REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies

Nora D. Volkow, M.D., and A. Thomas McLellan, Ph.D.

Chronic pain not caused by cancer is among the most prevalent and debilitating medical conditions but also among the most controversial and complex to manage. The urgency of patients' needs, the demonstrated effectiveness of opioid analgesics for the management of acute pain, and the limited therapeutic alternatives for chronic pain have combined to produce an overreliance on opioid medications in the United States, with associated alarming increases in diversion, overdose, and addiction. Given the lack of clinical consensus and research-supported guidance, physicians understandably have questions about whether, when, and how to prescribe opioid analgesics for chronic pain without increasing public health risks. Here, we draw on recent research to address common misconceptions regarding the abuse-related risks of opioid analgesics and highlight strategies to minimize those risks.

From the National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD (N.D.V.); and the Treatment Research Institute, Philadelphia (A.T.M.). Address reprint requests to Dr. Volkow at the National Institute on Drug Abuse, National Institutes of Health, 6001 Executive Blvd., Bethesda, MD 20892, or at nvolkow@nida.nih.gov.

N Engl J Med 2016;374:1253-63.
DOI: 10.1056/NEJMra1507771

SOURCE OF THE OPIOID EPIDEMIC

More than 30% of Americans have some form of acute or chronic pain.[1,2] Among older adults, the prevalence of chronic pain is more than 40%.[2] Given the prevalence of chronic pain and its often disabling effects, it is not surprising that opioid analgesics are now the most commonly prescribed class of medications in the United States.[3] In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers.[4,5] Of these prescriptions, 65% were for short-term therapy (<3 weeks),[6] but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.[7] Although opioid analgesics rapidly relieve many types of acute pain and improve function, the benefits of opioids when prescribed for chronic pain are much more questionable.[8]

However, two major facts can no longer be questioned. First, opioid analgesics are widely diverted and improperly used, and the widespread use of the drugs has resulted in a national epidemic of opioid overdose deaths and addictions. More than a third (37%) of the 44,000 drug-overdose deaths that were reported in 2013 (the most recent year for which estimates are available) were attributable to pharmaceutical opioids; heroin accounted for an additional 19%. At the same time, there has been a parallel increase in the rate of opioid addiction, affecting approximately 2.5 million adults in 2014.[9] Second, the major source of diverted opioids is physician prescriptions.[10,11] For these reasons, physicians and medical associations have begun questioning prescribing practices for opioids, particularly as they relate to the management of chronic pain. Moreover, many physicians admit that they are not confident about how to prescribe opioids safely,[12] how to detect abuse or emerging addiction, or even how to discuss these issues with their patients.[13]

This review is not intended as clinical instruction in chronic pain management;

Table 1. Misconceptions Regarding Opioids and Addiction.*

Addiction is the same as physical dependence and tolerance. This misconception leads some clinicians to avoid prescribing opioids to patients who would benefit from them and many patients to be afraid of taking opioids as prescribed.

Addiction is simply a set of bad choices. This misconception contributes to the discrimination against patients with addiction and to the willful ignorance by many in the health care system about modern treatment methods. It also promotes mistrust of patients by clinicians and prevents affected patients from seeking help for their addiction.

Pain protects patients from addiction to their opioid medications. This misconception can lead to overconfidence and overprescribing among clinicians as well as failure to monitor and recognize addictive behaviors or to intervene properly when they emerge. Research has shown that patients who are prescribed opioid medications for pain can become addicted to them even when the drugs are taken as prescribed.

Only long-term use of certain opioids produces addiction. The misconception that addiction is simply the property of certain opioid drugs promotes overprescribing of certain types of opioids that may be as risky as types that are well known to be associated with addiction. An improved prescribing practice in the management of acute pain is a necessary step in the control of opioid diversion and overdose, since the overprescription of opioids for acute pain is the main source of drug diversion.

Only patients with certain characteristics are vulnerable to addiction. Certain conditions do increase the vulnerability to addiction. These include substance-use disorder (including abuse of alcohol, nicotine, and illicit drugs), developmental stage (adolescents are more vulnerable than adults), and certain mental illnesses (e.g., attention deficit–hyperactivity disorder and major depressive disorder). Although some patients are more vulnerable than others, no patient is immune to addiction.

Medication-assisted therapies are just substitutes for heroin or opioids. The use of opioid-agonist medications such as methadone and buprenorphine for opioid addiction has led to the misconception that such drugs are just substitutes for the opioid being abused. Although these medications are opioid agonists, their slower brain pharmacokinetics along with their more stable concentrations help to stabilize physiologic processes that are disrupted by intermittent abuse of opioids. The use of these drugs also protects against risks associated with opioid abuse while facilitating recovery.[18-20]

* These misconceptions were drawn directly from questions submitted by physicians to two major websites for pain-management specialists (the American Academy of Pain Management and the American Pain Society).

for that, we suggest recent clinical guidelines.[14-17] Instead, this review focuses on the pharmacologic properties of opioids that underlie both their therapeutic effects and their abuse-producing effects and on the ways in which these properties should inform us in correcting common clinical misconceptions that interfere with the proper prescription and monitoring of opioids in the management of chronic pain (Table 1).

WHY OPIOID MEDICATIONS ARE DIVERTED AND ABUSED

Opioid medications exert their analgesic effects predominantly by binding to mu-opioid receptors. Mu-opioid receptors are densely concentrated in brain regions that regulate pain perception (periaqueductal gray, thalamus, cingulate cortex, and insula), including pain-induced emotional responses (amygdala), and in brain reward regions (ventral tegmental area and nucleus accumbens) that underlie the perception of pleasure and well-being. This explains why opioid medications can produce both analgesia and euphoria. Mu-opioid receptors in other brain regions and in peripheral organs account for other common opioid effects. In particular, mu-opioid receptors in the brain stem are mainly responsible for the respiratory depression associated with opioid-overdose incidents and deaths[21,22] (Fig. 1).

