Opioid Therapy in Acute and Chronic Pain

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Abstract

This is an article in the Core Entrustables in Clinical Pharmacology series that describes opioid therapy in acute and chronic pain. Opioid use during surgical procedures or anesthesia is not discussed. Basic pharmacokinetic and pharmacodynamic properties of opioids are reviewed. The safe and effective use of opioids, including clinical assessment and treatment plan, equianalgesic dosing, opioid rotation, opioid risks and side effects, and clinical adherence monitoring are discussed. Individualized opioid use can be a safe and effective component of a patient-specific multimodal treatment plan for acute or chronic pain. Adverse effects and risks can be prevented or effectively managed when anticipated and recognized. The article is followed by 4 clinical vignettes with discussions.

After reading this article, the reader will be familiar with the common classes of opioid agonists and partial agonists, the basics of pharmacokinetics and pharmacodynamics of opioids, the risks of opioid therapy, and the requirements for safe and effective use of opioids in acute and chronic pain. Opioid use during surgical procedures or anesthesia is not discussed. Various available opioid antagonists used for reversal of opioid overdose or treatment of opioid use disorder (including naloxone and naltrexone) are also not discussed. At the end, clinical vignettes are provided to enhance clinical understanding.

Opioid agonists ("opioids") are a group of medications that stimulate opioid receptors and exert their effects by mimicking endogenous opioid peptides known as endorphins.[1,2] Opioids are most often used for treatment of acute pain, including preoperative sedation, trauma, diagnostic and surgical procedures, labor, and acute medical problems such as renal or biliary colic. They are also commonly used for treatment of moderate and severe chronic cancer and noncancer pain that is unresponsive or less than adequately treated with nonopioid modalities.

Reasons for judicious opioid use in well-selected patients include their relative safety, multiple routes of administration, ease of titration, and reliability and effectiveness in somatic, visceral, and neuropathic pain. The goal of opioid use is to optimize effectiveness (ie, analgesia, daily functioning, and quality of life) and to minimize dose-limiting and troublesome nontherapeutic adverse effects. The US Centers for Disease Control and Prevention, the American Society of Interventional Pain Physicians, and the US Food and Drug Administration (via a risk evaluation and mitigation strategy program) are among those organizations that have issued guidelines to assist with opioid prescription in the outpatient setting.[3–8]

A serious public health problem has developed in the United States because of the misuse, abuse, and diversion of opioids. The development of widespread opioid use disorder has resulted in an increase in opioid-related deaths over the past 20 years,[9,10] and this has changed when and how we consider use of opioids. There are numerous federal and state regulations concerning opioid prescription, and a physician should always be familiar with both the federal laws and the laws of the state where he or she is prescribing.

Basics of Pharmacokinetics and Pharmacodynamics

Opioids can be pure agonists (eg, morphine, oxycodone, fentanyl), partial agonists (eg, buprenorphine), or mixed agonist-antagonists (eg, butorphanol, pentazocine,

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Table 1. Common Opioids by Class With Their Available Formulations and Routes of Administration[a]

Opioid	Natural or Synthetic	Routes of Administration	Formulations
Buprenorphine	Synthetic	IV, IM, SC, SD, TM, TD	Transmucosal[b]; solution for IV or IM; transdermal; SC depot; SD implant
Butorphanol	Synthetic	IM, IV, NS	Solution for IV or IM; nasal spray
Codeine	Natural	PO	IR;[c,d] oral liquids or suspension[c,d]
Fentanyl	Synthetic	IM, IV, NS, TD, TM	IV;[e] transdermal modified release[f]; oral transmucosal; nasal spray
Hydrocodone	Natural	PO	IR;[b] modified release; oral liquid or suspension
Hydromorphone	Semisynthetic	IM, IV, PO, R, SC	IR; modified release; oral liquid; suppository; regular and concentrated solution for IV or SC
Levorphanol	Synthetic	PO	IR
Meperidine	Synthetic	IM, IV, PO, SC	IR; solution for IV, IM, or SC; oral liquid
Methadone	Synthetic	IM, IV, PO, SC	IR; regular and concentrated oral liquid; solution for IV, IM, or SC
Morphine	Natural	EP, IM, IT, IV, PO, R, SC, TM	IR; modified release; regular and concentrated oral liquid; suppository; solution for EP, IT, IV, or SC; liposomal suspension for epidural injection; autoinjector; multiuse pen for SC injection; pellets for TM administration
Nalbuphine	Synthetic	IM, IV, SC	Solution for SC, IM, IV
Oxycodone	Synthetic	PO	IR; modified release; regular and concentrated oral liquid
Oxymorphone	Semisynthetic	IM, IV, PO, SC	IR; modified release; oral liquid; solution for IV, IM, or SC
Pentazocine	Synthetic	IM, IV, PO, SC	IR;[b,d] solution for IM, IV, or SC
Sufentanil	Synthetic	IV	Solution for IV
Tapentadol	Synthetic	PO	IR; modified release; oral liquid
Tramadol	Synthetic	IV, PO	IR;[d] modified release

EP indicates epidural; IM, intramuscular; IR, immediate release tablet or capsule; IT, intrathecal; IV, intravenous; NS, nasal spray; PO, oral; R, rectal; SC, subcutaneous; SD, subdermal; TD, transdermal; TM, transmucosal.

[a]Contents obtained from https://dailymed.nlm.nih.gov/dailymed/.

[b]Available as monotherapy and in combination with naloxone.

[c]Only available as a combination medication.

[d]Available in combination with another compound(s), which may include acetaminophen, aspirin, butalbital, caffeine, carisoprodol, chlorpheniramine, γ-aminobutyric acid, guaifenesin, homatropine, ibuprofen, phenylephrine, promethazine, pseudoephedrine, or triprolidine.

