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Basic Concepts in Opioid Prescribing and Current Concepts of Opioid-Mediated Effects on Driving

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ABSTRACT

Background: Many patients with chronic pain receive substandard analgesic therapy. Incomplete or inadequate care often stems from physician fears of patient addiction and/or drug toxicity. As a result, many chronic pain patients are undertreated and have unrelieved pain that tempts them to overuse or to abuse prescribed pharmacologic treatments. In the last few years, educational efforts have targeted physicians who treat chronic, nonmalignant pain with information to improve prescribing strategies and to appreciate side effects. Additionally, opioid prescribing guidelines and educational programs, including World Health Organization-published guidelines for the management of cancer pain in 1986 and the American Pain Society's promotion of pain as the 5th vital sign, have increased the propensity of pharmacists, physicians, and pain specialists to dispense pain treatments.

Methods: Controversial and evolving consequences from this explosion of prescription opioid use have emerged and are discussed in this review, including prescribing principles, opioid analgesic side effects, and driving concerns.

Conclusion: With additional appreciation for the untoward effects of chronic analgesia and a better understanding of opioid pharmacology, physicians can utilize pain management treatments in a safer and more effective manner.

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INTRODUCTION

Pain affects more Americans than diabetes, heart disease, and all cancers combined.[1] The majority of adults have pain that severely impacts the quality of their life, sleep, and overall well-being. Pain is the single most common reason for seeking medical treatment in the United States, yet it remains widely undertreated.[2]

Although physicians who are trained and certified in pain management practice in most communities, the majority of pain cases are managed by primary-care physicians who often do not have a specialized background in pain management but routinely prescribe high-dose and long-term opioid analgesics. Physicians must not underestimate the dangers associated with these powerful medications because morbidity and mortality are associated with their misuse and coadministration with other agents. Physicians and pharmacists must continue to educate patients and each other about the risks and benefits associated with pain management treatments.

HISTORY OF OPIATES

For several thousand years, opiates have been used for pain control. The Sumerians documented poppy in their pharmacopoeia and called it HU GIL, the plant of joy. In the third century BCE, Theophrastus referenced poppy juice. The word opium is derived from the Greek name for juice obtained from the poppy (papaver) and the Latin name for sleep inducing (somniferum). Opium was brought to the Orient by Arab traders as a treatment for dysentery. Opium contains approximately 20 distinct, naturally occurring alkaloid substances collectively termed opiates. In 1805, the German pharmacist Sertürner isolated morphine, which is named after Morpheus, the Greek god of dreams. Subsequently, Robiquet isolated codeine in 1832. In 1898, Bayer pharmaceu-

ticals sold diacetylmorphine or heroin, from the German word for hero. By the middle of the 19th century, pure opium alkaloids, rather than basic opium preparations, had spread throughout the medical community. Until the early 20th century, opioid abuse was rampant in the United States because of unrestricted availability of opium along with a massive influx of opium-smoking immigrants from the Orient. In fact, Thomas Jefferson grew opium poppies at Monticello. In 1942, the Opium Poppy Control Act banned opium production in the United States.[3]

Opioids are substances that act on the opiate receptor and are not the same as narcotics, substances such as cocaine, cannabis, and barbiturates that produce narcosis and can be abused. The word narcotic is derived from the Greek word for stupor. Narcotics were initially used for sleeping-aid medications. The word narcotic is now a legal term for different types of drugs that are abused.

CLINICAL AND PHARMACOLOGIC PRINCIPLES OF OPIATES

In recent years, acute and chronic management of pain has emerged as a unique aspect of medical practice. Newer treatment options have improved the success of pain management (analgesia) for many patients by increasing the duration and potency of pain relief.

Patients' pain is frequently associated with osteoarthritis, sports-related injuries, headaches, rheumatologic conditions, or even malignancy. Patients with musculoskeletal pain often require treatment with analgesics for intermittent pain exacerbations or constant disabling pain. Traditional options for noncancer pain treatment for most patients involve morphine-like or opioid medications and nonsteroidal antiinflammatory drugs (NSAIDs).

