Chapter 85: Substance Use Disorders I: Opioids, Cannabis, and Stimulants

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 71, Opioid Use Disorder.

KEY CONCEPTS

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1. The financial impact of the opioid crises is estimated to have totaled $504 billion in 2015, which accounted for approximately 2.8% of the gross domestic product (GDP).

2. Opioids accounted for over 70% of all overdose deaths in 2019. The Centers for Disease Control and Prevention (CDC) estimates each day at least 136 people in the United States die from an opioid overdose.

3. Between 2006 and 2012, opioid prescribing in the United States steadily increased with a peak annual opioid prescription count of 255 million prescriptions.

4. Opioid overdoses involving prescription opioids, synthetic opioids, and heroin have continued to increase while healthcare professionals, legislators, and the community have worked together to reverse this trend, by focusing on prevention, treatment, recovery, and enforcement.

5. The pathophysiology of opioid use disorder, as with other substance use disorders (SUDs), centers around the reward centers and mechanisms in the brain.

6. Opioid use disorder (OUD) is a chronic often relapsing condition. Viewing OUD as a disorder and providing medications for the treatment of OUD, patient education, and support have been shown to decrease the risk of accidental overdose or full relapse into opioid use.

7. There are three Food and Drug Administration (FDA)–approved medications used in OUD: buprenorphine, methadone, and naltrexone. All three medications have demonstrated superiority for substance use disorder over no treatment. Pharmacotherapy in combination with psychosocial therapy has been found to be more effective than either treatment alone.

8. Patients who achieve clinical stability have longer acting options that may improve adherence and quality of life.

9. While not a treatment for OUD, naloxone is an integral treatment option that has been shown to save lives. Naloxone is a mu-opioid receptor antagonist that can be used in the reversal of an opioid overdose. It can be administered by multiple routes and is available without a prescription in many states. Healthcare providers play an important educational role on the importance of naloxone use in an opioid overdose situation.

10. Benzodiazepine prescribing has increased by over 65% from 1996 to 2013 and continues to climb. Overdose rates have increased over sevenfold from 2002 to 2019, the peak occurring in 2017.

11. Symptomatic and supportive care is the standard of care for benzodiazepine intoxication. Flumazenil is an antagonizing antidote that can

be considered in select overdose situations. Treatment of benzodiazepine withdrawal is similar to treatment of alcohol withdrawal.

12 Stimulants including cocaine, methamphetamines, and newer derivatives continue to pose a significant issue to the population. Treatment of acute intoxication from these agents centers on supporting vital functions, while treatment for chronic use is less well described for such stimulants.

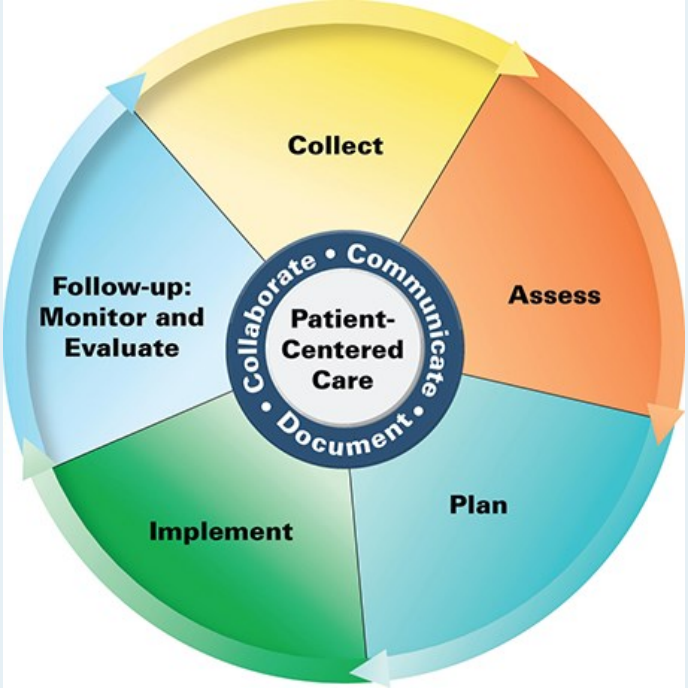
13 Expanded legalization of cannabis by individual states has brought an increase in chronic use. Emerging evidence supports the occurrence of an associated syndrome of effects known as cannabinoid use disorder (CUD). Treatment of CUD is in its infancy.

14 Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclical vomiting in individuals with habitual use of cannabis that abates after discontinuation of use. The pathophysiology underlying CHS is not completely elucidated.

15 Many individuals who experience CHS report that hot showers improve symptoms, but that the benefit is short-lived. If intravenous fluids and traditional antiemetics are unsuccessful, other treatment options that are less established have been reported. Dopamine antagonists like haloperidol have been used successfully as well as topical capsaicin products.

PATIENT CARE PROCESS

Patient Care Process for Opioid Use Disorder (OUD)



Collect

Objective Data

- Patient characteristics (eg, age, sex, pregnancy status)
- Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
- Prescription drug monitoring program (PDMP) data

- Practitioner observed pill counts
- Labs including urine or oral fluid drug testing, pregnancy test, liver function tests (LFTs), Hepatitis B and C serology, Human Immunodeficiency Virus (HIV) serology

Medication history

- Current medications including herbal products, dietary supplements, over-the-counter (OTC) medications, nonprescribed medications, prescription medications, illicit substances
- Known medication allergies or intolerances

Past medical history

- Past or current co-occurring illnesses (physical and mental), injuries, surgeries, and hospitalizations
- General state of current physical and mental health (eg, good, fair, poor, concern for suicidal ideation)

Social and environmental history

- Substance use (eg, tobacco/ethanol use, substance use, prescribed and/or non-prescribed medication use)
- Opioid use history (eg, age of first use, frequency and recentness of use, routes of use, overdose history, medication and drug mixing, withdrawal, tolerance, history of treatment for substance use disorder [SUD])
- Problems resulting from substance use
- Participation in high-risk activities for contracting sexually transmitted infections (STIs)
- Living environment and transportation resources
- Current support systems (eg, family, friends, group therapy)
- Family history of SUD (eg, parents, siblings, partners)
- Childhood or adolescent abuse (eg, emotional, sexual, physical, verbal)

Assess

Signs of opioid intoxication or withdrawal

- Physical
    - Dental caries, perforated septum, skin abscesses, needle track marks, swollen extremities, withdrawal (eg, goose bumps, nausea, abdominal cramps, tearing, yawning, runny nose, yawning) or intoxication (eg, drooping eyelids, constricted pupils, reduced respirations, itching, head nodding)
- Neurological
    - Dilated or constricted pupils, slurred or rapid speech, agitation, insomnia, falling asleep at inappropriate times, unstable gait
- Psychiatric and Behavioral
    - Depression, anxiety, low self-worth, mental health disorders, feelings of hopelessness or loss of control, resentment
    - Use of other substances, conduct disorders, impulsivity, alienation from others, involvement with the criminal justice system
- Risk stratification

- Assess patients for alcohol, tobacco, substance use, and substance use disorders
- Screening tools and symptom surveys may aid in determining opioid risk (eg, Pain Medication Questionnaire, Opioid Risk Tool, Current Opioid Misuse Measure), opioid withdrawal (eg, Clinical Opioid Withdrawal Scale, Objective Opioid Withdrawal Scale), alcohol use disorder (alcohol use disorder identification test), and respiratory depression (Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression).
- The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) criteria for diagnosis of SUD should be established by a provider prior to proceeding forward with treatment.

- Evaluate patient readiness
  - Highlight consequences that may motivate positive change
  - Identify patients' reasons to start treatment (eg, people, quality of life, self)
  - Determine the patients' preferred treatment setting (eg, opioid treatment programs, outpatient office visits with a prescriber)
  - Discuss potential barriers for patient access to treatment for OUD, mental health support, and laboratory tests for monitoring

Plan*

- Engage the patient in shared decision making regarding the risks and benefits of using medications to treatment of OUD, including alternative treatments
- Review medication options for the treatment of OUD (Tables 85-1, 85-2, and 85-3)
- Design a medication therapy regimen (eg, specific medication(s), dose, route, frequency, and anticipated duration of therapy (Tables 85-1, 85-2, 85-3, and 85-5)
- Communicate monitoring parameters including efficacy (eg, cravings, relapse, and withdrawal symptoms) and safety (eg, medication interactions, adverse medication effects); frequency and timing of follow-up
- Educate patients about their diagnosis, medication, and expectations (eg, purpose of treatment, possible adverse medication effects, importance of proper storage of medication, naloxone education, risk of overdose with discontinuation of treatment and return to substance use, notify other providers they are on this medication) (Table 85-4)
- Refer patient to other providers when appropriate (eg, behavioral health specialist, social worker)

Implement*

- Initiate individualized dosing focused on improving symptoms of withdrawal without over-sedation
- Titrate dosing over days to weeks to target cravings and blunt the euphoric responses from self-administered illicit opioids
- Review all elements of treatment plan with the patient and their support system (eg, friends, family, significant others)
- Continue to engage the patient with motivational interviewing, establish patient-centered goals and identify healthy coping strategies
- Provide a home naloxone device and complete proper education with the patient and their support system
- Schedule patient follow-up visit

Follow-up: Monitor and Evaluate

- Assess patient for changes in health (eg, pregnancy, pulmonary disease, hepatitis) and medications, including those non-prescribed

substances, prescribed medications, OTC, or herbals)

- Reevaluate medication therapy daily to weekly until stable
- Continue random drug testing, and monitoring for medication-related adverse medication effects

Collaborate with patient, caregivers, and other healthcare professionals.

BEYOND THE BOOK

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Watch the video entitled "Opioid Overdose-Administration of Naloxone" by NIH Pain Consortium Centers of Excellence in Pain Education at Saint Louis University Edwardsville. This brief video provides an overview of the three FDA-approved naloxone delivery methods for the treatment of opioid overdose.

https://tinyurl.com/slvh6fx

Determine if your state has approved use of cannabis for medical purposes and/or legalized recreational use. Determine if your state's governing board has issued a statement or policy about medical cannabis. Think about how your health system is affected by these state laws.

INTRODUCTION: OPIOIDS

In 1889, the Boston Medical and Surgical Journal published a piece by J.F. Adams, M.D., addressing the unique and indispensable place opium holds in the pharmacopeia. "While surpassing other remedies in its beneficent effects, it is alike remarkable in its power to harm. Hence, its medical use requires a degree of caution not less than that with which a surgeon handles a scalpel." Adams goes on to highlight his concerns with opioid use (eg, risk of overdose, significant side effect profile, and risk of dependence) advocating for judicious stewardship of these agents.[1] Negating Adams' previous concerns was a 1980 single paragraph letter to the Editor of the *New England Journal of Medicine* reporting the risk of physical dependence was rare in patients without a history.[2] A bibliometric analysis identified 600 citations of this letter occurring between 1981 and 2017. Interestingly, the majority of these citations occurred after the FDA approval of OxyContin© (extended-release oxycodone hydrochloride) in 1995.[3] OxyContin® promotion was done by targeting primary care providers claiming it was less addictive than traditional opioids. While this marketing sparked an exponential increase in prescribing, an intense morphine-like high could still be experienced when it was crushed and injected, snorted, or swallowed. This promotion of opioid prescribing and availability was further perpetuated in late 1990s by professional organizations (eg, American Pain Society, American Academy of Pain Medicine, and the American Geriatrics Society) who endorsed the use of opioids in chronic non-malignant pain.[4] In the early 2000s, the Joint Commission linked healthcare quality and patient satisfaction with pain control which prompted providers to take action in addressing patient-reported pain scores. The overall result from this series of overlapping events was increased opioid prescribing, increased non-medical use of prescription opioids, and an increase in opioid-related deaths.

In an attempt to regain equilibrium, national and global health organizations allocated efforts and resources to addressing what was now a public health issue. Clinical guidelines and safety measures regarding controlled substance prescribing, prescription drug monitoring programs, education on proper storage and disposal of opioids, and take-home naloxone were expanded.[5] While these actions resulted in decreased opioid prescribing beginning in 2006, opioid-related overdose deaths continued to increase. An epidemic once fueled by the use of pharmaceutical opioids is now overshadowed by illicit manufactured fentanyl (IMF), fentanyl analogs, and heroin use. Thus, diluting the previous progress made by organizations such as the Centers for Disease Control and Prevention (CDC), the National Institute on Drug Abuse (NIDA), and the FDA. As a result, OUD continues to plague individuals, their families, and their communities.[6]

Like the disease itself, solutions related to extinguishing the opioid epidemic are multifaceted and multifarious in nature. Confronting this epidemic begins with addressing the social stigma of SUDs, increasing patient access to treatment, and ensuring provider comfort with prescribing treatment.