[e]Available as monotherapy and in combination with bupivacaine.

[f]Modified-release formulations include extended-release and slow-release oral formulations.

nalbuphine). Pure agonists are typically used for pain management because they lack the ceiling for analgesia that occurs with partial agonists and mixed agonist-antagonists.

The analgesic effect of opioids is primarily the result of their binding to opioid μ-receptors, although binding also occurs at the κ and δ receptors with differing physiological effects. The primary sites of action are the brain, brainstem, spinal cord, and intestines, although there are also receptors in the peripheral nerves. An important feature of therapeutic opioid analgesia is that it occurs without loss of consciousness, although patients may become drowsy or euphoric.[1] Although the primary analgesic site of action is the central nervous system (CNS), only small amounts of opioids cross the blood-brain barrier.

Opioids are classified as naturally occurring, semisynthetic, or synthetic opioids, and this differentiation is primarily important when considering selection of a urine drug-testing assay. They can be administered by many different routes, and numerous formulations are available. Common opioids with available formulations and routes of administration are found in Table 1. Of note, some opioids are only available in combination with other compounds. This may enhance effectiveness

and cause fewer side effects but can be dose-limiting because of the combination.

In equianalgesic doses, most opioids should produce similar analgesia. Choosing a particular opioid is usually based on pharmacokinetic factors such as desired route of administration, duration of action (ie, half-life), metabolism (including individual responses that are genetically determined), and development of side effects. The morphine milligram equivalent (MME) is used to compare opioids, taking into account their potency. But "equivalent" doses are variable and require patient-specific monitoring and evaluation.

Once administered, opioids are rapidly removed from the blood and distributed into skeletal muscle, CNS, kidneys, lungs, and placenta. They undergo metabolism primarily in the liver but to a lesser extent may be metabolized in the kidney, small intestine, lungs, and placenta. They are primarily excreted in the urine as unchanged drug and metabolites. For this reason, attention must be paid if considering use in a patient with renal or hepatic impairment.

The pharmacokinetics of a chosen drug can differ within a patient (intraindividual variability) and between patients (interindividual variability). Absorption, distribution, metabolism, and excretion

are the primary pharmacokinetic parameters that are measured. Most pharmacokinetic variability is due to environmental and genetic factors. Environmental factors may include drug-drug interactions and food-drug interactions.[11] Genetic factors include drug transport across the intestinal mucosa and blood-brain barrier, cytochrome P450 enzymes, and phase II metabolic enzymes (conjugation reactions catalyzed by transferase enzymes such as glutathione S-transferase). The amount of pharmacokinetic variability can vary widely.[12] Significant interindividual variability exists in effectiveness and tolerability, and this leads to challenges in therapeutic use.[13] For example, plasma oxycodone concentrations that effect analgesia may vary more than 100-fold between individuals.[14] Some of the many factors that contribute to this variability include pharmacogenomics, environmental factors, and drug-drug interactions.[15] Table 2 lists opioids that are commonly used in adults along with selected pharmacokinetic and pharmacogenomic properties. Although most opioids are primarily metabolized by cytochrome P450 *CYP3A*, *CYP2D6* exhibits the greatest polymorphism with clinical significance. Opioids that are metabolized to a significant extent via *CYP2D6* can be expected to vary widely in both effectiveness and toxicity based on the individual patient's genetic constitution.

Patient characteristics influence pain tolerance, and the serum concentrations needed for analgesia vary depending on age, baseline anxiety, pain sensitivity, nicotine exposure, hepatorenal function, pulmonary function, and presence of chronic pain.

Pharmacodynamic effects include not only the primary desired outcome of analgesia but adverse effects of sedation, euphoria, dysphoria, nausea, vomiting, hypotension, gastrointestinal hypomotility (ie, constipation), QTc prolongation (eg, methadone), respiratory depression, pruritus, and urinary retention, among others.[16] Often, the prescriber must titrate the dose to balance the desired pharmacodynamic response of pain control with undesirable side effects. The mixed agonist-antagonist opioids (eg, butorphanol) have "ceiling effects" on analgesia (higher doses do not result in greater analgesia), whereas buprenorphine has a "ceiling effect" on respiratory depression that makes it safer for use in opioid use disorder.

Safe and Effective Use

Medication regimens should be patient-specific, patient-centered, and individualized based on clinical findings. Opioids are not the initial treatment of choice for outpatients. The risks and benefits of opioid use should always be weighed when initiating therapy and when deciding whether to pursue, modify, or continue treatment, and opioids should only be used when they

are expected to be effective.[17] Because of the current opioid crisis and concern about development of opioid use disorder, patients are at risk for undertreatment or being denied treatment of pain. Some specific populations (eg, the elderly[18], nonwhite minorities[19]) may be even more likely to have inadequate treatment of pain. Tailoring treatment for and with a patient should help to assure that benefits and risks are understood and balanced. A comprehensive treatment plan utilizes (when available) a complete metabolic profile, radiographic evaluation, social history, past treatment successes and failures, and patient allergies and side effects are documented.

For opioid-naive patients, one should prescribe the minimum quantity of opioids anticipated to be necessary for the expected severity and duration of pain. This may be a 3- to 5-day supply for acute pain.[17] Patients are considered opioid naive if they have used a continuous dose of opioid for fewer than 7 days (or intermittent opioids).[5,20] According to the US Food and Drug Administration, opioid-tolerant patients are those who have received a daily dose of greater than or equal to oral morphine 60 mg, oral oxymorphone 25 mg, oral oxycodone 30 mg, oral hydromorphone 8 mg, oral hydrocodone 60 mg, or transdermal fentanyl 25 μg/h for at least 7 days.[20] The difference between the opioid-naive versus -tolerant patient is important because naive patients are more sensitive to clinically important adverse effects such as respiratory depression. Modified-release formulations (eg, extended-release preparations, transdermal patches, transbuccal patches) should be avoided in opioid-naive patients. There are tables that provide recommended starting and maintenance doses for common opioids,[1,7] and these can be referenced if the prescriber is unfamiliar with a particular opioid.

