Opioid Use Disorder

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Introduction

Opioid use disorder is defined by the chronic use of opioids that leads to clinically significant impairment or distress [1]. Opioid use disorder is diagnosed when an individual meets two or more of the 11 criteria in the table below within a one-year period, and severity is based on the number of symptoms present (Table 7.1). An estimated 26.8 million people globally have opioid use disorder with over 100,000 overdose deaths reported each year [2]. In 2018, 10.3 million people or 3.7% of the US population aged 12 or older were estimated to have misused opioids, and two million of these individuals met criteria for opioid use disorder [3]. An estimated 446,000 American died from an opioid overdose from 1999 to 2018 and of those 233,000 died from a prescription opioid overdose [4]. During this same time period, there was a tenfold increase in overdose deaths caused by fentanyl [4], a synthetic opioid 30–50 times more potent than heroin [5, 6]. The prevalence of heroin use in the United States has increased significantly over the past two decades, doubling in number from 2002 to 2018 [7], and two thirds of individuals who use heroin also report use of prescription opioids [8]. Given the increasing rates of opioid overdose deaths and the human toll caused by this "opioid epidemic," in 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency, which increased public funding for treatment, overdose prevention, and training of first responders and other medical professionals to respond to the crisis [9].

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Table 7.1 DSM-5 diagnostic criteria for opioid use disorder [1]

Opioids are often taken in larger amounts or over a longer period of time than intended
There is a persistent desire or unsuccessful efforts to cut down or control opioid use
A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
Craving, or a strong desire to use opioids
Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home
Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
Important social, occupational, or recreational activities are given up or reduced because of opioid use
Recurrent opioid use in situations in which it is physically hazardous
Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids
Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect or (b) a markedly diminished effect with continued use of the same amount of an opioid
Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome or (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

Individuals develop opioid use disorder through a variety of pathways including legitimate use or abuse of prescription analgesics such as oxycodone and hydrocodone or through use of illicit substances such as heroin. Individuals at risk for developing opioid use disorder frequently have risk factors including current or past history of substance abuse, introduction to opioids at a younger age, untreated psychiatric disorders, and social and familial contexts where substance use is commonplace [10].

Medication-assisted treatment for opioid use disorder, when used in conjunction with psychosocial interventions and counseling, shows superior treatment outcomes in terms of treatment retention, lower mortality, and improved quality of life [11–14]. Despite strong evidence in support of MAT, it is underutilized [15, 16]. This can be explained in part due to stigma held by both patients and providers, lack of training for providers particularly in rural areas, and limited access to opioid treatment programs [17, 18]. One study found that less than 50% of privately funded substance use disorder treatment programs offer MAT as part of their treatment programs and of those only 34.4% of patients with opioid use disorder received MAT [19]. The goal of this chapter is to illustrate the evolution of an opioid use disorder (OUD) through a clinical case and to outline the pharmacologic treatment options to treat this illness including methadone, an opioid agonist; buprenorphine, an opioid partial agonist; and naltrexone, an opioid antagonist.

Clinical Case

Joe is a 45-year-old married man, working in construction, who sustained a work-related injury; while using a circular saw to cut a piece of wood, he accidentally sliced off his index finger. Fortunately, he salvaged his finger, and it was reattached at a nearby hospital. Dr. Frank, the surgeon who performed the procedure, prescribed Joe a one-month supply of oxycodone-acetaminophen (commonly known as Percocet) to treat his postoperative pain.

Prior to receiving this prescription for oxycodone-acetaminophen, Joe had never used any opioid analgesics nor any illicit opioids. He considered himself a "social drinker," but never drank on a daily basis, infrequently got drunk, and never blacked out from alcohol. His wife, however, did have a remote history of heroin addiction and was on methadone prescribed by an opioid treatment program (OTP) in a nearby town. Joe did not have any chronic medical conditions, nor did he have any relevant psychiatric history. He recalls his father being "an angry drunk," but his parents divorced at a young age, and he never maintained a relationship with his father after he left.

Joe began taking the opioid analgesic as his doctor had prescribed it. Initially, the medication adequately controlled Joe's pain, but within a few weeks, the pain in his finger became more intense. In an attempt to help alleviate Joe's pain, Dr. Frank renewed Joe's prescription and doubled his supply during the following 2 months.

