Chapter 10
Opioids: History, Pathophysiology, and Stewardship for Hospitalists

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History and Evolution of the Opioid Epidemic in America

History is studied to understand the error of our ways. It is learned so as not to repeat the same mistakes leading us down on a path of failure. Had we paid closer attention to the initial use of opioids and their effects, we may have avoided battling one of the biggest epidemics in America.

The first opioid epidemic in America dates to more than 100 years ago, during the Civil War era. It was not called an epidemic, but rather attributed as "soldier's disease," cluing its unique distinguishment to those that fought in the Civil War. Physicians at the time coined the term "morphinism" to explain the liberal injection of morphine in the sick and in wounded soldiers leading to their dependency for years to come [1]. Morphine clinics increased in number to attend the wounds and long-term care of those injured, while opium, morphine's oral counterpart, began to be universally given in all cases of wounds, gangrene, diarrhea, and dysentery. Opium was even given for malaria in conjunction with quinine due to its analgesic and tranquilizing properties; it was praised as the one medicine "which the Creator himself seems to prescribe" [1]. By 1900, America had approximately 200,000 opioid addicts.

Given the strong, long-term dependency on morphine and opium, there was a race to create an alkaloid derivative that provided the same analgesic effects with significantly less addiction. In 1895, Bayer Corp in Germany commercialized an

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alkaloid derivative synthesized by British scientist C. R. Wright; it was advertised as being more potent than morphine and without the addictive side-effect drug. The group also believed that it would make a valuable contribution to medicine as a cough suppressant in those with severe lung disease. Their conviction of its potential "heroic" deeds led to the drug's name "heroin" [2]. Heroin was marketed heavily in America. However, it was ultimately proven ineffective as a cough suppressant and less potent in its analgesic effects than morphine. It also saw no therapeutic success in patients with advanced lung disease. Due to the absence of any legislation to restrict the production and consumerism of heroin, the question of addiction became a widespread public concern in America [2]. Heroin was readily available and accessible over the counter, and it could be sniffed, smoked, swallowed, and even injected due to its higher water solubility compared to morphine salts, facilitating its street use. Using the anti-German sentiment prevalent at the time, Congress successfully passed the Harrison Narcotics Tax Act in 1914, introducing federal narcotic controls and making heroin illegal in America [2].

Despite the Harrison Narcotics Tax Act, the use of heroin among Americans did not slow down. The global-scale World Wars allowed soldiers to easily access heroin in its highest purity outside of America; this resulted in the third opioid epidemic in America, right after the Vietnam War. Heroin was high in purity and very cheap at $6 in Vietnam (as opposed to 10% purity and $20 in America), and American soldiers often used it to get high and distract themselves from boredom, homesickness, and disturbed sleep [3]. After the Vietnam War, there was more regular use of narcotics and of heroin (as opposed to codeine), and more addiction to other drugs, particularly cannabis, due to persistent social stigma, high cost, and low purity of heroin in America. Post-Vietnam War, substance use disorder was rampant among 20% of the general population, and this compelled President Ronald Reagan to declare the "war on drugs" [4].

Opioid Epidemic: An American Cultural Phenomenon

The "war on drugs" failed to curb opioid use in America. This futile result can be attributed to lobbying for opioid use in a medical setting during the late twentieth and early twenty-first centuries. In 1986, Dr. Russell Protenoy and Dr. Kathleen Foley published a retrospective study of 38 patients with chronic pain, in favor of opioid use. Opioid maintenance therapy was begun in these patients (with age range of 25–82 years; without any history of substance abuse and malignancy) after many failed attempts of analgesia by surgical or medical means. They reported that in their study, 58% of patients reported either adequate or partial relief of pain, and 63% of patients reported notable enhancement in comfort [5]. They argued that their study corroborated the findings of three other studies at the time in favor of opioid use in a medical setting. They ultimately recommended that opioid maintenance therapy should be considered only after exhausting all reasonable attempts at pain control and that the patient's pain is a significant impediment to their function [5].

Using Drs. Portenoy and Foley's study and similar studies alike, Purdue Pharma aggressively marketed OxyContin in the 1990s, particularly for non-malignant chronic pain. It conducted more than 40 national conferences on pain management and recruited more than 5000 health professionals for its national speaker bureau, grossly influencing physicians' prescription practices and causing the Federation of State Medical Boards to release policies assuring that physicians would not face regulatory action for prescribing opioids [6]. Sophisticated marketing, by utilizing a database that monitored physicians' opioid prescription practices, the promise of lucrative bonuses to its sales representatives, and the use of a coupon program offering free limited 7- to 30-day supply to patients, catapulted liberal use of OxyContin, especially in territories where substance abuse was either rampant or on the rise. In 2001 alone, Purdue spent $200 million in marketing and promotions; between 1996 and 2001, its sales grew from $48 million to $1.1 billion. By 2004, OxyContin had become a leading drug of abuse due to its high availability [6].

In December 2001, the Joint Commission and the National Pharmaceutical Council, which is supported by the nation's major research-based biopharmaceutical companies, published a booklet entitled *Pain: Current Understanding of Assessment, Management, and Treatments*. It added further fuel to the opioid epidemic in the early twenty-first century – a time when deaths from opioid use were increasing with each passing year [7]. First, it stated that the "patient, not clinician, is the authority on the pain and that their self-report is the most reliable indicator of pain," persuading physicians to trust that their patients would report pain accurately. Second, it incorrectly argued that opioids are non-addictive, and though the addiction risk is unknown, it is thought to be quite minimal. Third, it adopted "pain"' as the fifth vital sign and it is just as important to assess as the other four vital signs in all patients. This became a standard practice for almost the first decade of the twenty-first century, which permitted the use of opioids to treat every kind of pain [7].

The liberal prescription of opioids is the driver behind the opioid epidemic becoming an American cultural phenomenon. Though they are useful for short-term or acute pain management, opioids are continuously prescribed for the management of chronic pain despite their ineffectiveness. In fact, higher pain scores are reported in chronic opioid users compared to non-opioid users; one of the common side effects in chronic opioid users is ironically hyperalgesia, an increased sensitivity and responsiveness to pain. Additionally, they report decreased quality of life and employment due to their debilitating addiction to opioids, and consequently, rely increasingly on disability and healthcare utilization [8]. For example, in Louisiana, opioid abuse costs the state approximately $296 million per year in healthcare cost, and from 2010 to 2016, the state has averaged around 122 opioid prescriptions per 100 persons. The opioid epidemic also has direct, synergistic effects on HIV and drug-related mortalities [9]. In 2016, around 64,000 people in the United States had died from drug overdose. This number exploded to 90,000 in 2020, of which 70,000 are from opioid overdose-related deaths [10]. This is more than car accident deaths and breast cancer deaths – causes that receive consistent national attention every year. As healthcare institutions become more attentive and cut back on opioid

prescriptions, an increasing upward trend in heroin use has been observed, thereby highlighting that the opioid epidemic is not just a healthcare problem but rather a cultural problem that needs to be addressed aggressively by healthcare professionals, policy makers, and public health advocates.

