Substance Use and Cardiovascular Disease

By Robert L. Page II, Pharm.D., MSPH, FAHA, FCCP, FHFSA, FASHP, BCPS-AQ Cardiology

Reviewed by Sheryl L. Chow, Pharm.D., FCCP, FAHA, FHFSA; Christina Ruggia-Check, Pharm.D., BCPS, BCCP, BCTXP; and Michael A. Gillette, Pharm.D., FHFSA, AACC, BCPS, BCCP

LEARNING OBJECTIVES

1. Evaluate current trends within the United States regarding substance use, and using current diagnostic criteria, distinguish among specific substance use disorders.
2. Distinguish current state and national health policy regulations regarding medicinal or recreational cannabis use, and delineate the FDA's role in regulating cannabis products.
3. Given a patient with or without underlying cardiovascular disease (CVD) who is using cannabis, evaluate for specific cannabinoid-drug interactions, and devise a therapeutic plan to mitigate potential cardiac adverse effects.
4. Given a patient with or without underlying CVD who is misusing cannabis, opiates, or stimulants, evaluate for specific acute and chronic CV complications, and devise a therapeutic plan to mitigate or treat these complications.
5. Identify emerging substances of misuse, and estimate potential acute and chronic CV complications using electronic data resources.
6. Design appropriate education for patients and health care providers regarding the legal and CV issues surrounding substance use, particularly cannabis use.

ABBREVIATIONS IN THIS CHAPTER

ADHD	Attention-deficit/hyperactivity disorder
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CBD	Cannabidiol
CB1R	Cannabinoid receptor 1
CB2R	Cannabinoid receptor 2
CUD	Cannabis use disorder
CVD	Cardiovascular disease
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
GABA	γ-Aminobutyric acid
hERG	Human ether-à-go-go–related gene
HF	Heart failure
MI	Myocardial infarction
OUD	Opioid use disorder
SUD	Substance use disorder
TdP	Torsades de pointes
THC	Δ-9-tetrahydrocannabinol
TIA	Transient ischemic attack

Table of other common abbreviations.

INTRODUCTION

Substance Use in the United States

In the United States, misuse of substances such as cannabis, opiates or opioids, stimulants, and designer street drugs has not only become a major public health issue but is now also considered an epidemic. Moreover, not only has the prevalence of tobacco and alcohol use remained high, but the prevalence of substance misuse also continues to increase steadily and has particularly become more pervasive during COVID-19, especially among young adults. According to the Substance Abuse and Mental Health Services Administration, over 59.3 million Americans 12 years and older reported using one or more illicit substances during 2020, with the highest being cannabis (49.6 million); prescription pain relievers, often opiates (9.3 million); and cocaine (5.2 million) (Figure 1 A). Such misuse has led to over 40.3 million Americans developing a substance use disorder (SUD) (Figure 1, Panel B). Recreational use in individuals with and without cardiovascular disease (CVD) has been associated with many CV complications and death. Understanding SUD and its definitions, as well as the acute and chronic CV complications associated with substance misuse, is critical when assessing prevention, development, progression, and treatment of CVD. This chapter focuses on concepts and definitions of SUD, issues surrounding health policy

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Diagnosis and guideline-directed pharmacologic management of acute and chronic heart failure (HF) with reduced ejection fraction, acute coronary syndrome, hypertension, and endocarditis, as well as atrial and ventricular arrhythmias
- Presenting signs and symptoms, etiologies, and clinical sequelae of acute decompensated HF, acute coronary syndrome, hypertension, and endocarditis, as well as atrial and ventricular arrhythmias
- Pharmacologic management of adult cardiac arrest, including benzodiazepine, opiate, and stimulant overdose

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Heart Association (AHA). 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142:S337-S468.
- Dezfulian C, Orkin AM, Maron BA, et al. Opioid-associated out-of-hospital cardiac arrest: distinctive clinical features and implications for health care and public responses: a scientific statement from the American Heart Association. Circulation 2021;14:e836-e870.
- Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435.
- Martin JA, Campbell A, Killip T, et al. QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. Addict Dis 2011;30:283-306.
- McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction. A scientific statement from the American Heart Association Acute Cardiac Care Committee on the Council on Clinical Cardiology. Circulation 2008;117:1897-907.
- Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-227.

changes, and the acute and chronic CV complications associated with cannabis, opiate, and stimulant misuse.