Chronic opioid treatment (opioid prescribing for ≥90 days) is usually reserved for moderate to severe pain that is less than responsive to other medical and pharmacological treatments. After completion of an assessment (which should be comprehensive before opioids are started for chronic pain), a diagnosis, medical necessity, and treatment goals should be established. The importance of engaging with patients and their families to set realistic expectations and goals for opioid therapy cannot be overstated. Evaluation of the usefulness of opioids for the type of pain should be reviewed when determining medical necessity. Opioids have limited or no benefit for widespread soft tissue pain (eg, fibromyalgia), migraine headache, and functional pain (eg, functional gastrointestinal pain)[21] and are minimally to moderately beneficial for nociceptive pain and neuropathic pain.[5] An exception is tapentadol, which has a Food and Drug Administration (FDA) indication for diabetic peripheral neuropathy.[22]

Table 2. Selected Pharmacokinetic and Pharmacogenomic Properties of Opioids Commonly Used in Adults

Opioid	Half-Life for IR or Parenteral Formulations (h)	Primary Route of Metabolism	Primary Route of Clearance	Unique Pharmacodynamic Properties
Buprenorphine	TD: 16–27 TM: 24–35 IV: 1.2–7.2	Hepatic (CYP3A, phase 2)	Fecal 70% to 90% Renal 10% to 30%	Ceiling effect on respiratory depression; poor oral bioavailability; partial μ-receptor agonist and therefore patients may require higher-than-usual doses of full opioid agonists with administered concurrently or within 48 h of buprenorphine dosing; use with full agonists may cause precipitated withdrawal in opioid dependent patients
Butorphanol	IV: 2–9 NS: 3–9	Hepatic	Renal 70% to 80% Fecal 15%	Mixed agonist/antagonist with ceiling on analgesic effects; use with full agonists may cause precipitated withdrawal in opioid-dependent patients
Codeine	IR: 2.9	Hepatic (UGT 2B7, CYP2D6, CYP3A, CYP2E1, CYP1A2)	Renal	Requires CYP2D6 conversion to morphine, resulting in risk of no therapeutic benefit or overdose/increased adverse effects/limited pain control[57]; should be avoided in hepatic failure
Fentanyl	IV: 2–4 TD: 20–27 TM: 7	Hepatic and intestinal (CYP3A4)	Renal	Highly lipophilic; every 2- to 3-day dosing with transdermal preparation; may be less likely to cause pruritus
Hydrocodone	IR: 3.5–4	Hepatic (CYP3A, CYP2D6)	Renal	Active metabolite: hydromorphone
Hydromorphone	IV: 2.3 IR: 2–3 ER: 8–15	Hepatic (phase 2)	Renal	Highly hydrophilic[58]
Levorphanol	IR: 11–18	Hepatic (phase 2)	Renal	
Meperidine	IV: 2–5 IR: 3–8	Hepatic (CYP3A, CYP2B6, CYP2D6, CYP2C19)	Renal	Toxic metabolite (normeperidine) with half-life of 30-85 h, is not reversible by naloxone, and accumulates with renal dysfunction or high doses; should be avoided in most patients
Methadone	IR: 8–59 and variable	Hepatic (CYP2B6, CYP3A, CYP2C19, CYP2C9, CYP2D6)	Renal	Highest risk of accumulation and overdosage during titration and dose adjustment; potential for QTc prolongation; induces its own metabolism; lack of active metabolites
Morphine	IV: 2.5–3 IR: 2–4 ER: 11–29	Hepatic (CYP3A, CYP1A2, CYP2C9, CYP2D6, phase 2, and other minor pathways)	Renal	M-3-G metabolite is associated with neurotoxicity M-6-G metabolite is associated with analgesia
Nalbuphine	IV: 5	Hepatic	Renal	Mixed agonist/antagonist with ceiling on analgesic effects; use with full agonists may cause precipitated withdrawal in opioid-dependent patients
Oxycodone	IR: 1–4	Hepatic (CYP3A, CYP2D6, CYP2C9)	Renal	Low rate of metabolism to oxymorphone or noroxycodone, with questionable clinical effects[59]
Oxymorphone	IR: 7–9 ER: 9–11	Hepatic (phase 2), intestinal	Renal	Low propensity to release histamine[20]
Pentazocine	IR: 1.5–10	Hepatic	Renal	Mixed agonist/antagonist with ceiling on analgesic effects; use with full agonists may cause precipitated withdrawal in opioid-dependent patients
Tapentadol	IR: 4 ER: 4–8	Hepatic (phase 2 85%, CYP2C9, CYP2C19, and CYP2D6 15%)	Renal	Mixed mechanism of action (μ-opioid receptor agonist and norepinephrine reuptake inhibitor); low histamine release; low abuse potential; indicated for diabetic peripheral neuropathy
Tramadol	IR: 5–8 ER: 10–11	CYP2D6, CYP3A, CYP2B6	Renal	Mixed mechanism of action (μ-opioid receptor agonist and norepinephrine and serotonin reuptake inhibitor); active metabolite n-desmethyltramadol has a long ($\sim$9-h) half-life; maximum dose of 400 mg/day; lowers seizure threshold; only partial antagonism by naloxone; does not cause histamine release

CYP indicates cytochrome P450; ER, modified release, including extended release and slow release; IR, immediate release; IV, intravenous; M-3-G, morphine-3-glucuronide; M-6-G, morphine-6-glucuronide; NS, nasal spray; TD, transdermal; TM, transmucosal.

