A clinical guide to

OPIOID ANALGESIA
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A clinical guide to

OPIOID ANALGESIA

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HISTORICAL NOTES AND PERSPECTIVES

CHAPTER 1
HISTORICAL NOTES AND PERSPECTIVES

“The pre-eminent place in any history of drugs must be assigned to opium.”
Richard Davenport-Hines

Opium derivatives have been used continuously throughout the ages for a variety of perception-altering purposes. Their therapeutic capacity as potent analgesics has made this drug class uniquely valuable. Indeed, the capability of medical providers to meet the imperative to relieve suffering would be largely unmet were it not for these drugs. This unmatched benefit to humankind, however, has come with a price. Recreational use, and compulsive use that becomes sustained by uncontrollable cravings, can undermine public health and can be viewed (and is judged) in medical, legal, social, and anthropologic contexts. The dichotomous and sometimes paradoxical reality of the potential “good” and the unlikely but ever-lurking “bad” of opioids used in a medical context has confronted, and no less confounded, physicians for centuries.

The history of man’s relationship with opioids is replete with ambivalence and highly mixed emotions, tensions, and strained—if not downright inconsistent—attitudes and policies. During the past three decades, the medical profession has become more attuned to these issues and its awareness has been increased by the advancing knowledge of pharmacology and the disquieting recognition of the large-scale public health tragedy of needless yet treatable pain.

More recently, there also has been increased insight into the fundamental risks associated with exposure to these drugs, particularly as they relate to the genetic, psychosocial, and situational predispositions toward abuse and addiction. It is a challenging era, characterized by both growing outrage over the undertreatment of pain and an evolving clarity that our most effective treatment, the opioid drugs, will be increasingly problematic unless the risks are fully understood and managed.

The need to identify and then nurture the proper balance between expanded access and a proactive effort to limit misuse, abuse, addiction, and diversion has never been more critical. Indeed, this “principle of balance” has been invoked as the most
effective and cogent means to create positive change in this arena (table 1). Increasingly, the scientific, clinical, and regulatory communities have jointly expressed a multilateral commitment to simultaneously ensure access to the therapeutic use of opioid drugs (and to expand this use as appropriate) while addressing the potential for harm. Efforts are being made to create balanced clinical guidelines and regulatory policies. Even the most challenging clinical confounds—such as treating the known substance abuser with opioids in an effort to relieve suffering and improve functional outcomes—are undergoing fresh appraisal.

Compelling need to implement the principle of balance motivated the Federation of State Medical Boards of the United States to create *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain*. The guidelines, which

<table>
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<th>Table 1. The principle of balance in opioid use</th>
</tr>
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<tbody>
<tr>
<td><strong>Medical availability</strong></td>
</tr>
<tr>
<td>While opioid analgesics are controlled substances, they are also essential medications and are absolutely necessary for relief of pain</td>
</tr>
<tr>
<td>Opioid analgesics should be accessible to all patients who need them for relief of pain</td>
</tr>
<tr>
<td>Governments must take steps to ensure adequate availability of opioids for medical and scientific purposes, including:</td>
</tr>
<tr>
<td>• Empowering medical practitioners to provide opioids in the course of professional practice</td>
</tr>
<tr>
<td>• Allowing practitioners to prescribe, dispense, and administer according to the individual medical needs of patients</td>
</tr>
<tr>
<td>• Ensuring that a sufficient supply of opioids is available to meet medical demand</td>
</tr>
</tbody>
</table>

**Drug control**

- When misused, opioids pose a threat to society

Clinicians must recognize that a system of controls is necessary to prevent abuse and diversion. Although the system of controls is not intended to interfere with legitimate medical use, controls are necessary to protect public health and should be understood, and supported, by the clinical community

- Minimizing risk of abuse and diversion during treatment of individual patients is part of the essential skill set needed for safe and effective clinical use of opioid drugs

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are endorsed by various federal and state regulatory bodies, professional organizations, and patient advocacy groups, have been a signal event among many educational, regulatory, and policy initiatives designed to promote a balanced perspective. A recent report card on regulatory issues, published by the University of Wisconsin’s Pain and Policy Studies Group (“Achieving Balance in State Pain Policy: A Progress Report Card,” available at http://www.medsch.wisc.edu/painpolicy), describes many positive changes that have emerged from this effort but overall suggests that there is still considerable room for improvement (table 2).

The intent of this book is to help clinicians make practical sense of the varied and often conflicting pharmacologic, clinical, and regulatory issues to promote the most healthful outcomes possible for patients in pain. The aim is to improve knowledge and skills related to both the principles of prescribing and the management of risk. In this way, healthcare professionals and those they serve may benefit increasingly from the unique therapeutic potential of this drug class and fear less the undeniable, yet manageable, potential for harm.

Table 2. Number of states with policy language that has potential to impede pain management

<table>
<thead>
<tr>
<th>Negative provisions</th>
<th>Number of states</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids are considered a treatment of last resort</td>
<td>10</td>
</tr>
<tr>
<td>Medical use of opioids is implied to be outside legitimate professional practice</td>
<td>14</td>
</tr>
<tr>
<td>The belief that opioids hasten death is perpetuated</td>
<td>15</td>
</tr>
<tr>
<td>Physical dependence or analgesic tolerance is confused with addiction</td>
<td>18</td>
</tr>
<tr>
<td>Medical decisions are restricted on the basis of patient characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Medical decisions are restricted on the basis of mandated consultation</td>
<td>11</td>
</tr>
<tr>
<td>Medical decisions are restricted on the basis of quantity prescribed or dispensed</td>
<td>10</td>
</tr>
<tr>
<td>Length of prescription validity is restricted</td>
<td>7</td>
</tr>
<tr>
<td>Practitioners are subject to additional prescription requirements</td>
<td>3</td>
</tr>
<tr>
<td>Other provisions may impede pain management</td>
<td>15</td>
</tr>
<tr>
<td>Provisions are ambiguous</td>
<td>33</td>
</tr>
</tbody>
</table>

Lessons from history
The history of opioids provides context for education predicated on the principle of balance. The history dates back millennia and provides many relevant lessons. It highlights elements that are unique to our contemporary times and issues that almost eerily recapitulate the experiences of other eras. The logical place to start this history discussion is with the “ontogeny” of opioids, a class of drugs originally derived from *Papaver somniferum*. Evidence found in a Sumerian ideogram, depicting the opium poppy as “the plant of joy,” suggests that this flowering plant was domesticated for its pharmacologically active milky white juice as long as 8,000 years ago. A papyrus dated 1552 BC advises Theban physicians about the use of opium in hundreds of potions for myriad “medicinal” purposes. Arab, Greek, and Roman physicians described opiate toxicity in the 2nd century BC, and Nero, the Roman emperor, took advantage of this quality of opium by intentionally overdosing Britannicus in AD 55, taking his throne. Egyptian documents describe the use of opium for pain relief, as do Roman documents, around this same epoch.

During ancient times, consumption of opiates (a term referring to the alkaloid derivatives of opium) became routine, even commonplace, among many seemingly upstanding citizens, and there is documentation that this occurred without the pathognomonic dose escalation and dysfunction attributed to addiction. Galen, for instance, reported that the political leaders of the day could distinguish the quality of the ingredients of their opiate concoctions, reducing consumption when necessary to execute their duties.

In the 16th century, both German and British physicians commonly prescribed opium admixtures, under the rubric of laudanum, for a variety of ailments. This practice soon became associated with quackery, since it was purported to be a panacea for all ills at a time when at least some rigor in medicine was being demanded. It was also around this time that there were observations describing tolerance and physical dependence.

By the turn of the next century, 2 schools of medicine had diverged in France. In the southern regions, physicians preferred tonics, whereas northern practices influenced by Parisian schools of thought placed great reliance on bloodletting and purging. The former approach was adopted by the English physician Thomas Sydenham. He, too, used the term *laudanum* for his alcohol-opium tinture. He wrote, “So necessary an instrument is opium in the hand of a skillful man, that medicine would be a cripple without it.”
During the 17th and 18th centuries, physicians and pharmacists throughout England, France, and Germany experimented with a variety of formulations and means of administration in both humans and animals. Physical dependence, manifested by an acute abstinence syndrome, became well known, mostly in persons using opiates for what would probably be classified as mood disorders today (ie, anxiety and depressive illness). This era is marked by a substantial increase in the use of psychoactive drugs in Europe for purely experiential purposes.

Concurrently, British commercial interests expanded the opium trade from India to China. This trade became a major revenue generator and offset the trade deficit from Chinese silk, spices, and other commodities. The opium trade had a devastating effect on productivity of Chinese peasants, however, and in 1799, the emperor of China issued a proclamation that prohibited importation of opium. This ban had limited effect, because market demand exceeded the capacity of imperial rule to stop the trade.

In 1805, Friederich Wilhelm Sertürner, an apothecary’s assistant in Hanover, Germany, isolated from opium a white crystalline powder that he thought would explain the sleep-inducing quality of the parent compound. He called this purified product morphium, after the Greek god of dreams and sleep, Morpheus. Apparently, Sertürner was not a disciplined scientist, and his eccentricities delayed appreciation of his discovery for more than a decade.

The Parisian pharmacist Pierre-Jean Robiquet perfected an extraction process for morphine, and morphine was soon promoted as both an analgesic and a cure for opium addiction. Commercial morphine appeared in London in 1821, and wholesale production by the German pharmacist Heinrich Emanuel Merck began a few years later.

With the development of the hypodermic syringe in the mid 19th century, morphine could be injected directly into painful areas, termed neuralgias, which was done with the thought that the injection would induce localized anesthesia.

**Public concern and legislation**

Early in the 20th century, growing use and abuse of opioids and other drugs in the United States led to increasing public concern and to reaction by politicians. In 1906, the Pure Food and Drug Act was passed, which gave the government the obligation of regulating drugs and establishing their safety and efficacy before their entry into the US market. This was followed in 1914 by the far-reaching Harrison Narcotics Act, which applied controls to
opioid anagesics and, among other features, prohibited physicians from prescribing opioids for addicts.

In 1919, the Supreme Court upheld this law (*Webb et al vs the United States*) and stated that a physician must not provide opioids for maintenance of an addict. Dispensing centers for maintenance were closed, driving procurement underground. Addicts who obtained drugs illegally became criminals, and drug use was increasingly viewed as being under the purview of the criminal justice system rather than the healthcare system. In 1937, the Marijuana Tax Act outlawed cannabis and heroin, adding further aspects of drug use to the criminal code.

Throughout the 20th century, efforts to stem abuse and addiction by law and regulation surged in the United States. In 1970, the Federal Controlled Substances Act increased the monitoring of the manufacturing, prescribing, and dispensing of opioids and other controlled substances. It required registration of all prescribers of controlled substances and categorized potentially abusable drugs into 5 schedules, each with different regulatory mandates. The law stipulated that drugs in Schedule II, such as morphine, could not be prescribed by telephone, nor could morphine prescriptions be refilled without a new written prescription. These federal efforts were mirrored at the state level, where a complex array of laws and regulations created further requirements for prescribers and patients and enacted an additional set of civil and criminal penalties that could be applied to those prosecuted.

This societal decision to regulate medical practice and criminalize the administration of opioid medications in some contexts led to secondary phenomena, which had effects of their own. Prescribers became increasingly concerned about the potential for investigation and sanction or prosecution. To some degree, this concern has contributed to the underuse of opioid medications. Equally important, the criminalization of opioid addiction fostered an illicit drug trade that, in turn, brought new problems, including the involvement of organized crime and violent gangs in drug trafficking. Over time, all these problems—undertreatment of pain, occurrence of opioid abuse and addiction, and criminal activities surrounding opioid trafficking—have increasingly undermined public health. Clearly, pursuant to pain management and opioid analgesia, there is a pressing need for rational and consistent policies, initial and continuing education of healthcare professionals, and application of sound principles of assessment, prescription, and management.
Conclusion
There is growing tension between clinicians’ needs to support therapeutic use of opioids, to address abuse and addiction as conditions that are fundamentally medical rather than legal, and to minimize societal harm resulting from drug abuse, addiction, and trafficking. These contemporary issues reflect an iterative evolution that dates back thousands of years. With the advantage of hindsight, it is apparent that the current medical, sociopolitical, and economic issues surrounding opioid use, misuse, and abuse do not depart much from those of previous eras. A new paradigm that brings historically adversarial parties together is needed. The principle of balance supports this paradigm and has potential to inform the creation of clinical guidelines, regulations, and laws that meet the needs of patients without compromising the appropriate societal demand for control of potentially abusable substances.

Suggested readings


Sydenham T. Medical observations concerning the history and cure of acute diseases. London, 1676
CHAPTER 2
THE ENDOGENOUS OPIOID SYSTEMS

The complex effects, both beneficial and adverse, of opioid analgesics can be traced to the interaction of these agents with endogenous opioid systems. Opioid compounds and their receptors exist throughout the central and peripheral nervous systems and in other tissues. Opioid systems are involved in a diverse array of homeostatic functions and movement control as well as the processing of noxious sensory input. The antinociceptive system, involved in pain modulation, is itself exceedingly complex. Information about this system is useful background for an understanding of the effects of opioid analgesics.

Mechanisms of opioid analgesia
Pain transmission in the spinal cord is regulated by a balance of facilitatory and inhibitory influences operating on the neural circuits of the somatosensory system. Noxious stimuli activate high-threshold primary sensory neurons in the periphery. This activity is conducted to their central terminals, which synapse on second-order nociceptive neurons in the spinal cord. Although opioid compounds are active in the periphery as well, they produce analgesia primarily by inhibiting nociceptive transmission in the central nervous system (CNS).

Opioid receptors located presynaptically and postsynaptically at the first central synapse in the spinal cord have been most extensively studied. Those located on the presynaptic nerve terminal decrease the release of excitatory neurotransmitters from nociceptive neurons, specifically the neurons that send small C-fibers and A-delta fibers into the periphery and respond to a variety of noxious stimuli. This presynaptic inhibition is caused by the effects of opioid receptor activation on ion channels. Specifically, opioid activation leads to hyperpolarization of the terminal through the opening of potassium channels or closing of calcium channels. These hyperpolarized neurons are less likely to have spontaneous discharge or evoked responses.

Opioid receptors located postsynaptically have similar effects on the second-order neuron. Hyperpolarization caused by changes in ion fluxes leads to a reduced response of this neuron as it receives excitatory input from first-order nociceptive neurons.
Signal transduction from opioid receptors occurs through binding to inhibitory G proteins. One opioid receptor can regulate several G proteins, and multiple receptors can activate a single G protein. Likewise, a single G protein can regulate several effectors, and a single effector can be activated by several G proteins. Through these mechanisms, a cascade of complex processes can be initiated, involving activation of protein kinases, stimulation of genes, and generation of other neuromodulators. These processes in turn alter the response characteristics of the neuron and lead to synthetic processes that can change various receptors or other structures. The interactions and outcomes remain poorly understood and are undergoing intensive investigation.

**Endogenous opioid systems and analgesia**

Opioids exert their analgesic effects by binding to and activating receptors that comprise part of an endogenous opioid system. This system normally operates to modulate sensory input caused by noxious stimuli, its response activated by endogenous peptide neurotransmitters. Opioids mimic and amplify the actions of these neurotransmitters.

**Endogenous opioid peptides**

The endogenous opioid system includes a large number of opioid peptides that are ligands for numerous types of opioid receptors. Some of these naturally occurring peptides produce morphinelike effects and can be displaced from their binding sites by opioid antagonists.

Three distinct families of endogenous opioid peptides have been well characterized: the endorphins, the enkephalins, and the dynorphins, which derive from the precursor polypeptides pro-opiomelanocortin, proenkephalin, and prodynorphin, respectively. More recently, 2 additional short peptides that display a high affinity and selectivity for μ opioid receptors have been identified. These peptides, endomorphin-1 and endomorphin-2, produce potent and prolonged analgesia in animals. However, the gene coding for them is yet unknown.

The endogenous opioid peptides bind to opioid receptors. In the CNS, there are 3 primary opioid receptor types that mediate analgesia, which are designated μ, κ, and δ (see table 3). Preferentially, enkephalins interact with the δ receptor, dynorphins interact with the κ receptor, and endorphins bind to both μ and δ receptors with comparable affinity. As noted previously, these peptides have diverse physiologic functions, one of which involves antinociception. In different systems and settings, they
can appear to function as neurotransmitters, neuromodulators or, in some cases, neurohormones. Research during the past 3 decades has only just begun to elucidate the physiologic roles of these peptides and the receptors with which they interact.

**Opioid receptors**

Opioid receptors, like other G protein–coupled receptors, are characterized by 7 transmembrane domains. High densities of opioid receptors are located in all areas of the CNS known to be involved in integrating information about pain—the brainstem, the medial thalamus, the spinal cord, the hypothalamus, and the limbic system. Opioid receptors also have been identified in the periphery. Recently, the μ, κ, and δ receptors have been cloned and their cDNA sequenced, yielding invaluable information about receptor structure and function.

Drugs that bind to opioid receptors are classified as agonists, partial agonists, mixed agonist-antagonists, and antagonists. Receptor activation by an agonist initiates pharmacologic actions (table 3), whereas an antagonist occupies the receptor without these effects. In patients with physical dependence, displacement of an agonist drug by an antagonist is associated with abstinence (withdrawal). The ability of the drug-receptor complex to initiate a pharmacologic effect is defined by the intrinsic activity of a drug. The intrinsic activity is further

<table>
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<th>Receptor</th>
<th>CNS location</th>
<th>Response on activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>Brain (laminæ III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)</td>
<td>μ₁: supraspinal analgesia, physical dependence; μ₂: respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence</td>
</tr>
<tr>
<td>κ</td>
<td>Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)</td>
<td>Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release</td>
</tr>
<tr>
<td>δ</td>
<td>Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)</td>
<td>Analgesia, euphoria, physical dependence</td>
</tr>
</tbody>
</table>

*CNS, central nervous system.*

described by the receptor occupancy required to yield a defined effect. If a drug has a sufficiently low intrinsic activity, high receptor occupancy still produces less than a maximal response, these drugs are called partial agonists. Partial agonists may also have antagonistic properties, because they compete with pure agonists for occupancy of opioid receptor sites. The degree to which they compete is determined by their affinity for the receptor. Buprenorphine hydrochloride, an analgesic now also used for addiction therapy, is a partial agonist with very high affinity for the \( \mu \) receptor; it can compete for the receptor and have antagonist properties and also is difficult to displace from the receptor once bound.

The opioid analgesics most commonly used in clinical practice bind selectively to the \( \mu \) receptor and are called \( \mu \)-agonists. Morphine is considered the prototypical \( \mu \)-agonist. Although there are many similarities between morphine and the other \( \mu \)-agonists, the different drugs can produce varied effects in the individual patient. For example, when a patient who is chronically exposed to one \( \mu \)-agonist is switched to another, pain can often be controlled by doses of the second drug that are far lower than predicted by their relative potencies, and both the pattern and severity of nonanalgesic effects can be distinct. This observation, now known as incomplete cross-tolerance, suggests that these \( \mu \)-agonists are not acting through identical receptors.

Pharmacologic studies completed more than a decade ago demonstrated that there were at least 2 \( \mu \) receptors, which were labeled \( \mu_1 \) and \( \mu_2 \) receptors. After the cloning of the \( \mu \) receptor, MOR-1, investigators have evaluated the possibility of different alleles in the gene coding for MOR-1 and different phenotypes from these genes based on single nucleotide polymorphisms (so-called splice variants). Studies have confirmed the existence of different alleles in the population, and antisense mapping of gene-coding fragments known as exons has established the existence of multiple polymorphisms. To date, 15 splice variants of the original gene encoding the \( \mu \) receptor (Oprm) have been identified, and at least 10 show high affinity and selectivity for \( \mu \) opioids in receptor-binding assays.

Considering the potential for both multiple opioid receptors distinguished by gene sequence (alleles) and multiple receptors distinguished by gene expression (polymorphisms produced by splice variants), it is likely that the \( \mu \) receptor actually comprises literally dozens of versions within the population. In an individual, different \( \mu \)-agonists may lead to different clinical effects, depending on the predominating form of the receptor. Recent studies
using ultra-low doses of μ-antagonists have identified an intriguing paradox. At these doses the antagonists are actually analgesic and they reverse opioid tolerance. Combined with a μ-agonist, they provide enhanced analgesia. These findings have suggested that the opioid receptor, which is widely recognized as a mediator of inhibitory actions, can exist in a form that is excitatory. This excitatory opioid receptor is blocked by ultra-low doses of the antagonist. Further research into this mechanism may lead to the use of antagonists at ultra-low doses in clinical practice.

Most recently, a receptor that is structurally similar to the opioid receptor was discovered. This receptor has been classified as opioid-receptor-like 1 (ORL₁). The natural ligand has been termed orphanin FQ (OFQ), or nociceptin. The physiology of this system is yet poorly understood. It appears to be involved in the central modulation of pain but does not appear to be implicated in respiratory depression.

**Clinical implications**

In the future, it may be possible to “type” a patient according to the predominant opioid receptor and select the drug that is most likely to have favorable effects. Combinations of opioids may ultimately be preferred in some patients to optimally activate the opioid system (some clinicians are empirically trying such combination therapy now). It is even possible that studies may allow development of opioids that activate antinociceptive systems without involving the “reinforcement and reward” brain systems that become problematic in persons genetically predisposed to addiction.

Research into the interaction between specific pain pathophys- iologies and opioid systems may illuminate the phenomenon of poor opioid sensitivity and allow development of therapies that can convert a patient’s poor response into a beneficial one. Studies have already shown that neuropathic pain is relatively less responsive to opioid therapy than pain of other types, a phenomenon that may be due, at least in part, to involvement of the N-methyl-D-aspartate (NMDA) receptor in the pathogenesis of neuropathic pain. Activation of the NMDA receptor has been shown to lessen the sensitivity of the opioid receptor, and NMDA receptor blockers reverse opioid tolerance in animal models. Further study of these interactions may yield useful combinations of drugs or preferred opioid treatment approaches in patients with relatively poor opioid responsiveness.

As receptors continue to be identified and characterized, the potential for development of highly selective agents increases. These drugs may have fewer unwanted effects or a better therapeu- peutic index. For example, some agents have more affinity for the
μ or κ receptor and thus might be expected to have different actions on the gastrointestinal tract. At present, knowledge of the complexity of the opioid system involved in analgesia should be a continuing reminder of the need for clinical flexibility. Opioid rotation, the process of switching opioid drugs in an effort to identify the one with the most favorable balance between analgesia and side effects, is a rational approach, given the multiple phenotypes of the μ receptor.

**Peripheral opioid mechanisms**

Recently, opioid receptors that are capable of mediating analgesia in humans have been discovered on peripheral sensory nerve terminals. The prevailing peptides found in the periphery are the endorphins and enkephalins. Pharmacologic experiments indicate that the characteristics of receptors located in the periphery are very similar to those of receptors in the brain.

This peripheral opioid system interacts with immune functions. During inflammation, opioid peptides secreted by immune cells can activate opioid receptors on sensory nerve terminals to inhibit nociception. In addition, humans have been shown to possess a peptide called enkelytin (proenkephalin A), which has a potent antibacterial action. It has been suggested that immune or neural signaling leads to enhanced proenkephalin proteolytic cleaving, thereby causing the release of both opioid peptides and enkelytin simultaneously. These findings constitute a new concept of intrinsic pain control that involves mechanisms traditionally used by the immune system for mounting a host response to fight pathogens. The potential effects of exogenously administered opioids on the immune system require further study.

Existence of peripheral opioid mechanisms has suggested the potential utility of peripherally administered opioid medications. For example, some placebo-controlled studies have demonstrated that relatively low doses of morphine, when administered into a site of peripheral injury (eg, a joint space after surgery), can produce analgesia. Other studies suggest a similar outcome from morphine applied topically to painful wounds, a result that is independent of systemic drug uptake. Further studies are needed to clarify the efficacy of peripherally administered opioid medications and to explain why there is such interindividual variance in responses.

**Conclusion**

The physiologic modulation of noxious stimuli involves a highly complex system that integrates the actions of multiple opioid
receptors and endogenous opioid peptides. The interaction of this system with different opioids is similarly complex. Future research that elucidates the pharmacology and molecular biology of the endogenous system holds great promise for development of new selective drugs, rational selection of treatments for individual patients, and fashioning of novel drug combinations to optimize the benefit and minimize the risks associated with opioid therapy.

**Suggested readings**
Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine’s analgesic potency and attenuate opioid tolerance/dependence liability. Pain 2000;84:121-31


The opioid analgesics can be divided into agonists, agonist-antagonists, and antagonists on the basis of their interaction with opioid receptors (table 4).

**Pure agonists**
Pure μ-agonists are generally preferred over agonist-antagonist drugs for management of moderate to severe pain. With no ceiling effect for analgesia and the availability of multiple formulations (table 5), they offer great flexibility to prescribers. Clinical experience with these medications throughout the ages for treatment of acute and chronic pain is extensive.

**Clinical pharmacology**
Although there is great intraindividual variation in the response to the different pure μ-agonists, the pharmacodynamic profile is similar across them. For analgesia, there is a concentration-response relationship that continues to slope upward until the patient becomes unconscious. Side effects are very common, and the clinical challenge is to identify a dose associated with a favorable balance between analgesia and side effects.

The concept of relative potency has important implications for the clinical use of opioid analgesics. All the opioids differ in potency, which is defined as the dose required to generate a given effect. If the doses of 2 opioids are appropriately adjusted, the same level of effect should be obtainable. In this context, therefore, potency does not mean strength of effect or efficacy. The efficacy of 2 opioids, one more potent than the other, is the same if the doses used are equianalgesic.

Numerous controlled trials have been done in populations with relatively little opioid exposure, to calculate the relative potencies between different opioids and between the same opioids given by different routes of administration. These studies have allowed the construction of an equianalgesic dose table (see table 5). The table describes relative potencies by listing the doses of different drugs and the administration routes that are equianalgesic to a standard, usually 10 mg of morphine given intravenously or intramuscularly. The equianalgesic dose table represents the best science but was developed from studies in selected populations.
Guidelines for switching opioids and routes of administration have been developed and are based on use of the table as a starting point for dose selection (see chapter 5, page 40).

