ANNUAL REVIEWS

Annual Review of Medicine

Use and Misuse of Opioids in Chronic Pain

Nora Volkow,[1] Helene Benveniste,[2] and A. Thomas McLellan[3]

[1]National Institute on Drug Abuse, Rockville, Maryland 20852; email: nvolkow@nida.nih.gov

[2]Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut 06510; email: helene.benveniste@yale.edu

[3]Treatment Research Institute, Philadelphia, Pennsylvania 19106; email: tmclellan@tresearch.org

Annu. Rev. Med. 2018. 69:451–65

First published as a Review in Advance on October 13, 2017

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-011817-044739

Keywords

overdose, respiratory depression, addiction, diversion, hyperalgesia, dependence

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.

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 ($\geq$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
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	Evaluate risk of harm Observe patient for overdose symptoms Evaluate for overdose risk. If yes, taper dose
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)	Continue to ensure that nonopioid treatment is optimized
Assess baseline pain and function (dependent on diagnosis, e.g., PEG scale)	Reassess pain and function (e.g., PEG) and compare with baseline results
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	Check for opioid-use disorder—if suspected, consider early intervention
Check PDMP	Check PDMP
Check urine drug screen	Calculate MME/day and ensure that it is ≤90
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	Determine whether to continue, taper or stop
Schedule reassessment 1–4 weeks after initiation of treatment	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.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Merskey H, Bond M, Bonica J, et al., International Association for the Study of Pain, Subcommittee on Taxonomy. 1986. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle: Intl. Assoc. Stud. Pain
2. Andersson GB. 1999. Epidemiological features of chronic low-back pain. *Lancet* 354(9178):581–85
3. Institute of Medicine. 2011. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research*. Washington, DC: Natl. Acad. Press

4. Johannes CB, Le TK, Zhou X, et al. 2010. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J. Pain* 11(11):1230–39
5. Centers for Disease Control and Prevention. 2001. Prevalence of disabilities and associated health conditions among adults—United States, 1999. *Morb. Mortal. Wkly. Rep.* 50(7):120–25
6. Gureje O, Von Korff M, Simon GE, Gater R. 1998. Persistent pain and well-being: a World Health Organization Study in Primary Care. *JAMA* 280(2):147–51
7. Centers for Disease Control and Prevention. 2011. Vital signs: overdoses of prescription opioid relievers. United States 1999–2008. *Morb. Mortal. Wkly. Rep.* 60(43):1487–92
8. Chou R, Fanciullo GJ, Fine PG, et al. 2009. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J. Pain* 10(2):113–30
9. Allan L, Richarz U, Simpson K, Slappendel R. 2005. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. *Spine* 30(22):2484–90
10. Kalso E, Edwards JE, Moore RA, McQuay HJ. 2004. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 112(3):372–80
11. Moore RA, McQuay HJ. 2005. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res. Ther.* 7(5):R1046–51
12. Noble M, Tregear SJ, Treadwell JR, Schoelles K. 2008. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J. Pain Symptom Manag.* 35(2):214–28
13. Centers for Disease Control and Prevention. 2016. *Prescription opioid overdose data*. **https://www.cdc.gov/drugoverdose/data/overdose.html**
14. Knowlton A, Weir BW, Hazzard F, et al. 2013. EMS runs for suspected opioid overdose: implications for surveillance and prevention. *Prehosp. Emerg. Care* 17(3):317–29
15. Substance Abuse and Mental Health Services Administration. 2016. *Key substance use and mental health indicators in the United States: results from the 2015 National Survey on Drug Use and Health*. **https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf**
16. Deshpande A, Furlan A, Mailis-Gagnon A, et al. 2007. Opioids for chronic low-back pain. *Cochrane Database Syst. Rev.* 3:CD004959
17. Devulder J, Richarz U, Nataraja SH. 2005. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Curr. Med. Res. Opin.* 21(10):1555–68
18. Eisenberg E, McNicol ED, Carr DB. 2005. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA* 293(24):3043–52
19. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. 2006. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Can. Med. Assoc. J.* 174(11):1589–94
20. Hollingshead J, Duhmke RM, Cornblath DR. 2006. Tramadol for neuropathic pain. *Cochrane Database Syst. Rev.*3:CD003726
21. Martell BA, O'Connor PG, Kerns RD, et al. 2007. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann. Intern. Med.* 146(2):116–27
22. Sandoval JA, Furlan AD, Mailis-Gagnon A. 2005. Oral methadone for chronic noncancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness, and side effects. *Clin. J. Pain* 21(6):503–12
23. Lee BH, Park JO, Suk KS, et al. 2013. Pre-emptive and multi-modal perioperative pain management may improve quality of life in patients undergoing spinal surgery. *Pain Physician* 16(3):E217–26
24. Prabhakar A, Cefalu JN, Rowe JS, et al. 2017. Techniques to optimize multimodal analgesia in ambulatory surgery. *Curr. Pain Headache Rep.* 21(5):24
25. Varrassi G, Hanna M, Macheras G, et al. 2017. Multimodal analgesia in moderate-to-severe pain: a role for a new fixed combination of dexketoprofen and tramadol. *Curr. Med. Res. Opin.* 33:1165–73
26. Chou R, Turner JA, Devine EB, et al. 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann. Intern. Med.* 162(4):276–86

