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Management of Opioid Use Disorder

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Increased abuse of prescription opioids and subsequent increases in accidental opioid-related deaths have caught the attention of policy makers in the United States (U.S.) and in Oregon. On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs and improve community access to naloxone.[1] In January 2017, the Oregon Health Plan (OHP) removed restrictions for Suboxone®, and its generic sublingual tablet and film formulations, and for Vivitrol®, a naltrexone extended-release injectable formulation, in fee-for-service patients.[2] This article will summarize medication treatment options for patients with opioid use disorder.

Substance Use Disorders

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.* (DSM-V), substance use disorders (SUDs) are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life.[3] In persons with an SUD, there is an underlying change in the way the brain functions that can persist beyond detoxification and result in repeated relapses and intense cravings when exposed to certain stimuli.[3] These addictive substances alter brain circuitry involved in complex functions like motivation and decision-making and diminish natural reward mechanisms for essential substances like food and water.[4] Pleasure normally experienced with stimuli like food or social interactions is diminished with repeated use of addicting substances.[4] A specific example of an SUD is opioid use disorder which is a result of opioid abuse. It is a chronic, relapsing disease that often occurs with other SUDs and has had significant economic, personal and public health consequences for many victims.[5]

Opioid Use Disorder

Opioid analgesics have been used for decades to manage pain, but they can also produce feelings of dysphoria and sedation which places them at high risk for misuse and abuse. In addition, tolerance to regular use of an opioid analgesic can result in the need over time for higher doses to achieve analgesia. From 2007 to 2014, the number of private insurance claim lines with an opioid dependence diagnosis increased 3,203%, with most of the claims associated with persons between 19-35 years of age.[6] With ease of accessibility to opioids, it is imperative that physicians understand how to recognize opioid use disorder and navigate treatment strategies with their patients. Opioid use disorder is defined by DSM–V when at least 2 criteria outlined in Table 1 are met in the last 12 months.[3]

Table 1. DSM-V Criteria for Opioid Use Disorder (≥2 met in last 12 months).[3]

1. Opioid(s) often taken in larger amounts or over a longer time than intended.
2. Persistent desire or unsuccessful efforts to cut down or control opioid use.
3. Excessive time spent to obtain or use an opioid, or recover from its effects.
4. Urge to use opioids; opioid craving.
5. Failure to fulfill important obligations at work, school, or home because of recurrent opioid use.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous (e.g., while driving).
9. Continued opioid use despite knowledge of such use being a persistent physical or psychological problem.
10. Opioid tolerance (need for increased amounts of opioid for effect or diminished effect with same dose).*
11. Opioid withdrawal or need opioid to relieve withdrawal.*

*Note: These criteria not considered to be met when taking opioids as prescribed.

Treatment Strategies

For patients who seek help for opioid use disorder, a thorough patient medical and mental health evaluation should be performed before treatment is started. This should include screening for other SUDs, infectious diseases (e.g., hepatitis C, HIV, tuberculosis) and pregnancy.[5] Patients with concomitant SUDs or concurrent use of alcohol, sedatives, hypnotics or anxiolytics may require a higher level of care and closer monitoring.[5]

The setting in which treatment is provided is just as important as the specific medication selected.[5] For treatment of opioid withdrawal (detoxification), symptoms may be monitored closely at the appropriate level of care (inpatient or outpatient setting). For maintenance therapy, opioid treatment programs (i.e., 'methadone clinics') offer daily supervised dosing of methadone, and increasingly of buprenorphine. Office-based maintenance treatment, which is limited to buprenorphine by Federal law, provides dispensing of medication periodically on an individualized basis. Naltrexone can be prescribed in any setting by any clinician with prescribing privileges. The most appropriate setting and choice of therapy largely depends on patient preference, their psychosocial situation, concomitant disorders, and risk of diversion. All factors are considered in order to make treatment as successful as possible.

Goals for maintenance therapy include improvement in health and ability to work, decreased use of contaminated needles and risk for HIV or Hepatitis C infection, reduced opioid cravings, decreased use of illicit opioids, and crime reduction.[6] Long-acting opioids methadone and buprenorphine are the most studied. Methadone and buprenorphine have similar efficacy in patients with opioid use disorder when outcomes like self-reported opioid use, positive opioid urine drug screens, and patient retention in opioid treatment programs were studied.[8] Overall rates of adverse events between methadone and buprenorphine also appear to be similar when used for maintenance treatment.[8] Oral and extended-release injectable naltrexone formulations are also approved by the U.S. Food and Drug Administration (FDA) for opioid dependence in patients who can abstain from all opioids. Formulations approved for opioid use disorder are listed in Table 2.

Table 2. Drugs FDA-Approved for Patients with Opioid Use Disorder.

Drug	Proprietary Name	Formulation	AAAC for 30-day supply
Buprenorphine/ Naloxone	Buprenorphine/ Naloxone	SL Tablet	$47
	Suboxone®	SL Film/Buccal	$227
	Zubsolv®	SL Tablet	$233
	Bunavail®	Buccal Film	$229
Buprenorphine	Buprenorphine	SL Tablet	$22
	Probuphine®	Implant Device‡	$5940*
Methadone	Methadone	Tablet, Solution	$7
	Dolophine®	Tablet, Solution	$67*
Naltrexone	Naltrexone	Tablet	$15
	Vivitrol®	ER Injection	$1571*

Key: AAAC = average actual acquisition cost; ER = extended–release; SL = sublingual
‡Available as a 6-month implant; *Prices from Lexicomp Database. Accessed 4/24/17.