Four months after Joe's procedure, despite ongoing complaints of intense "dagger-like" pain in his reattached index finger, Dr. Frank informed Joe that he could no longer continue to prescribe oxycodone-acetaminophen, explaining "the medical community is cracking down on narcotic prescriptions, so you should try to cope without the medication." At this point, Joe had been consuming oxycodone-acetaminophen 5–325 mg up to six times daily for several months. He was worried about being suddenly cut off from his prescription, recalling a time when he had forgotten his pain medication at home during a work day, and he experienced flu-like symptoms of opioid withdrawal. He expressed these concerns to his doctor who offered to refer him to a pain management specialist, but the next available appointment was in 3 months' time.

In the week following his last appointment with Dr. Frank, Joe attempted to cut back on his oxycodone-acetaminophen use. He had about 30 pills remaining, and he attempted to reduce his use from six pills daily to three pills daily. He succeeded at this, despite enduring numerous symptoms of opioid withdrawal: chills, muscle aches, nausea, and diarrhea. Joe felt like he had come down with a terrible bout of influenza. His wife, concerned about his state, suggested he enroll at her opioid treatment program and initiate methadone. Joe refused. He had always regarded methadone as "legal heroin" and had been encouraging his wife to taper off of it.

As he only had a few days' supply of pain medications remaining, and his pain management appointment was still ten weeks away, Joe felt that he had to find an interim solution. He took to the Internet to search his options, and he found a compound called kratom (*Mitragyna speciosa*), which could be bought legally, marketed itself as an effective painkiller, and had opioid-like properties that would soften the impact of opioid withdrawal.

Joe found relief in kratom – a powder he brewed into hot water – which he consumed multiple times daily. It lessened his symptoms of opioid withdrawal and dulled the pain in his finger. He noticed, however, that he quickly became tolerant of kratom. He began by drinking three cups of kratom daily, and within a few weeks, he was drinking six cups daily to achieve the same desired effect.

Joe started to worry about the financial implications of his new kratom habit. His wife approached him again and suggested that he come to her Opioid Treatment Program and hear about the available treatment options, assuring him that methadone is not the only option for his condition. Joe agreed.

Pharmacologic Interventions

When Joe arrives at the clinic, he meets with a psychiatrist to discuss treatment options and shares that he last used kratom yesterday morning and is already experiencing withdrawal symptoms and cravings to use again. During the visit a Clinical Opiate Withdrawal Scale (COWS) is administered, which is an 11-item scale designed to assess withdrawal symptoms over time, rating withdrawal symptoms from mild, moderate, moderately severe, and severe [20]. Joe's vitals are taken and blood pressure is 125/90 mm Hg and pulse rate 110 beats per minute. He blows his nose several times as he enters the exam room and reports feeling anxious and restless with strong urges to use kratom. He is noted to be sweating and yawns twice during the session. He also reports experiencing severe muscle and bone pain and gets up several times during the interview to use the bathroom due to nausea and severe diarrhea. Based on these symptoms of opioid withdrawal, Joe's COWS score is 16, indicating moderate withdrawal. He is not noted to have any tremor or gooseflesh skin, and pupils appear normal-sized. Joe initially states he wants to "tough it out" and detox from kratom without MAT due to concern for "getting addicted to something else." Detox options are discussed, specifically non-opioid symptomatic treatment of opioid withdrawal including clonidine 0.1–0.2 mg four times daily to treat Joe's tachycardia, anxiety, sweating, and hypertension. Metoclopramide 10 mg every 6 hours as needed is offered for nausea and loperamide 4 mg initially, and then 2 mg thereafter (up to 16 mg/day) is offered for diarrhea. Ibuprofen 400 mg three times daily as needed is offered for pain, and he is also prescribed trazodone 50 mg nightly as needed for insomnia which he also reported experiencing due to the withdrawal [21].