Terminology of Substance Use

The terminology surrounding substance use can be confusing, is often used incorrectly, and continues to evolve. Although *drug misuse*, *abuse*, and *addiction* are all serious public health challenges, their definitions can vary depending on the federal or medical organization. Because each of these issues deals with the use of illegal drugs and inappropriate use of legal drugs (e.g., tobacco, alcohol, prescription medication), these terms are commonly used interchangeably; however, their interventions vary. *Drug misuse* is generally associated with prescription medicines in which substances are taken for a purpose that is inconsistent with legal or medical guidelines, whereas *abuse* refers to repeated use to produce pleasure, alleviate stress, and/or alter or avoid reality. In 2013, the American Psychiatric Association updated the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) and replaced the categories of substance abuse and substance dependence with a single category: SUD, with three subclassifications – mild, moderate, and severe. The symptoms associated with a SUD fall into four major groupings: impaired control, social impairment, risky use, and pharmacologic criteria (i.e., tolerance and withdrawal). Box 1 summarizes the *DSM-5* criteria for cannabis use disorder (CUD), opioid use disorder (OUD), and stimulant use disorder.

Physical dependence can occur with regular (daily or almost daily) use of any substance, legal or illegal, even when taken as prescribed, as the body adapts to regular exposure. Once removed, withdrawal symptoms can emerge as the body readjusts to the substance loss. Physical dependence can lead to craving the substance to relieve the withdrawal symptoms, whereas tolerance is the need to take higher doses of a drug to achieve the same effect. To this end, tolerance accompanies dependence, thus often making them indistinguishable. Addiction is defined as a chronic, relapsing disorder characterized by compulsive drug seeking, continued use despite harmful consequences, and long-lasting changes in the brain.

CANNABIS

Terminology and Formulations

Marijuana and hemp plants are cultivars of the genus *Cannabis* and have been used for centuries because of their potential therapeutic and medicinal properties. Also known as "pot" and "weed," their properties are derived from the natural cannabinoids in cannabis. Although not standardized, cannabinoids can be divided into either the plant derived from the flower, stem, or leaf of the cannabis plant (e.g., phytocannabinoids) or synthetic. Although more than 100 different phytocannabinoids have been identified, Δ-9-tetrahydrocannabinol