Cardinal Features of the Opioid Epidemic

Over-prescription of opioid medications in the last 25 years is responsible for the progression of the opioid overdose epidemic, diversions of tablets in communities, and overutilization of healthcare resources. Opioid-dependent patients have complex psychiatric and medical illnesses, and most of them are also socially complex, lacking social support and frequently homeless. Opioids are known to topple neuroanatomical pathways that are responsible for Pavlovian learning, memory formation, judgment, and emotional control [11]. As a result, the impulsive (drug-seeking) behavior that may be seen in chronic opioid users is a drug-induced phenomenon, not a lack of moral character. Understanding the origins of chronic pain, withdrawal pain, and central sensitization is essential to treating these patients with evidence-based therapies and to tackle the features of the opioid epidemic: chronic pain, overutilization, substance use disorder, psychiatric illness, and diversion of tablets. A learning dive into the brain disease model of addiction, the pain matrix of a normal functioning brain, the effects of opioids on brain structures, and the neurophysiologic origins of central sensitization and central pain syndromes will serve as effective tools to gain such understanding.

The Brain Disease Model of Addiction

While it is debatable whether addiction and opioid dependence is a disease, or a normal response to the effect of opiates on brain tissue, the “Brain Disease Model of Addiction” serves as a great place to start learning the effects of opioids on the brain. The areas involved are noted in Fig. 10.1. The brain disease model of addiction as outlined was derived from years of neuropsychopharmacology research. Pavlovian learning, a type of learning that occurs due to the subject’s instinctive responses, is driven by the ventral tegmental area and the nucleus accumbens, i.e., the learning and pleasure centers of the brain, respectively. Given the intertwined connection, a pleasure signal entices to repeat action to stimulate remembrance [12]. The signal begins with a dopamine flash in these two areas when a person learns something new, and this is followed by a weak dopamine signal sent to the prefrontal cortex.

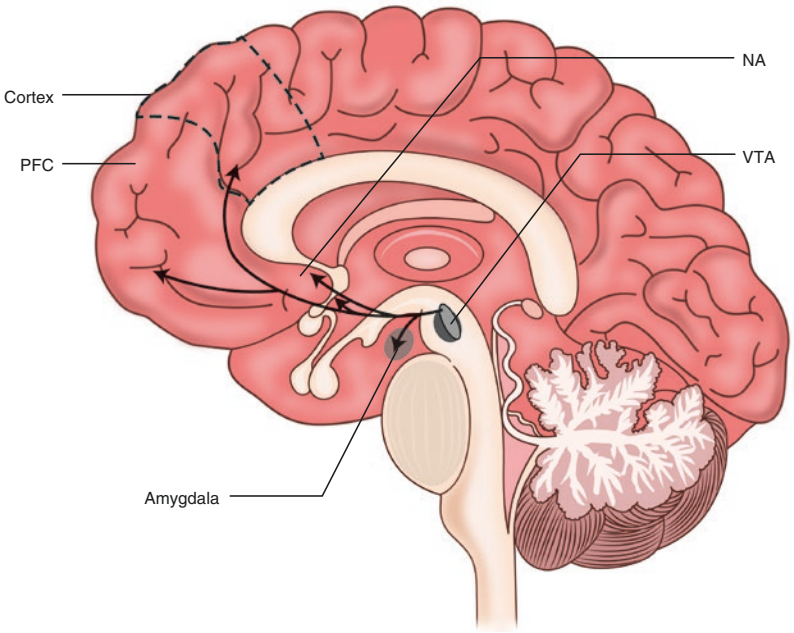

Fig. 10.1 Brain disease model of addiction. PFC prefrontal cortex, NA nucleus accumbens, VTA ventral tegmental area

The prefrontal cortex then begins to make connections with cortical nerve fibers to create memory and feedback loops to the emotional center of the brain, the amygdala. The amygdala does not fully mature until the age of 24, and without prefrontal control, it tips the balance of behavior toward impulsive actions [11, 12].

Opioid use induces euphoria, through a dopamine "blast" instead of a healthy pleasurable "flash" in the ventral tegmental area and nucleus accumbens. As a result of overstimulation, the brain undergoes several adaptive changes, intracellularly and within the synapse, in order to reduce the effects of dopamine; this causes an increasing requirement of opioid dose to achieve the same effect [11, 12]. The adaptive response in the prefrontal cortex is recession of affected neuron dendrites, which consequently impairs memory formation and disconnects control over the amygdala. This causes an individual to lose their impulse control and their ability to progress academically and intellectually, putting them at a risk for progressive psychiatric disorders [11, 12].

Hypofrontality has been observed in the prefrontal cortex as well as in the regions of anterior cingulate and ventral orbital cortex in addicted individuals. The development of enduring neuroplasticity was observed through neuroimaging with functional MRI scans and direct visualization of reduced prefrontal cortical measures of

blood flow, metabolism, and striatal levels of dopamine D2 receptors. The capacity for biologically relevant stimuli to activate the prefrontal cortex is impaired in patients with prolonged opioid use; however, drug-associated stimuli continue to markedly activate the prefrontal cortex [11]. The role of dopamine transitions from promoting new learning to enabling the use of learned information to execute adaptive behavioral response. Behavior evolves from a declarative process into a habitual behavior utilizing working memory circuits, which lead to automatic behaviors that lack conscious control and cause compulsive relapse [11]. The ability of prefrontal, declarative circuit to intrude and disrupt drug-seeking habit is also impaired. Over time, adaptive changes that occur early in disease progression promote behaviors toward addiction but can resolve with abstinence; however, later in the disease, habit circuitry is fully formed [11].

Addiction is a progression of brain pathology, and lack of behavioral control is a pharmacologically induced phenomenon. There is a hierarchy of events, a 3-tiered progression, that occurs with repeated exposure over time. Addiction progresses from intracellular changes to changes in function and anatomy of neural circuits, establishment of permanent unconscious behaviors and drug-related memories, and loss of unconscious control from conscious dependence [11]. Given that neuroplasticity leads to permanent drug-associated memories, addiction should be recognized as a chronic relapsing disease, not as an acute episodic illness.

The Pain Matrix

As seen in Fig. 10.2, the pain pathway involves the parts of the brain that control and modulate sensory input from the dorsolateral spinothalamic tract of the spinal cord. It consists of a constellation of brain regions, a multi-tiered hierarchical neural network, and the pattern or neural activation created by the sensory input that represents the *pain signature* of the experience. The stream of input is continuous, and the brain interprets it, gives it meaning, and then reflects it back to the original source [12].