27. Hale ME, Fleischmann R, Salzman R, et al. 1999. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin. J. Pain* 15(3):179–83
28. Matsumoto AK, Babul N, Ahdieh H. 2005. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain Med.* 6(5):357–66
29. Nicholson B, Ross E, Sasaki J, Weil A. 2006. Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone HCl in moderate to severe nonmalignant pain. *Curr. Med. Res. Opin.* 22(8):1503–14
30. Niemann T, Madsen LG, Larsen S, Thorsgaard N. 2000. Opioid treatment of painful chronic pancreatitis. *Int. J. Pancreatol.* 27(3):235–40
31. Rauck RL, Bookbinder SA, Bunker TR, et al. 2007. A randomized, open-label, multicenter trial comparing once-a-day AVINZA (morphine sulfate extended-release capsules) versus twice-a-day OxyContin (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: improved physical functioning in the ACTION trial. *J. Opioid Manag.* 3(1):35–43
32. Rauck RL, Bookbinder SA, Bunker TR, et al. 2006. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J. Opioid Manag.* 2(3):155–66
33. Skolnick P, Volkow ND. 2016. Re-energizing the development of pain therapeutics in light of the opioid epidemic. *Neuron* 92(2):294–97
34. Finnerup NB, Attal N, Haroutounian S, et al. 2015. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 14(2):162–73
35. Derry S, Gill D, Phillips T, Moore RA. 2012. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst. Rev.* 3:CD008244
36. Arnold LM, Russell IJ, Diri EW, et al. 2008. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J. Pain* 9(9):792–805
37. Linde K, Allais G, Brinkhaus B, et al. 2016. Acupuncture for the prevention of tension-type headache. *Cochrane Database Syst. Rev.* 4:CD007587
38. Sun Y, Gan TJ, Dubose JW, Habib AS. 2008. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. *Br. J. Anaesth.* 101(2):151–60
39. Smeets RJ, Vlaeyen JW, Kester AD, Knottnerus JA. 2006. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. *J. Pain* 7(4):261–71
40. Boris-Karpel S. 2010. Policy and practice issues in pain management. In *Behavioral and Psychopharmacologic Pain Management*, ed. MH Ebert, RD Kerns, pp. 407–33. New York: Cambridge Univ. Press
41. Freye E. 2008. *Opioids in Medicine. A Comprehensive Review on the Mode of Action and the Use of Analgesics in Different Clinical Pain States*. Dordrecht, Neth.: Springer
42. Zubieta JK, Smith YR, Bueller JA, et al. 2001. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science* 293(5528):311–15
43. Pattinson KT. 2008. Opioids and the control of respiration. *Br. J. Anaesth.* 100(6):747–58
44. Volkow ND, McLellan AT. 2016. Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N. Engl. J. Med.* 374(13):1253–63
45. Butler SF, Black RA, Cassidy TA, et al. 2011. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduct. J.* 8:29
46. Mastropietro DJ, Omidian H. 2015. Abuse-deterrent formulations. Pt. 2: Commercial products and proprietary technologies. *Expert Opin. Pharmacother.* 16(3):305–23
47. Raffa RB, Pergolizzi JV Jr. 2010. Opioid formulations designed to resist/deter abuse. *Drugs* 70(13):1657–75
48. Bailey CP, Connor M. 2005. Opioids: cellular mechanisms of tolerance and physical dependence. *Curr. Opin. Pharmacol.* 5(1):60–68
49. Roeckel LA, Le Coz GM, Gaveriaux-Ruff C, Simonin F. 2016. Opioid-induced hyperalgesia: cellular and molecular mechanisms. *Neuroscience* 338:160–82