Informed decision making with patient consent and agreement is recommended before starting treatment for chronic pain, and sample controlled substance treatment agreements are readily available.[7,23] The 2012 American Society of Interventional Pain Physicians guidelines have a 6-step algorithm for initiation and use of opioid therapy in patients with chronic noncancer pain.[7]

At the start of treatment, an immediate-release (short-acting) formulation should be used on an

as-needed basis, with gradual titration as necessary. Titrations are directed at increased functionality and activities of daily living and decreases in side effects. This process is achieved by bilateral, open, ongoing dialogue. The patient's expectation of "pain-free" is accomplished by anesthesia. By contrast, analgesia is not "pain-free," and is directed at decreasing pain quality and intensity but not at total ablation of pain. Long-acting opioids should be avoided in opioid-naive patients.

Oral administration is recommended when possible, and combination products to enhance analgesia should be used when they are available and appropriate. Generally, one should start with the lowest effective dose and increase the dose cautiously. MMEs may be used to estimate equivalent doses of different opioids. Some recommendations are to limit new opioid users to <50 MME/day.[24] Additional care is needed for dose escalations to ≥50 MME/day. Patients who are without a therapeutic response to low or moderate doses of opioids are unlikely to respond to high doses. The increased risk of side effects, including overdose at doses of ≥90 MME/day, should be carefully justified and the rationale for high dose use documented. The highest frequency of overdose is found among patients on high daily doses.[5] There is not uniform agreement about what constitutes a high MME dose, with 90-120 mg MME per day being used by different guidelines.[7,24] A number of states have legislated guidelines to limit the total daily dose of an opioid to ≤120 MME daily dose. There will be patients who require a higher dose of opioid to achieve treatment goals, and referral to a pain specialist for a second opinion should be considered in those circumstances.

Over time, tolerance or pathology progression may develop and lead to the need for higher doses to achieve the same level of pain control or the addition of supplemental doses for breakthrough pain.[25] Opioid tolerance describes the physical adaptation of opioid receptors that results in the need for higher doses to achieve the same level of analgesia. Tolerance may develop rapidly (within a few doses) or slowly (over weeks to months).[25,26] If patients are unable to use oral preparations, transmucosal (sublingual, buccal), transdermal, subcutaneous, or rectal formulations can be used. Tamper-resistant and abuse-deterrent formulations are available for some opioids and should be considered for use, especially when there is concern about the environment, misuse, abuse, or diversion.[27]

With chronic treatment of moderate to severe pain, consideration can be given to use of modified-release formulations. Long-acting or modified-release formulations (eg, extended-release tablets or capsules, transdermal patches that result in a slow-release skin membrane reservoir, or transbuccal patches) have the potential advantages of more consistent pain control (with fewer troughs and peaks) and better overnight pain control, and these require fewer doses each day. These are the situations when modified-release formulations may be considered, but the prescriber should be aware that they may not be covered by insurance. There is a lack of evidence that long-acting opioids have higher efficacy in pain control than short-acting opioids, so their use is primarily for patient compliance and convenience. When long-acting drugs are used, patients may need immediate-release medication for breakthrough pain. These "rescue" doses should provide approximately 10% to 20% of the total daily dose or 25% to 30% of the single-standing dose.[28]

It is imperative that the prescriber understand differences in modified-release (ie, extended-release) versus immediate-release formulations. Among modified-release formulations, time to peak concentration is longer, duration of action is longer, and there is a larger amount of drug in a single dosage form. These factors may present risks. When these dosage forms are broken, crushed, chewed, or dissolved, the delivery mechanism of the modified-release formulation is damaged, rapid drug release ensues, rapid absorption follows, and there is potential for overdose and death. Simply swallowing multiple doses of modified-release "abuse deterrent" dosage forms with an intent for abuse is also dangerous and creates challenges for opioid reversal.

Use of methadone in opioid-naive patients is not recommended. Use of methadone for pain should be reserved for patients who have failed other opioids. Methadone is recognized as possessing unique pharmacokinetic and pharmacodynamic properties (eg, autoinduction of CYP450 metabolism, long and variable half-life, risk of early drug accumulation, numerous drug-drug interactions),[29] significant adverse effects (such as QTc prolongation and higher rates of overdose), and the potential for abuse and diversion. Methadone should be used only by clinicians with specific training and experience in its risks and uses.[7] Switches to methadone as part of opioid rotation are not recommended unless the prescriber has a thorough working knowledge of how to use methadone. Methadone pharmacokinetics differs from those of all other opioid agonists, making initiation and rotation to methadone more challenging (for example, you should lower the calculated dose of the new opioid by 75% to 90% rather than 25% to 50%).[30]

Treatment with opioids should be at the lowest effective dose for the briefest time possible. Reevaluation of risks and benefits should be done within the first 4 weeks after starting treatment or increasing a dose and every 3 months thereafter.[31] If risks exceed benefits at any time, then appropriate changes to therapy

are needed. This may include decreasing the dose or discontinuing the opioid while avoiding withdrawal symptoms. There are guidelines for opioid tapering and discontinuation that are intended to avoid withdrawal symptoms.[32] If a patient is on more than 90 MME/day, consideration should be given to lowering the daily dose to the lowest effective dose.[24]

