CHAPTER 5
COMORBID POLYSUBSTANCE USE

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5.1. Introduction

Many patients with Opioid Use Disorder (OUD) are also using, or are addicted to, other substances (see Table 5.1.1) [138, 139]. Caring for these patients presents many additional challenges: they are at higher risk for a range of infections including HIV, HCV, MRSA, and infectious endocarditis [138], which in turn predisposes them to various cardiovascular and cerebral vascular diseases like myocardial infarction and stroke [139].

People with polysubstance use disorders suffer a high level of psychological and socio-economic stresses from loss of employment, housing and social support [138]. Their treatment responses are accordingly poorer as well. When used concurrently, substances can interact with medications used in the treatment of OUD, further complicating the treatment process, and can contribute to intentional and unintentional overdoses. Many clinicians, in part out of concern for these patients' safely, simply avoid prescribing medications to treat these patients' OUD. (Miller) Those who do prescribe medications, like methadone and buprenorphine, often do so with reluctance and stringent precautions such as regular drug screens, short prescriptions, and frequent clinic visits.

Clearly, the added complexity and difficulty of treating patients with OUD and polysubstance use requires careful treatment planning and caution. In many cases a more intense level of care, such as day treatment or residential treatment, may be needed. In practice, a standard patient with OUD tends to engage in polysubstance use when accounting for tobacco, alcohol, and cannabis are considered. Over 80 percent of people with opioid use disorder use tobacco, and a majority of them also drink (see Table 5.1.1) [140].

The DSM-5 removed polysubstance use disorder from the diagnostic listing. Instead each mind-altering substance is rated individually using the 11 criteria to determine whether there is a use disorder and its severity on the continuum from mild to severe, as explained in Chapter 1 of this Guideline describing the changes from DSM IV to DSM-5.

5.2. Recommendations for Treatment for Other Substances

5.2.1. Methamphetamine and Cocaine

Pharmacology and Types

Methamphetamine (MA) is the secondary drug most commonly used by patients with OUD. Use of methamphetamine and cocaine (including crack cocaine) has increased nationally (Table 5.1.1). MA and cocaine are both psychomotor stimulants with similar effects in increasing dopamine availability in the reward pathway in the nucleus accumbens [142]. The combination of either of these stimulants with an opioid is known as a "speedball" [143]. The stimulant-opioid combination produces greater positive subjective effects than either drug alone. Among those using heroin, up to 92 percent report concomitant use of cocaine [143].

Psychiatric Signs and Symptoms

Psychiatric indicators of stimulant intoxication include euphoria, anxiety, agitation, irritability, paranoia, psychosis and suicidal states [144]. Signs and symptoms of stimulant withdrawal include anxiety, depression, fatigue, and possibly

Table 5.1.1

Type of Secondary Drug for Opioid Use with Methadone/ Buprenorphine Detoxification in CA, 2016 [143]

Secondary Drug	Frequency	%
None	18243	50.2
Methamphetamine	8716	24.0
Cannabis	2311	6.4
Cocaine/Crack	1693	4.7
Other opiates/Synthetics	1400	3.9
Alcohol	1281	3.5
Oxycodone/Oxycontin	944	2.6
Tranquilizers (Benzodiazepines)	610	1.7
Heroin	391	1.1
Non-prescription Methadone	261	0.7
Other	227	1.3

higher suicidal states. This withdrawal period may last three to five days and may contribute to clinic absences. Patients may feel they are "not addicted" because withdrawal is less obvious than with opioids, although craving is severe. Patients may present with sedation if they come to clinic while "crashing."

Epidemiology

Physiologically, cocaine use increases risks for strokes [145] especially among young adults and in crack smokers [146]. Young adults who use cocaine often experience chest pain, myocardial infarction, congestive heart failure, arrhythmias, and renal failure [147]. Methamphetamine also causes cardiovascular [148] and cerebrovascular disease, especially in younger adults [149].

Psychologically, patients who use stimulants and opioids together often have concomitant psychological distress and increased risk of non-fatal overdoses [150]. Stimulant use has long been recognized for its links with infectious diseases following condomless sex with multiple and concurrent partners under the influence [151, 152]. The powerful synthetic opioid, fentanyl, is frequently used as an adulterant for street heroin, methamphetamine and cocaine, contributing significantly to overdoses [153]. In 2016, over 7,200 people in the U.S. died from combining cocaine with opioids [154].

