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Use and Misuse of Opioids in Chronic Pain

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Abstract

The prescribing of opioid analgesics for pain management—particularly for management of chronic noncancer pain (CNCP)—has increased more than fourfold in the United States since the mid-1990s. Yet there is mounting evidence that opioids have only limited effectiveness in the management of CNCP, and the increased availability of prescribed opioids has contributed to upsurges in opioid-related addiction cases and overdose deaths. These concerns have led to critical revisiting and modification of prior pain management practices (e.g., guidelines from the Centers for Disease Control and Prevention), but the much-needed changes in clinical practice will be facilitated by a better understanding of the pharmacology and behavioral effects of opioids that underlie both their therapeutic effects (analgesia) and their adverse effects (addiction and overdose). With these goals in mind, this review first presents an overview of the contemporary problems associated with opioid management of CNCP and the related public health issues of opioid diversion, overdose, and addiction. It then discusses the pharmacology underlying the therapeutic and main adverse effects of opioids and its implications for clinical management of CNCP within the framework of recent clinical guidelines for prescribing opioids in the management of CNCP.



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ISSUES IN CHRONIC PAIN MANAGEMENT WITH OPIOIDS

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” and defines chronic pain as “pain that persists beyond normal tissue healing time, which is assumed to be three months” (1). Chronic noncancer pain (CNCP) is pain lasting more than three months that stems from injuries or illnesses other than cancer (see sidebar titled Chronic Pain Conditions). Pain is the most common and prevalent symptom reported among patients in primary care, and ~50% of pain cases are treated by primary care physicians (2). CNCP is reported by >30% of Americans and by >50% of older adult Americans (3, 4). Within CNCP, low back pain is the most common type, followed by arthritis (5). Chronic pain is also frequently associated with depression and anxiety (6), explaining why CNCP is the major factor in disability and extended impairment among adults under 45 years of age (2).

CHRONIC PAIN CONDITIONS

Common conditions causing chronic pain include neuropathic pain (NP), fibromyalgia (FM), low back pain (LBP), and osteoarthritis (OA). NP includes diabetic neuropathy, lumbar nerve root compression, cancer-related NP, HIV-related NP, trigeminal neuralgia, and phantom limb pain, among others. It typically presents as continuous or intermittent spontaneous pain, described as burning, aching or shooting. An IASP (International Association for the Study of Pain) consensus panel recommends the following first-line treatments for NP: antidepressants (i.e., tricyclics and serotonin norepinephrine reuptake inhibitors), α_2 - δ calcium channel ligand anticonvulsants (i.e., gabapentin and pregabalin), and topical lidocaine. In certain cases (e.g., intercostal nerve involvement in cancer-related NP or lumbosacral radiculopathy), neural blockade can be used effectively (84). Opioids are recommended by the IASP as second-line treatments. This panel noted that no medications have demonstrated efficacy for lumbosacral radiculopathy, a common NP condition, and that little is known about long-term effectiveness since the duration of trials was less than three months.

Fibromyalgia (FM) is characterized by generalized, widespread chronic pain (≥ 3 months) with multiple tender points upon physical examination. It is believed that the primary problem is inadequate filtering of signaling from nociceptors by descending antinociceptive pathways, which is described as central sensitization (85). Effective medications for FM include antidepressants, the muscle relaxant cyclobenzaprine, the opioid tramadol, and the α_2 - δ calcium channel antiepileptics. The strongest evidence is for pregabalin, duloxetine, and milnacipran, all of which are approved by the US Food and Drug Administration for FM.

Low back pain (LBP) and osteoarthritis (OA) are the most common chronic musculoskeletal pain disorders and among the most frequent causes of chronic noncancer pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, and opioid analgesics are the most commonly prescribed medications for LBP (86). Although there is no good-quality evidence, lower-level evidence suggests that acetaminophen, NSAIDs, tramadol, and tricyclics can be effective. The effectiveness of physical activity for LBP has not been fully demonstrated, based on the quality of the available evidence (87). However, there is high-quality evidence that epidural blockade is effective for treating LBP and lower-extremity pain (88). In addition, there are other minimally invasive treatments for certain cases of LBP, which are opioid-sparing. The evidence for the benefits of opioids in LBP is inconclusive (21).

