Chapter 23
Pain and Addiction

Ivanshu N. Jain, Adriane dela Cruz, and Sidarth Wakhlu

Substance Abuse Terminology

To understand treatment strategies for patients with addictive disorders, physicians need to understand substance abuse terminology. The terms physical dependence and tolerance have been inappropriately used in the past to define addiction. Physical dependence is defined as development of a physical withdrawal syndrome following abrupt dose reduction. Its presence does not indicate the presence of addiction, but rather it is a normal physiologic response to chronic use of opioid analgesics. Tolerance likewise is not indicative of addiction but can be defined as a normal physiologic response at the cellular level to the chronic use of opioid analgesics that results in requiring more drug to elicit the same physiologic response. Physical dependence and tolerance to opioids are normal and predictable physiologic events that are the natural consequences of chronic opioid use. Their development can be expected after extended use of these drugs (several days to a few weeks) and does not imply the presence of addiction.

Addiction Addiction is a chronic brain disease characterized by chronic, relapsing disorder that has been characterized by (a) a compulsion to seek and take drugs, (b) loss of control over drug intake, and (c) emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome when access to the drug is prevented [1]. The occasional, limited, recreational use of a drug is clinically distinct from the loss of control over drug intake and the emergence of compulsive drug-seeking behavior that characterize addiction.

I. N. Jain (✉) · A. dela Cruz · S. Wakhlu
Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Sidarth.Wakhlu@UTSouthwestern.edu

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Tolerance Tolerance is defined as a decrease in pharmacologic response following repeated or prolonged drug administration. It is either innate or acquired. Innate tolerance due to pharmacogenetic makeup of the patient and is usually evident after the initial dose administration. Acquired is due to repeated exposure to opioids and is considered due to pharmacokinetic, pharmacodynamic, or learned mechanism [2]. Pharmacokinetic mechanism occurs as a consequence of drug being inducer or inhibitor of metabolic enzyme or transporter system. Diminishing response of intrinsic opioid receptor system over time results in pharmacokinetic tolerance. Finally, learned tolerance is either behavioral or conditioned learning and is attributed to learning, either behavioral or conditioned. Behavioral tolerance occurs when an individual learns to function despite repeated exposure to a drug. Eventually incremental amount of opioid is needed to produce pleasure comparable to that provided in previous drug use episodes.

Dependence and Withdrawals Altered physiological state characterized by manifestation of opposite physiological effects of drug when it is removed. It is intricately associated with tolerance, and the adaptive changes associated with tolerance predominate and become profoundly nonadaptive when drug levels drop below certain threshold. In human brain, the locus ceruleus (LC) is responsible for release of noradrenaline (NA), which in turn is responsible for effects including breathing, wakefulness, blood pressure modulation, and alertness. Opioid intake via linking to mu receptors on LC suppresses the release of NA and resultant decrease in alertness, respiratory drive, and blood pressure. With time, this suppression is offset by the augmented activity of LC brain cells. When opioids are not present, this enhanced activity is postulated to be causative of withdrawal symptoms like agitation, anxiety, muscle cramps, and diarrhea due to excess of NA [3].

Hyperalgesia It is defined as a state of nociceptive receptor sensitization caused by exposure to opioids. The condition is described as a paradoxical increase in pain perception after prolonged use of opioids whereby patient becomes more sensitive to certain pain stimuli.

Allodynia Allodynia is pain due to a normally innocuous stimulus that does not usually provoke pain. Stimuli could be mechanical or thermal in nature. It is caused by peripheral and central sensitization of receptors, which is described later in this chapter.

Understanding Stages of Pain

As per Task force on taxonomy of the International Association for the Study of Pain (IASP), pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Below mentioned are physiological processes involved in generation of pain and sensitization.

Stage 1: Nociception It is the ability to feel pain, caused by a noxious stimulus (mechanical, chemical, or thermal); if strong enough or repetitive, it causes depolarization of nociceptors or afferent pain fibers (A-delta and C fibers). This message is transmitted from peripheral tissue to dorsal horn of spinal cord and then to second-order neurons, which send the message rostral to the lateral and medial thalamus. Thalamic projections to somatosensory cortex convey localization and intensity information, resulting in the conscious perception of pain, and limbic system is responsible for the emotional aspect of pain [1].