First, the nociceptive input arrives to the thalamus. Second, perceptual-attentional areas of the cortex interpret it; this is known as *conscious modulation* and is shown in Fig. 10.3. Third, the nociceptive input is reflected into reappraisal-emotional areas so that importance can be assigned to the information; this is known as *unconscious modulation* and is shown in Fig. 10.4. After the sensory input is filtered through these three regions, *descending modulation* of the pain signature occurs. The signal first enters the periaqueductal gray zone, where a high concentration of opioid receptors either inhibits or facilitates the pain signature in order to tone down or increase the response. The altered signature enters the rostral ventral medulla, which contains “on” cells and “off” cells, before traveling back to the dorsal horn and then to the original source. These midbrain structures are analogous to “volume

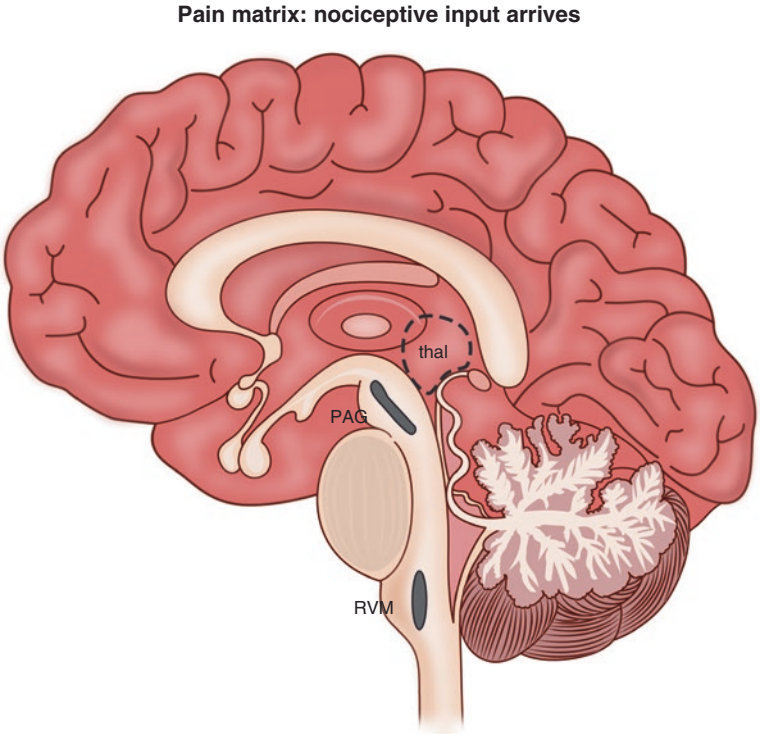

Fig. 10.2 Nociceptive input arrives

control" and "on/off switch" for pain; the pain signature deintensifies with time and distraction before it is reflected back to the original source.

Opioids inhibit the reflection of the pain signature at the levels of periaqueductal gray zone and rostral ventral medulla, where the function of "on" cells is blocked. In addition, opioids cause release of cytokines, interleukins, and glutamate from microglial cells, thereby intensifying neuroinflammation and leading to cell dysfunction and death in these areas [13]. Opioids are also known to disrupt the function of glial cells in the dorsal horn of spinal cord, causing spontaneous neuronal firing and leading to hyperalgesia and chronic pain. The pain associated with neuroinflammation is known as *central sensitization* [13].

Opioids also intensify the pleasure signal through stimulation of the ventral tegmental and nucleus accumbens areas [11]. When the effect of opioids begins to wear off, the rostral ventral medulla and the periaqueductal gray zone relieve the signal and the pleasure signal also disappears; the patient's perception of pain gets worse. This triggers intense fear and avoidance behaviors in patients that clinically manifest as *pain catastrophizing* behavior; it is the behavior focused on the

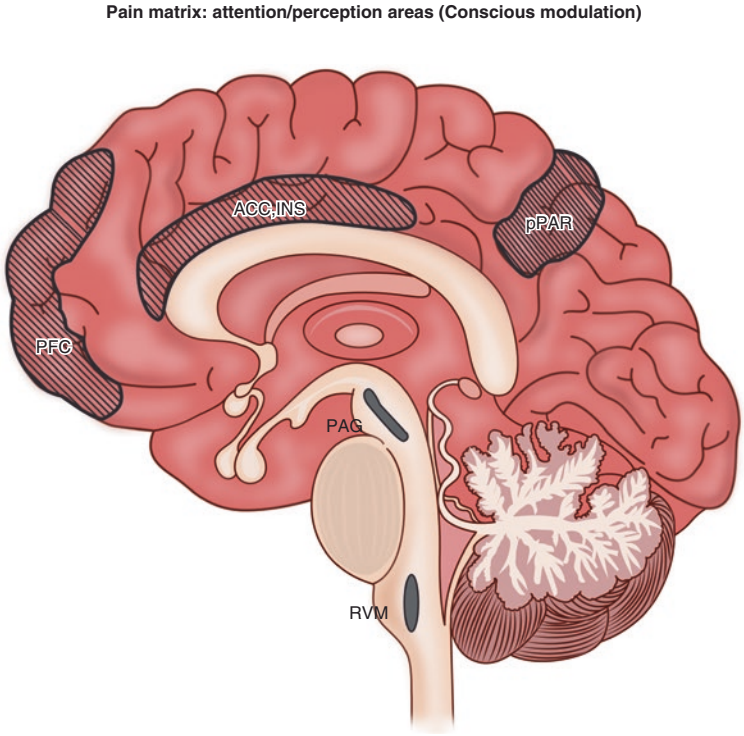

Fig. 10.3 Attention/perception areas (conscious modulation)

anticipation of the worst possible outcome, with increased attention to pain and associated symptoms [14]. The repeated use of opioids progresses maladaptive neuroplastic changes seen in the addiction pathway over time, inhibiting prefrontal cortex control over both the amygdala and the periaqueductal gray zone, strengthening habit circuity, and ultimately leading to highly emotional patients in constant pain.

Shared Neural Networks

The pain matrix and learning reward system share overlapping neural networks, mainly between the medial prefrontal cortex and nucleus accumbens. Prefrontal brain regions are involved in nociceptive inhibition and in the transition from declarative memories to habitual working memory circuits. The periaqueductal gray zone is located right next to the ventral tegmental area and receives input from the prefrontal cortex, insula, and other important structures. Because of the proximity of these regions to one another, the systems of human learning, pleasure, and pain are intimately connected. This is necessary since learning to avoid painful events deters risky behavior and stimulates the seeking of healthy, safe environments as well as cooperation within human communities.