**Adverse effects.** The most important potential adverse effect from use of the pure agonists is respiratory depression. These

**Table 4. Classification of opioid analgesics for pain management in the United States**

<table>
<thead>
<tr>
<th>Opioid type</th>
<th>Medications</th>
<th>Notes about therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure agonists</td>
<td>Codeine</td>
<td>• No clinically relevant ceiling effect to analgesia; as dose is raised, analgesic effects increase until analgesia is achieved or dose-limiting side effects supervene</td>
</tr>
<tr>
<td></td>
<td>Dihydrocodeine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levorphanol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meperidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymorphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propoxyphene</td>
<td></td>
</tr>
<tr>
<td>Agonist-antagonists</td>
<td>Partial agonists</td>
<td>• µ-Agonist with lower intrinsic efficacy (partial agonists) or agents that produce agonist effects at one receptor and antagonist effects at another (mixed agonist-antagonists)</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed agonist-antagonists</td>
<td>• Ceiling effect for analgesia</td>
</tr>
<tr>
<td></td>
<td>Butorphanol</td>
<td>• Some produce psychotomimetic side effects more readily than do pure agonist opioids</td>
</tr>
<tr>
<td></td>
<td>Dezocine</td>
<td>• Potential to induce acute abstinence in patients with physical dependency to agonist opioids</td>
</tr>
<tr>
<td></td>
<td>Nalbuphine</td>
<td>• In general, less preferred by patients with opioid addiction disorder</td>
</tr>
<tr>
<td></td>
<td>Pentazocine</td>
<td></td>
</tr>
<tr>
<td>Pure antagonists</td>
<td>Alvimopan*</td>
<td>• Compete with endogenous and exogenous opioids at µ receptor sites</td>
</tr>
<tr>
<td></td>
<td>Methylnaltrexone*</td>
<td>• Administered for prevention or reversal of opioid effects</td>
</tr>
<tr>
<td></td>
<td>Naloxone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Tramadol</td>
<td>• µ-Agonist distinguished by a mechanism of action that includes effects on monoamines, such as serotonin</td>
</tr>
</tbody>
</table>

* Not yet commercially available; minimal systemic absorption by enteral route.
<table>
<thead>
<tr>
<th>Opioid Analgesic</th>
<th>Equianalgesic Doses*† (mg)</th>
<th>Half-life (hr)</th>
<th>Peak Effect (hr)</th>
<th>Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 IM/IV/SQ</td>
<td>2-3</td>
<td>0.5-1</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td>20-30 PO†</td>
<td>2-3</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Controlled-release morphine</td>
<td>20-30 PO†</td>
<td>2-3</td>
<td>NA</td>
<td>8-12</td>
</tr>
<tr>
<td>Sustained-release morphine</td>
<td>20-30 PO†</td>
<td>2-3</td>
<td>NA</td>
<td>12-24</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 IM/IV/SQ</td>
<td>2-3</td>
<td>0.5-1</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td>7.5 PO</td>
<td>2-3</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20-30 PO</td>
<td>2-3</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Controlled-release oxycodone</td>
<td>20-30 PO</td>
<td>NA</td>
<td>3-4</td>
<td>8-12</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1 IM/IV/SQ</td>
<td>NA</td>
<td>0.5-1</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>10 PR</td>
<td>NA</td>
<td>1.5-3</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>15 PO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2 IM/IV/SQ</td>
<td>12-15</td>
<td>0.5-1</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>4 PO</td>
<td>12-15</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Methadone</td>
<td>Variable</td>
<td>12-150</td>
<td>1-2</td>
<td>6-8</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 PO</td>
<td>2-4</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50-100 µg IV/SQ</td>
<td>7-12</td>
<td>&lt;10 min</td>
<td>1-2</td>
</tr>
<tr>
<td>Fentanyl transdermal system</td>
<td>NA</td>
<td>NA</td>
<td>12-24</td>
<td>48-72 per patch</td>
</tr>
<tr>
<td>Oral transmucosal fentanyl citrate</td>
<td>NA</td>
<td>7-12</td>
<td>15-30 min</td>
<td>1-2</td>
</tr>
</tbody>
</table>

FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; NA, not applicable; PO, by mouth; PR, per rectum; SQ, subcutaneous.

* Dose provides analgesia equivalent to 10 mg of morphine given by IM route. These ratios are useful guides when switching drugs or routes of administration. In clinical practice, the potency of the IM route is considered to be identical to IV and SQ routes.

† When switching from one opioid to another, incomplete cross-tolerance requires a reduction in the dose of the new drug by 25% to 50%, to prevent excessive opioid effects. Provision of “rescue” medication during the conversion period (a few days) prevents breakthrough pain.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation, nausea, sedation are most common; respiratory depression is rare when titrated to effect</td>
<td>Standard for comparison of opioids; multiple routes available</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Once-a-day morphine recently approved in United States</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Potency and high solubility may be beneficial for patients requiring high opioid doses and for SQ administration</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Available as single entity or combined with aspirin or acetaminophen</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Oral immediate release and extended release formulations are currently under FDA review</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>With long half-life, accumulation possible after beginning or increasing dose</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Highly variable half-life and potential for accumulation require increased vigilance for development of opioid toxicity; can prolong QTc interval</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Available only in combination with acetaminophen or aspirin</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Can be administered as continuous IV or SQ infusion</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Refer to package insert for equianalgesic dosing guidelines for oral and parenteral medication; currently available doses not usually recommended for opioid-naïve patients; not recommended for acute pain</td>
</tr>
<tr>
<td>Typical opioid effects</td>
<td>Not recommended for opioid-naïve patients; recommended starting dose for breakthrough pain is 200-400 µg, even with high “baseline” opioid</td>
</tr>
</tbody>
</table>

that might result from relative underdosing. When switching to methadone from another drug, the reduction in the equianalgesic dose should be greater, usually 75% to 90%.
‡ Extensive survey data suggest that the relative potency ratio of IM to PO morphine, which has been shown to be 1:6 in an acute dosing study, is 1:2 to 1:3 with chronic dosing.
opioids produce a concentration-dependent shift in the carbon dioxide response curve. At clinically appropriate doses, compensation for the shift occurs and respiratory rate typically does not decline. Tolerance to the respiratory effects usually develops quickly, and doses can be steadily increased without risk. If some other cardiopulmonary insult occurs, however, the patient’s response may be greater than it would have been without the opioid present.

Clinical evidence of this phenomenon is observed when patients receiving long-term therapy experience respiratory compromise associated with a new insult, such as pneumonia, and show improvement after administration of naloxone. The response to the opioid antagonist in this situation does not mean that the opioid was the primary driver for the respiratory problem, but it does show that there is some ongoing effect on respiratory reserve even after opioid therapy has continued for a time.

Other side effects more commonly have clinical impact (see chapter 6, page 53). Nausea and mental clouding or sedation are common, but tolerance to these effects usually develops within days to weeks. Constipation is also very common, and adaptation to this effect occurs much less reliably. Many patients require ongoing laxative therapy during long-term treatment.

Some patients experience fatigue, confusion, or other psychotomimetic effects (such as nightmares or hallucinations), myoclonus, other gastrointestinal effects (such as bloating, symptoms of reflux, or anorexia), dysphoria or other mood effects (such as mood lability), headache, urinary retention, or sexual dysfunction. Itch is relatively common during acute administration and rarely reflects a true allergic response. Many factors may predispose to adverse effects, including advanced age, medical comorbidities, and concurrent administration of other drugs. Successful management of side effects increases the likelihood of a favorable outcome and potentially allows the use of a more efficacious opioid dose over time.

Outcomes generally considered under the rubric of chemical dependency or drug abuse should also be considered potential adverse effects of opioid use. All opioids that have agonist effects interact with deep brain structures that subserve “reinforcement and reward” mechanisms. It has been estimated that at least 5% to 10% of people have variants of this system that predispose to addiction to opioids or other drugs with potentially reinforcing effects (see chapter 9, page 67). Presumably, these individuals represent a group that is more likely to experience euphoric effects when an opioid is first taken. The likelihood of
addiction is thought to increase if this biologic predisposition occurs in tandem with a complex and poorly understood set of psychologic, social, and situational factors.

In most patients, the disease of addiction presents at an early age. A patient who has reached middle age without developing compulsive use behaviors to potentially abusable drugs, including alcohol and nicotine, appears to be at very low risk. This is particularly true if there is also no family history of addiction. Patients who may be at relatively increased risk must be identified so that opioid administration can be structured in a manner that lessens the liability.

Development of true addiction is not the only concern during long-term opioid administration and it indeed appears to be far less common than problems related to misuse and abuse. Drug diversion, a criminal act, also is rarely encountered but must be considered among the risks of therapy. To date, there are very few empirical data to help define the patterns of these behaviors or their clinical meaning. However, acute short-term administration is clearly less likely than long-term administration to be associated with any of these potential outcomes. Healthcare providers, patients, and families require reassurance about these concerns, but at the same time, prescribers must be aware of the need for careful monitoring for nontherapeutic outcomes.

Members of the drug class

Morphine. Morphine is often considered the prototype pure \( \mu \)-agonist. It is available in multiple formulations and has been extensively used in management of both acute and chronic pain.

Morphine has 2 biologically active metabolites, morphine-6-glucuronide and morphine-3-glucuronide. Morphine-6-glucuronide binds to the opioid receptor and is believed to contribute to the effects of the parent compound. Morphine-3-glucuronide does not bind to the receptor and is believed to contribute in some cases to adverse effects such as myoclonus and confusion. Usually, the metabolites are considered a clinical issue only when their concentrations in the blood are likely to fluctuate differently than the concentration of the parent compound. This can occur during renal insufficiency, in which concentrations of the renally cleared metabolites relative to the parent compound can become very high. Patients with fluctuating renal insufficiency are, on theoretical grounds, the most likely patients to be at risk for unpredictable morphine effects because of a changing ratio between metabolite and parent compound.

Morphine is available in immediate-release and modified-release formulations. The latter formulations have an 8-
24-hour duration of effect, depending on the specific drug and individual variation.

**Hydromorphone.** Hydromorphone is significantly more potent than morphine, permitting smaller volumes to be used when injecting equianalgesic doses. Like morphine, it can be administered through oral, parenteral (subcutaneous, intramuscular, and intravenous), rectal, or intraspinal (epidural and intrathecal) routes. Its relatively short half-life of elimination (2 to 3 hours) facilitates dose titration but complicates efforts to use hydromorphone for chronic pain. Modified-release formulations, which will increase the convenience of oral therapy for chronic pain, are in development and are currently being reviewed by the US Food and Drug Administration (FDA).

Because hydromorphone is very soluble in water, high-concentration solutions can be made and are particularly suitable for subcutaneous administration, including continuous subcutaneous infusion. A high-potency preparation (10 mg/mL) is commercially available. Side effects associated with hydromorphone are qualitatively similar to those associated with opioids in general, and most often include constipation, nausea, and sedation. Hydromorphone may be preferred over morphine for patients with decreased renal clearance, to preempt the potential for toxicity from morphine metabolite accumulation.

**Oxycodone.** Oxycodone is available in both an immediate-release and a modified-release (8- to 12-hour duration) preparation. The immediate-release formulation is available as a single entity and in combination with acetaminophen or aspirin. Lower doses of oxycodone (eg, 2.5 mg, 5 mg, 7.5 mg, 10 mg) in combination with a nonopioid coanalgesic are frequently used for management of acute pain in patients with limited prior opioid exposure. When these drugs are used, care must be taken not to exceed the recommended maximal dose of the coanalgesic (for example, 4 g or less of acetaminophen per day). The modified-release formulation of oxycodone is now widely used for management of chronic pain.

**Oxymorphone.** Oxymorphone has a short half-life and is both a potent congener of morphine and an active metabolite of oxycodone. It is presently available in suppository and injectable forms. Although an oral form is not yet available, immediate-release and modified-release formulations are in development and are currently under review by the FDA. Oxymorphone may have particular utility for patients subject to drug-drug interactions since it does not affect the CYP2D6 or CYP3A4 enzymes.

**Meperidine.** Meperidine is not preferred for long-term use because of the risk of toxicity associated with accumulation of
the metabolite normeperidine. Normeperidine can cause dysphoria, tremulousness, hyperreflexia, and seizures. It is renally cleared, and use of meperidine in patients with kidney disease is not recommended.

**Methadone.** In the United States, methadone is commercially available as a racemic mixture. The \(l\)-isomer is the opioid compound; the \(d\)-isomer does not bind to the opioid receptor but instead blocks the \(N\)-methyl-\(d\)-aspartate (NMDA) receptor. This pharmacology has been adduced to explain methadone’s apparent increased potency when it is administered to a patient who is already receiving another opioid. There are anecdotal observations suggesting particularly good efficacy against some pains that were otherwise poorly responsive to opioids.

The unique pharmacology of methadone, its potential efficacy, and its low cost have combined to increase interest in the drug. This is appropriate as long as the challenges inherent in dosing a medication with an uncertain potency and a long and variable half-life (from 12 to more than 150 hours, with the usual half-life approximating 24 hours) are appreciated. It is recommended that a switch to methadone be accompanied by a large (75% to 90%) decrease in the calculated equianalgesic dose, to account for the potential for high potency. Because the plasma concentration of methadone rises to steady-state levels over 4 to 5 half-lives, rapid titration to an effective dose can subsequently be followed by continued escalation of the plasma concentration, ultimately leading to toxicity (known as accumulation).

Finally, there are recent reports linking methadone to prolongation of the QTc interval. At a critical point, this prolongation can predispose to life-threatening cardiac arrhythmia. In short, methadone dosing requires close monitoring, use of low starting doses, an adequate interval between dose changes, and caution in patients who have heart disease or medications with concurrent effects on the QTc interval.

**Levorphanol.** Levorphanol is another opioid with a long half-life (usually 12 to 15 hours). It generally can be administered at an interval of 6 hours and may be useful particularly in patients who are unable to tolerate, or access, modified-release opioids.

**Codeine.** Codeine is the most commonly used opioid for mild or moderate acute pain. It is typically used in combination with aspirin or acetaminophen. Clinical experience suggests that nausea and constipation are more commonly encountered with codeine than with equianalgesic doses of other opioids.

**Propoxyphene.** Propoxyphene is a weak opioid agonist that, when administered at typical doses, has an efficacy similar to that of aspirin or acetaminophen. Like meperidine, propoxyphene
has an excitotoxic metabolite that can accumulate, particularly in the setting of renal insufficiency. It is not preferred for management of chronic pain or for use in older patients.

**Hydrocodone, dihydrocodeine.** The oral analgesic potency of hydrocodone and dihydro-codeine is approximately 50% to 100% that of oral morphine. In the United States, they are available only in combination with acetaminophen or aspirin. The doses provided in these combination products are such that these medications typically are used for treatment of acute moderate to severe pain in patients with limited opioid exposure.

**Fentanyl.** Fentanyl is a synthetic opioid that is characterized by both high potency and comparatively high lipid solubility. A transdermal fentanyl patch is available for continuous opioid analgesia, and an oral transmucosal formulation is available for relief of brief, episodic severe pain (e.g., breakthrough pain). Each transdermal fentanyl patch provides 48 to 72 hours of pain relief at steady state. Some patients consider the patch delivery form and the long dosing interval to be favorable characteristics. The fentanyl patch is particularly useful for patients who are unable to swallow or absorb an orally administered opioid, and studies that suggest a lesser potential for constipation provide support for a trial treatment with fentanyl when this symptom is especially problematic.

The pharmacokinetics of the transdermal system are complex and may be variable across patients. The formulation produces a subcutaneous depot, resulting in a slow onset of effect after a dose change and in a prolonged apparent elimination half-life (usually 24 hours) after the patch is removed. Steady-state concentrations are not approached for 1 to 3 days and sometimes longer. Oral transmucosal fentanyl is approved for treatment of cancer-related breakthrough pain but has been used for other types of episodic severe pains in opioid-tolerant patients. This formulation incorporates fentanyl into a lozenge that is sucked, allowing partial absorption through the buccal mucosa. The formulation has been shown to be effective and well tolerated and has an onset of effect faster than comparable doses of “immediate-release” oral opioids.

**Agonist-antagonists**
Use of agonist-antagonists for persistent pain generally is not preferred because of their ceiling dose for analgesia and the potential for inducing an acute abstinence syndrome in patients taking opioid agonists. Some of these medications, such as pentazocine and butorphanol, also have a higher likelihood of psychotomimetic side effects than the pure agonists. Studies sug-
gest that these opioids have a lower abuse potential than the pure opioid agonists in the known addict population, but this property has limited relevance in the general patient population. Buprenorphine, a partial agonist, is now available in the United States for office-based substitution treatment of opioid addiction.

**Pure antagonists**

Opioid antagonists exert their pharmacologic effect by competing with endogenous and exogenous opioids at μ receptor sites. Their role in pain management is primarily to prevent or reverse opioid-induced adverse effects. Low doses of oral naloxone have been shown to reverse opioid-induced bowel dysmotility without reversing analgesia. Use of naloxone, however, is not without risk, because some patients experience uncomfortable signs of systemic opioid withdrawal. Methylaltrexone and alvimopan, opioid antagonists whose activity is restricted to peripheral receptors when ingested orally, are currently undergoing investigation for prevention or reversal of opioid-induced bowel effects without reversal of analgesia or precipitation of withdrawal symptoms. Some studies suggest that ultra-low doses of opioid antagonist drugs have analgesic effects (see chapter 2, page 9). The clinical utility of this observation is currently under study.

**Drug metabolism and potential interactions**

Most opioids are metabolized through the liver microsomal cytochrome P-450 (CYP) system. The enzymes CYP2D6 and CYP3A4, which are responsible for metabolism of a wide variety of drugs, are the most important enzymes for opioid metabolism. Patients may lack normal levels of enzymatic activity to metabolize opioids at expected rates because of genetic factors, severe liver disease, or competition with other medications.

The potential importance of enzyme activity is illustrated by codeine. Codeine is actually a prodrug that requires metabolic transformation to morphine. Patients who are slow metabolizers at the CYP2D6 isozyme produce little morphine from codeine and are unlikely to benefit after codeine administration.

Concomitant treatment with an inducer of a particular enzyme may lead to decreased levels of medications that are metabolized by that enzyme; treatment with an inhibitor may lead to increased levels. There are many potential interactions (table 6). It is likely that these interactions can produce clinically relevant effects, warranting closer monitoring, but further research is necessary to clarify their clinical implications.
Conclusion
There is an ever-enlarging pharmacopeia of opioid analgesics in a variety of formulations and delivery systems. A fundamental understanding of the clinical pharmacology of opioids can inform drug selection and assist in anticipating, and managing, both favorable and adverse opioid effects.

Table 6. Potential drug interactions for major cytochrome P-450 enzymes CYP2D6 and CYP3A4

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Amitriptyline, bupropion, clomipramine, clonazepam, codeine, desipramine,</td>
<td>Citalopram (weak), desipramine, fluoxetine, olanzapine (weak), paroxetine,</td>
<td>Carbamazepine, phenobarbital,</td>
</tr>
<tr>
<td></td>
<td>dextromethorphan, doxepin, fluoxetine, haloperidol, hydrocodone, imipramine,</td>
<td>sertraline, venlafaxine (weak)</td>
<td>phenytoin</td>
</tr>
<tr>
<td></td>
<td>methadone, modafinil, morphine, nortriptyline, olanzapine, oxycodone,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>paroxetine, sertraline, tiagabine, tramadol, venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Alfentanil, alprazolam, amitriptyline, bupropion, citalopram, clozapine,</td>
<td>Dexamethasone, dextromethorphan, fluoxetine, paroxetine (weak), sertraline,</td>
<td>Carbamazepine, dexamethasone,</td>
</tr>
<tr>
<td></td>
<td>cyclosporin, dexamethasone, dextromethorphan, etoposide, fentanyl, fluoxetine,</td>
<td>venlafaxine</td>
<td>erythromycin, modafinil,</td>
</tr>
<tr>
<td></td>
<td>ifosfamide, imipramine, ketamine, lidocaine, meperidine, modafinil, paclitaxel,</td>
<td></td>
<td>phenobarbital, phenytoin</td>
</tr>
<tr>
<td></td>
<td>prednisone, sertraline, tamoxifen, tiagabine, venlafaxine, vincristine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Suggested readings
Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. J Pain Symptom Manage 2002;24:71-90


CHAPTER 4
POSITIONING THERAPY
BY COMPREHENSIVE PAIN ASSESSMENT

Treatment strategies for chronic pain may involve a primary therapy directed against the etiology of the pain and 1 or more specific analgesic therapies (table 7). A comprehensive pain assessment provides the information necessary to determine the feasibility and appropriateness of primary therapy and create a therapeutic strategy focused on pain relief, improved function, and enhanced quality of life. In the absence of comparative studies of single or combined therapies, the selection of 1 or more treatments usually is a matter of clinical judgment. In some cases, a single therapy, such as an analgesic medication, meets the needs of the patient. If this approach proves inadequate, or the assessment indicates a degree of complexity unlikely to be optimally treated by one approach alone, the clinician must promote a multimodality strategy, the details of which may vary from patient to patient or evolve over time in the individual.

The decision to undertake a trial of opioid therapy is challenging, given the paucity of studies that have evaluated or compared outcomes. To some extent, positioning of therapy is based on conventional practice, but this has been evolving during the past 2 decades and there is no clearly defined standard of care in most cases.

The positioning of opioid therapy, therefore, is fundamentally a clinical judgment based on an understanding of the evolving nature of clinical practice, a rapidly changing body of medical literature pertaining to risks and benefits, the specific information gleaned from a comprehensive patient assessment, and an appraisal of the clinician’s own skills in the use of this approach. Given the great variability in the populations with chronic pain, the most suitable guideline for positioning opioid therapy involves a general strategy based on a series of questions that should be considered by the clinician (table 8).

Conventional practice
It is useful in discussing the positioning of opioid therapy to consider cancer pain first. A worldwide consensus has evolved concerning the utility of opioid therapy in cancer pain management,
### Table 7. Categories of pain treatments

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapy</td>
<td></td>
</tr>
<tr>
<td>Nonopioid drugs</td>
<td>Acetaminophen, nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Adjuvant analgesics</td>
<td>Antidepressants, anticonvulsants</td>
</tr>
<tr>
<td>Opioids</td>
<td>Morphine, oxycodone, fentanyl, methadone, oxymorphone, hydromorphone</td>
</tr>
<tr>
<td>Rehabilitative approaches</td>
<td>Modalities (heat, cold), physical therapy, occupational therapy</td>
</tr>
<tr>
<td>Psychologic approaches</td>
<td>Cognitive techniques (biofeedback, hypnosis, relaxation), behavior therapy, other psychotherapies</td>
</tr>
<tr>
<td>Injection therapies and</td>
<td>Trigger point injections, spinal injections, neural blockade, neuraxial infusion</td>
</tr>
<tr>
<td>anesthesiologic approaches</td>
<td></td>
</tr>
<tr>
<td>Neurostimulatory approaches</td>
<td>Transcutaneous electrical nerve stimulation, spinal cord stimulation</td>
</tr>
<tr>
<td>Surgical approaches</td>
<td>Cordotomy, neuroablation</td>
</tr>
<tr>
<td>Complementary and alternative</td>
<td>Acupuncture, chiropractic therapy, massage, nutritional approaches and nutraceuticals, energy therapies</td>
</tr>
<tr>
<td>medicine approaches</td>
<td></td>
</tr>
<tr>
<td>Lifestyle changes</td>
<td>Weight loss, exercise</td>
</tr>
</tbody>
</table>

### Table 8. Strategy for appropriate positioning of opioid therapy for chronic pain

Consider a trial of opioid therapy for any patient with chronic or frequently recurrent pain of moderate to severe intensity, on the basis of responses to the following questions:

1. What is conventional practice for pain of this type?
2. Are opioids likely to work well?
3. Is the patient at relatively increased risk of side effects by virtue of medical comorbidities or treatments?
4. Are there other available therapies that might be considered in lieu of an opioid trial, for which there is evidence of the same or better efficacy at no greater risk?
5. Are there therapies that would be appropriate to try before opioid therapy or that should be undertaken in tandem with a trial of opioid therapy?
6. Is the patient likely to manage opioid therapy responsibly?
7. Does this patient have a pain problem for which opioid therapy could be administered with a likelihood that the treatment strategies employed are within the clinician’s knowledge and skills? If not, could the clinician prescribe the therapy with the help of a consultant, or should referral be considered?
and this provides an informative backdrop for decision making in other populations. Specifically, pharmacotherapy is widely considered the mainstay approach to management of cancer pain, and opioid therapy specifically is considered the standard of care for management of moderate to severe chronic pain. This approach became accepted after the dissemination of a broad paradigm for drug selection by a committee of the World Health Organization in the mid 1980s. Surveys of cancer patients treated according to this paradigm have concluded that opioids can provide adequate pain control for more than three quarters of these patients.

Many studies have found that cancer pain is undertreated despite the acceptance of opioid therapy. Populations at relatively increased risk of undertreatment include women, minority populations, and persons with a history of substance abuse. Efforts to educate clinicians as a means to lessen undertreatment have been ongoing for many years. Progress has been made, but more needs to be done.

As a result of a positive experience in the treatment of cancer pain, a consensus also has evolved that opioid therapy should be considered a mainstay for treatment of chronic pain associated with other life-threatening illnesses. Studies have shown that advanced AIDS is similar to metastatic cancer in the prevalence and variety of chronic pain syndromes. Opioid therapy for moderate to severe chronic AIDS-related pain is preferred, notwithstanding the challenges of this approach in patients with a history of drug abuse. Again, safe and effective therapy in this population requires skills in the assessment and management of substance abuse.