Successful pain relief usually involves, in part, using a few different medications of various strengths and durations of action to provide an effective regimen for the patient's condition. Most patients have a combination of mild to severe pain that occurs constantly, along with sudden peaks or exacerbations that often occur after certain activities and require quick-onset medications. Specific medications are available to provide immediate but temporary pain relief, while other medications can provide a longer duration of pain relief with a slower onset of action. An understanding of the medication options available and knowledge of the patient's daily pain occurrences allow for the development of an effective pain regimen. Consultation with a pain specialist may be useful in cases of complicated pain conditions or for treatment-resistant patients.

On September 10, 2013, the US Food and Drug Administration (FDA) announced an update to its Risk Evaluation and Mitigation Strategy for Long-Acting and Extended-Release Opioid Products.[4] This class of medications is now indicated only for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Two opioids commonly used to treat nonmalignant pain are hydrocodone and oxycodone. These medications are available in various preparations, including both immediate- and extended-release formulations with the latter. The successful selection and adjustment of these therapies can not only reduce pain and suffering, but can also improve quality of life and emotional well-being by providing analgesia arising from both acute and chronic conditions. Acutely, opioids are most commonly used to treat pain following injury, surgery, or labor and delivery. They are also used to treat discomfort arising from exacerbations of medical disorders such as osteoarthritis or rheumatoid diseases. In addition, opiates such as codeine have been used in lower doses to treat cough, and weaker opioids such as diphenoxylate with atropine (Lomotil) can be effective in treating diarrhea. Opioids such as methadone and buprenorpine are often used to treat pain and even maintain addicted patients in opiate substitution therapy. It is important to remember, however, that opiates merely treat these symptoms; the underlying disease remains.

Opioid analgesic prescribing principles in acute settings are based on a variety of factors; no standard therapy exists. Opioid doses should be titrated to a response. Some patients may require considerably more than the average dose of a drug to experience part or complete relief from pain; others may require dosing at more frequent intervals. Treatment often depends on the patient, is multifactorial, and can be heavily influenced by prior experience with opiates (opioid naivety) and other adjuvant agents. Pain is a subjective symptom and often difficult to quantify by individual patients. Consequently, accurately assessing pain and precisely understanding the meaning of pain both within and across populations are challenging for physicians.

Response to opioid medications varies widely in terms of pain relief, side effects, and complications. Some patients' unique biology may limit the effectiveness of certain classes of analgesic agents. For example, some patients metabolize opiates poorly. It is now understood that poor metabolizers of cytochrome P450 2D6 (CYP2D6), a key enzyme in the opiate medications codeine and dihydrocodeine, may not experience successful analgesia. Conversely,

ultra-rapid metabolizers (high or normal activity variants) may metabolize codeine too efficiently, leading to opioid intoxication.[5]

Clinical signs such as tachycardia and hypertension may indicate that a patient is in acute pain. Likewise, a constellation of signs and symptoms, including tachycardia and hypertension, can be seen with opiate withdrawal and central nervous system hyperarousal states. Because of great individual patient variables, pain physicians should be careful in assuming abuse if the patient reports pain despite receiving medication. Underdosing pain patients can lead to treatment failure as well.

Chronic opioid therapy usually involves the use of either weak or strong opiates; often both are prescribed in conjunction to adequately control acute pain. Weak opiates typically come in oral preparations and are combined with other everyday medications in varying formulations to augment the response. These combinations often include acetaminophen (Tylenol, acetyl-para-aminophenol [APAP], paracetamol), aspirin, or ibuprofen. All of these drugs have ceiling doses related to the nonopioid ingredient. Acetaminophen is included in a multitude of opioid formulations; its popularity is due to its property of not irritating the stomach.

The limitations of these preparations come from the potential side effects of larger doses of the second drug, along with the dose-dependent side effects of the opiate. The popularity of NSAIDs has declined over the last decade because of reports of cardiovascular complications with COX-2 inhibitors (NSAIDs that selectively inhibit cyclooxygenase-2). Even short-term use of a drug combination with aspirin or ibuprofen can result in gastrointestinal issues, including bleeding. Another limitation is the possibility of acetaminophen poisoning, one of the common causes of acute liver failure in the United States and often the result of deliberate misuse or attempted suicide. Patients with hepatitis or known alcoholism and patients on acetaminophen-containing opiates require extra scrutiny. Medications such as methotrexate, propylthiouracil (PTU), and isoniazid should not be prescribed for patients on APAP because of the potential for additive hepatic damage.