Stage 2: Peripheral Sensitization Intense and prolonged tissue damage, inflammation, and cell death cause stimulation of the previously dormant nociceptors, which may spontaneously discharge and become more sensitive to peripheral stimulation. Inflammatory mediators like bradykinin, prostaglandins, serotonin, and histamine activate secondary messenger system, which causes phosphorylation of receptors, influx of calcium ions, and release of chemicals like substance P, which furthers continued release of inflammatory mediators. Several receptors including opioid, γ-aminobutyric acid (GABA), bradykinin, histamine, serotonin, and capsaicin have also been identified on the surface membrane of sensory axons [1].

It is important to understand the consequences of peripheral sensitization at this point. Now spontaneous or subthreshold would be enough to cause depolarization of primary afferent pain fibers, leading to firing without a noxious stimulus present. This codes for an increase in the pain signal to the spinal cord and brain, causing increased pain from a given noxious stimulus—this is termed *hyperalgesia*. Also, normal light touch or stimulus (that does not usually provoke pain) would cause pain due to peripheral sensitization and is termed as *allodynia*.

Stage 3: Central Sensitization Persistent noxious stimulus enhances the responsiveness of neurons in dorsal horn, and it is independent of primary afferent drive which leads to secondary hyperalgesia and allodynia. Multitude of neurotransmitters are responsible for this process, including excitatory amino acid glutamate, substance P, calcitonin gene–related peptide, vasoactive intestinal peptide, somatostatin, and others. Inhibition of this nociceptive circuit is mediated by 5-hydroxytryptamine, GABA, and glycine as well as neuropeptides such as enkephalins. This manifests as chronic pain states generally characterized as maldynia or bad pain. Maldynia is exaggerated intensity of pain, which is spontaneously triggered by innocuous physical or physiological stimuli. It is still not clear whether genetic, cognitive, or emotional factors play a role in stage 3 pain [1].

Neuroscientific View of Addiction

Addiction to opioids and pain share the common neurochemicals and neuropathways in the brain. Addiction affects mood, behavior, physical health, and social aspects of life, and it worsens the quality and perception of pain. Their relationship is pretty complex as opioids are attributed to cause both analgesia and hyperalgesia.

Brain abnormalities resulting from chronic use of opioids are underlying causes of opioid dependence (the need to keep taking drugs to avoid a withdrawal syndrome) and addiction (intense drug craving and compulsive use). Brain changes that produce dependence appear to resolve after detoxification, within days or weeks after opioid use is stopped. The changes that produce addiction, however, are more wide-ranging, complex, and long-lasting [3]. Interaction of environmental effects can occur between stress, the social context of initial opiate use, and psychological conditioning, and a genetic predilection in the form of brain pathways that were abnormal even before the first dose of opioid was taken. These interactions can precipitate craving that might steer future relapse months or years after the individual is no longer opioid dependent [1].

Standard diagnostic criteria for opioid or other drug and alcohol use rely on physiologic responses to chronic drug use, behavioral consequences as loss of control over drug use, and significant disruptions in social and occupational functioning.

Active addiction goes through three stages: (1) binging and/or intoxication, (2) withdrawal/negative affect, and (3) preoccupation/anticipation. It has been hypothesized that both classical conditionings and operant conditioning play a significant role in addiction. In addition, social psychology (self-regulation failure framework) and neurobiology (counteradaptation and sensitization frameworks) can be superimposed on the stages of the addiction cycle. These processes are enmeshed with each other and intensify with time, leading to a pathological state called *addiction* [1].

Agonist activity at mu-opioid receptors (MOR) provides a robust and unfailing analgesia and, hence, makes them the most powerful and effective treatment for pain known to man. Opioid analgesics bind to mu-opioid receptor (MOR) on opioid neurons. One such area of the brain that gets activated by opioids is the mesolimbic (midbrain) reward system. This system generates signals in a part of the brain called the ventral tegmental area (VTA) that results in the release of the chemical dopamine (DA) in another part of the brain, the nucleus accumbens. DA is the same neurotransmitter that rewards people with feelings of pleasure when they engage in activities that promote basic life functions, such as eating and sex. When opioids, prescribed for pain, activate these reward processes in the absence of significant pain, they can motivate repeated use of the drug simply for pleasure. Amygdala and other areas of the brain create a lasting record or memory that associates these good feelings with the circumstances and environment in which they occur. This positive conditioning often leads to the craving for drugs when the user reencounters those persons, places, or things, and they drive users to seek out more drugs in spite of many obstacles [3].