In contrast to the use of opioids for treatment of cancer pain or pain associated with other serious illnesses, the role of long-term opioid therapy for most other chronic pain conditions has not achieved widespread consensus. Nonetheless, much has changed during the past 20 years. Most notably, there is now widespread agreement within the international community of pain specialists that opioids can yield highly favorable responses in selected patients with chronic pain. Pain specialists accept the view that some patients with chronic pain of virtually any type may respond to opioid therapy in a manner identical to the cancer pain population. In the United States, consensus documents from several professional societies, including the American Pain Society, the American Academy of Pain Medicine, and the American Society of Addiction Medicine, endorse this view.

Nevertheless, use of opioid therapy for management of chronic nonmalignant pain continues to be ill-defined and controversial.
Unfortunately, there is limited evidence of long-term efficacy or safety from controlled trials, few data confirming a positive effect on function or quality of life, and very little information about the risks of misuse, abuse, or addiction among different opioid-treated populations. There also are no validated methods for selecting patients who are likely to benefit or to take the medications responsibly over a period that may extend to many years.

Yet, pain specialists have accumulated a large amount of clinical experience, which is supported by the available data and strongly endorses the view that opioid therapy should be tried in selected patients with chronic pain. The decision to proceed requires a detailed assessment of the patient, an understanding of the existing data pertaining to the potential for pain relief and the risk of adverse outcomes (including misuse, abuse, and addiction), and the skills to undertake the approach in a manner that optimizes benefit (table 9).

Effectiveness and risk
Many studies have evaluated opioid therapy for chronic nonmalignant pain. Controlled clinical trials have established the efficacy of different opioids in a variety of pain syndromes, including neuropathic pains. For example, placebo-controlled trials of several weeks’ duration have confirmed the efficacy of oxycodone in populations with painful osteoarthritis and low back pain. Studies that evaluated treatment over a period of many weeks have confirmed that morphine is more effective than a tricyclic antidepressant (and both were more effective than placebo) for postherpetic neuralgia and oxycodone is more effective than placebo for painful diabetic neuropathy. A randomized, open-label study that extended over a year documented a modest benefit from morphine over conventional therapy in patients with varied chronic pain syndromes, particularly improvements in the psychologic domain. Other long-term, open-label studies showed continued benefit with a modest or no dose increase as well as tolerable side effects for a subset of patients receiving fentanyl or oxycodone.

The results of these studies should be interpreted with caution, because study methodology and duration of treatment may not apply to usual clinical scenarios. Most important, there are relevant selection criteria for studies, such as no overt history of substance abuse, that may limit the generalizability of the results.

It is also important to recognize that earlier literature pertaining to opioid therapy for chronic pain, which largely originated from pain treatment centers, documented the potential for negative outcomes associated with treatment. These outcomes included more severe disability, less effectiveness of rehabilitative therapy, and drug misuse.
The available literature thus suggests a spectrum of outcomes associated with opioid therapy. Although treatment may become a problem in some disabled patients, a subpopulation of patients...
with chronic nonmalignant pain appears to attain at least partial relief from opioid analgesics for a prolonged period, without development of opioid toxicity, clinically significant tolerance, or abuse behaviors. Some patients who experience pain relief have significant improvement in functional status, but others do not. Although opioid responsiveness can vary with characteristics of the patient or pain syndrome, no subgroup of patients with chronic pain appears to be inherently resistant to this therapy.

Risk of adverse pharmacologic outcomes

The risk of major organ dysfunction and the incidence of persistent side effects are 2 major considerations that must be taken into account when prescribing opioids to patients with chronic nonmalignant pain. Subtle neuropsychologic impairment is a particularly important potential side effect, because its presence could undermine concurrent rehabilitative efforts.

Major organ toxicity after exposure to opioid analgesics has not been observed among cancer patients or patients receiving methadone maintenance. Pulmonary edema has been reported in several dying cancer patients who were receiving high doses of an opioid, but this phenomenon is not relevant to the routine treatment setting. A variety of dysimmune effects have been reported in animal models, but human data are yet minimal and studies also have demonstrated immunosuppressive effects from unrelieved pain. In sum, there is no evidence that long-term opioid therapy produces major organ dysfunction.

In contrast, reversible side effects are common during opioid therapy. Acute administration of an opioid produces changes in the central nervous system, hypothalamic-pituitary axis, peripheral vasculature, gastrointestinal tract, urinary tract, and skin. These actions may produce side effects such as nausea, constipation, mental clouding or confusion, urinary retention, or itch. With long-term opioid administration, tolerance develops at different rates to each effect. On the basis of clinical observations, constipation is the most common opioid side effect over the long term; tolerance to constipation may develop very slowly or not at all. Cognitive impairment is commonly observed after acute administration of opioids in opioid-naïve patients or dose escalation in patients receiving chronic therapy. However, these effects typically wane with stable long-term therapy. In studies of cancer patients, cognitive impairment is generally not problematic after a few weeks of opioid treatment, and several studies have confirmed that the ability to drive is preserved in most patients during long-term therapy. In fact, one study
suggested that unrelieved pain was more likely to contribute to impaired driving skills than was opioid treatment.

In a small proportion of patients, cognitive impairment may persist. Given the high prevalence of polypharmacy and significant medical comorbidities in the population with chronic pain, it is likely that the problem actually is multifactorial in many patients. More research is needed to clarify this issue, and the potential for cognitive impairment must be evaluated when opioids are employed in the clinical setting.

**Risk of addiction**
The potential for misuse, abuse, and addiction is the most significant issue to address in the assessment of chronic opioid therapy for nonmalignant pain. This concern is ubiquitous in all clinical settings but has had the greatest impact on the management of this population. Overall, the literature provides evidence that the outcomes of drug abuse and addiction are rare among patients who receive opioids for a short period (ie, for acute pain) and among those with no history of abuse who receive long-term therapy for medical indications. The risk should not be assumed to be nil, however, and it may vary with specific characteristics of the patient. Assessing the risk of addiction, administering therapy in a manner consistent with the level of risk, and responding appropriately to the possibility that problems are developing are fundamental elements to safe and effective use of opioid therapy and are discussed later in this volume.

**Patient assessment**
All patients with chronic pain should undergo a comprehensive pain assessment that includes thorough medical history taking, physical examination, and confirmatory laboratory and radiographic procedures, if appropriate. The assessment should be used to characterize the pain and prioritize other physical and psychosocial problems that may influence pain therapy or be amenable to primary treatment. It permits the development of a treatment strategy that addresses the major clinical issues and facilitates decision making about the role of opioid therapy.

**Characterizing the pain complaint**
Because pain is inherently subjective, patient self-report is the “gold standard” for assessment. The information elicited from the patient should focus on:
- Temporal features (onset, daily pattern, and course)
- Location (primary sites and patterns of pain radiation)
• Severity
• Quality
• Associated factors that exacerbate or relieve the pain

Other relevant information that should be collected includes details about medical and surgical conditions (related or unrelated to the pain), history of persistent pain, previous pain treatments, and prior use of licit drugs (including alcohol, tobacco, and over-the-counter and prescription medicines) and illicit drugs.

**Clarifying etiology, pathophysiology, and pain syndrome**

The history, examination findings, and results of laboratory or imaging studies provide the data necessary to characterize the patient’s pain. Identifying the etiology, syndrome, and pathophysiology of pain is extremely useful, because it may inform judgments about underlying organic processes, suggest the need for further evaluation, guide the selection of treatments, and indicate prognosis.

A discrete etiology for the pain may clarify the nature of the disease and suggest a primary therapy. An etiology that appears sufficient to explain the pain may or may not be evident. In some cases, an etiology may be identified that appears to be one factor among others contributing to the pain, and in other cases, an appropriate evaluation yields no clear evidence of a disease process capable of sustaining the pain. When pain appears to be disproportionate to any identifiable pathologic process, it usually is real (that is, truly experienced) to the patient. The clinical challenge is to interpret the nature of the pain in the absence of objective findings. In some cases, there is evidence that the pain is sustained by some functional disturbance in the nervous system (eg, neuropathic pains, headache), and in others, there is evidence that the pain is predominantly related to psychologic factors. These processes can coexist. If no reasonable inference can be drawn about the cause of the pain, the problem should be labeled idiopathic.

Inferences about the putative mechanisms that may be sustaining the pain are linked to the search for responsible etiologies and are valuable in the assessment of pain. Although in many cases pathophysiologic labels cannot be proven and undoubtedly oversimplify very complex processes, they are now widely accepted in clinical practice. Additional evaluation by behavioral medicine experts (eg, psychologist, psychiatrist) and rehabilitation experts (eg, physiatrist, physical therapist, occupational therapist) with training in chronic pain, if possible, can be very helpful in providing important supplementary information, concurrent diagnoses, and comanagement strategies.
Pain with a predominating organic contribution can be described as nociceptive or neuropathic. Nociceptive pain is pain that is perceived to be commensurate with tissue damage associated with an identifiable somatic or visceral lesion. Such pain originating from somatic structures (somatic pain) is usually well localized and described as sharp, aching, throbbing, or pressure-like. Nociceptive pain arising from visceral structures (visceral pain) is generally more diffuse and is often described as gnawing or cramping when due to obstruction of a viscus and as aching, sharp, or throbbing when due to disturbance of organ capsules or mesentery. Pain caused by tumor invasion of bone and pain due to degenerative changes in joints are examples of nociceptive pain. If interventions that improve the peripheral nociceptive lesion are feasible, these types of pains usually respond. For example, radiotherapy often can eliminate pain from a bony metastasis, and joint replacement usually can alleviate severe joint pain from destructive arthritis. This type of pain also generally responds well to nonsteroidal anti-inflammatory drugs and opioids.

Neuropathic pain refers to syndromes that may be related to aberrant somatosensory processing in either the peripheral or central nervous system. There are many subtypes and, presumably, varied mechanisms are involved. These pains are disproportionate to any nociceptive lesion identified during the evaluation and may be described with words such as abnormal, unusual, strange, or unfamiliar compared with the patient’s experiences with tissue-injury pain (a phenomenon termed dysesthesia). The diagnosis of neuropathic pain may suggest the use of selected types of analgesic medications or other pain-relieving interventions.

Pain that is inferred to be predominantly related to psychologic processes has been termed psychogenic. Greater specificity can be attained using an accepted taxonomy, such as the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition text revision (*DSM-IV-TR*), of the American Psychiatric Association. It is important to emphasize that these diagnoses imply that the pain is truly experienced but is best explained by psychiatric disease. A complaint of pain that is factitious, or even feigned, is possible but appears to be extremely rare in clinical practice. Both the patient and the clinician are best served if the clinician believes the patient and then exercises skill and judgment in assessing the problem and developing an appropriate treatment strategy.

Syndrome identification is another important element in the assessment of pain. The cancer literature has highlighted its importance. In one survey, an unrecognized organic lesion was discovered in 64% of cancer patients with pain, which led to the
use of primary therapy (ie, antineoplastic drugs or antibiotics) in almost 20%. Likewise, recognizing a neuropathic pain syndrome may lead to an intervention that might not be considered otherwise, such as neurectomy for a painful neuroma or sympathetic nerve blocks for suspected sympathetically maintained pain.

**Clarifying pain-related impact and comorbidities**

Pain assessment should focus on disturbances in varied domains that link in some direct way to the pain or present as relevant comorbidities. The domains that should be explored are those that contribute to quality of life (table 10). For the patient with

<table>
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<tr>
<th>Dimension</th>
<th>Examples of concerns</th>
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<tr>
<td>Physical well-being</td>
<td>• Other physical symptoms (eg, fatigue, nausea, constipation, anorexia, itch)</td>
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<td></td>
<td>• Sleep quality</td>
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<td></td>
<td>• Performance status, “up time,” and ability to perform activities of daily living, household activities, and vocational and recreational activities</td>
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<td></td>
<td>• Specific impairments (eg, paresis)</td>
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<td>• Practical needs</td>
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<td>Psychologic well-being</td>
<td>• Mood and psychologic symptoms</td>
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<td></td>
<td>• Coping</td>
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<td></td>
<td>• Past and present psychiatric disorders</td>
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<td>• Personality variables</td>
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<td>• Body image</td>
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<td></td>
<td>• Intimacy or sexuality</td>
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<td>Social well-being</td>
<td>• Interpersonal contacts</td>
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<td>• Social support</td>
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<td></td>
<td>• Family integrity</td>
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<td></td>
<td>• Marital relationship</td>
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<tr>
<td>Spiritual or religious</td>
<td>• Meaning of disease</td>
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<tr>
<td>Role functioning</td>
<td>• Involvement with church</td>
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<tr>
<td>Relationship with</td>
<td>• Ability to work</td>
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<tr>
<td>healthcare providers</td>
<td>• Ability to perform housekeeping tasks</td>
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<td></td>
<td>• Ability to maintain role in family</td>
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<tr>
<td>Financial</td>
<td>• Access and trust</td>
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<tr>
<td></td>
<td>• Cost of care</td>
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<td></td>
<td>• Lost wages</td>
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<td></td>
<td>• Other responsibilities</td>
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chronic nonmalignant pain, the details of this assessment also should provide a measure of the patient’s overall disability.

Among the most medically important historical elements to clarify as part of the history taking of pain are substance use and abuse. History taking should explore both the specific pattern of licit and illicit drug use and any relationship between these behaviors and the pain.

**Conclusion**

Comprehensive assessment of pain and comorbidities is an essential foundation for the selection of a treatment strategy targeted to improve comfort and functioning in order to provide a better quality of life. Just as treatment of tissue injury alone may not reduce pain sustained by other nonnociceptive factors, a therapeutic approach focused solely on pain may not meaningfully benefit a patient whose suffering is caused by other disturbances.

Ultimately, the clinical judgment to explore the value of opioid therapy rests on the accuracy of this comprehensive assessment. Over time, it is only by assessment and reassessment that the clinician can continue to be reassured that opioid therapy is in the patient’s best interest and is being used as part of a treatment strategy that optimizes the likelihood of a favorable long-term outcome.

**Suggested readings**


Once a decision is made to undertake a trial of opioid therapy, the clinician’s obligation should be to implement therapy according to accepted principles of prescribing. These principles have been refined over decades of experience treating patients with cancer pain (table 11).

Selecting an opioid

In the approach to cancer pain management popularized by the World Health Organization, patients with moderate pain who are relatively opioid-naïve should receive an opioid from among a group that has been conventionally used for pain of this severity. In practice, opioid-naïve patients with severe pain also may be offered a trial of one of these drugs. In the United States, this group of medications includes codeine, oxycodone (when combined with aspirin or acetaminophen), hydrocodone (available in combination with acetaminophen or ibuprofen), dihydrocodeine (available in combination with aspirin), and tramadol (either alone or combined with acetaminophen). All of these opioids have a short half-life and short duration of action, typically 2 to 4 hours, and usually are prescribed on an as-needed basis. The total daily dose of those that are combined with a nonopioid coanalgesic should not exceed the maximal safe dose of the latter drug (for example, 4 g of acetaminophen per day and less in patients with known liver disease or high alcohol consumption).

The traditional use of the short-acting combination products for moderate cancer pain is not based on any empirical demonstration of superiority over other treatment approaches, and there is now substantial clinical experience in the use of long-acting, modified-release opioids for pain of this type. These formulations improve the convenience of therapy when the opioid is required repeatedly during the day and should be considered as a potential first-line approach in patients with constant or frequently recurring pain.

Several other opioids, such as oral pentazocine, propoxyphene and meperidine, historically have been used for managing moderate pain. However, these drugs are generally not recommended for long-term opioid therapy.
The single-entity pure μ-agonist opioids usually are preferred for management of severe pain. In the United States, these medications include:

- Morphine
- Hydromorphone
- Oxycodone
- Oxymorphone
- Fentanyl
- Levorphanol
- Methadone

### Table 11. Principles of opioid prescribing

<table>
<thead>
<tr>
<th>Selection of opioid</th>
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<tr>
<td>Consider:</td>
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<tr>
<td>• Severity and pattern of pain</td>
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<tr>
<td>• Age, medical comorbidities, individual differences, previous experience with opioids</td>
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<tr>
<td>• Drug-specific differences</td>
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<tr>
<td>• Available formulations and cost</td>
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<tr>
<th>Route selection</th>
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<tbody>
<tr>
<td>• Use the least invasive route possible</td>
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<td>• Consider patient convenience and adherence</td>
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<tr>
<th>Dosing</th>
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<tr>
<td>• Consider previous dosing requirements and relative analgesic potencies when initiating therapy</td>
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<tr>
<td>• Start with lowest likely effective dose</td>
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<tr>
<td>• Increase the dose incrementally (usually by 30% to 100%), with both the size of the increment and the time interval between increments influenced by the severity of pain and side effects</td>
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<tr>
<td>• Increase the dose until adequate analgesia occurs or dose-limiting side effects are encountered</td>
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<tr>
<td>• Consider dosing schedule (eg, around the clock and/or as needed), depending on temporal patterns of pain</td>
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<tr>
<td>• Consider “rescue” medication for breakthrough pain</td>
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<tr>
<th>Treatment of side effects</th>
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<tr>
<td>• Consider treatment of constipation, nausea, mental clouding or somnolence, itch, or other side effects</td>
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<tr>
<th>Monitoring</th>
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<tr>
<td>• Monitor treatment efficacy, side effects, and other responses over time and consider modification, if necessary; frequency of follow-up should be individually tailored according to each patient’s clinical and social circumstances</td>
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Few relevant comparative studies of these medications have been conducted, and there is very substantial individual variation in the response to each one. Indeed, sequential opioid trials (ie, opioid rotation [see chapter 7]) may be necessary to identify the drug that yields the most favorable balance between analgesia and side effects. For example, in one prospective survey of 100 consecutive inpatients with cancer pain, 44 patients required trials of 2 or more systemically administered opioid analgesics, and 20 required sequential trials of 3 or more opioids to optimize the balance between analgesia and side effects. Despite the lack of data and the likelihood of individual variation in response, several factors should be considered in selecting an opioid (see table 11). If pain is very severe and rapid oral titration of the dose is needed, the medications that have a short half-life and are available in immediate-release oral formulations (morphine, hydromorphone, and oxycodone) are generally favored because they require a shorter period to approach steady-state plasma concentrations than either the modified-release opioids or medications with a long half-life. If pain is very acute, delivery of a medication with a short half-life by oral transmucosal administration (for fentanyl only) or the intravenous route may be preferable, because these routes provide the fastest onset of effect.

A patient’s response to previous trials of opioid therapy should be reviewed when selecting a new opioid. Given the marked variability in the analgesic effectiveness and occurrence of side effects with each drug, a patient who had a favorable prior experience with a particular opioid should be considered for treatment with this drug again. If the current opioid is well tolerated, it usually is continued unless difficulties in dose titration occur or the required dose cannot be administered conveniently. The exception to this is meperidine; a favorable experience with short-term intravenous exposure for management of acute pain in the past does not prefigure a similar response during oral therapy.

Patients with renal impairment may accumulate the active metabolites of propoxyphene (norpropoxyphene), meperidine (normeperidine), and morphine (morphine-6-glucuronide, morphine-3-glucuronide). Caution is required in the administration of these medications, particularly in the setting of changing renal function.

Some caution is also appropriate in the use of levorphanol or methadone in patients who are difficult to monitor (eg, patients who do not adhere to treatment regimens, those who live alone or at a distance, older patients without highly capable caregivers) and those predisposed to opioid side effects. Since 4 or 5 half-lives with repeated dosing must pass before steady state is
approached, these opioids with a long half-life require relatively close monitoring for a prolonged period, to avoid unanticipated delayed toxicity resulting from gradual drug accumulation in the plasma with repeated administration. This need for monitoring is most critical in patients predisposed to opioid side effects, including patients with advanced age or major organ failure (ie, encephalopathy or disturbances in pulmonary, hepatic, or renal function). Clinically, most problems appear to develop with methadone, which has a highly variable half-life that ranges from less than 24 hours to more than 150 hours.

Availability of modified-release opioids has increased the role of dosing interval as a consideration in opioid analgesic selection. Most standard opioid preparations require a dosing interval of 3 to 4 hours. Methadone often can be administered every 6 hours and even less often in some patients. The modified-release oral formulations are effective at an 8- to 24-hour dosing interval, and the transdermal fentanyl system can be administered at an interval of 48 to 72 hours. These medications have met with great patient acceptance and presumably enhance patient adherence to therapy.

Other drug-specific characteristics also may influence decision making. There is evidence that transdermal fentanyl is less likely to produce constipation, and patients with preexisting constipation or gastrointestinal comorbidities may be especially good candidates for a trial of this formulation. The unique and somewhat difficult pharmacology of methadone supports the conclusion that it should be a second-line agent. Given the theoretical potential for efficacy that may be based, in part, on reversal of opioid tolerance (resulting from the blocking effect on the \( N \)-methyl-\( \beta \)-aspartate receptor caused by the \( d \)-isomer), it is reasonable to consider a trial of this drug after another has proved ineffective. Finally, patients with a history of addiction might be considered for treatment with opioids that are less likely to be preferred by substance abusers, either because they are not pure \( \mu \)-agonists (eg, buprenorphine, one of the agonist-antagonists) or because they have less potential for abuse and diversion (eg, transdermal fentanyl, methadone).

**Selecting a route of administration**
The least invasive and most convenient route that can provide adequate analgesia should be used to administer opioids. For chronic pain, the oral and transdermal routes usually are preferred.

**Noninvasive routes**
- **Oral.** The oral route for opioid delivery is simple and effective in most patients with chronic pain. It should be avoided in
INITIATING AND OPTIMIZING OPIOID THERAPY

patients with impaired swallowing or gastrointestinal obstruction and also may become problematic if very high doses are needed or rapid onset of action after a dose is essential. Orally administered medications have a slower onset of action and a more delayed time to peak than parenterally administered drugs. Most immediate-release oral formulations have a peak effect that is typically achieved after 60 minutes. The peak effects of the modified-release formulations generally occur between 3 and 5 hours after administration.

**Transdermal.** The transdermal formulation of fentanyl, which delivers 25, 50, 75, or 100 µg per hour, has become widely used for long-term treatment. Some patients prefer this route, and some are good candidates by virtue of impaired swallowing or gastrointestinal disease, nonadherence with oral regimens, or poor response to other opioids. The dosing interval for each transdermal patch is typically 72 hours, but as with other opioids, individual pharmacokinetic variation is large, and patients may require a dosing interval of 48 hours. Transdermal fentanyl is not indicated for management of acute pain, particularly in patients who are relatively opioid naïve.

**Sublingual.** A sublingual preparation of buprenorphine is available in some countries, but in the United States, prescriptive authority is limited to persons with special certification for its use in addiction therapy. Sublingual absorption occurs to some extent with any opioid, but bioavailability is very poor with drugs that are not highly lipophilic, such as morphine. Although there is considerable experience in the use of sublingual administration of concentrated oral morphine solution during the care of patients at the end of life, it is likely that most of the effects obtained by this route occur following enteral absorption after swallowing. Lipophilic opioids, such as fentanyl and methadone, are relatively well absorbed sublingually, and sublingual administration of an injectable formulation may be a useful approach in some patients who transiently lose the option of oral dosing.

**Rectal.** The rectal route usually is considered for patients who are relatively opioid nontolerant and become temporarily unable to take oral medications. In the United States, rectal suppositories containing morphine, hydromorphone, or oxymorphone are available. There also is anecdotal experience with rectal administration of controlled-release morphine or oxycodone tablets. The potency of opioids administered rectally is believed to approximate oral dosing. However, absorption is variable, and relative potency may be higher or lower than expected, depending on a variety of factors, including location of the suppository (low in the
rectum, where the blood supply is systemic, or high in the rectum, where blood flows through the portal circulation) and contents of the rectum at the time of dosing.

**Oral transmucosal.** An oral transmucosal formulation of fentanyl citrate is available for breakthrough pain. The fentanyl, which is incorporated into a hard lozenge, is rapidly absorbed through the oral mucosa. This formulation has been shown to have an onset of pain relief similar to intravenous morphine, and its safety and efficacy have been demonstrated in several clinical trials.

**Intranasal and inhaled.** An intranasal formulation of butorphanol is available. This mixed agonist-antagonist drug is not preferred for management of chronic pain. Theoretically, any lipophilic drug could be rapidly absorbed from the nasal cavity, and there is anecdotal experience in the use of others, such as fentanyl. Also, research is ongoing to develop an aerosolized opioid that will be administered through a metered dose inhaler. These formulations potentially could play a role in treatment of acute pain, including breakthrough pain.

**Invasive routes**
The parenteral route of administration should be considered for patients who require a very rapid onset of effect, have impaired swallowing or gastrointestinal obstruction, or require high doses that cannot otherwise be conveniently administered. However, because of the cost, invasiveness, and nursing requirements for parenteral administration of opioids, these routes typically are limited to patients who are unable to swallow or to absorb opioid drugs administered by enteral routes.

**Intramuscular.** Repetitive intramuscular injections are painful and offer no pharmacokinetic advantage. Consequently, their use is not recommended. Repeated bolus doses, if required, can be accomplished without frequent skin punctures, through use of an indwelling intravenous or subcutaneous infusion device.

**Subcutaneous.** The clearest indication for using the subcutaneous route is the inability to tolerate the oral route. Repeated bolus injections can be delivered painlessly through a 27-gauge infusion needle that is left under the skin and can remain there for up to a week. Continuous infusions can be performed using morphine, hydromorphone, fentanyl, or oxymorphone and are widely used in populations with far-advanced cancer or other illnesses. Methadone appears to be relatively irritating and is not preferred for subcutaneous infusion. Ambulatory infusion devices vary in complexity, cost, and ability to provide patient-controlled “rescue” doses as an adjunct to a continuous basal infusion.
To maintain the comfort of an infusion site, the subcutaneous infusion rate should not exceed 5 mL per hour.