Opioids not only directly activate these brain analgesia and reward regions but also concurrently mediate a learned association between receipt of the drug and the physiological and perceptual effects of the drug — a type of Pavlovian conditioning.[23] Repeated receipt of opioids strengthens these learned associations and over time becomes part of the desire (craving) for the drug's effects — analgesic or pleasurable.[24] For a patient in chronic pain, even mild levels of pain can trigger the learned associations between pain and drug relief, which are manifested as an urge for relief. Such a conditioned urge for relief from even mild pain can lead to the early, inappropriate use of an opioid outside prescribed scheduling.

Opioid medications vary with respect to their affinity and selectivity for the mu-opioid receptor, since some also bind to kappa- or delta-opioid receptors or to other neurotransmitter receptors and transporters. There is also considerable variation among the drugs with respect to their pharmacokinetics and bioavailability. When combined, these pharmacologic properties affect the rapidity of onset, potency, and duration of both the analgesic and pleasurable effects of opioids.

The effects of opioids — particularly their rewarding effects — are accentuated most when the drugs are delivered rapidly into the brain.[25] This is why diverted opioids that are taken for their rewarding effects are frequently injected. This also explains why the Food and Drug Administration has encouraged and approved abuse-deterrent formulations that are designed to prevent the injection of pharmaceutical opioids[26] (Table 2).

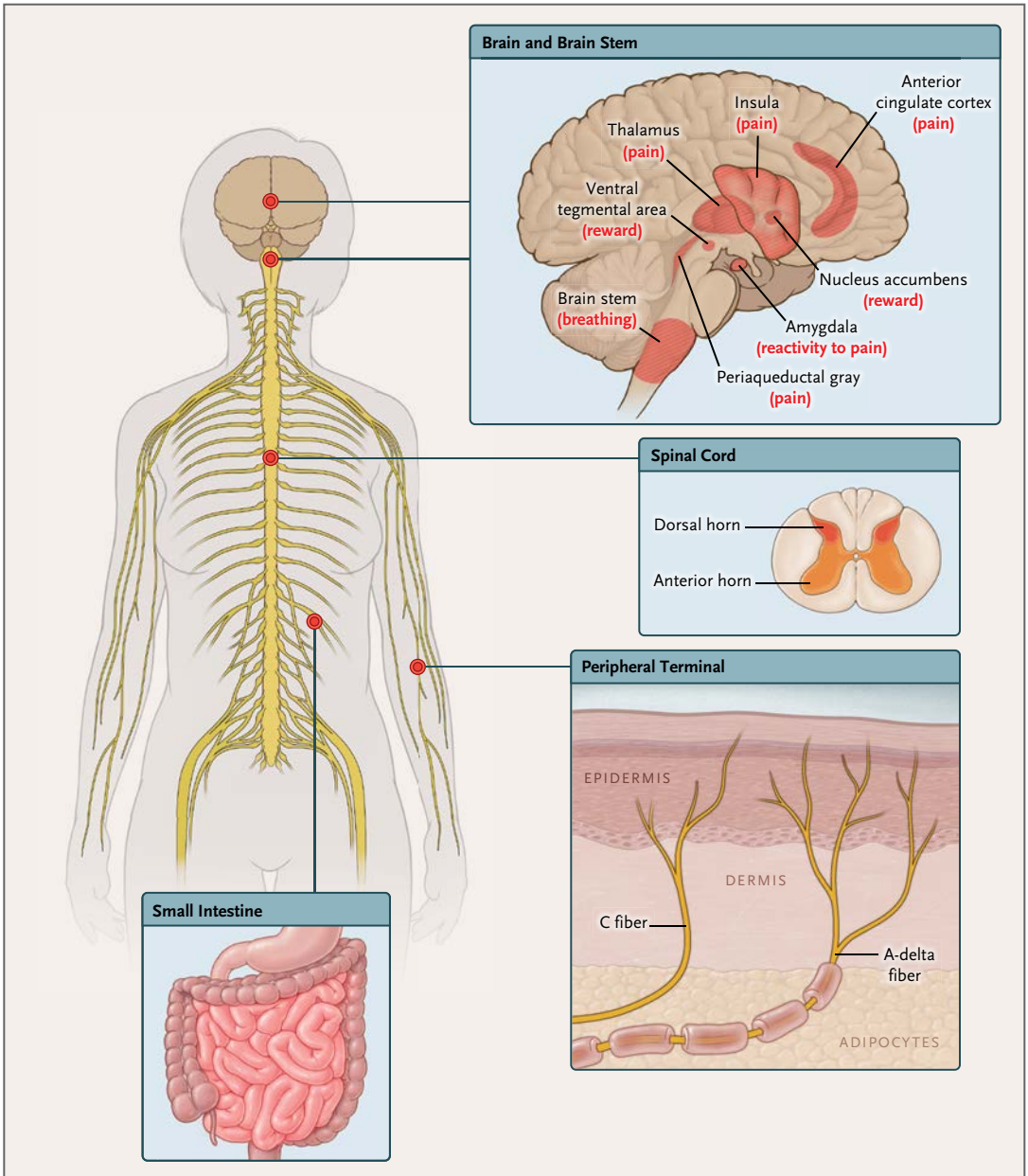

Figure 1. Location of Mu-Opioid Receptors.

Shown are the locations of mu-opioid receptors in the human brain, with high concentration in the thalamus, periaqueductal gray, insula, and anterior cingulate (regions involved with pain perception), in the ventral tegmental area and nucleus accumbens (regions involved with reward), in the amygdala (a region involved with emotional reactivity to pain), and in the brain stem (nuclei that regulate breathing). In the spinal cord, a high concentration of mu-opioid receptors is located in the dorsal horn. Mu-opioid receptors in peripheral terminals modulate the perception of pain, and receptors in the small intestine regulate gut motility.