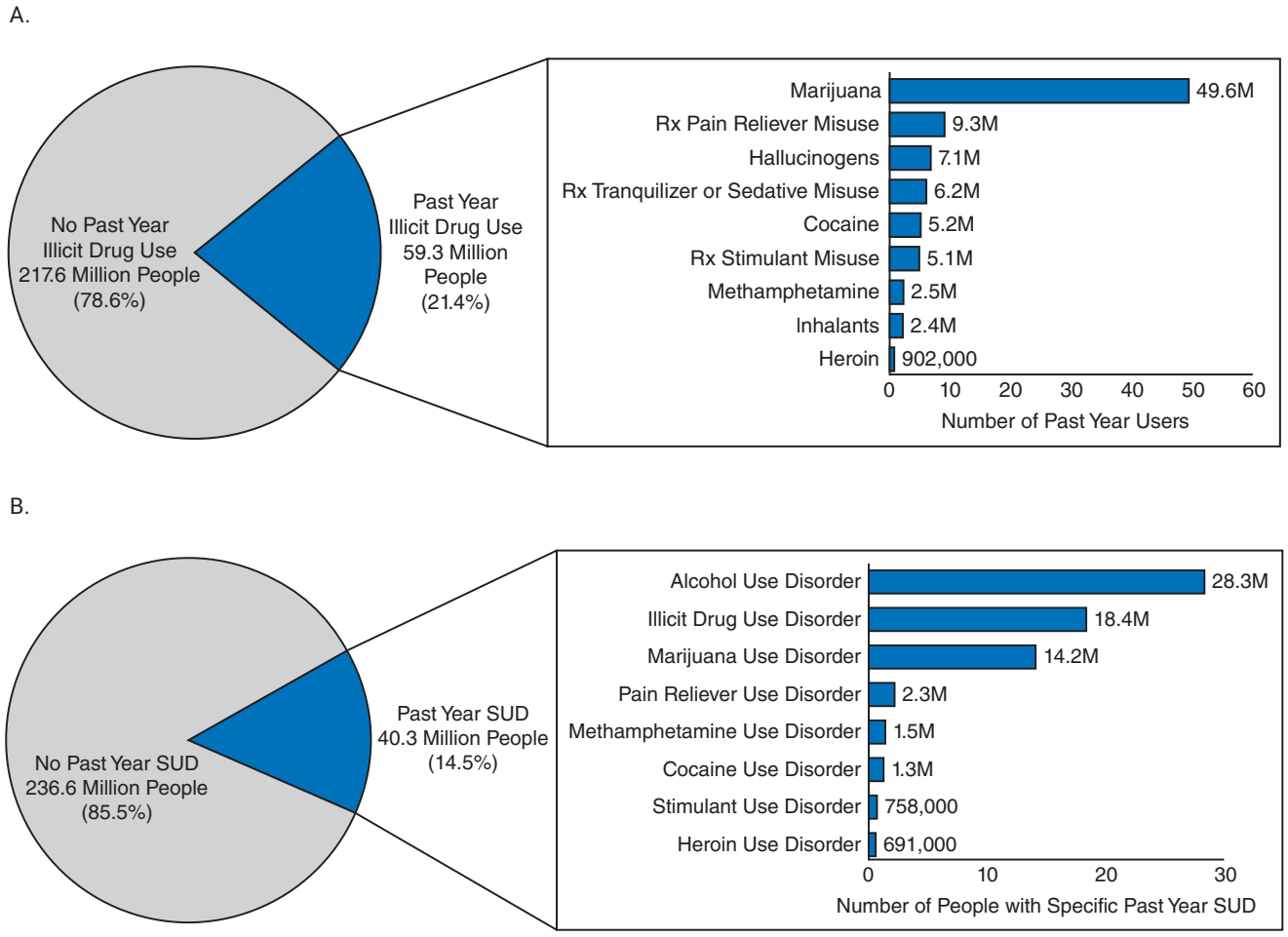


Figure 1. Trends of (A) substance use; and (B) substance use disorder in the United States among people 12 years or older in 2020.

M = million; Rx = prescription; SUD = substance use disorder.

Hallucinogens = dimethyltryptamine, ecstasy, ketamine, lysergic acid diethylamide, mescaline, peyote, phencyclidine, psilocybin, *Salvia divinorum*.

Inhalants = amyl nitrate; correction fluid, degreaser, or cleaning fluid; gasoline or lighter fluid; glue, shoe polish, or toluene; halothane, ether, or other anesthetics; lacquer thinner or paint solvents; lighter gases such as butane or propane; nitrous oxides; magic markers; spray paints; computer keyboard cleaner.

Reprinted from: Substance Abuse and Mental Health Services Administration (SAMHSA). Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health. October 2021.

(THC) and cannabidiol (CBD) have been the most studied. The three commonly recognized strains of cannabis used recreationally and medicinally are *Cannabis sativa*, *C. indica*, and *C. ruderalis*. Botanists use physical differences such as variations in height, branching patterns, and shape of the leaves to identify different strains of plants (Figure 2). Indica plants are shorter than sativa plants and have a woody, not fibrous, stalk, whereas sativa strains are tall and thin with finger-like leaves. Cannabis dispensaries often characterize these plants as sativa, a high-THC-containing plant; indica, or a mixed THC-CBD plant; and ruderalis, a high-CBD-containing plant. Although rudimentary, sativa appears to provide more stimulating, uplifting, and energizing effects, whereas indica is more relaxing, sedating, and pain reducing (VanDolah 2019). Cannabis plants can also be classified on the basis of their ratio of THC to CBD, consisting of chemotype I or drug-type plants, which have a high THC/CBD ratio (>>1.0); chemo-type II or intermediate-type plants, which have a balanced THC/CBD ratio close to 1.0; and chemotype III or hemp-type plants, which have a low THC/CBD ratio (<<1.0) in which the THC percentage of less than 0.30% is below the level of detectability (Hillig 2004).