**Intravenous.** Intravenous opioid infusion is commonly used in the hospital setting. Long-term intravenous infusions are possible if a permanent venous access device is available. As with the subcutaneous route, repeated bolus injections and patient-controlled analgesia may be coadministered with a continuous infusion. Infusions of drug combinations may also be indicated when pain is accompanied by nausea, anxiety, or agitation. In such cases, an antiemetic, neuroleptic, or anxiolytic agent may be combined with an opioid, provided it is nonirritating, miscible, and stable in combined solution. Experience has been reported with infusions of an opioid combined with metoclopramide, haloperidol, scopolamine, cyclizine, methotrimeprazine, chlorpromazine, or midazolam.

**Intraspinal.** Properly selected patients can benefit greatly from intraspinal opioid administration. A recent randomized trial in the cancer population found that intrathecal drug administration through an implanted programmable pump yielded better pain relief and fewer side effects than conventional analgesic therapy in patients with an extended prognosis.

The clearest indication for intraspinal opioid administration is pain below the midthorax that cannot be adequately relieved by systemic opioids because of development of central nervous system toxicity (eg, intolerable somnolence, confusion). Many methods may be used. If therapy is expected to be given in the relative short term (no longer than several months), the preferred system usually involves placement, in the epidural or intrathecal space, of a catheter that is tunneled subcutaneously and either brought through the skin or connected to a subcutaneous portal. Infusions that are expected to continue for a longer period than this are better accomplished by the intrathecal route using a totally implanted pump.

The preferred opioids for neuraxial infusion are morphine and hydromorphone. Others, such as fentanyl, methadone, and sufentanil, have been used. The opioid can be combined with a local anesthetic agent, such as bupivacaine. Clonidine is commercially available for intrathecal use and has been shown in controlled trials to be more effective for neuropathic than nociceptive pain, and ziconotide is currently being reviewed by the FDA in the United States. Other agents have been tried, but experience is too limited to recommend their use.

**Switching routes**
During long-term treatment, it may be necessary to switch routes of administration. One survey of patients with advanced cancer,
for example, found that more than half of the patients required 2 or more routes of administration prior to death, and almost a quarter needed 3 or more. All such changes require careful attention to relative potency. It is generally prudent to perform the switch in a gradual, stepwise manner over 2 to 3 days.

Selecting an initial dose
Opioid-naïve patients with severe pain should generally begin one of the opioids conventionally used for severe pain, at a dose equivalent to 5 to 10 mg of parenteral morphine every 3 to 4 hours. Equivalent doses of these opioids are calculated from the relative potency ratios published in equianalgesic dose tables (see chapter 3).

A switch to a new pure µ-agonist opioid, or a new route of administration, can be guided by consulting an equianalgesic table. The doses indicated on this table should be viewed as broad guidelines, the use of which must be tempered by clinical judgment and the condition of the patient (table 12). As a first step, the calculated equianalgesic dose typically is reduced to account for incomplete cross-tolerance between opioids and for individual variation. To be prudent, and respectful of patient variability, the calculated dose also is usually decreased when switching routes with the same drug.

Initial reduction in the calculated dose is typically 25% to 50%, with two important exceptions. First, the dose reduction is larger (ie, 75% to 90%) when switching to methadone. Second, there typically is no reduction required when a switch is made from another opioid to transdermal fentanyl if the equianalgesic dose table provided by the manufacturer is used, because a reduction has already been built into the calculation.

This initial adjustment in equianalgesic dose should be altered on the basis of the patient’s condition. Specifically, the reduction in equianalgesic dose should be augmented in patients with relatively good pain control and either severe side effects or serious medical comorbidities. The reduction should be diminished if the patient has severe pain and is not expected to have any undue toxicity from the new opioid. For example, a patient with severe pain and no comorbidities who is being switched from morphine to oxycodone might be started at an oxycodone dose equal to the calculated equianalgesic dose, or just 10% less, whereas a patient with mild pain and severe comorbidities might be started at an oxycodone dose that is 66% to 75% less than the calculated equianalgesic dose.

After any change from one opioid to another or from one route to another, patients must be monitored carefully to assess the
adequacy of analgesia and to detect the development of side effects. Subsequent dose adjustments are usually necessary.

**Titrating the dose**

Once an opioid and route of administration are selected, the dose should be increased until adequate analgesia occurs or intolerable and unmanageable side effects supervene. Titration of the opioid dose may be necessary at the start of therapy and repeatedly during the patient’s course of treatment. Inadequate pain relief usually should be addressed through gradual escalation of the dose until adequate analgesia is reported or intolerable and unmanageable side effects limit further dose escalation. Adherence to this guideline requires repeated assessment and the ongoing management of side effects.

The concentration-response relationship for opioid drugs is best characterized as a log-linear relationship. Accordingly, dose increments are best considered as percentages of the existing dose, rather than any absolute amount. A dose increment of 30% to 50% is safe and usually large enough to observe a meaningful change in effects. If pain is severe and the patient is not predisposed to opioid toxicity, a higher increment—up to 100% of the existing dose—may be considered.

An alternative approach to dose titration is possible in patients who receive a coadministered, as-needed opioid dose (such as an oral rescue dose or patient-controlled analgesia) during fixed-schedule administration of an oral, transdermal, or parenteral opioid. The total amount of supplemental drug used during the

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**Table 12. Empirical guidelines for opioid rotation**

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Use the equianalgesic table to calculate a dose of the new opioid that is roughly equivalent to the dose of the current opioid.</td>
</tr>
</tbody>
</table>
| 2.   | Determine the clinically relevant starting point.  
|      | a. If switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%.  
|      | b. If switching to methadone, reduce the equianalgesic dose by 75% to 90%.  
|      | c. If switching to transdermal fentanyl, do not reduce the equianalgesic dose. |
| 3.   | Consider further dose adjustments on the basis of medical condition and pain.  
|      | a. If the patient is elderly or has significant organ failure, consider further dose reduction.  
|      | b. If the patient has severe pain, consider a lesser dose reduction. |
| 4.   | Calculate a “rescue” dose as 5% to 15% of the total daily dose and administer at an appropriate interval. |
| 5.   | Reassess and titrate the new opioids according to therapeutic response and side effects. |
previous day or two can be summed and converted into the fixed-schedule administration. Whatever the amount, safety is assured if the patient has tolerated it during the previous day.

The use of a percentage dose increment applies irrespective of the specific opioid or route of administration. When patients are receiving a drug by fixed-schedule dosing (such as a long-acting, modified-release oral formulation, a transdermal formulation, or a continuous infusion) and a drug by as-needed administration, both the fixed-schedule drug and the as-needed drug should be increased concurrently.

In most cases, gradual dose escalation identifies a favorable balance between analgesia and side effects that remains stable for a prolonged period. There is no ceiling effect to analgesia provided by the pure \(\mu\)-agonist opioids, and the maximal dose is immaterial as long as the patient attains a favorable balance of analgesia, other functional goals, and side effects. This implies that the opioid responsiveness of a specific pain can be ascertained only if the dose is gradually increased until treatment-limiting side effects occur.

In clinical practice, the range of opioid doses required by patients is enormous. Occasionally, doses can become extremely large (equivalent to grams of morphine per day) during the process of dose titration. The absolute dose is irrelevant, however, as long as therapy is not compromised by dose-limiting toxicity, cost, or excessive inconvenience produced by the number of pills. In a retrospective study of 100 patients with advanced cancer, the average daily opioid requirement was equivalent to 400 to 600 mg of morphine given parenterally, but approximately 10% of patients required more than 2,000 mg and 1 patient required more than 30,000 mg per 24 hours. According to most surveys, patients with chronic nonmalignant pain usually require less than a dose equivalent to few hundred milligrams of oral morphine per day. If a patient requires a relatively high dose, careful assessment is needed to ensure that the outcomes, including analgesia and side effects, are consistently favorable and the drug is taken responsibly.

Although doses typically stabilize for prolonged periods during long-term management, dose escalation is usually required at intervals to maintain analgesia. Studies of patients with pain due to medical illness have indicated that the need for a dose increase usually can be explained by some change in clinical status. In this setting, analgesic tolerance cannot be invoked as the dominant factor in the need for opioid dose escalation.

This observation has two important implications. First, concerns about tolerance should not impede the use of opioids.
Clinically significant tolerance may or may not ever occur, and if it does, analgesia usually can be recaptured through dose escalation. Second, worsening pain in a patient receiving a stable dose of opioids should be assessed as presumptive evidence of a new process, such as disease progression or increasing psychologic distress or delirium. This potential for a changing opioid requirement over time underscores the need for repeated assessment. Given the inherently subjective nature of the critical end points (ie, adequate analgesia and intolerable side effects), careful patient assessment is essential.

**Scheduled versus as-needed dosing**
Because experts generally agree that the more effective approach to pain management is to prevent the recurrence of pain than to abort it once it appears, by-the-clock dosing has replaced as-needed dosing in treatment of continuous or frequently recurring pain. As-needed dosing still plays a role, however, and should be considered during initiation of therapy in opioid nontolerant patients, in those with rapidly changing pain, and in patients with intermittent pains separated by pain-free intervals. (Given the risk of gradual accumulation, methadone is often started with 1 to 2 weeks of as-needed dosing and at least a 6-hour interval between doses.) As-needed administration of a rescue drug also is commonly combined with fixed-schedule administration to manage intermittent breakthrough pains. This is considered a standard of care in management of cancer pain and an option to consider in management of nonmalignant pain syndromes. In most cases, the rescue drug can be the same as the drug administered by fixed-schedule dosing. If a rapid onset of action is essential, treatment with the oral transmucosal fentanyl formulation should be considered. The long and variable half-life of methadone complicates its use as a rescue drug, and an alternative opioid with a short half-life is usually offered to supplement a methadone regimen.

On the basis of clinical experience, the size of the most effective rescue dose usually is selected to be equivalent to 5% to 15% of the total daily opioid dose. The lower end of this range is used if the patient is medically frail or has moderately intense breakthrough pain. The upper end is used if the breakthrough pains are anticipated to be severe and the risk is not excessive, considering factors such as advanced age or major organ failure that predispose to opioid toxicity.

Use of oral transmucosal fentanyl presents an exception to the 5% to 15% rule for rescue medication. In several clinical trials, there was no relationship between the effective dose of oral transmucosal fentanyl and the total daily opioid dose. Therefore, oral
transmucosal fentanyl should be initiated at one of the lower available doses (200 or 400 µg) and the dose should be titrated until the appropriate dose is identified.

In cancer care and for acute pain management (eg, postoperative care), oral rescue doses typically are offered at intervals up to every 1 to 2 hours as needed, and parenteral rescue doses can be offered at intervals up to every 15 to 30 minutes. As noted, the number of rescue doses required daily can be used to guide the size of the increment in the regularly scheduled dose as it is titrated upward. Use of rescue doses for pain flares in management of noncancer chronic pain syndromes remains controversial but, if determined to be indicated, is generally restricted to a few doses per day.

**Rate of dose titration**
The severity of the pain should determine the rate of dose titration. Patients with very severe pain who need rapid relief can be managed by repeated parenteral dosing every 15 to 30 minutes until pain is partially relieved. After parenteral loading using an opioid with a short half-life, an approximate hourly maintenance dose can be calculated by dividing the total loading dose by twice the elimination half-life of the drug. For example, the starting maintenance dose for a patient who has required an intravenous loading dose of 30 mg of morphine sulphate (half-life, approximately 3 hours) would be 5 mg per hour, (ie, 30 mg ÷ [3 hours × 2]). Patients with less severe pain can undergo more gradual dose escalation. Aggressive dose titration is rarely indicated in patients with a stable chronic-pain syndrome treated in the outpatient setting.

**Treatment of side effects**
Treatment of opioid-induced side effects is an integral part of effective opioid administration (see chapter 6). Successful amelioration of symptoms both enhances patient comfort and improves the likelihood that a favorable balance between analgesia and side effects will be found.

**Risk assessment and management strategies**
These pharmacologic principles must be complemented by proactive and ongoing efforts to assess and manage another potential set of negative outcomes, specifically outcomes associated with abuse, addiction, and diversion (see chapter 10). This is true in all populations, particularly those that include patients at relatively high risk. Given the prevalence of substance abuse in US society, it is best to incorporate risk assessment and
management as part of the routine approach to opioid therapy in all patient populations.

**Suggested readings**


CHAPTER 6
MANAGEMENT OF ADVERSE EFFECTS

One of the goals of opioid therapy is to maintain a favorable balance between analgesia and side effects. Effective treatment of side effects increases the likelihood of a favorable outcome and potentially allows the use of higher opioid doses, which may be necessary to control pain. Moreover, unrelieved side effects can themselves substantially impair quality of life, negating benefits derived from pain control. If intolerable side effects occur, the analgesic regimen has failed, reassessment is necessary, and an alternative therapy is indicated.

Unfortunately, studies designed to improve the management of opioid-related side effects have been limited. Management strategies are largely anecdotal and most of the recommended approaches represent an extrapolation of treatments directed against similar symptoms caused by different pathophysiologic conditions. Broad guidelines based on clinical experience also do not capture the nuances encountered in the clinical setting, such as the extent to which side effects may be influenced by expectation and learning.

These limitations notwithstanding, strategies to address the common side effects associated with opioid analgesics can be developed. Ongoing assessment and treatment of these problems are an essential element in the effort to optimize outcomes.

Constipation
The most common and persistent side effect from opioid analgesics is bowel dysmotility, leading to constipation. Diminished frequency of defecation associated with difficult or painful elimination may also contribute to abdominal discomfort, bloating and distention, and sometimes nausea and anorexia. Rarely, constipation progresses to the serious complications of obstruction and bowel obstruction.

The clinical evaluation of the patient with constipation depends on the time course of its development and on the medical setting. Without prophylaxis of some sort, most patients develop some degree of constipation after initiation or escalation of opioid therapy. Often, the relationship to the drug is clear, and other contributing factors, such as inactivity or dehydration, are apparent. In such cases, further evaluation may not be warranted
unless the clinician strongly suspects another cause that may be amenable to treatment. However, when constipation develops or worsens without a clear precipitant, a thorough evaluation of potential etiologies is necessary. Depending on the clinical situation, the history taking and physical examination (including rectal examination) may be supplemented by a laboratory evaluation, a plain radiograph of the abdomen, other imaging approaches (computed tomography, magnetic resonance imaging, or ultrasound), or a colonoscopy.

**Management of opioid-induced constipation**

Tolerance to the effects of opioids develops very slowly, and a large proportion of patients require laxative therapy as long as they are receiving opioid therapy. Some patients are able to improve bowel function by dietary modifications, and others may habituate to the constipating effects of these drugs and require no intervention.

The epidemiology of opioid-induced constipation is not well understood, but it is likely that younger, active patients without concurrent risk factors for constipation are least likely to have problems, whereas older patients and those with other risk factors, such as inactivity, use of other constipating drugs, and intrinsic bowel disease, are more likely to encounter difficulties. Because the use of laxatives can be expensive and burdensome, it is reasonable to limit constipation prophylaxis to patients with these other risk factors. Those who are likely at the lowest risk for this side effect can be managed expectantly.

For some patients with opioid-induced bowel dysfunction, nonpharmacologic interventions are sufficient. If possible, dietary fiber intake should be increased by adding fruits or high-fiber cereals or by using a commercially available fiber supplement. Fiber or bulking agents should be avoided if the patient is debilitated, fluid intake is limited, partial bowel obstruction is suspected, or a change in diet is impeded by anorexia or some other intercurrent medical problem. If fiber worsens symptoms, it should be discontinued.

Patients with opioid-induced constipation should be encouraged to increase their fluid intake irrespective of their fiber consumption. Generally, an intake of 2 to 3 L per day should be adequate. Whenever possible, patients who receive opioids should be encouraged to increase their activity level. Inactivity has been associated with decreasing colonic motility, and regular exercise can be important in the prevention of constipation. Patient comfort, privacy, and convenience during defecation should be ensured. In the institutional setting, use of a bedside commode
and prompt nursing response may be beneficial. Patients with limited self-reporting ability should undergo evaluation for anal fissures or hemorrhoids.

Given the individual variation in the response to different opioid analgesics, a switch from one opioid to another (opioid rotation) should be considered among the strategies used for refractory constipation. Recent surveys suggest that the transdermal fentanyl system may produce less constipation than oral morphine, and this formulation may be preferred for a trial in this setting. Very rarely, severe and refractory constipation may require the use of an alternative means of pain control (eg, neuraxial techniques) to reduce or eliminate the need for systemic opioids. In these cases, consideration must be given to the patient’s overall quality of life and goals of care.

Pharmacologic strategies for constipation vary with the medical status, expectations, and responses of the patient. Various options should be discussed with the patient and treatments that are consistent with patient preference should be initiated (table 13). If the response to one approach is not favorable, an alternative should be selected.

Laxative therapy should not be initiated in patients with existing severe constipation until serious problems, such as bowel obstruction, have been excluded and the clinician is reasonably certain that impaction is not present. Examination of the rectum can reveal low impaction, but high impaction requires abdominal imaging for evaluation. Management of impaction may require physical disimpaction, repeated enemas, and a combination of rectal and oral laxatives. Routine laxative therapy can begin once impaction is ruled out or cleared.

**Rectal therapies.** Rectal therapies are not generally recommended for long-term management of constipation because of the inconvenience, the potential for local trauma, and the efficacy of alternative oral therapies. Enemas and suppositories are typically used for acute short-term management of more severe episodes of constipation. Nonetheless, some patients prefer the regular use of rectally administered therapy, and these measures should be available to them.

Rectal suppositories may contain an inert (eg, glycerine) or active (eg, bisacodyl) ingredient. Inert suppositories draw fluid into the rectum and act as a stimulus to defecation. Active suppositories contain a contact cathartic. Enemas may consist of a small volume containing sodium phosphate or oil or may consist of a large volume containing tap water, soap suds, or saline (table 14).

**Oral therapies.** Selection of a laxative therapy is largely a trial-and-error process and must be based on a comprehensive
assessment of the patient’s medical needs, capabilities, and expectations. Currently available oral laxatives include bulk-forming agents, osmotic agents, lubricants, surfactants, contact cathartics, prokinetic drugs, agents for colonic lavage, and oral naloxone (table 15). Dosing guidelines for oral agents are summarized in table 16.

The contact cathartics are most commonly used for long-term treatment of opioid-induced constipation. Castor oil acts on the small bowel and is often poorly tolerated. The clinical experience with senna and bisacodyl is extensive, and these drugs are available over the counter. Treatment should begin with a relatively low dose (e.g., 1 senna tablet at bedtime), which can then be increased every 2 to 3 days (at bedtime or in divided doses) until constipation is relieved, the patient reports side effects, or the therapy becomes too burdensome or costly to continue. Some patients prefer to use a contact cathartic intermittently, such as every 3 to 4 days if needed.

Although sodium docusate is a contact cathartic at relatively high doses, the doses used clinically only produce a surfactant effect that allows fat to mix with feces, softening the stool. This drug may be used alone or in combination with another type of laxative.

### Table 13. Stepwise approach for managing opioid-induced constipation

1. Nonpharmacologic approaches for all patients
   - Increase fluid intake as tolerated
   - Increase dietary fiber as tolerated (unless patient is severely debilitated or bowel obstruction is suspected)
   - Encourage mobility and ambulation if appropriate
   - Ensure comfort and privacy for defecation
   - Encourage bowel movements at the same time each day
   - Rule out or treat impaction
2. Consider pharmacologic interventions and discuss approaches with patient
   - Intermittent use (every 2-3 days) of an osmotic laxative, such as magnesium hydroxide, magnesium citrate, or sodium phosphate
   - Trial of a daily softening agent (sodium docusate) alone
   - Intermittent use (every 2-3 days) of a contact cathartic, such as senna or bisacodyl
   - Daily use of a contact cathartic preparation (with or without a concurrent softening agent)
   - Daily use of lactulose or sorbitol
   - Daily use of polyethylene glycol
3. Adjust dose and dosing schedule of selected therapy to optimize effects
4. Switch or combine conventional approaches if initial therapy is inadequate
The risks associated with short-term use of a contact cathartic are minimal. Long-term ingestion, however, may result in a syndrome that has been termed laxative bowel and cathartic bowel, a condition characterized by dependence on laxatives for bowel function. Risk of this syndrome is not a contraindication to therapy in the setting of advanced disease, but it should be considered in patients with long life expectancies. In the latter situation, an alternative approach to constipation—or alternate use of the contact cathartics with laxatives that have other mechanisms of action—should be considered.

Long-term treatment of constipation also may be accomplished by regular oral administration of a highly osmotic sugar,
## Table 15. Agents used for opioid-induced constipation

<table>
<thead>
<tr>
<th>Class / Mechanism</th>
<th>Class / Mechanism</th>
<th>Class / Mechanism</th>
<th>Class / Mechanism</th>
<th>Class / Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming laxatives</td>
<td>Osmotic/saline cathartics</td>
<td>Lubricants</td>
<td>Surfactants</td>
<td>Oral lavage</td>
</tr>
<tr>
<td>(cellulose, psyllium seeds)</td>
<td>(magnesium salts, sodium salts, lactulose, sorbitol)</td>
<td>(mineral oil)</td>
<td>(docusate sodium)</td>
<td>(polyethylene glycol)</td>
</tr>
<tr>
<td><strong>Use</strong></td>
<td><strong>Use</strong></td>
<td><strong>Use</strong></td>
<td><strong>Use</strong></td>
<td><strong>Use</strong></td>
</tr>
<tr>
<td>• Increase water in bowel</td>
<td>• Increase water in bowel</td>
<td>• Soften stool</td>
<td>• Facilitate mixture of fat and stool</td>
<td>• Flushes colon</td>
</tr>
<tr>
<td>• Decrease transit time</td>
<td>• Decrease transit time</td>
<td>• Not generally recommended for chronic constipation</td>
<td>• Doses used clinically (usually 200-400 mg/day) produce a distinct effect rather than contact cathartic effect</td>
<td>• Generally recognized as safe and well tolerated for management of chronic constipation</td>
</tr>
<tr>
<td>• Lactulose and sorbitol attract water into colon, acidify contents</td>
<td>• Lactulose and sorbitol have slower onset and greater flexibility than magnesium or sodium salts</td>
<td>• Usually combined with contact cathartic as first-line therapy for opioid-induced constipation</td>
<td>• Often used for bowel cleansing before medical procedures</td>
<td>• Not generally recommended for long-term use</td>
</tr>
<tr>
<td>• May be used for acute constipation or fecal impaction</td>
<td>• May be used for acute constipation or fecal impaction</td>
<td>• Minimal risks</td>
<td>• Available powdered formulation can be used daily for long-term management</td>
<td>• Experience is limited, and trial should be considered only when constipation has responded poorly to more conventional measures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Problems/Comments</strong></th>
<th><strong>Problems/Comments</strong></th>
<th><strong>Problems/Comments</strong></th>
<th><strong>Problems/Comments</strong></th>
<th><strong>Problems/Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased flatulence, distension, bloating, or abdominal pain in patients with intra-abdominal disease</td>
<td>• Increased flatulence, distension, bloating, or abdominal pain in patients with intra-abdominal disease</td>
<td>• Long-term use may impair absorption of fat-soluble vitamins</td>
<td>• Diarrhea and dehydration are possible side effects</td>
<td>• Cramping and diarrhea are common with long-term use, malabsorption of nutrients may occur</td>
</tr>
<tr>
<td>• Avoid use in patients who are severely debilitated or have partial bowel obstruction</td>
<td>• Avoid use in patients who are severely debilitated or have partial bowel obstruction</td>
<td>• Irritation of perianal area may occur</td>
<td>• Minimal risks</td>
<td>• Some patients absorb sufficient naloxone and experience uncomfortable signs of abstinence</td>
</tr>
<tr>
<td>• Significant allergies have been reported</td>
<td>• Significant allergies have been reported</td>
<td>• Potential for serious lipoid pneumonia if aspiration occurs</td>
<td>• Minimal risks</td>
<td>• Some patients absorb sufficient naloxone and experience uncomfortable signs of abstinence</td>
</tr>
<tr>
<td>• May worsen flatulence, distension, bloating, or abdominal pain in patients with intra-abdominal disease</td>
<td>• May worsen flatulence, distension, bloating, or abdominal pain in patients with intra-abdominal disease</td>
<td>• Apparent insensitivity to repeated bowel cleansing</td>
<td>• Diarrhea and dehydration are possible side effects</td>
<td>• Cramping and diarrhea are common with long-term use, malabsorption of nutrients may occur</td>
</tr>
<tr>
<td>• Risks are generally minor</td>
<td>• Risks are generally minor</td>
<td>• Risk of systemic opioid withdrawal</td>
<td>• Minimal risks</td>
<td>• Some patients absorb sufficient naloxone and experience uncomfortable signs of abstinence</td>
</tr>
</tbody>
</table>
specifically lactulose or sorbitol. Some patients are unable to tolerate this approach because of unpalatability or the occurrence of flatulence and bloating. An alternative strategy is daily use of a powdered form of polyethylene glycol. This compound is an oral lavage agent that is not absorbed and can flush the colon. Consumption of a large volume of polyethylene glycol fluid is used for colonic lavage before bowel procedures. Both the osmotic sugars and polyethylene glycol require dose titration in an effort to find a level associated with comfortable laxation.