Methadone

Methadone is a mu-opioid agonist and an N-methyl-D-aspartate (NMDA) antagonist. The recommended initial dose ranges from 10 to 30 mg for

management of withdrawal, with reassessment every 3 to 4 hours.[5] Federal law mandates that the initial dose cannot exceed 30 mg. Methadone has a high potential for misuse and diversion. As maintenance therapy, it is recommended for patients who could benefit from single daily dosing and supervision provided in an opioid treatment program.[5] Opioid treatment programs have strict guidelines for dosing, supervised treatment and associated services. Doses can usually be anywhere from 60 to 120 mg per day.[5] There is no recommended limit to duration of maintenance therapy.

Methadone has strong evidence to support reducing mortality and substance abuse, improving physical and mental health outcomes, reducing criminal activity and reducing risk for HIV and risk behaviors.[8] However, methadone is not without risk for harm. Patients with cardiac or respiratory disease should avoid methadone. Adverse effects may include prolongation of the QT-interval which rarely may result in Torsade de pointes, a fatal arrhythmia. Respiratory depression can occur when the drug is titrated too quickly due to drug accumulation and methadone's complicated pharmacokinetic profile. Depending on clinical response, dose increases of 5 to 10 mg increments should occur no more frequently than every 7 days.[5]

Buprenorphine

Buprenorphine is a partial opioid agonist with lower intrinsic activity at the mu-opioid receptor than a full agonist, but due to its very high affinity for the receptor, buprenorphine possesses antagonist properties that can block the effects of other opioids if used concurrently. Buprenorphine (C-III) is not as highly controlled as methadone (C-II) and can be provided in clinician offices. Qualifying physicians, nurse practitioners (NP), or physician assistants (PA) must have a waiver from the Substance Abuse and Mental Health Services Administration (SAMSHA), completed the required buprenorphine training, and obtained a unique Drug Enforcement Administration (DEA) number. Physicians may provide care for up to 275 patients and NPs and PAs may care for up to 30 patients.[1]

Buprenorphine is formulated alone or with naloxone in a 4:1 ratio to discourage injection of the drug. The low dose of naloxone does not precipitate withdrawal symptoms unless it is injected. Buprenorphine has poor oral bioavailability due to extensive first-pass metabolism so formulations are dissolved against the tongue and buccal mucosa.

Buprenorphine reduces self-reported opioid use, reduces positive opioid urine drug screens, improves treatment retention, and has similar evidence for survival benefit as methadone.[8] Buprenorphine is safer than methadone due to its limited effects on the respiratory system, fewer drug interactions, and more predictable pharmacokinetics. However, buprenorphine is not the best option for everyone. Office-based treatment with buprenorphine may not be suitable for patients who regularly use alcohol or sedatives.[5] Physicians can reduce risk of diversion with buprenorphine with frequent office visits, urine drug testing, and recall visits for pill counts.[5] Another consideration is cost. Buprenorphine is more expensive than methadone, and private office charges for buprenorphine might exceed the usual costs of a methadone clinic.[7]

Opioid-dependent patients should wait until they are experiencing mild to moderate withdrawal before starting buprenorphine at a dose of 2 to 4 mg.[5] Doses can be increased in increments of 2 to 4 mg until it is determined to be well tolerated.[5] Maintenance therapy with buprenorphine should exceed 8 mg per day but no more than 24 mg per day.[5] Higher doses are not more effective but can increase risk of diversion. Buprenorphine taper and discontinuation is a slow process, without a defined duration, but can take several months. Close monitoring is advised even after buprenorphine is stopped. Accessing the Oregon Prescription Drug Monitoring Program (PDMP) data can be helpful to know what other controlled substances, if any, are being prescribed.

Naltrexone

Extended-release injectable opioid antagonist naltrexone can also be successfully used to treat opioid use disorder as evidenced by one randomized, placebo-controlled trial.[9] The long-acting formulation is given intramuscularly every 4 weeks. Success with oral naltrexone is often adversely affected by poor medication adherence because it requires a highly motivated patient. Oral naltrexone has not consistently demonstrated superiority to control groups at treatment retention or opioid consumption because of high attrition in clinical trials and so there is insufficient evidence to recommend it routinely in patients at this time.[4] Patients who initiate parenteral or oral naltrexone treatment or switch from methadone or buprenorphine must be free of opioid dependence (7-14 days without acute withdrawal symptoms), which can be confirmed with an opioid-free urine sample and a naloxone challenge (intramuscular or intravenous administration of 0.8 to 1.6 mg of naloxone; or alternatively, 50 mg of oral naloxone with no subsequent withdrawal symptoms).[7] Length of treatment with oral or extended-release injectable naltrexone depends on clinical judgement, but there is no physical dependence and it can be stopped abruptly without withdrawal symptoms.[5]

Guideline Resources

Cost of therapy, concomitant medical and psychiatric conditions, availability of methadone clinics, clinicians trained in administering buprenorphine or naltrexone, and risk of diversion are all factors that play a role in considering which drug is appropriate for an individual patient. Both the American Society of Addiction Medicine and the U.S. Department of Veteran Affairs and Department of Defense have published helpful guidelines that describe the nuances for each drug therapy.[4,5] Importantly, the guidelines emphasize that drug therapy alone is insufficient. Concomitant psychosocial interventions are described which should be applied to address the psychological and social circumstances that often hinder treatment from being successful.[4,5]

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