When without drug, the addicted individual suffers from negative symptoms such as anhedonia, prolonged dysphoria, and irritability, which have been attributed to dopamine-depleted state in the reward pathways and also to recruitment of the brain stress or antireward systems. The antireward system triggers the release of chemicals like corticotropin-releasing factor (CRF), norepinephrine, and dynorphin, producing aversive or stress-like states. Simultaneously, within the positive

motivational circuits of the ventral striatum and extended amygdala, reward function is weakened, resulting in a powerful negative reinforcement that perpetuates a compulsive drug-seeking behavior and long-term addiction. Evidently, the negative feeling states associated with drug withdrawal can augment the subjective discomfort associated with pain. Interestingly, as many research studies have pointed out, anticipation of pain and pain in itself can create a negative emotional state that can intensify the negative emotional state of addiction and vice versa. In order to maintain a homeostatic level of reward system activity, antireward systems are recruited to counteract drug effects, which become stronger with each exposure of the drug and extinguish more slowly than the original response. Opioid addiction worsens over time, is influenced by environmental factors, and leaves a neuroadaptive trace that allows rapid "readdiction" even after detoxification and years of abstinence [1].

Long-term opioid use may have a drug opposite response such that the euphoria associated with acute opioid effects is lost and a negative mood response prevails, much like the drug opposite effect with opioid-induced hyperalgesia [4], which is further discussed in the next section.

Risks and Associations

Depression is a risk factor for prolonged opioid treatment for postoperative pain. The self-loathing factors (past failure, guilty feelings, self-dislike, self-criticalness, suicidal thoughts, and worthlessness) on the Beck Depression Inventory-II are most predictive of continuing opioid use [5]. In a 16-week trial of opioids for chronic back pain, higher doses of opioids were associated with improved anxiety, depression, irritability, and pain [6]. Results of another study show that opioids may contribute to depression in patients with chronic pain who are treated with opioids [7], which contradicts the above findings. Opioids have a dose-dependent association with depression, and duration of opioid exposure is correlated with depression. Opioids are associated with antidepressant failure, and opioid dose reduction is associated with mood improvement.

Opioid overdoses increased 30% from July 2016 through September 2017 in 52 areas in 45 states [8]. Fifty-one percent of opioid prescriptions are prescribed to patients with depression or other mental health condition [9]. Suicide is a significant factor in the death rate associated with the opioid overdose epidemic [10]. Prescription pain reliever overdose deaths among women increased more than 400% from 1999 to 2010, compared to 237% among men. Forty-eight thousand women died of prescription pain reliever overdoses between 1999 and 2010. It has been discovered that overdose and suicide have shared risk factors [11]. In one study, suicidal ideation is reported in 36.5% of patients with chronic pain who were treated with opioids. 16.4% and 2.5% had made an attempt in their lifetime and within the past 12 months, respectively [12]. The risk of suicide by any means and by overdose with opioids is dose dependent. The risk doubles from doses

below 20 MME and above 100 MME [13]. An alarming study reported that more than half of overdoses occur within 90 days of starting opioids and one third of overdoses occur on doses below 50 mg of morphine equivalents per day [14]. It is important to note that as per one of the study, the overdose death risk is highest among patients with substance use disorder compared to the groups of patients with cancer pain, chronic pain, and acute pain [15]. It is all the more important that the physicians should be trained in assessing opioid use during every visit if patients are on controlled substance prescription. On the contrary, physicians are not trained to screen patients who are high risk for opioid treatment. One study showed that physicians identified only 5% of patients as high risk in a population of exclusively high-risk patients [16]. One study showed that 91% of patients were prescribed opioids again after a nonfatal overdose [17]. Finally, in a study of chronic opioid users, it was found that most patients on chronic opioid therapy began opioids after surgery or trauma [18].