Opioid rotation is a strategy whereby the patient is switched from 1 opioid to another opioid (possibly with a different mechanism of action). Opioid rotation can improve pain control when there is inadequate efficacy or need for a different potency, allow lowering of the opioid dose, use of a smaller quantity (ie, higher potency), decrease intolerable side effects, allow for use of a different formulation (eg, subcutaneous vs oral administration), or because of practical considerations (eg, availability or cost).[28,33] To convert a patient from 1 opioid to another, a different opioid is chosen, and an estimated equianalgesic dose is calculated.[34–36] Because of incomplete opioid cross-tolerance, the dose of the new opioid should be decreased by approximately 25% to 50% and then adjusted to meet pain control goals and minimize adverse effects such as sedation.[30] Many tables used for opioid rotation are available for calculation of analgesic equivalency, but they should be used cautiously because data from opioid-naive patients are frequently used in these tables, and most patients appropriate for opioid rotation are on chronic dosing.[28,33] When a patient has been on chronic opioid dosing, these tables can result in overestimating the equianalgesic dose. There are limited data on opioid equivalence during chronic dosing, and these are not readily available.[37] These tables also reflect variable patient populations, and many tables are unidirectional (eg, from intravenous to oral) and not bidirectional in their conversion figures. There are also differences in opioid receptor affinity and occupancy that may influence dose conversions but are not included in these tables.[38–40]

Referral to a pain clinic should be considered when opioids are best avoided based on pretreatment screening (and other nonpharmacological and pharmacological treatments have been tried), opioid treatment does not achieve goals for pain relief, there is a need for invasive treatments (eg, intrathecal pumps, spinal cord stimulators, nerve blocks), or there is evidence of aberrant behavior. If there is evidence of a substance use disorder, the Substance Abuse and Mental Health Service Administration substance abuse treatment facility locator (https://www.samhsa.gov/) can be used for patient referrals.

Coprescription of naloxone should be considered for patients who are on high doses of opioids, have children in the environment or home, are on formulations that increase the risk of overdose (eg, fentanyl patch, long-acting formulations), have experienced an overdose, or have a diagnosis of substance use disorder but need to take opioids. Because of the recent increase of opioid overdose deaths due to synthetic opioids such as fentanyl and carfentanyl,[9,41] the recommendation has been made to administer a standard initial intramuscular dose of naloxone 2 mg (rather than 0.4 mg) or 4 mg by intranasal administration.[42] There are no safety concerns with the higher naloxone dose.[43]

Asking patients about their existing home opioid supply and educating patients and families about proper drug disposal are essential. Guidance on disposal of prescription drugs is available for patients from the FDA[44] and Drug Enforcement Agency (https://takebackday.dea.gov/).

Special Populations

In the setting of reduced metabolism (eg, hepatic impairment), reduced clearance (eg, renal impairment, diabetes mellitus, neonates, elderly patients), patients with severe CNS or respiratory depression or at risk of such (eg, patients with head injury, hypoxia, hypercapnia, sleep apnea), or challenging psychopathology, reduced dosage is indicated or use of opioids may be contraindicated. For pregnant women or those of childbearing potential, there may be increased risk to the fetus (eg, low birth weight, premature birth, neonatal death, neonatal abstinence syndrome),[31] and caution is advised.

Adherence Monitoring

During chronic therapy, adherence monitoring should be done for therapeutic outcomes, misuse, abuse, development of opioid use disorder, and diversion. The most commonly recommended monitoring techniques are use of qualitative and confirmatory urine drug testing (UDT), consulting state prescription drug-monitoring databases before each prescription, medication reconciliations ("pill counts"), behavioral assessments, and repeated administration of questionnaires (eg, Current Opioid Misuse Measure,[45] Pain Assessment and Documentation Tool,[46] or Pain Medication Questionnaire[47]).

UDT requires an understanding of types of opioids (eg, natural vs synthetic), the specific testing, and opioid pharmacokinetics including metabolism. Most UDT is done as qualitative testing (positive/negative) and may or may not be followed with confirmatory testing. UDT should be used in conjunction with clinical history and observations with the goal of optimizing treatment by measuring risk and monitoring compliance. Positive results can support recent use, but knowledge of how long the medication is expected to remain in the urine after administration (metabolism and pharmacokinetics) is essential. In addition, urine drug concentrations

cannot be used to determine how much medication has been taken (ie, cannot be used to tell if the patient is taking the dose of medication prescribed).[15] Tables containing this information are readily available.[7] Most qualitative, immunoassay tests identify classes of drugs (eg, "opiates," "benzodiazepines") above a certain cut-off concentration, and confirmatory testing is required to establish the specific molecule (eg, morphine, hydrocodone). They are subject to cross-reactivity and variability, and false positives may be common.[48] In addition, some semisynthetics do not cross-react with the "opiate" assay, and synthetic opioids require testing specific to the medication you expect to find (eg, fentanyl, methadone, oxycodone). One needs to understand how to interpret immunoassays, quantitative assays, and the limitations of the specific testing methods. Positive test results can provide evidence of exposure but not duration of exposure, dose taken, or frequency of use.[15] Measures of temperature, urinary creatinine, pH, and specific gravity are often included to confirm integrity of the specimen (that it is human and has not been tampered with).[48]

Qualitative UDT can be by point-of-care or laboratory-based immunoassay. Gas chromatography mass spectrometry-mass spectrometry, liquid chromatography mass spectrometry-mass spectrometry, or ultraperformance liquid chromatography mass spectrometry is usually used for confirmatory, quantitative testing. Even with confirmatory testing and quantification of urine drug or metabolite, it is not possible to determine whether the patient is taking a specific medication precisely as prescribed.[15] Christo et al have published an algorithm for steps in UDT.[49] Most physicians lack the thorough knowledge that is necessary for UDT interpretation and may need assistance from clinical experts.[50] If UDT interpretation is unclear, clinical experts at the reference laboratory may usually provide information and clarification.