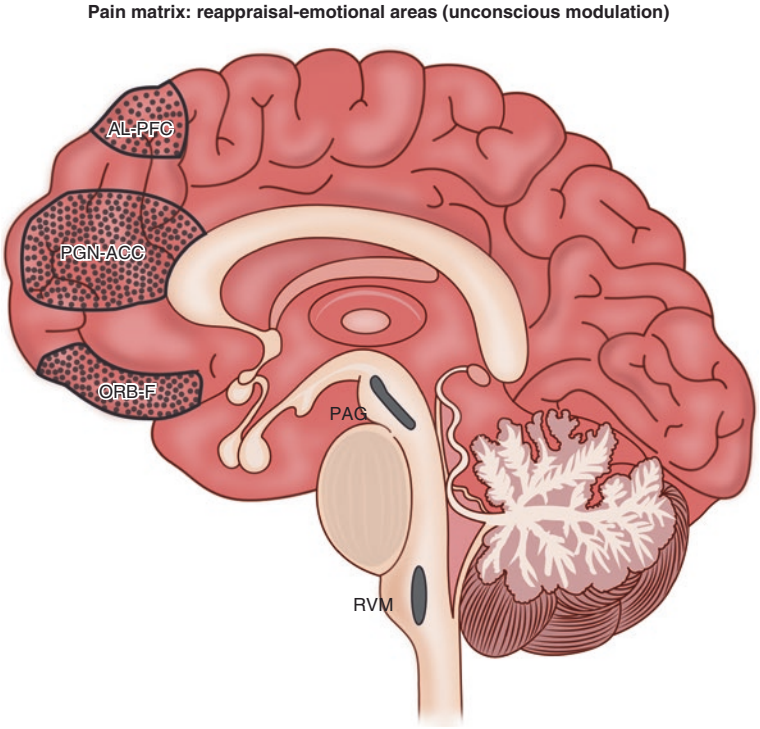

Fig. 10.4 Reappraisal-emotional areas (unconscious modulation). PAG periaqueductal gray zone, RVM rostral ventral medulla, thal thalamus ACC, INS anterior cingulate cortex, insula, pPAR posterior parietal lobe, PFC prefrontal cortex, AL-PFC anterior lateral prefrontal cortex, PGN-ACC perigenual anterior cingulate cortex, ORB-F orbital frontal lobe

On the other hand, chronic pain and psychiatric disorders also share neural mechanisms, and their relationship is bidirectional. For example, chronic pain leads to depression, and depression leads to chronic pain. In the opioid epidemic context, chronic pain leads to substance use disorders, and substance use disorders, including cannabis use, lead to chronic pain [14]. Additionally, suicide risk factors have increased prevalence among patients with chronic pain. Patients with personality disorders and neuroticism (negative thoughts) have increased sensitivity to pain, greater disability, and a lower quality of life, further signifying the shared neural networks between chronic pain and psychiatric disorders [14].

A third condition – addiction – is also intimately intertwined with chronic pain and psychiatric disorders within the brain. With prolonged, persistent use of opioids, acute pain progresses to chronic pain, eventually resulting in conscious opioid dependence and then finally to unconscious addiction. The prefrontal cortex dysfunction coupled with prolonged fear of withdrawal leads to chronic anxiety and the development of personality disorders. Due to the intertwined connection among chronic pain, psychiatric disorders, and addiction, these ultimately cannot be

separated in clinical practice; they must be considered as the same disease process and treated together.

Chronic Pain, Central Pain Syndromes, Hyperalgesia, and Withdrawal Pain

Chronic pain is pain lasting for more than 3 months. It is not the same disease as acute pain. It has association with fear and avoidance behaviors, so psychosocial issues come under scrutiny. It also has a different pathophysiology than acute pain and, therefore, it needs a multimodal approach [15]. Chronic pain can impact many body systems: gastrointestinal, psychological, endocrine, and sleep. Its presence implies that neuroinflammation and neuroplastic changes in the brain have begun to develop. Its pathophysiology may include central pain syndromes, central sensitization of the periaqueductal gray zone and rostral ventral medulla of the midbrain, or a failure of descending modulation of glial cells in the dorsal horn of the spinal cord (complex regional pain syndrome). It may also be peripheral in origin, as in peripheral neuropathy or osteoarthritis [15].

Some examples of central pain syndromes include phantom limb pain, pain associated with Parkinson's disease, pain associated with spinal cord injury, and multiple sclerosis. This form of pain arises when the brain constructs painful reality within unconscious brain structures as the pain signature is born and persists from direct insult to nerve tissue. Microglial cells activate and induce neuroinflammation with the release of cytokines, interleukins, and glutamate, which ultimately lead to mental dysfunction and depression as a result of cell death. Opioid use fails to provide relief and can actually potentiate the central pain [13].

Complex regional pain syndrome is due to failure of descending modulation of signal by glial cells in the dorsal horn of the spinal cord. These cases require a multimodal treatment approach, as the perception of pain is real to the patient. Although the pain signature arises from a peripheral nerve, it is amplified at the level of spinal cord. As noted in its name, this form of pain syndrome is complex, difficult to treat, and requires a referral to a chronic pain specialist [13].

Opioids are often the go-to treatment to treat pain. However, not all pain can be treated with them. The opioid-induced hyperalgesia is an important cause of pain and is often overlooked. It is also greatly associated with fear and avoidance behavior and with pain catastrophizing. Opioid-induced hyperalgesia was first reported in the medical literature in 1870 and has persistently been noted since. It is characterized by increased sensitization to painful stimuli after exposure to opioids and often mimics the patient's original pain condition [15]. Opioid-induced hyperalgesia may have both a central and a spinal origin. Central sensitization in opioid-induced hyperalgesia is caused by neuroinflammation in the midbrain structures. Function of glial cells is also disrupted, where the mitigation of the pain signal in the dorsal horn of the spinal cord is compromised [15]. Opioid-induced hyperalgesia needs to

be considered when a patient fails to resolve their pain with opioid use. A thorough history of pain, opioid use, and psychiatric issues is critical to the formation of a treatment plan for a patient who has a history of opioid use.

Pain from opioid withdrawal is also chronic, cyclical, associated with anxiety, and often unrecognized. It has a similar pathophysiology to opioid-induced hyperalgesia and should be considered when opioid therapy fails [15]. Opioids turn off the natural endogenous opioid system in the brain, and it may take 3–5 days to recover after the opioid is discontinued. The pain perception of central sensitization can take 1 month to resolve [13]. Due to the pharmacologic effects of opioids, the withdrawal pain can be greater than the original painful event. As the opioids wear off, the midbrain structures release the pain signature and the pleasure signal in the nucleus accumbens also diminishes, enhancing pain perception. As a result, objective monitoring of the patient's functional status (rather than use of a subjective pain scale) is crucial to dictate the pace of the weaning process. Opioids also induce fear and anxiety, which amplify pain perception, so patients typically are very emotional and expressive when they present with withdrawal [15]. During this sensitive period, a patient will need reassurance, motivational interviewing, and guidance to overcome their withdrawal. They may respond well to dialog about the central origins of their pain and reaffirmation that their pain perception is real, although their physical condition is stable. A useful analogy that a patients may understand is when one moves their hand from a cold bath to a warm one, the temperature may initially feel very hot but will stabilize in time. Many patients are willing to endure this sensitive, suffering period, if the goal is independence from pharmacotherapy and improved quality of life. Additionally, distraction is a known treatment method that can assist with this endeavor [13].

Opioid Stewardship for Hospitalists

The rest of this chapter will discuss the common risks, such as respiratory depression and behavioral disturbances, involved with opioid use, the special complications of opioid use, the characteristics that put an individual at a greater risk, and the management necessary to mitigate these risks. This lays down the clinical foundation for opioid stewardship for hospitalists and provides guidance on the multimodal approach to treat opioid dependency and withdrawal.