Doctors and patients often look for midrange products that provide moderate pain relief without a major risk of dependency or addiction. Examples include hydrocodone (Vicodin, Norco) and codeine (Tylenol with Codeine). These products are effective for acute injuries, but the duration of pain relief is often brief.[6]

Many patients do not obtain full pain relief and ultimately require and request larger doses in an attempt to manage escalating pain. Because larger doses of opioid products are associated with potentially daunting toxicities, practitioners often utilize secondary agents including nonopioid adjuvant therapies including NSAIDs, skeletal muscle relaxants, antidepressant and anticonvulsant medications, topical/local anesthetic patches, and injected nerve blocks (usually given as a combination of glucocorticosteroids and anesthetics) among others. The phenomenon of tolerance—the need for increasing doses of the same drug to achieve the same effect—can develop over time, adding to the challenges of dosing opiate medications because larger doses increase the risk of potential side effects and toxicity.[5]

In the hospital setting, morphine, meperidine, fentanyl, and hydromorphone are used for patient-controlled analgesia machines and postoperative acute pain treatment. Morphine is available in various formulations, including immediate-release tablets, oral liquid, sustained-release tablets, suppositories, and parenteral (injectable) formulations. Physicians and patients are often tempted to utilize longer-acting agents in an attempt to minimize highs and lows and to prevent frequent breakthrough pain. Variable responses to medications in this class are often due to subtle differences in patient's absorption, metabolism, tolerances, and pain levels.

MS-Contin and Oramorph SR (morphine sulfate controlled-release) provide 12 hours of relief in most patients but lack a quick onset of action. Kadian, a newer morphine product formulated in sustained-release pellets, provides prolonged pain relief for up to 24 hours in selected patients. Morphine is also available in immediate-release and extended-release bead formulations (Avinza) that offer continuous opioid pain relief for up to 24 hours. Avinza is not effective for immediate or as-needed use (for breakthrough pain) and requires properly educating the patient about issues such as the avoidance of alcohol.

Meperidine (Demerol) is an agent that is one-tenth as potent as morphine and possesses high addiction potential due to its rapid but short duration of action after parenteral administration. Physicians often feel pressured by patients to administer this rapid-acting drug. The drug's frequent abuse by healthcare workers has given it the unfortunate moniker of "the doctors' and nurses' addiction." Although meperidine tablets for oral administration are available, toxicity from the metabolite normeperidine limits its long-term use, so it is rarely used to manage chronic pain.

Fentanyl, 75-125 times as potent as morphine, is available in myriad dosage formulations, including buccal soluble film (Onsolis), buccal tablet (Fentora),

transdermal patch (Duragesic), lollipop (Actiq), and parenteral formulation (Sublimaze).

Hydromorphone (Dilaudid), 5-6 times as potent as morphine, is an effective analgesic that has been formulated in the past in an extended-release formulation (Palladone). Palladone was removed from the US market because of FDA concerns about dose dumping—substantial release from its controlled-release formulation—in patients who took it with alcoholic beverages. A once-daily extended-release formulation without this complication has recently been introduced (Exalgo).

Hydrocodone, oxycodone, and oxymorphone preparations have also had a major role in pain management. Hydrocodone is the most prescribed medication in the United States, according to the IMS Institute for Healthcare Informatics, a pharmaceutical market intelligence firm. A staggering 135.3 million prescriptions were written for hydrocodone/paracetamol in the United States in 2012.[7] Hydrocodone is available in many formulations with acetaminophen (Norco, Lortab, Vicodin) and ibuprofen (Vicoprofen, Ibudone). Because a controlled-release hydrocodone product is not available at present, typical dosing is every 4-6 hours to maintain effective pain relief. The potential for acetaminophen-induced hepatic injury requires regular monitoring of liver function.

Oxycodone (OxyIR, Oxycontin) is dosed every 12 hours for extended-release formulations; the immediate-release formulations are often given more frequently than every 6 hours as needed for acute pain. Multiple prescribing options (with long- and short-acting treatments) are often utilized for pain management based on physician experience. Immediate-release liquid is also available for patients unable or unwilling to swallow tablets or capsules. Percodan and Percocet, short-duration or breakthrough pain agents dosed every 4-6 hours, offer formulations that include either aspirin or acetaminophen combined with oxycodone in immediate-release tablets. With its acetaminophen concentration of 325-650 mg per tablet, Percocet has the potential for causing liver damage. Oxymorphone (Opana, Opana ER, Numorphan, Numorphone) was developed a century ago and induces less euphoria, sedation, and itching than other opioids. Oxymorphone is also produced within the human body when the liver metabolizes oxycodone by means of O demethylation catalysed by the CYP2D6 enzyme. Consuming alcohol can alter absorption of oxymorphone significantly and be associated with a lethal dose-dumping phenomenon.[8,9]