OPIOID-INDUCED TOLERANCE AND PHYSICAL DEPENDENCE

There is lingering misunderstanding among some physicians about the important differences between physical dependence and addiction. The repeated administration of any opioid almost inevitably results in the development of tolerance and physical dependence. These predictable phenomena reflect counter-adaptations in opioid

Table 2. Formulations for Deterrence of Abuse.

When opioids are diverted because of their rewarding effects, they are typically taken at higher doses than were originally prescribed. In other cases, the pills are crushed so that the drug can be snorted, smoked, or injected. These routes of administration result in faster drug delivery into the brain, which in turn is associated with a rapid and more intense drug effect. Thus, strategies for abuse-deterrent formulations have been developed to minimize the likelihood that the opioids will be injected or snorted or taken at higher doses than prescribed.[27,28] These strategies include the following:

Combining the opioid agonist with an antagonist. Mixing the opioid with naloxone or naltrexone will interfere with the opioid effects if the drug is injected but not if it is taken orally or sublingually. Examples include Embeda (morphine sulfate plus naltrexone hydrochloride) and Targiniq ER (oxycodone plus naloxone).

Delivering the opioid in a form that cannot be crushed and extracted. Examples of such drug-delivery technologies include opioids approved by Food and Drug Administration (FDA) in abuse-deterrent formulations such as Hysingla (hydrocodone) and the new formulation of OxyContin (oxycodone), as well as opioids not approved as abuse-deterrent formulations, including Exalgo (hydromorphone), Nucynta ER (tapentadol), Opana ER (oxymorphone), Oxecta (oxycodone), and Xartemis (oxycodone and acetaminophen).

Combining the opioid with a substance that triggers an adverse response. If the drug is tampered with or used at a higher dose than indicated, such formulations are designed to produce adverse results. Examples include Lomotil (diphenoxylate hydrochloride plus atropine) and Acurox (oxycodone plus niacin).

Developing prodrugs that require enzymatic activation. Such formulations could provide a chemical barrier to in vitro conversion into the active opioid. There are currently no abuse-deterrent formulations approved by the FDA that use this strategy. Examples being developed include prodrugs for hydrocodone, oxycodone, and hydromorphone that require molecular cleavage by trypsin in the digestive system to release the parent opioid.

receptors and their intracellular signaling cascades.[29] These short-term results of repeated opioid administration resolve rapidly after discontinuation of the opioid (i.e., in a few days to a few weeks, depending on the duration of exposure, type of opioid, and dose). In contrast, addiction will occur in only a small percentage of patients exposed to opioids. Addiction develops slowly, usually only after months of exposure, but once addiction develops, it is a separate, often chronic medical illness that will typically not remit simply with opioid discontinuation and will carry a high risk of relapse for years without proper treatment. The molecular processes responsible for addiction are also distinct from those underlying tolerance and physical dependence, and so are the clinical consequences.

Tolerance leads to a decrease in opioid potency with repeated administration. Thus, prescribing opioids long-term for their analgesic effects will typically require increasingly higher doses in order to maintain the initial level of analgesia — up to 10 times the original dose.[30] Similarly, tolerance with respect to the rewarding effects of opioids leads to the characteristic dose escalation seen in opioid addiction, which can result in daily doses of up to 800 morphine milligram equivalents (MME, the conversion factor used to facilitate comparison of potency among opioids).[31]

Some opioid effects show tolerance after a single dose,[32] whereas for others, tolerance occurs more slowly.[29] In particular, tolerance to the analgesic and euphoric effects of opioids develops quickly, whereas tolerance to respiratory depression develops more slowly,[33,34] which explains why increases in dose by the prescriber or patient to maintain analgesia (or reward) can markedly increase the risk of overdose.

Physical dependence underlies the physiological adaptations that are responsible for the emergence of withdrawal symptoms on the abrupt discontinuation of opioids. Withdrawal symptoms (e.g., piloerection, chills, insomnia, diarrhea, nausea, vomiting, and muscle aches) vary appreciably in severity (from not noticeable to quite uncomfortable) and duration (1 to 14 days) on the basis of the type, dose, and duration of opioid prescribed.[35,36]

In the context of chronic pain management, the discontinuation of opioids requires dose tapering in order to prevent the emergence of such withdrawal symptoms. In some patients, the repeated use of opioids can also lead to hyperalgesia, which is a state of heightened pain sensitivity.[37,38] In the clinical context, hyperalgesia can lead to inappropriate increases in opioid doses, which further exacerbate rather than ameliorate pain.[39] In the case of hyperalgesia, dose tapering or tapering to discontinuation is a better pain-relief strategy.[40]

Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with preexisting vulnerabilities (Table 3). Older medical texts and several versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) either overemphasized the role of tolerance and physical dependence in the definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct

from those responsible for tolerance and physical dependence, in that they evolve much more slowly, last much longer, and disrupt multiple brain processes.[57]

Cardinal features of addiction include a pronounced craving for the drug, obsessive thinking about the drug, erosion of inhibitory control over efforts to refrain from drug use, and compulsive drug taking (DSM-5). These behavioral changes in turn are associated with structural and functional changes in the reward, inhibitory, and emotional circuits of the brain.[58,59] Clinical studies have also shown that the ability of opioids to produce addiction is genetically modulated, with heritability rates similar to those of diabetes, asthma, and hypertension.[60,61] For these reasons, we do not know the total dose or the duration of opioid administration that will reliably produce addiction. However, we do know that the risk of opioid addiction varies substantially among persons, that genetic vulnerability accounts for at least 35 to 40% of the risk associated with addiction,[62-64] and that adolescents are at increased risk because of the enhanced neuroplasticity of their brains and their underdeveloped frontal cortex, which is necessary for self-control.[52,62] Hence, in adolescents, the risks and benefits of prescribing opioids for pain management need to be even more carefully weighed than in adults.