By the end of the 45-minute session, Joe appeared even more restless and was noted to have a new onset tremor and a COWS score of 23. As he rose to leave the

Table 7.2 Pros and cons of the three FDA-approved treatments for OUD

Medication	Pros	Cons
Methadone	Medication cost is affordable [50] Straightforward induction process Reduction in infectious disease transmission and criminal activity [51] Safely used in pregnancy [52] Some find benefit to the structure of an OTP Low risk of diversion due to strict initial frequent attendance policy	Initially 6 day/week attendance expected at most OTPs No office-based treatment, must have access to OTP [24] Cardiac arrhythmias [53] Overdose risk [24] Stigmatized High abuse potential At high doses: sedation, constipation, sexual dysfunction [54]
Buprenorphine	Ceiling effect: low risk of overdose, less abuse potential Daily or alternate-day dosing Increased flexibility: office-based prescribing Less stigmatized than methadone Safely used in pregnancy [55]	Costly: medication is moderately expensive, and DEA-X waivered physicians usually in private practice Moderate abuse potential [55] Diversion risk with office-based prescribing Risk of precipitated withdrawal during induction [55]
Naltrexone	Blocks high from any opioid use Relieves cravings No risk of naltrexone withdrawal Less stigmatized than methadone Minimal abuse potential	Risk of precipitated withdrawal during induction Decreases tolerance, therefore increases overdose risk Common side effect: nausea

office, he walked to the door then stopped and turned around and said "I'd actually like to hear about the other treatment options. I can't continue withdrawing like this."

The psychiatrist welcomed Joe back into the room and provided supportive listening about how much Joe has struggled with his chronic pain and resultant opioid dependence. She then reviewed the three FDA-approved medication options for opioid use disorder that work by reducing cravings: methadone, buprenorphine, and naltrexone [22].

The psychiatrist, aware that Joe's wife was treated with methadone for opioid use disorder, began by discussing this option. Methadone, she explained, is a long-acting opioid agonist that is FDA-approved for both opioid use disorder and pain management, which could be helpful for Joe's finger pain [23]. She also shared that methadone can only be dispensed by a SAMHSA-certified Opioid Treatment Program (OTP) that would provide on-site administration of methadone in liquid form six days a week along with individual sessions with a counselor, regular urine toxicology, and group therapy. Additional pros and cons of methadone were reviewed with Joe (Table 7.2) [24].

Joe expressed interest in the pain management aspects of methadone though expressed hesitance that methadone was not for him, saying "it seems like yet another drug to abuse."

Next the psychiatrist reviewed naltrexone, a synthetic opioid antagonist, as a treatment option given that there is no abuse potential with this medication [25]. She explained how this medication was available as a tablet or in an extended-release

monthly injection called Vivitrol that could be prescribed in an outpatient clinic setting. Naltrexone functions by binding to and blocking the opioid receptor [25] and by extension would block opioid-like substances such as kratom, which has agonist effects on the opioid receptor. Naltrexone therefore reduces opioid cravings and compulsive opioid use [3]. Joe seemed interested initially, though when he learned that he would have to remain abstinent from opioids or opioid-like substances for 6 days prior to induction on naltrexone, he declined this option.

Aware that Joe was seeking a more immediate treatment for his opioid cravings and withdrawal, the psychiatrist then recommended buprenorphine, an opioid partial agonist that can be prescribed in an outpatient clinic setting. Given Joe's current withdrawal symptoms, he could safely be induced on buprenorphine today in the office. The treatment, it was explained, would reduce his opioid cravings and withdrawal symptoms as well as reduce some of his finger pain given its action at the opioid receptor. The pros and cons of this treatment were reviewed with Joe including risk for precipitated withdrawal – if he had recently consumed opioids – and potential side effects. Various formulation options were reviewed including buprenorphine sublingual tablets (Subutex), buprenorphine-naloxone combination sublingual films (Suboxone) and tablets (Zubsolv), as well as longer-acting forms of buprenorphine such as extended-release injection (Sublocade). Given Joe's concern about the abuse potential of his treatment, he opted to try a buprenorphine-naloxone compound, since naloxone reduces misuse of buprenorphine. Joe agreed to start buprenorphine-naloxone combination sublingual films (Suboxone) 4 mg in the office and would return home with an additional 4 mg to take that evening if withdrawal symptoms persisted. He agreed to return the following morning for assessment and potential dose adjustment. See treatment Algorithm 7.1 for additional guidance of initiating MAT for the treatment of opioid use disorder.