50. Williams JT, Christie MJ, Manzoni O. 2001. Cellular and synaptic adaptations mediating opioid dependence. *Physiol. Rev.* 81(1):299–343
51. Kornetsky C, Bain G. 1968. Morphine: single-dose tolerance. *Science* 162(3857):1011–12
52. Cortazzo MH, Fishman SM. 2008. Major opioids and chronic opioid therapy. In *Raj's Practical Management of Pain*, ed. HT Benzon, JP Rathmell, CL Wu, et al., pp. 597–611. Philadelphia: Mosby Elsevier. 4th ed.
53. Wax P, Ruha A-M. 2003. Withdrawal syndromes. Opioid withdrawal. In *Irwin and Rippe's Intensive Care Medicine*, ed. RS Irwin, JM Rippe, pp. 1707–16. Philadelphia: Lippincott Williams & Wilkins. 5th ed.
54. Ling GS, Paul D, Simantov R, Pasternak GW. 1989. Differential development of acute tolerance to analgesia, respiratory depression, gastrointestinal transit and hormone release in a morphine infusion model. *Life Sci.* 45(18):1627–36
55. Hill R, Lyndon A, Withey S, et al. 2016. Ethanol reversal of tolerance to the respiratory depressant effects of morphine. *Neuropsychopharmacology* 41(3):762–73
56. Arout CA, Edens E, Petrakis IL, Sofuoglu M. 2015. Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. *CNS Drugs* 29(6):465–86
57. Miller M, Barber CW, Leatherman S, et al. 2015. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern. Med.* 175(4):608–15
58. Centers for Disease Control and Prevention. 2013. Number of poisoning deaths involving opioid analgesics and other drugs or substances—United States, 1999–2010. *Morb. Mortal. Wkly. Rep.* 62:234
59. Von Korff M, Saunders K, Thomas Ray G, et al. 2008. De facto long-term opioid therapy for noncancer pain. *Clin. J. Pain* 24(6):521–27
60. Jones CM, Paulozzi LJ, Mack KA, Centers for Disease Control and Prevention. 2014. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths—United States, 2010. *Morb. Mortal. Wkly. Rep.* 63(40):881–85
61. Hall AJ, Logan JE, Toblin RL, et al. 2008. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 300(22):2613–20
62. Correa D, Farney RJ, Chung F, et al. 2015. Chronic opioid use and central sleep apnea: a review of the prevalence, mechanisms, and perioperative considerations. *Anesth. Analg.* 120(6):1273–85
63. Darke S, Kaye S, Duflou J. 2006. Systemic disease among cases of fatal opioid toxicity. *Addiction* 101(9):1299–305
64. Cheatle MD. 2011. Depression, chronic pain, and suicide by overdose: on the edge. *Pain Med.* 12(Suppl. 2):S43–S48
65. Madadi P, Persaud N. 2014. Suicide by means of opioid overdose in patients with chronic pain. *Curr. Pain Headache Rep.* 18(11):460
66. Wheeler E, Jones TS, Gilbert MK, Davidson PJ, Centers for Disease Control and Prevention. 2015. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *Morb. Mortal. Wkly. Rep.* 64(23):631–35
67. Ewan EE, Martin TJ. 2013. Analgesics as reinforcers with chronic pain: evidence from operant studies. *Neurosci. Lett.* 557(Pt. A):60–64
68. Hou YY, Cai YQ, Pan ZZ. 2015. Persistent pain maintains morphine-seeking behavior after morphine withdrawal through reduced MeCP2 repression of GluA1 in rat central amygdala. *J. Neurosci.* 35(8):3689–700
69. Zhang Z, Tao W, Hou YY, et al. 2014. Persistent pain facilitates response to morphine reward by down-regulation of central amygdala GABAergic function. *Neuropsychopharmacology* 39(9):2263–71
70. Volkow ND, Koob GF, McLellan AT. 2016. Neurobiologic advances from the brain disease model of addiction. *N. Engl. J. Med.* 374(4):363–71
71. Banta-Green CJ, Merrill JO, Doyle SR. 2009. Opioid use behaviors, mental health and pain—development of a typology of chronic pain patients. *Drug Alcohol Depend.* 104(1–2):34–42
72. Fishbain DA, Cole B, Lewis J, et al. 2008. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med.* 9(4):444–59
73. Vowles KE, McEntee ML, Julnes PS. 2015. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 156(4):569–76