In a person with an opioid addiction, discontinuation of the opioid will rapidly reverse the tolerance and physical dependence within days or a couple of weeks. In contrast, the underlying changes that are associated with addiction will persist for months and even years after the discontinuation of opioids.[65] This finding is clinically relevant, because after abstinence from opioids, addicted patients are particularly vulnerable to overdosing: their intense drive to take the drug persists, but the tolerance that previously protected them from overdosing is no longer present. These effects explain the high risk of overdosing among persons with an opioid addiction after they have been released from prison or from a detoxification program.[66,67]

Table 3. Factors Associated with the Risk of Opioid Overdose or Addiction.

Factor	Risk
Medication-related	
Daily dose >100 MME*	Overdose,[8] addiction[8]
Long-acting or extended-release formulation (e.g., methadone, fentanyl patch)	Overdose[14,41]
Combination of opioids with benzodiazepines	Overdose[42]
Long-term opioid use (>3 mo)†	Overdose,[43] addiction[44]
Period shortly after initiation of long-acting or extended-release formulation (<2 wk)	Overdose[45]
Patient-related	
Age >65 yr	Overdose[46]
Sleep-disordered breathing‡	Overdose[47]
Renal or hepatic impairment§	Overdose[48]
Depression	Overdose, addiction[49]
Substance-use disorder (including alcohol)	Overdose,[50] addiction[49]
History of overdose	Overdose[51]
Adolescence	Addiction[52]

* The risk of opioid overdose increases in a dose–response manner at opioid doses of more than 20 morphine milligram equivalents (MME).
† Although addiction is associated with long-term but not short-term opioid use, the prescription of a higher quantity of opioids than is needed for acute pain contributes substantially to the availability of opioids for diversion and abuse.
‡ Sleep-disordered breathing refers to conditions that manifest as abnormal breathing patterns during sleep and includes obstructive sleep apnea and central sleep apnea.[53]
§ Patients with these disorders are at increased risk because the disposition of various opioid drugs is affected by hepatic and renal impairments, which reduce drug clearance and increase bioavailability.[54-56]

MITIGATION STRATEGIES

The rewarding effects of opioids play a major role in the risks of opioid diversion, overdose, and addiction. However, the likelihood and severity of these risks are largely independent and governed by different factors. All these risks are present to some degree with all opioids and with all pain diagnoses. This means that no single or simple change in prescribing behavior can be expected to alleviate all risks while properly managing pain. For example, these risks cannot be mitigated simply by restricting prescribing to a particular type of opioid or by avoiding the prescription of opioids to a particular type of patient. However, there are common strategies that can help mitigate all risks, including limiting the prescribed opioid to the lowest effective dose for the shortest effective duration (for both acute and chronic pain) without compromising effective analgesia. Regular monitoring and reassessment provide opportunities to minimize the risks associated with long-term opioid use by allowing for the tapering and discontinuing of opioids among patients who are not receiving a

Table 4. Mitigation Strategies against Opioid Diversion and Misuse.

Several mitigation strategies for risk assessment of opioid misuse have been proposed.[74] These include the following:

Screening tools to identify patients with a substance-use disorder. Such tools include the Opioid Risk Tool; the Screener and Opioid Assessment for Patients with Pain (SOAPP), version 1.0; SOAPP-Revised; and the Brief Risk Interview; or the use of a simple question such as "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" since patients who score above a certain threshold (e.g., ≥1 to the sample question) may be at increased risk for opioid abuse.[75]

Use of data from the Prescription Drug Monitoring Program. Such data can be used to identify doctor shopping, which is frequently an indication of drug misuse or diversion.

Use of urine drug screening. Such screening, which can be performed before prescription of opioids and periodically as part of regular follow-up, can provide information on drug use not reported by patients and may help in identifying patients who are not taking their prescribed opioids and might be diverting them.

Doctor–patient agreement on adherence. Such personal contracts can help doctors in monitoring a patient's adherence to prescribed opioid medications.

However, a recent review of the evidence showed that only limited data are available regarding the efficacy of any of these strategies.[76]

clear benefit or among those who are engaging in practices that increase the risk of overdose (e.g., consumption of high doses of alcohol, concurrent use of benzodiazepines, and poor adherence to opiate medications).[68]

PREVENTING DRUG DIVERSION

The most common form of diversion is the transfer of opioid analgesics by patients who have received legitimately prescribed opioids to family members or friends who are usually trying to self-medicate a generic pain.[69] This type of diversion applies to prescriptions given for the management of either chronic or acute pain and would be best managed by educating patients on the dangers of sharing their medications and on the importance of safe storage and disposal.[70]

Approximately 7 to 10% of diversion occurs among patients who feign pain to acquire prescribed opioids,[71] usually with the goal of maintaining their addiction, and who will often attempt to acquire opioids from multiple physicians (doctor shopping).[71-73] Physicians have attempted to identify dissembling or addicted patients through screening instruments or through detection of so-called aberrant behaviors that are thought to be indicative of addiction (Table 4).[77] However, the most recent review of patient screening efforts showed no evidence that any scale or procedure was effective.[8] Risks of diversion through doctor shopping are best mitigated by the full participation of all prescribers in Prescription Drug Monitoring Programs (PDMPs). PDMPs are statewide electronic databases that collect information on prescription and dispensing of controlled prescription drugs (including opioid drugs) and were designed to monitor information pertaining to suspected abuse or diversion.[78] Although these data have been shown to help health care professionals reduce doctor shopping and overdoses,[79-81] their use by health care providers is inconsistent.[82-84] This in part reflects the fact that PDMPs are voluntary programs in many states. Although 25 states and the District of Columbia update their databases daily, as of this writing, only Oklahoma provides real-time reporting.[85] In addition, only 22 of 49 PDMPs share information across states.[86] Another obstacle is that access to PDMP data requires a computer that is separate from that used to access electronic health records. However, implementation and consistent use will be facilitated by rapid changes in laws to require mandatory consultation of a PDMP before prescribing, advances in electronic technologies to deliver PDMP information in real time, better integration of PDMPs with electronic health records, and access of PDMP data across state lines.[87]