Table 10.1 Risk factors and monitoring of respiratory suppression

Respiratory suppression risk factors and monitoring	
Risk factors	Monitoring
Renal and pulmonary conditions Neurologic or psychiatric conditions Higher dose First 24 hours of opioid therapy Prolonged surgery Polypharmacy Substance use disorder	Capnography Telemetry Naloxone reversal orders Neurological checks periodically Quick weaning protocols

Understanding Opioid Risk

Respiratory Depression

Respiratory depression is a very well-known side effect associated with opioid medication. However, as noted in Table 10.1, there are risk factors that make certain patient populations more likely to experience opioid-induced respiratory depression (OIRD) [16]. OIRD is due to the decreased respiratory drive and reduced supraglottic airway tone induced by opioids. If left untreated, OIRD may be fatal.

Risk Factors

Risk factors for OIRD include patient characteristics, certain comorbidities, and iatrogenic risks. Presence of one or more of these risk factors should prompt the hospitalist to institute an appropriate monitoring system to assess and, if necessary, reverse opioid toxicity.

Patients who are female, greater than 60 years of age, or less than 24 hours post-surgery are at an increased risk of OIRD. Orthopedic, transplant, and general surgery patients are particularly at high risk for OIRD, as are patients with an American Society of Anesthesia (ASA) score of 3–4 prior to their surgery. As an example, a patient with a remote history of a myocardial infarction (MI) or cerebral vascular accident (CVA) would likely have an ASA score of 3, while a patient with a recent MI or CVA would have an ASA score of 4 [17]. Patients who are opioid dependent at baseline are also at increased risk.

Patients with underlying renal disease, liver disease, neurologic disease (e.g., stroke, dementia), pulmonary disease (including chronic obstructive pulmonary disease), or cardiac disease (including coronary artery disease, congestive heart failure, and arrhythmias) are at an increased risk for OIRD. Diagnosed or suspected obstructive sleep apnea, obesity, and diabetes mellitus are also comorbidities associated with OIRD.

Finally, iatrogenic factors associated with OIRD include concomitant use of sedatives, multiple prescribers, multiple routes of administration, and excessive doses.

Management

Management of opioid patients at high risk for respiratory suppression includes monitoring for changes in clinical picture, as well as the placement of naloxone reversal orders. High-risk patients should be treated in a step-down unit, where capnography and telemetry are available. For these patients, as well as patients at lower risk for OIRD, periodic neurologic checks and alternative treatment modalities for pain should be considered. Finally, protocols for the rapid weaning of opioids should be in place for all patients at risk of OIRD.

Behavioral Disturbances

The neuropathological effects of opioids, as discussed previously, generate behavior in patients that is disruptive or counter-productive to the goals of care, or perhaps to the point of endangering the safety of hospital staff.

Risk Factors

Perhaps unsurprisingly, patients with a history of substance use disorder (SUD), persistent refusal to take medication-assisted therapy (MAT), and opioid dependence are at an increased risk of behavioral disturbances in the hospital setting. Patients who demonstrate poor frontal lobe function, refusal of self-care, or self-mutilation behaviors are also at risk for behavioral disturbances.

An adversarial relationship with the healthcare system, such as a history of verbal abuse of staff or non-adherence to medical or psychiatric care, is predictive of behavioral disturbances.

Similarly, patients with recurrent administrations to the same hospital, with frequent short stays at multiple hospitals (so-called “hospital shopping”), or who have been terminated from a practice in the past are more likely to cause behavioral disturbances.

Behavioral management is a very delicate task that can make or break the therapeutic relationship between the patient and hospital staff. Addressing behavioral disturbances compassionately requires clear communication to the patient and among the staff to ensure that therapeutic goals can be met while also maintaining the safety and well-being of all parties.

Table 10.2 Behavioral disturbances risk factors and monitoring

Risk factors	Monitoring
History of SUD/opioid dependence Persistent non-adherence to medical care History of engaging in verbal abuse Evidence of poor frontal lobe function Persistent refusal for self-care Self-mutilation Persistent refusal to take MAT Recurrent admissions to the hospital/hospital shopping Receipt of a seek care elsewhere policy	Proactive violence prevention strategies De-escalation Joint rounding with nursing and security Collate patients Communicate risk to nursing Create and utilize long-term care plans Develop a multi-disciplinary care team Steer patients into treatment programs

Management

As noted in Table 10.2, strategies for management of behavioral disturbances may be divided into those that directly involve the patient and those which inform the structure and coordination of the hospital care team.

For a patient with a history of behavioral disturbances, the most effective approaches are preventative in nature. These may include creation of a long-term care plan with the patient, and counselling to steer patients into treatment programs. Long-term care plans create a point of consensus and mutual understanding that reduces the discontinuity between patient and staff about routine medical care, such as blood draws or neurological checks.

A multi-disciplinary team consisting of psychiatry, medicine, pharmacy, and infectious disease staff allows for a consistent and holistic approach to patient care that minimizes the perception or actual presence of conflicting medical recommendations. Similarly, communication among nursing and physician teams regarding the patient's risk of behavioral disturbances ensures that all members of the care team are prepared when interacting with that patient. This is especially important if there are particular triggers for a patient's outbursts. Finally, all staff should be trained in verbal de-escalation strategies so that they respond to a patient's behavior appropriately.

At an administrative level, joint rounding, which is rounding within a team framework, with hospital security and representatives from the patient provider relations department may reduce risk to healthcare workers. Ensuring effective and adequate communication is key to proper medical care and well-being of all caregivers. The collation of patients at risk of behavioral disturbances to a designated set of beds on the hospital floor can allow for the centralization of properly trained staff and resources. Furthermore, these strategies reduce the impact of behavioral disturbances on all other patients on that floor.

Key Points

- OIRD is a serious and potentially fatal complication of opioid use.
  - Postsurgical patients and chronically ill patients are at high risk of OIRD.
  - Monitoring, multimodal therapies, early mobilization prevent respiratory depression.
- Behavioral disturbances disrupt patient care and can pose a threat to staff.
  - De-escalation training is recommended for all staff.
  - Foster patient buy-in to treatment plans.
  - Joint rounding and care team communication reduce risk of violence.

Stewardship and Acute Pain

The emergency department is often the first port of call for many patients seeking treatment for pain and, therefore, a critical point for opioid stewardship.

Acute vs Chronic Pain

Acute pain management begins with the decision to treat with opioid or non-opioid therapy. Multimodal pain management including acute nerve blocks should be the mainstay therapy whenever possible. In the event that opioid therapy is indicated, the Centers for Disease Control (CDC) recommends using the lowest effective dose with the shortest duration of treatment [18]. Ideally, a treatment plan should be established with the patient to ascertain the goals of opioid therapy as well as risks and benefits.

Once the decision to utilize opioid therapy for acute pain has been made, physicians should assess opioid risk. This can be accomplished by checking the prescription monitoring program, performing a pain, psychiatry, and drug history, and performing a urine drug screen. When considering which opioid medication to prescribe, short-acting opioids should be preferred. Finally, a comprehensive review of the patient's medications should be undertaken to avoid co-prescribing opioids with benzodiazepines or other sedatives.