Risks

Common Adverse Effects

Common opioid adverse effects include gastrointestinal side effects (constipation, nausea, vomiting), fatigue, central nervous system effects (dizziness, confusion, sedation, euphoria, dysphoria, restlessness), genitourinary effects (urinary retention), cholinergic effects (xerostomia, bradycardia), as well as weight gain, diaphoresis, flushing, pruritus, urticaria, and suppression of the cough reflex. Constipation is frequent, and it is imperative that a bowel regimen be started as soon as constipation becomes apparent because patients do not develop tolerance to opioid-induced constipation.[51] Stimulants such as sennosides and polyethylene glycol, along with increased water intake and dietary measures

are typically the first interventions for constipation.[52] There are also specific treatments for opioid-induced constipation, including naloxegol, lubiprostone, methylnaltrexone, and naldemedine.[53] Adverse effects that are less common but important to recognize include respiratory depression, hyperalgesia, and endocrinopathies (eg, decreased libido, hypogonadism, osteoporosis).

Perhaps the most common side effect of chronic opioid use is physical dependence. Dependence describes the need to continue to take opioids to prevent withdrawal symptoms. The physiological changes that occur with dependence typically resolve within days to weeks of discontinuing opioids, and withdrawal symptoms can be prevented by dose tapering.[25]

Although respiratory depression is not a common side effect of judicious use of opioids, respiratory depression is a serious and potentially life-threatening adverse effect. Risk of respiratory depression is increased in the setting of underlying pulmonary compromise (eg, severe chronic obstructive pulmonary disease, central and obstructive sleep apnea) or when used in conjunction with sedatives (eg, benzodiazepines, alcohol).[5,18,31] The FDA placed boxed warnings on all opioids and benzodiazepines on August 31, 2016 to discourage their concurrent use.[54] Because of the high frequency of neurological effects, especially with initiation of opioids, patients should be educated about avoiding concurrent use of sedative/hypnotics and alcohol and avoidance of driving motor vehicles or using heavy machinery until it is evident that the opioid does not cause sedation or impairment of judgment.

Use of cannabis with opioids may not be fully therapeutic and is accompanied by risks such as greater sensory and cognitive impairment. Although the majority of side effects for opioids are minor and resolve with continued use, some are long-lasting, serious, or may increase with ongoing use. Therefore, it is important to be able to recognize and manage adverse effects.

Drug Interactions

As with other medications, drug-drug interactions may be anticipated when a concurrently administered drug is an inhibitor or inducer of a metabolic pathway of an opioid. Many, but not all, opioids are metabolized by cytochrome P450 (CYP) enzymes, and other medications, dietary intake, and environmental exposures can alter opioid elimination via the CYP pathways (see table 2). CYP3A is the most common metabolic pathway and numerous medications inhibit (eg, ritonavir, indinavir, clarithromycin, fluconazole) or induce (eg, carbamazepine, glucocorticoids, rifampin) this pathway. Competitive inhibition may also occur. In addition, opioids can potentiate the effects of other CNS depressants and must be used very cautiously in conjunction with CNS depressants such as alcohol, sedatives, hypnotics,

H_1-receptor antagonists (eg, hydroxyzine, diphenhydramine), barbiturates, or antipsychotics. Although monoamine oxidase inhibitors are infrequently used, potentially lethal interactions may occur when they are combined with opioids and thus should be avoided except in exceptional circumstances.

Tolerance, Dependence, and Withdrawal

Tolerance and physical dependence are expected with chronic administration of opioids. Tolerance develops with repeated administration and may manifest as reduced analgesia at a stable dose, shorter duration of analgesia, less sedative effect, or less euphoria. Physical dependence results in withdrawal symptoms if an opioid is abruptly discontinued or a patient receives an opioid antagonist. Withdrawal symptoms include restlessness, lacrimation, rhinorrhea, sneezing, yawning, piloerection, sweating, insomnia, tremor, myalgias (especially in the back and legs), nausea, vomiting, diarrhea, abdominal pain, fever, hypertension, tachycardia, and increased respiratory rate.[55]

Misuse, Abuse, Substance Use Disorder, and Diversion

Opioids work by activating μ-opioid receptors in the brain to produce pleasure (reward) and pain relief (brain and spinal cord). Because of opioid effects on mood and reward behaviors, some patients may misuse or abuse them.

Screening to identify potential for development of opioid use disorder (drug addiction and abuse) and awareness that even 1 dose can result in opioid misuse are needed before treatment begins. The longer a patient takes opioids, the greater the likelihood of dependence and incident opioid use disorder.[5] Because it is so difficult to determine which patient may develop an opioid use disorder, appropriate boundary setting in the doctor-patient relationship is crucial at the time of the initial opioid prescription.[32,56,57] Boundary setting is also important when a physician assumes care of a patient on chronic opioid therapy started by another prescriber.[58]

Before the start of therapy, each patient should be assessed for risk for aberrant drug use behavior and development of a substance use disorder. Numerous screening tools are readily available for clinic use, including online prescription drug monitoring programs (mandatory in many states), the Opioid Risk Tool, and Screener and Opioid Assessment for Patients with Pain.[59] Screening should be followed by verbal and sometimes written informed consent that includes anticipated benefits and foreseeable risks (ie, treatment agreement).[5,60] In addition, having a treatment agreement and urine drug testing before initiating opioids, or at the time of the first visit for an "inherited" patient, assists in modification of or discontinuance of treatment if either is appropriate. Next, documentation of pre- and posttreatment pain assessment and level of function are essential and need to be done on an ongoing basis. If a patient is identified as having aberrant drug use behaviors or a substance use disorder, screening, brief intervention, and referral to treatment are recommended.[61,62]