Enlisting the help of communities through education on proper storage and disposal of opioids, as well as training on the use of the rescue medication naloxone[7] will be essential in reducing opioid-related deaths. These interventions will be costly, but they are needed to mitigate the cost of the ongoing crisis.

1 The council of economic advisers, an agency to the executive office of the president estimates the financial impact of the opioid crises (both fatality- and non-fatality–related costs) to have totaled $504 billion in 2015, a figure which accounts for approximately 2.8% of the gross domestic product (GDP) that year.[8]

Epidemiology

Despite the focus on prescription opiates, the opioid issue continues to worsen. Between 1999 and 2019, the number of overdose deaths in the United States more than quadrupled. 2 Opioids accounted for over 70% of all overdose deaths in 2019 and the CDC now estimates each day at least 136 people in the United States die from an opioid overdose.[9,10] These overdoses often involve poly-substance use making it difficult to interpret and classify mortality data. Over the last 20 years, the United States has seen three different waves of opioid overdose-related deaths. The first wave started in 1999 with prescription opioids (eg, natural opioids, semi-synthetic opioids, and methadone) and continued to rise as the second wave began in 2010 marked by a substantial increase in heroin overdoses. In 2013, a third wave created an exponential rise in synthetic opioid overdoses predominantly driven by IMF compounds in cocaine, heroin, and counterfeit pharmaceuticals.[9,10]

SUD is associated with comorbidities such as cardiovascular disease, stroke, cancer, lung disease, hepatitis, and infection with the human immunodeficiency virus. These healthcare issues occur without regard to the amount or frequency of substance use by an individual. The interplay between mental health and co-occurring SUD has yet to be fully elucidated. However, the National Survey of Drug Use and Health (NSDUH)[11] indicates an association between the two, with 397,000 adolescents aged 12 to 17 reporting major depressive episodes plus SUD. Along with 9.5 million reporting having both a mental illness and SUD. The impact of this disease combination is known to further inhibit functional ability, reduce treatment success rates, increase risk of homelessness, suicidality, incarceration, morbidity, mortality, and healthcare costs when compared to individuals with a single diagnosis. While current guidelines support addressing both disorders congruently, only 1.3% of adolescents with SUD and major depressive disorder (MDD) and 7.8% of adults with SUD and acute mental health issues received concomitant treatment in 2019.[11]

The Opioid Epidemic

3 Opioid prescribing in the United States steadily increased beginning in 2006 and peaked in 2012 with 255 million prescriptions dispensed annually. Between 2012 and 2019 the rate of opioid prescribing was nearly cut in half going from 81.3 prescriptions per 100 people to 46.7 per 100 in 2019.[12] However, in 2017 over 17% of the US population still had at least one opioid prescription filled. The greater than 19% decrease in prescribing may be attributable to a combination of factors including increased regulatory oversight, enhanced awareness of opioid-related risks, educational initiatives, and new legislative efforts to improve the prescribing and dispensing of controlled substances.

A large contributor to oversight improvement came with the implementation of statewide prescription drug monitoring programs (PDMPs), which are now operational in 49 of 50 states.[13] The PDMPs are electronic systems used for tracking controlled substance prescriptions with the intent to prevent diversion (eg, patients obtaining opioids from multiple providers) and improving patient safety, while still maintaining access.[14] Pharmacies are required to report dispensing information routinely to the program in the states that participate and over 40 states also require healthcare practitioners to access this database prior to prescribing a controlled substance. Specific requirements vary by state; however, interstate communication between programs has also become common. In an effort to optimize the use of PDMPs, some states have allowed incorporation of the PDMPs into the electronic health record (EHR) systems, decreased barriers to the registration process, and the ability for prescribers to assign delegates to review the PDMP under their license.[14]

Another measure focused on promoting opioid safety and reducing related harms (eg, OUD, overdose) included the CDC's 2016 publication of a Guideline for Prescribing Opioids for Chronic Pain.[15] This document provides recommendations for primary care physicians treating adults with chronic non-malignant pain in the outpatient setting (eg, excluding malignant pain, palliative care, and end-of life care). This guideline intended to (1) improve safety and effectiveness of long-term opioid therapy and pain treatment, (2) reduce the risks associated with opioid therapy, and (3) improve communication. The publication outlines three major areas of clinical consideration: (1) determining when to initiate or continue opioids for chronic

pain; (2) opioid selection, dosage, duration, follow-up, and discontinuation; (3) assessing risk and addressing harms of opioid use (see Chapter 78, Table 85-1).[15] While this guidance was originally labeled as "voluntary," many states, organizations, and third-party payers have adopted them as their foundation for policy development and legislative change related to opioid prescribing.

TABLE 85-1

Differences Between the Medications Used to Treat OUD

	Methadone	Extended-Release Injectable Naltrexone (XR-NTX)	Buprenorphine
Pharmacology in OUD	Full opioid agonist at mu-opioid receptor with long half-life to allow for once daily dosing for OUD	Antagonist at mu-opioid receptor (*note:* does not provide analgesia)	Partial agonist at mu-opioid receptor with long half-life (up to 36 hours via sublingual administration); blocks intoxicating effects of other opioids
Phase of treatment in OUD; effect	Medically supervised withdrawal, maintenance; reduces or eliminates withdrawal symptoms and cravings to use opioids, blocks or blunts the effects of illicit opioids	Prevention of relapse to opioid dependence following medically supervised withdrawal; reduces or eliminates cravings to use opioids and blunts or blocks the effects of opioids	Medically supervised withdrawal, maintenance; reduces or eliminates withdrawal symptoms and cravings to use opioids and blocks or blunts the effects of opioids
Route of administration	Provided orally once daily: Commonly given as liquid concentrate in treatment programs, but current guidelines also allow use of solid oral-dosage forms	IM extended-release (depot naltrexone)	Sublingual, buccal tablet, buccal film
		(*note:* oral not as effective and its use is not common in the treatment of OUD due to insufficient evidence of efficacy and poor medication adherence)	Other routes of administration available after meeting specific criteria: subdermal implant, subcutaneous extended-release injection
Restrictions for prescribing each product	CII; patient must meet Federal Opioid-Treatment Program standards; can be used in hospital settings for OUD treatment	Not a controlled substance but requires a prescription. All naltrexone products can be prescribed by general practitioners and in OUD treatment	CIII; requires waiver to prescribe outside of a treatment program. Prescribers will receive a separate DEA number with a "X" upon meeting requirements of DATA 2000. They may prescribe for up to 275 individuals. To confirm practitioner verification: https://www.samhsa.gov/bupe/lookup-form
			Implant: Prescribers must be certified in buprenorphine REMS program to insert/remove implants
			Subcutaneous: Healthcare settings and pharmacies must be certified in the Sublocade REMS program and the medication is only dispensed directly to a provider for administration
Patients that are commonly considered for this type of therapy	Patients with OUD; physically dependent on opioids and meet federal OTP admission criteria	Patients with OUD; those who are abstinent from short-acting opioids for 7-10 days and long-acting opioids 10-14 days	Patients with OUD; physically dependent on opioids

Major side effects	Constipation, vomiting, dizziness, sedation, QTc prolongation, respiratory depression (risk is highest during methadone initiation, dose titration or with concurrent benzodiazepines or alcohol use)	Injection site pain and tenderness, risk of injection site induration, toothache, LFT elevation, insomnia, nasopharyngitis	Constipation, vomiting, dizziness, sedation, insomnia, blurred vision, respiratory depression (highest risk with concurrent use of CNS depressants including benzodiazepines); sublingual buprenorphine/naloxone sublingual and buccal film: oral hypoesthesia, oral mucosal erythema, glossodynia

CII, Schedule II Prescription; CIII, Schedule III Prescription; Federal Drug Addiction Treatment Act (DATA 2000); IM, Intramuscular; LFT, Liver Function Test.

Data from Reference 5.

Implementation inconsistencies surrounding the application of these recommendations in clinical practice has remained a point of controversy. Examples of these inconsistencies include reports of applying the guidelines to patients outside of the primary care setting (eg, patients with cancer, sickle cell disease, or recent surgery), imposing opioid prescribing limitations (eg, quantity, dosage, or duration), and tapering or discontinuing opioids without patient involvement, or adequate preparation.[16] In response to a consensus panel which outlined these challenges, the CDC issued clarification reiterating the importance of implementing the guidelines as they were intended and stressed that treatment be individualized to each patient.[17]

The FDA also launched a broad campaign in partnership with the Department of Health and Human Services (HHS), the National Academy of Medicine (NAM), and the National Institute of Health (NIH) to develop a systematic framework for the review of opioid medications that addresses their potential public health consequences (eg, long-term risk of addiction, diversion risk, and adverse effect profiles), and to expedite the approval pipeline for non-opioid analgesics and use deterrent formulations.[18] Several opioids with use-deterrent labeling and formulations have come to market since, which are designed to make it more difficult to administer the product via intravenous injection, nasal snorting, or chewing. Unfortunately, despite preliminary enthusiasm, conflicting evidence exists regarding the ability of these formulations to substantially reduce opioid use, OUD, overdose or death.[19] Further post-marketing analysis of these agents will add to the current body of evidence in determining the impact of these formulations on adverse events. Another measure to reduce opioid-related deaths by the FDA was the expansion of boxed warnings on benzodiazepines, opioid analgesics, and opioid-containing cough medicines notifying patients and their caregivers of the increased risk associated when opioids and benzodiazepines are taken concurrently.[20]

In 2018, the Risk Evaluation and Mitigation Strategy (REMS) program was expanded to include both short-acting and long-acting opioid formulations. Included with this was a requirement that training be available to all healthcare practitioners involved in pain management. The Opioid REMS Education Blueprint for Health Care Providers delivers education on pain assessment and management strategies for providers managing acute or chronic pain in the primary care setting to reduce inappropriate prescribing and adverse outcomes, while continuing to maintain access to pain medications.[21] For those healthcare practitioners still in training, the Association of American Medical Colleges continues to advance educational content related to pain assessment and management, SUDs, and responsible opioid prescribing.[22]

In 2018, the Substance Use Disorder Prevention That Promotes Opioid Recovery and Treatment (SUPPORT) for Patient and Communities Act[23] was enacted to focus on prevention, treatment, recovery, and enforcement to help combat the opioid epidemic of the opioid epidemic. This bill has many policy changes but major policy changes include the following:

- Remove restrictions on medications used for the treatment of OUD and expand prescribing rights of these agents to select physician extenders.
- Direct Center for Medicare and Medicaid Services (CMS) to look for further options in providing telehealth services for SUDs for Medicaid and Medicare patients.
- Expand existing programs allowing more first responders to carry and use naloxone.
- Allow more federal agencies to pursue expanded research projects related to pain, substance use, and risk for addiction.
- Adjust Medicare and Medicaid processes to limit overprescribing of opioids and allow expansion of substance use treatments including adjusting

restrictions to improve access to care.

- Authorize SAMHSA[24] grant programs for "Comprehensive Opioid Recovery Centers" for communities.
- Improve initiatives for education and awareness for healthcare providers on proper pain treatment.
- Improve coordination between federal agencies to test, detect, and stop substances often used at the border.
- Increase penalties for medication manufacturers and distributers related to overprescribing of opioid.
- Create incentive programs for students to pursue a career in the SUD treatment field.

Since 2018, several additional bills introduced to congress have focused on reducing barriers to the prescribing and dispensing of buprenorphine for the treatment of OUD. Accompanying these is a proposal for a national education campaign encouraging practitioners to integrate SUD treatment into practice.[25]

Etiology

Overall, the true etiology behind OUD is still unknown, as there is no way to predict why some individuals exposed to an opioid develop an OUD, while others may not. In general, it is felt that there needs to be a triad of the right patient, with the right genetic risk factors, being exposed to the right substances in order for an OUD to occur.

4 The high bioavailability, near immediate onset of action, and increased potency of IMF and its respective analogs is thought to play a causal role in overdose fatalities.[10] This postulation is affirmed by the 1,040% increase in synthetic-opioid–related deaths observed from 2013 to 2019. Death rates related to prescription opioids, and heroin correspondingly have continued to rise in the presence of synthetic opioids. These combined upward trends imply that medication-related overdoses are continuing to intensify across the United States.[26]

Pathophysiology

5 Understanding of OUD pathophysiology is growing and, like with other SUDs, focuses on the reward center and mechanism in the brain. Substances or activities that release dopamine (DA) in the nucleus accumbens (NAc) have been clearly linked to disordered use. The current understanding is that the rapid release of DA following an opioid reaches the NAc to stimulate D1 receptors which in turn activates cyclic AMP (cAMP). This leads to the downstream effects such as euphoria and pleasure. This feeling conditions the person to associate using the substance and their surrounding environment and situation with the euphoric and pleasurable sensations. Receptors for *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in the synapse are also conditioned by the DA release to increase glutamate signaling. These changes further modify the interconnected neural loops that lead to habit formation and disordered response to opioids. While DA and glutamate are direct signals in this system, emerging evidence seems to implicate indirect signaling via γ-aminobutyric acid (GABA), serotonin, acetylcholine, endogenous opioids, and endogenous cannabinoid compounds.[27]

Clinical Presentation

CLINICAL PRESENTATION: Acute Opioid Withdrawal and Intoxication

See Chapter e84, "Introduction to Substance Use Disorders" for complete *DSM-5* diagnostic criteria.