Discussion

Joe's story is similar to that of many thousands of Americans who have developed an opioid use disorder over the past 30 years. In 1995, the American Pain Society (APS) set out guidelines that encouraged medical providers to record patients' reports of pain, with the goal of improving the diagnosis and treatment of pain. They recommended that patients' reports of pain should be taken as seriously as vital sign measurements, thereby coining this initiative *pain as the fifth vital sign* [32]. Not surprisingly, an increase in pain assessments brought on an increase in opioid analgesic prescribing; opioid prescriptions increased from 76 million in 1991 to 219 million in 2011. Unfortunately, during this time of widespread opioid prescribing, pharmaceutical companies marketed opioid analgesics to the medical community as non-addictive [33], which we now recognize is not the case. The increase in opioid prescriptions led to an increase in opioid-related emergency room visits, treatment admissions, and overdose fatalities [34].

In response to the increasing rates of controlled substance misuse in the United States, prescription drug monitoring programs (PDMPs) were implemented in most

American states. With the implementation of PDMPs, there was a corresponding 30 percent decrease in the rates of prescribing Schedule II opioids (which includes most prescription opioids) [35]. Physicians became increasingly aware of the addictive nature of prescription opioids, and many abruptly changed their prescribing practices, sometimes to the detriment of their patients.

Naloxone, a rapid-acting opioid receptor antagonist, was introduced to the market in a more user-friendly form in recent years. In the past, this medication had been used only in medical settings such as emergency rooms, since it was only available in intravenous or intramuscular form. Importantly, the key to reversing an opioid overdose is prompt timing of naloxone administration, so the recent creation and wider distribution of an easy-to-use intranasal naloxone spray have been an important step in overdose prevention [36]. Naloxone should be prescribed to anyone considered high risk of opioid overdose – such as individuals with an opioid use disorder who have recently been released from a period of incarceration or those who are prescribed high doses of long-acting opioid analgesics – and a doctor or pharmacist can show patients, their family members, or caregivers how to administer intranasal naloxone [37].

As was seen in Joe's case, his doctor abruptly stopped his opioid prescription, leaving Joe without access to a medication he was physiologically dependent on. It is at this juncture that many people make the transition to heroin due to its widespread availability, adequate analgesic effect, and affordability. In Joe's case, however, he harbored considerable stigma about illicit drugs and their treatments, such as methadone, so he sought out kratom, an opioid-like compound that is sold legally online and in head shops. Kratom (*Mitragyna speciosa*) is harvested from a tree indigenous to Southeast Asia and is a relative of the coffee plant. It is sold as a powder that can be stirred into a beverage or put in individual capsules for consumption. At lower doses, kratom has stimulant-like properties, and at higher doses it behaves like an opioid, and in fact is an agonist on the major opioid receptors. In recent years it has gained popularity as a recreational drug that is marketed to improve mood, relieve pain, and may provide benefit in opioid addiction [38]. As we saw in the above case, Joe became tolerant of kratom and began to use higher doses to achieve the same effect. Upon recognizing this, he agreed to visit his wife's OTP and consider a medication-assisted treatment for opioid use disorder.

Upon learning about the three FDA-approved treatments for opioid use disorder, Joe found himself most partial to buprenorphine-naloxone combination therapy (Suboxone). He told the psychiatrist that he heard that methadone causes dental and bone decay. The OTP psychiatrist explained that methadone can reduce the production of saliva, which prevents dental caries. Therefore, initiating methadone can cause dry mouth, which may increase risk of cavities; however, methadone does not directly act on the teeth to cause dental decay. Additionally, until arriving at a therapeutic dose of methadone, opioid withdrawal symptoms may cause musculoskeletal pain, which may be misconstrued as bone breakdown. Methadone does not directly act on bones to break them down, however. Joe mentioned that he is also worried that people would regard him as "weak and without willpower" if he agreed to methadone or another MAT [39]. His wife has been on methadone for nearly a

decade, and he is worried that if he were to start it, he would never get off. While the OTP psychiatrist understood that there is considerable stigma against people with substance use disorders and those on MAT, she assured Joe that most providers he would be working with at the clinic would see his seeking treatment as a sign of willpower: he is asking for help with a habit that has become destructive. She also assured Joe that every patient is different: some patients use MAT as a bridge to transitioning off opioids altogether, and others need to be on MAT for many years, given how susceptible they are to relapse on opioids.