Chronic pain has a different pathophysiology than acute pain. Although there is significant overlap between the two, chronic pain is associated with fear, avoidance behaviors, and additional psychosocial factors such as substance use disorder and dependency. Patients who are expected to be admitted to the hospital for a short period of time and are otherwise stable, without any signs of substance use disorder

and dependency, on a chronic pain regimen should be kept on their long-term medicine regimen and discharged to follow-up with the provider who prescribes their opioid medications.

During the course of hospitalization, complications and side effects of opioids, such as hyperalgesia, gastroparesis, and nausea, should be anticipated and addressed. Hospitalization is an opportunity to screen patients for these complications. If present, the patient's medications should be discontinued, as ongoing use will lead to debilitation, adverse outcomes, and readmission. The patient will need other options for pain management. If weaning of opioids is not possible, then palliative care consultation is warranted. Care should be taken to avoid making a patient opioid-dependent, including weaning and education on the risks of long-term opioid use.

American College of Emergency Physicians Opioid Recommendations [19]

Several questions need to be considered before prescribing opioids in the emergency department:

- In adult patients experiencing an acute painful condition, do the benefits of prescribing a short course of opioids on discharge from the emergency department outweigh the potential harms?
  - Preferentially prescribe nonopioid analgesic therapies (nonpharmacologic and pharmacologic) rather than opioids as the initial treatment of acute pain in patients discharged from the emergency department.
  - For cases in which opioid medications are deemed necessary, prescribe the lowest effective dose of a short-acting opioid for the shortest time indicated.
- In adult patients with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing a short course of opioids on discharge from the emergency department outweigh the potential harms?
  - Do not routinely prescribe opioids to treat an acute exacerbation of noncancer chronic pain for patients discharged from the emergency department. Nonopioid analgesic therapies (nonpharmacologic and pharmacologic) should be used preferentially.
  - For cases in which opioid medications are deemed appropriate, prescribe the lowest indicated dose of a short-acting opioid for the shortest time that is feasible.
- In adult patients with an acute episode of pain being discharged from the emergency department, do the harms of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics outweigh the benefits?
  - Do not routinely prescribe, or knowingly cause to be co-prescribed, a simultaneous course of opioids and benzodiazepines (as well as other muscle relaxants/sedative-hypnotics) for treatment of an acute episode of pain in patients discharged from the emergency department.

- In adult patients experiencing opioid withdrawal, is emergency department-administered buprenorphine as effective for the management of opioid withdrawal compared with alternative management strategies?
  - When possible, treat opioid withdrawal in the emergency department with buprenorphine or methadone as a more effective option compared with nonopioid-based management strategies such as the combination of α2-adrenergic agonists and antiemetics.
  - Preferentially treat opioid withdrawal in the emergency department with buprenorphine rather than methadone.
- As per the US Substance Abuse and Mental Health Services Administration recommendations, physicians should prescribe naloxone to at-risk patients such as the following [20]:
  - Discharged from the emergency department following opioid intoxication or poisoning
  - Taking high doses of opioids or undergoing chronic pain management
  - Receiving rotating opioid medication regimens
  - Having legitimate need for analgesia combined with history of substance abuse
  - Using extended release/long-acting opioid preparations
  - Completing mandatory opioid detoxification or abstinence programs
  - Recent release from incarceration and past abuser of opioids

Key Points
- Avoid prescribing opioids in the emergency department whenever possible.
- ACEP guidelines apply to hospitals for treatment of acute pain.
- Prescribe naloxone in the emergency department and hospital.
- Prescribe two doses due to short-acting effect.
- Distribute to patient, family, caretakers.

Special Complications of Opioids

Unique to opioids is the development of pain sensitization and catastrophizing of pain. Hyperalgesia due to opioid use should be suspected in patients for whom opioids paradoxically make the patient's pain worse. For hospitalists, this syndrome is often seen in postoperative settings and cannot be treated with additional opioids. In fact, treatment entails removing the opioid. A short-term prescription for antiseizure medication for neuropathy may reduce the hyperactivity and reduce symptoms of pain and emotionality. Recognition of opioid-induced hyperalgesia is important because any delay in treatment leads to unnecessary suffering of the patient.

Opioid-withdrawal hypersensitivity is an allodynia-like sensation of pain in the patient's typical location which flares when the dosage of opioids is reduced. This hypersensitivity lasts approximately 24–72 hours after a change in dosing and is associated with a spike in the patient's anxiety and catastrophizing about the nature of their pain.

Multimodal Therapy

Multimodal therapy is the synergistic utilization of non-opioid analgesics to address pain, as an alternative to opioids [21]. Multimodal therapy comprises both general (i.e., systemic medications) and regional (i.e., field blocks and neuraxial blocks) approaches to pain management. Unless contraindicated, patients should receive an around-the-clock regimen of non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (COXIBs), or acetaminophen. The choice of medication, dose, route, and duration of therapy should be individualized, and dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events. When appropriate, or prior to a surgical procedure, regional blockade with local anesthetic should be considered [22].

Classes of Multimodal Therapy

Each class of medication used in the context of multimodal therapy is briefly discussed below.

NSAID use decreases opioid consumption and provides superior analgesia when combined with opioids [23, 24]. These drugs are considered first-line medications for mild-to-moderate pain. Adverse effects include gastric bleeding, colonic or diverticular bleeding, and renal impairment [25, 26]. COXIBS have a lower risk of bleeding compared with traditional NSAIDs but have an increased risk for cardiovascular events [27].

Acetaminophen is a non-opioid antipyretic analgesic without anti-inflammatory activity [28]. It has an incompletely understood mechanism of action, but studies show a synergistic effect with NSAIDs [29]. Acetaminophen is recommended to be administered using a dosing schedule. Both PO and IV routes of administration are equally efficacious for moderate-to-severe pain, but IV administration is recommended when oral medications are contraindicated, e.g., nausea and vomiting [30].

Tramadol is a weak opioid agonist which acts on the μ-opioid receptor. It also acts as a selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) [31]. Tramadol is a cytochrome p450 (CYP450) substrate and may cause interactions with other medications that are processed via the

CYP450 system [32]. Because of the SSRI capacity of tramadol, it should be used with caution on patients who take other SSRI medications to prevent serotonin syndrome. Presently, evidence does not support the concept that tramadol is less addictive than other opioid medications [33].

N-methyl-D-aspartate (NMDA) receptor antagonists include drugs like ketamine, magnesium, methadone, and dexamethasone [34, 35]. The NMDA receptor is associated with central sensitization of nociceptive signals and is therefore an important target in the treatment of chronic and postoperative pain. Ketamine is particularly versatile, with intranasal administration as a safe and efficacious alternative to intranasal fentanyl [36].

Anticonvulsant agents such as gabanoids, gabapentin, and pregabalin are neuromodulators that reduce excitability of pre-synaptic calcium-gated channels. This class of therapy promotes opioid cessation after surgery, but has no effect on postoperative pain [37]. However, gabanoids are effective first-line agents for neuropathic pain [38]. Of note, evidence suggests that diversion and abuse of gabanoids occur in approximately 1% of the general population and at higher rates among patients with opioid use disorder [39].