Current State of Opioid Addiction

The misuse of and addiction to opioids including prescription pain relievers, heroin, and synthetic opioids such as fentanyl are a serious national crisis that affects public health as well as social and economic welfare [19]. The current opioid epidemic has had three waves. The first wave began with increased prescribing of opioids for chronic pain in 1990s followed by a heroin wave in 2010, which resulted in increased overdose deaths [20]. The third wave has been illicit fentanyl use started in 2013, which again spiked overdose death numbers. According to the 2015 National Survey on Drug Use and Health (NSDUH) [21], the majority of people (87.2%) who take prescription pain relievers do not misuse them and the most common reason for their last misuse was to relieve physical pain (63.4%) [22]. It has been noted that 4.2% of the total US population misuses opioids and 92% of the people who misuse are taking prescription opioids either legally or illegally [23]. The risk of opioid-use disorder is dose dependent and increases by a factor of 15 on low doses, 29 on moderate doses, and 122 on high doses [24]. Every day, more than 130 people in the United States die after overdosing on opioids [25]. According to another study published in *Journal of International Association for the Study of Pain*, roughly 21–29% of patients who are prescribed opioids for chronic pain misuse them [26]. Between 8% and 12% of patients develop an opioid use disorder [27–29]. An estimated 4–6% of patients who misuse prescription opioids transition to heroin [27–29]. Paradoxically, patients who should not be prescribed opioids are more likely to be prescribed opioids. Patients with a history of substance use disorder have been able to obtain prescription opioids during the opioid epidemic [30]. It has been shown that longer duration of initial opioid therapy prescribed is associated with an increased risk of long-term opioid use [31].

Management Strategies

Medication-assisted treatment (MAT) for opioid-use disorders is the use of medications in combination with behavioral therapies. There are several FDA-approved medications for opioid-use disorders, that is, methadone, buprenorphine/naloxone combination, buprenorphine monotherapy, and naltrexone, both as oral tablets and monthly injectable preparation. MAT has been shown to improve patient survival with decrease in or complete elimination of illicit opioid use, increase retention in treatment, increase patients' ability to gain and maintain employment, and improve birth outcomes among pregnant women addicted to opioids.

Methadone is a full mu agonist, NMDA antagonist, and an SNRI. It usually exists as a racemic mixture of its two enantiomers, S-methadone (d-isomer) and R-methadone (l-isomer). The d-isomer (S-methadone) antagonizes the NMDA receptor and prevents 5-hydroxytryptamine and norepinephrine reuptake, while the l-isomer has significant opioid agonist properties.

Methadone's oral bioavailability is approximately 80% (range 40–99%), which is three-fold that of oral morphine. Methadone appears to be extensively distributed throughout peripheral tissues, perhaps related to its high degree of lipophilicity. Likewise, its volume of distribution has been reported to be high. Given its large volume of distribution (mean 6.7 l/kg), the plasma elimination of methadone usually occurs slowly (mean half-life 26.8 hours). Methadone's slow clearance from the body (mean 3.1 ml/min/kg) provides the rationale for dosing it once per day in methadone maintenance therapy, thereby preventing the onset of opioid withdrawal syndrome for 24 hours or more. Unfortunately, prolonged pain relief is not similarly sustained. Methadone undergoes a biphasic pattern of elimination, with an alpha-elimination phase persisting 8–12 hours and a beta-elimination phase ranging from 30 to 60 hours. The alpha-elimination phase equates to the period of analgesia that typically does not exceed 6–8 hours. Initial dosing for analgesia may need to be frequent, because steady-state kinetics are required for reaching the biphasic profile. Although the 30- to 60-hour beta-elimination phase can prevent withdrawal symptoms, it is usually subanalgesic. Thus, the biphasic elimination probably accounts for the dissociation between the brief analgesic effect and the longer plasma-elimination half-life.

This likely underscores why methadone is prescribed every 24 hours for opioid maintenance therapy and every 4–8 hours for analgesia. Unlike morphine and other opioids whose breakdown products are associated with neurotoxicity, methadone has no known active metabolites.

Buprenorphine is a semisynthetic highly lipophilic opioid that is derived from the baine, one of the alkaloids in raw opium. Buprenorphine is a partial agonist at the mu-opioid receptor and a weak antagonist at the kappa opioid receptor. Being a partial mu agonist, buprenorphine has a higher safety profile compared to full mu agonists, especially with regard to respiratory depression. Buprenorphine has higher affinity at the mu-opioid receptor as compared to other full mu agonists.