The likelihood of OA increases with age and frequently involves joints in the fingers, knees, hips, and cervical and lumbar regions of the spine. NSAIDs and acetaminophen are the main pharmacotherapies for OA (89). A meta-analysis of 18 trials of opioids in the treatment of OA showed moderate efficacy for decreasing pain intensity but small efficacy for improving function.

Increases in Opioid Use, Misuse, Overdose, and Addiction

The goals of pain management are relief of pain and improvement in function and general health. To foster improved recognition and treatment of pain, the US Congress declared 2000–2010 the Decade of Pain Control and Research. The most visible consequence was that prescriptions for opioid analgesics increased 300% during this period (7) despite limited research on the efficacy of opioids for CNCP (8). Systematic reviews of opioids in the treatment of most types of CNCP (discussed below) show high rates of patient attrition due to their side effects, as well as modest rates of improved analgesia or patient function (9–12).

While there are significant questions about the effectiveness of opioids in the management of CNCP (see below), there is no doubt that increased opioid prescribing has resulted in serious public health problems, such as diversion (see sidebar titled Opioid Diversion and Mitigation Strategies), overdose, and addiction. Most notable are the fatalities from prescription opioid overdoses, which quadrupled between 1999 and 2015 in the United States to >15,000 (13). Even more prevalent are the nonlethal opioid overdose incidents that require medical care in a hospital or emergency care

OPIOID DIVERSION AND MITIGATION STRATEGIES

Opioid diversion refers to the transfer or sale of an opioid from a prescriber or (usually) a legitimately prescribed patient to another individual for use in an illicit or nonprescribed manner. The most common form of diversion is transfer of an opioid from a patient to a family member or friend to self-medicate a generic pain (44). This type of diversion is best managed by educating patients on the dangers of sharing medications and on the importance of safe storage and disposal. Another 7–10% of diversion is due to dissembling patients who feign pain to acquire prescribed opioids—often from multiple physicians (doctor shopping)—for their rewarding effects. Although effort has been put toward screening practices to identify dissembling patients, the most recent review found no evidence that any scale or procedure was effective (90). Risks of diversion through doctor shopping are best mitigated by patient contracts and full participation in Prescription Drug Monitoring Programs (PDMPs).

Opioid contracts are formal written agreements between prescribers and patients that define key aspects of opioid therapy, including potential risks and benefits of treatment, prescribing policies, methods for monitoring opioid use, expected behaviors, and consequences of violating the contract (91, 92). Contracts can help enhance adherence to opioid therapy and reduce aberrant drug-related behaviors. They document the informed consent process, reduce clinicians' legal risk, and improve practice efficiency (91, 92). Opioid contracts also allow physicians to stop prescribing if there is no treatment benefit. Potential harms are uncertain: possible undertreatment of pain or negative effects on patient–clinician relationships (93).

PDMPs are statewide electronic databases that collect information on prescription of controlled prescription drugs designed to monitor information pertaining to suspected abuse or diversion. They help reduce doctor shopping and overdoses (94–96), but their utilization is inconsistent, in part because only 22 of 49 PDMPs share information across states (<http://www.namsdl.org/library/4475CD3E-1372-636C-DD2E5186156DFB6F>) and because some of the PDMPs do not report information in real time.

To mitigate diversion and abuse, the US Food and Drug Administration grants “abuse-deterrent formulation” (ADF) labeling to opioids that cannot be extracted for snorting or injection. There are limited data supporting an impact of ADFs in decreasing diversion except for the ADF OxyContin, for which 10 postmarketing studies documented decreases in diversion, abuse, and overdoses (97). However, OxyContin, which is the most frequently prescribed ADF, accounts for <3% of all prescriptions, and all of the new opioid ADFs combined account for an even lower percentage. Currently, there are no immediate-release ADFs and no generic formulations of ADFs, which in some settings precludes insurance coverage.

setting, ~1,000 per day in the United States (14). Addiction to prescription opioids has also led to an increase in heroin abuse (increasingly being laced with synthetic opioids such as fentanyl), as heroin is cheaper and more accessible, along with marked increases in heroin- and fentanyl-associated fatalities, which in 2015 corresponded to 13,000 and 9,500 deaths, respectively (13).