Fixed-dose combinations of opioid and non-opioid medications are an important element in multimodal therapy that decrease pill burden on patients by combining NSAID medications with small doses of opioids [40]. Common drug pairings include oxycodone/ibuprofen, hydrocodone/ibuprofen, and hydrocodone/acetaminophen, which decreases the liver toxicity associated with acetaminophen [41].

Regional anesthesia is an effective option to reduce or eliminate the need for opioids. Administration is via continuous local infiltration in patients requiring prolonged analgesia, and benefits include a reduction in hospital resource utilization, decreased nausea and vomiting, and an improvement in patient satisfaction [42]. Additional medications added to the regional anesthetic can provide additional benefit to patients. Anti-inflammatory medications, such as COX-2 inhibitors and steroids, or motor and sensory blocks such as liposomal bupivacaine may be used when indicated [43].

Field blocks are a non-specific subset of regional anesthesia, in which local anesthetic is administered into fascial planes. A single injection may last hours but requires ultrasound-guidance and a larger volume of anesthetic compared to peripheral nerve blocks [44].

Key Points

- There are multiple methods to address acute and chronic pain in patients.
- Opioids are often inferior to other analgesic agents such as NSAIDs.
- Appropriate combinations of two or more methods can be safe and effective.
- Be aware of drug-drug interactions and potential complications.

Compassionate Withdrawal of Opiates

Overview

The most effective strategy for the treatment of opioid use disorder is that of prevention. Early weaning of opioid medication and transition to multimodal therapy after acute pain are paramount to opioid stewardship. Failing to wean a patient from their opioid medications prior to discharge is one of the biggest mistakes a hospitalist can make. For patients who are already taking opioids, the decision to taper or completely stop opioids should be made when there is evidence of complications, dependence, or substance use disorder. Doing so in a compassionate manner requires making a correct diagnosis and understanding the complications of opioid withdrawal. Strategies to address the psychological components of a patient's pain are often as important as the medication regimens themselves. Peer recovery coaches, nurses, case managers, therapists, clinical psychologists, inpatient and chronic pain specialists, addiction medicine specialists, and hospitalists should all be capable of recognizing complications, performing motivational interviews and bedside cognitive behavioral therapies to help guide the patient's progress through opioid withdrawal.

Empathic Strategies

Validation and reassurance should be used frequently when withdrawing patients from opioids. The sensation of worsening pain may be temporary, but the pain itself is very real, and dismissing patient complaints of pain can negatively affect the physician-patient relationship. All patients should be given the time and space to express themselves and feel respected by the care team. The role of the clinician is often that of a coach, helping to redirect the patient's attention away from the immediate pain of withdrawal and toward their future state.

Coping strategies are also helpful for many patients during this time, and mind-body therapies have some evidence for a decrease in opioid-treated pain [45]. Meditation, hypnosis, relaxation, guided imagery, therapeutic suggestion, and cognitive behavioral therapy are all options to discuss with patients. A variety of strategies not only gives the patient agency in deciding the approach to their treatment, but it also avoids the tendency for patient to succumb to treatment nihilism should the first approaches prove unsuccessful. If all else fails, simply walking the halls of the unit can offer a change of scenery, however brief, that can precipitate a change in focus away from the patient's current sensation of withdrawal. Early mobility in a safe environment builds confidence, documents functional status, and prepares a patient for a safe discharge.

Providing patients with education materials is another helpful strategy during the withdrawal of opioids. Understanding the pain pathways and how pain is generated can help reinforce validation and reassurance. Furthermore, tying the education

materials into the pain-reducing strategies currently being used by the patient can improve the patient's buy-in to the clinical plan. Finally, documenting the education provided to the patient can ensure that the next provider who sees the patient does not make assumptions about what the patient does or does not know about their condition. This helps the patient to feel that they are being seen, heard, and understood by their care team.

Suggested Stepwise Withdrawal

The first step in withdrawing prescription opioids from a patient is to establish a provider-patient relationship. Buy-in to the care plan from both the patient and their family is critical to a successful withdrawal. The provider should also document reasoning for withdrawal recommendation, including patient behavior, as well as a complete medical and surgical evaluation.

Once the patient and family agree with the care team regarding the recommendation to withdraw opioids, the next step is education. Handouts may be useful to allow all parties to consider the decision, as well as to formulate any questions or concerns about the process. A discussion about the anticipated symptoms is warranted, especially the concept of hyperalgesia, i.e., the increased sensation of pain is not indicative of new pathology. Nursing staff, caretakers, and family should all be informed of the decision to withdraw opioids, as discussed previously.

Once withdrawal is initiated, the transition period should involve close monitoring for new issues and treatment of symptoms as they arise. Chronic pain and withdrawal hypersensitivity pain should be treated with non-opioid alternatives, as discussed previously. Non-pharmacologic approaches such as physical and occupational therapy, as well as cognitive behavioral therapy and ongoing education about the neurologic effects of opioids, should be utilized where appropriate.

Documentation of symptom progression is an important component in managing the withdrawal period. Functional status of patients and any occurrence of aberrant behaviors should be recorded and addressed. As patients withdrawing from opioids have a higher risk of leaving against medical advice (AMA), decision-making capacity assessments should be documented daily and before the AMA discharge. Additionally, hydration and electrolyte status should be monitored, especially in patients with ongoing diarrhea or vomiting due to the withdrawal.

Timeline of Withdrawal

Clinicians should be aware that while acute physical withdrawal lasts between 3 and 5 days, physical withdrawal symptoms can last for up to 3 months, and psychological dependence lasts years. Patients need close monitoring in the period after withdrawal to screen for relapse and ensure adequate psychosocial support. Over 90% of

patients go through opioid withdrawal relapse within a month [46]. Removing any habit may take numerous attempts before success is attained.

With regard to the trajectory of medications, benzodiazepines should be weaned first to eliminate the risk of seizures. Opioids may be weaned by 25% every other day and more if tolerated. The tapering of medications for central sensitization should begin at least 1 month after cessation to give time for neural activity to calm down. They may be tapered slowly according to the patient's symptoms. All patients should be supported with naloxone, given the risk of death from relapse.

Key Points

- Withdrawal of opioids should be conducted in a stepwise fashion, with buy-in from patient and family followed by education, monitoring, and treatment of symptoms.
- Risk of overdose and death is highest in the post-hospital period – all patients should be supported with naloxone.

Opioid Use Disorder: Diagnosis and Treatment Strategies

The correct diagnosis of opioid use disorder is only the first step of treatment. The DSM-5 classification of opioid use disorder is outlined in Table 10.3. It is also important to communicate this diagnosis to other providers, nursing staff, and insurance companies to ensure appropriate care for each patient.

OUD encompasses both opioid dependence and the more severe opioid use disorder. Dependence is associated with either physiologic or psychologic withdrawal. In contrast, opioid use disorder is characterized by compulsive drug-seeking behavior, dysfunction, and the persistent use of opioids despite adverse consequences.