Conclusions

The pharmacotherapeutic management of acute and chronic pain is a process that engages an individualized multimodal treatment plan. The judicious prescribing of opioids can be considered in the pain management plan when pain is less than adequately controlled following the prescribing of nonopioid medications. The opioid selection process is a function of a patient-specific care plan. A comprehensive treatment plan is made and includes discussion and documentation of opioid risks and benefits. The categories of pain (nociceptive, neuropathic, and visceral), medical, surgical history, psychiatric history, social history, and patient's past opioid experiences are evaluated. A controlled substance agreement, review of state(s) prescription drug-monitoring programs, and clinical UDT are part of the opioid treatment plan. Follow-up clinical visits may be monthly initially and extended up to every 3 months once stability of the treatment plan has been achieved. Incremental and decremental titrations are directed at increased functionality and activities of daily living and decreases in side effects. A thorough knowledge of the opioids used is essential and requisite on continuing medical education (ie, training, knowledge, clinical experience, and wisdom). As a rule of thumb, the practitioner would be wise to become an expert on a few opioids and their formulations and then prescribe those medications. Referral to a pain specialist is warranted if there is difficulty achieving acceptable results or care becomes more complex than the practitioner is trained to manage.

Clinical Vignettes

Case 1

A 33-year-old white woman has come to your primary care clinic seeking treatment for fibromyalgia. She reports 5 years of diffuse pain and "terrible" fatigue that started after she wrenched her neck in a spill from her bicycle. She has 3 children under the age of 8 and says that she cannot keep up with her home and child-care responsibilities because she doesn't sleep well and cannot concentrate during the day. She is not employed outside the home and says that her life is very stressful. "The pain is unbelievable. People act like I'm making this up." You recently referred her to a rheumatologist who diagnosed her fibromyalgia.

She says that she has "done everything and been on everything, and nothing helps." Physical examination is remarkable for an anxious, overweight woman with 14/18 tender points consistent with fibromyalgia on her neck, shoulders, upper back, elbows, hips, and knees. She has been to physical therapy and taken 4 different nonopioid medications (duloxetine, fluoxetine, milnacipran, and pregabalin) at therapeutic doses for adequate trials without evident benefit or with unacceptable side effects. Currently she practices yoga for 20 minutes 5 days a week and walks for 30 minutes twice a day.

Commentary. Your initial step should be to review nonpharmacological and pharmacological therapy and consider recommending any remaining options that are reasonable. These might include cognitive behavioral therapy, massage, a sedating antidepressant (eg, tricyclic antidepressant, mirtazapine) to improve sleep quality and duration as well as the potential for primary treatment of fibromyalgia and graded exercise to increase exercise intensity and duration.

This patient has been actively participating in her care, as evidenced by the number of interventions she has tried or is actively engaged in. Once the nonpharmacological treatments have been tried and determined to lack adequate efficacy, you could consider a trial of opioid therapy.

Because this patient is potentially facing long-term use of opioids, this vignette illustrates the importance of patient-specific evaluation and tailoring of treatment, ensuring that the patient is involved in decision making. Baseline risk assessment and education are essential. You need a clear, established plan for early and repeated evaluation of treatment to determine if you are reaching therapeutic goals for pain relief and functioning as well as a plan for opioid tapering and discontinuation if these goals are not met.

Case 2

A 24-year-old man presents to the emergency department with reported severe abdominal pain, sweats and chills, and 2 episodes of vomiting. He says that his pain is "15 out of 10" and "excruciating." He has had moderately severe Crohn disease for the past 6 years, with intermittent flares of disease in the ileum, cecum, midcolon, and perianal regions. Two years ago, he had a right-sided colectomy. He is currently treated with oral budesonide and oxycodone/acetaminophen. He smokes a pack of cigarettes daily. On physical examination, he is afebrile, blood pressure 126/64, pulse 110, respirations 16, and pulse oximetry 98%. He is anxious, gripping his abdomen, curled onto his right side, and writhing on the stretcher. Abdominal examination reveals active bowel sounds, guarding, and diffuse tenderness to palpation. There are no masses. Rectal exam is tender with brown, hemoccult-negative stool. The complete blood count shows mild microcytic anemia, and his complete metabolic profile is unremarkable. A urine drug test is positive for tetrahydrocannabinol (a cannabis metabolite) and oxycodone. A computed tomographic scan of the abdomen and pelvis shows changes consistent with the former partial colectomy, stool in the colon, and no evidence of active inflammatory bowel disease. The remainder of the CT scan is unremarkable. Intravenous fluids are started, and patient is given 1 dose of intravenous ketorolac. An hour later, his physical examination is unchanged, and you do not have a diagnosis other than "abdominal pain." He is given a dose of intravenous morphine, and his pain subsides.

Commentary. This man has responded to administration of morphine because his symptoms are secondary to opioid withdrawal. The symptoms of opioid withdrawal are anxiety or irritability, hot and cold flushes (often described by patients as "sweats and chills"), restlessness, nasal stuffiness, myalgias, and arthralgias. The Subjective Opioid Withdrawal Scale can be used to score symptoms for severity of withdrawal.[63] The signs of opioid withdrawal are tachycardia, gastrointestinal upset (stomach cramps, nausea, vomiting, diarrhea), diaphoresis, tremor, restlessness, yawning, dilated pupils, observable irritability and anxiety, piloerection, rhinorrhea, and lacrimation. The Clinical Opioid Withdrawal Scale can be used to score examination findings for severity of withdrawal.[63] Combining the initial history, physical findings, laboratory and radiological data, and his response to pain medications allows you to return to the patient for additional history. You can also consult your prescription drug-monitoring program to learn when this patient last filled a prescription for oxycodone/acetaminophen and how many doses he obtained.