General

- Opioid withdrawal presents with similar signs and symptoms across the agents in the class.
- Onset, duration, and severity of withdrawal may differ depending on the opioid agent, chronicity of use, and dosage consumed.
- Onset of the acute phase of withdrawal ranges from 8 to 24 hours for short-acting opioids and 36 to 72 hours for long-acting opioids.
- The duration of withdrawal ranges from days to weeks for short-acting and long-acting opioids, respectively.
- Similarly, duration and severity of opioid intoxication is dependent on the agent, dosage, and frequency of use.

Symptoms

- Opioid intoxication: euphoria, dysphoria, apathy, lethargy, somnolence, and impaired motor skills. Individual agents may also have idiosyncratic presentations (eg, seizures with tramadol, QTc prolongation with methadone).
- Opioid withdrawal: insomnia, muscle or bone aches, abdominal cramps, vomiting, diarrhea, and anxiety or agitation. The Clinical Opiate Withdrawal Scale (COWS) or the Objective Opioid Withdrawal Scale (OOWS) are clinician-rated assessment tools used to trend the severity of opioid withdrawal symptoms and medication efficacy.

Signs

- Opioid intoxication: miotic pupils, drooping eyelids, scratching due to histamine release, decreased respiratory drive, pulmonary edema, loss of consciousness, and death.
- Opioid withdrawal: tachycardia, hypertension, hyperthermia, abnormally heightened reflexes, lacrimation, increased respiratory rate, restlessness, tremor, nausea/vomiting, diarrhea, irritability/anxiety, rhinorrhea, yawning, insomnia, dilated pupils, gooseflesh, and perspiration.

Laboratory Tests

- A comprehensive metabolic panel, complete blood count, urine toxicology screen, physical exam, electrocardiogram (EKG), and pregnancy screening will help guide medication selection for management of withdrawal symptoms and identification of potential medications for OUD treatment.
- For suspected opioid intoxication, blood gas, pulse oximetry, and capnography assist in monitoring for opioid-induced respiratory depression and can be used as appropriate.
- Abnormal findings may require further evaluation or referral.

Management

- To avoid needless suffering during opioid withdrawal, clinicians should attempt to manage patients in discomfort with supportive therapies.
- Patients presenting with acute opioid intoxication may require naloxone administered intermittently or in more severe cases as an intravenous infusion.

Data from References 28,29,31,32.

After repeated exposure to opioids, the nervous system adapts by creating a level of tolerance. When this repeated exposure is removed a hyper-

excitable state results. Opioid withdrawal presents with similar signs and symptoms no matter the agent(s) used. Onset, duration, and severity of withdrawal may differ depending on the pharmacokinetics of the opioid agent, chronicity of use, and dosage consumed. Opioid withdrawal itself is not life-threatening; however, consequences of withdrawal can be significant. Patients can experience uncontrolled pain, miscarriages, premature delivery, and increased risk of suicide due to psychological distress. To avoid needless suffering during the withdrawal period supportive therapies (eg, clonidine, buprenorphine) can be implemented as appropriate to mitigate severity of discomfort. To assess withdrawal severity several validated assessment tools are available (eg, COWS, OOWS). Frequent reassessment will be prudent, as the onset, duration, and peak effects of withdrawal are dependent on the substance involved. Typically, withdrawal symptoms begin within 8 to 24 hours for opioids with a short half-life (eg, heroin), and can last up to 7 to 10 days. For agents with a long half-life (eg, methadone), symptoms can begin as early as 24 hours following the last dose but takes up to 96 hours to peak with gradual reduction of symptoms over 2 weeks or longer. The post-acute phase of withdrawal can last for weeks, months, or even longer leading to symptoms such as opioid craving and a negative affect including symptoms such as fear and irritability. It is also important to remember patients who have withdrawn from opioids will have a reduced opioid tolerance that could increase the risk of opioid overdose.[30]

Methadone

In 2014, methadone accounted for one in four prescription opioid-related deaths despite only accounting for 1% of all opioids prescribed.[31] Methadone has pharmacologic properties that are unique among opioids, and a lack of knowledge by practitioners and patients regarding these unique properties is thought to contribute to methadone-related deaths. Methadone's elimination half-life (15-60 hours; some reports as long as 120 hours) is longer than its duration of analgesic action (4-8 hours) and its full analgesic effect is usually not achieved for 3 to 5 days.[32] Doses should not be increased more frequently than every 5 to 7 days according to recent guidelines.[32] Fatal errors have been reported during conversion from other opioid agonists to methadone, as it has wide variability in equianalgesic dosing compared to other opioids. Therefore, vigilance is necessary during treatment initiation, during conversion between opioids, and during dose adjustments. Medications administered concomitantly with methadone should be evaluated for potential interactions, as methadone has many. Due to its association with prolongation of the QTc interval (in the most severe cases leading to torsades de pointes) it is prudent to monitor a patient's ECG prior to initiation and after significant dose adjustments of methadone.

Heroin

Heroin, also known as diacetylmorphine, is a serious threat to the United States and its use has increased since 2007. Since 2016 the number of heroin-related deaths has trended down, but in 2019, an estimated 14,019 Americans died from heroin-related overdoses. It remains to be seen if this is a temporary plateauing of annual deaths or the beginning of a more prolonged decrease. Overdose deaths involving co-ingestion of psychostimulants (primarily methamphetamine or derivatives) and opioids has continued to increase since 2016, which may also be contributing to the reduced mortality.[28]

The main factors associated with increases in heroin use are increased availability, low cost, and increased purity.[28,29] The DEA expects that high-purity heroin, commonly referred to as white powder heroin, will continue to be available in the United States. Now exacerbating the overdose deaths is heroin laced or adulterated with fentanyl and related derivatives that are 50 to 100 times more potent than heroin. There are conflicting opinions about whether policy changes implemented to reduce nonmedical prescription opioid use had unintended consequences by increasing the use of heroin in the United States. Opioid prescribing policies could help decrease heroin overdose deaths.[33]

Heroin is hydrolyzed to 6-acetyl morphine and subsequently morphine. It acts as an agonist at opioid receptors including the mu, kappa, and delta receptors. Administration can occur via multiple routes including intranasal, intravenous, subcutaneous, intramuscular routes, or smoking. Heroin is very lipophilic and crosses the blood brain barrier (BBB) quickly which leads to very rapid absorption and arrival at the site of action; 5 to 10 minutes when administered subcutaneously, 3 to 5 minutes intranasally and intramuscularly, and <1 minute when administered intravenously.[34] Although the initial half-life is approximately 8 hours, the ultimate duration of effect from heroin is dependent on the person's history with the medication and how it is administered. The oral route is typically not preferred due to first pass metabolism to morphine which leads to less rapid onset of action.[34]

As tolerance develops, the half-life decreases leading to earlier withdrawal symptoms including dilated pupils, hostility, sweating, vomiting, diarrhea, yawning, and piloerection. Those that use heroin increase doses and rates of administration to avoid these withdrawal symptoms, which increases their overdose risk. Symptoms of heroin use include sedation, decreased respiration, apnea, cardiac arrest, and death without medical treatment such as administration of naloxone.[35] Testing for heroin in urine, blood, or other biological samples is difficult due to the very short half-life of intact heroin

(2-6 minutes). Unfortunately, the next metabolite, 6-acetylmorphine (6-AM) is only present in urine and blood for approximately 6 to 25 minutes before it is hydrolyzed to morphine and other metabolites. As morphine and other metabolites can be detected on a urine screen after heroin use, as well as after use of certain prescription opioids, results from urine screens are often misinterpreted and require confirmatory secondary testing and a thorough clinical evaluation.[35,36]

Fentanyl

Fentanyl is a synthetic short-acting opioid analgesic, that is 50 to 100 times more potent than morphine and is approved for managing acute or chronic pain, as well as pain associated with advanced cancer. Although pharmaceutical fentanyl can be diverted for use, most cases of fentanyl-related morbidity and mortality have been linked to illicitly manufactured fentanyl and fentanyl analogs (IMF). Since 2015, there have been almost yearly CDC public health fentanyl advisories including a public health advisory regarding increased fentanyl-related overdose deaths, a warning that fentanyl was found in counterfeit pills in the United States, and a report regarding the rise in fentanyl analogs contributing to opioid overdose deaths.[37]

Generally, the IMF products are sold via illicit markets, with individuals seeking them out for their heroin-like effect. Additionally these illegal products are often mixed with heroin and cocaine and marketed as an oral opioid or benzodiazepine.[37] Deaths from counterfeit opioids and benzodiazepine pills laced with fentanyl have been reported and are believed to be contributing to the increased overdose rates. A CDC analysis from 31 states and Washington DC from 2015 to 2016 showed that overdose death rates increased by 21.5%, and the death rates from synthetic opioids (presumed to be IMF) more than doubled. The death rates for heroin, cocaine, and psychostimulants also increased by 19.5%, 52.4%, and 33.3%, respectively, and the CDC attributes a portion of rate increases to the presence of IMF in the respective products.[38]

Other Opioid-Related Substances

Intoxication from the OTC cough suppressant, dextromethorphan[39] occurs from consuming large doses of liquid cough syrup that is known as “robodosing” or “robotripping” and those who use the cough syrup in this manner are sometimes called “syrup heads.”[39] Additionally, “skittles” is a term used to describe use of other cough and cold remedies because they look similar to the popular candy. As dextromethorphan is an opioid analog, large doses can create a depressant and sometimes profound hallucinogenic effect, and since it is available OTC it is easily procured by adolescents.[39]

Loperamide is also another dangerous example of OTC medication that is often used. Pharmacologically this medication acts as an intestinal mu-opioid agonist that works locally for the short-term treatment of diarrhea. When used in this fashion, at normal recommended doses, it does not cross the blood brain barrier and will not have any CNS effects.[40] When taken at high doses, or with concomitant medications that inhibit the P-glycoprotein efflux transporter, CNS effects can be seen.

Treatment

Desired Outcomes

6 As with any use disorder the desired treatment outcomes for OUD are reduction in use of the substance, reduction in substance-induced disorders, and prevention of death from the substance. The course and prognosis of OUD is variable. Getting patients to stop misusing can be quite difficult, and many patients return to opioid use even after treatment. It has been reported that as many as 40% to 60% of treated patients with an SUD will relapse within 1 year.[41] However, many patients can achieve recovery with proper treatment and continued care in counseling programs or 12-step programs such as Narcotics Anonymous. It is important to note that the treatment of OUD is a chronic condition that needs proper medical treatment and appropriate follow-up, as relapses are common. Therefore, providing medication for long-term maintenance decreases the risk of an accidental overdose or full relapse into opioid use. Continued patient education and support is vital to helping patients continue their set treatment goals.

Pharmacologic Therapy

A variety of treatment regimens are used for patients during the acute opioid withdrawal phase. Initiating buprenorphine in the emergency room for patients who present with opioid withdrawal symptoms has become a treatment option. The reader is directed to Cisewski et al.[42] for a detailed review outlining the process for establishing this stepwise treatment practice.

Methadone has also been used as a long-acting opioid option to aid in treatment of withdrawal symptoms.[43] The use of clonidine, an alpha-2 agonist, has commonly been used to attenuate withdrawal symptoms such as anxiety, tachycardia, hypertension, chills, and piloerection. Patients must be monitored for side effects including hypotension, dizziness, and sedation following administration of clonidine.[43] Lofexidine, also an alpha-2 agonist, has been found to be more effective than placebo in managing withdrawal from methadone or heroin and has demonstrated a better safety profile compared to clonidine.[43,44] Replacement of fluids due to losses from perspiration, vomiting, and diarrhea is crucial during withdrawal and other patient-specific supportive care measures should be provided until the patient stabilizes. Ongoing follow-up is important since post-acute withdrawal can continue for an extended period of time. This can increase risk of relapse and heighten the risk of overdose.