Treatment

Early identification of stimulant use in patients receiving treatment for opioid addiction is critical for ensuring patient safety and effective treatment. A thorough history and physical, as well as urine drug screen can help identify the specific stimulant(s) involved, which should be addressed in the initial treatment plan. Proper evaluation may include requiring some period of abstinence from stimulant use to test for the ability to stop using stimulants. This may require stimulant-specific program interventions, such as mandated treatment in groups focused specifically on stimulant use. Treatment of psychosis and paranoia should not be delayed because of ongoing use.

Treatments for stimulant use disorders are almost entirely behavioral, as there are no drugs approved for the treatment of cocaine or methamphetamine [155]. Methadone or buprenorphine can be an appropriate treatment option when used in conjunction with a multi-pronged approach including behavioral intervention, support groups, and motivational enhancement for people with co-occurring stimulant use disorders and opioid use disorders [142].

More research is necessary to determine buprenorphine's effectiveness over long periods of time, if there a dose- and/or administration-dependent relationship, and if there are significant side effects or issues with safety that providers should be aware of when managing patients with opioid and stimulant addiction [156].

5.2.2. Alcohol

Epidemiology

Alcohol use disorder (AUD) is a common problem among patients with OUD, and contributes significantly to the high mortality rate in this population. About 20% of patients receiving treatment (OUD) with methadone or buprenorphine/ naloxone also have AUD [157]. Moreover, Superscript reference AUD is a risk factor for increased overdose and mortality in patients with OUD—accounting for about 40% of deaths in these patients. AUD is also associated with poor compliance with

Table 5.2.1

Stimulants – Other Important Information

- The major difference between cocaine and methamphetamine is that cocaine acts extracelluarly, but methamphetamine acts both extracellulary and intracellularly. Clinically, this means methamphetamine's effects last much longer, are more severe, and potentially more neurotoxic and destructive.
- Patients suffering acute effects of methamphetamine may appear like patients with acute schizophrenic psychosis, but they are often at least vaguely aware that what is happening to them is connected to the drug they took. These patients often respond to the "talking down" strategy (quiet room, low light and noise level, calm,reassurance).
- Consider hospitalizing the patient when you see: danger to self or others; inability to safely travel from clinic.
- Psychosis from chronic methamphetamine use can persist and often be "encapsulated," meaning that it isn't obvious until the subject of their delusion is brought up in conversation.
- Methamphetamine psychosis can be induced in almost everyone; it is dependent mostly on total lifetime exposure.
- There is no real evidence that methamphetamine can cause schizophrenia, but persistent psychosis is more likely in people with a family history of psychiatric disorders.

pharmacotherapy, increased risk of relapse, increased risk of hepatotoxicity leading to cirrhosis, and exacerbation of psychiatric comorbidities among patients receiving opioid agonist treatment (OAT) [157, 158]. Alcohol withdrawal may pose serious health complications among patients with co-occurring OUD and AUD during and outside of treatment [159].

Treatment

Given the prevalence of health and safety risks for patients with OUD, treatment for AUD needs to be an important component in their treatment plans. Patients with OUD and AUD should be screened for hepatotoxicity. Patients with OUD and AUD have heightened risk of opioid overdose, and may require administration of naloxone to block opioid receptors and restore normal respiration [160]. Patients with OUD and AUD who are at risk of developing severe, complicated alcohol withdrawal should be identified, as they may require inpatient care or benzodiazepine therapy for withdrawal management before proceeding with treatment of OUD [159].