Methadone, closely related to the relatively weaker analgesic propoxyphene, has become a commonly used agent in pain management because of its inexpensive and long-acting pharmacokinetics.[10] Careful use and titration are necessary because of the drug's various severe adverse effects including heart rhythm abnormalities. An independent advisory panel to the FDA recommended pretreatment electrocardiography (ECG) due to methadone-related cardiac conduction effects, including QTc interval prolongation and torsades de pointes. Additional follow-up ECG at 30 days and then annually is encouraged, although the panel recommended more frequent ECG monitoring for patients taking doses in excess of 100 mg/d and patients whose QT interval $>$450 milliseconds.[11,12]

Propoxyphene (Darvocet, Darvon) was a commonly prescribed analgesic structurally similar to methadone. Nausea, upset stomach, and constipation were minimal compared to other opioids, but so was the degree of analgesia. Propoxyphene remained a popular analgesic for many years despite its many potential side effects including heart damage, delusions, and convulsions. When given in combination with aspirin or acetaminophen, propoxyphene is thought to provide less analgesia than the aspirin or acetaminophen alone.[13] After reports of potentially fatal heart rhythm abnormalities (ECG data from a clinical study revealed QT interval abnormalities occurred in healthy people taking normal doses of the drugs), the FDA and its advisory groups recommended removal from the market after concluding that the pain relief benefits of the drugs did not outweigh the significant risk of side effects related to overdose and addiction. The FDA banned propoxyphene use in the United States in 2010.[10]

NONOPIOID ANALGESICS

Tramadol (Ultram) and tramadol with acetaminophen (Ultracet) are nonopioid dual-action analgesics that produce many of the same benefits and potential side effects of opioids. Interactions with other medicines, including some antidepressants, and a patient's history of seizures may increase the seizure risk associated with tramadol. Tapentadol (Nucynta) is a newer and similar type of product that produces powerful pain relief.[8,14]

Noncontrolled local anesthetics patches such as Lidoderm; topical NSAID products such as the Flector Patch (diclofenac patch), Voltaren Gel (diclofenac topical gel), and PENNSAID (diclofenac sodium topical solution); and the antidepressant Cymbalta (duloxetine, a serotonin-norepinephrine reuptake inhibitor) provide adequate pain relief to many chronic pain patients.

OPIOID-INDUCED SIDE EFFECTS

Diligent monitoring of patients is necessary to prevent serious side effects including life-threatening bradycardia and respiratory depression. Constipation, nausea, and pruritus can often be minimized by pharmacologic adjustment. Physical dependence is to be expected with high-dose chronic opioid therapy. Addiction can occur in patients who overuse or misuse these powerful medications. Opioid-induced hyperalgesia (OIH)—often defined as abnormal, increased, or extreme pain sensitivity—is one of the most difficult and undesirable effects of opioid therapy. Opioid reduction is considered the most useful intervention to treat this unpleasant consequence.

The common adverse effects of opioid medications, including sedation, constipation, and nausea, must be understood to minimize medication complications. Constipation is a long-term complication, and chronic use of laxatives is often necessary with either polyethylene glycol-electrolyte solution (MiraLAX) or stimulant laxatives such as senna glycosides or sennosides, available with or without the popular stool softener docusate sodium (Senokot, Senokot-S).

Lesser-known potential toxicities associated with high doses of opioid-containing medications include ototoxicity and sensorineural hearing loss, side effects not commonly recognized as associated with opioid medications. Since the late 1990s, otolaryngologists have warned physicians and pain patients of a possible correlation between permanent hearing loss and high-dose opioid administration.[15,16] A case study from 2007 reports rapidly progressive bilateral sensorineural hearing loss without vestibular symptoms in 5 patients with a history of hydrocodone use and abuse. The admitted doses ranged from 10-300 mg daily. Hepatitis C was noted as a comorbidity in 3 of the 5 patients.[15] Oddly, after thousands of years of opioid use and abuse by societies around the world, the phenomenon of rapid and progressive sensorineural hearing loss was not well known or frequently reported until the last few decades.