7 Although OUD can range from mild to severe, it often requires continual care including patient-centered care involving mental health services, medical services, counseling, and the use of medications for treatment. The three FDA-approved medications used in OUD include methadone, buprenorphine, and naltrexone that work by blunting or blocking the effects of opioids and reducing or eliminating craving. All three agents have demonstrated superiority over no treatment in reducing opioid use,[30,45,46] and methadone and buprenorphine decrease the risk of overdose deaths. All of these medications have unique characteristics that healthcare providers must be aware of, including differences in mechanism of action, routes of administration, and side effects. It is also important to understand in what phase of treatment each of these agents is used, and the regulations associated with their use (Table 85-1).

Methadone

Methadone is a mu-opioid agonist that suppresses withdrawal symptoms and controls the craving for opioids in maintenance therapy. Controlled trials have shown that methadone use in patients with OUD is superior to placebo and has demonstrated a reduction of mortality, incidence of HIV infection, and criminality.[10] Recommended once daily dosing of methadone on the first day of treatment for patients tolerant to opioids can range from 10 to 30 mg, depending on the patient's use pattern. The patient should be reassessed in 2 to 4 hours after this initial dose for signs of sedation or symptoms of withdrawal. Additional monitoring and/or treatment can continue if needed during the first day based on the initial response. Although rare, if the dose does exceed 30 mg on the first day of treatment, monitoring for over-sedation should occur for multiple days.[30] In patients who are older than 60 years of age, have identified medication interactions, or have other medical conditions that can lead to increased risk of hypoxia, it is recommended to limit the initial maximum methadone daily dosing to 10 to 20 mg. Dosing ranges for stabilization that eliminate withdrawal and craving, block euphoric effects of illicit opioids, and that are not normally associated with sedation are commonly between 60 and 120 mg administered once a day for most patients but this can vary considerably.[30] Titrating the methadone dose must be individualized and based on a full assessment of the patient. Due to its long half-life and extended time to reach steady state, daily dose adjustments should not occur, as they can result in over-sedation and possible increased risk of toxicity. It is recommended that dose adjustments of 5 to 10 mg should occur gradually, with each adjustment occurring no sooner than every 4 to 7 days based on clinical response. This will allow for achievement of steady state and account for the other numerous factors that can impact serum levels.[30,32] Concerns with methadone include medication interactions due to the variety of concomitant cytochrome P450 (CYP 450) inducers that can reduce methadone levels. Concomitant use of alcohol or benzodiazepines can lead to overdose and use should be assessed. Additionally, the risk of QT prolongation is increased with methadone use, especially when given with other medications that also prolong the QT interval. The use of methadone for the treatment of OUD is only approved through the opioid treatment programs controlled by the DEA and SAMHSA. However, methadone for the treatment of OUD may be provided to patients during a hospital admission for the treatment of other health conditions such as pain. Patients who as part of an opioid treatment program most often receive it on a daily basis with daily onsite administration; however, some patients are allowed to take doses at home if they meet a list of criteria set by federal regulations.[47]

Naltrexone

Naltrexone is a mu-opioid antagonist available as both an oral tablet and an extended-release injectable formulation for the treatment of OUD.[48,49] It is important to note that while the oral tablet has not been found to be any more effective than placebo in a meta-analysis of 13 studies,[50] naltrexone reduces opioid use and retained treatment participation compared to placebo.[45]

To use the oral formulation, patients need to have confirmation of being opioid free for 7 to 10 days as assessed through the use of a urine drug screen or naloxone challenge. The initial dose given is 25 mg once daily and if no symptoms of withdrawal are demonstrated, this can be increased to the target dose of 50 mg once daily.[48] Extended-release injectable naltrexone (Vivitrol ®) is FDA-approved for use following opioid detoxification to help

prevent relapse.[49] It is important to review all medication-associated adverse effects with patients, including education on the length of time naltrexone is active and their vulnerability to opioid effects at the end of a dosing interval, after a missed dose, or with treatment discontinuation. Patients should be informed to contact their provider if any excessive swelling, bruising, or pruritus occurs at the injection site since this could be a sign of improper subcutaneous injection and may require medical treatment. The REMS information highlights the risk of severe injection site reactions and provides education for healthcare providers including proper techniques to reduce severe injection site reactions as well as important counseling points to use with patients to identify any signs or symptoms of injection site reactions.[49] Naltrexone is not a controlled substance and is not included in the opioid treatment program regulations, but it does require a prescription and a monthly medical office visit. The use of extended-release injectable naltrexone should be part of a comprehensive patient program that includes psychological counseling and support.

Buprenorphine

Buprenorphine is a partial mu-receptor agonist that is very lipophilic and available as buprenorphine alone or in combination with naloxone. These products have been shown in numerous studies and clinical trials to be effective treatment options for OUD both in reducing opioid use and treatment retention.[47] It is now recommended by the Best Practice Guidelines (TIP 63) expert panel[30] and the Department of Veterans Affairs Guidelines[51] that FDA-approved buprenorphine formulations should be offered to patients with OUD who are appropriate candidates. As buprenorphine is a partial mu-receptor agonist, it does provide some intrinsic pain control. Additionally, due to the partial agonist activity, it also has a ceiling effect for respiratory depression, except when combined with CNS depressants such as benzodiazepines or alcohol, where there have been reports of increased risk of respiratory depression. Furthermore, due to the partial agonist activity, any full agonist activity will be blunted, such as that provided from heroin or other opioids. This effect will be prolonged due to the long half-life and prolonged receptor dissociation properties of buprenorphine.[52] At the time of this writing there are buprenorphine/naloxone sublingual tablets and films, buprenorphine/naloxone buccal films, buprenorphine implants, buprenorphine tablets, and a buprenorphine extended-release injection.[52] Newer products have greater bioavailability compared to previous products, making product selection and conversion between buprenorphine products an important consideration for healthcare providers (Tables 85-2 and 85-3).[52,53]

TABLE 85-2

Oral Buprenorphine Products Used in Treatment of Opioid Use Disorder

	Buprenorphine Tablet	Suboxone SL Tablet	Zubsolv SL Tablet	Suboxone SL Film	Bunavail Buccal Film
Strengths of products commercially available/Routes of Administration	**Sublingual Tablet:** 2 mg 8 mg	**Sublingual Tablet:** 2/0.5 mg 8/2 mg	**Sublingual Tablet:** 0.7/0.18 mg 1.4/0.36 mg 2.9/0.71 mg 5.7/1.4 mg 8.6/2.1 mg 11.4/2.9 mg	**Sublingual or Buccal Film:** 2-0.5 mg 4-1 mg 8-2 mg 12-3 mg	**Buccal Film:** 2.1-0.3 mg 4.2-0.7 mg 6.3-1 mg
Recommended Once-Daily Target Maintenance Dose and Dosing Ranges	**Target Maintenance Dose:** 16 mg **Dosing Range:** 4-24 mg[a]	**Target Maintenance Dose:** 16/4 mg **Dosing Range:** 4/1 to 24/6 mg[a]	**Target Maintenance Dose:** 11.4/2.9 mg **Dosing Range:** 2.9/0.71 to 17.2/4.2 mg[b]	**Target Maintenance Dose:** 16/4 mg **Dosing Range:** 4/1 to 24/6 mg[a]	**Target Maintenance Dose:** 8.4/1.4 mg **Dosing Range:** 2.1/0.3 to 12.6/2.1 mg

SL, sublingual.

[a]Doses higher than 24/6 mg do not offer any further benefit.

[b]Doses higher than 17.2/4.2 mg do not offer any added benefit.

Note: Refer to individual product dosing information when switching formulations due to possible bioequivalence variability. Monitoring is recommended following a switch in products due to possible variation in response to different formulations.

Data from References 32,54-57,63,64.

TABLE 85-3

Patient Education Points for Buprenorphine Treatment

Prior to starting buprenorphine therapy and repeated at induction
• **Communication with prescriber:** Tell your prescribers all medications including over-the-counter (OTC), herbal, creams, injections, inhalants, street medications, etc. that you are currently taking. This is important so your healthcare team is aware of what is in your body and if there are any chances of a dangerous medication interactions. Additionally, it is important to tell all of your prescriber and healthcare team you are taking buprenorphine, especially if you are being treated for pain. • **Goals of therapy:** The goal of your first week of treatment is to improve withdrawal symptoms without causing any over-sedation (making you too tired or feeling over medicated). It is important to notify your prescriber if you are feeling overly tired/sedated or euphoric within 1 to 4 hours of your dose. Dose adjustments might occur initially and it will take a little time for the buprenorphine to become stable in your system. The goals of therapy include finding the right dose to eliminate withdrawal, decrease or even eliminate cravings for opioids, and block the effects of other opioids without

severe adverse medication effects.

- **Product use:**
  - Buprenorphine products (tablets, sublingual film, and buccal film) are not equivalent. If you have to transition to a new buprenorphine product, a dose adjustment might be required.
  - Take your dose at regular intervals and only as prescribed.
  - If you miss a dose, take the dose as soon as possible. If it is almost time for the next dose, do not double your dose, take only the dose that is prescribed.
  - Leave medication in packaging until you are ready to use.
  - Do not swallow sublingual tablets or film. This can lead to a decreased effect of buprenorphine that can lead to withdrawal symptoms.
    - Sublingual tablets:
      1. Place tablets under tongue and allow the tablet to fully dissolve which can take several minutes.
      2. If your dose requires multiple tablets, all tablets can be placed under the tongue at one time. If this is uncomfortable, only place two tablets under the tongue at a time.
    - Sublingual film:
      1. Drink water prior to placing the film to help the film dissolve easily.
      2. Place film under the tongue, to the left or right of the center of the tongue, and allow to completely dissolve
      3. If you are prescribed 2 films at a time, place the second film on the opposite side of the tongue. Do not allow the films to touch.
      4. If you are prescribed more than 2 films at a time, wait until previous films have dissolved and repeat the process.
    - Buccal film:
      1. Wet the inside of your cheek with your tongue or rinse with water prior to placing film.
      2. Hold the film by the edges with two fingers and place on inside of cheek until fully dissolved that can take up to 30 minutes.
      3. If you are prescribed two films, place the second film inside the opposite cheek.
      4. Do not adjust the film placement or touch the film, do not chew or swallow the film.
      5. Do not drink or eat until the film has completely dissolved.
- **Common adverse medication effects:** These do not happen all of the time and do not happen to everyone. If you are experiencing any of these adverse medication effects please tell your healthcare team immediately. Do not stop taking buprenorphine without first speaking to your prescriber. The most common adverse medication effects that have been experienced include headache, nausea, constipation, abdominal pain, insomnia, sweating, and a possible feeling of weakness or lack of energy.
- **Precautions and warnings:**
  - Using benzodiazepines or alcohol while taking buprenorphine is very dangerous and can lead to increased risk of overdose and possibly death.
  - Using tobacco products prior to using buprenorphine has been shown to decrease the absorption of buprenorphine decreasing its effectiveness.
  - Long-term buprenorphine maintenance is recommended in many cases. If you stop buprenorphine, there is a high risk of overdose if you return to misusing opioids.
  - Buprenorphine is an opioid that can cause physical dependence. Do not stop taking buprenorphine without consulting your prescriber. If you stop buprenorphine abruptly, you could experience withdrawal symptoms.
  - All medications, including buprenorphine, should be stored in a secure area, preferably in a locked cabinet or safe. It is important to keep medication away from children.
  - It is recommended that you do not drive, operate heavy machinery, or perform any dangerous activities until you are fully aware of how this medication affects you.
  - If you feel you have taken too much buprenorphine, you will need emergency medical attention immediately. Some possible signs include dizziness, confusion, unsteady or faint, slowed reflexes, or breathing slower.
  - Do not inject these products. Serious life-threatening infections could occur. Additionally, serious withdrawal reactions can also occur upon injecting many of these buprenorphine products.
- **Pregnancy:** It is very important to inform your healthcare team if you become pregnant.
- **Counseling options:** Recovery resources and counseling resources are available for you and your family. We can give you further information on this when you are ready.

Maintenance

- **Adherence assessment:** If any discrepancies arise, initiate discussion to identify reasons for discrepancies.
  - Complete pill/film count.
  - Review Prescription Drug Monitoring Program.
  - Confirm current buprenorphine dose.
  - Review results of urine drug analysis.
- **Treatment assessment and counseling:**
  - Review treatment goals and assess progress.
  - Review and assess benefits and risks of continuing buprenorphine treatment.
  - Discuss participation in counseling or encourage counseling if not receiving counseling.

Data from References 30,43,58.