Box 1. Criteria for Substance Use Disorders According to the *DSM-5*

Cannabis Use Disorder

A pattern of cannabis use for at least 1 yr, with the presence of at least two of the following symptoms, accompanied by significant impairment of functioning and distress:

- Difficulty containing use of cannabis – the drug is used in larger amounts and over a longer period than intended
- Repeated failed efforts to discontinue or reduce the amount of cannabis that is used
- An inordinate amount of time is occupied acquiring, using, or recovering from the effects of cannabis
- Cravings or desires to use cannabis. These can include intrusive thoughts, images, and dreams about cannabis or olfactory perceptions of the smell of cannabis because of preoccupation with cannabis
- Continued use of cannabis despite adverse consequences from its use, such as criminal charges, ultimatums of abandonment from spouse/partner/friends, and poor productivity
- Other important activities in life (e.g., work, school, hygiene, and responsibility to family and friends) are superseded by the desire to use cannabis
- Cannabis is used in contexts that are potentially dangerous, such as operating a motor vehicle
- Use of cannabis continues despite awareness of physical or psychological problems attributed to use (e.g., anergia, amotivation, chronic cough)
- Tolerance to cannabis, as defined by progressively larger amounts of cannabis needed to obtain the psychoactive effect experienced when use first commenced, or, noticeably reduced effect of use of the same amount of cannabis
- Withdrawal defined as the typical withdrawal syndrome associated with cannabis, or cannabis or a similar substance is used to prevent withdrawal symptoms[a]

Opioid Use Disorder

A problematic pattern of opioid use for at least 1 yr, leading to clinically significant impairment or distress, as manifested by at least two of the following:

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

Stimulant Use Disorder

A pattern of amphetamine-type substance, cocaine, or other stimulant use for at least 1 yr leading to clinically significant impairment or distress, as manifested by at least two of the following:

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

Mild: 2or 3 criteria; moderate: 4 or 5 criteria; severe: ≥ 6 criteria.

[a]Withdrawal signs and symptoms: cannabis = insomnia, anorexia, anxiety, irritability, restlessness, dysphoria, nightmares, nausea, or physical pain and discomfort when using less than usual (may persist for weeks or months in attenuated form for long-time users); opiates = GI distress (e.g., abdominal cramps, diarrhea, nausea, and/or vomiting); flu-like symptoms (e.g., lacrimation, rhinorrhea, diaphoresis, shivering, and piloerection (goosebumps); sympathetic nerve and CNS arousal (e.g., mydriasis, mild hypertension, and tachycardia, anxiety and irritability, insomnia, agitation, restless legs syndrome, general restlessness, tremor, and, less commonly, low-grade temperature and tactile sensitivity); and other (e.g., yawning, sneezing, anorexia, dizziness, myalgias/arthralgias, and leg cramps; stimulant, specifically methamphetamines: acute (first 24 hr): dehydration, insomnia, nausea, headaches, irritability, sweating, mood swings; subacute (2 wk to months): anxiety, paranoia, depression, cravings, and increased eating and sleeping.

Information from: American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 5th ed. APA, 2013.

