- Grape S, Tramer MR. Do we need preemptive analgesia for the treatment of postoperative pain? *Best Pract Res Clin Anaesthesiol.* 2007; 21:51-63.
- Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. *Can J Anaesth.* 2001; 48:1091-101.
- Møiniche S, Kehlet J, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. *Anesthesiology*. 2002; 96:725-41.
- Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol*. 2009; 22:588-93.
- Ritchey RM. Optimizing postoperative pain management. *Cleve Clin J Med.* 2006; 73:S72-6.
- 15. Food and Drug Administration. FDA drug safety communication: safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy (February 20, 2013). www.fda.gov/Drugs/Drug-Safety/ucm339112.htm (accessed 2013 Oct 29).
- 16. Food and Drug Administration. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. www.fda. gov/downloads/Drugs/DrugSafety/ UCM339116.pdf (accessed 2013 Nov 7).
- 17. Roe BB. Are postoperative narcotics necessary? *Arch Surg.* 1963; 87:912-5.
- Sechzer PH. Studies in pain with the analgesic-demand system. *Anesth Analg.* 1971; 50:1-10.
- Bujedo BM. A clinical approach to neuraxial morphine for the treatment of postoperative pain. *Pain Res Treat*. 2012; 2012:612145.
- Bourne N. Managing acute pain in opioid tolerant patients. J Perioper Pract. 2008; 18:498-503.
- Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med.* 2006; 144:127-34.
- 22. McPherson ML. Demystifying opioid conversion calculations: a guide for effective dosing. Bethesda, MD: American Society of Health-System Pharmacists; 2010.
- Colson J, Koyyalagunta D, Falco FJ et al. A systematic review of observational studies on the effectiveness of opioid therapy for cancer pain. *Pain Physician*. 2011; 14:E85-102.

- 24. Trescot AM, Datta S, Lee M et al. Opioid pharmacology. *Pain Physician*. 2008; 11(suppl 2):S133-53.
- Berland D, Rodgers P. Rational use of opioids for management of chronic nonterminal pain. *Am Fam Physician*. 2012; 86:252-8.
- Utah Department of Health. Utah clinical guidelines on prescribing opioids for treatment of pain, 2009. http://health. utah.gov/prescription/guidelines.html (accessed 2013 Oct 18).
- Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009; 10:113-30.
- Kwong TC, Dasgupta A, Magnani BJ. Drug screening by immunoassays. In: Kwong TC, Magnani BJ, Rosano T, Shaw L, eds. The clinical toxicology laboratory: contemporary practice of poisoning evaluations. 2nd ed. Washington, DC: AACC Press; 2013:411-22.
- 29. Huestis MA, Verstraete A, Kwong TC et al. Oral fluid testing: promises and pit-falls. *Clin Chem.* 2012; 57:805-10.
- 30. Kwong TC, Magnani BJ. Urine drug testing in opioid therapy for chronic pain management. In: Kwong TC, Magnani BJ, Rosano T, Shaw L, eds. The clinical toxicology laboratory: contemporary practice of poisoning evaluations. 2nd ed. Washington, DC: AACC Press; 2013:447-58.
- Hammett-Stabler CA, Magnani BJ. Supporting the pain service. In: Magnani BJ, Bissell M, Kwong TC, Wu AH, eds. Clinical toxicology testing: a guide for laboratory professionals. Northfield, IL: College of American Pathologists; 2012:15-26.
- Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. *Clin Pharmacol Ther*. 2007; 81:429-44.
- Cone EJ, Caplan YH, Moser F et al. Evidence that morphine is metabolized to hydromorphone but not to oxymorphone. J Analyt Tox. 2008; 319-23.
- West R, Crews B, Almazan P et al. Anomalous observations of hydrocodone in patients on oxycodone. *Clin Chim Acta*. 2011; 412:29-32.
- West R, Crews B, Mikel C et al. Anomalous observations of codeine in patients on morphine. *Ther Drug Monit.* 2009; 31:776-8.
- Centers for Disease Control and Prevention. Overdose deaths involving prescription opioids among Medicaid enrollees—Washington, 2004–2007. MMWR. 2009; 58:1171-5.
- Budnitz DS, Pollock DA, Weidenbach KN et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006; 296:1858-66.
- Centers for Disease Control and Prevention. Emergency department visits involving nonmedical use of selected prescription drugs—United States, 2004–2008. MMWR. 2010; 59:705-9.
- 39. Centers for Disease Control and Prevention. Vital signs: overdoses of