Patients who achieve clinical stability have longer acting options that may improve adherence and improve quality of life (Table 85-3). Buprenorphine is a Schedule III controlled substance with specific prescribing restrictions. Table 85-1 outlines some of these restrictions. Recent legislation has extended regulations to allow physician assistants, nurse practitioners, clinical nurse specialists, certified nurse midwives, and certified registered nurse anesthetists to prescribe buprenorphine. This practice varies by state based on laws and regulations, therefore each state licensing board should be consulted for the most up to date laws and regulations.

Prior to prescribing buprenorphine, a full assessment including reviewing the PDMP database and a full medication review should be completed. Care should be taken to screen for medication interactions including HIV medications, benzodiazepines, CNS depressants, and CYP 450 inducers/inhibitors. Additionally, a urine drug screen, informed consent, and treatment agreement should be completed. Comprehensive patient education is very important to help improve adherence to the treatment plan and improve patient safety (Table 85-4).

TABLE 85-4

Extended-Release Products Approved by FDA for Opioid Use Disorder

Medication	Trade Name	Dose	Comments
Naltrexone Tablets	Revia	Following 7-10 day opioid-free period for short-acting opioids or 10-14 day opioid-free period for long-acting opioids: begin with dose of 25 mg daily with food. If no signs of withdrawal, increase dose to 50 mg PO daily.	• Should be part of a comprehensive treatment plan that includes psychosocial support • Although specific dosage adjustments are not available for patient with hepatic dysfunction, reports of elevated LFTs have been reported; use with caution • Use with caution in patients with renal impairment, although data is limited, naltrexone and active metabolite are renally excreted
Naltrexone XR Injection	Vivitrol	Following 7-10 day opioid-free period for short-acting opioids or 10-14 day opioid-free period for long-acting opioids: 380-mg IM in gluteal area alternating buttocks; every 4 weeks or once a month.	• Must be administered by a healthcare provider • Must use manufacture provided needle and assess body size of patient at each visit so proper needle size is used • Monitor injection site closely for any signs of abnormal pain and contact healthcare provider immediately if this occurs • Dose adjustment is required in mild or moderate hepatic impairment. No data available in severe

			hepatic impairment • No dose adjustments in mild renal impairment; use caution in patients with moderate-to-severe renal impairment; naltrexone and active metabolite are renally excreted

Buprenorphine	Probuphine	Four implants are inserted subdermally in the inner side of the upper arm and should remain in place for 6 months.	• Patients must meet specific criteria for use of Probuphine:
			  ○ Only indicated for patients who are opioid tolerant
			  ○ Demonstrates clinical stability on transmucosal buprenorphie with Subutex or Suboxone 8 mg/day or less (or transmucosal equivalent) for 3 months or longer without requiring supplemental dose adjustments
			• Probuphine must be inserted or removed within a facility and by a certified provider who has completed the required live training
			• It is recommended to not prescribe prn transmucosal buprenorphine products. If patient is requesting these products, reassessment is indicated
			• Moderate-to-severe hepatic impairment: use not recommended
			• Limited data in renal impairment, currently no dosage adjustments listed

Buprenorphine	Sublocade	For patients who have achieved clinical stability on equivalent of 8-24 mg of a transmucosal buprenorphine product daily.
		Available in two extended-release solutions:
		  ○ *100 mg/0.5 mL*
		  ○ *300 mg/1.5 mL*
		Directions: Inject 300 mg subcutaneously once a month in abdominal area for 2 months, then decrease dose to 100 mg once monthly in abdominal area.
			• Must be administered by a healthcare provider
			• Steady state occurs after 4-6 months; after discontinuation of detectable buprenorphine levels could occur 12 months or longer; urine and plasma concentration correlations are not known
			• Injections must occur at least 26 days apart. Follow all manufacturers' direction for preparation and injection
			• Do not give the injection at the belt or waistband area where pressure will occur
			• It is important to counsel the patient that there will be a small bump at the injection site that will decrease in size over the next several weeks. It is important not to rub or massage this area.
			• If needed, the most recently injected depot can be removed within the 14 days of injection under local anesthesia.
			• Doses can be adjusted back to 300 mg monthly for patients in which benefits exceed risks.
			• Examine injection site each month for evidence of tampering
			• Moderate-to-severe hepatic impairment: use not

			recommended • Limited data in renal impairment, currently no dosage adjustments listed

mg, milligram; IM, intramuscularly; mL, milliliters.

Data from References 5,51,58,59.

When the patient presents to begin buprenorphine, it is important for the clinician to assess the patient carefully for signs of sedation or intoxication since buprenorphine should not be started under these circumstances. As the patient should be present in the beginning stages of withdrawal to start buprenorphine, a validated assessment scale, such as the Clinical Opiate Withdrawal Scale (COWS), can be used for assessment. It is recommended that treatment start with a COWS score of 12 or higher for the first dose, based on buprenorphine REMS.[30]

Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase, followed by maintenance.[30] Best practice guidelines are periodically issued for treatment of OUDs. The TIP 40[52] (entitled "The Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction") provides consensus- and evidence-based guidance on the use of buprenorphine and the TIP 63 provides similar guidelines as outlined below for buprenorphine treatment.[30] Induction is the first stage of buprenorphine treatment and involves helping patients begin the process of switching from the used opioid to buprenorphine. The goal of this phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no withdrawal symptoms, minimal or no adverse medication effects, and no craving for the used substance. This phase is commonly initiated in the physician office when the patient is in mild to moderate withdrawal with the last dose of opioid use occurring 6 to 12 hours prior for heroin or short-acting opioids. For longer-acting opioids such as methadone, it is recommended to wait 24 to 72 hours after the last dose. Patients are typically monitored in the office at approximately 2-hour intervals after the first dose of buprenorphine with continued dose titration until the withdrawal symptoms are eliminated. Guidelines recommend weekly follow-up until the patient is stable and then monthly follow-up can be considered.[52] Although office-based induction has traditionally been recommended, home induction is an alternative growing in use.[30] The American Society of Addiction Medicine National Practice Guidelines recommends that both the patient and prescriber have prior experience with the medications used to treat OUD, in order to consider this option.[52,60]

The stabilization phase begins when a patient is experiencing no withdrawal symptoms, is experiencing minimal or no adverse medication effects, and no longer has uncontrollable cravings for opioid agonists. Buprenorphine dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance. Ongoing psychological evaluation for mental health or psychological issues is recommended so proper medical assistance can be provided immediately if needed.[30]

Maintenance is the longest phase of treatment as this period may be indefinite and longer treatment has been associated with positive treatment outcomes.[61] During the maintenance phase, attention must be focused on the psychosocial and family issues that have been identified during the course of treatment that contribute to a patient's OUD.[61] Other issues related to OUD that need to be addressed during maintenance treatment include, but are not limited to, psychiatric comorbidity, consequences of drug use, family support issues, structuring of time in prosocial activities, employment and financial issues, legal consequences of medication use, and the use of other substances. Ongoing monitoring will continue to include urine drug tests, and patient education regarding this aspect is important so there is understanding that this testing is used more to help them meet treatment goals and not as a tool for punishment.[30]

Naloxone

9 Naloxone is a key strategy in reducing opioid-related deaths,[62] as patients who are being treated for OUD, or who are not taking medications for OUD but are at high risk of returning to opioid use, are at substantial risk of overdose. It is imperative that patients and their caregivers are educated on the availability of naloxone and the proper use of this agent. Pharmacologically, naloxone hydrochloride is a competitive mu-opioid receptor antagonist that can be used in the reversal of an opioid overdose. It can be administered through a variety of routes including intravenous (IV), intramuscular (IM), subcutaneous Unapproved abbreviation, intraosseous, (IO), and intranasal (IN).[63] The onset of action when delivered via intravenous route can be as fast as 60 seconds, but is approximately 2 to 5 minutes when delivered IN.[63] The duration of effect is dependent upon the

dose and the specific opioid naloxone is reversing. It is important for interested parties to know that if a long-acting opioid such as methadone is involved, the patient could show decompensation after initial improvement due to the long half-life of methadone and comparatively short half-life of naloxone.

The FDA has approved two devices to deliver naloxone that can be administered by nonmedical bystanders: the intramuscular autoinjector Evzio® and an intranasal delivery device, Narcan®. A third option readily available prior to these new devices, the generic injectable naloxone solution used with a mucosal atomization device, is used in the community setting, although it is not approved by the FDA. For this device, extra education is necessary on how to connect the components and then administer the 1-mg dose per nostril.[63] Table 85-5 includes more information about naloxone delivery options and counseling information.

TABLE 85-5

Delivery Options for Naloxone

	Intramuscular Injection	Auto-Injector (Evzio)	Nasal Spray (Narcan)	Intranasal Spray (Atomizer)
Description of device or what is provided	Two single use 0.4-mg/mL naloxone vials Two single use 3-mL syringe 23-25 gauge 1-1.5 in. needles	One box 2-mg/0.4-mL prefilled auto injector that include 2 devices and a trainer devices	One box that contains two 4-mg/0.1-mL intranasal devices	2-mg/2-mL prefilled naloxone needleless syringe Two mucosal atomizer devices
Directions for use	Inject 1-mL intramuscularly in shoulder or thigh upon signs of opioid overdose. Call 911 immediately. May repeat once more in 2-3 minutes if inadequate response.	Apply one auto-injector to the outer thigh by depressing and holding for 5 seconds. The voice automation will direct the patient with this device. Call 911. May repeat once more in 2-3 minutes if inadequate response.	Use full contents of nasal spray in one nostril upon signs of opioid overdose. Call 911. May repeat once more in 2-3 minutes if inadequate response using the other nostril.	Spray one-half of contents of syringe into each nostril upon signs of opioid overdose. Call 911. May repeat once more in 2-3 minutes if inadequate response.

Naloxone pearls:

- Naloxone has not been shown to cause severe effects or adverse medication effects if administered to patients who are currently not taking opioids.
- Naloxone should be given if the patient is intoxicated by a combination of products since the naloxone will still work for the opioid but not for other products such as benzodiazepines or alcohol.

Naloxone counseling topics that should be covered:

- Overdose recognition, response, prevention
- Importance of seeking emergency medical care
- Proper device use and counseling of family members and caregivers
- Proper storage, shelf life. Periodically check expiration date
- Potential adverse medication effects associated with naloxone
- Availability of substance use disorder treatment program

General opioid safety counseling:

- Take medication only prescribed for you, only take prescribed doses
- Do not mix opioids with alcohol or sleeping pills
- Always store all medications in a locked and secure place
- Dispose of unused medications appropriately
- Do not use opioids/medications in seclusion. Never buy opioids/medications from unknown source
- Do not restart opioid at same dose if there is a period of abstinence. Overdose is possible due to lower tolerance

Data from References 63–65.

Inadequate response to less sensitive opioids such as buprenorphine, fentanyl, or other synthetic opioids may be seen with take-home naloxone (THN).[62,64] Higher doses of naloxone may be needed in such a scenario; therefore, it is vital that emergency services are contacted to provide ongoing care.[62,65] However, the THN products might provide time for arrival of medical professionals and/or transportation to medical facilities for more definitive treatment.

Controversy exists regarding concerns that distribution of naloxone may increase drug use, as some authors feel naloxone has contributed by "providing a safety net that encourages riskier use."[66] However, data from communities that have implemented overdose programs prior to this report have documented a decrease in overdose death rates. In fact, overdose education and naloxone distribution (OEND) programs in the community have been occurring since 1996, and this practice was embraced by the World Health Organization (WHO) guidelines which recommend that anyone who might witness an overdose have access to naloxone and proper training.[66]

As the number of opioid overdoses has continued to increase, CDC guidelines have recommended increasing use of THN. In fact, improving access has become a goal of many states through expanding those able to distribute naloxone or simplifying the process of obtaining the naloxone. Additionally, improved education of healthcare providers and the community as a whole has also been a primary goal.[67]

Opioid Use Disorder in Pregnancy

As the rates of opioid use in the United States have increased, the number of pregnant women diagnosed with OUD has increased substantially.[68] The occurrence of opioid use during pregnancy results in an increased risk of preterm labor, neonatal abstinence syndrome, and maternal mortality. The CDC reported the rate of OUDs in women at delivery has more than quadrupled between 1999 and 2014.[68] Current recommendations for a pregnant woman with an OUD requesting treatment includes methadone or buprenorphine, and behavioral interventions. Now, the safety of extended-release injectable naltrexone is still under study. For patients taking naltrexone, it is recommended that it be converted to buprenorphine or methadone during the pregnancy.[69] More specifics regarding treatment in this population can be obtained from recently released guidance documents for healthcare providers entitled "Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants."[69]

Key to the success of OUD treatments in this population is patient education, which should include topics such as the risks and benefits of the chosen medication. During this discussion, it is important to stress to the patient there are some disagreements on the risks associated with these medications. Now, research efforts have not linked buprenorphine or methadone use with an increased risk of birth defects and or issues with long-term neurodevelopment.[69] Other important topics to discuss with the patient include risk of neonatal abstinence syndrome and details associated with this syndrome, as well as important strategies for improving the patient's health and the pregnancy. Due to the large number of pregnant women presenting with OUDs, all healthcare providers should look for substance use behaviors in their pregnant patients, and if identified, provide a referral for therapy as quickly as possible to improve the outcome for both the mother and the baby.[69]

INTRODUCTION: BENZODIAZEPINES AND OTHER SEDATIVE-HYPNOTICS

Benzodiazepines, while not first-line treatment options, are commonly prescribed for anxiety, muscle spasms, and insomnia in a variety of practices. While their therapeutic use can be quite helpful to patients, similar to opioids, their CNS effects can make them substances commonly misused.