Table 5.2.2

Health Risks of Excessive Alcohol Use

System	Effects
Brain	■ Interferes with brain's communication pathways ■ Altered mood and behavior ■ Impaired thinking, movement, coordination
Heart	■ Cardiomyopathy ■ Arrhythmias ■ Stroke ■ Hypertension
Liver	■ Steatosis ■ Alcoholic hepatitis ■ Fibrosis ■ Cirrhosis
Pancreas	■ Pancreatitis
Immune system	■ Weakening of the immune system ■ Increased susceptibility to infection (e.g., pneumonia, tuberculosis, etc.)
Cancer	■ Head and neck cancer ■ Esophageal cancer ■ Liver cancer ■ Breast cancer ■ Colorectal cancer

Alcohol Testing

An alcohol history should be part of the initial admission evaluation; standardized screening instruments such as the CAGE or AUDIT may be used. For patients who present in alcohol withdrawal, a CIWA should be used to document need for acute withdrawal treatment using benzodiazepines. Alcohol breathalyzer testing can be used to identify patients who are unable to control their drinking. It may also help clarify a patient's drinking pattern (daily versus weekend or holiday binges). Be aware that some patients are able to titrate their alcohol consumption, stopping early enough in the day to avoid a positive breath test in clinic the next day; urine screens can be helpful in this situation, especially for detecting episodes of binge drinking, as urine remains positive longer than breath.

Alcohol and Methadone Treatment

AUD impacts methadone in two specific ways: acute use, specially combined with methadone, leads to synergistic sedative effects. Chronic use stimulates the metabolic activity of the P450 enzymes leading to more rapid methadone metabolism, and thus a reduced methadone blood level. Achieving a stabilized methadone dose may be complicated by the concomitant use of alcohol. Early screening, intervention and treatment planning are essential to effect change in this potentially lethal behavior.

Alcohol Testing and Methadone Treatment

The patient who presents for dosing with a positive Breathalyzer test poses a clinical dilemma. Safety is the critical issue. A dose of methadone on top of an unknown quantity of alcohol puts the patient at risk for sedation or overdose. Missing a dose of methadone increases the likelihood that the patient will use heroin in addition to alcohol. Serial Breathalyzer tests (i.e. two tests about 30 minutes apart) may be used to determine whether the patient's serum alcohol level is on the way up or down. The physician's role is to determine whether it is safe for the patient to receive his/her regular dose of methadone or some portion of it. There is no body of literature establishing the best course of action, and physician practices vary.

Some physicians decline to administer a dose of methadone to a patient who has any positive Breathalyzer score. This practice may deter patients from coming to clinic to dose when they have been drinking. Other physicians withhold the dose if the patient appears under the influence or has a Breathalyzer >.04. Intoxicated patients should be advised not to drive and assisted to arrange other transportation home. Some physicians will order a partial dose (half) for patients with a positive Breathalyzer that is <. 04 provided they do not appear under the influence. When the Breathalyzer is <. 02, it may be reasonable to continue the regular dose. See also Methadone Section for more specific dosing guidance.

These protocols depend partly on clinic philosophy. Because of the high prevalence of hepatitis C, some clinics have a lower threshold for holding the dose to discourage alcohol use in this group. The clinic's policy regarding alcohol use, BAC levels and dosing should be established and discussed with patients during the initial orientation process.

In the alcohol-tolerant patient, blood alcohol levels do not necessarily correlate with functional impairment. Even if the patient is alert with alcohol "on board," the effect of methadone in synergism with the alcohol may significantly reduce alertness after dosing.

When alcohol use is identified, the patient's treatment plan should reflect this and include approaches to address it. Frequent follow-ups may be offered in order to provide brief interventions (see CSAT Tip 34) and possibly pharmacotherapy. Withdrawal from alcohol can be medically dangerous. Patients whose Breathalyzer results are positive on more than one occasion should be evaluated for the presence of physical dependence and assisted to obtain medical detoxification from alcohol when needed. Some programs offer outpatient detoxification from alcohol with phenobarbital or benzodiazepine. Patients whose past history includes severe alcohol withdrawal, such as seizures, blackouts or DTs, or patients who are medically fragile or pregnant, require hospitalization for detoxification from alcohol use. (ASAM *Principles of Addiction Medicine*) [161] In some communities the prevalent stigma associated with MMT, even in some addiction treatment programs, makes it difficult to place methadone maintained patients in inpatient alcohol treatment facilities.