Despite the OTP psychiatrist debunking many of Joe's preconceived notions about methadone, and recommending it for the dual treatment of opioid use disorder and pain management, Joe opted to initiate suboxone. While he could initiate suboxone at his wife's OTP, he preferred to find an office-based suboxone provider in the future, so he would not be subject to the initial six-day-per-week pickup schedule of the OTP.

Despite substantial evidence for its efficacy, safety, and relative ease of use, buprenorphine remains vastly underutilized [40]. In order to become a licensed buprenorphine prescriber, one must provide MAT in a qualified practice setting or hold board certification in addiction medicine or addiction psychiatry. Buprenorphine training is typically eight hours in duration and grants those a DEA X waiver to prescribe buprenorphine [41]. As of 2017, more than half (56.3%) of US counties were without a buprenorphine prescriber [42]. In addition, most waivered physicians treat far fewer than the potential maximum of 275 patients they are eligible to treat. Studies suggest a lack of prescriber experience and education in the use of buprenorphine as a reason for its underutilization [43]. Buprenorphine has also been criticized as being marketed to a specifically white, affluent, college-educated population [44]. Notably its advertising campaigns do not target an underserved population with low socioeconomic status, where rates of substance use disorders are highest. In addition, many state-funded Medicaid programs do not cover reimbursements for buprenorphine, thereby narrowing the scope of prescribing to more affluent subsections of the population with private insurance [45].

Psychotherapeutic and Psychosocial Interventions

The treatment of opioid use disorder includes medication-assisted treatment as well as a range of behavioral interventions aimed at helping patients to reduce urges to use opioids, maintain abstinence, and develop coping skills [46]. Studies have shown superior clinical outcomes in the treatment of opioid use disorder when medication management was combined with psychosocial interventions [47]. These interventions take the form of individual and group therapies including cognitive behavioral therapy, acceptance and commitment therapy, couples and family