prescription opioid pain relievers— United States, 1999–2008. *MMWR*. 2011; 60:1487-92.

- Hall AJ, Logan JE, Toblin RL et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008; 300:2613-20.
- Centers for Disease Control and Prevention. Drug overdose deaths— Florida, 2003–2009. MMWR. 2011; 60:869-72.
- 42. Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012; 367:146-55.
- Glick C, Evans OB, Parks BR. Muscle rigidity due to fentanyl infusion in the pediatric patient. *South Med J.* 1996; 89:1119-20.
- Goetting MG, Thirman MJ. Neurotoxicity of meperidine. Ann Emerg Med. 1985; 14:1007-9.
- Murphy DB, Sutton JA, Prescott LF et al. Opioid-induced delay in gastric emptying. *Anesthesiology*. 1997; 87:765-70.
- Hoffman JR, Schriger DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med.* 1991; 20:246-52.
- Manini AF, Jacobs MM, Vlahov D et al. Opioid receptor polymorphism A118G associated with clinical severity in a drug overdose population. *J Med Toxicol.* 2013; 9:148-54.
- 48. Pedapati EV, Bateman ST. Toddlers requiring pediatric intensive care unit admission following at-home exposure to buprenorphine/naloxone. *Pediatr Crit Care Med.* 2011; 12:e102-7.
- Lavonas EJ, Banner W, Bradt P et al. Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children. *J Pediatr.* 2013; 163:1377-83.
- Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict*. 2010; 19:89-95.
- 51. Soyka M. Buprenorphine and buprenorphine/naloxone intoxication in children—how strong is the risk. *Curr Drug Abuse Rev.* 2013; 6:63-70.
- 52. Bailey JE, Campagna E, Dart RC et al. The underrecognized toll of prescription opioid abuse on young children. *Ann Emerg Med.* 2009; 53:419-24.
- 53. Fentanyl mechanism of action and pharmacokinetics [monograph]. In: Micromedex, version 2.0 [online database]. Greenwood Village, CO: Truven Health Analytics; 2013 (accessed 2013 Nov 14).
- 54. Mrvos R, Feuchter AC, Katz KD et al. Whole fentanyl patch ingestion: a multicenter case series. *J Emerg Med.* 2012; 42:549-52.
- Woodall KL, Martin TL, McLellan BA. Oral abuse of fentanyl patches (Duragesic): seven case reports. *J Forensic Sci.* 2008; 53:222-5.
- Moon JM, Chun BJ. Fentanyl intoxication caused by abuse of transdermal fentanyl. J Emerg Med. 2011; 40:37-40.
- 57. D'Orazio JL, Fischel JA. Recurrent respiratory depression associated with

fentanyl transdermal patch gel reservoir ingestion. *J Emerg Med.* 2012; 42:543-8.