Most physicians are aware of the alarming elevations in national rates of opioid-related public health problems, but many find it hard to believe that their own prescribing behaviors could be related to these national problems. Data from the 2015 National Survey on Drug Use and Health (15) support both perceptions. In this survey, 97.5 million Americans admitted to “taking an opioid in the past year” (~36% of US adults)—confirming the remarkable prevalence of opioid use in the United States. Approximately 12.5 million of those individuals (~13%) admitted “misusing” an opioid in nonprescribed ways, and two million met diagnostic criteria for a prescribed-opioid-use disorder (about 2% of all users). These figures comport with the impressions of many physicians that most of their patients take opioid medications as directed. However, because of the magnitude of opioid use in the US population, even modest rates of misuse can constitute a serious public health concern. Physicians bear partial responsibility because about one third of those who misused opioids got them directly from a physician’s prescription, and 57% got them from a friend or relative who had been prescribed opioids (15). The “flooding” of US communities with opioid prescriptions has facilitated diversion of these medications and caused serious public health consequences. Thus, there is a need for physicians to reconsider the management of CNCP with opioids and to better understand the separate but related effects of opioids on analgesia, overdose, and addiction.

Effectiveness of Opioids for Relieving Pain and Improving Function

The effectiveness of the most commonly prescribed opioids for CNCP, including codeine, morphine, oxycodone and tramadol, has been evaluated in several systematic reviews (10–12, 16–22). The most common kinds of CNCP represented in these reviews were low back pain, osteoarthritis, and neuropathic pain. Opioids had significantly greater analgesic effect than placebo—approximately a 30% reduction in reported pain—regardless of type of pain and/or type of opioid prescribed. Improvements in functional status were not as consistent nor as great in magnitude as the analgesic effects (8), although this was confounded by the lack of standardized measurements. It is well known from the acute pain literature that, although opioid analgesics are effective for resting pain, they are ineffective for pain associated with activities. This is why multi-modal analgesia paradigms supplemented with NSAIDs and other pharmaceutical targets have been suggested (23–25). Overall, the results from these reviews showed no consistent differences in effectiveness among different types of opioids (26). Specifically, six carefully controlled studies comparing different types of opioids, equating for both dose and levels of additional support services, found no clear advantage in efficacy or side-effect prevalence for any specific opioid (9, 27–32). Five of these six studies failed to show a significant difference between short- and long-acting or between immediate- and extended-release opioids.

Research reviews have documented multiple gastrointestinal and central nervous system adverse effects associated with opioids, particularly when prescribed at higher doses [>80 mg/day morphine milligram equivalent (MME)], for longer periods of time, or for patients with known risk factors for adverse effects. The most common adverse effects are dry mouth, nausea, constipation, sedation, dizziness, hyperalgesia, pruritus, and dermatological rashes. Tolerance (discussed in detail below) develops to most of these adverse effects, but not to constipation, which requires therapeutic measures to improve laxation.

About half of patients treated with opioids in the review studies reported adverse events, and nearly one-quarter withdrew because of those side effects (12). In the longest randomized

NONOPIOID ANALGESICS

Nonsteroidal anti-inflammatory drugs (NSAIDs): These analgesics have anti-inflammatory and antipyretic properties. NSAIDs' inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) accounts for both their therapeutic and their adverse effects. Gastrointestinal and cardiovascular adverse effects are the most common and worrisome. NSAID use is limited to patients not at risk for coronary artery disease.

Antidepressants: These include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), which exert analgesic effects by enhancing monoaminergic neurotransmission. There is strong evidence for their analgesic effects (98). However, the cardiovascular side effects of TCAs (e.g., hypertension, postural hypotension, arrhythmias) limit their use.

Anticonvulsants: Gabapentin and pregabalin are considered the first-line anticonvulsants for the treatment of neuropathic pain other than trigeminal neuralgia (34). They are believed to exert analgesic effects by binding to calcium channels (α - δ subunits) in the brain and spinal cord, thereby inhibiting release of excitatory neurotransmitters implicated in pain. Gabapentin and pregabalin are also approved for fibromyalgia. Their most bothersome side effects are somnolence, dizziness, and weight gain.