In patients whose condition has been refractory to other types of laxative therapy, several other treatment approaches should be considered. Oral naloxone may ameliorate opioid-induced

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Starting dose</th>
<th>Effects/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming laxatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psyllium</td>
<td>1 tbsp tid</td>
<td>2-4 days Must be taken with at least 8 oz of water</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>1 tbsp tid</td>
<td>2-4 days Must be taken with fluids</td>
</tr>
<tr>
<td>Osmotic (saline) cathartics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>1/2-1 bottle</td>
<td>3-6 hr</td>
</tr>
<tr>
<td>Magnesium sulfate (Epsom salts)</td>
<td>5-15 g</td>
<td>3-6 hr</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>30-60 mL</td>
<td>30 min-6 hr</td>
</tr>
<tr>
<td>Sodium phosphate</td>
<td>45 mL</td>
<td>30 min-6 hr Useful as prep for colonoscopy</td>
</tr>
<tr>
<td>Lactulose, sorbitol</td>
<td>30 mL</td>
<td>24-48 hr</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>1 capful/day</td>
<td>Variable</td>
</tr>
<tr>
<td>Lubricants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral oil</td>
<td>1-2 tbsp</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Surfactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docusate</td>
<td>300 mg</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Contact cathartics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenylmethane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>1-2 tabs</td>
<td>6-12 hr</td>
</tr>
<tr>
<td>Anthraquinones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cascara, senna</td>
<td>1-2 tabs</td>
<td>6-12 hr</td>
</tr>
<tr>
<td>Castor oil</td>
<td>1-2 tbsp</td>
<td>3-6 hr</td>
</tr>
<tr>
<td>Prokinetic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg qid</td>
<td></td>
</tr>
<tr>
<td>Oral naloxone</td>
<td>1 mg bid</td>
<td>Titrate dose; monitor for withdrawal symptoms</td>
</tr>
</tbody>
</table>
constipation with little risk of systemic withdrawal. The compound is about 3% bioavailable. Dosing usually starts with 1 mg twice daily and is then increased gradually; some patients do not benefit until doses above 20 mg per day are reached. Use of naloxone is not without risk; some patients develop painful cramping while others absorb enough of the drug to have symptoms of systemic abstinence. This outcome is more likely to occur in patients receiving high doses of an opioid.

Although not yet commercially available, 2 promising agents are currently undergoing investigation for reversing opioid-induced bowel dysfunction without reversing analgesia or precipitating abstinence. Methylnaltrexone and alvimopan are quaternary opioid antagonists with activity that is restricted to peripheral receptors. Early studies have indicated that these agents are effective at normalizing bowel function in opioid-treated patients without affecting analgesia. If clinical trials continue to demonstrate the safety and efficacy of these products, they may allow for more aggressive use of opioid analgesics with fewer adverse effects and eliminate the need for more complicated and burdensome bowel regimens.

Nausea and vomiting
Nausea may occur after the administration of an opioid. However, tolerance usually develops rapidly, and routine prophylactic administration of an antiemetic agent is not typically indicated except in patients with a history of severe opioid-induced nausea. Some patients experience symptoms severe enough to interrupt treatment, and a small proportion have symptoms that are persistent and difficult to manage despite a trial of different agents.

Nausea and vomiting have many etiologies, and potential contributing factors should be evaluated if it is suspected that the opioid is not the entire explanation. If the assessment suggests that factors other than opioid use are contributing to the problems, antiemetic therapy may be combined with specific interventions to reverse or minimize these factors. If possible, nonessential drugs that may contribute to nausea, such as nonsteroidal anti-inflammatory drugs, should be eliminated. Constipation should be treated. Other abnormalities, such as electrolyte disturbances, gastritis, gastroesophageal reflux, or other intra-abdominal pathology, also should be addressed.

Several opioid effects may interact to produce nausea. These include direct effects on the chemoreceptor trigger zone in the lower brainstem, enhanced vestibular sensitivity, and delayed gastric emptying. Based on clinical observations, it is possible to postulate a link between the specific complaints of the patient
and the putative mechanism underlying the problem. Specifically, nausea associated with enhanced vestibular sensitivity may be accompanied by vertigo or may worsen markedly with movement. Nausea associated with delayed gastric emptying may be most severe postprandially and be associated with early satiety and bloating. These symptoms, in turn, may suggest the utility of specific treatment approaches.

Management of opioid-related nausea and vomiting

Nausea is highly noxious and must be treated promptly. Beyond the immediate benefits to the patient, prompt treatment may reduce the likelihood of conditioned responses that can complicate future management of symptoms. Conditioned nausea is suggested if the symptoms occur from the mere sight or taste of the opioid. The conditioned response may become generalized to the extent that other therapies or characteristics of the clinical situation or surroundings induce nausea. Once established, conditioned nausea can mimic pharmacologic outcomes and contribute to a poor therapeutic response.

For most patients, opioid-related nausea is adequately managed by the administration of an antiemetic agent at the time the nausea occurs, assuming that this treatment can be initiated promptly. Because opioid-induced nausea typically wanes in a period of days to weeks, interventions that may not be feasible for the long term can be tried as short-term therapeutic strategies. For example, some patients experience relief from a change in diet, including consumption of smaller, more frequent, and less spicy or pungent meals. This approach to managing opioid-induced nausea is obviously inappropriate if the symptom persists, but it may be tolerable for a period of days to weeks. If symptoms do not gradually improve during this time, the therapy must be changed.

Antiemetic therapy can be administered on either an as-needed or fixed-schedule basis. If nausea is intermittent and relatively mild, access to a drug on an as-needed basis may be sufficient. However, if the symptom is persistent and severe, continuous dosing is preferred. Should nausea be entirely controlled in the latter setting, the dose should be tapered after 1 week to determine whether tolerance has developed to the emetogenic effects of the opioid. If nausea returns as the dose is lowered, treatment should be resumed and continued for another week or so before a trial without the antiemetic is again undertaken.

There are numerous options when selecting a medication for treatment of opioid-induced nausea (table 17). However, no comparative trials have been conducted on these options, and
aside from a rationale for drug selection based on putative mechanisms (table 18), the decision to try one agent over another is based on clinical judgment, patient preference, availability, and cost. The dose-response relationships of the antiemetic drugs are not known, and treatment should explore this relationship at least to the extent of doubling the standard starting dose if the initial antiemetic response is inadequate and no adverse effects are noted. Patients differ substantially in their response to different medications, and sequential trials are sometimes needed to identify the most salutary treatment.

Based on the observation that antiemetic drugs differ in their mechanisms of action, the use of drug combinations may be reasonable. It should be appreciated, however, that no controlled clinical trials have established the safety and efficacy of any specific combination therapy. The use of concurrent therapy from unrelated classes could be justified on theoretical grounds in difficult cases.

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Initial dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Prochlorperazine</td>
<td>10 mg PO q6h; 25 mg PR q6h</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine</td>
<td>12.5-25 mg PO q8h</td>
</tr>
<tr>
<td>Butyrophenones</td>
<td>Haloperidol</td>
<td>0.5 mg IV q6h; 1 mg PO q6h</td>
</tr>
<tr>
<td>Anticholinergic drugs</td>
<td>Scopolamine</td>
<td>1.5 mg q3d</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Promethazine</td>
<td>25 mg PO/PR q6h</td>
</tr>
<tr>
<td></td>
<td>Meclizine</td>
<td>25 mg PO q6h</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>25 mg PO/IV q6h</td>
</tr>
<tr>
<td></td>
<td>Dimenhydrinate</td>
<td>25 mg PO/IV q6h</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
<td>25 mg PO/IV q6h</td>
</tr>
<tr>
<td></td>
<td>Trimethobenzamide</td>
<td>250 mg PO; 200 mg PR q6h</td>
</tr>
<tr>
<td>Prokinetic drugs</td>
<td>Metoclopramide</td>
<td>10 mg PO/IV q6h</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
<td>1-4 mg PO/IV q8h</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Lorazepam</td>
<td>0.5-1 mg SL/PO/IV q4-6h</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Dronabinol</td>
<td>2.5 mg PO q12h</td>
</tr>
<tr>
<td>5-HT3 receptor</td>
<td>Ondansetron</td>
<td>4-8 mg PO/SL/IV q8h</td>
</tr>
<tr>
<td>antagonists</td>
<td>Granisetron</td>
<td>1 mg PO/SL/IV q12h</td>
</tr>
<tr>
<td></td>
<td>Dolasetron</td>
<td>50-100 mg PO/IV q12h</td>
</tr>
</tbody>
</table>

IV, intravenous; PO, by mouth; PR, parenteral; SL, sublingual.

* May start at lower dose in older patients.
Some patients with severe opioid-induced nausea benefit from a change in the opioid medication (opioid rotation) or in the route of opioid administration. Specifically, patients who become nauseated from an oral opioid sometimes benefit from a switch to transdermal or parenteral administration. If this strategy is successful, it should be continued for a week or so, at which time a trial of oral therapy can be reinstituted if appropriate.

Patients who experience severe opioid-induced nausea and vomiting also should be considered for cognitive therapy, particularly if the nausea appears at least partly generated by behavioral factors. Cognitive therapies have established efficacy in treatment of chemotherapy-induced emesis, and the techniques developed for this setting may be adaptable to other situations.
Somnolence and cognitive impairment
Initiation of opioid therapy or significant dose escalation can cause somnolence or mental clouding, which typically wanes over a period of days or weeks. However, some patients continue to have problems, particularly if other contributing factors exist.

Somnolence can range from mild (merely a tendency to fall asleep when not active) to severe. Cognitive impairment may range from slight inattention or befuddlement to disorientation, severe memory impairment, or extreme confusion. Perceptual disorders may accompany confusion and be limited to increased dreaming or hypnologic illusions, or involve frank hallucinations. Some patients also experience mood disturbances associated with opioid use. These may be dysphoric (extending to depression) or euphoric (extending to episodes of hypomania) occurrences; dysphoria is more common.

As with other symptoms associated with opioid therapy, the decision to pursue additional evaluation is a clinical judgment influenced by the likelihood that other factors may be contributing. If the relationship to the drug or to other factors is clear, further evaluation may not be warranted. However, if the degree of impairment or its persistence is atypical, a thorough assessment of other potential etiologies is indicated.

Management of somnolence and cognitive impairment
The approach to persistent somnolence or cognitive impairment associated with opioid therapy is best taken in a stepwise fashion based on the assessment. First, contributing causes that may be relatively simple to address should be treated. This usually involves both the elimination of nonessential medications that can depress the central nervous system and treatment of metabolic disturbances, if any are found. Second, the opioid regimen should be evaluated. If analgesia is satisfactory, it may be possible to reduce the opioid dose. An empirical 25% reduction in dose will determine whether pain will worsen or side effects will clear. Third, drug treatment directed at the symptom should be considered.

There is a large body of clinical experience in the use of psychostimulants to treat opioid-induced cognitive impairment. The most extensive experience is with methylphenidate, which is usually initiated at a starting dose of 5 mg in the morning and at noon, or a comparable dose of one of the long-acting, modified-release formulations. The dose is gradually increased until benefits occur or side effects supervene. Most patients benefit at doses well below 60 mg per day, but some require considerably
higher doses. Therapeutic effects sometimes wane over time—a phenomenon that could reflect tolerance or the cumulative effects of higher opioid doses, other drugs, or intercurrent neurologic insults. Benefit can sometimes be regained after the dose is increased.

Other psychostimulants are also commonly tried. Patients seem to react more positively to one stimulant drug than another, and a trial of a different drug should be considered if the initial therapeutic response is poor, if benefits decline over time and cannot be regained by a modest dose increase, or if side effects occur. Dextroamphetamine and a compound of amphetamine congeners are dosed in a manner identical to methylphenidate. Modafinil, a newer drug, has less risk of sympathomimetic effects, and treatment is usually initiated at a dose of 100 to 200 mg per day and then titrated. Pemoline, an older drug, is used less commonly because of an association with a rare hepatopathy.

The potential for adverse effects during psychostimulant therapy must be carefully monitored. Consequences of toxicity include tremulousness, anorexia, anxiety or other mood disturbance, insomnia, and tachycardia or hypertension. Given the potential for these adverse effects, relative contraindications for therapy include preexisting anorexia, severe insomnia, psychiatric disorder characterized by anxiety or paranoid ideation, significant cardiac disease, or poorly controlled hypertension. Older patients and those with early dementing illness are especially susceptible to untoward psychotomimetic and cognitive disturbances.

Other strategies also should be considered. Any treatment that reduces the opioid requirement might allow a degree of dose reduction that would lessen or eliminate the somnolence or cognitive impairment. Accordingly, a patient with somnolence or cognitive disturbance should be considered for any of a variety of pharmacologic therapies (eg, addition of a nonopioid or adjuvant analgesic, a trial of neuraxial drugs) or nonpharmacologic therapies (eg, a psychologic approach, another interventional strategy), as suggested by the assessment.

Other side effects
Patients receiving opioid therapy for pain management may experience a variety of other adverse effects.

Myoclonus
Myoclonus is a common dose-related adverse effect of opioids. It is associated with somnolence and cognitive impairment and, like these problems, is often determined by multiple factors. If sponta-
neous muscle contractions or spasms interfere with usual functions, cause sleep disturbance, or are in any other way distressing, symptoms can be treated empirically with a low-dose benzodiazepine (eg, clonazepam, 0.5 mg PO q6-8h) or an anticonvulsant. Based on anecdotal observations, baclofen also may be tried if treatment is needed, starting with a 5-mg dose. Similar to treatment of other opioid-related symptom complexes, strategies such as opioid rotation or nonopioid treatments that allow lowering of the opioid dose also should be considered.

**Pruritus**
Pruritus can occur with any opioid and is believed to be caused by opioid-mediated release of histamine from mast cells. Studies have shown that fentanyl is relatively less likely to have this effect than other pure µ-agonists. Regardless of the opioid used, itch appears to be more likely during neuraxial administration than systemic administration. The pharmacologic management of opioid-induced pruritus begins with a trial of an antihistamine, such as diphenhydramine (25-50 mg PO/IV q6h) or hydroxyzine (25 mg PO q6h). If this is ineffective, empirical trials with other medications, administered on the basis of clinical experience, might be considered. These agents include sedative hypnotics (eg, lorazepam, 1 mg SL/PO/IV q6h) and selective serotonin reuptake inhibitors (eg, paroxetine). Opioid rotation and strategies to reduce the opioid requirement may be considered as well.

**Neuroendocrine effects**
Opioids can interfere with the functioning of the hypothalamic-pituitary-adrenal axis and result in increased levels of prolactin or decreased levels of sex hormones, or both. The prevalence of clinically significant effects related to these changes, including sexual dysfunction, fatigue, accelerated bone loss, and mood disturbance, is only now coming under investigation. Further study is required to determine the need for systematic endocrine evaluation in these patients. Measurement of sex hormones and prolactin is reasonable should a patient describe symptoms that may be explained by these neuroendocrine effects. The role of replacement therapy is ill-defined, but again, a trial of replacement therapy could be justified if pain relief is satisfactory and symptoms that could be addressed by exogenous hormone therapy undermine quality of life.

**Dysimmune effects**
Opioid analgesics have effects on immune function, and studies indicate that these effects involve both cell-mediated and humoral
immunity. Peripheral effects may be mediated in some fashion by the now-confirmed existence of opioid receptors on lymphocytes. Other effects may be mediated centrally. Neither the durability (that is, the rapidity with which tolerance occurs) nor the clinical significance of opioid-related immunosuppression is yet understood. Confirmation in preclinical models that untreated nociception also suppresses immune functions, an outcome that can be reversed by opioid use, further complicates the interpretation of these effects. At present, the risk of clinically significant dysimmune effects has not been sufficiently established to recommend any change in guidelines for opioid therapy.

**Respiratory depression**

Respiratory depression is rarely a problem when opioids are administered according to accepted guidelines. Tolerance to this effect usually develops quickly, allowing rapid escalation of the dose by typical increments in the range of 30% to 100% of total daily dose. Combination of opioids with benzodiazepines, barbiturates, and other sleep-inducing or hypnotic drugs requires an added measure of caution because of synergistic blunting of hypoxic ventilatory drive. If the opioid dose is being increased too quickly, the risk of adverse respiratory effects is presaged by slowed respirations and other signs of central nervous system depression, including somnolence, cognitive impairment, and myoclonus. These signs usually provide a warning that the patient is at risk.

Tolerance notwithstanding, it also is true that some degree of opioid effect on respiratory function may persist over time, even if respiratory rate is normal. (Maintenance of respiratory rate is a normal compensatory mechanism and can occur even with significant shift in the carbon dioxide response curve.) The evidence for this effect is the occasional observation that patients receiving stable opioid therapy may experience respiratory depression after some other intervention that markedly reduces nociception and pain (e.g., nerve block, radiotherapy to a painful metastasis, pharmacologic treatment such as high-dose steroids). To prepare for this possibility, it is prudent to monitor patients closely if this type of intervention is planned and, in the case of nerve blocks, to proactively lower the opioid dose by about 50% immediately after the procedure.

In the clinical setting, it is common for healthcare staff to attribute any respiratory problem experienced by opioid-treated patients to the opioid agent. This may lead to inadequate assessment of other contributing factors. It is important to understand that respiratory distress associated with tachypnea and anxiety is
never a primary opioid event. In this setting, an alternative explanation, such as pneumonia or pulmonary embolism, must be sought. Moreover, respiratory depression with bradypnea and somnolence that occurs in the setting of stable opioid dosing should never be assumed to be the result of the opioid alone. Even if naloxone reverses the effect, the occurrence of a problem during a stable period argues against a primary role for the opioid and should impel a search for some other cause, which may have combined with subclinical opioid effects.

Naloxone should be administered only for symptomatic respiratory depression, because of the risk of systemic withdrawal and the return of pain. If peak plasma levels of the opioid have already been reached and the patient is arousable, naloxone should not be administered; instead, the next opioid dose should be withheld and the patient monitored until improved. If the patient is becoming progressively obtunded and is unarousable, naloxone should be administered using small bolus injections of dilute solution (eg, 1-mL doses of 0.4 mg of naloxone diluted in 10 mL of saline), which are titrated against respiratory rate. Patients receiving sustained-release opioid formulations or drugs with a long half-life (eg, methadone, levorphanol) may require a naloxone infusion to prevent recurrence of respiratory depression.

Suggested readings


Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs 2003;63:649-71


Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. JAMA 2000;283:367-72
Most patients attain a favorable balance between analgesia and side effects with gradual escalation of the opioid dose. However, some do not. The balance between analgesia and side effects varies from patient to patient given the same opioid and from opioid to opioid within the same individual. Some patients achieve analgesia that is maintained with few dosage adjustments; others are completely unresponsive and experience no pain relief at doses associated with intractable adverse effects. Opioid responsiveness refers to the probability that satisfactory relief without intolerable and unmanageable side effects can be attained during gradual dose titration.

Although some patients respond so poorly to multiple opioid trials that the term opioid resistant can be applied, the variability observed in responsiveness is such that this term should be avoided. No factor or group of factors is so predictive that either a negative or positive outcome can be known in advance of a therapeutic trial. Likewise, within-patient responsiveness to different opioids varies considerably, and a poor response to one opioid should not be interpreted as a poor response to opioid therapy overall.

Factors that influence opioid responsiveness
Several factors influence responsiveness to opioids. Recognition of these factors may help in the development of strategies to improve the outcome of therapy.

Individual characteristics
Demographic and disease-related factors may predispose to side effects, thereby reducing therapeutic responsiveness. For example, older patients may be less likely to experience a favorable outcome during opioid therapy because of a propensity to experience cognitive impairment from centrally acting agents. Comorbidities, such as brain metastases in cancer patients or dementia, may have the same effects.

Neuropathic pain
Although several controlled trials have now shown that patients with certain types of neuropathic pain, such as painful diabetic polyneuropathy, can respond well to opioid analgesics, there is
some evidence that, overall, patients with neuropathic pain may be relatively less responsive than patients with nociceptive pain. Opioid therapy should not be withheld merely on the assumption that its mechanism precludes a favorable response, but the clinician should be prepared with alternative therapeutic strategies to use if needed.

**Breakthrough (incident) pain**

Breakthrough pains are transitory episodes that occur in the setting of an otherwise controlled or stabilized painful condition. The term *incident pain* is most commonly applied to breakthrough pains that occur as a result of a voluntary action (ie, effort-dependent pains). Opioid responsiveness may be impaired in patients with frequent and severe breakthrough pains, particularly when the onset is rapid and the duration is too short to allow effective use of supplemental doses of an oral opioid drug. For example, a patient with incident pain related to standing may not be able to achieve adequate control of pain with an oral opioid because severe pain flares that occur immediately with every effort to stand cannot be addressed in a timely way by the medication. In these cases, a trial of a rapidly acting “rescue” opioid (eg, oral transmucosal fentanyl, intravenous patient-controlled analgesia) or a completely different analgesic modality may be needed.

**Tolerance**

Opioid responsiveness would be impaired if analgesic effects declined rapidly, driving dose escalation ultimately to a level associated with intolerable side effects. The need for dose escalation to maintain effects is a complex phenomenon. It could be caused by analgesic tolerance or by any factor that induces more pain and, hence, the need for more analgesia.

If the requirement for dose escalation is driven by a factor that causes worsening pain, such as progression of a disease, then the phenomenon cannot be attributed to opioid tolerance alone. Surveys in the clinical setting have identified these alternative explanations as the norm. In the setting of nonprogressive disease, doses typically stabilize for prolonged periods. Concern about tolerance, therefore, should not inhibit opioid prescription to appropriate patients.

**Opioid metabolites and drug-drug interactions**

Morphine's metabolites, morphine-3-glucuronide and morphine-6-glucuronide, are active and accumulate in the setting of renal insufficiency. Although the importance of these metabolites in determining opioid responsiveness is not yet clear, accumulation could be a
cause of poor morphine responsiveness in some patients. A similar situation presumably could occur with other opioids that have active metabolites and is widely recognized with those that have neurotoxic metabolites, notably meperidine and propoxyphene.

The potential for drug-drug interactions exists with some of the opioid analgesics, but little is yet known about the impact of these interactions on responsiveness. Codeine is metabolized to the active metabolite morphine by the CYP2D6 enzyme of the cytochrome P-450 hepatic enzyme system. Persons who are slow metabolizers at this isozyme site (about 7% of the US population) may have poor codeine responsiveness because of limited metabolism to morphine. It also is possible that drugs that compete at the CYP2D6 site, such as quinidine, may change the patient’s drug responsiveness. Any drug that induces enzymatic activity at opioid metabolic (deactivation) sites could, in effect, reduce responsiveness.

**Improving the balance between analgesia and side effects**

Patients with poorly responsive pain must be comprehensively assessed to identify the most rational therapeutic course. The selection of an approach is empirical; there are very few comparative trials, and every case suggests a variety of strategies that could be undertaken in an effort to improve pain control (table 19).

**Opening the therapeutic window**

Management of side effects should be considered a routine part of opioid therapy. In the context of poor responsiveness, more aggressive management may be entertained in an effort to open the therapeutic window and potentially allow higher opioid doses (see chapter 6).

**Opioid rotation**

Poor responsiveness during treatment with one opioid does not predict response to another. Sequential opioid trials—called opioid rotation—is now widely accepted for addressing poorly responsive pain (see chapter 5). When switching from one opioid to another, calculated equianalgesic doses (see chapter 3) are used as a starting point to reduce the risk of overdosing or underdosing (see table 12).

**Pharmacologic techniques that reduce the systemic opioid requirement**

A reduction in the opioid dose necessary to yield therapeutic benefit may allow for a clinically relevant dose that is in the range
not associated with treatment-limiting toxicity. Two pharmacologic strategies derive from this concept: systemic administration of a coanalgesic and delivery of the opioid intraspinally (neuraxial infusion).

**Systemic administration of coanalgesics.** Potential coanalgesics include the nonsteroidal anti-inflammatory drugs (NSAIDs) and the so-called adjuvant analgesics. NSAIDs (selective and nonselective agents) produce additive analgesia when combined with opioids, and the combination of an opioid and an NSAID has been included in widely accepted guidelines for treatment of both acute and cancer pain.

Adjuvant analgesic agents are drugs that have a primary indication other than pain relief but are known to have an analgesic effect in specific circumstances. They include numerous drugs in diverse drug classes. A simple taxonomy divides these classes by their current uses (table 20). The multipurpose drugs include a large number of analgesic antidepressants, $\alpha_2$-adrenergic agonists and corticosteroids and a variety of topical agents.

Drug classes used selectively for neuropathic pain include all the multipurpose analgesics plus the analgesic anticonvulsants, $\gamma$-aminobutyric acid agonists, oral local anesthetics, and $N$-methyl-$d$-aspartate receptor antagonists. Drugs that are indicated for musculoskeletal pains comprise the so-called muscle relaxants and benzodiazepines. Drug classes used for headache include the NSAIDs, the multipurpose agents and anticonvulsants,
and numerous classes specifically prescribed for vascular headache, including the vasoactive drugs, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

Finally, there are some adjuvant analgesics used for certain types of cancer pain, specifically drugs for pain from bone metastases and those for pain associated with malignant bowel obstruction. Given the extraordinary variety of coanalgesics available, and the limited data on each, selection of specific drugs for trials in the patient with poorly responsive pain requires good clinical judgment informed by a comprehensive evaluation of the patient and a grounding in pharmacology.

**Neuraxial infusion.** The clearest indication for intraspinal opioid delivery is intolerable somnolence or confusion in patients who are not experiencing adequate analgesia and have pain located below the level of midchest. Intraspinal administration of local anesthetics or other agents (eg, clonidine) in combination with an opioid may provide additional analgesia and permit the successful treatment of patients whose pain is unresponsive to spinal morphine alone.

**Nonpharmacologic techniques that reduce the systemic opioid requirement**

Numerous nonpharmacologic approaches can be used to reduce the systemic opioid requirement (table 21). Like the pharmacologic strategies, selection of one or more of these approaches must be informed by an understanding of the available options and a detailed assessment of the patient.

**Anesthesiologic approaches.** Invasive therapies performed with a needle may be under the purview of a variety of medical disciplines. The more challenging and potentially risky of these approaches historically have been performed by anesthesiologists, whose training includes becoming skilled at regional anesthetic techniques. Injection therapies include trigger point injections, joint injections, and spinal injections of varied types. Neural blockade subsumes a broad array of procedures that target somatic or sympathetic nerves. Use of implanted analgesic devices, including spinal cord stimulators and neuraxial infusion pumps, is often considered under this category as well.

**Neurostimulatory approaches.** The neurostimulatory procedures include transcutaneous electrical nerve stimulation and invasive therapies—most importantly, spinal cord stimulation. The latter approach is considered most often for patients with refractory neuropathic pain.