When physical dependence is not, or no longer an issue, pharmacotherapy with disulfiram (Antabuse®) may be considered. The typical dose is 250 mg to 500 mg per day. The first dose should not be given until the patient has been alcohol free for at least 48 hours. Patients should be given information about inadvertent alcohol ingestion in mouthwash, sauces, vinegars, cough suppressants, cosmetics, etc. [162] and sign a consent that explains the potential adverse physical reaction to alcohol exposure while on disulfiram. The physician must make sure that the patient understands the purpose and effects of the medication before prescribing or dispensing it. Dispensing the medication at the clinic's dosing window increases the likelihood of compliance. The use of this deterrent medicine has been shown to be effective in several studies with methadone patients, but requires regular liver function testing [162]. It is explained more fully in Chapter 6 of the textbook, *Methadone Treatment for Opioid Dependence* [163] The chapter title is "Other substance use disorders in methadone treatment: prevalence, consequences, detection and management."

Alcohol and Buprenorphine Treatment

Alcohol use has not been generally highlighted as a serious clinical concern in patients receiving buprenorphine for treatment of OUD; the literature suggests that buprenorphine may even reduce alcohol intake [164]. However, in the present context, alcohol use should be discouraged, and where signs of excessive use exist, appropriately addressed, because of the effects of alcohol on treatment adherence, which, in turn, may have deleterious effects on other aspects of treatment.

Alcohol, Other Opioid Agonist Treatments (OAT) and Other Interventions

Other effective interventions for AUD include the patient receiving OAT plus clinician-delivered brief intervention, motivational interviewing, and cognitive-behavioral coping skills [165, 166]. While there are medications that have shown effectiveness for alcohol prevention in the general population, generally their effectiveness in the OAT population has not been studied or their use is contraindicated. For example, naltrexone should not be administered to patients receiving OAT as it can precipitate opioid withdrawal, acamprosate has not been studied in the OAT population and disulfiram has yielded unclear results [167]. Medications like gabapentin, baclofen, and topiramate are promising options for medication assisted therapy but more research is necessary to determine if they are feasible treatment options.

5.2.3. Nicotine

Nicotine Use is Ubiquitous

People who use opioids overwhelmingly use nicotine-containing products as well, especially cigarettes. Nicotine likely serves as a primer for other drugs, including opioids, prolonging the action of other substance and potentiating their effects [168]. Cigarettes are the most common nicotine product used in the United States, but cigars, cigarillos, hookah pipes, smokeless tobacco, and electronic-nicotine delivery systems (i.e. e-cigarettes) are also common [169]. The prevalence of tobacco use among OUD patients is higher than in other addictions and almost five times greater than in the general population [168]. In a study of OAT patients on methadone or buprenorphine, 97% used cigarettes, smoking on average 20 cigarettes per day [169].

Nicotine and Methadone Treatment

Nicotine and methadone have a synergistic action. Patients on nicotine replacement therapy have been observed to have decreased opioid withdrawal symptoms and patients on methadone seem to have decreased nicotine withdrawal symptoms and increased euphoria [169].

Nicotine Treatment

Although the high morbidity and mortality of smoking is generally understood, many patients do not recognize the specific impact that smoking is already having on their own health, nor are they aware of the inevitability of lung disease in everyone who smokes for 30-40 years.

Many patients express an interest in quitting and find the recovery skills they are learning to address opioid addiction to be useful in addressing nicotine addiction. Some patients will cut down, temporarily quit, or repeatedly try to quit, and may be discouraged if they have been unable to quit.

Nicotine Treatment Pharmacotherapy

Nicotine Replacement Therapy (NRT), bupropion and varenicline are three medications that have been approved in the United States as treatment for smoking cessation [170]. The Cochrane's (2013) review of pharmacological interventions revealed the following:

- NRT and bupropion are more effective than placebo. For every 10 people who quit with placebo, about 18 people quit smoking when using NRT or bupropion.
- Varenicline more than doubled the likelihood of quitting when compared with placebo.
- Varenicline is more effective than NRT (including the patch, lozenges, gum, tablets, sprays and inhalers).
- Combining two types of NRT is as effective as varenicline, and more effective than using a single type of NRT.

The efficacy of pharmacotherapy increases when patients attend a cessation support group. The OTP can encourage smoking cessation by having cessation support groups on site and by prohibiting smoking on clinic premises, so that patients do not have to see and smell cigarettes when they come to the clinic. Addressing smoking behavior in treatment plans and at annual examinations and offering smoking cessation interventions on-site encourages patients to cut down and eventually quit smoking.