Skeletal muscle relaxants: These medications are approved for spasticity and musculoskeletal conditions (99). However, most trials have involved acute rather than chronic pain, except that cyclobenzaprine has shown benefit for fibromyalgia. There has been concern that some of these medications can lead to abuse and addiction.

Topical analgesics: These can be used to treat localized areas of pain, including neuropathic or osteoarthritic pain. Lidocaine, salicylate, and capsaicin have been the most investigated.

Inflammatory mediators: These are not analgesics, but we include them because they are used to treat chronic pain conditions. They work by interfering with inflammatory signals responsible for pain generation. These include antagonism of nerve growth factor and tumor necrosis factor inhibitors, as well as chemokine antagonists or neutralizing antibodies that modulate nociceptors.

trial (13 months), 90% of patients (N=680) who received either transdermal fentanyl or sustained-release morphine experienced at least one opioid-related adverse event; and 34% consequently withdrew (9). The most serious opioid-related side effects are overdose and addiction, discussed in the sections below.

Given the questionable effectiveness and the high rates of side effects, why there has been such dramatic growth in opioid prescribing for CNCP? Among the major reasons is the limited number of available alternative medications or treatments for chronic pain (33). The US Food and Drug Administration (FDA) has approved nonopioid medications for treating CNCP (see sidebar titled Nonopioid Analgesics), such as cyclooxygenase inhibitors (ibuprofen, celecoxib), amine uptake inhibitors (amitriptyline, duloxetine, milnacipran), and calcium channel blockers (e.g., pregabalin, gabapentin), but all of these also have clinical limitations, including partial efficacy and side effects, and tend to have a slower onset of action than most opioids.

The relative efficacy of analgesics is evaluated by comparing the number needed to treat (NNT) to achieve moderate benefit, defined as >30% pain relief. For example, for amine uptake inhibitors and calcium channel blockers, which are recommended as first-line treatments for neuropathic pain, a meta-analysis of 229 studies derived an NNT value of 6–7 (34). That is, for every patient achieving this degree of pain relief, five to six would receive less (or no) benefit. In the treatment of fibromyalgia, the NNT of the serotonin-norepinephrine reuptake inhibitor (SNRI) milnacipran was 8, according to a meta-analysis on >4,000 patients (35). The NNT of the antiepileptic drug pregabalin, based on a randomized clinical trial, was 6–9 (36).

Complementary and alternative medical treatments, including physical therapy, exercise, stress management, and cognitive behavioral therapy, have also been proposed for the management

Table 1 Overview of CDC opioid guidelines for chronic pain in adults (source: <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>)

When considering long-term opioid treatment	When reassessing patient at return visit
<ul style="list-style-type: none"> Complete and document H & P Conduct focused history Review diagnostic work-up for underlying course Consider contributing factors (e.g., sleep, psychosocial stressors) Consider pain consultation 	<ul style="list-style-type: none"> Evaluate risk of harm Observe patient for overdose symptoms Evaluate for overdose risk. If yes, taper dose
<ul style="list-style-type: none"> Assure that nonopioid therapies have been tried and optimized Physical therapy CBT and other behavioral therapies Exercise therapy (if possible) Interventional approaches (e.g., pain consultation) 	<ul style="list-style-type: none"> Continue to ensure that nonopioid treatment is optimized
<ul style="list-style-type: none"> Assess baseline pain and function (dependent on diagnosis, e.g., PEG scale) 	<ul style="list-style-type: none"> Reassess pain and function (e.g., PEG) and compare with baseline results
<ul style="list-style-type: none"> Discuss and set realistic goals for pain and function with patient Discuss realistic benefits of opioid therapy Clarify that there is no good evidence that long-term opioids improve pain and function Discuss risks of long-term opioid therapy including risk of serious harms: death from respiratory depression, potential lifelong serious opioid-use disorder, cognitive limitations, common side effects that will interfere with well-being in daily life. Discuss increased risk if opioids are taken with other drugs and alcohol; risk to household members, e.g., children; importance of regular reassessment 	<ul style="list-style-type: none"> Check for opioid-use disorder—if suspected, consider early intervention
<ul style="list-style-type: none"> Check PDMP 	<ul style="list-style-type: none"> Check PDMP
<ul style="list-style-type: none"> Check urine drug screen 	<ul style="list-style-type: none"> Calculate MME/day and ensure that it is ≤ 90
<ul style="list-style-type: none"> Prescribe lowest possible dose of short-acting opioid Do not prescribe ≥ 50 MME/day (for patients already on opioids) Do not prescribe ER/LA opioids 	<ul style="list-style-type: none"> Determine whether to continue, taper or stop
<ul style="list-style-type: none"> Schedule reassessment 1–4 weeks after initiation of treatment 	<ul style="list-style-type: none"> Evaluate benefits and harm of continued opioid treatment with patient every 3 months