- Lyttle MD, Verma S, Isaac R. Transdermal fentanyl in deliberate overdose in pediatrics. *Pediatr Emerg Care*. 2012; 28:463-4.
- 59. Sindali K, Sherry K, Sen S et al. Lifethreatening coma and full-thickness sunburn in a patient treated with transdermal fentanyl patches: a case report. *J Med Case Rep.* 2012; 6:220.
- 60. Singla A, Sloan P. Pharmacokinetic evaluation of hydrocodone/acetaminophen for pain management. *J Opioid Manag.* 2013; 9:71-80.
- 61. Stoops WW, Hatton KW, Lofwall MR et al. Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. *Psychopharmacol.* 2010; 212:193-203.
- 62. Food and Drug Administration. FDA approves extended-release, single-entity hydrocodone product (October 25, 2013). www.fda.gov/newsevents/newsroom/pressannouncements/ucm372287.htm (accessed 2014 Jun 4).
- 63. Doyon S, Klein-Schwartz W, Lee S et al. Fatalities involving acetaminophen combination products reported to United States poison centers. *Clin Toxicol.* 2013; 51:941-8.
- 64. Krenzelok EP. Repeated supratherapeutic acetaminophen (paracetamol) use resulting in a fatality. *Ther Pharmacol Clin Toxicol*. 2011; 15:156-9.
- Methadone hydrochloride [monograph]. In: AHFS DI Essentials [online database]. Hudson, OH: Lexi-Comp; 2013 (accessed 2013 Nov 14).
- 66. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emerg Med J.* 2005; 22:612-6.
- Lee S, Klein-Schwartz W, Welsh C et al. Medical outcomes associated with nonmedical use of methadone and buprenorphine. *J Emerg Med.* 2013; 45:199-205.
- Darke S, Dufluo J, Torok M. The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. *Drug Alcohol Depend*. 2010; 106:1-6.
- 69. Caplehorn JR, Drummer OH. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. *Aust N Z J Public Health*. 2002; 26:358-62, discussion 362-3.
- Fareed A, Vayalapalli S, Scheinberg K et al. QTc interval prolongation for patients in methadone maintenance treatment: a five years follow-up study. *Am J Drug Alcohol Abuse*. 2013; 39:235-40.
- Al Sardar H. Methadone-associated QT prolongation and torsades de pointes. Br J Hosp Med (Lond). 2007; 68:221. Comment (author reply, 221).
- Abramson DW, Quinn DK, Stern TA. Methadone-associated QTc prolongation: a case report and review of the literature. Prim Care Companion J Clin Psychiatry. 2008; 10:470-6.

- SPECIAL FEATURE Opioid abuse and misuse
- 73. Bateman DN. Opioids. *Medicine*. 2011; 40:141-3.
- Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2001– 2004. J Pain. 2005; 6:662-72.
- 75. Aquina CT, Marques-Baptista A, Bridgman P et al. Oxycontin abuse and overdose. *Postgrad Med.* 2009; 121(2):163-7.
- Wolf BC, Lavezzi WA, Sullivan LM et al. One hundred seventy two deaths involving the use of oxycodone in Palm Beach County. *J Forensic Sci.* 2005; 50:192-5.
- Darke S, Duflou J, Torok M. Toxicology and characteristics of fatal oxycodone toxicity cases in New South Wales, Australia 1999–2008. J Forensic Sci. 2011; 56:690-3.
- Fanoe S, Jensen GB, Sjogren P et al. Oxycodone is associated with dosedependent QTc prolongation in patients and low-affinity inhibiting of jERG activity in vitro. *Br J Clin Pharmacol.* 2009; 67:172-9.
- Berling I, Whyte IM, Isbister GK. Oxycodone overdose causes naloxone responsive coma and QT prolongation. *QJM*. 2013; 106:35-41.
- Bauman BM, Patterson RA, Parone DA et al. Use and efficacy of nebulized naloxone in patients with suspected opioid intoxication. *Am J Emerg Med.* 2013; 31:585-8.
- Robertson TM, Hendey GW, Stroh G et al. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care*. 2009; 13:512-5.
- Merlin MA, Saybolt M, Kapitanyan R et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *Am J Emerg Med.* 2010; 28:296-303.
- Doe-Simkins M, Walley AY, Epstein A et al. Saved by the nose: bystanderadministered intranasal naloxone hydrochloride for opioid overdose. *Am J Public Health.* 2009; 99:788-91.
- 84. Walley AY, Xuan Z, Hackmanb HH et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *Br Med J.* 2013; 346:f174.
- Kim HK, Nelson LS. Effectiveness of low dose naloxone to reverse respiratory depression in opioid intoxication. *Clin Toxicol.* 2012; 50:577-8.
- 86. Food and Drug Administration. FDA approves new hand-held auto-injector to reverse opioid overdose (April 3, 2014). www.fda.gov/newsevents/newsroom/pressannouncements/ucm391465.htm (accessed 2014 Jul 17).
- Krenzelok EP, Vale JA. Position paper: single-dose activated charcoal. *Clin Toxicol*. 2005; 43:61-87.
- Milone MC. Laboratory testing for prescription opioids. J Med Toxicol. 2012; 8:408-16.