Recently, attention has been focused on opioid-induced androgen deficiency (OPIAD) also known as opioid-induced hypogonadism. All opioids can cause some degree of endocrine dysfunction, and higher relative doses of sustained-release opioids may result in greater impairment.[17] Opioid-induced endocrinopathy affects both men and women but exerts greater effects in men. With the recent increase in promotions for topical testosterone formulations, monitoring and treatment for OPIAD has increased. Gonadal sex hormones, cortisol, and growth hormone dysfunction are only some of the known endocrinopathy reported. The primary mechanism for opiate-induced sex hormone deficiency is suppression of the hypothalamic-pituitary-gonadal axis.[18] The hypothalamic-pituitary-gonadal axis has multiple effects on adrenal androgen and endocrine production and deficiency. Opioids, both endogenous and exogenous, modulate gonadal function primarily by acting on opioid receptors in the hypothalamus.[19] Some studies show that opioids may act directly at the gonadal tissue, suppressing testosterone secretion. Low serum testosterone concentrations in male heroin and methadone users were first reported in the 1970s.[20] Symptoms of opioid-induced deficiencies include decreased libido, erectile dysfunction, decreased muscle mass, fatigue, weight gain, osteopenia, osteoporosis, depression, and, additionally in women, hyperprolactinemia, menstrual irregularities including amenorrhea, flushing, and sweating.

After opioid treatment is initiated, possible signs or symptoms of endocrine deficiency including sexual dysfunction should be monitored. Physicians and pharmacists may encourage diagnostic laboratory testing to assess androgenic deficiency in both men and women. A morning total testosterone is a suggested screening test for those on chronic opiate therapy. Data from one study reveal a high frequency (73%-89%) of apparently symptomatic hypogonadotropic hypogonadism in community-dwelling men consuming multiple daily doses of commonly prescribed opioids.[21] After identification of opioid hypogonadism or other endocrinopathies, a reduction of dose or substitution with other analgesics may restore proper endocrine function. If this approach is not successful, hormone replacement with testosterone for men and progesterone and other hormonal treatments for women may provide symptomatic improvement. Transdermal/topical androgen replacement for hypogonadotropic hypogonadism has improved libido and also mood.[17]

The Food and Drug Administration Amendments Act of 2007 was an attempt by the FDA to reduce the dangers of long-acting opioids that requires manufacturers to provide a risk evaluation and mitigation strategy to demonstrate that the benefits of a drug (opioid-analgesic) outweigh its risks. Tamper-resistant (also called abuse-resistant) formulations for opioid painkillers feature specific oral long-acting prescription formulations that are less likely to be able to be crushed, snorted, or injected. It remains to be seen if these modifications will significantly reduce overdoses and deaths or simply shift abuse patterns to immediate-release opioid products.

Examples of the various modifications and formulations that have been developed include Embeda

(morphine and naltrexone), Suboxone (buprenorphine and naloxone), and Talwin-Nx (pentazocine and naloxone). Recently, Oxycontin has been reformulated to "prevent the opioid medication from being cut, broken, chewed, crushed or dissolved to release more medication."[22] The new formulation involves the addition of a substance that makes the tablet too sticky and difficult to crush and prevents it from being able to be snorted or injected.[22]

The abuse of prescription-controlled substances for pain management, particularly opioids, is on the rise. Consequently, all physicians must be cautious with patients who request opioid therapy without actually having documented moderate or severe pain because such requests may be indicative of abuse or diversion potential.

Recent attention has been given to the additive risk of opiate addiction in patients with simultaneous mental health issues. Extra precautions should be taken with pain patients who have diagnoses such as schizophrenia, anxiety, depression, attention deficit disorder, bipolar disorder, posttraumatic stress disorder, or alcoholism. With such patients, consider the following prudent practices:

- Prescribe reduced quantities of tablets or capsules at one time to minimize the potential for overuse.
- Hesitate to prescribe more than a 7- to 14-day supply of controlled substances to patients with a history of overdose or suicide attempts.
- Use less powerful medications when possible, including noncontrolled prescription adjuvants.
- Increase monitoring of patients for aberrant drug-taking behaviors for the duration of the pain management therapy.
- For patients requiring long-term treatment with opiate medications, require an opiate contract (pain contract) signed by the patient and the practitioner. These contracts clarify the dangers and risks associated with these powerful agents and warn of dismissal from the physician's practice if the patient fails to follow the rules for medication compliance or if the patient uses multiple prescribers or pharmacies.