Co-existing depression is a factor that reduces success in smoking cessation. It is advisable to assess for depression before a patient launches an attempt to quit. Those already on antidepressants may require a dose adjustment once they quit. Interventions demonstrated to increase likelihood of nicotine cessation include:

1. Brief counseling provided by a clinician. (This intervention has been shown to improve the likelihood that a smoker will successfully quit and remain a nonsmoker for subsequent 12 months.) [171]
2. Smoking cessation group counseling and individual therapy based on cognitive behavioral therapy [172].
3. Pharmacological interventions [170].
4. Referral to toll-free telephone quit-line numbers such as 1-800-NO-BUTTS or 1-800-QUIT-NOW [173].

In November of 2007, the FDA required a black box warning regarding the possibility of serious neuropsychiatric symptoms observed in post-marketing surveillance when using varenicline for smoking cessation that involved hostility, suicidal thoughts and agitation. In 2016, the FDA reviewed data on efficacy and adverse events (the EAGLES trial) [174] in an RCT evaluating varenicline, bupropion, nicotine replacement and placebo in a large sample of controls and of psychiatric patients who were seeking smoking cessation. Findings showed no higher rates of adverse events for varenicline and showed superior smoking cessation outcomes for varenicline across control and psychiatric groups. This led the FDA to recommend removal of the black box warning and to include a statement that varenicline produces superior smoking cessation outcomes compared to bupropion and nicotine replacement. Best practice would involve a discussion of the risks and benefits with patients willing to start another quit attempt using varenicline.

5.2.4. Benzodiazepines, Sleep Drugs, and Muscle Relaxants

Benzodiazepines (particularly clonazepam (Klonopin®) and alprazolam (Xanax®) are often and increasingly used with opioids as they seem to amplify and prolong the opioid effects [175]. This is particularly problematic because benzodiazepine produces synergistic sedative effects with opioids such as methadone. Patients may use benzodiazepine to suppress the agitation produced by stimulant abuse or to potentiate an opioid high. Some patients say that they abuse benzodiazepine because "it makes the methadone feel like heroin."

Unfortunately, patients may use benzodiazepines with other sedating substances, such as muscle-relaxants (combination of an opioid, a benzodiazepine and carisoprodol) or antihistamines (combination of an opioid, a benzodiazepine and an antihistamine) (see Table 1 in Polysubstance Abuse Section for statistics.) [176, 177]

Assessment and Testing

Due to the frequency of abuse and patients' inconsistent reporting at admission, adding benzodiazepine to the admission drug screen is recommended and to subsequent screens in patients whose history is suggestive or who screen positive at admission. Note that testing for clonazepam (Klonopin®) and lorazepam (Ativan®) requires special assays; routine benzodiazepine screens will not detect them. In addition, routine drug screenings also do not identify carisoprodol. Patients who present for dosing appearing under the influence of a sedative must be carefully interviewed and assessed. It may be necessary to have the patient transported to a local emergency room for evaluation of altered mental status and observation. If the patient has already been dosed before the sedation is noted, the patient will need to be under observation until the methadone has peaked (3-4 hours). The patient should relinquish their car keys and arrange other transportation home.

Adverse Effects

Concurrent use of benzodiazepines and opioids can lead to respiratory depression, CNS depression, overdose and overdose fatalities [175]. Respiratory depression is the chief mechanism leading to overdose mortality. It is estimated that 40 and 80 percent of methadone- or heroin-related deaths are associated with benzodiazepines.

Pharmacology

Opioids act through μ- and δ-receptors while benzodiazepines act on the GABA receptors to inhibit the respiratory center in the medulla. [Jones] Thus, when used concurrently they have an additive effect on respiratory depression, placing the patient at higher risk for overdose.

Benzodiazepines and Buprenorphine

Buprenorphine is safer than methadone when used alone due to its "ceiling effect" on respiratory depression. Unlike barbituates, benzodiazepines, when used alone, do not cause respiratory depression. **However, when buprenorphine and benzodiazepines are used concurrently, the protective "ceiling effect" on respiratory drive is eliminated** [178, 179].