- 89. Forgione DA, Neuenschwander P, Vermeer TE. Diversion of prescription drugs to the black market: what the states are doing to curb the tide. *J Health Care Finance*. 2001; 27:65-78.
- 90. Food and Drug Administration. FDA announces safety labeling changes and postmarketing study requirements for extended-release and long-acting opioid analgesics (September 10, 2013). www.fda.gov/newsevents/newsroom/ pressannouncements/ucm367726.htm (accessed 2014 Jul 17).
- 91. National Alliance for Model State Drug Laws. Status of state prescription drug monitoring programs (July 2013). www. namsdl.org/library/13999269-1C23-D4F9-74EF032677373B17 (accessed 2013 Oct 31).
- National Alliance for Model State Drug Laws. Prescription drug monitoring programs: a brief overview (March 2011). www.namsdl.org/library/2C1D3D84-1372-636C-DD7AA3FC63B30DB9/ (accessed 2013 Oct 31).
- National Alliance for Model State Drug Laws. Status of state prescription drug monitoring programs (PDMPs). www.namsdl.org/library/1E4808C8-1372-636C-DD0293F829471A7E/ (accessed 2013 Oct 31).
- Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. *Pain Med.* 2011; 12:747-54.
- 95. Reifler LM, Droz D, Bailey JE et al. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Med.* 2012; 13:434-42.
- 96. Morgan L, Weaver M, Sayeed Z et al. The use of prescription monitoring programs to reduce opioid diversion and improve patient safety. *J Pain Palliat Care Pharmacother*. 2013; 27:4-9.
- Baehren DF, Marco CA, Droz DE et al. A state-wide prescription monitoring program affects emergency department prescribing behaviors. *Ann Emerg Med.* 2010; 56:19-23.
- 98. Prescription Drug Monitoring Program Center of Excellence. Keeping patients safe: a case study on using prescription monitoring program data in an outpatient addictions treatment setting (March 2011). www.pdmpexcellence.org/ sites/all/pdfs/methadone_treatment_ nff_%203_2_11.pdf (accessed 2013 Oct 31).
- 99. Prescription Drug Monitoring Program Center of Excellence. Prescription drug monitoring programs: an assessment of the evidence for best practices (September 20, 2012). www.pdmpexcellence. org/sites/all/pdfs/Brandeis_PDMP_ Report_final.pdf (accessed 2013 Oct 31).
- 100. Blumenschein K, Fink JL, Freeman PR et al., for the KASPER Evaluation Team. Independent evaluation of the impact and effectiveness of the Kentucky All Schedule Prescription Electronic Reporting Program (KASPER). http://chfs. ky.gov/NR/rdonlyres/2449 3B2E-B1A1-

4399-89AD-1625953BAD43/0/KASPER EvaluationFinalReport10152010.pdf (accessed 2013 Oct 31).