Abbreviations: CBT, cognitive behavioral therapy; CDC, Centers for Disease Control and Prevention; ER/LA, extended release/long acting; H & P, history and physical examination; MME, morphine milligram equivalent; PEG, pain, enjoyment, general activity; PDMP, Prescription Drug Monitoring Program.

of CNCP [see CDC guidelines (<https://www.cdc.gov/drugoverdose/prescribing/guideline.html>), Table 1, and VA guidelines (<https://www.healthquality.va.gov/guidelines/pain/cot>)]. For example, acupuncture has shown benefit in the management of postoperative pain and in patients with tension headaches (37, 38). Similarly, cognitive behavioral therapy has shown benefit in the management of chronic low back pain (39). Comprehensive multidisciplinary pain management programs also show benefit in pain management and improved function in patients with CNCP (39), including low back pain (40). Unfortunately, such comprehensive programs are not covered by all insurance programs, do not have the rapid analgesic effects of most opioids, and require more active patient participation as a basis for their benefits.

The limited options currently available for the management of chronic pain conditions highlight the need for more research on the neurobiology of pain and the development of new

medications and therapeutics (33). Structural changes in the healthcare system are needed to support nonpharmacological comprehensive treatments for chronic pain conditions.

PHARMACOLOGY OF OPIOIDS UNDERLYING THEIR THERAPEUTIC AND ADVERSE EFFECTS

The analgesic effects of opioid medications are predominantly mediated through agonist effects at mu opioid receptors (MORs), although for some compounds, their binding to delta and kappa opioid receptors also contributes to analgesic effects (41). Brain regions that regulate pain perception (periaqueductal gray, thalamus, cingulate cortex, and insula) and pain-induced emotional responses (amygdala) contain high MOR levels (42). This observation explains why opioid medications can be so effective in the management of severe acute pain. However, MORs are also highly expressed in brain regions associated with the experience of pleasure or reward (ventral tegmental area, nucleus accumbens), which helps explain why opioid medications can be perceived as highly pleasurable or rewarding and can cause addiction (42). Finally, MORs are also located in the brainstem respiratory center (pre-Bötzinger complex), which explains why opioids are able to depress respiration and can result in overdose-induced death (43).

Opioid medications vary in their binding affinity and selectivity for the mu, kappa, and delta opioid receptors, and therefore they vary in potency (41). They also differ in their pharmacokinetics and bioavailability, which determine the rapidity and duration of action (41). Opioid pharmacokinetics also influence their reward and addiction potentials; both are stronger when an opioid is rapidly delivered into the brain (44). This is why most diverted opioid medications are snorted or injected, as these routes of administration produce the most direct and rapid stimulation of brain reward centers (45). Because of this, the FDA has encouraged abuse-deterrent formulations (ADFs) of opioid medications designed to prevent opioids from being snorted or injected (see sidebar titled Opioid Diversion and Mitigation Strategies) (46, 47). For example, the technology associated with certain ADFs ensures that if the drug is dissolved for intravenous injection, it will produce a viscous, gelatinous mixture, making it ineffectual for injection. In other ADFs, the active drug is released with an opioid antagonist that can precipitate withdrawal—but only if injected. Still other ADFs use an osmotic delivery system that releases the opioid at a slow rate. Barriers to wider use of ADFs include lack of insurance coverage and absence of generic formulations at prices competitive with those of other opioid analgesics. Also, although ADFs prevent administration by non-oral routes (injection, snorting), they can still be consumed at high doses orally and result in addiction and/or overdoses.