Use in Treatment

Benzodiazepines, opioids and OAT are still being prescribed concurrently. Although there is a theoretical risk of over-sedation or overdose in patients undergoing concurrent opioid and alcohol withdrawal treatment, no research to date has demonstrated clear interactions or quantified the risk of administering these treatments simultaneously. [Nolan] Thus, all MAT patients with AUD should be offered treatment, monitored closely in a setting where methadone or buprenorphine doses can be promptly adjusted and monitored closely for any other adverse effects. [Nolan] An FDA Drug Safety Communication was issued in 2017 recommending not to withhold MAT for patients who are being treated with benzodiazepines or CNS depressants. The statement recognizes the potential harms of the combined medications, but cautions that these are likely outweighed by the certain harms of withholding MAT. The Communication also contains recommendations for clinicians to address with patients their use of benzodiazepines and CNS depressants in MAT.

Patients may obtain benzodiazepine illicitly or by prescription from a physician unaware the patient is on MAT. Benzodiazepines and other CNS depressants are often requested to combat anxiety and insomnia associated with withdrawal [180]. The MAT physician should meet with a patient who is taking a prescription benzodiazepine or CNS depressant to discuss the risk of overdose and misuse/addiction and to explore the possibility of alternative medical and behavioral treatments. The patient should be asked to sign a release allowing the MAT physician to communicate with the physician prescribing the benzodiazepine or CNS depressants. Because of the potential for overdose when a benzodiazepine is mixed with another/other sedatives, it is appropriate to discuss the risks and benefits of continuing use of the benzodiazepine or depressants with the patient and to make an agreement that use of the medication will be monitored. As well, the physician treating anxiety using benzodiazepines should be made aware that the patient is on opioid agonist therapy. Careful tracking of prescription records using the prescription drug monitoring program (CURES) and urine screening tests provide information that can alert both the MAT physician and the prescribing physician to prescription drug misuse.

Carisoprodol (Soma®), a non-benzodiazepine sedative-hypnotic drug, is a frequently found, concomitantly abused drug. Its use in the context of a maintenance program should be strongly discouraged. The prescribing physician needs to be aware that the patient is on MAT, so the patient should be asked to sign a release allowing communication and coordination with the prescribing physician, using procedures identical to those for benzodiazepines and other CNS depressants. Routine drug screenings do not identify carisoprodol; special testing is required to detect it.

When a patient is using benzodiazepines, alcohol or other sedatives and is seeking admission to MAT or is currently receiving MAT, it is the responsibility of the OTP physician to weigh the risks and benefits of initiating or continuing methadone or buprenorphine given the specifics of the patient's situation. In the event that the risk is felt to be too great (such as when a patient is repeatedly presenting to clinic appearing too sedated to dose or has had ER visits/ICU stays for overdose), an alternative plan for treatment should be offered to safely address the opioid and sedative use disorders.

Recommendations for treating patients with concurrent use of benzodiazepines, other CNS depressants and opioids include [181]:

1. Educate patients about the risks (including risk of death) inherent when benzodiazepines, depressants and opioid agonists are combined.
2. Diligently assess for benzodiazepine use, including asking about substances used, dose, and frequency of use.
3. Consider and discuss adjustments in induction procedures and requirements for monitoring patients.
4. For treatment of anxiety, consider use of non-benzodiazepine medications, which have a better safety profile, like SSRIs and SNRIs in combination with behavioral therapy. Benzodiazepines should not be the treatment of choice for anxiety.
5. If a patient has a history of long-term benzodiazepine use, he/she should be evaluated to determine the safest treatment plan. In some, taper/detox and monitoring at

a higher level of care may be indicated prior to initiating OAT. In others, gradually decreasing to the lowest effective dose is indicated.

6. Generally, medication-assisted treatment should not be discontinued for persistent benzodiazepine use, however, close monitoring and risk management strategies should be implemented.
7. Once OAT is initiated, if a patient presents to clinic appearing sedated, consider holding or decreasing the methadone or buprenorphine dose until further medical assessment can be performed.
8. Assessment for diversion or abuse should be carried out regularly for patients with controlled substance prescriptions. Toxicology screening may help to determine whether a patient is taking the prescribed medication and whether illegal drugs are being used. Confirmatory testing should be considered if there are concerns about misuse or substitution.
9. Routine review of the Prescription Monitoring Drug Program, CURES in California, should be carried to confirm one single provider, one single pharmacy and reduce the risk for misuse, abuse or diversion.