- 101. General Accounting Office. Prescription drugs: state monitoring programs may help to reduce illegal diversion. Testimony before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives (March 4, 2004). www.gao.gov/new.items/d04524t. pdf (accessed 2013 Oct 31).
- 102. Fass JA, Hardigan PC. Attitudes of Florida pharmacists toward implementing a state prescription drug monitoring program for controlled substances. J Manag Care Pharm. 2011; 17:430-8.
- 103. Trust for America's Health. Prescription drug abuse: strategies to stop the epidemic (October 7, 2013). http://healthyamericans.org/reports/drugabuse2013/ (accessed 2013 Oct 31).
- 104. National Alliance for Model State Drug Laws. Components of a strong prescription drug monitoring (PMP) program/ statute (revised June 2012). www. namsdl.org/library/85740FEB-19B9-E1C5-31AA3E9A59034388/ (accessed 2013 Oct 31).
- 105. Institute for Safe Medication Practices. ISMP's list of high-alert medications. www.ismp.org/Tools/institutional highAlert.asp (accessed 2013 Oct 25).
- 106. American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. 6th ed. Glenview, IL: American Pain Society; 2008:32.
- 107. Latta KS, Ginsberg B, Barkin RL. Meperidine: a critical review. *Am J Ther.* 2002; 9:53-68.
- 108. Gudin J. Opioid therapies and cytochrome p450 interactions. J Pain Symptom Manage. 2012; 44:S4-14.
- 109. Kelly LE, Rieder M, van den Anker J et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012; 129:e1343-7.
- 110. Albert S, Brason FW 2nd, Sanford CK et al. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Med.* 2011; 12(suppl 2):S77-85.
- 111. Community Care of North Carolina. www.communitycarenc.com/media/ related-downloads/pl-toolkit-eds.pdf (accessed 2013 Oct 21).
- 112. Wilsey BL, Fishman SM, Tsodikov A et al. Psychological comorbidities predicting prescription opioid abuse among patients in chronic pain presenting to the emergency department. *Pain Med.* 2008; 9:1107-17.
- 113. Wasan AD, Butler SF, Budman SH et al. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007; 23:307-15.
- 114. Edlund MJ, Martin BC, Fan MY et al. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP

study. Drug Alcohol Depend. 2010; 112:90-8.

- 115. Sullivan MD, Edlund MJ, Zhang L et al. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006; 166:2087-93.
- 116. Kirschner N, Ginsburg J, Snyder Sulmasy L, for the Health and Public Policy Committee of the American College of Physicians. Prescription drug abuse: executive summary of a policy position paper from the American College of Physicians. Ann Intern Med. 2014; 160:198-200.
- 117. Joint Commission. Sentinel event alert issue 49: safe use of opioids in hospitals (August 8, 2012). www.jointcommission. org/sea_issue_49/ (accessed 2013 Apr 13).
- Betses M, Brennan T. Abusive prescribing of controlled substances—a pharmacy view. N Engl J Med. 2013; 369:989-91.
- 119. Office of Diversion Control, Drug Enforcement Administration. An informational outline of the Controlled Substances Act (revised 2010). www. deadiversion.usdoj.gov/pubs/manuals/ pharm2/ (accessed 2013 Oct 26).
- 120. Berge KH, Dillon KR, Sikkink KM et al. Diversion of drugs within health care facilities, a multiple-victim crime: patterns of diversion, scope, consequences, detection, and prevention. *Mayo Clin Proc.* 2012; 87:674-82.

Appendix A—Key considerations in analgesic selection⁶

- Cause of the patient's pain
- Patient's age and general health, and the presence of comorbidities
- Potential for adverse outcomes associated with medication-related adverse effects
- Potential drug interactions
- Comorbidities that may be relieved by the nonanalgesic effects of the medications (e.g., sleep disturbances, depression, anxiety)
- Comorbidities that may be exacerbated by the nonanalgesic effects of the medications (e.g., hypertension, gastrointestinal ulceration, renal impairment, sleep apnea, cognitive impairment)
- · Costs of therapy
- · Potential risks for medication abuse
- · Risks of intentional or unintentional overdose

Appendix B—Summary of American Pain Society–American Academy of Pain Medicine recommendations on use of chronic opioid therapy in chronic noncancer pain⁷

Patient selection and risk stratification. Before beginning opioid therapy, clinicians should conduct a history and a physical examination and collect other information as appropriate, including a risk assessment for opioid use. Chronic opioid therapy should be started only when the perceived benefit outweighs any real or potential risk.