REDUCING RISK OF OVERDOSE

The rate of death from opioid overdose has quadrupled during the past 15 years in the United States.[88] Researchers at the Centers for Disease Control and Prevention have estimated that 28,647 drug overdose deaths (61%) in 2014 in the United States involved some type of opioid, including heroin.[89] Even more prevalent are nonfatal opioid overdoses that require medical care in a hospital or emergency department. Such events have increased by a factor of six in the past 15 years.[90]

The contributing factors associated with overdose can be divided into those associated with the opioid itself (type, dose, potency, and duration of action) and those associated with critical features of the patient (Table 3). Although the use of any opioid can lead to overdose, research suggests that exposure to higher doses of all opioids increases the risk of overdose. Opioid doses of more than 100 MME[91,92] are disproportionately associated with overdose-related hospital

admissions and deaths[45] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The use of long-acting opioids, such as methadone and oxycodone, has also been associated with an increased risk of overdose.[45]

Several identifiable characteristics among patients have been reliably associated with an elevated risk of opioid overdose (Table 3). Included among these factors are a history of overdose,[51,93] a history of addiction to any substance (but particularly alcohol, benzodiazepines, or opioids),[93] and health problems associated with respiratory depression or concurrent prescription of any medication that has a depressive effect on the respiratory system, such as benzodiazepines and sedative hypnotics.[88] The presence of renal or hepatic dysfunction also increases the risk of overdose, since in patients with either of these conditions, the clearance of many opioid drugs is impaired, which leads to higher and longer-lasting drug levels in blood.[54,55] Finally, because some cases of overdose may be purposeful suicide attempts,[94,95] a history of suicidal thoughts or attempts and a diagnosis of major depression are also markers for an elevated risk of overdose.

Recommended mitigation strategies include an overdose risk assessment (Table 3) and urine drug screening before prescription or represcription of opioids (to verify absence of drugs of abuse). The identification of these risks does not automatically rule out opioids as part of effective pain management. However, these risks do indicate the needs for much greater education of the patient (and the patient's family) about overdose risks, the use of an opioid treatment agreement,[96] increased caution in prescribing high opioid doses or long-acting opioids, more frequent clinical follow-up, and, potentially, a prescription for and instruction in the use of naloxone, an opioid antagonist that can reverse an opioid-induced overdose. Indeed, expanding access to naloxone has been shown to significantly reduce the rate of death from opioid overdoses.[97]

MINIMIZING THE RISK OF ADDICTION

For many years, it was believed that pain protected against the development of addiction to opioid medications. However, epidemiologic studies of opioid addiction among patients in pain, as well as preclinical studies of addiction in animal models of chronic pain,[24,98,99] have disproved this belief. Although published estimates of iatrogenic addiction vary substantially from less than 1% to more than 26% of cases,[100] part of this variability is due to confusion in definition. Rates of carefully diagnosed addiction have averaged less than 8% in published studies, whereas rates of misuse, abuse, and addiction-related aberrant behaviors have ranged from 15 to 26%.[101-103] A small (estimated at 4%) but growing percentage of persons who are addicted to prescription opioids transition to heroin,[1] mainly because heroin is typically cheaper and in some instances easier to obtain than opioids.

Clinical efforts to prevent the emergence of addiction can be initiated in primary care settings. Assessment of addiction risks before opiates are prescribed is recommended as a mitigation strategy (Table 3). Emerging signs of addiction can be identified and managed through regular monitoring, including urine drug testing before every prescription is written, to assess for the presence of other opioids or drugs of abuse. Responsible physicians should be prepared to make a referral for specialty addiction treatment when indicated. Although addiction is a serious chronic condition, recovery is a predictable result of comprehensive, continuing care and monitoring.[104] In particular, the use of medication-assisted therapy in managing opioid addiction among patients with co-occurring pain significantly improves outcomes.[105]

On the basis of research and clinical evidence, the Department of Health and Human Services recently launched an initiative to reduce opioid overdoses and addiction that focuses on improving opioid prescribing practices to reduce opioid-use disorders and overdoses, expanding the use of naloxone to prevent overdoses, and extending the use of medication-assisted treatment to reduce opioid-use disorders and overdoses.[106]

CONCLUSIONS

It is no longer possible to simply continue previous practices with respect to the management of chronic pain. The associated risks of opioid diversion, overdose, and addiction demand change. Although there are no simple solutions, we recommend three practice and policy changes that can reduce abuse-related risks and improve the treatment of chronic pain.

Table 5. Alternative Treatments for Chronic Pain.*

Nonpharmacologic
Cognitive-behavioral therapy[109]
Exercise therapy[110-113]
Complementary medicine[114] (e.g., yoga, meditation, acupuncture)
Nonopioid analgesics
Acetaminophen
Nonselective nonsteroidal antiinflammatory drugs; recommended as first-line pharmacotherapy for osteoarthritis[115] and low back pain[116] in multiple guidelines
Cyclooxygenase-2 inhibitors
Anticonvulsants (gabapentin or pregabalin)†
Antidepressants (tricyclics and serotonin and norepinephrine reuptake inhibitors)†
Interventional and neural-stimulation therapies
Epidural injection; may provide short-term improvement for certain pain-associated conditions (e.g., lumbar radiculopathy)[1]
Brain, spinal cord, and nerve stimulation, including transcranial magnetic stimulation, transcranial direct current stimulation, electrical deep-brain stimulation, and stimulation devices for peripheral nerves or tissues[117-120]
Biofeedback
Electromyography to help patients learn to control muscle tension and electroencephalography to help patients learn to influence brain electrical signals in order to modulate pain; may be beneficial in treatment of headaches, some forms of chronic back pain, and other pain disorders[121]
Neurofeedback with the use of functional magnetic resonance imaging as a supplemental approach for chronic pain management[122]

* Evidence of efficacy varies for these strategies, and research is ongoing to assess their value in the management of chronic pain.
† Multiple guidelines recommend the use of antidepressant and anticonvulsant medications as either first-line or second-line treatment for neuropathic pain.[123]