Epidemiology

10 Benzodiazepine prescribing has increased by over 65% from 1996 to 2013 and continues to climb. Overdose rates have increased over sevenfold from 2002 to 2019, the peak occurring in 2017.[28] When benzodiazepines are given concomitantly with an opioid, the combination can lead to increased CNS effects such as dizziness and sedation but also deadly respiratory depression. A cohort study that included over 2 million opioid prescriptions in 1 year demonstrated 80% of these were co-prescribed with a benzodiazepine and the rates of overdose deaths in this group were 10 times higher than opioid analgesics alone.[70] In 2016, the FDA announced a class-wide medication labeling change for both opioids and benzodiazepines requiring both classes to include black box warning indicating that concurrent use could cause sedation, respiratory depression, coma, and death.[71] Additionally, the CDC Guidelines for prescribing opioids for chronic pain recommends avoiding concurrent benzodiazepine and opioid prescriptions whenever possible highlighting the dangers of using this combination.[15]

Etiology

Pharmacologically, the benzodiazepines increase the affinity of gamma amino butyric acid (GABA) for its receptor and augment GABA-mediated inhibitory signaling. This occurs by targeting the $GABA_A$ receptor that has multiple subunits. Activation of these subunits leads to an increase in

frequency of ion channel opening that leads to an influx of chloride ions and membrane hyperpolarization.[72] Benzodiazepines vary in pharmacokinetic properties, with additional details being found in Chapters 90 and 91.

A class of medications related to the benzodiazepines include eszopiclone, zaleplon, and zolpidem, which are prescribed for insomnia, and commonly known as the Z-hypnotics. While pharmacologically they may differ from benzodiazepines, tolerance and withdrawal have been reported with their use and they should be used with caution.[73] Additionally, this class of medication is required by the FDA to include labeling that warns of a variety of psychological and behavioral adverse medication effects that include sleep driving. Depression and suicidal thoughts have also been linked to these products, although this has been seen mainly in patients taking both sedatives and hypnotics concurrently.[73]

Pathophysiology

Benzodiazepines have been shown to cause release of dopamine in the mesolimbic region of the brain, which is a hallmark of substances that can lead to use disorders.[73] Additionally, benzodiazepines have demonstrated an ability to activate dopaminergic neurons in the ventral tegmental area through $GABA_A$ interactions involving interneurons in the region. These two neuronal pathways within the addiction centers of the brain explain their potential for developing disordered use of this medication class. Due to their use liability, patients cannot be switched from one benzodiazepine to another in hopes of decreasing this behavior pattern. Additionally, long-term use of even therapeutic doses of these agents can cause physical dependence and withdrawal symptoms after abrupt discontinuation, including seizures. In general, shorter-acting benzodiazepines have higher risk of use potential due to the immediate “rush” or “high” feeling. Gradual tapering (4 weeks or longer) of dosage is also associated with less withdrawal and rebound anxiety than abrupt discontinuation.[73]

Clinical Presentation

CLINICAL PRESENTATION: Benzodiazepine Intoxication and Withdrawal

General

- The intoxicated patient may be in acute distress during overdoses or when benzodiazepines are combined with alcohol.
- Patients in withdrawal may be in acute distress and should be treated with a benzodiazepine taper to prevent seizures.

Symptoms

- Symptoms of intoxication may include memory impairment, drowsiness, visual disturbances, confusion, and gastrointestinal disturbances. Patient may appear intoxicated, with slurred speech, poor coordination, swaying, and bloodshot eyes, with or without the odor of alcohol.
- Symptoms of withdrawal can include agitation and restlessness, confusion, anxiety, sleep disturbances, dizziness, flu-like symptoms, impaired memory and concentration, irritability, nausea and vomiting, nightmares, visual disturbances, convulsions, hallucinations, and psychosis.

Signs

- Hypotension or nystagmus may be observed and urinary retention may occur.
- Nervousness, sweating, trembling, hypertension, tachycardia, weakness, tremors, and seizures are examples of possible signs in acute withdrawal.

Laboratory Tests

- Qualitative testing to confirm presence of benzodiazepines is useful for diagnostic purposes, but quantitative plasma concentrations are usually not clinically useful due to the length of time required for results to be obtained at most institutions.

Treatment

Desired Outcomes

Similar to the desired outcomes for individuals misusing opioids, the overall goals of treatment are to reduce dependency, the incidence of substance-induced disorders, and death.

Non-pharmacological management as a primary treatment for benzodiazepine intoxication or withdrawal is not indicated. Rather, direct pharmacologic care of an individual intoxicated with a benzodiaepines includes the use of supportive care. For patients undergoing benzodiazepine withdrawal, supportive care should be provided in combination with pharmacologic therapy.

Pharmacologic Therapy for Benzodiazepine Intoxication and Withdrawal

11 Symptomatic and supportive care is the standard of care for benzodiazepine intoxication. Management primarily includes support of bodily functions to allow for metabolism and excretion of the medication from the system. For individuals that use short-term, withdrawal is not expected and thus flumazenil can be considered. Flumazenil reverses the intoxicating effects of benzodiazepines and Z-hypnotics by competitively inhibiting the GABA/benzodiazepine receptor complex. However, caution should be exercised as indiscriminate use can potentiate seizures in those that have used benzodiazepines chronically and those who have co-ingested a seizure-potentiating substance (eg, bupropion, tricyclic antidepressants, and lithium). The dosing scheme is to give 0.2 mg of flumazenil IV, then 0.3-mg IV if there is an insufficient response, then repeated doses of 0.5-mg IV up to a maximum of 3 mg.[74]

Treatment of benzodiazepine withdrawal is very similar to the treatment of alcohol withdrawal. The major differences in management is the length of treatment.[73] The duration of withdrawal symptoms in patients physically dependent on benzodiazepines can be variable due to multiple factors including benzodiazepine dose, duration of use, duration of taper, and pharmacokinetic half-life.[75] Current recommendations suggest a gradual taper extending over 4 to 8 weeks and sometimes longer depending on the duration of use. It is recommended to reduce the daily dose approximately 10% to 25% every 2 weeks to decrease the risk of severe withdrawal reactions and seizures.[73] If a patient is taking multiple benzodiazepines, it is recommended to convert the patient to an equivalent single dose of diazepam, given its long half-life, and begin the taper as directed. There is limited evidence for converting a patient from a single short half-life benzodiazepine to a long half-life benzodiazepine so this practice is generally not recommended. With all benzodiazepines, protracted minor abstinence symptoms—such as anxiety, insomnia, irritability, sensitivity to light and sound, and muscle spasms—can remain for several weeks or longer in patients with a history of long-term exposure. This can occur even after the acute phase of benzodiazepine withdrawal is complete.[76] Additional information on benzodiazepine tapers can be found in Chapter 90.

INTRODUCTION: STIMULANTS, HALLUCINOGENS, AND CANNABINOIDS

12 Acute intoxication with stimulants, hallucinogens, cannabinoids, and other mind-altering substances continues to be a relevant issue around the world. Improved outcomes are achieved through prompt recognition of symptoms and supportive care. At the time of writing, no antidotes or targeted therapies are available for these agents. Active monitoring and management of vital organ function is often sufficient for a positive outcome. Chronic use disorder and withdrawal from these agents are complex disease states that can require inpatient monitoring. No medication-assisted therapy is available for the treatment of chronic use involving these agents. Data involving successful treatment of SUDs involving stimulants, cannabinoids, and cathinones is in its infancy. It likely requires outpatient follow-up and psychosocial intervention for long-term sustained recovery.

Stimulants

The physiologic and psychologic effects of amphetamines and other stimulants are qualitatively similar, as they diminish fatigue, increase alertness, and suppress appetite. In higher doses stimulants can lead to behavioral changes, perception disturbances, and frank psychosis. Pharmacologically, amphetamines increase the activity of catecholamine neurotransmitters (eg, norepinephrine and dopamine) by stimulating release, decreasing reuptake into the neuron through blocking of vesicular monoamine transporters (VMAT2), and by inhibiting the degradation via monoamine oxidase (MAO). Stimulants improve mood, self-confidence, energy levels, alertness, concentration, and physical performance. Negative consequences of stimulant use range from headache, palpitations, hypertension, tachycardia, dizziness, anxiety and insomnia to confusion, agitation, paranoia, convulsions, and delirium.

Methamphetamine

The pathophysiology of methamphetamine use disorder (MUD) results from dopamine, serotonin, norepinephrine, and epinephrine release from the synaptic vesicle into the cytosol.[77] Dopamine is also increased through several mechanisms such as the inhibition of monoamine oxidase and increase in tyrosine hydroxylase activity. However, excessive dopamine can also increase reactive oxygen species that lead to cell structure damage. With this damage, the brain's metabolic state is altered through acidification of the microenvironment, and dysregulation of cell signaling via reactive oxygen species. This mirrors degenerative central nervous system diseases. The resultant neuronal and microglia cellular dysregulation is associated with dysfunctional neural processing, altered reward motivation, and reduced prefrontal control. Through this, the imbalance in the orbitofrontal cortex of the brain leads to cognitive deterioration affecting valuation and decision making. This results in poor task performance, and inattention, which facilitates continued-seeking behavior. Mortality from MUD is commonly associated with cerebrovascular disease such as stroke, and cardiovascular disease such as cardiac collapse.[77] Because methamphetamine elevates mood, people who experiment with it tend to use it with increasing frequency and in increasing doses, despite their original intent.[78]

Methamphetamine is used orally, intranasally, rectally, intravenously, and by smoking. Immediately after inhalation or intravenous injection, the individual using methamphetamine experiences an intense sensation, called a "rush" or "flash," that lasts only a few minutes and is described as extremely pleasurable. The timing and intensity of the "rush" that accompanies methamphetamine use results from the release of high levels of dopamine in the brain, but this depends in part on the method of administration. Specifically, the effect is almost instantaneous when smoked or injected, whereas it takes approximately 5 minutes after snorting or 20 minutes after oral ingestion.[79] The duration of effect is about 12 hours per administration but can be altered by route of administration and individual characteristics.[78]

Methamphetamine-induced caries, or "meth mouth," is a characteristic pattern of dental decay commonly observed in patients that smoke methamphetamine. Prolonged use of methamphetamine can result in a tolerance for the medication and increased use at higher dosage levels, creating dependence. Such continual use of the medication with little or no sleep may lead to an extremely irritable and paranoid state. Discontinuing use of methamphetamine often results in a state of depression, as well as fatigue, anergia, and some types of cognitive impairment that can last from 2 days to several months.[79]

Healthcare providers working in the retail setting, such as pharmacists, should be wary of persons wishing to purchase large quantities of products containing nonprescription sympathomimetic products such as pseudoephedrine, as this is a key ingredient for methamphetamine production. As a precaution, federal legislation now limits the quantities that can be purchased, along with mandating pseudoephedrine-containing products be kept behind a counter, and suitable identification be shown before purchasing.