Informed consent and opioid management plans. When starting opioid therapy, the risks and benefits of therapy should be explicitly discussed with the patient. The patient needs to have a clear understanding of the goals of therapy, probable outcomes, and alternatives to chronic opioid therapy. For many if not most chronic noncancer pain conditions, nonpharmacologic therapies (e.g., physical, cognitive behavioral) and nonopioid therapies (e.g., adjuvant analgesics) are critically important to the overall success of the therapeutic plan, and patients must be willing to attempt a trial of these interventions in addition to opioid therapy.

Initiation and titration of chronic opioid therapy. The initiation of opioid therapy should be considered a short-term therapeutic trial, with frequent assessment of whether or not the goal is achieved. It is critically important that practitioners set realistic therapeutic goals in treating chronic noncancer pain, which include not only a reduction in pain severity but demonstrated improvement in functioning. Selection of a specific opioid to treat chronic noncancer pain is also a patient-specific decision based on patient- and drug-related variables. Patientrelated variables include considerations such as renal and hepatic functions, body habitus (for transdermal opioids), ability to swallow tablets or capsules, history of responsiveness to opioids in the past (positive and negative), and history of opioid allergy or intolerance, among others. The six opioids recommended for the management of chronic severe pain in the elderly by an international expert panel are buprenorphine, fentanyl, hydromorphone, methadone, morphine, and oxycodone.

Methadone. Methadone is an opioid with complicated and variable pharmacokinetic and pharmacodynamic parameters. Clinicians who choose to use methadone for chronic opioid therapy must become expert in the use of this agent. This includes a keen understanding of whether or not a patient is an appropriate candidate for methadone after performing a careful risk assessment, including a cardiac assessment; dosing strategies for both opioid-naive and opioid-tolerant patients; and how to monitor a patient receiving methadone. Methadone has a very long and variable half-life; therefore, starting doses should be conservative, patients should be monitored closely, and doses should not be adjusted before four to seven days.

Monitoring. Patients receiving chronic opioid therapy must be regularly monitored to ensure progress is being made toward achieving therapeutic goals, adherence to the prescribed therapy, and avoidance of adverse effects. Efforts (e.g., urine drug screening) to ensure the prescribed opioid is not being abused or diverted may be part of the monitoring plan.

High-risk patients. Patients with a concurrent history of drug abuse, psychiatric issues, or aberrant drug-related behaviors should only receive chronic opioid therapy if the clinician is able to implement more stringent and frequent monitoring. In difficult cases, patients may benefit from referral to an appropriate healthcare provider.

Dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy. When repeated dosage escalations have occurred or the patient experiences adverse effects from opioid therapy, the clinician should reevaluate the benefits and burdens of therapy. Patients may require tapering and discontinuation of opioid therapy or conversion to a different opioid.

Opioid-related adverse effects. Practitioners should be knowledgeable of opioid-related adverse effects and prevent, identify, and manage such adverse effects as they occur.

Use of psychotherapeutic cointerventions. Psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and nonopioid therapies should routinely be integrated into the patient's plan of care.

Driving and work safety. Patients should be counseled about the risks of driving and work safety while taking opioids and counseled about avoiding unsafe behaviors.

Identifying a medical home and when to obtain consultation. If the patient's primary care provider is not prescribing the chronic opioid therapy, there should be close communication between this provider and other prescribers. Patients with chronic pain often benefit from interdisciplinary pain management.

Breakthrough pain. Patients with persistent pain that requires around-the-clock opioid therapy should be evaluated for a trial of "as-needed" opioid therapy after considering the risks and benefits of such an intervention.

Opioids in pregnancy. Women of childbearing age should be counseled about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. The use of opioids during pregnancy is not encouraged, and risks to the patient and newborn must be considered and dealt with.

Opioid policies. Practitioners need to be aware of state and federal laws and guidelines as they pertain to chronic opioid therapy. Opioids are an effective tool in the management of acute and chronic pain, but as with all pharmacotherapeutic interventions, risks and benefits must be assessed before and during therapy to ensure safe and effective outcomes for patients.