An important characteristic of all opioids is that both the direct physical and perceptual effects of an initial administration diminish significantly with repeated administrations, resulting in tolerance, physical dependence, and hyperalgesia (48). All these characteristics of repeated opioid administration are affected by the potency, route of administration, latency of onset, and analgesic duration of the particular opioid. The mechanisms responsible for tolerance, physical dependence, and hyperalgesia are not completely understood but involve molecular- and circuit-level adaptations as well as counter-adaptations in opioid receptors and their intracellular signaling cascades (49, 50). Some of these effects develop gradually, but some can emerge after even a few administrations (51). Tolerance, physical dependence, and hyperalgesia in general resolve relatively rapidly after opioid discontinuation, depending on the opioid drug, its dose, and treatment duration (52, 53); in contrast, the state of addiction (described below) does not resolve promptly. Each of these three characteristics of repeated opioid administration are described individually below.

Tolerance

The physical changes (respiration, gastric motility, pupillary constriction, etc.) and the perceptual changes (analgesia, calmness, somnolence, pleasure, etc.) produced by the initial dose of an opioid are progressively reduced with repeated administrations of the same opioid dose. The decreased sensitivity to most opioid effects typically necessitates increasingly larger doses to achieve the initial level of analgesia in pain management—or of reward if the opioid is being abused. Importantly, tolerance to opioids does not develop to the same extent or at the same rate across all physiological responses. In particular, tolerance to analgesia and reward appears to develop faster than tolerance to respiratory depression (54, 55). This makes management of CNCP with opioids particularly challenging because the dose escalation necessary to maintain analgesic efficacy can increase the risk of overdose and potentially the risk of addiction.

Physical Dependence

Repeated exposure to opioids also results in the development of physical dependence, which manifests as the emergence of withdrawal symptoms (e.g., piloerection, chills, insomnia, cramps, diarrhea, nausea, vomiting, aches, dysphoria, anxiety, irritability, seizures, etc.) upon abrupt discontinuation of the opioid analgesic. The severity of the withdrawal symptoms varies depending on the opioid medication (stronger withdrawal upon discontinuation of more potent and shorter-acting drugs) and the duration of treatment (stronger with chronic treatments) from being hardly noticeable to quite uncomfortable (52). Physical dependence is an expected response for patients treated with opioids over an extended period, but these symptoms typically resolve quickly (3–7 days). Withdrawal symptoms can also be averted by tapering the drug slowly.

Some physicians and patients erroneously equate “physical dependence” or “dependence” with “addiction.” Addiction, discussed below, is different from physical dependence because it occurs infrequently, develops much more gradually, and often requires chronic care to produce recovery. Nevertheless, physical dependence can lead to a desire to avoid withdrawal symptoms and a strong patient drive to maintain an opioid prescription.

Hyperalgesia

Repeated exposure to opioid analgesics can, in susceptible individuals, result in heightened pain sensitivity (hyperalgesia) (56), which can lead to inappropriate increases in opioid doses that further exacerbate the pain. This cycle explains why, in some patients, dose tapering or opioid discontinuation is associated with amelioration of pain. The development of opioid tolerance that necessitates increasing the dose facilitates the emergence of hyperalgesia. Consequently, when patients complain of pain, it is challenging for clinicians to decide whether to increase or decrease the opioid dose. There is limited evidence of the effectiveness of clinical strategies used to prevent hyperalgesia, which include switching to a different opioid and the use of nonopioid analgesics (pregabalin, propofol, or COX-2 inhibitors) (49).

MANAGING PUBLIC HEALTH RISKS ASSOCIATED WITH OPIOIDS: OVERDOSE AND ADDICTION

Although all opioids can produce respiratory depression and reward/euphoria—and thus carry the risks of overdose and abuse/addiction, respectively—two prescribing considerations are very important to highlight. First, because of differences in the metabolism and pharmacodynamics

of various opioids, there are pronounced differences in their individual risks for overdose and addiction. In general, high-potency opioids carry the highest risks of both overdose and addiction, and at initiation of therapy, long-acting opioids carry higher overdose risk than short-acting opioids (57). Second, the risks for overdose are not identical to the risks for addiction. Patients most vulnerable to respiratory depression and overdose may not necessarily be most vulnerable to developing addiction—and vice versa. This means that no simple change in prescribing behavior (e.g., choosing a short-acting versus long-acting opioid) or in patient selection can be expected to alleviate all risks while properly managing pain.