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## Table 20. Adjuvant analgesic agents

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multipurpose analgesics</strong></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, desipramine, imipramine, nortriptyline, doxepin</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Paroxetine, citalopram, fluoxetine, sertraline, fluvoxamine</td>
</tr>
<tr>
<td>Serotonin/norepinephrine reuptake inhibitors</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>α2-Adrenergic agonists</td>
<td>Clonidine, tizanidine, dexametomidine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone, prednisone, methylprednisolone</td>
</tr>
<tr>
<td>Topical analgesics</td>
<td>Capsaicin (eg, prilocaine/lidocaine cream, lidocaine 5% patch)</td>
</tr>
<tr>
<td><strong>Drugs used for neuropathic pain</strong></td>
<td></td>
</tr>
<tr>
<td>All multipurpose analgesics</td>
<td>See drugs listed above</td>
</tr>
<tr>
<td>Anticonvulsant agents</td>
<td>Clonazepam (also a benzodiazapine), carbamazapine, gabapentin, phenytoin, valproate, lamotrigine, topiramate, trileptal</td>
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<td>GABA agonists</td>
<td>Tiagabine</td>
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<td>Oral local anesthetic agents</td>
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<td>NMDA receptor antagonists</td>
<td>Ketamine, dextromethorphan, amantadine, memantine</td>
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<td><strong>Drugs used for musculoskeletal pain</strong></td>
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<td>Muscle relaxants</td>
<td>Methocarbamol, baclofen</td>
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<tr>
<td>Benzodiazapines</td>
<td>Diazepam, clonazapam</td>
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<td><strong>Drugs used for headache</strong></td>
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<td>Nonsteroidal anti-inflammatory drugs</td>
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<td>Nonselective agents</td>
<td>Aspirin, ibuprofen, ketorolac, ketoprofen, naproxen</td>
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<td>COX-2 selective agents</td>
<td>Celecoxib, rofecoxib, valdecoxib</td>
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<tr>
<td>Multipurpose analgesics</td>
<td>See drugs listed above</td>
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<tr>
<td>Anticonvulsants</td>
<td>See drugs listed above</td>
</tr>
<tr>
<td><strong>Drugs for vascular headache</strong></td>
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<tr>
<td>Vasoactive drugs</td>
<td>Triptans (eg, sumatriptan, zolmitriptan, rizatriptan, naratriptan), ergots (eg, ergotamine, dihydroergotamine)</td>
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<tr>
<td>β-Blockers</td>
<td>Propranolol, timolol, metoprolol, nadolol</td>
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<tr>
<td>Calcium channel blockers</td>
<td>Verapamil, diltiazem, nifedipine</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Captopril, enalapril</td>
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</table>
**Table 20. Adjuvant analgesic agents** (continued)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>Losartan, valsartan, irbesartan</td>
</tr>
<tr>
<td><strong>Drugs used for cancer pain</strong></td>
<td></td>
</tr>
<tr>
<td>Drugs used for bone pain</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>See drugs listed above</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Injectable and intranasal formulations</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Pamidronate, zoledronic acid, clondronate</td>
</tr>
<tr>
<td>Radiopharmaceuticals</td>
<td>Strontium Sr 89, samarium Sm 153</td>
</tr>
<tr>
<td><strong>Drugs used for bowel obstruction</strong></td>
<td></td>
</tr>
<tr>
<td>Synthetic hormonelike drugs</td>
<td>Octreotide</td>
</tr>
<tr>
<td>Anticholinergic agents</td>
<td>Hyoscine, scopolamine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>See drugs listed above</td>
</tr>
</tbody>
</table>

**COX, cyclooxygenase; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate.**

**Surgical neuroablative procedures.** Surgical therapies that isolate the painful part from the central nervous system are now rarely performed. The most widely used procedure, cordotomy (spinothalamic tractotomy), is sometimes considered in the setting of refractory cancer pain in the lower body. Neuraxial infusion techniques have largely replaced the need for surgical cordotomy.

**Physiatric techniques.** Many patients with painful conditions benefit from physical or occupational therapy, and the use of orthoses or prostheses in selected patients may have important analgesic consequences. Modalities used for analgesic purposes include heat and cold, vibration, and ultrasound.

**Psychologic approaches.** There is substantial evidence that cognitive therapies can have an analgesic effect in some populations of patients with chronic pain. These approaches include relaxation training, hypnosis, and biofeedback. Behavioral approaches may be useful to optimize function, which itself may have pain-reducing consequences.

**Complementary and alternative medicine (CAM) approaches.** CAM therapies are commonly pursued by patients. Some of these treatments have sufficient evidence to consider under the broad rubric of a multimodality therapeutic approach. Physicians often suggest a trial of acupuncture, therapeutic massage, chiropractic therapy, or movement or stretching therapies (eg, tai chi chuan, yoga). Several nutritional supplements, such as...
### Table 21. Nonpharmacologic techniques to reduce the systemic opioid requirement

<table>
<thead>
<tr>
<th>Approach</th>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiologic</td>
<td>Neuraxial infusion</td>
<td>Epidural or intrathecal infusion of local anesthetics and other drugs</td>
</tr>
<tr>
<td></td>
<td>Neural blockade</td>
<td>Temporary nerve blocks, neurolytic blocks</td>
</tr>
<tr>
<td></td>
<td>Injection therapies</td>
<td>Spinal injections, trigger point injections</td>
</tr>
<tr>
<td>Neurostimulatory</td>
<td>Superficial</td>
<td>Transcutaneous electrical nerve stimulation, counterirritation</td>
</tr>
<tr>
<td></td>
<td>Invasive</td>
<td>Dorsal column stimulation</td>
</tr>
<tr>
<td>Surgical</td>
<td>Neurolytic lesions</td>
<td>Peripheral neurectomy, rhizotomy, cordotomy, and other lesions in brain or spinal cord</td>
</tr>
<tr>
<td>Physiatric</td>
<td>Orthoses/prostheses</td>
<td>Spinal or limb-bracing techniques</td>
</tr>
<tr>
<td></td>
<td>Physical/occupational therapy</td>
<td>Therapeutic exercise</td>
</tr>
<tr>
<td></td>
<td>Modalities</td>
<td>Heat, cold</td>
</tr>
<tr>
<td>Psychologic</td>
<td>Cognitive</td>
<td>Relaxation techniques, psychotherapy</td>
</tr>
<tr>
<td></td>
<td>Psychoeducational</td>
<td>Structured support groups</td>
</tr>
<tr>
<td>Complementary and alternative medicine</td>
<td>Some nutraceuticals</td>
<td>Possibly glucosamine</td>
</tr>
<tr>
<td></td>
<td>Acupuncture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chiropractic therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Massage</td>
<td></td>
</tr>
</tbody>
</table>

Glucosamine, may have sufficient evidence to warrant recommendation. Other popular but untested therapies, including the so-called energy approaches such as craniosacral manipulation, treatments included under non-Western medical systems (eg, traditional Chinese medicine, Ayurvedic medicine), and unproven nutraceuticals or supplements, are not usually recommended as part of a conventional strategy for pain. If patients desire such treatments, however, and there is no evidence of a safety concern, it may be best to be supportive and to try to integrate all strategies into an approach focused on comfort and functional restoration.
Suggested readings


The relationship between medical use and abuse of opioids cannot be clarified without a precise characterization of terms. Confusion about physical dependence, tolerance, and addiction augments the fear of opioid analgesic use and contributes to a physician’s reluctance to prescribe opioids and a patient’s reluctance to take the medications. Conversely, failure to understand the characteristics that truly constitute addiction or other forms of problematic drug-related behavior may hinder recognition of the syndrome when it does occur in the clinical setting.

**Tolerance**

As described previously, tolerance is a pharmacologic property of opioid drugs defined by the need for increasing doses to maintain effects. It is a complex phenomenon that may include both physiologic changes and learning (known as pharmacologic and associative tolerance, respectively). Opioid tolerance is assumed to primarily involve changes in the mechanisms initiated after binding of the drug to the receptor. Recent research has elucidated a mechanism that involves the N-methyl-D-aspartate (NMDA) receptor and can be reversed by NMDA receptor blockers. Other processes, such as changes in second messengers unrelated to the NMDA receptor and a change in receptor number, also may be involved. Tolerance may develop to any opioid effect, and both the rate of development and the degree of tolerance varies from effect to effect and from individual to individual.

Although tolerance is commonly portrayed as a potential problem during long-term therapy, tolerance to adverse effects actually is a favorable phenomenon. This type of tolerance allows dose escalation to levels associated with improved analgesia.

Tolerance to analgesic effects can occur and, theoretically, could be a major impediment to the clinical use of opioid drugs. In the clinical setting, however, the need for dose escalation has several potential drivers, only one of which is tolerance. Progression of disease (leading to greater nociception), a change in pain mechanism (e.g., a shift over time from a predominating nociceptive mechanism to a predominating neuropathic mechanism), and psychologic processes that lead to increased pain all
may result in declining efficacy and a need to increase the dose to maintain analgesia. The need for dose escalation can be ascribed to tolerance only if an alternative explanation cannot be discerned. This occurrence appears to be uncommon in most clinical situations.

Patients who benefit from opioid therapy for a prolonged period often have stable doses for very prolonged periods. Those who experience worsening pain from time to time may require temporary dose escalation to maintain effects. At least for this subpopulation, tolerance does not preclude effective long-term therapy.

Tolerance must be distinguished from both physical dependence and addiction. Although tolerance to the positive psychic effects of a self-administered drug has been perceived as an element in the genesis of addiction, patients who receive opioids for pain do not commonly express significant effects of this type, and the development of tolerance to any mood effect rarely influences the course of therapy. In short, addiction can occur without evidence of tolerance, and tolerance can be inferred in the clinical setting without any of the behavioral problems consistent with abuse or addiction.

**Physical dependence**

Physical dependence is also a pharmacologic property of opioids as well as other medications, defined by the occurrence of an abstinence syndrome after abrupt dose reduction, a decreasing blood level of the drug, or administration of an antagonist. Some degree of physical dependence is usually produced with very little opioid exposure, and neither the opioid dose nor the duration of administration required to produce clinically significant physical dependence in humans is known. Therefore, most practitioners assume that the potential for an abstinence syndrome exists after opioids have been administered regularly for only a few days. Physical dependence is not problematic as long as patients are instructed not to abruptly discontinue therapy after long-term use and no antagonist drugs are administered.

The distinction between physical dependence and addiction has been a source of confusion for patients and clinicians alike. It is probably true that individuals who are predisposed to addiction and begin compulsive drug use to feel a positive psychic effect may make the transition and have compulsive use maintained by a need to avoid uncomfortable withdrawal. However, this phenomenon should not be taken as evidence that physical dependence itself results in addiction. In medically ill populations using opioid analgesics on a regular basis, physical dependence is common
but addiction is rare, and uncomplicated discontinuation of opioid therapy can be achieved easily if a tapering schedule is used when cessation is indicated.

A patient who is presumed to be physically dependent should never be labeled an addict. Misuse of the latter term reinforces the stigma associated with opioid therapy and should be abandoned. Likewise, referring to the patient as dependent should also be discouraged, since it creates confusion between physical dependence and the type of psychologic dependence that is associated with addiction.

**Abuse and addiction**

During the past half century, numerous definitions for abuse and addiction have been developed. Each definition has generated criticism, and each has been followed by an attempt at some later time to redefine the construct. Until recently, all definitions emerged from the field of addiction medicine, without input from pain specialists.

According to one definition, the term *drug abuse* should apply to the use of any drug that is outside of accepted norms. Although it is true that normative behavior reflects culture and is not constant, this definition has utility in the clinical setting. It labels any use of an illicit drug and any misuse of a prescribed drug (use in a manner not intended by the clinician) as abuse.

In a more complex definition, the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition text revision (DSM-IV-TR), classifies substance abuse as 1 of 2 psychoactive substance use disorders and defines it as a maladaptive pattern of drug use that results in harm or places the individual at risk. Considered broadly, this definition and the one discussed before it describe very similar phenomena.

Early definitions of addiction developed by expert committees of the World Health Organization were problematic because they included tolerance and physical dependence as cardinal signs of addiction. These criteria clearly do not apply to patients who receive a drug for medical indications.

The *DSM-IV-TR* does not include the term *addiction* but defines a syndrome of psychoactive substance dependence under the category of psychoactive substance use disorders. This diagnosis is characterized by a maladaptive pattern of drug use that persists for at least 1 month and includes at least 3 of 9 criteria. Although the criteria include descriptions of craving, compulsive use, and use despite harm (which could be used to establish the diagnosis of addiction in the absence of any other criteria), they also refer to
tolerance and physical dependence. These ambiguities have led to criticisms of this definition by pain specialists.

Recently, the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine established a task force that created consensus definitions of addiction, physical dependence, and tolerance (table 22). The definition of addiction states that the syndrome is a psychologic and behavioral disorder that has a genetic substrate and is characterized by drug craving, compulsive use, a strong tendency to relapse after withdrawal, and continued use despite harm to the user or those around him or her. This definition appropriately focuses on behavior as the relevant assessment for the diagnosis of addiction, rather than on phenomena related to tolerance or physical dependence.

Pseudoaddiction

In clinical practice, the diagnosis of addiction involving use of a pharmacotherapy may be particularly challenging, because the drug in question is legal and prescribed for an appropriate medical condition. This challenge is underscored by a phenomenon that has been termed pseudoaddiction. Pseudoaddiction refers to the development of abuselike behaviors that are driven by desperation surrounding unrelieved pain and are eliminated by measures that relieve the pain, such as an increase in medication dose.

The term pseudoaddiction was originally coined on the basis of observations of patients with cancer pain. It referred

<table>
<thead>
<tr>
<th>Table 22. Terminology of substance abuse</th>
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<tbody>
<tr>
<td><strong>Tolerance</strong></td>
</tr>
<tr>
<td>A state of adaptation in which exposure to a drug induces changes that result in diminution of 1 or more of the drug’s effects over time</td>
</tr>
<tr>
<td><strong>Physical dependence</strong></td>
</tr>
<tr>
<td>A state of adaptation that is manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, a decreasing blood level of the drug, and/or administration of an antagonist</td>
</tr>
<tr>
<td><strong>Addiction</strong></td>
</tr>
<tr>
<td>A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving</td>
</tr>
</tbody>
</table>

specifically to behaviors such as drug-seeking and expressions of distress. Over time, however, it has been applied to all populations with chronic pain and sometimes used to describe behaviors that are highly problematic, such as the acquisition of street drugs to treat a pain problem.

In ascribing more overt and potentially harmful drug-related behaviors to pseudoaddiction, there is a risk of ignoring a concurrent addiction. This risk is a serious concern. It is important to recognize that addiction and pseudoaddiction can coexist and that the report of unrelieved pain does not give license to behaviors that are inappropriate or illegal. Even if the term pseudoaddiction is applied, it is necessary to gain control over behaviors that place the patient, the physician, or others at risk.

**Aberrant drug-related behavior**
The dual phenomenon of addiction and pseudoaddiction, either of which may explain a set of drug-related behaviors, indicates that problematic behaviors in the clinical setting have a differential diagnosis (table 23). In addition to addiction and pseudoaddiction, problematic behaviors may reflect a variety of other psychiatric disorders, family disturbances, or possibly even criminal intent. For some patients with psychiatric disorders and some with high distress but no clear psychiatric diagnosis, inappropriate opioid use may reflect self-medication (sometimes called chemical coping) or an effort to communicate anger or misery. Appropriate treatment requires a proper diagnosis based on a detailed assessment.

The concept of aberrant drug-related behavior has been developed to explore the observation that drug-related behav-

<table>
<thead>
<tr>
<th>Table 23. Differential diagnosis of aberrant drug-related behavior</th>
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<tbody>
<tr>
<td><strong>Addiction</strong></td>
</tr>
<tr>
<td><strong>Pseudoaddiction</strong></td>
</tr>
<tr>
<td><strong>Other psychiatric disorder</strong></td>
</tr>
<tr>
<td>Axis I disorder (eg, anxiety disorders, major depression)</td>
</tr>
<tr>
<td>Axis II disorder (eg, personality disorders such as borderline personality, sociopathic personality)</td>
</tr>
<tr>
<td>Encephalopathy (eg, associated with medication toxicity)</td>
</tr>
<tr>
<td><strong>Other psychosocial/emotional issues</strong> (eg, family discord, financial worries, work-related discontent, “rebellion”)</td>
</tr>
<tr>
<td>Recreational use (eg, experimentation, pleasure, escape, peer pressure)</td>
</tr>
<tr>
<td><strong>Criminal intent</strong></td>
</tr>
</tbody>
</table>
Behaviors, and the meaning of these behaviors, vary greatly from individual to individual. In the clinical setting, aberrant drug-related behavior is synonymous with other terms, including problematic behavior, misuse and abuse behaviors and nonadherence behavior. It refers to the phenomenon of drug-related behavior that is inconsistent with the expressed intentions of the prescriber.

Aberrant drug-related behavior exists on a continuum. Some behaviors are very worrisome and probably quite suggestive of an addiction; others are less worrisome and may reflect other causes (table 24). Routine evaluation of patients using opioids must include monitoring for the development of these behaviors. Should problematic behaviors occur, the assessment must yield information that supports a specific diagnosis and facilitates an appropriate therapeutic response.

### Table 24. Behaviors suggestive of addiction

<table>
<thead>
<tr>
<th>Behaviors probably more suggestive of addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Selling prescription drugs</td>
</tr>
<tr>
<td>• Forging prescriptions</td>
</tr>
<tr>
<td>• Stealing or “borrowing” drugs from others</td>
</tr>
<tr>
<td>• Injecting or inhaling (snorting, smoking) oral formulations</td>
</tr>
<tr>
<td>• Obtaining prescription drugs from nonmedical sources</td>
</tr>
<tr>
<td>• Concurrently abusing alcohol or illicit drugs</td>
</tr>
<tr>
<td>• Having multiple dose escalations or other nonadherence with therapy, despite warnings</td>
</tr>
<tr>
<td>• Repeatedly “losing” prescriptions</td>
</tr>
<tr>
<td>• Repeatedly seeking prescriptions from other clinicians or from emergency department staff without informing prescriber or after warnings to desist</td>
</tr>
<tr>
<td>• Showing evidence of deterioration in ability to function at work, in the family, or socially that appears to be related to drug use</td>
</tr>
<tr>
<td>• Repeatedly resisting changes in therapy, despite clear evidence of adverse physical or psychologic effects from the drug</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behaviors probably less suggestive of addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aggressive complaining about the need for more drug</td>
</tr>
<tr>
<td>• Drug hoarding during periods of reduced symptoms</td>
</tr>
<tr>
<td>• Requesting specific drugs</td>
</tr>
<tr>
<td>• Openly acquiring similar drugs from other medical sources</td>
</tr>
<tr>
<td>• Having unsanctioned dose escalation or other nonadherence with therapy on 1 or 2 occasions</td>
</tr>
<tr>
<td>• Using the drug, without approval, to treat another symptom</td>
</tr>
<tr>
<td>• Reporting psychic effects not intended by the clinician</td>
</tr>
<tr>
<td>• Resisting a change in therapy associated with “tolerable” adverse effects with expressions of anxiety related to the return of severe symptoms</td>
</tr>
</tbody>
</table>
The diagnosis of aberrant drug-related behavior, and subsequent control and monitoring should opioid therapy be continued, may require the input of a professional skilled in addiction medicine. Referral should be considered if the issues raised by the patient are beyond the skills of the prescriber.

**Suggested readings**


CHAPTER 9

OPIOID MISUSE, ABUSE, AND ADDICTION

Extensive experience in management of cancer pain has suggested that long-term opioid therapy of an older population with no history of substance abuse is rarely associated with de novo development of abuse or addiction. Similarly, very large surveys of patients who receive opioids to treat acute pain indicate that this therapy has a very low risk of precipitating addiction. In the cancer pain and acute pain populations, there are considerable challenges in treating patients with a known history of drug abuse, but the risk of iatrogenic addiction among those without this history appears to be very low.

Importantly, the reassuring data concerning development of addiction in the nonabusing cancer pain and acute pain populations do not mean that the incidence, prevalence, or impact of various aberrant drug-related behaviors are known. The rates of all types of aberrant drug-related behavior within these diverse populations are not known and remain an important topic of future research.

Even less is known about the larger population with chronic nonmalignant pain. Surveys have shown that the occurrence of aberrant drug-related behavior during opioid therapy is common among patients who were referred to pain specialists. For example, studies of urine drug screens suggest that as many as one third of patients who are referred to specialized multidisciplinary pain clinics are prescribed opioid analgesics, and those who are not subsequently suspected of abuse may be using other drugs without the clinician’s knowledge. Because patients referred to pain specialists are far more likely than the general population with chronic pain to have comorbid psychiatric disease, including prior substance abuse, it is reasonable to assume that this observation reflects the worst-case scenario.

It must be recognized that the base rate of addictive disease in the general US population is relatively high (estimated to be about 15% for alcoholism and about 5% for cocaine or heroin addiction). On this basis, it has been estimated that at least 10% of adults (and probably more) have a genetic susceptibility to addiction. With this level of genetic vulnerability, and with other psychologic and social factors also potentially driving aberrant drug-related behavior, it is prudent to acknowledge the risk of
problematic behavior and even addiction whenever opioids (or other abusable drugs) are prescribed. Although the risk may be low in some subpopulations, it can never be said to be zero, and clinicians who prescribe opioids must incorporate risk assessment—and management, if needed—at the start of therapy and repeatedly during its course.

Surveys have established that patients with a past history of substance abuse or addiction are at higher risk of having a problem with prescribed opioids. Recent studies have attempted to go beyond this characterization and identify other patient characteristics that can be useful in predicting aberrant drug-related behavior or addiction during opioid therapy for chronic pain. Several screening tools have recently been developed; all require additional validation in large prospective studies.

A survey by Chabal and colleagues suggested that 5 criteria could be used to judge the risk of prescription drug abuse in a patient: (1) a focus on opioids during clinic visits, (2) a pattern of early refills or dose escalation, (3) multiple telephone calls or visits pertaining to opioid therapy, (4) other prescription problems, and (5) acquisition of opioids from other sources. A survey by Compton and coworkers evaluated a 42-item interview and identified 3 items that were most predictive of drug misuse and abuse: (1) having a tendency to increase the dose, (2) having a preference for a specific route of administration, and (3) considering oneself addicted.

Coambs and associates developed the Screening Instrument for Substance Abuse Potential (SISAP) (table 25). This instrument was designed for use when a physician already knows the patient or has sufficient collateral data to confirm the patient’s

<table>
<thead>
<tr>
<th>SISAP questions predictive of aberrant behavior</th>
<th>Use caution when prescribing opioids to these patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If you drink alcohol, how many drinks do you have on a typical day?</td>
<td>Men who drink more than 4 alcoholic beverages per day or 16 per week</td>
</tr>
<tr>
<td>2. How many drinks do you have in a typical week?</td>
<td>Women who drink more than 3 alcoholic beverages per day or 12 per week</td>
</tr>
<tr>
<td>3. Have you used marijuana or hashish in the past year?</td>
<td>Persons who admit to recreational use of marijuana or hashish in the previous year</td>
</tr>
<tr>
<td>4. Have you ever smoked cigarettes?</td>
<td>Persons who are younger than 40 years and smoke</td>
</tr>
<tr>
<td>5. What is your age?</td>
<td></td>
</tr>
</tbody>
</table>

SISAP: Screening Instrument for Substance Abuse Potential.
responses. This tool has a low false-negative rate but results in a fairly high percentage of patients who are falsely labeled as being at higher risk (ie, high sensitivity and low specificity).

The CAGE questionnaire (Cut down, Annoyed, Guilty, and Eye-opener), which was originally developed as a screening tool for alcoholism, has been adapted to include drugs (CAGE-AID) (table 26). Two or more positive responses should be followed by a detailed assessment.

A single question has been identified as having good predictive validity for prior addiction: “Has your use of alcohol or other drugs ever caused a problem for you or those close to you?” Given the relationship between prior drug abuse and problems with prescription drugs, an affirmative response to this question should initiate a more detailed assessment.

Recently, Adams and colleagues developed a 26-item pain medicine questionnaire. In a formal validation study, questionnaire scores were highly associated with abuse history.

Patient characteristics other than those identified in these instruments also may help a clinician define the degree of risk (table 27). Although there is yet no standard approach to the prediction of risk, this effort to examine a range of characteristics and validate screening tools reflects the importance of risk assessment before and during opioid therapy. Hopefully, future research will yield a highly valid, brief screening instrument that can be easily adapted for clinical use.

For the present, clinicians should ensure that assessment of the patient with chronic pain includes a variety of items related to the risk of abuse and addiction. In this way, patients may be

<table>
<thead>
<tr>
<th>In the past have you ever:</th>
<th>Implications for prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tried to Cut down or Change your pattern of drinking or drug abuse?</td>
<td>• One positive response to any question suggests caution</td>
</tr>
<tr>
<td>2. Been Annoyed or Angry by others’ concern about you drinking or drug use?</td>
<td>• Two or more positive responses may have a sensitivity of 60%-95% and specificity of 40%-95% for diagnosing alcohol or drug problems and strongly suggest assessment by an addiction specialist before opioids are prescribed</td>
</tr>
<tr>
<td>3. Felt Guilty about the consequences of your drinking or drug use?</td>
<td>• CAGE screen may have less predictive value in the elderly, college students, women, and certain ethnic groups</td>
</tr>
<tr>
<td>4. Had a drink or used a drug in the morning (Eye-opener) to decrease hangover or withdrawal symptoms?</td>
<td></td>
</tr>
</tbody>
</table>

* “AID” refers to “adapted to include drugs.”
Table 27. Additional risk factors for substance abuse

1. History of physical, emotional, or sexual abuse
2. Personal history or family history of a severe depression or anxiety disorder
3. Personality disorders with poor impulse control (borderline, antisocial, psychopathic)
4. Family history of substance abuse/dependence or antisocial personality disorder
5. Low threshold for any adverse bodily symptoms (stimulus augmenter)
6. Limited stress management skills and previous episodes of “chemical coping”
7. Current dysfunctional or chaotic living environment (drug abuse in a close family member)
8. Regular contact with high-risk people (eg, drug-using friends) or involvement with high-risk activities (eg, regular time spent in a bar or on the street)
9. Previous criminal behavior
10. Prior tobacco abuse
11. Previous treatment in a drug or alcohol rehabilitation facility
12. Treatment in another pain clinic
13. Many previous automobile accidents

Information from RD Jovey. Presentation at the International Conference on Pain and Chemical Dependency, Jun 6-8, 2002, New York.

classified as being at relatively low versus high risk for future problems, and this classification in turn can inform the approach used to administer and monitor therapy over time.