Cocaine

Cocaine is perhaps the most behaviorally reinforcing of all used substances. It acts as a local anesthetic through inhibition of voltage-gated sodium channels when topically applied. Cocaine also acts as a sympathetic nervous system stimulator through α- and β-adrenergic stimulation which can precipitate chest pain and myocardial infarction. In the CNS, the stimulant and euphoric effects occur through inhibition of dopamine and norepinephrine reuptake. The excess dopamine in the ventral tegmental area (VTA) leads to the psychostimulant properties, contributes to psychotic behavior, and portends a high rate of addiction.[80]

For many years, cocaine has been administered as the hydrochloride salt form, usually by insufflation, but also by injection. Conversion to the cocaine base, also known as "crack" or "rock," allows for smoke inhalation. This is generally a more inexpensive form and thus more widely available. The time to peak concentration is rapid for all routes but is fastest by intravenous injection (instantaneous), then smoking (6 minutes), and then finally nasal insufflation (45 minutes).[80] Smoking the drug leads to almost instant absorption and intense euphoria. The high from insufflating is more prolonged lasting 15 to 30 minutes, whereas the high from smoking rapidly dissipates lasting only 5 to 10 minutes. Cocaine is metabolized and eliminated rapidly, with a half-life of approximately 1 hour contributing to its very short duration of effect.[81] Therefore, the rapid onset and short duration combined provide a powerful incentive for repeated use of the drug. The primary cocaine metabolite (benzoylecgonine) may be detected for up to 5 days in a urine sample with little cross-reactivity.[82] Increased use can reduce the period of stimulation and an appreciable tolerance to the high can develop. Many individuals that use cocaine report failing to achieve as much pleasure as they did from their first exposure with continued use which may lead to intense drug-use cycling, sometimes lasting days, characterized by rapidly repeating doses of cocaine until their money or supply is exhausted.

Other patterns of use such as consumption of alcohol along with cocaine are common and add to the toxicity. Such drug use would seem

counterintuitive based on the counteracting effects of the two substances; however, in the presence of alcohol, cocaine is metabolized to cocaethylene, a longer-acting but potent psychoactive compound compared to the parent drug. The risk of death from cocaethylene is greater than from cocaine alone and this combination is one of the most common among individuals who come to hospital emergency departments with acute substance abuse problems.[81]

CLINICAL PRESENTATION: Cocaine Intoxication and Withdrawal

General

- In overdoses, cocaine is a CNS and cardiac stimulant.
- Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest.

Symptoms

- Symptoms of intoxication include motor agitation, elation, euphoria, hypervigilance, sweating, nausea, and vomiting.
- Symptoms of withdrawal include fatigue, sleep disturbances, nightmares, depression, and changes in appetite.

Signs

- Tachycardia, mydriasis, and elevated blood pressure may be observed with overdose.
- Cardiac abnormalities (eg, arrhythmias, infarction) and respiratory depression may be observed with overdose.
- Bradyarrhythmias and tremors may be observed in acute withdrawal.

Laboratory Tests

- Qualitative urine screening tests are available; however, they do not change clinical treatment significantly.

Other Diagnostic Tests

- Markers of organ dysfunction may be ordered as clinically indicated.

CLINICAL PRESENTATION: Amphetamine Intoxication and Withdrawal

General

- Amphetamine intoxication is an acute condition that may result in death. Pharmacotherapy may be indicated for symptomatic control of agitation, psychosis, and seizures.
- Patients may experience withdrawal symptoms for several days but are usually not in acute distress. Treatment of withdrawal is supportive in nature.

Symptoms

- Amphetamine intoxication may present as increased wakefulness, increased physical activity, decreased appetite, increased respiration, hyperthermia, and euphoria. Other CNS effects include irritability, insomnia, confusion, tremors, convulsions, anxiety, paranoia, chest pain, and aggressiveness. Hyperthermia and convulsions can result in death.
- Depression, altered mental status, substance craving, dyssomnia, and fatigue are all symptoms of withdrawal.

Signs

- Patients with amphetamine intoxication may present with tachycardia, hypertension, seizures, or stroke.

Laboratory Tests

- A qualitative urine screening can identify patients who have been exposed to amphetamines. However, false positives are common and the diagnostic benefit is limited.

Ecstasy

There are several dozen analogs of amphetamine and methamphetamine that are mildly hallucinogenic. Two methamphetamine analogs of most concern are 3,4-methylenedioxyamphetamine and especially 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy or Molly). Ecstasy usually refers to a tablet or pill formulation, whereas Molly is most often a powdered form that can be insufflated or smoked. Trends in MDMA use have been declining since its peak in 2001; however, the annual prevalence of use has held steady.[11]

Individuals that use MDMA report feelings of trust and empathy with others, decreased inhibition when socializing, and enhanced proprioception in addition to stimulating effects that MDMA shares with amphetamines. These effects are due to the preferential selectivity of MDMA for serotonergic over dopaminergic neurotransmission.[83] In addition to these positively reinforcing effects, MDMA use can result in negative effects such as panic, anxiety, depression, paranoid thinking, and psychosis. Physical symptoms include muscle tension, nausea, blurred vision, faintness, chills, and sweating, as well as vomiting, hyperthermia, dehydration, tremors, insomnia, and convulsions. Furthermore, MDMA also increases heart rate and blood pressure due to its structural similarities with amphetamines.[84]

In general, those that use MDMA perceive it to be a harmless drug, based in part on the fact that the risk of death is low compared with other drugs such as heroin and cocaine. However, mounting evidence points to MDMA's neurotoxic effects, involving a complex and incompletely understood mechanism. Mechanistically MDMA has been shown to destroy serotonergic neurons in animals, but further research is needed to understand the mechanism behind this loss of serotonin following MDMA exposure.[84] Recent publication of small studies exploring ecstasy being used therapeutically further complicates the assessment of MDMA's risks and benefits, as preliminary studies have been conducted in posttraumatic stress disorder (PTSD), anxiety disorders, and social anxiety in autism. It should be noted that most of these studies also include psychotherapy as part of the treatment regimen.[85,86]

Hallucinogens

The drugs commonly classified as hallucinogens are lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), mescaline, phencyclidine (PCP), ketamine, and other related compounds. Approximately 1.4 million people aged 12 or older are estimated to be currently using hallucinogens, with variability seen in each age ranging from 0.6%, 1.7%, and 0.3% for adolescents, young adults, and adults, respectively.[11] These statistics may not include ketamine use as this was recently added to the NSDUH Survey. Pharmacologically, LSD and related drugs stimulate both presynaptic (5-HT_{1A} and 5-HT_{1B}) and postsynaptic (5-HT_2) serotonin receptors in the brain, which functionally can cause either agonist or antagonist effects on serotonin activity. Precisely how the hallucinogens exert their effects remains unclear. Overall, LSD is an extraordinarily potent compound, producing observable CNS effects at doses as low as 25 mcg. For an in-depth review of the history, current status, and future uses of LSD, the reader is directed to a review by Smith and colleagues.[87]

Cannabinoids

Cannabis use is common in the United States. Despite a multitude of states passing laws allowing medical use and recreational use, cannabis is still an illegal substance according to federal law. In addition, increased media attention surrounding potential medical uses has also contributed to the public's evolving beliefs surrounding its use. In 2019, an estimated 48 million (a steady increase since 2002) Americans aged 12 or older used cannabis which corresponds to 17.5% of this population.[11] This use is likely to increase for the foreseeable future making abuse and subsequent treatment an increasingly important topic for healthcare providers. Cannabinoids are the active compounds within most available products or preparations. One chemical component of cannabis is δ-9-tetrahydrocannabinol (THC) which interacts with the two cannabinoid receptors within the CNS to cause its euphoric and psychoactive effects. Cannabidiol (CBD) does not have psychoactive effects. Epidiolex™ is a CBD preparation, FDA approved to treat Lennox-Gastaut syndrome and Dravet syndrome, two disorders that leave the afflicted with refractory seizures.[88]

As a group, cannabinoids interact with two subsets of cannabinoid receptors in the body: cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). Anandamide and 2-arachidonoylglycerol are the endogenous complements to the CB receptors, although their effects have not been completely described. The CB1 receptors are found in presynaptic neurons of the prefrontal cortex and in the hippocampus, and the CB2 receptors are located in smaller numbers in the prefrontal cortex, hippocampus, and hypothalamus. However, they are thought to play a much larger role in systemic effects of cannabinoids due to their abundance in the immune, peripheral nervous, and gastrointestinal systems.[89] Since THC is a partial agonist at CB1 and CB2 receptors, it is thought to create its psychoactive effects through CB1 receptors. In contrast, CBD binds less tightly with CB receptors and may interact with other receptors within and outside of the CNS.[90] Although the knowledge base surrounding the pharmacology and pharmacodynamics of cannabinoids is rapidly expanding, the current knowledge regarding their therapeutic effects is relatively incomplete compared to other FDA-approved medications. While cannabis is most commonly smoked, it can be ingested orally with THC and CBD extracts now being incorporated into many other usable forms including edible candies/snacks and vaporizable liquids that can be more palatable for new, young, or those not experienced in using cannabis. Cannabinoid pharmacokinetic properties are not well characterized, but they do show highly variable effects that are greatly affected by route of use. After inhalation of smoke or vapors, peak blood concentrations occur in about 10 minutes and although bioavailability is higher through inhalation relative to oral ingestion, many factors can affect this. Both THC and CBD are poorly bioavailable due to extensive first-pass metabolism by the liver; therefore, peak concentrations occur at about 2 hours when taken via the oral route. The terminal half-life of THC and CBD after a single use is about 24 hours; however, in those that use chronically, the terminal half-life is highly altered due to accumulation and subsequent redistribution from fatty tissues after chronic use.[90]

Cannabis use disorder (CUD) is loss of control over use, repeated failures to quit, and continuous usage despite negative consequences. The pathophysiology of CUD lies in chronic neuroadaptation over time. The primary euphoric psychoactive component of cannabis THC targets the body's natural endogenous endocannabinoid system leading to downregulation in those that use chronically. This downregulation results in alterations to the processes that regulate cognition, emotional processing, stress sensitivity, and reward goal directed behavior occurs. Additionally, THC-induced alterations modify synaptic plasticity, specifically leading to a reduction in synapses of the hippocampal neurons.[91]

13 According to the *DSM-5*, CUD leads to significant social impairment and or psychological distress in spite of negative personal consequences.[92] It is often associated with multiple failed attempts at halting cannabis use, with the rate of occurrence in North America being estimated to be as high as 749 in 100,000.[93] Although CUD has quite a high incidence, its detection and treatment are limited in part by beliefs that cannabis is safe and natural.[91] Abrupt discontinuation of cannabis use can elicit a withdrawal syndrome including anxiety, dysphoria, sleep changes, irritability, and anorexia. Although not life threatening, these withdrawal symptoms can make permanent discontinuation difficult. Treatment of CUD most often centers around

psychosocial interventions such as cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), or a combination there of. Both CBT and MET have been shown to decrease the number of days of cannabis use, and improve the severity of CUD. Additionally, CBT has been shown to increase abstinence rates where MET has yet to show this effect in clinical studies. Regardless, the combination of CBT and MET is synergistic.[91] Attempts at using pharmacotherapeutic agents to alleviate CUD have been mostly unsuccessful with escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, valproate, baclofen, modafinil, atomoxetine, buspirone, and naltrexone all proving ineffective. However, several therapeutic candidates have met with some success. Cannabinoid receptor agonists including dronabinol, nabilone (a synthetic THC analogue), and nabiximols (Sativex, a combination THC/CBD product) have had varying degrees of success in improving withdrawal symptoms in CUD. One small study found gabapentin was effective in decreasing cannabis use in addition to abating withdrawal symptoms. N-Acetylcysteine, a cysteine precursor thought to affect glutamate transmission, decreased rates of cannabis use in adolescents. However, follow-up studies in adults did not confirm these results. Regardless these studies should be interpreted and extrapolated cautiously due to the low number of patients involved.[91]

Synthetic Cannabinoids

A growing collection of synthetically derived cannabinoids are being misused for their psychoactive effects. Following identification of THC in 1964, and the endogenous cannabinoid receptors in the 1980s, there was a pharmaceutical effort to synthesize cannabinoid receptor agonists for potential therapeutic indications like nausea and pain. However, the vast majority of these efforts never reached commercial fruition, and they have begun showing up in the illicit market. To increase their attractiveness, they are often brightly packaged and given colorful names such as “K2,” “Spice,” “Aroma,” “Mr. Smiley,” “Zohai,” “Eclipse,” “Black Mamba,” “Red X Dawn,” “Blaze,” and “Dream.” Due to unclear laws regarding their legality, these products had been readily available at gas stations and convenience stores. However, since being listed as a schedule I controlled substance, the overt availability has decreased but they are still readily available.[94] Some synthetic cannabinoids produce a combination of intended effects, as well as unintended adverse effects, that resemble intoxication from THC. However, synthetic cannabinoids appear to be more potent than natural cannabinoids, and may interact with CB receptors for longer than THC. Symptoms of synthetic cannabinoid toxicity are similar to the euphoric and psychoactive effects of THC. The adverse effects of synthetic cannabinoids include severe agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremors, seizures, hallucinations, paranoid behavior, and nonresponsiveness. These effects are likely due to complex CB1 receptor interactions, direct and indirect, with dopaminergic, serotonergic, and glutaminergic pathways within the parts of the brain linked to psychosis.[95] However, it must not be forgotten that most reported adverse experiences with synthetic cannabinoids are troubled by incomplete knowledge of the specific cannabinoid product used, as well as adulteration with other substances.