The only exception being fentanyl. Induction with buprenorphine requires a patient to be in at least mild opioid withdrawal, premature induction with the full mu agonist still occupied to the receptor site will cause a precipitated withdrawal. Because of its high affinity, it offers an "opioid blockade" to other opioids that typically lasts in excess of 24 hours. Oral bioavailability of buprenorphine is low because of extensive first-pass hepatic metabolism. The administration of buprenorphine by the sublingual route allows for bypassing of the first-pass hepatic metabolism, thus increasing bioavailability. Buprenorphine is well-absorbed sublingually, with 60–70% of the bioavailability of intravenous doses. It is highly bound to plasma proteins and is inactivated by enzymatic transformation via N-dealkylation and conjugation. Buprenorphine is mainly metabolized to inactive conjugated metabolites (80–90%), but norbuprenorphine, a product of N-dealkylation by the cytochrome P450 3A4 enzyme, has more potent respiratory depressive effects than the parent drug. The combination product contains buprenorphine and naloxone in a 4:1 ratio. The tablets are available in 8 and 2 mg and the films in 12, 8, 4, and 2 mg. The naloxone is poorly absorbed sublingually and may precipitate a withdrawal if the combination product is administered parenterally, thus reducing the risk of misuse and diversion. The monoproduct contains buprenorphine only. In 2016, FDA approved the first buprenorphine subdermal implant and the next year the monthly buprenorphine injection, which is administered subcutaneously in the abdomen.

A clinical challenge is how to treat pain in a patient who is on MAT for their opioid use disorder. Pain can be categorized as anticipated acute pain, unanticipated acute pain, acute pain superimposed on chronic pain, and chronic pain.

Anticipated Acute Pain

Painful procedures such as elective surgery can be anticipated. This is an opportunity for both the patient and the treatment team to plan and optimize the management of this acute pain [32]. If the elective procedure is associated with mild-to-moderate pain, the dose of methadone or buprenorphine can be titrated upward with TID dosing. If the postoperative pain is severe, patients can be maintained on the same dose of methadone/buprenorphine and a high-potency full mu agonist like hydrocodone or hydromorphone can be added to the treatment regimen until the acute pain resolves.

Unanticipated Acute Pain

Some patients may experience pain secondary to trauma such as a motor vehicle accident or other acute, surgical emergencies. If the pain is mild-to-moderate pain, the dose of methadone or buprenorphine can be titrated upward with TID dosing. If the pain is severe, patients can be maintained on the same dose of

methadone/buprenorphine and a high-potency full mu agonist like hydrocodone or hydromorphone can be added to the treatment regimen until the acute pain resolves.

Acute Pain Superimposed on Chronic Pain

If patients with a history of opioid-use disorder and chronic pain syndrome on methadone or buprenorphine TID dosing experience acute pain, a high-potency full mu agonist like hydrocodone or hydromorphone can be added to the treatment regimen until the acute pain resolves.

Chronic Pain

Patients on MAT who are taking methadone or buprenorphine once daily dosing and who experience chronic pain may divide the total dose and take it on a TID dosing schedule. Then, like any other chronic pain patient, the dose of methadone or buprenorphine is titrated to effect.

References

1. Ries RK. The ASAM principles of addiction medicine: Wolters Kluwer. Retrieved from https://wolterskluwer.vitalsource.com/#/books/9781469883816/.
2. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. AAPS J. 2008;10(4):537–51. https://doi.org/10.1208/s12248-008-9056-1.
3. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002;1(1):13–20.
4. White JM. Pleasure into pain: the consequences of long-term opioid use. Addict Behav. 2004;29:1311–24.
5. Hah JM, Mackey S, Barelka PL, et al. Self-loathing aspects of depression reduce postoperative opioid cessation rate. Pain Med. 2014;15(6):954–64.
6. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain: a randomized prospective study. Spine. 1998;23(23):2591–600.
7. Mazereeuw G, Sullivan MD, Juurlink DN. Depression in chronic pain might opioids be responsible? Pain. 2018;159(11):2142–5. https://doi.org/10.1097/j.pain.0000000000001305.
8. Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital signs: trends in emergency department visits for suspected opioid overdoses–United States, July 2016–September 2017: Centers for Disease Control and Prevention.
9. Davis MA, Lin LA, Liu H, Sites BD. Prescription opioid use among adults with mental health disorders in the United States. J Am Board Fam Med. 2017;30:407. https://doi.org/10.3122/jabfm.2017.04.170112.
10. Oquendo MA, Volkow ND. Suicide: a silent contributor to opioid-overdose deaths. N Engl J Med. 2018;378:1567–9. https://doi.org/10.1056/NEJMp1801417.
11. Bohnert ASB, Ilgen MA. Understanding links among opioid use, overdose, and suicide. N Engl J Med. 2019;380:71–9. https://doi.org/10.1056/NEJMra1802148.