Opioid Overdose

Opioids induce respiratory depression by activating MORs on brainstem neurons that control breathing (43). However, fatal opioid-induced respiratory depression is preventable with correct administration/titrations, patient education, frequent monitoring, and timely intervention with Narcan. Although all opioids can lead to overdose in certain settings, research suggests that overdose risks increase with higher daily doses. Specifically, opioid doses greater than 80–100 MME are disproportionally associated with overdose-related hospital/emergency department admissions and deaths (57–59). Further, the use of long-acting opioids, such as methadone and oxycodone, has also been associated with increased risk for overdose (57). The combination of opioids with alcohol, or with sedative hypnotics such as benzodiazepines and antihistamines, increases the risk of overdose (60), so clinicians should thoroughly review what other drugs their patients are taking prior to prescribing an opioid medication.

Certain clinical characteristics are predictive of opioid overdose risk. First, a history of a prior overdose increases future overdose risk (61); second, a history of addiction to any substance (but particularly alcohol, benzodiazepines, or opioids) is a major risk factor (61). Third, health problems associated with respiratory compromise and/or concurrent prescription of any medication having respiratory-depressing effects, such as benzodiazepines or sedative hypnotics, impose increased risk for overdose (60). In addition, central sleep apnea is a risk factor for opioid overdose (62). Renal or hepatic dysfunction also increases risks for overdose because the clearance of many opioid drugs is impaired, leaving higher and longer-lasting drug levels in the blood (63). Finally, because some proportion of overdoses may be purposeful suicide attempts (64, 65), prior suicidal thoughts/attempts or a diagnosis of major depression are also markers for elevated risk of overdose.

Recommended strategies to prevent overdose include a thorough risk assessment as well as urine drug screens prior to prescribing or represcribing. The urine test ensures no presence of other drugs that may magnify opioid effects on respiration. The identification of these risks does not automatically rule out opioids as part of effective pain management, but the finding of any such risk factors will require (*a*) much greater patient (and family) education about overdose risks, (*b*) the use of an opioid treatment contract (see sidebar titled Opioid Diversion and Mitigation Strategies), (*c*) greater caution in prescribing high opioid doses or long-acting opioids, (*d*) more frequent clinical follow-up, and, potentially, (*e*) a prescription for and instruction in the use of naloxone, an opioid antagonist that can reverse opioid-induced overdoses. Indeed, expanding access to naloxone has been shown to significantly reduce opioid overdose fatalities (66).

Opioid Addiction

For many years, it was mistakenly believed that pain protected against development of addiction to opioid medications. It is now recognized that patients suffering from acute or chronic pain can potentially become addicted to their opioid pain medications. Moreover, preclinical studies have

shown that chronic pain can enhance the reinforcing effects of opioids in a dose-dependent manner (67–69). We again emphasize the distinction between opioid tolerance and physical dependence, on the one hand, and opioid addiction, on the other. Tolerance and physical dependence are a common and expected consequence of repeated opioid exposure, regardless of the type of opioid and the characteristics of the patient, and they develop rapidly. In contrast, addiction to opioid medications occurs far more rarely and develops much more slowly, usually after months of exposure (70).

Prevalence estimates of iatrogenic addiction vary substantially from <1% to >26% of patients prescribed (71). Much of this variability is due to confusion about the definition, particularly the equation of so-called “aberrant behaviors” or “withdrawal symptoms” and “dependence” with a true addiction diagnosis (44). Rates of carefully diagnosed addiction in published studies average <8% of cases, whereas prevalence of “misuse” and addiction-related “aberrant behaviors” have been reported in 15–26% of cases (21, 72, 73). A small (4–6%) but growing percentage of individuals addicted to prescription opioids transition to heroin, mainly because it is typically cheaper and more available (74).