Additional questions reveal that this patient has increased his oxycodone/acetaminophen intake from the prescribed maximum of 4 tablets a day to 6-10 tablets a day and took his last dose 5 days ago. He has misused his opioid, has opioid dependence, and possibly an opioid use disorder. His pain resolved with morphine because you treated his withdrawal syndrome. Further acute workup is not necessary. The patient should be referred back to his primary care provider and opioid prescriber for further evaluation and treatment of his opioid dependence, possible opioid use disorder, and Crohn disease.

Case 3

An 81-year-old man with hypertension, hypercholesterolemia, osteoarthritis of the hips and knees,

moderate chronic obstructive pulmonary disease (stage 2), and chronic insomnia is admitted to the surgical floor after left total hip replacement. His chronic medical problems are stable and controlled on his home medications. Of note, he takes zolpidem every night to assist him with sleep and has done so for years. On postoperative day 1, he receives low doses of hydromorphone IV by nursing staff as needed. His home medications are continued in the hospital once he is able to take oral medications. The morning of postoperative day 2, the nursing staff have difficulty arousing him, his respiratory rate is 12 breaths per minute, and his pulse oximetry has decreased from 95% on admission to 88%.

Commentary. Concurrent administration of opioids with benzodiazepines is contraindicated in most circumstances (and only to be used in careful medication management when a patient is receiving medication-assisted treatment for opioid use disorder).[64] The markedly increased risk for respiratory depression and fatal overdose is emphasized by the boxed warnings the FDA added to the product labels of prescription opioids and benzodiazepines in 2016.[65]

This patient appeared to have a stable respiratory status before surgery even with moderate chronic obstructive pulmonary disease and chronic use of a benzodiazepine (zolpidem). The addition of hydromorphone for pain control likely resulted in his respiratory decompensation. Supportive treatment, and possibly naloxone, should result in improvement and recovery of his respiratory status.

Case 4

A 64-year-old man has a primary complaint of low back pain that had been worsening for the past 5 weeks. He had long-standing low back pain that had been relieved at the time of a L_3-L_5 lumbar laminectomy 7 weeks ago. Two weeks after the laminectomy, he developed a new pain that he describes an intense burning and prickling, pins-and-needles sensation, with radiation into both legs. The pain is constant, dull, achy, and worsens with walking. Self-reported pain score is 8/10 with medication. He has been on daily opioids since his surgery.

His past medical history includes chronic low back pain, migraine headaches, hypercholesterolemia, osteoarthritis of the knees, and gastroesophageal reflux. Behavioral health history includes generalized anxiety disorder and insomnia. Surgical history includes cholecystectomy, appendectomy, dental implants, and arthrodesis of L_3-L_5. Current medications include sumatriptan 50 mg as needed, hydrocodone/acetaminophen 10/325 mg eight tablets daily, rosuvastatin 10 mg daily, omeprazole 20 mg daily,

diclofenac topical gel 3% to knees twice daily, and trazodone 100 mg at bedtime as needed for sleep. He has no known drug allergies but has seasonal allergies. He does not drink alcohol, smoke cigarettes or cannabis, or use any substances of abuse. On physical examination, he has a height of 180 cm (71 in), weight 95 kg (210 lb), body mass index 29.3 kg/m^2, and unremarkable vital signs. His complete metabolic profile is within normal limits, creatinine clearance = 61 mL/min, QTc = 405 milliseconds, and magnetic resonance imaging of the lumbar spine shows that the fusion site is in place and there is no disk protrusion or herniation.

Previous treatment of his pain has included hydrocodone/acetaminophen 5/325 mg (not more than 10 tablets per day), anticonvulsants, antidepressants (fluoxetine and nortriptyline), and complementary therapies (massage, chiropractic therapy, turmeric). In addition, he has tried over-the-counter treatments for his pain (aspirin 81 mg daily, lidocaine patches, glucosamine chondroitin) and treatment side effects (sennosides, bisacodyl, bran, diphenhydramine, melatonin). He is not satisfied with these prior therapies and has had side effects that included constipation, pruritus, and daily episodes of euphoria. The patient wants to be able to increase his mobility, vocational and avocational functioning, and avoid itching, daytime drowsiness, and constipation. His wife accompanies him and validates that he has pain and limitations as well as significant side effects that are impairing his quality of life and states that he has made an "honest try" to use the above-mentioned methods to control his pain.

In concert with the patient and his wife, a plan is made to discontinue his hydrocodone/acetaminophen, begin pregabalin, duloxetine, and tapentadol (introduced over the course of a couple of weeks), refer for physical therapy and occupational therapy, and refer to a sleep disorder center for evaluation of his insomnia.

Commentary. This patient has significant neuropathic pain, is currently opioid dependent, and is experiencing unacceptable side effects from his current treatment. Pregabalin is indicated for neuropathic pain with spinal cord injury. Duloxetine is approved for diabetic neuropathic pain and chronic musculoskeletal pain. This patient may see benefit for his knee pain, as well as his back pain.

There is limited evidence that most opioids are useful for neuropathic pain. In this patient, his ongoing pain, escalating daily hydrocodone dose, and dose-limiting side effects (constipation, pruritus) illustrate the need to taper and discontinue the hydrocodone. Tapentadol can be used to treat neuropathic pain, and causes less

constipation, a lower incidence of pruritus (secondary to less histamine release), and less euphoria.

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