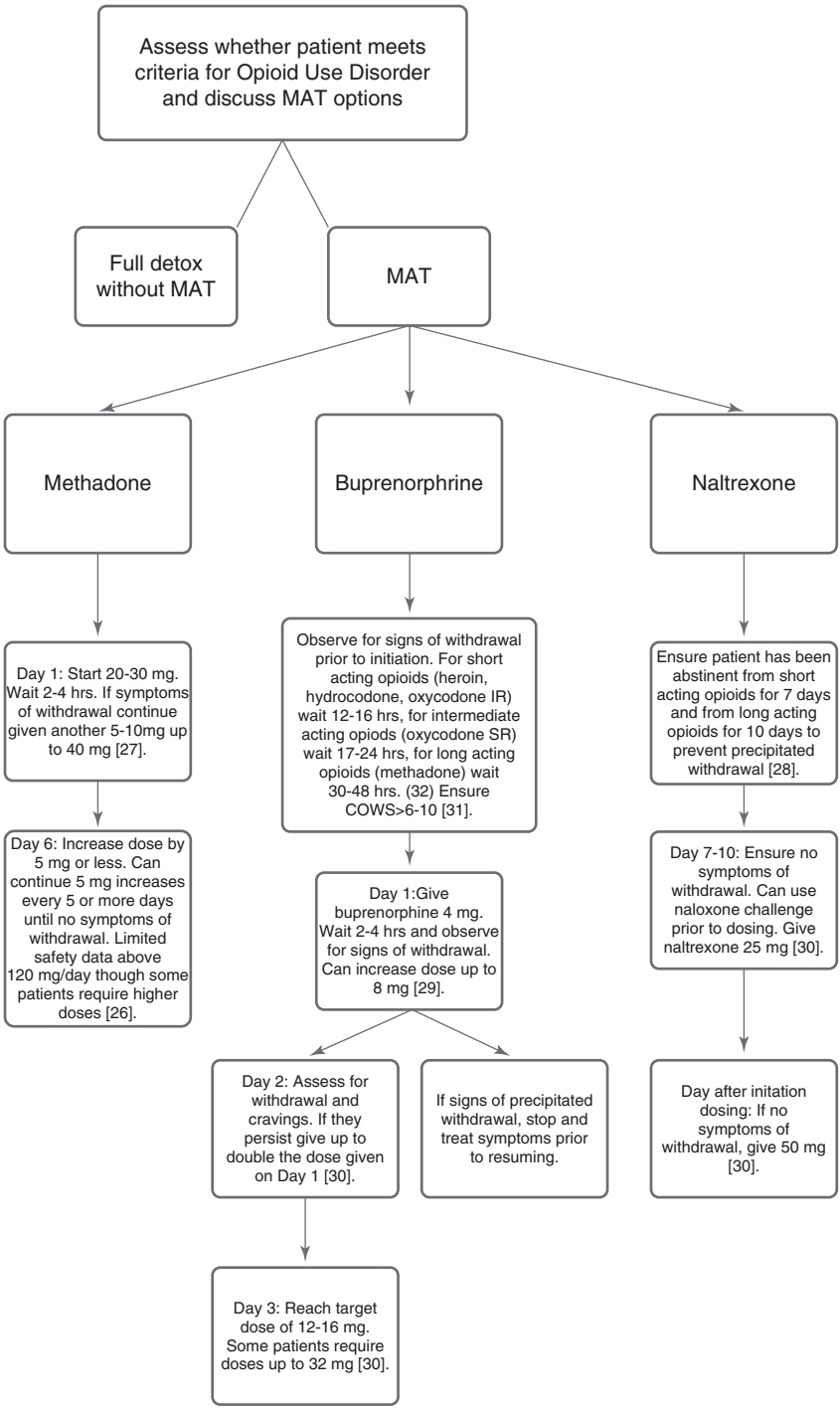
therapy including network therapy, contingency management, motivational interviewing, social skills training, harm reduction counseling, and 12-step facilitation therapy [48]. Some treatments such as 12-step facilitation therapy (such as Narcotics Anonymous, with almost 20,000 groups worldwide) promote an abstinence-only recovery approach, while others such as harm reduction counseling seek primarily to reduce the negative sequelae of substance use, such as infectious disease transmission or criminal behavior.

Joe's case provides a good example of where motivational interviewing could be used to help Joe recognize problems associated with his kratom use, explore and resolve ambivalence about his use, and explore both the benefits of changing his addictive behaviors and the costs of not changing. In this case, the OTP psychiatrist could take a nonjudgmental stance and use empathy to align with Joe in his struggle to stop using kratom. She could employ open-ended questioning and reflections to help Joe to see the gap between his kratom use and his personal goals and values. The psychiatrist could elicit Joe's own reasons for change referred to as "change talk" rather than trying to persuade him that he should stop using kratom. She could also explore his belief about MAT being a sign of weakness rather than as a sign of strength in his recovery.

Conclusion

The opioid epidemic is one of the most profound public health crises that the United States has faced over the course of its history. An increase in opioid analgesic prescribing in the late 1990s and early 2000s led to an increase in misuse and abuse of prescription opioids, which commonly became a gateway to developing a heroin addiction [49]. There are three medication-assisted treatments [13] for opioid use disorder – methadone, buprenorphine, and naltrexone – and they are all underprescribed and heavily stigmatized, both by the lay public, by patients with opioid use disorders, and even by medical providers. This chapter has attempted to illustrate how a middle-aged man without a prior history of addiction developed an opioid use disorder through a legitimate prescription by his own physician. Within a short period of time, he was physiologically dependent on opioid analgesics and later on kratom, an opioid-like compound that reduces opioid withdrawal symptoms. The patient's own long-held beliefs about MAT prevented him from seeking treatment immediately and from weighing all three approved treatment options equally. While the psychiatrist in this case was well-versed on each approved MAT for the patient's opioid use disorder, MAT in general is vastly underprescribed, possibly due to prescriber lack of training and experience in MAT prescribing. Additional efforts in educating medical providers and the general public on the disease of addiction and its treatments are a necessary step in tackling the opioid epidemic.

Algorithm 7.1 Treatment of Opioid Use Disorder



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