74. Compton WM, Jones CM, Baldwin GT. 2016. Nonmedical prescription-opioid use and heroin use. *N. Engl. J. Med.* 374(13):1296
75. Volkow ND, Morales M. 2015. The brain on drugs: from reward to addiction. *Cell* 162(4):712–25
76. Woody GE. 2017. Advances in the treatment of opioid use disorders. *F1000Research* 6:87
77. Korthuis PT, McCarty D, Weimer M, et al. 2017. Primary care-based models for the treatment of opioid use disorder: a scoping review. *Ann. Intern. Med.*166(4):268–78
78. Mistry CJ, Bawor M, Desai D, et al. 2014. Genetics of opioid dependence: a review of the genetic contribution to opioid dependence. *Curr. Psychiatry Rev.* 10(2):156–67
79. Conrod PJ, Nikolaou K. 2016. Annual research review: on the developmental neuropsychology of substance use disorders. *J. Child Psychol. Psychiatry* 57(3):371–94
80. American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: Am. Psychiatr. Assoc. 5th ed.
81. McLellan AT, Skipper GS, Campbell M, DuPont RL. 2008. Five year outcomes in a cohort study of physicians treated for substance use disorders in the United States. *BMJ* 337:a2038
82. Office of the Surgeon General. 2016. *Facing Addiction in America. The Surgeon General's Report on Alcohol, Drugs, and Health*. Washington, DC: US Dep. Health Hum. Serv.
83. Weiss RD, Potter JS, Griffin ML, et al. 2015. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Depend.* 150:112–19
84. Manchikanti L, Helm S 2nd, Fellows B, et al. 2012. Opioid epidemic in the United States. *Pain Physician* 15(3 Suppl.):ES9–ES38
85. Abeles AM, Pillinger MH, Solitar BM, Abeles M. 2007. Narrative review: the pathophysiology of fibromyalgia. *Ann. Intern. Med.* 146(10):726–34
86. Keller A, Hayden J, Bombardier C, van Tulder M. 2007. Effect sizes of non-surgical treatments of non-specific low-back pain. *Eur. Spine J.* 16(11):1776–88
87. Geneen LJ, Moore RA, Clarke C, et al. 2017. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst. Rev.* 1:CD011279
88. Zhai J, Zhang L, Li M, et al. 2015. Epidural injection with or without steroid in managing chronic low-back and lower extremity pain: a meta-analysis of 10 randomized controlled trials. *Am. J. Ther.* 24(3):e259–69
89. Richette P, Latourte A, Frazier A. 2015. Safety and efficacy of paracetamol and NSAIDs in osteoarthritis: Which drug to recommend? *Expert Opin. Drug Saf.* 14(8):1259–68
90. Jones T, Moore T, Levy JL, et al. 2012. A comparison of various risk screening methods in predicting discharge from opioid treatment. *Clin. J. Pain* 28(2):93–100
91. Arnold RM, Han PK, Seltzer D. 2006. Opioid contracts in chronic nonmalignant pain management: objectives and uncertainties. *Am. J. Med.* 119(4):292–96
92. Fishman SM, Bandman TB, Edwards A, Borsook D. 1999. The opioid contract in the management of chronic pain. *J. Pain Symptom Manag.* 18(1):27–37
93. Tobin DG, Keough Forte K, Johnson McGee S. 2016. Breaking the pain contract: a better controlled-substance agreement for patients on chronic opioid therapy. *Cleve. Clin. J. Med.* 83(11):827–35
94. Delcher C, Wagenaar AC, Goldberger BA, et al. 2015. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. *Drug Alcohol Depend.*150:63–68
95. Paulozzi LJ, Kilbourne EM, Desai HA. 2011. Prescription drug monitoring programs and death rates from drug overdose. *Pain Med.* 12(5):747–54
96. Surratt HL, O'Grady C, Kurtz SP, et al. 2014. Reductions in prescription opioid diversion following recent legislative interventions in Florida. *Pharmacoepidemiol. Drug Saf.* 23(3):314–20
97. Coplan PM, Chilcoat HD, Butler SF, et al. 2016. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. *Clin. Pharmacol. Ther.* 100(3):275–86
98. O'Malley PG, Jackson JL, Santoro J, et al. 1999. Antidepressant therapy for unexplained symptoms and symptom syndromes. *J. Fam. Pract.* 48(12):980–90
99. Chou R, Peterson K. 2005. *Drug class review on skeletal muscle relaxants*. Final rep., Oregon Health Sci. Univ., Portland, OR

Annual Review of Medicine

Volume 69, 2018

Contents

Precision Medicine: Functional Advancements
Thomas Caskey 1

Refinement of the Affordable Care Act
Vivian Ho 19

Refinement of the Affordable Care Act: A Progressive Perspective
Olveen Carrasquillo and Michael Mueller 29