INCREASED USE OF SCIENCE-SUPPORTED PRESCRIBING AND MANAGEMENT PRACTICES

The extended prescription of opioids (>8 weeks) for the treatment of chronic pain has questionable benefits for individual patients and presents substantial public health risks.[8] The risks of overdose and addiction from this prescribing practice — both among patients with chronic pain and the public at large — increase with higher doses (>100 MME), longer duration of prescribing, and perhaps the use of long-acting opioids. Despite these facts, a Medicaid study showed that more than 50% of opioid prescriptions were for doses higher than 90 MME and for periods of more than 6 months.[107] Better results can be obtained by using the most contemporary guidelines for pain management.[14]

INCREASED MEDICAL SCHOOL TRAINING ON PAIN AND ADDICTION

Very few medical schools offer adequate training in pain management, and still fewer offer even one course in addiction. The result is that even experienced clinicians are unsure about how to deal with fundamental and omnipresent clinical issues in their practices. Many motivated, well-intentioned physicians do not know whether to prescribe opioids for pain management and, if so, which ones and for how long. Still fewer understand the pharmacologic or clinical relationships among tolerance, physical dependence, and addiction.[108] This education is particularly critical for primary care practitioners, who prescribe more than 70% of opioid analgesics.

INCREASED RESEARCH ON PAIN

At a recent workshop at the National Institutes of Health on the role of opioids in the treatment of chronic pain, attendants recommended several areas of research that are needed for improved clinical practice guidelines. These areas included how to differentiate the unique properties of acute and chronic pain and how to describe the process by which acute pain transitions into chronic pain.[8] Discovery-oriented research was also recommended to identify new, potent nonopioid analgesics and other pain-treatment strategies (Table 5). Access to biomarkers of pain and analgesia that take advantage of neuroimaging technologies or genetic analyses would accelerate the development of new medications and allow for more personalized clinical interventions for pain management.

Dr. McLellan reports receiving fees for serving on the board of directors of Indivior Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education and research. Washington, DC: National Academies Press, 2011.
2. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. J Pain 2010;11:1230-9.
3. Centers for Disease Control and Prevention. FastStats. Therapeutic drug use. 2014 (http://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm).
4. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med 2015;49:409-13.

5. National Institute on Drug Abuse. The latest prescription trends for controlled prescription drugs. 2015 (http://www.drugabuse.gov/news-events/meetings-events/2015/09/latest-prescription-trends-controlled-prescription-drugs).
6. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. JAMA 2011;305:1299-301.
7. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009;18:1166-75.
8. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik J. The effectiveness and risks of long-term opioid treatment of chronic pain: Evidence Report/Technology Assessment. Rockville, MD: Agency for Healthcare Research and Quality, 2014. No. 218 (AHRQ publication no. 14-E005-EF).
9. Results from the 2013 National Survey on Drug Use and Health: summary of national findings. NSDUH series H-48. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014. HHS publication no. (SMA) 14-4863.
10. Compton WM, Boyle M, Wargo E. Prescription opioid abuse: problems and responses. Prev Med 2015;80:5-9.
11. Shei A, Rice JB, Kirson NY, et al. Sources of prescription opioids among diagnosed opioid abusers. Curr Med Res Opin 2015;31:779-84.
12. Keller CE, Ashrafioun L, Neumann AM, Van Klein J, Fox CH, Blondell RD. Practices, perceptions, and concerns of primary care physicians about opioid dependence associated with the treatment of chronic pain. Subst Abus 2012;33:103-13.
13. Hagemeier NE, Gray JA, Pack RP. Prescription drug abuse: a comparison of prescriber and pharmacist perspectives. Subst Use Misuse 2013;48:761-8.
14. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med 2014; 160:38-47.
15. American Pain Society, American Academy of Pain Medicine Opioids Guidelines Panel. Guideline for the use of chronic opioid therapy in chronic noncancer pain: evidence review (http://americanpainsociety.org/uploads/education/guidelines/chronic-opioid-therapy-cncp.pdf).
16. The Management of Opioid Therapy for Chronic Pain Working Group. VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. Washington, DC: Department of Veterans Affairs, Department of Defense, 2010.
17. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1): 1-49.
18. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-171.
19. Kreek MJ. Methadone-related opioid agonist pharmacotherapy for heroin addiction: history, recent molecular and neurochemical research and future in mainstream medicine. Ann N Y Acad Sci 2000;909:186-216.
20. Nutt DJ. Considerations on the role of buprenorphine in recovery from heroin addiction from a UK perspective. J Psychopharmacol 2015;29:43-9.
21. Akil H, Watson SJ, Young E, Lewis ME, Khachaturian H, Walker JM. Endogenous opioids: biology and function. Annu Rev Neurosci 1984;7:223-55.
22. Pattinson KT. Opioids and the control of respiration. Br J Anaesth 2008;100:747-58.
23. Miguez G, Laborda MA, Miller RR. Classical conditioning and pain: conditioned analgesia and hyperalgesia. Acta Psychol (Amst) 2014;145:10-20.
24. Ewan EE, Martin TJ. Analgesics as reinforcers with chronic pain: evidence from operant studies. Neurosci Lett 2013; 557 Pt A:60-4.
25. Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. Harm Reduct J 2011;8:29.
26. Department of Health and Human Services. Guidance for industry: abuse-deterrent opioids: evaluation and labeling. April 2015 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf).
27. Mastropietro DJ, Omidian H. Abuse-deterrent formulations: part 2: commercial products and proprietary technologies. Expert Opin Pharmacother 2015;16: 305-23.
28. Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs 2010;70:1657-75.
29. Williams JT, Christie MJ, Manzoni O. Cellular and synaptic adaptations mediating opioid dependence. Physiol Rev 2001; 81:299-343.
30. Buntin-Mushock C, Phillip L, Moriyama K, Palmer PP. Age-dependent opioid escalation in chronic pain patients. Anesth Analg 2005;100:1740-5.
31. Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. Addiction 2005;100: 1101-9.
32. Kornetsky C, Bain G. Morphine: single-dose tolerance. Science 1968;162:1011-2.
33. Hill R, Lyndon A, Withey S, et al. Ethanol reversal of tolerance to the respiratory depressant effects of morphine. Neuropsychopharmacology 2016;41:762-73.
34. Ling GS, Paul D, Simantov R, Pasternak GW. Differential development of acute tolerance to analgesia, respiratory depression, gastrointestinal transit and hormone release in a morphine infusion model. Life Sci 1989;45:1627-36.
35. Argoff C, Turk D, Benzon H. Major opioids and chronic opioid therapy. Philadelphia: Mosby Elsevier, 2008.
36. Wax P, Ruha A. Withdrawal syndromes: opioid withdrawal. In: Irwin RS, Rippe JM, eds. Irwin & Rippe's intensive care medicine. Philadelphia: Lippincott Williams & Wilkins, 2003.
37. Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. CNS Drugs 2015; 29:465-86.
38. Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. Front Pharmacol 2014;5:108.
39. Chen L, Sein M, Vo T, et al. Clinical interpretation of opioid tolerance versus opioid-induced hyperalgesia. J Opioid Manag 2014;10:383-93.
40. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011;14:145-61.
41. Lev R, Petro S, Lee A, et al. Methadone related deaths compared to all prescription related deaths. Forensic Sci Int 2015; 257:347-52.
42. Paulozzi LJ. Prescription drug overdoses: a review. J Safety Res 2012;43:283-9.
43. Paulozzi LJ, Zhang K, Jones CM, Mack KA. Risk of adverse health outcomes with increasing duration and regularity of opioid therapy. J Am Board Fam Med 2014; 27:329-38.
44. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain 2014;30:557-64.
45. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Intern Med 2015;175:608-15.
46. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 2008;8: 287-313.
47. Cheatle MD, Webster LR. Opioid therapy and sleep disorders: risks and mitigation strategies. Pain Med 2015;16:Suppl 1: S22-6.