OPIOID-MEDIATED DRIVING EFFECTS

Although it seems likely that studies would consistently demonstrate similar opioid-mediated effects on driving, controversy still exists.[23-26] Driving under the influence of drugs (DUID) is a term used to designate the action of driving an automobile after the consumption of drugs or medications other than alcohol that interfere with the capacity to operate a vehicle safely.[26] The development of tolerance from stable chronic administration of prescription opioids is a well-described phenomenon that may help explain some patients' ability to drive safely after long-term use. Evolving data have focused on the driving competence and motor coordination of patients on chronic opioid medications. Despite the significant evidence that opioids provide efficacious and safe pain management benefits, many people, especially those in law enforcement positions, believe that any type of opioid, whether administered over a short or long term, results in dysfunction in cognitive abilities.

The ability to drive safely requires a wide range of cognitive and psychomotor abilities. Visual deficiencies and lapses of attention contribute specifically to the dangers of driving, and driving skills can be depressed in tolerant patients operating a motor vehicle who are not stabilized on chronic doses. A literature review of opioid-dependent/tolerant patients and driving-related skills produced 48 relevant studies in the structured review. In these studies, subjects were tested for reaction time, visual orientation, motor coordination, and vigilance at time intervals following varying doses of opioids and were compared to drivers not taking opioid medicines. The results showed generally consistent evidence for no impairment of psychomotor abilities in opioid-maintained patients. Strong, consistent evidence showed no greater incidence in motor vehicle violations/motor vehicle accidents (MVAs) among drivers taking opioids compared to drivers not taking opioid medications. These studies also demonstrated no impairment when drivers were measured in driving simulators.[23-26]

A structured evidence-based literature review designed to look for evidence of an association between opioid use and intoxicated driving, MVAs, and MVA fatalities indicates that opioids probably are not associated with intoxicated driving. The literature indicates that opioids are not associated with MVA.[23] Patients develop tolerance rapidly to any sedative or cognitive impairment related to controlled-release medications. Sustained blood levels of long-acting opioid medications were not associated with altered driving capacity.

While most physicians and pharmacists continue to warn patients of potential sedation and impairment of the neuromuscular skills required to drive, the results of this systematic review support the contention that patients taking opioids, assuming their cognitive and physical resources are intact, may be allowed to drive. A pivotal point in many disability suits and settlements is the argument that the need for opioids serves as the reason why the claimant cannot return to the workforce. Cognitive assessment in the context of taking opioid medications may better

represent the true level of disability in the present and future of these patients.

Functionality, including the capacity to work, provides a delicate challenge for the clinician prescribing opioid analgesics. Existing data suggest that driving capacity is not reduced when patients take opioid analgesics in appropriate doses over extended periods of time.

With a sizable percentage of the driving public having detectable levels of opioids within their bodies, policymakers must account for scientific evidence when balancing the benefit of pain relief against the need for public roadway protection when drafting DUID legislation. The best available evidence demonstrates psychomotor impairment following acute administration of opioids or an increase in opioid dosage, but impairment diminishes with chronic, stable opioid usage.[27]

CONCLUSION

Effective pain management requires a delicate balance of adjusting and titrating powerful medications to levels sufficient to provide sustained relief of debilitating pain. Because of the widespread distribution of opioid receptors, precise knowledge of opioid-induced toxicities is imperative for ensuring patient safety. Unwanted side effects are common and include agonizing constipation, pruritus, dizziness, or drowsiness. Overdose and misuse can cause life-threatening bradycardia and respiratory depression. Continuous monitoring of patients for physical dependence, addiction, and OIH are a necessity with chronic use of opioids.

In summary, physicians have improved their understanding of clinical issues related to opioid administration in recent years. By carefully weighing critical clinical factors, including patient-specific responses to a given medication, duration of the medicine, and onset of pain relief, the best choices and regimens for safe opioid administration are ensured. Clinicians need to be educated on lesser-known toxicity issues related to opioid administration. Finally, knowledge of pharmacological principles related to long-term tolerance and patient functionality (such as driving and cognitive abilities) with these agents is important in many aspects, including disability and workforce issues.

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