12. Campbell G, Bruno R, Darke S, Shand F, Hall W, Farrell M, Degenhardt L. Prevalence and correlates of suicidal thoughts and suicide attempts in people prescribed pharmaceutical opioids for chronic pain. Clin J Pain. 2016;32(4):292–301. https://doi.org/10.1097/AJP.0000000000000283.
13. Ilgen MA, Bohnert AS, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid dose and risk of suicide. Pain. 2016;157(5):1079–84.
14. Fulton-Kehoe D, Garg RK, Turner JA, Bauer AM, Sullivan MD, Wickizer TM, Franklin GM. Opioid poisonings and opioid adverse effects in workers in Washington state. Am J Ind Med. 2013;56:1452–62. https://doi.org/10.1002/ajim.22266.
15. Bohnert ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305(13):1315–21. https://doi.org/10.1001/jama.2011.370.
16. Brown J, Setnik B, Lee K, Wase L, Roland CL, Cleveland JM, Siegel S, Katz N. Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. J Opioid Manag. 2011;7:467–83.
17. Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF. Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. Ann Intern Med. 2016;164:1–9. https://doi.org/10.7326/M15-0038.
18. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The initiation of chronic opioids: a survey of chronic pain patients. J Pain. 2017;18(4):360–5, ISSN 1526–5900. https://doi.org/10.1016/j.jpain.2016.11.001.
19. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care. 2016;54(10):901–6. https://doi.org/10.1097/MLR.0000000000000625.
20. Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public Health tragedy. Am J Public Health. 2009;99(2):221–7. https://doi.org/10.2105/AJPH.2007.131714.
21. Center for Behavioral Health Statistics and Quality (CBHSQ). National survey on drug use and health: detailed tables. Rockville: Substance Abuse and Mental Health Services Administration; 2017. p. 2018.
22. Lipari RN, Williams M, Van Horn SL. Why do adults misuse prescription drugs? Source The CBHSQ Report. Rockville: Substance Abuse and Mental Health Services Administration (US); 2013–2017 Jul 27.
23. Ashburn MA, Fleisher LA. Increasing evidence for the limited role of opioids to treat chronic noncancer pain. JAMA. 2018;320(23):2427–8. https://doi.org/10.1001/jama.2018.19327.
24. 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(7):557–64.
25. CDC WONDER. CDC/NCHS, National Vital Statistics System, Mortality. Atlanta: US Department of Health and Human Services, CDC; 2018. https://wonder.cdc.gov.
26. 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(4):569–76. https://doi.org/10.1097/01.j.pain.0000460357.01998.f1.
27. Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Rev. August 2013.
28. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiat. 2014;71(7):821–6. https://doi.org/10.1001/jamapsychiatry.2014.366.
29. Carlson RG, Nahhas RW, Martins SS, Daniulaityte R. Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: a natural history study. Drug Alcohol Depend. 2016;160:127–34. https://doi.org/10.1016/j.drugalcdep.2015.12.026.
30. Quinn PD, Hur K, Chang Z, Krebs EE, Bair MJ, Scott EL, Rickert ME, Gibbons RD, Kroenke K, D'Onofrio BM. Incident and long-term opioid therapy among patients with psychi-

atric conditions and medications: a national study of commercial health care claims. Pain. 2017;158(1):140–8.
31. Deyo RA, Hallvik SE, Hildebran C, et al. J Gen Intern Med. 2017;32:21. https://doi.org/10.1007/s11606-016-3810-3.
32. Morone NE, Weiner DK. Pain as the fifth vital sign: exposing the vital need for pain education. Clin Ther. 2013;35(11):1728–32. https://doi.org/10.1016/j.clinthera.2013.10.001.