Patients with OUD are often hospitalized due to the presence of new complications secondary to drug use. For these patients, the decision to wean, educate, and discontinue opioids versus the commencement of medication assisted therapy is crucial. Opioid risk assessment tools can be helpful to differentiate between acute and chronic pain and between iatrogenic opioid dependency and substance use disorder.

When considering opioid withdrawal, medications are recommended over abrupt cessation ("quitting cold-turkey"). Tapering schedules for opioid withdrawal usually last between 6 and 10 days, depending on the patient's individual need. For iatrogenic opioid dependence, a gradual taper of the patient's prescription can be undertaken. For patients with substance use disorder, a long-term approach is needed. Medication-assisted therapy may include methadone, buprenorphine, or extended-release naloxone. For the management of side effects, clonidine,

Table 10.3 DSM-5 opioid use disorder (OUD) [46]

Opiate use AND the recurrence within 12 months of ≥2 of the following:
Continued use despite worsening physical or psychological health
Continued use leading to social and interpersonal consequences
Decreased social or recreational activities
Difficulty fulfilling professional duties at school or work
Excessive time to obtain opioids or recover from taking them
More taken than intended
Presence of cravings
Withdrawal
Inability to decrease amount used
Development of tolerance
Use despite physically dangerous settings

loperamide, ondansetron, acetaminophen, and NSAIDs are appropriate [46]. The help of an addiction medicine specialists is indicated.

Patients should also be counseled on the risks of relapse and overdose, especially following discharge from the hospital, as a loss of tolerance to their usual dose of opioids can result in fatal respiratory depression if that dose is resumed. A best practice is to include a prescription of naloxone at the time of discharge. Medications that reduce the sensation of craving and thus the risk of relapse are discussed in detail below.

Medication-Assisted Therapy (MAT)

Overview

Patients with iatrogenic opioid dependence deserve a trial of abstinence (with naloxone), especially if they do not have an underlying psychiatric or attachment disorder. However, for patients with longstanding opioid use disorder, MAT has been shown to be highly effective. Chief among the benefits of MAT such as buprenorphine/naloxone is the lower rate of overdose, the decreased risk of abuse or diversion, and the increased retention of patients in treatment programs where, ideally, the psychosocial factors may also be addressed.

Importantly, if a patient is admitted to the hospital and is already on MAT, it is appropriate to continue their medication regimen throughout their stay. Whenever possible, confirm with the prescribing provider the patient's dosage schedule and active status of treatment.

Medications of MAT

Methadone is an orally administered long-acting full agonist at the mu-opioid receptor, appropriate for use in medically supervised withdrawal and maintenance of abstinence from opioids [47]. Due to the duration of occupation of the opioid receptor, methadone reduces cravings and withdrawal symptoms for an extended period of time. Additionally, methadone's occupation of the opioid receptor blunts the effects of additional opioids. Methadone is classified as a Schedule II controlled substance and, therefore, administration is limited to the acute inpatient setting and certified outpatient clinics [48].

Buprenorphine is a partial agonist at the mu-opioid receptor, weaker than full agonists such as methadone. For this reason, buprenorphine has a lower potential for misuse than other opioids [46]. By occupying the opioid receptor, buprenorphine reduces the symptoms associated with physiological dependence on opioids, such as cravings and withdrawal. Suboxone is a common formulation of buprenorphine and naloxone, which precipitates withdrawal when injected but not when taken orally. Buprenorphine is classified as a Schedule III controlled substance, which requires a waiver for physicians to prescribe, as discussed below [48].

Unlike methadone and buprenorphine, naltrexone is a competitive antagonist at the mu-opioid receptor. Its chief utility is to prevent relapse in patients who have completed medically supervised withdrawal and are no longer taking opioids. Because it binds and antagonizes the opioid receptor, naltrexone blunts both the sedative and euphoric effects of opioids but may precipitate withdrawal in patients who have unmetabolized opioids still in their system. Because it is not a controlled substance, naltrexone does not have the prescribing restrictions of other drugs used in MAT.

Barriers to MAT

Like any therapy, MAT does have its downsides. Chief among these is the need for patients to secure follow-up after their discharge from the hospital. This is compounded by the relative lack of providers with the X-license necessary to prescribe MAT. Recent announcements suggest that X-licenses may not be required for physicians in the future, but as of this writing, this is hypothetical [49].

Discharge disposition is also often a barrier, since many long-term acute care facilities and nursing homes are reluctant to take patients on MAT, due to the stereotype of opioid patients as "difficult." Paradoxically, patients receiving closer clinical attention at such facilities would be less likely to have unmet medical needs, be more adherent with enhanced supervision, and have improved outcomes and behaviors. Achieving adherence in a supervised setting is more likely to improve long-term care arrangement in the outpatient drug treatment program.

Among clinicians, there is a lack of education about the efficacy and elements of MAT, leading to a perception of a high risk involved in its use. Providers have medical legal concerns about complex laws restricting the use of medications, stigmatize and treat substance use disorders. Stemming perhaps in part from this lack of understanding, providers can be reluctant to assume the kind of partnership with their patients that is a necessary component of effective MAT [50].

In addition to individual-level stigma, access to MAT in the United States is often accompanied by structural-level stigma that negatively impacts utilization and retention in MAT programs. This is best characterized by patterns of restricted access to MAT services and low tolerance of patient noncompliance [51]. For example, MAT is not commonly provided in correctional facilities [47]. In the community setting, MAT is often administered by specialty clinics physically and ideologically separate from clinics, which treat other forms of chronic illness that are more easily treated in a primary care setting.

Further commentary on the racial and socioeconomic barriers to MAT is beyond the scope of this chapter. Clinicians should be mindful of the conditions that patients are likely to face in their communities once discharged.

Initiation of Buprenorphine

As mentioned previously, buprenorphine is a partial agonist at the mu-opioid receptor commonly used for MAT. Initiation of buprenorphine can increase the risk of precipitating acute withdrawal in patients who take opioids. It is recommended that buprenorphine be started only after current opioid medications are stopped and mild to moderate symptoms of withdrawal begin, as measured using a validated tool like the Clinical Opioid Withdrawal Scale (COWS) [52].

A typical starting dose is 2–4 mg by mouth once or twice a day, though this should be titrated up in increments of 2–4 mg until symptoms are managed for 24 hours [53]. An average daily dose of buprenorphine is 8 mg but can be as high as 16–24 mg [54]. Psychosocial treatment, such as motivational interviewing and bedside CBT, is an important adjunct to initiation of buprenorphine, as patients may benefit from the coping strategies as they adjust to a new medication regimen.

As mentioned previously, the transition of care from hospital to outpatient setting can be difficult and potentially dangerous. Ensuring the patient's seamless transition to an outpatient provider of MAT is the responsibility of the hospitalist. Once in the outpatient setting, the decision to taper off of buprenorphine may be considered. Should the patient desire tapering and eventual discontinuation of MAT, the process should be done slowly with close monitoring for symptoms of withdrawal. This is because patients are at the highest risk of mortality in the first month after discontinuation of treatment [55].

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