Suggested readings


Clinicians who prescribe opioid analgesics for the treatment of chronic pain have an obligation to implement therapy according to accepted principles of prescribing and to minimize the risk of misuse, abuse, addiction, and diversion through individualized application of risk assessment and management strategies. The necessity of a basic skill set in addiction medicine to prescribe opioid therapy safely has been highlighted in recent years by a documented increase in prescription drug abuse, the devastating consequences of endemic abuse of specific drugs (eg, oxycodone abuse in varied regions of the United States), and the strong call for “balance” by both pain specialists and those in the regulatory and law enforcement communities. Clinicians must understand the regulations and laws that govern the use of controlled prescription drugs and must be able to structure a prescription regimen that is consistent with the perceived risk of abuse or addiction and includes the monitoring necessary to identify problems if they occur.

Laws and regulations governing prescription drugs
Uncertainty regarding regulatory issues and a fear of potential disciplinary action may give physicians pause when considering whether to prescribe long-term opioid therapy. Surveys have shown that physicians have a very real fear of disciplinary action for prescribing controlled substances, particularly if the patient has nonmalignant pain or a history of drug abuse. Even in patients with cancer pain or HIV-related pain, for which there is wide acceptance of opioid therapy, concerns about regulatory scrutiny are believed to be a significant cause of undertreatment.

The framework of laws and regulations governing the use of opioids and other controlled substances has 3 tiers: (1) international laws and treaties, (2) federal laws and regulations, and (3) state laws and regulations. National governments are obligated to ensure the availability of opioid medications for legitimate medical and scientific purposes. International treaties have been designed to achieve a balance between ensuring the availability of controlled substances for medical purposes and preventing illegal diversion.

The International Narcotics Control Board was established in 1968 as an independent and quasi-judicial body empowered to
implement the United Nations drug conventions. It attempts to ensure that adequate supplies are available for medical and scientific uses and that leakages from licit sources to illicit traffic do not occur. To accomplish this, the board administers an estimates system for opioids and monitors international trade in drugs. It also monitors government control over chemicals used in the illicit manufacture of drugs, and assists governments in preventing diversion of these chemicals into illicit traffic. Finally, the board also attempts to identify where weaknesses in the national and international control systems exist.

At the federal level, the FDA and the Drug Enforcement Agency (DEA) work together to regulate drugs and thereby prevent drug diversion and abuse. Before a pain medication can become available to patients, the FDA must assess its efficacy and safety, including its potential for abuse. If a product does not receive marketing approval (or an exemption) from the agency, it cannot be legally produced or prescribed.

The Controlled Substances Act empowers the DEA to classify drugs into different schedules based on the risk of abuse and diversion, medical use, and safety. Controlled substance schedules range from I to V. Schedule I drugs (e.g., heroin, LSD, marijuana) have a high potential for abuse, a lack of accepted safety, and no current federally accepted medical use. Schedule II drugs (e.g., morphine, fentanyl, hydromorphone, levorphanol, methadone, oxycodone, oxymorphone, methylphenidate, dextroamphetamine, dronabinol) have a high potential for abuse, produce severe psychologic or physical dependence liability, and have current accepted medical uses. Drugs classified into schedules III through V (e.g., hydrocodone, codeine, diazepam) represent substances considered to have progressively less abuse potential and relatively reduced psychologic or physical dependence.

The DEA enforces the Controlled Substances Act and the laws regulating the manufacture, distribution, dispensing, and record-keeping requirements for controlled substances. It also sets production quotas for controlled drugs, which are intended to accommodate all legitimate medical and scientific uses of scheduled drugs.

Each state works with the federal government to oversee the movement of controlled prescription drugs and minimize abuse and diversion. Each also has sole responsibility for maintaining standards of healthcare practice through licensure of professionals. Law enforcement involvement occurs at the local and the state level through numerous agencies. Medical practice and licensure is governed through state medical boards, whose members are appointed by the governor.
Historically, the policies, laws, and regulations that govern the use of controlled prescription drugs in most states have been skewed toward enforcement and not patient care. The principle of balance found in international and federal law has not been central to the oversight efforts of the states. During the past 5 years, however, many states have attempted to redress the major concerns and explicitly recognize the need to protect clinical practice while reducing opioid abuse and diversion. In the area of medical practice, for example, the Federation of State Medical Boards, a national organization, has drafted model regulations for the medical use of controlled substances (“Model Guidelines for the Use of Controlled Substances for the Treatment of Pain”), which have now been adopted, at least in part, by almost half of the states.

Progress has been made in establishing a dialogue with members of the federal and state regulatory and law enforcement communities about the evolving role of opioid analgesics in pain management. However, physician concerns about investigation, and potential sanction, are not unfounded. The number and complexity of the agencies that can initiate an investigation after a complaint, the variation in laws and regulations from jurisdiction to jurisdiction, the lack of certainty that local investigators follow the intentions of senior management in any agency, and the potential to be duped by those who would divert drugs into the illicit market combine to create an irreducible level of prescriber risk associated with prescribing controlled drugs. Anecdotal reports of physicians who have been investigated (a costly and highly stressful process, even if the outcome is favorable), disciplined by their licensing boards, or prosecuted for alleged criminal activities further lead to a high level of concern and may produce a chilling effect that contributes to the undertreatment of pain.

To minimize risk, prescribers must follow laws and regulations when prescribing, prescribe in accordance with accepted medical practice, and document appropriately. A clinician who recognizes the necessity of risk assessment and management is best able to maintain the controls necessary to prescribe in a manner consistent with federal and state requirements.

**Structuring therapy to reduce risk**

Just as opioid treatment must be individualized from the perspective of medication selection and dosing, treatment strategies must be individually fashioned to minimize the likelihood of misuse, abuse, addiction, and diversion and must create an appropriate level of monitoring for these potential adverse
outcomes. Although the science of prediction is still limited, the clinician must rely on the assessment to ascertain whether the patient should be categorized as having a relatively low risk of abuse or a high risk of abuse. Proactive strategies should be adopted at the start of therapy on the basis of perceived level of this risk (table 28).

During the course of treatment, all patients should be monitored for development of aberrant drug-related behaviors (see chapter 8, page 80). If problematic behavior is identified, reassessment usually is needed to clarify the meaning of the behavior and to generate one or more potential diagnoses (eg, addiction, pseudoaddiction, another psychiatric disorder associated with impulsive drug taking, family disturbances, criminal activity). Often, the meaning of the behavior is not clear when the behavior first occurs. If involvement with the patient continues, the diagnosis may become evident over time as the patient deals with new contingencies.

On the basis of the severity of the problematic behavior, patient history, and the findings of the reassessment, the clinician must decide about continuation of treatment and referral. Pain treatment may be continued with opioids (using a different structure for prescribing) or continued without opioids, or the patient may be discharged from the practice. The decision to again continue treatment with the opioid is based on the severity of the problematic behavior and the reassessment. Treatment should not be continued unless (1) favorable outcomes (ie, pain relief and maintained function) are manifest, (2) there is a high likelihood that control over the therapy can be reacquired, and (3) restructuring allows better monitoring of drug-related behavior. Discharge from the practice may be warranted if the possibility of therapeutic progress has been severely undermined by mistrust or the assessment reveals that the patient lacks interest in treatments other than the opioid agent.

When aberrant drug-related behavior occurs, the clinician must also decide about the need for referral. If a diagnosis of addiction is tenable, referral to a specialist in addiction medicine or an addiction program should be strongly considered. Addiction is a disease like any other, and it is no more appropriate to neglect referral for this disorder once it is suspected than it is to neglect referral for any other complex, potentially life-threatening disease. The clinician also might consider referral to a pain specialist or to a mental healthcare provider (other than an addiction specialist), depending on the needs identified.

If the decision is made to continue prescribing the opioid, strategies should be implemented to reduce the risk of further
Table 28. Proactive and reactive strategies to minimize risk of abuse and enhance monitoring

**Proactive strategies**
- Written agreement after detailed consent discussion
- Prescribe long-acting drug without “rescue” dose
- Frequent visits and small quantities prescribed
- Urine drug screen at baseline and expressed intention to request occasional screens in the future
- Requirement that only one pharmacy be used (with permission to contact)
- Instruction to bring pill bottle to appointment (for count)
- Instruction that there will be no early refills and no replacement of lost prescription without a police report documenting loss
- Requirement for nonopioid therapies, including psychotherapy
- Requirement for all prior records and permission to contact all other healthcare providers prior to prescribing
- Required referral to addiction medicine specialist for all at-risk patients
- Requirement that others (eg, spouse) be allowed to give feedback to the physician
- In states with electronic prescription reporting/tracking, intention to query the database initially and on a regular basis

**Reactive strategies**
- Written agreement that addresses specific behaviors and outlines consequences going forward
- Discontinue rescue dose
- Frequent visits and small quantities prescribed
- Urine drug screen at baseline and expressed intention to request screens in the future
- Requirement that only one pharmacy be used (with permission to contact)
- Instruction to bring pill bottle to appointment (for count)
- Instruction that there will be no early refills and no replacement of lost prescription without a police report documenting loss
- Requirement for nonopioid therapies, including psychotherapy
- Requirement that all other healthcare providers be contacted
- Required referral to addiction medicine specialist, with follow-up treatment for aberrant behaviors
- Requirement that others (eg, spouse) be allowed to give feedback to the physician
- In states with electronic prescription reporting, intention to query the database on a regular basis going forward
problems and to monitor therapy. For patients who are vulnerable to abuse or addiction, a more rigid structure for therapy, such as frequent visits, small quantities prescribed, and use of urine drug screens (see table 28), may be helpful in maintaining control. This structure also provides the clinician with the reassurance necessary to continue to act in the patient’s best interest. Patients who are taught that a new structure for prescribing is not punitive but instead is fundamentally therapeutic are more likely to accept the new restrictions without difficulty. Indeed, patients may express gratitude that the clinician is willing to continue a helpful therapy and assist them in maintaining control.

If therapy must be restructured, it is important that documentation be comprehensive and complete. The medical record should reflect the thoughtful reassessment, and the written plan should be explicit. It may be useful to provide the patient with a letter that clarifies the next steps, his or her obligations, and the consequences should problems recur.

The role of opioid agreements or contracts

A formal written agreement between the patient and the physician at the start of opioid therapy also is becoming a common tool for defining expectations and documenting informed consent. These agreements are often called contracts, although they have no force of law.

Pain specialists differ in their views of this approach. On the positive side, these agreements outline the clinician’s policy for providing controlled prescription drugs and describe the consequences of problematic drug-related behavior. They can reinforce that opioid medications must be used responsibly and also assure patients that medication will be prescribed as long as there is adherence to the plan of care. They can be used as educational tools.

On the negative side, these agreements can contribute to the stigmatization of opioid therapy and possibly reduce the likelihood of success. If they are framed in a manner that the patient perceives as threatening, they may contribute to assessment difficulties as the patient withholds or skews information in an effort to meet expectations. If the agreements make demands (such as no driving) that are inconsistent with the literature and would compromise function if accepted, they could undermine the goals of therapy or encourage the patient to lie. If they give a clinician a false sense of security and thereby reduce the vigilance, monitoring, and use of appropriate proactive and reactive strategies that are essential to risk management, they could paradoxically increase risk. Finally, if the agreements implicitly hold a clinician
to a certain level of clinical performance, they could ultimately be used adversely in a medicolegal dispute. Given these potential negatives—and the lack of consensus about the role of this approach—each clinician must decide whether the use of an agreement is appropriate and likely to be beneficial.

<table>
<thead>
<tr>
<th>Statement category</th>
<th>Contracts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Avoid improper use of controlled substances (includes overdosing, seeking medication elsewhere, selling medication, stopping medication abruptly)</td>
<td>95</td>
</tr>
<tr>
<td>2. Terms of disciplinary termination (medication abuse, missed appointments, contract violation, inappropriate behavior)</td>
<td>92</td>
</tr>
<tr>
<td>3. Limitations for replacing medication or changing prescriptions</td>
<td>85</td>
</tr>
<tr>
<td>4. Inform physician of relevant information (ie, side effects, other medications, changes in condition)</td>
<td>74</td>
</tr>
<tr>
<td>5. Submit to random drug screens</td>
<td>69</td>
</tr>
<tr>
<td>6. Terms regarding appointments (missing appointment follow-up, appearing without appointment)</td>
<td>62</td>
</tr>
<tr>
<td>7. Include additional healthcare providers involved in care (eg, primary care physician, physical therapist, psychologist)</td>
<td>59</td>
</tr>
<tr>
<td>8. Limits on drug refills (phone allowances, only in person, call in advance, normal office hours)</td>
<td>56</td>
</tr>
<tr>
<td>9. Education about side effects (including withdrawal)</td>
<td>56</td>
</tr>
<tr>
<td>10. Terms of nondisciplinary termination (eg, no improvement, pregnancy, tolerance, toxicity)</td>
<td>51</td>
</tr>
<tr>
<td>11. Education on addiction risks and behavior</td>
<td>49</td>
</tr>
<tr>
<td>12. Education on opioids and chronic pain</td>
<td>49</td>
</tr>
<tr>
<td>13. Healthcare providers informed of prescription (eg, primary care physician, pharmacist)</td>
<td>46</td>
</tr>
<tr>
<td>14. Pharmacy issues included (use of only one pharmacy, use of in-state pharmacy)</td>
<td>44</td>
</tr>
<tr>
<td>15. Goals (outline goals)</td>
<td>38</td>
</tr>
<tr>
<td>16. Additional risks discussed (eg, other drug use, misuse, pregnancy)</td>
<td>38</td>
</tr>
<tr>
<td>17. Necessity of contract discussed (reasons why necessary, including federal guidelines and abuse)</td>
<td>36</td>
</tr>
<tr>
<td>18. Legal considerations discussed</td>
<td>33</td>
</tr>
<tr>
<td>19. Single prescriber for all opioid prescriptions</td>
<td>33</td>
</tr>
<tr>
<td>20. Dosing limitation (how much, interval between prescriptions, “rescue” dosing, as-needed use, dose escalation)</td>
<td>31</td>
</tr>
</tbody>
</table>

Long-term controlled substances therapy for chronic pain

SAMPLE AGREEMENT

A consent form from the American Academy of Pain Medicine (AAPM)

The purpose of this agreement is to protect your access to controlled substances and to protect our ability to prescribe for you.

The long-term use of such substances as opioids (narcotic analgesics), benzodiazepine tranquilizers, and barbiturate sedatives is controversial because of uncertainty regarding the extent to which they provide long-term benefit. There is also the risk of an addictive disorder developing or of relapse occurring in a person with a prior addiction. The extent of this risk is not certain.

Because these drugs have potential for abuse or diversion, strict accountability is necessary when use is prolonged. For this reason the following policies are agreed to by you, the patient, as consideration for, and a condition of, the willingness of the physician whose signature appears below to consider the initial and/or continued prescription of controlled substances to treat your chronic pain.

1. All controlled substances must come from the physician whose signature appears below or, during his or her absence, by the covering physician, unless specific authorization is obtained for an exception. (Multiple sources can lead to untoward drug interactions or poor coordination of treatment.)

2. All controlled substances must be obtained at the same pharmacy, where possible. Should the need arise to change pharmacies, our office must be informed.

The pharmacy that you have selected is:__________________________   Phone: _____________________

3. You are expected to inform our office of any new medications or medical conditions and of any adverse effects you experience from any of the medications that you take.

4. The prescribing physician has permission to discuss all diagnostic and treatment details with dispensing pharmacists or other professionals who provide your healthcare, for purposes of maintaining accountability.

5. You may not share, sell, or otherwise permit others to have access to these medications.

6. These drugs should not be stopped abruptly, as an abstinence syndrome will likely develop.

7. Unannounced urine or serum toxicology screens may be requested, and your cooperation is required. Presence of unauthorized substances may prompt referral for assessment for addictive disorder.

8. Prescriptions and bottles of these medications may be sought by other individuals with chemical dependency and should be closely safeguarded. It is expected that you will take the highest possible degree of care with your medication and prescription. They should not be left where others might see or otherwise have access to them.

9. Original containers of medications should be brought in to each office visit.

10. Since the drugs may be hazardous or lethal to a person who is not tolerant to their effects, especially a child, you must keep them out of reach of such people.

11. Medications may not be replaced if they are lost, get wet, are destroyed, left on an airplane, etc. If your medication has been stolen and you complete a police report regarding the theft, an exception may be made.

12. Early refills will generally not be given.

13. Prescriptions may be issued early if the physician or patient will be out of town when a refill is due. These prescriptions will contain instructions to the pharmacist that they not be filled prior to the appropriate date.

14. If the responsible legal authorities have questions concerning your treatment, as might occur, for example, if you were obtaining medications at several pharmacies, all confidentiality is waived and these authorities may be given full access to our records of controlled substances administration.

15. It is understood that failure to adhere to these policies may result in cessation of therapy with controlled substance prescribing by this physician or referral for further specialty assessment.

Figure 1. Sample opioid agreement by the American Academy of Pain Medicine.
Use of opioid agreements may be informed by a recent survey that identified the most common elements used by 39 university-affiliated pain management centers (table 29). This work highlighted the necessity for careful consideration of prohibitions endorsed. For example, rather than prohibiting patients from driving while taking long-term opioid therapy, it may be prudent to prohibit driving during periods of initial opioid dosing or after dose escalations. Likewise, rather than prohibiting pregnancy during treatment, the agreement may outline the prescriber’s concerns about pregnancy and require notification should pregnancy occur or be anticipated, so that counseling and appropriate perinatal referral can be provided. In an effort to further clarify the type of language that may be most appropriate for these agreements, the American Academy of Pain Medicine developed a model approach (figure 1).
Suggested readings


CHAPTER 11
OPIOID THERAPY IN SUBSTANCE ABUSERS

A history of serious drug abuse or addiction complicates treatment that incorporates potentially abusable drugs, including opioids. However, it is not a contraindication for such therapy. Short-term opioid therapy for acute pain, particularly in a monitored setting, usually can proceed without difficulty. Indeed, undertreatment is widely considered to be a serious challenge among these patients and may relate to both the reticence to prescribe on the part of clinicians and nonadherence with therapy on the part of the patient.

Long-term opioid therapy presents a more challenging issue. A trial of opioid treatment for pain related to serious medical illness, such as cancer or AIDS, is generally appropriate. Treatment of patients with severe nonmalignant pain syndromes is best considered on a case-by-case basis. In all situations, the decision to implement a trial must be based on a careful evaluation, which must be clearly documented. Treatment requires ongoing assessment and skillful adaptation of the principles that have proved essential in the optimal management of patients with no history of drug abuse. Although there are very few data pertaining to the outcome of long-term therapy in populations with drug abuse or addiction, the observations of specialists suggest both that the risks are increased, particularly among patients with recent or active drug abuse, and that many patients have the ability to respond favorably.

Assessment issues
History taking that reviews substance use should be part of every pain assessment and must be detailed whenever a patient has a suspected or known history of drug abuse. Highly comprehensive, structured interviews have been developed for this assessment but are used only in research settings. Clinicians should ask nonjudgmental questions about past and present drug use, both licit and illicit. These questions should attempt to clarify the nature of this use and its impact on varied domains of function. Questions about the nature of use should focus on quantity and frequency of drug intake and the extent to which it appears controlled or compulsive and out of control. Those focused on the impact of use should explore physical effects (such as hospitalizations or visits to the emergency department),
legal problems, trouble at work, interference in relationships, and other pertinent outcomes.

Extensive experience suggests that matter-of-fact questioning usually yields openness and responses that appear accurate over time. Some patients dissemble, of course, and when it is crucial to be sure, confirmatory information should be sought. Generally, however, this substance use history yields information sufficient to categorize the patient in terms of current risk and to clarify the type of structure that will be needed should treatment with a controlled substance be pursued.

Categories of substance abusers
To help categorize patients according to risk, it is worthwhile to broadly distinguish into 3 groups those with a history of substance abuse.

Drug-free recovery
The first group, patients in an established drug-free recovery, often appears clinically to present more of a problem with undertreatment than abuse. If opioids are necessary, such as after surgery or trauma, or if long-term treatment is considered for chronic pain, a history of abuse may increase both the risk of inadequate prescribing and a reluctance of the patient to accept the therapy.

Notwithstanding the risk of undertreatment, these patients also should be viewed as being at relatively higher risk of aberrant drug-related behavior than those without such a history. For this reason, consideration must be given to creating a more defined structure for prescribing at the start of therapy (see chapter 10). This structure may be reassuring to both the treating clinician and the patient and may assist the at-risk patient in maintaining control. The specifics depend on the assessment. For example, the patient who has been in recovery from a primary alcoholism for more than 20 years and still attends daily peer support meetings probably requires less structure than a patient with a polysubstance abuse history whose recovery spans less than a year.

History of opioid abuse
The second group includes patients with a history of opioid abuse who are currently in substitution therapy with methadone or buprenorphine. These patients also are at high risk for undertreatment. Negative attitudes of the clinician may combine with some degree of analgesic tolerance to limit the efficacy of therapy. Assessment of a patient who requires substantially higher
starting doses than most and complains about persistent pain may be very challenging. At times, an empirical approach centered on a therapeutic trial of higher doses and close monitoring of subsequent behavior is the only reasonable, and humane, strategy. This may be a justifiable indication for inpatient care.

There are important differences between the use of methadone as an analgesic and its use as a substitution therapy for opioid addiction. In pain management, doses of methadone must be titrated according to patient response; there is no predefined appropriate dose range, and most patients require doses 3 to 6 times per day to maintain consistent analgesia. The latter observation is supported by studies that demonstrate a duration of analgesia that is typically much briefer than would be expected from the half-life of this drug. When methadone is used to block craving in addiction, a once-daily dose is sufficient, and most patients require doses less than or equal to 120 mg per day.

Methadone can be used to treat pain in patients receiving methadone maintenance, but the clinical distinctions and the parallel regulatory issues must be understood. Any clinician can prescribe methadone for pain, but maintenance for addiction treatment requires a federal license. If methadone is used for pain management in the patient receiving methadone maintenance, clear documentation is required that describes this use and distinguishes it from addiction treatment. If it is used as an analgesic, dosing frequency should be increased and the dose should be titrated against pain.

Patients with a history of opioid addiction who are given long-acting opioids, including methadone, for pain do not also need substitution therapy with methadone or buprenorphine to block drug craving. Nonetheless, some patients prefer to continue in a program during pain treatment with an opioid. The reasons for this are varied and may involve support systems provided by some programs or a persistent fear of relapse into addiction. Patients can remain in programs and also receive an opioid for pain as long as the 2 treatments adhere to regulations and the various clinicians are communicating.

Office-based buprenorphine therapy is beginning to be used in the United States. Although many of the issues surrounding pain management are likely to mirror those encountered in the methadone-maintained population, there are several unique considerations. Buprenorphine has an affinity for the opioid receptor that far exceeds the affinity of other agonist opioids. To treat acute pain, and presumably chronic pain, it will probably be necessary to use doses of another opioid that are substantially higher than those required by patients who are not receiving
buprenorphine. Experience is yet too limited to develop guidelines for this treatment, but the known pharmacology suggests that clinicians must be prepared to titrate the dose of a second opioid agonist aggressively or risk undertreatment. Substitution therapy with buprenorphine may pose additional challenges for pain treatment, because it is an office-based treatment and depends largely on the efforts of a single clinician. If these patients are referred for pain management, the need for communication and documentation is apparent.

**Ongoing abuse**
The third group of drug abusers broadly includes patients with an active ongoing abuse problem. This is obviously a highly diverse population that includes addicts and nonaddicts, single-drug abusers and polydrug abusers, and those with various medical and psychiatric comorbidities. In varied subpopulations, comorbid psychiatric disease and adverse situational factors may be profound enough to undermine any effort to implement an effective pain management strategy.

**Management strategies for opioid therapy**
Clinicians who learn to implement strategies to manage risk should be comfortable implementing a necessary opioid regimen for acute pain or chronic pain in severe medical illness. They also may feel empowered to consider opioid therapy in other patients with chronic pain. The specific management strategies must be individualized on the basis of patient assessment. A broad framework that recognizes the special challenges that might be posed by a patient with a known history of substance abuse includes the following considerations.

**Accept the patient’s self-report of distress**
The dictates of humane and compassionate care should support a bias that patients generally should be believed. Although addiction, other psychiatric disorders, and psychosocial factors can profoundly influence pain presentation, malingering and factitious pain complaints appear to be rare even among patients with a history of substance abuse. Unless the evidence is compelling, it is more productive simply to believe the patient’s complaint and thoughtfully assess the degree to which it can be explained by physical and psychologic determinants.

**Consider opioids within a multimodality approach**
A multimodality approach should be considered for all patients with chronic pain. When the risk of problematic drug-related
behavior is relatively high, the need to consider alternative strategies or concurrent therapies that may reduce the opioid requirement is especially important.

**Define and use a treatment team**
A treatment team typically is developed ad hoc depending on the complexity of the problems posed by the patient. The team may involve a specialist in addiction, the patient’s sponsor, a pharmacist, the patient’s spouse or significant other, and various clinicians who can address different pain management approaches. Agreement on the treatment plan by the entire team enhances patient care, and communication among the team is essential to prevent mixed messages, duplication of prescriptions, or inadvertent violations of the opioid treatment plan. If the treatment plan includes continued attendance at peer support meetings, the clinician can demand from the patient signed slips that document attendance.