48. Beaudoin FL, Merchant RC, Janicki A, McKaig DM, Babu KM. Preventing iatrogenic overdose: a review of in-emergency department opioid-related adverse drug events and medication errors. Ann Emerg Med 2015;65:423-31.
49. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction 2010;105:1776-82.
50. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths — United States, 2010. MMWR Morb Mortal Wkly Rep 2014;63:881-5.
51. Hasegawa K, Brown DF, Tsugawa Y, Camargo CA Jr. Epidemiology of emergency department visits for opioid overdose: a population-based study. Mayo Clin Proc 2014;89:462-71.
52. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry 2003;160:1041-52.
53. Callop N, Cassel DK. Snoring and sleep disordered breathing. In: Lee-Chiong T Jr, Sateia M, Carskadon M, eds. Sleep medicine. Philadelphia: Hanley & Belfus, 2002.
54. Bosilkovska M, Walder B, Besson M, Daali Y, Desmeules J. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. Drugs 2012;72:1645-69.
55. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64:1147-61.
56. Mercadante S, Arcuri E. Opioids and renal function. J Pain 2004;5:2-19.
57. Christie MJ. Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. Br J Pharmacol 2008;154:384-96.
58. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005;162:1403-13.
59. Volkow ND, Morales M. The brain on drugs: from reward to addiction. Cell 2015;162:712-25.
60. Uhl GR, Drgo T. Genetic contributions to individual differences in vulnerability to addiction and abilities to quit. In: Verster JC, Brady K, Galanter M, Conrad P, eds. Drug abuse and addiction in medical illness: causes, consequences and treatment. New York: Springer, 2012:95-105.
61. Hall FS, Drgonova J, Jain S, Uhl GR. Implications of genome wide association studies for addiction: are our a priori assumptions all wrong? Pharmacol Ther 2013;140:267-79.
62. Mistry CJ, Bawor M, Desai D, Marsh DC, Samaan Z. Genetics of opioid dependence: a review of the genetic contribution to opioid dependence. Curr Psychiatry Rev 2014;10:156-67.
63. Tsuang MT, Lyons MJ, Meyer JM, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry 1998;55:967-72.
64. Xian H, Chantarujikapong SI, Scherrer JF, et al. Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. Drug Alcohol Depend 2000;61:95-102.
65. Public policy statement on rapid and ultra rapid opioid detoxification. Chevy Chase, MD: American Society of Addiction Medicine, 2005.
66. Seaman SR, Brettle RP, Gore SM. Mortality from overdose among injecting drug users recently released from prison: database linkage study. BMJ 1998;316:426-8.
67. Wines JD Jr, Saitz R, Horton NJ, Lloyd-Travaglini C, Samet JH. Overdose after detoxification: a prospective study. Drug Alcohol Depend 2007;89:161-9.
68. Common elements in guidelines for prescribing opioids for chronic pain. Atlanta: Centers for Disease Control and Prevention, 2015.
69. McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. Addict Behav 2007;32:562-75.
70. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10:113-30.
71. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. JAMA Intern Med 2014;174:796-801.
72. Manchikanti L, Helm S II, Fellows B, et al. Opioid epidemic in the United States. Pain Physician 2012;15:Suppl:ES9-38.
73. McDonald DC, Carlson KE. Estimating the prevalence of opioid diversion by "doctor shoppers" in the United States. PLoS One 2013;8(7):e69241.
74. Chou R, Turner JA, Devine EB, et al. 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 2015;162:276-86.
75. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. Arch Intern Med 2010;170:1155-60.
76. Executive summary. Pathways to prevention workshop: the role of opioids in the treatment of chronic pain. Bethesda, MD: National Institutes of Health, September 2014 (https://prevention.nih.gov/docs/programs/p2p/ODPPainPanelStatementFinal_10-02-14.pdf).
77. Jones T, Moore T, Levy JL, et al. A comparison of various risk screening methods in predicting discharge from opioid treatment. Clin J Pain 2012;28:93-100.
78. Wang J, Christo PJ. The influence of prescription monitoring programs on chronic pain management. Pain Physician 2009;12:507-15.
79. Delcher C, Wagenaar AC, Goldberger BA, Cook RL, Maldonado-Molina MM. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. Drug Alcohol Depend 2015;150:63-8.
80. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. Pain Med 2011;12:747-54.
81. Surratt HL, O'Grady C, Kurtz SP, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. Pharmacoepidemiol Drug Saf 2014;23:314-20.
82. Deyo RA, Irvine JM, Hallvik SE, et al. Leading a horse to water: facilitating registration and use of a prescription drug monitoring program. Clin J Pain 2014 November 7 (Epub ahead of print).
83. Hildebran C, Cohen DJ, Irvine JM, et al. How clinicians use prescription drug monitoring programs: a qualitative inquiry. Pain Med 2014;15:1179-86.
84. Irvine JM, Hallvik SE, Hildebran C, Marino M, Beran T, Deyo RA. Who uses a prescription drug monitoring program and how? Insights from a statewide survey of Oregon clinicians. J Pain 2014;15:747-55.
85. Prescription Drug Monitoring Program Training and Technical Assistance Center. State profiles reports. Waltham, MA: Brandeis University (http://www.pdmpassist.org/pdf/Collection_Frequency.pdf).
86. Model Alcohol and Other Drug Abuse Policy and Planning Coordination Act. Charlottesville, VA: National Alliance for Model State Drug Laws (http://www.namsdl.org/library/).
87. Perrone J, Nelson LS. Medication reconciliation for controlled substances — an "ideal" prescription-drug monitoring program. N Engl J Med 2012;366:2341-3.
88. Calcaterra S, Glanz J, Binswanger IA. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. Drug Alcohol Depend 2013;131:263-70.
89. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths — United States, 2000–2014. MMWR Morb Mortal Wkly Rep 2016;64:1378-82.
90. Knowlton A, Weir BW, Hazzard F, et al. EMS runs for suspected opioid over-