Cannabis Hyperemesis Syndrome

14 Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclical vomiting in individuals with habitual use of cannabis that abates after discontinuation of use. Although first officially recognized in 2004, the syndrome has likely existed much longer. The pathophysiology underlying CHS is not completely elucidated and several hypotheses are being explored. Since cannabinoids are used therapeutically to treat chemotherapy associated nausea and vomiting, current hypotheses indicate that pathway signaling may be altered in a way that leads to excessive nausea and vomiting. Cannabinoids are also known to alter gastrointestinal hormones, potentially leading to aberrant GI function such as emesis. Other potential explanations include non-THC metabolite interactions, genetic variations in metabolism of cannabinoids, and vasodilation of splanchnic vascular beds.[96] Overall, CHS can be difficult to diagnose as nausea and vomiting are symptoms of many issues, and patients may not be forthcoming with their cannabis use due to its questionable legality. One interesting symptom, that often sets CHS apart from other causes of severe vomiting, is that CHS sufferers often report relief from hot baths or showers.

A systematic review found that CHS is diagnosed in males with greater frequency. The median age when cannabis use started was 16 years and the median age when symptoms developed was 24 years. The fact there is a long pattern of use before CHS develops which makes it harder to diagnose as both the person using as well as the clinician are likely to consider more recent changes or developments over chronic use. In the same review, all people diagnosed with CHS self-identified as using it at least weekly and a large majority (~75%) used daily. There are no consensus diagnostic criteria now.[96] Treatment of CHS is also far from standardized due to an incomplete delineation of causative mechanism. Abstinence from cannabis is the most effective treatment option, but takes several days to weeks for the cyclic vomiting to abate. While the use of hot bathing is effective for some people, its benefit is short-lived and it is not a sustainable treatment modality.[97] If intravenous fluids and traditional antiemetics are unsuccessful at improving CHS symptoms, other treatment options that are less established have been reported. Dopamine antagonists like haloperidol have been used successfully in small case reports.[98] A growing number of case reports have shown some benefit with topical capsaicin application which is

thought to interact with the transient receptor potential cation channel subfamily V member 1 or vanilloid receptor 1 (TRVP1 or VR1) to improve nausea and vomiting, although the mechanism isn't clearly understood.[96,97,99,100] The incidence of CHS is likely to increase as the availability of cannabis use increases and the potency of THC-containing products increases.

EVALUATION OF THERAPEUTIC OUTCOMES

There are a range of situations and substances where patients can present in regards to substance use. When considering overall therapeutic outcomes, each treatment must be evaluated to determine its efficacy and safety as there are a variety of factors that must be considered based on the current stage of therapy and the patient's specific treatment goals. Each of the medications used in the acute or the chronic setting have unique qualities that must be evaluated for each individual patient. Consistent monitoring for efficacy and appropriateness through treatment is critical. Monitoring for withdrawal reactions utilizing proper assessment scales (ie, COWS) can aid in evaluating the patient appropriately. When developing the treatment plans, the unique adverse effect profiles and medication and drug-interaction concerns for the selected treatment regimen must be considered. Data from urine drug screens and profiles from the Prescription Drug Monitoring Program (PDMP) can also help provide critical information on the full clinical picture for each patient. Patient education must occur throughout treatment to ensure proper medication administration and safety as therapy continues. SUD is a chronic disorder that will need not only pharmacological treatment but also ongoing psychosocial and educational support. It is important for healthcare providers working in this setting, to partner closely with the patient to continue setting appropriate goals in order to achieve favorable treatment outcomes.

CONCLUSION

OUD along with other SUDs continue to be escalating health problem in the United States. The true scope of the problem has only recently been explored. Management of OUD and SUD, whether through pharmacotherapy or behavioral therapy, is a rapidly progressing field. Healthcare providers can help in all aspects of tackling this problem, from identifying those with SUD, directing pharmacotherapy, assisting with treatment, and patient education using a patient-centered model.

ABBREVIATIONS

5-HT	5-hydroxytryptamine
6-AM	6-acetylmorphine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASAM	The American Society of Addiction Medicine
BBB	blood brain barrier
BP	blood pressure
cAMP	cyclic adenosine monophosphate
CB1 and CB2	cannabinoid receptor 1 and 2
CBD	cannabidiol
CBT	cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention

CHS	cannabinoid hyperemesis syndrome
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
CUD	cannabis use disorder
CYP450	cytochrome P450 isoenzyme
DA	dopamine
DEA	Drug Enforcement Administration
DMT	dimethyltryptamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GDP	gross domestic product
GI	gastrointestinal
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
HR	heart rate
IM	intramuscular
IMF	illicitly manufactured fentanyl
IN	intranasal
IO	intraosseous
IV	intravenous
LFT	liver function test
MAO	monoamine oxidase
MDD	major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine

MET	motivation enhancement therapy
MME	morphine milligram equivalents
MUD	methamphetamine use disorder
NAc	nucleus accumbens
NAM	National Academy of Medicine
NIDA	National Institute on Drug Abuse
NIH	National Institute of Health
NMDA	*N*-methyl-D-aspartate
NSDUH	National Survey on Drug Use and Health
OEND	overdose education and naloxone distribution
OTC	over-the-counter
OTP	opioid-treatment programs
OUD	opioid use disorder
PCP	phencyclidine
REMS	Risk Evaluation and Mitigation Strategy
SAMHSA	Substance Abuse and Mental Health Services Administration
SCr	serum creatinine
STI	sexually transmitted infection
SUD	substance use disorder
THC	δ-9-tetrahydrocannabinol
THN	take home naloxone
TIPS	Treatment Improvement Protocols
TJC	The Joint Commission
TRVP1 or VR1	transient receptor potential cation channel subfamily V member 1 or vanilloid receptor 1
VMAT2	vesicular monoamine transporter
VTA	ventral tegmental area

WHO	World Health Organization
XR-NTX	extended-release injectable naltrexone

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SELF-ASSESSMENT QUESTIONS

1. In which year did opioid prescriptions peak in the United States?

   A. 2010

   B. 2011

   C. 2012

   D. 2016

2. Which of the following statements is FALSE regarding fentanyl products?

   A. Most opioid overdose deaths attributed to fentanyl have been linked to prescription fentanyl products.

   B. llicit manufactured fentanyl (IMF) is often mixed with heroin or cocaine which is leading to increases in overdose deaths across America as per data released in 2018.

   C. IMF has been identified in counterfeit opioids and benzodiazepines pills and capsules.

   D. Carfentanil is 10,000 times more potent than morphine and poses a severe threat to first responders due to the potency of the opioid.

3. Which medication treatment for OUD requires the patient to be abstinent from short- acting opioids for 7 to 10 days or long-acting opioids for 10 to 14 days?

   A. Methadone

   B. Buphrenorphine

   C. Extended-release Naloxone

   D. Ketamine

4. What is a key counseling point that should be covered regarding buprenorphine therapy?

   A. All symptoms of craving will be immediately eliminated after starting this medication.

   B. There are very few side effects to this medication so no need for follow-up.

   C. The goal of the first week is to improve withdrawal symptoms without over-sedation.

   D. There are no drug-drug interactions with this medication so no need to worry about this.

5. Which of the following statements is TRUE regarding naloxone?

   A. Naloxone can be very dangerous if administered to a patient who is not currently taking an opioid.

   B. The Narcan Nasal Spray and the Evzio auto-injector are approved by the FDA for community distribution.

   C. Naloxone is effective at reversing benzodiazepine overdoses and opioids.

   D. If a patient is overdosing on opioids and is also suffering from alcohol poisoning, then there is no reason to use the naloxone since it is ineffective.

6. Which of the following is FALSE regarding prescribing restrictions for buprenorphine?

   A. Based on recent legislation, certified nurse midwives can prescribe buprenorphine if allowed by state prescribing laws.

   B. Practitioners who are in compliance with DATA 2000 and have been confirmed to have the “X” DEA number can prescribe buprenorphine for up

to 300 patients.

C. Buprenorphine is a schedule III controlled substance with very specific prescribing restrictions.

D. Physician assistants and nurse practitioners are authorized to prescribe buprenorphine as long as it is approved by state licensing.

7. Which of the following routes of cocaine use has the fastest time of onset and highest peak blood concentration?

A. Oral ingestion of crack cocaine

B. Nasal insufflation of cocaine

C. Smoking crack cocaine

D. Intravenous injection of cocaine

8. Which of the following neurotransmitter systems plays a major role in the toxicity of stimulants, such as cocaine, based on current understanding?

A. Histamine

B. Dopamine

C. Norepinephrine

D. GABA

9. Which of the following is the cannabinoid associated with the psychoactive effects of cannabis?

A. Anandamide

B. 2-arachidonoylglycerol

C. Cannabidiol

D. Tetrahydrocannabinol

10. Symptoms of cannabis hyperemesis syndrome (CHS) are potentially relieved by which of the following treatments.

A. Warm showers

B. Smoking cannabis

C. Gabapentin

D. Cold showers

11. What is the incidence of opioids and benzodiazepines being co-prescribed?

A. 20%

B. 40%

C. 60%

D. 80%

12. Which over-the-counter (OTC) medication is regulated in an effort to prevent the production of methamphetamine?

A. Certrizine

B. Pseudoephedrine

C. Diphenhydramine

D. Epinephrine

13. Use of which of the following substances can lead to adverse effects similar to amphetamine toxicity based on similar structural elements?

A. Cannabis

B. Ecstasy

C. Carfentanyl

D. Heroin

14. Current recommendations for a pregnant woman with an OUD requesting treatment includes:

A. Naloxone.

B. Methadone.

C. Extended-release injectable naltrexone.

D. No medications are recommended.

15. What is the main difference between the treatment of benzodazepine withdrawal and alcohol withdrawal?

A. The half-life of the benzodiazepine used.

B. The length of treatment.

C. Alcohol withdrawal protocols only start if withdrawal symptoms are seen.

D. Treatment for withdrawal from a benzodiazpine is not medically managed.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** In 2012, opioid prescriptions in the United States peaked at 255 million annual prescriptions.

2. **A.** Most fentanyl linked overdoses have been associated with IMF. For more information see the "Fentanyl" section.

3. **C.** Patients starting extended-release naloxone must have an adequate time period of opioid abstinence before starting this medication as opioids in the system can precipitate withdrawal necessitating hospitalization. For further information, see the chapter text and Table 85-1.

4. **C.** The first week is focused on identifying a dose that will help withdrawal symptoms without over-sedating the patient. Moving forward, it will be important to work on stabilizing the patient and working to encourage behavioral therapy to go with the pharmacotherapy treatment.

5. **B.** Narcan Nasal Spray and Evzio auto injectors are both approved by the FDA for community distribution. For further information see the text and Table 85-2.

6. **C.** This bill codified that waivered physicians can prescribe MAT for 275 patients. For more information see the "Buprenorphine" section.

7. **D.** Since IV administration of cocaine bypasses the first pass effect, this results in the fastest time of onset and highest peak blood concentration. For more information see the "Cocaine" section.

8. **C.** While dopamine plays a key role in the reward and addiction pathways, norepinephrine is responsible for the toxic sympathomimetic effects

experienced by users of cocaine. For more information see the "Cocaine" section.

9. **D.** Tetrahydrocannabinol is the primary cannabinol associated with the psychoactive effects of cannabis.

10. **A.** Warm showers can help alleviate the vomiting and can be a diagnostic clue if reported by the patient.

11. **D.** A cohort study that included over 2 million opioid prescriptions in one year demonstrated 80% of these were co-prescribed with a benzodiazepine and the rates of overdose deaths in this group were 10 times higher than opioid analgesics alone. See "Epidemiology" in "Benzodiazepines and Other Sedative-hypnotics" section.

12. **B.** Small laboratories use OTC products containing pseudoephedrine as starting product for the clandestine manufacture of methamphetamine. See the "Stimulant" section for more information

13. **B.** Ecstasy or 3,4-methylenedioxymethamphetamine (MDMA) is a structural analog of methamphetamine and can lead to hypertension, tachycardia, agitation, and psychosis. For more information, see the "Stimulants" section.

14. **B.** Current recommendations for a pregnant woman with an OUD requesting treatment includes methadone or buprenorphine, and behavioral interventions. Now, the safety of extended-release injectable naltrexone is still under study. See "Opioid Use Disorder" in "Pregnancy" section.

15. **B.** Treatment of benzodiazepine withdrawal is very similar to the treatment of alcohol withdrawal. The major differences in management is the length of treatment. See the "Pharmacologic Therapy for Benzodiazepine Intoxication and Withdrawal" section.