5.2.5. Cannabis and Cannabinoids

Over the past decades, cannabis use has become almost as prevalent as tobacco use in California. Cannabis contains over 80 cannabinoids. Its effects on the brain are characterized by the altered sense of time, mood, movement, thinking, and memory [182]. In the brain, the CB1 receptors are responsible for THC's psych-activity. The CB2 receptors are not psychoactive and are related to the immune system's anti-inflammatory effects. Delta-9-tetrahydrocannabinol (THC) is the psychoactive cannabinoid found in cannabis and likely responsible for the euphoria and increased sociability associated with cannabis use [183]. Cannabidiol (CBD), the other cannabinoid of therapeutic interest, is not psychoactive and does not act on the cannabinoid receptors [183]. It has effects opposing those of THC. The ratio between THC and CBD is thus important in any cannabis product. The concentration of THC is rising from selective cultivation [184]. There are new risks emerging from ongoing use of synthetic cannabinoids, which are compounds created in the laboratory and often sprayed on spices or other organic material that can be smoked or ingested [184].

Cannabis and Opioids – A Limited, Mixed Bag

There are only a few things known about cannabis that are supported by scientific findings, even fewer that are relevant to SUD in general and to OUD in particular. Cannabis use among patients receiving opioid agonist therapy in California is highly prevalent. Though cannabis remains classified as a Schedule 1 drug, it is now legal in California. It is imperative to consider the possible effects cannabis use might have on public health. Certain research studies have shown a positive effect of cannabis legalization, particularly among patients receiving opioid agonist therapy [185]. Cannabis use has been associated with lower opioid overdose mortality rates, and less opioid use and increased quality of life among patients with chronic pain [186, 187]. On the other hand, cannabis use is associated with polysubstance use, impaired cognition, and psychotic episodes and disorders in specific groups in the population [188, 189]. There are harmful impacts on the developing brain that are not seen in the adult brain. In addition, population based studies suggest that using cannabis at baseline is associated with increased rather than decreased use of prescription opioids in follow up [190].

Among patients receiving opioid agonist therapy, research study findings seem to be contradictory. In general, OAT patients tended to use cannabis heavily and are at increased risk of premature dropout from treatment [185]. However, other studies have found contradictory evidence. Thus, differences in gender, demographics, and age should be considered. More research is necessary to determine the long-term effects of concurrent cannabis use and OAT.

Relevant Clinical Use

Cannabis has primarily been used in combination with opioids for pain relief [191] (Academy of Medicine report). Epidemiological evidence suggests use of cannabis may reduce opioid use in some patients, though findings have yet to be demonstrated in a randomized controlled trial.

Cannabis Use Disorder

Cannabis use can lead to a SUD, which is likely to increase with its availability and rising potency. Symptoms of cannabis use disorder can include disruptions in daily functioning, tolerance, cravings, and withdrawal symptoms, such as sleep disturbance, restlessness, nervousness, anger, or depression [192]. There is ongoing debate about whether or not cannabis is a "gateway drug," however in practice, it is commonly used in conjunction with alcohol and other substances.

Cannabis Adverse Effect

Daily or nearly-daily use has been associated with several adverse health outcomes including anxiety, dysphoria, paranoia, cannabis addiction, poorer cognitive performance, higher association with psychotic symptoms, increased risk of myocardial infarctions, respiratory infections, and higher risk of mouth, tongue, esophagus, and bladder cancer [193].

Still, there can be no argument that the adverse consequences of cannabis are far less than with opioids, which argues in favor of its being a potentially effective harm reduction strategy. Of particular interest are two facts:

1. There are few, if any, deaths by cannabis overdose. This is largely because there are no CB1 receptors in the lower respiratory centers.
2. States with medical cannabis laws have generally seen a fall in opioid overdose deaths. [194]

Advice to Patients

Physicians might have difficulty deciding how to address the use of cannabis by their patients on MAT. Ideally, share the facts about the lack of evidence and the risks associated with use and impact on recovery. Avoid judgment, but explore fears of stopping cannabis use. Regardless, focus on pragmatic outcomes such as improved functioning in various domains, better mental health, progressing in recovery (being/becoming someone who does not meet criteria for OUD or cannibus use disorder) and participating in the program. After all, if recovery is to be considered, getting high every day is still getting high every day.