The Affordable Care Act: What's Next?
Mark McClellan and Mark Japinga 41

Atrial Fibrillation Ablation
Rakesh Latchamsetty and Fred Morady 53

Heart Failure with Preserved Ejection Fraction
James D. Gladden, Antoine H. Chaanine, and Margaret M. Redfield 65

Impact of the SPRINT Trial on Hypertension Management
Lama Ghazi and Suzanne Oparil 81

Common Cardiovascular Complications of Cancer Therapy: Epidemiology, Risk Prediction, and Prevention
Vivek Narayan and Bonnie Ky 97

New Therapeutic Approaches for Familial Hypercholesterolemia
Ezim Ajufo and Daniel J. Rader 113

PCSK9 Inhibitors: Mechanisms of Action, Metabolic Effects, and Clinical Outcomes
Connie N. Hess, Cecilia C. Low Wang, and William R. Hiatt 133

Risk Stratification for Sudden Cardiac Death After Myocardial Infarction
Jonathan W. Waks and Alfred E. Buxton 147

Understanding Peripartum Cardiomyopathy
Zoltan Arany 165

Updated Recommendations for Athletes with Heart Disease
Rachel Lampert and Douglas P. Zipes 177

Antibody–Drug Conjugates for Cancer Treatment
John M. Lambert and Anna Berkenblit 191

Modern Systemic Therapy for Metastatic Renal Cell Carcinoma of the Clear Cell Type
Mamta Parikh and Primo N. Lara Jr. 209

Circulating Tumor DNA: Measurement and Clinical Utility
Joshua Donaldson and Ben Ho Park 223

Computed Tomography Scanning for Early Detection of Lung Cancer
Francine L. Jacobson and Michael T. Jaklitsch 235

Evidence for Genetic Risk Contributing to Long-Term Adverse Treatment Effects in Childhood Cancer Survivors
Maria Monica Gramatges and Smita Bhatia 247

Lymphedema: Pathogenesis and Novel Therapies
Joseph H. Dayan, Catherine L. Ly, Raghu P. Kataru, and Babak J. Mehrara 263

Novel Radiotherapy Techniques for Breast Cancer
Julie A. Bradley and Nancy P. Mendenhall 277

Recombinant Poliovirus for Cancer Immunotherapy
Matthias Gromeier and Smita K. Nair 289

CD8 T Cell Exhaustion in Chronic Infection and Cancer: Opportunities for Interventions
Masao Hashimoto, Alice O. Kamphorst, Se Jin Im, Haydn T. Kissick, Rathi N. Pillai, Suresh S. Ramalingam, Koichi Araki, and Rafi Ahmed 301

Basket Studies: Redefining Clinical Trials in the Era of Genome-Driven Oncology
Jessica J. Tao, Alison M. Schram, and David M. Hyman 319

Molecular and Genomic Determinants of Response to Immune Checkpoint Inhibition in Cancer
Russell W. Jenkins, Rohit Thummalapalli, Jacob Carter, Israel Cañadas, and David A. Barbie 333

Targeting RAGE Signaling in Inflammatory Disease
Barry I. Hudson and Marc E. Lippman 349

New Concepts in the Treatment of Malignant Pleural Mesothelioma
Ori Wald and David J. Sugarbaker 365

New Molecular Diagnostic Approaches to Bacterial Infections and Antibacterial Resistance
Ephraim L. Tsalik, Robert A. Bonomo, and Vance G. Fowler Jr. 379

Zika, Chikungunya, and Other Emerging Vector-Borne Viral Diseases
Scott C. Weaver, Caroline Charlier, Nikos Vasilakis, and Marc Lecuit 395

New-Generation High-Potency and Designer Antibodies: Role in HIV-1 Treatment
Lucio Gama and Richard A. Koup 409

Novel Latency Reversal Agents for HIV-1 Cure
Adam M. Spivak and Vicente Planelles 421

Innate Immunity and Neurodegeneration
Larisa I. Labzin, Michael T. Heneka, and Eicke Latz 437

Use and Misuse of Opioids in Chronic Pain
Nora Volkow, Helene Benveniste, and A. Thomas McLellan 451

Measuring Patient-Reported Outcomes: Key Metrics in Reconstructive Surgery
Sophocles H. Voineskos, Jonas A. Nelson, Anne F. Klassen, and Andrea L. Pusic 467

What Metrics Accurately Reflect Surgical Quality?
Andrew M. Ibrahim and Justin B. Dimick 481

Indexes

Cumulative Index of Contributing Authors, Volumes 65–69 493

Cumulative Index of Article Titles, Volumes 65–69 497

Errata

An online log of corrections to *Annual Review of Medicine* articles may be found at http://www.annualreviews.org/errata/med