The development of addiction to opioids (or to other drugs) is now understood to involve several neurobiological processes, including learning mechanisms that consolidate automatic behaviors in response to the drug and stimuli associated with it. Specifically, the pleasurable effects of opioids (and many other addictive drugs) are triggered by release of dopamine in the nucleus accumbens, a key reward region (75). This in turn results in a learned association between the drug administration and the experience of pleasure. This type of learning is referred to as conditioning. Additionally, conditioning to opioids can occur as a result of the relief of pain due to their inherent analgesic effects, and because they curb abstinence symptoms. Although in most patients physical dependence resolves with proper tapering and drug discontinuation, in some patients conditioning to the relief of withdrawal symptoms makes it hard to discontinue the medication. Repeated exposures to opioid medications will strengthen all of these learned associations and, with time and repetition, can result in the desire (craving) for the drug’s effects and the strong motivation to seek them (67).

As a result of conditioning, even mild pain or withdrawal symptoms can trigger the motivation for relief, leading to an unnecessarily early administration of the opioid and more frequent dosing. Repetition of drug exposures disrupts dopamine-modulated striatocortical pathways, thus impairing the function of prefrontal cortical regions necessary for self-regulation and control. Especially among those who are genetically or otherwise vulnerable, these neuroadaptations can lead to escalation of opioid use and the compulsive drug intake and impaired self-control that characterize addiction (70).

These symptoms reflect functional changes not only in brain circuits involved with reward, conditioning, and self-regulation but also in circuits that regulate stress reactivity—circuits that render the addicted person vulnerable to dysphoria, anxiety, and irritability (70). These changes persist even years after drug discontinuation (75), which is why addiction is considered a chronic disease of the brain and why its treatment requires continuous care. In the case of opioid addiction, there are effective medications (methadone, buprenorphine, and naltrexone) that significantly improve outcomes (i.e., reduce relapse, prevent overdoses, prevent HIV) (76). Despite the evidence of their therapeutic benefits, medications for the treatment of opioid-use disorders are underutilized (77).

Opioid addiction is etiologically complex and has a long latency of expression, which makes it difficult to predict in advance of the initial opioid prescription. However, research suggests that current or past substance-use disorders or psychiatric comorbidities (e.g., anxiety, depression) and/or a family history of these disorders are clinically relevant warning signs (78). Brain

development is also a vulnerability factor, and adolescents are at particularly high risk because of the enhanced neuroplasticity of their brains, which allows them to learn more rapidly but also leads them to condition to drugs more rapidly (79). Although there are no guidelines on the use of opioid medications in adolescents, their higher risk for addiction means opioids should be used only when other analgesics are not effective, and duration of opioid use should be kept as short as possible.

Risks for opioid addiction increase with the dose and duration of treatment. The Centers for Disease Control and Prevention (CDC) guidelines (<https://www.cdc.gov/drugoverdose/prescribing/guideline.html>) direct prescribers to reevaluate addiction risks regularly during the course of pain management and especially at the time of represcribing opioids (**Table 1**). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (80), addiction should be suspected when there is a pronounced craving for the drug, obsessive preoccupation with it, inability to refrain from using it, and escalation of drug taking. Again, the presence of risk factors does not rule out opioid analgesia but should alert clinicians to the necessity for more active education, monitoring, and management.

When elevated risks for addiction are identified, clinical interventions to halt progression toward addiction can be initiated within primary care settings. Responsible physicians should be prepared to make a referral for specialty addiction treatment when indicated. Although addiction is a serious chronic condition, recovery is an expectable result of comprehensive, continuing care and monitoring (81, 82). In particular, Weiss et al. (83) report that the use of medication-assisted therapy in managing opioid addiction among patients with co-occurring pain significantly improved outcomes. The findings from this study also highlighted the need for continuous treatment to avoid relapse and are consistent with the management of opioid addiction as a chronic condition.

SUMMARY AND CONCLUSIONS

Training of physicians in the proper prescription of opioid analgesics for both acute and chronic pain, as well as in the proper management of CNCP, is an important first step to control the negative public health consequences of overprescription of opioid medications. However, this will require concomitant structural changes in insurance reimbursement for the management of CNCP, along with the infrastructure needed to provide for multidisciplinary care as recommended by the CDC guidelines (**Table 1**). Additionally, investment in research and development of safer effective analgesics for CNCP is necessary to improve the outcomes in those suffering from chronic pain conditions.

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