dose: implications for surveillance and prevention. Prehosp Emerg Care 2013;17:317-29.
91. Centers for Medicare and Medicaid Services. Opioid morphine equivalent conversion factors (https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf).
92. Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain 2008;24:521-7.
93. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 2008;300:2613-20.
94. Madadi P, Persaud N. Suicide by means of opioid overdose in patients with chronic pain. Curr Pain Headache Rep 2014;18:460.
95. Cheatle MD. Depression, chronic pain, and suicide by overdose: on the edge. Pain Med 2011;12:Suppl 2:S43-8.
96. Starrels JL, Wu B, Peyser D, et al. It made my life a little easier: primary care providers' beliefs and attitudes about using opioid treatment agreements. J Opioid Manag 2014;10:95-102.
97. Opioid overdose prevention programs providing naloxone to laypersons — United States, 2014. MMWR Morb Mortal Wkly Rep 2015;64:631-5.
98. Hou YY, Cai YQ, Pan ZZ. Persistent pain maintains morphine-seeking behavior after morphine withdrawal through reduced MeCP2 repression of GluA1 in rat central amygdala. J Neurosci 2015;35:3689-700.
99. Zhang Z, Tao W, Hou YY, Wang W, Lu YG, Pan ZZ. Persistent pain facilitates response to morphine reward by downregulation of central amygdala GABAergic function. Neuropsychopharmacology 2014;39:2263-71.
100. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain — development of a typology of chronic pain patients. Drug Alcohol Depend 2009;104:34-42.
101. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. 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 2008;9:444-59.
102. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med 2007;146:116-27.
103. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 2015;156:569-76.
104. McLellan AT, Skipper GS, Campbell M, DuPont RL. Five year outcomes in a cohort study of physicians treated for substance use disorders in the United States. BMJ 2008;337:a2038.
105. Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. Drug Alcohol Depend 2015;150:112-9.
106. Office of the Assistant Secretary for Planning and Evaluation. Opioid abuse in the U.S. and HHS actions to address opioid-drug related overdoses and deaths. Washington, DC: Department of Health and Human Services, March 26, 2015 (https://aspe.hhs.gov/basic-report/opioid-abuse-us-and-hhs-actions-address-opioid-drug-related-overdoses-and-deaths).
107. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. Pain 2008;138:440-9.
108. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. JAMA 2011;305:1346-7.
109. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2012;11:CD007407.
110. Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2007;4:CD003786.
111. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1:CD004376.
112. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014;4:CD007912.
113. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. Cochrane Database Syst Rev 2005;3:CD000335.
114. Simpson CA. Complementary medicine in chronic pain treatment. Phys Med Rehabil Clin N Am 2015;26:321-47.
115. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64:669-81.
116. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med 2007;147:478-91.
117. Boccard SG, Pereira EA, Aziz TZ. Deep brain stimulation for chronic pain. J Clin Neurosci 2015;22:1537-43.
118. Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. Neuromodulation 2015;18:24-32.
119. Moreno-Duarte I, Morse LR, Alam M, Bikson M, Zafonte R, Fregni F. Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury. Neuroimage 2014;85:1003-13.
120. Treister R, Lang M, Klein MM, Oaklander AL. Non-invasive transcranial magnetic stimulation (TMS) of the motor cortex for neuropathic pain — at the tipping point? Rambam Maimonides Med J 2013;4(4):e0023.
121. Glombiewski JA, Bernardy K, Hauser W. Efficacy of EMG- and EEG-biofeedback in fibromyalgia syndrome: a meta-analysis and a systematic review of randomized controlled trials. Evid Based Complement Alternat Med 2013;2013:962741.
122. Guan M, Ma L, Li L, et al. Self-regulation of brain activity in patients with postherpetic neuralgia: a double-blind randomized study using real-time FMRI neurofeedback. PLoS One 2015;10(4):e0123675.
123. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009;122:Suppl:S22-32.