**Consider pharmacologic issues**
Patients with a history of active opioid abuse or ongoing substitution therapy may require higher doses or more rapid titration. Specifically, drug tolerance and the higher opioid receptor affinity of buprenorphine may alter dosing expectations when prescribing opioids for pain in patients taking buprenorphine substitution therapy.

**Structure therapy based on the perceived level of risk**
As discussed in Chapter 10, a variety of strategies can be implemented to increase the likelihood that the therapy will be controlled and to enhance the opportunity for monitoring outcomes. Consideration of these strategies is essential in the population of known drug abusers. Treatment of chronic pain often requires more intensive elements, such as the use of a written agreement, urine drug screens, and prescriptions for small amounts with frequent visits. Similar to the management of the patient without a drug abuse history, the structure of prescribing can be made less strict over time should a patient demonstrate consistently responsible drug use.

**Suggested reading**
CHAPTER 12
OPIOID ANALGESIA IN THE VERY YOUNG AND THE VERY OLD

The young and the elderly have the most to fear from pain because they are the most defenseless against it.
Liebeskind and Melzack, 1989

The very young and the very old may respond to opioid drugs in a manner different than the typical adult patient. To use these drugs safely in these populations, clinicians should be aware of these differences and appropriately alter the routine approach to prescribing.

Opioids in the very young
In children, long-term opioid therapy is most commonly used to treat cancer-related pain or pain associated with other serious illnesses, such as AIDS or neurodegenerative disorders. Although few studies have evaluated the risk-benefit of long-term opioid use in children, experienced clinicians endorse the need for this treatment in selected patients with other chronic debilitating conditions, such as sickle cell disease, neuropathic pain, and severe headache.

Assessment of pain in children
Assessment is the cornerstone of adequate pain management. The process in children is similar to that in adults but must additionally consider developmental stage and parental knowledge.

The ability of a child to understand and describe pain changes with age. Self-report is the “gold standard” for evaluating pain, and several instruments have been validated to help children describe pain intensity. These include faces in photographs, cartoon faces, colors, and a poker chip tool (ie, child chooses 1 to 4 chips [“pieces of pain”]). Generally, children who are at least 8 years of age can assess their pain using standard numeric or visual analog scales commonly accepted by adults. Beginning at about 3 years of age, children can usually assess their pain if given developmentally appropriate instruments.

Parental attitudes are central to the assessment of pain in children. The reactions of parents strongly influence the child’s expression of pain, and treatment usually depends on the parents’ capacity to evaluate and their willingness to offer therapy. To
ensure adequate treatment, parental attitudes must be understood and an effort must be made to educate. This is particularly important when therapy is unusual or potentially stigmatizing.

Some of the information gleaned from the pain assessment is particularly relevant to children.

This information includes:

- The magnitude of distress for the child and family that is attributed to the pain and the impact of the pain on the child’s cognitive functioning, anxiety, depression, and feelings of hopelessness
- The child’s and family’s perceptions of the cause of the pain and their respective response to it
- The child’s perception of what the pain means (eg, punishment, harbinger of more visits to the doctor or hospital)
- A history of pain problems in the child and other family members
- The child’s history of birth and early childhood and the family’s medical and social history
- Recent stressful events, such as deaths, marital disruption, moves, or other changes in life circumstances

**Principles of opioid pharmacotherapy in children**

As with adults who have challenging pain syndromes, children with chronic pain appear to respond best to a treatment approach that is multimodal, involving both pharmacologic and nonpharmacologic methods of pain control and a team that is multidisciplinary. Children with complex or refractory problems should be referred to a pediatric pain program, if possible, to ensure that treatment strategies are safe and appropriate and are implemented with a focus on developmental stage and family concerns.

The decision to implement a trial of opioid therapy should be based on the severity of the pain, its associated distress, and other factors elaborated in the pain assessment. Similar to making the decision in adults, clinicians should evaluate the nature of conventional practice and explore the potential risks and benefits of opioid therapy and available alternative treatments. If the decision is made to proceed with opioid therapy, the parents and, if possible, the child should be fully informed about the nature of the therapy, the risk of side effects, the need for communication and adherence, and the issues surrounding abuse and addiction.

Few studies have evaluated opioid pharmacokinetics and pharmacodynamics in children, and dosing recommendations are based primarily on experience in adults (table 30). In the younger or opioid-naïve child, both age and weight influence selection of drug formulation and route of administration.
Table 30. Initial dosing guidelines for opioid analgesics in pediatric patients*

<table>
<thead>
<tr>
<th>Opioid analgesic</th>
<th>Usual starting intravenous or subcutaneous doses and intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child &lt;50 kg</td>
</tr>
<tr>
<td>Codeine</td>
<td>NR</td>
</tr>
<tr>
<td>Morphine</td>
<td>Bolus: 0.1 mg/kg q2-4h</td>
</tr>
<tr>
<td></td>
<td>Infusion: 0.03 mg/kg/hr</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
</tr>
<tr>
<td>Methadone†</td>
<td>0.1 mg/kg q4-8h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Bolus: 0.5-1.0 µg/kg q1-2h</td>
</tr>
<tr>
<td></td>
<td>Infusion: 0.5-2.0 µg/kg/hr</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Bolus: 0.02 mg q2-4h</td>
</tr>
<tr>
<td></td>
<td>Infusion: 0.006 mg/kg/hr</td>
</tr>
<tr>
<td>Meperidine‡</td>
<td>Bolus: 0.8-1.0 mg/kg q2-3h</td>
</tr>
</tbody>
</table>

NA, not applicable; NR, not recommended.

* Doses are for patients older than 6 months. In infants younger than 6 months, initial per-kg doses should begin at roughly 25% of the per-kg doses recommended here. Higher doses are often required for patients receiving mechanical ventilation. All doses are approximate and should be adjusted according to clinical circumstances. Recommendations are adapted from summary tables, including those of a consensus statement from the World Health Organization and the International Association for the Study of Pain (World Health Organization, 1998).

† Methadone requires additional vigilance because it can accumulate and produce delayed sedation. If sedation occurs, doses should be withheld until sedation resolves. Thereafter, doses should be substantially reduced or the interval between doses should be extended to 8 to 12 hours, or both.

‡ Use of meperidine should be avoided if other opioids are available, especially for long-term use, because its metabolite can cause seizures.


For most children, long-term opioid therapy is best implemented using the oral or transdermal routes. Modified-release preparations of opioids must be swallowed whole, which may preclude their use in younger children. If these drugs are prescribed, parents must be educated that crushing or chewing such formulations releases the full dose immediately, potentially leading to overdose. Transdermal fentanyl also must be used cautiously, because the smallest patch...
currently available, which delivers 25 µg of fentanyl per hour, provides a dose that is too high for younger, opioid-naïve children. Parents also must be told that the patch cannot be cut into smaller pieces in an attempt to reduce the dose.

Use of painful injections should be avoided in children, because it may lead to the underreporting of pain. Rectal administration also is uncomfortable and should be limited. If short-term parenteral administration is needed, the intravenous route is preferred.

Individualization of the dose is as important in children as it is in adults. This requires repeated assessment of analgesia and side effects. It may be necessary to ask very specifically about side effects, such as constipation or unpleasant dreams, because children may be reluctant to report them. Side effects must be managed aggressively.

**Opioids in the very old**
Chronic pain is highly prevalent in older patients and has multiple etiologies. Painful osteoarthritis and degenerative spinal disorders are very common in the older US population, and the

<table>
<thead>
<tr>
<th>Usual starting oral doses and intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &lt;50 kg</td>
</tr>
<tr>
<td>0.5-1.0 mg/kg q3-4h</td>
</tr>
<tr>
<td>Immediate release:</td>
</tr>
<tr>
<td>15-20 mg q3-4h</td>
</tr>
<tr>
<td>Sustained release:</td>
</tr>
<tr>
<td>20-35 kg, 10-15 mg q8-12h;</td>
</tr>
<tr>
<td>36-50 kg, 15-30 mg q8-12h</td>
</tr>
<tr>
<td>0.1-0.2 mg/kg q3-4h</td>
</tr>
<tr>
<td>0.1-0.2 mg/kg q4-8h</td>
</tr>
<tr>
<td>NA</td>
</tr>
<tr>
<td>0.04-0.08 mg/kg q3-4h</td>
</tr>
<tr>
<td>2-3 mg/kg q3-4h</td>
</tr>
</tbody>
</table>
prevalence of many painful medical disorders, including cancer, postherpetic neuralgia, and painful diabetic polyneuropathy, increases with age. Large surveys have suggested that, unfortunately, pain in older adults is often undertreated.

Treatment of pain in the geriatric population can be complicated by cognitive impairment and other sources of communication difficulties, gait and balance disturbances, deconditioning, sensory impairments, and comorbidities that increase the risk of therapy (eg, cardiovascular disease, pulmonary disease). As a result, the ill effects of pain, such as mood disorder (especially depression), social isolation, poor sleep, gait disturbance, and inability to perform routine activities of daily living, can be compounded.

Use of analgesics in older patients also may be complicated by concurrent treatment with multiple medications for comorbid disease and symptom management. In this group of patients, drug-drug and drug-disease interactions are a far more significant concern and the consequences of drug-related adverse effects, such as falls, confusion, or obstipation, can have much graver consequences than in younger patients.

Aging and opioid pharmacology
Sensitivity to both the analgesic effects and the side effects of opioids increases with age. Studies in postoperative patients older than 40 years demonstrate a linear age-related increase in the analgesic response to fixed morphine doses. This relationship is explained by both pharmacokinetic and pharmacodynamic factors.

Opioid kinetics change as a result of age-related alteration in drug absorption, distribution, metabolism, and clearance, all of which are influenced by body composition changes (eg, a reduced muscle-to-fat ratio) and reductions in serum protein levels, cardiac output, and organ perfusion. Pharmacodynamic changes relate to poorly understood central nervous system processes that increase sensitivity to both analgesic and adverse effects. The few studies that have evaluated pharmacodynamic effects of analgesic drugs in older patients found that the rate of drug delivery, rather than the absolute dose of drug over time, influences both analgesia and adverse effects, including the risk of respiratory depression.

Assessment in patients who cannot self-report
A significant challenge in geriatric care is the management of symptoms in patients who cannot communicate. Typically, these are patients with advanced dementia, such as Alzheimer’s disease or multi-infarct dementia. Patients with dementing diseases
who lack the cognitive capacity to describe their pain have been shown to receive for the same clinical conditions significantly less opioid analgesic than nondemented patients receive.

When self-report is impossible, pain assessment must rely on other measures. Observable behaviors and bodily changes suggesting pain include:

- Facial expressions or body posturing (eg, grimacing, guarding, rigidity)
- New or changed vocalizations
- Change in sleep patterns
- Agitation or restlessness
- Withdrawal from social interaction
- Decreased interest in previous enjoyments (eg, music, feeding, massage, bathing)
- Inconsolability
- Tachycardia, tachypnea, hypertension, diaphoresis

Although the absence of these phenomena does not imply comfort, their presence suggests distress and, in the right context, pain. When other assessments are impossible, an analgesic trial may be appropriate when these observations are made.

Managing the noncommunicative patient

To treat pain in a population that cannot communicate, clinicians must develop the skills necessary to anticipate and recognize nonverbal indicators of distress, treat empirically, and monitor the outcomes of therapy. In some cases, initiating a trial of an opioid may be the best means of testing the hypothesis that a patient who cannot communicate is experiencing pain. Changes in usual behaviors, vocalizations, various forms of agitation, and alterations in eating, sleeping, or interpersonal response patterns may be modifiable by both pharmacologic and nonpharmacologic analgesic therapies. Agitation that responds to analgesics does not require treatment with psychotropics, the effects of which may be to mask the symptoms rather than treat the source of distress. This type of empirical pain management may protect the dignity of these vulnerable patients and provide sensitive and humanistic care.

Principles of pharmacotherapy in older persons

All older patients with functional impairment or diminished quality of life resulting from persistent pain are candidates for pharmacologic therapy. Generally, the same principles applied in younger adults when selecting an opioid trial and implementing therapy may be used in geriatric patients. However, age-related factors must be considered and suggest the following guidelines
and specific dosing recommendations when opioids are used (Table 31).

- Slowly and carefully titrate opioids, having specific subjective and objective end points in mind. (ie, 50% of usual adult starting dose).
- Prevent and treat adverse events, particularly constipation, sedation, ataxia (dysmobility and falls), nausea, and cognitive disturbances, including delirium.
- For patients experiencing severely debilitating pain, titrate the opioid rapidly and consider hospital admission for diagnosis, aggressive treatment, and close monitoring.
- Simplify drug regimens as much as possible and adjust regimens to meet individual needs, lifestyle, and care settings.
- Be aware of common economic barriers, including limitations of Medicare reimbursement for outpatient oral medications, limited formularies, and delays from mail-order pharmacies in some managed-care programs. (A noteworthy exception is that the Medicare Hospice Benefit covers the cost of all medications associated with the diagnosis that prompted admittance into the hospice.)
- Do not prescribe propoxyphene or meperidine for older patients; neuroexcitatory side effects may be more likely in this population because of central sensitivity and subclinical renal insufficiency.
- Use methadone very cautiously, because its long and variable half-life makes it especially problematic in older patients. Adverse effects from drug accumulation may arise several days after regular dosing begins.
- If the patient drives, consider restricting driving until doses are stable and cognitive capacity is reassessed.
- For patients with borderline mobility capabilities and a propensity for falls, monitor carefully for increasing gait and balance disturbances.
- Warn patients that chewing or crushing continuous-release tablets destroys their controlled-release properties and causes rapid absorption of the entire dose, which may result in overdose.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral equivalent</th>
<th>Starting dose</th>
<th>Aging effects</th>
<th>Precautions and recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>30 mg</td>
<td>5-15 mg q4h</td>
<td>Intermediate half-life</td>
<td>Anticipate increased sensitivity and duration of action with advancing age</td>
</tr>
<tr>
<td>Codeine</td>
<td>120 mg</td>
<td>15-30 mg q4h</td>
<td>Acetaminophen-NSAID combinations limit dose</td>
<td>Constipation is a major issue</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
<td>5-10 mg q3-4h</td>
<td>Acetaminophen-NSAID combinations limit dose</td>
<td>Toxicity similar to morphine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20-30 mg</td>
<td>5-10 mg q3-4h</td>
<td>Acetaminophen-NSAID combinations limit dose</td>
<td>Toxicity similar to morphine</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
<td>1-2 mg q3-4h</td>
<td>Half-life may be shorter than morphine (3 hr)</td>
<td>Available as a single agent</td>
</tr>
<tr>
<td>Long-acting drugs*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified-release morphine</td>
<td>30 mg</td>
<td>15-30 mg q12-24h</td>
<td>Occasionally requires more frequent dosing than recommended on package insert</td>
<td>Anticipate increased sensitivity and duration of action with advancing age</td>
</tr>
<tr>
<td>Modified-release oxycodone</td>
<td>20-30 mg</td>
<td>10 mg q12-24h</td>
<td>Similar to sustained-release morphine</td>
<td>Anticipate increased sensitivity and duration of action with advancing age</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>See package insert for recommended dose equivalences</td>
<td>25-mg patch is lowest available dose</td>
<td>Effective activity may exceed 72-hr usual duration of action</td>
<td>Not recommended for opioid-naive patients</td>
</tr>
</tbody>
</table>

- Anticipate and prevent side effects
- Begin bowel program early
- Do not exceed recommended maximum dose of fixed-dose combination formulations
- Anticipate and prevent side effects
- Begin bowel program early
- Do not exceed recommended maximum dose of fixed-dose combination formulations
- Anticipate and prevent side effects
- Begin bowel program early
- Do not exceed recommended maximum dose of fixed-dose combination formulations
- Similar to morphine
- Start low and titrate to comfort and functional goals
- Best for continuous pain
- Always commence a bowel stimulant regimen (eg, senna compounds, bisacodyl) when initiating opioid therapy
- Escalate dose slowly because of possible drug accumulation
- Short-acting opioid analgesic often necessary for breakthrough pain, especially for patients with pain related to movement or weight-bearing activity (incident pain)
- Similar to sustained-release morphine

NSAIDS: nonsteroidal anti-inflammatory drugs.

1 Some practitioners favor the use of methadone because of its comparatively low cost. However, very careful monitoring and ample clinical experience are needed because of propensity for drug accumulation and the wide variation in apparent relative potency, especially in older patients. A responsible caregiver should be available for monitoring during dose titration and dose escalation phases of treatment.

Suggested readings


CHAPTER 13

OPIOID THERAPY IN ADVANCED MEDICAL ILLNESS

Pain is a common manifestation of many advanced illnesses. Among these clinical settings, pain in cancer has been the most studied and best characterized. However, limited surveys in other diseases, including AIDS, advanced congestive heart failure, and advanced lung disease, suggest that the prevalence and impact of pain are significant in all advanced disease.

Although death is inevitable, a painful death is not. When attention is focused on relief of pain, and care is rendered by clinicians with even basic skills in opioid pharmacotherapy, the promise of a comfortable death can be realized in most cases. Opioids usually are considered the mainstay therapy for moderate to severe pain. With knowledge of opioid pharmacology and the principles of prescribing, the outcomes of treatment can be optimized, and a major barrier in pain control—clinician fear of inflicting harm or hastening death—can be eliminated.

Relevant constructs and palliative care
In the context of a progressive, incurable illness, pain must be considered from the perspective of a set of broad constructs, including suffering, quality of life, and goals of care. An understanding of these constructs continually informs decision making and supports the treatment of pain within a therapeutic model known as palliative care.

Suffering and quality of life
Suffering has been described as a perceived threat to the integrity of the person, as a type of total pain, or as overall impairment in quality of life. Suffering may be related to physical symptoms or losses, to psychiatric disorders or psychologic processes, to social or family disruptions, to spiritual concerns, or to other factors, such as financial loss. Quality of life is related to the construct of suffering but has been more formally characterized for research. Most of the instruments created to measure quality of life codify the inherent subjectivity and multidimensionality of this construct by using self-report to ascertain well-being in these physical, psychosocial, and spiritual domains.

Comprehensive pain assessment in the setting of advanced illness must address issues related to suffering by evaluating the
physical, psychologic, social, and spiritual issues important to the patient. A therapeutic approach that is focused only on pain may not meaningfully benefit a patient whose suffering is caused by other disturbances.

**Goals of care**
From the medical perspective, the therapeutic approach to a patient with far-advanced disease usually is guided by several goals.

- Slow the progression of disease, if possible, with the least burdensome means possible
- Optimize function
- Provide comfort and relieve symptoms
- Provide treatments and resources to reduce suffering and improve quality of life

These goals are dynamic and evolve over time. They are strongly influenced by the attitudes and expectations of the patient and family, the vagaries of the disease, the availability of disease-modifying treatments, and expertise in palliative care. Immediate and longer-term goals must be continually reassessed. The goals of care may influence every therapeutic decision. For example, some patients with advanced illness express the desire to limit diagnostic procedures. Without tests, the etiology of the pain may remain obscure and opportunities for primary therapy directed against the etiology will not be realized. Although the clinician may relate concerns about a decision to forego evaluation, the patient’s desires must be respected and should not preclude aggressive symptomatic therapy.

**Palliative care**
In populations with advanced illnesses, pain management is best understood as a component of a larger therapeutic model known as palliative care. Palliative care aims to enhance the quality of life of the patient and family throughout the course of the disease by addressing problems in the physical, psychologic, social, and spiritual domains. It views the family as the unit of care and attempts to ensure that (1) the patient’s values and decisions are respected, (2) comfort is a priority, (3) psychosocial and spiritual issues are addressed, (4) practical support (eg, homemaking services, assistive devices for self-care) in the home is available, and (5) opportunities for closure—and even growth—are available at the end of life. The need for palliative care usually intensifies at the end of life, at which time the goals include preparation for the dying process and bereavement support for the family. Patients and families with a high need for pal-
Palliative care interventions should have access to specialized programs, which include hospital-based palliative care services (now offered in about 30% of US hospitals) and several thousand hospice programs.

Despite the development of these specialized programs, there is considerable evidence that expertise in palliative care is not routinely available for patients with advanced illness and, consequently, symptoms like pain continue to be undertreated. Although hospice programs could help with pain control by providing much-needed support for patients and families in their homes, most patients with advanced disease are not referred into these programs, and those who are referred typically access the care very late in the course of the disease—oftentimes only days before death. Services funded by the Medicare Hospice Benefit, as well as most commercial insurance plans and Medicaid, include durable medical equipment, supplies, and drugs. However, the majority of eligible patients (and their families) who could benefit from these services do not obtain this help.

Managing pain in dying patients
In patients for whom death is imminent, expertise in pain management should be part of a therapeutic approach that attempts to address the full range of concerns and challenges that may occur at this critical time. Ideally, all dying patients and their families should receive specialist-level help through expert hospice care.

In the best case, patients have prepared for a time when decision making is impaired and have openly expressed their preferences and priorities (in a living will, for example) and appointed a surrogate decision maker. The laws that govern these procedures vary from state to state, and clinicians should understand and support the use of these advance directives.

When opioids are used to manage pain in advanced illness, the routine principles of prescribing apply (see chapter 5). These principles should be framed within considerations that are particularly relevant to this population.

- The opioid should be delivered using an approach that is the least invasive, most readily available, and most acceptable to the patient and caregiver. This is usually the oral or transdermal route. If the oral route is used, it is prudent to plan for an alternative should the patient lose the ability to swallow or absorb drugs. Planning in advance can avert pain crises. If there is some question that oral and transdermal delivery may not suffice, parenteral access should be established and a trial of intravenous or subcutaneous administration offered.
• Caregivers must be educated about the chosen approach to pain management. In the setting of advanced illness, it may be the caregiver who is most able to assure continued administration of an analgesic.

• Pain should be distinguished from delirium (terminal agitation) or anxiety, if possible. In the noncommunicative patient, this may require a trial of opioid therapy. Terminal restlessness or agitation unresponsive to rapid titration of opioids may respond to a neuroleptic or sedative-hypnotic agent.

• Pain crises that respond poorly to basic analgesic approaches merit consultation with a pain management consultant as soon as possible. More aggressive therapeutic methods may be warranted. Intervetional techniques, such as epidural or intrathecal catheterization, certain types of nerve blocks or neurolytic procedures, or use of drugs such as ketamine, may be appropriate in selected patients.

**Ethical imperatives and safeguards**

The obligation to relieve suffering is an ethical imperative of the medical profession and is especially important in the care of patients who are dying. Among the greatest harms to dying patients, and their loved ones, is to abandon them in their need for comfort, of which relief from pain is paramount. Patients and family members expect that physicians will honor this need by effectively treating pain.

When providing opioid therapy to patients who are near death, the ethical principle of double effect must be understood and clearly communicated. This principle is particularly important in addressing the fear that aggressive opioid therapy at the end of life could potentially hasten death. According to the principle of double effect, a foreseeable “bad” outcome of an action (such as a potentially hastened death) is ethically acceptable if the intention (relief of suffering) is beneficent, and the need to accomplish the good is more important than the need to avoid the bad. At the end of life, this principle guides the aggressive use of opioids and other interventions. Physicians must defend the ethical nature of aggressive pain control and clearly distinguish pain treatment from euthanasia.

Although clinicians should understand and invoke the principle of double effect when using opioids in dying patients, it is nonetheless reassuring to know that there is no convincing scientific evidence that demonstrates a significant risk of hastened death if the opioid dose is appropriately titrated at the end of life. Indeed, there is more anecdotal evidence to the contrary. Given these reassuring observations and the well-recognized
adverse physiologic and psychologic effects from unrelieved pain, aggressive titration of the opioid dose to maintain relief of pain is warranted until the very end of life.

Suggested readings
Fine PG. The ethical imperative to relieve pain at life’s end. J Pain Symptom Manage 2002;23:273-7


Liebeskind JC. Pain can kill. (Editorial) Pain 1991;44:3-4


Resources

Web sites
Beth Israel Medical Center
Department Pain Medicine and Palliative Care
http://www.stoppain.org

University of Wisconsin Comprehensive Cancer Center
Pain and Policy Studies Group
http://www.medsch.wisc.edu/painpolicy

American Academy of Pain Medicine
http://www.painmed.org

National Initiative on Pain Control
http://www.painedu.org

National Pain Education Council
http://www.npecweb.org

Professional Societies

American Academy of Pain Medicine
4700 W Lake Ave
Glenview, IL 60025
Phone: (847) 375-4731
Fax: (847) 375-4777
E-mail: aapm@amctec.com
http://www.painmed.org

American Pain Society
4700 W Lake Ave
Glenview, IL 60025
Phone: (847) 375-4715
Fax: (847) 375-4777
E-mail: info@ampainsoc.org
http://www.ampainsoc.org

International Association for the Study of Pain
909 NE 43rd St, Suite 306
Seattle, WA 98105-6020
Phone: (206) 547-6409
Fax: (206) 547-1703
E-mail: IASP@locke.hs.washington.edu
http://www.iasp-pain.org
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A clinical guide to
OPIOID ANALGESIA

This handbook is intended as a guide to the responsible use of opioid analgesics for the treatment of pain. It is designed to help clinicians make practical sense of the varied pharmacologic, clinical, and regulatory issues surrounding opioid therapy, with the objective of obtaining the most different outcomes possible for patients.

Opioid analgesics can provide effective relief to many patients suffering from acute and chronic pain. Still, these are potent medications whose use needs to be managed carefully and targeted responsibly. A proper balance between appropriate access to opioids and a proactive effort to prevent misuse is inherent to responsible prescribing.

The authors provide an in-depth review of opioid therapy including patient assessment and management, comparisons of various opioids and their respective benefits/risks, and appropriate regimens for optimizing the effectiveness of opioid analgesia. The handbook features extensive tables, algorithms, and patient questionnaires to help improve clinicians’ knowledge and skills related to both the principles of prescribing and the management of risk. In this way, healthcare professionals and their patients may benefit from the therapeutic potential of this class of medications while managing the risks of potential associated adverse effects.