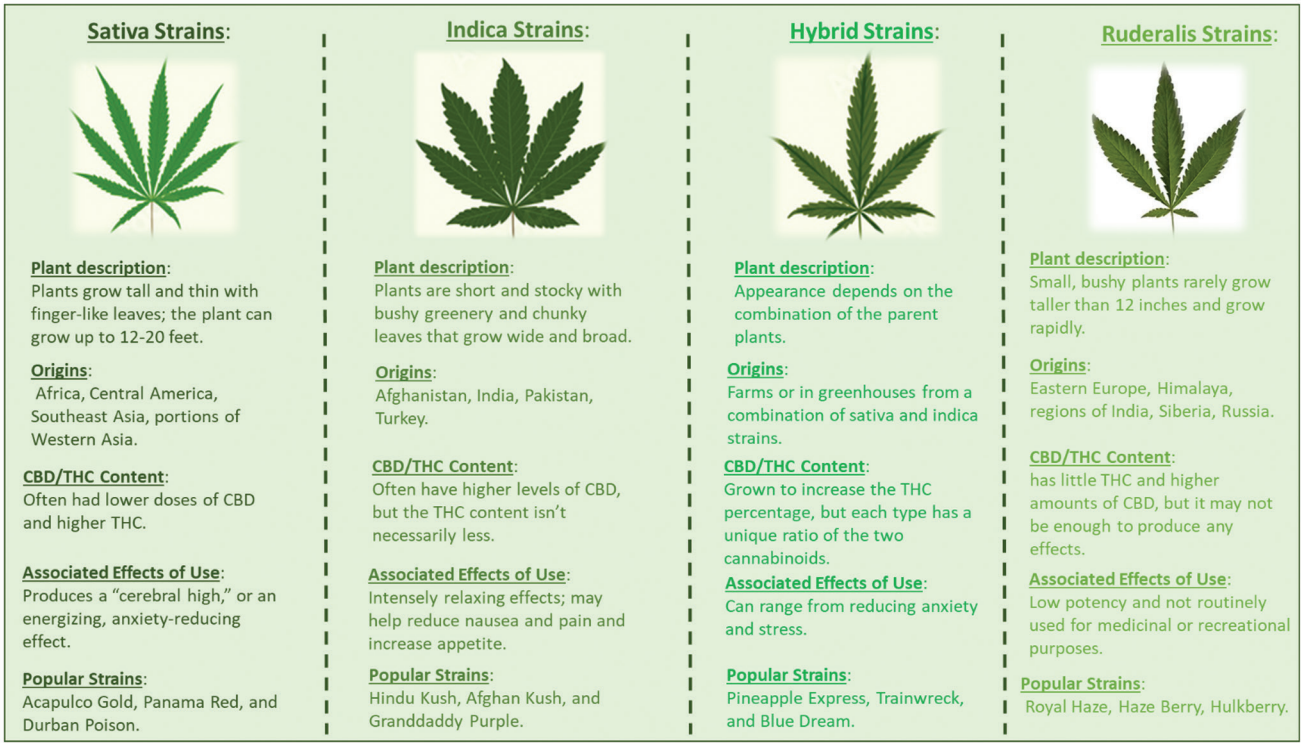


Figure 2. Description of various types of cannabis.

CBD = cannabidiol; THC = Δ-9-tetrahydrocannabinol.

Information from: Committee on the Health Effects of Marijuana. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies Press, 2017.

Synthetic cannabinoids are a class of designer molecules that are arbitrarily divided into prescription and illicit. Four synthetic prescription cannabinoids are currently marketed as Marinol (dronabinol) and Cesamet (nabilone) in the United States and Canada, Epidiolex (CBD) in the United States, and Sativex (CBD plus THC) in Canada. In 2008, synthetic illicit cannabinoids, initially designed to study the pharmacology of the endogenous cannabinoid system and not designed for human consumption, emerged on the gray market. Known as K-2 and Spice, these extremely potent products contain 2–100 times more THC than typical cannabis products and are now classified as new psychoactive drugs. Because of their overwhelming content of THC as well as the significant cardiotoxicities associated with illicit synthetic cannabinoids, many states have banned these substances since 2010 (Pacher 2018)

With the advent of cannabis dispensaries and changes in state policies, phytocannabinoids can also be arbitrarily delineated into first and second generations. Compared with first-generation phytocannabinoids (gray market before 1996), second-generation phytocannabinoids are bred to be more potent and have higher THC and CBD concentrations. For example, between 1995 and 2018, the average THC concentration in a single leaf of cannabis increased by more than 4-fold – from 3.96% to 15.61% (National Institute on Drug Abuse 2021). Finally, depending on its use, cannabis is considered either medical or recreational, the definitions of which are based on state policy.

Regardless of use, many cannabis formulations have entered onto the market and can be used orally, sublingually, rectally, vaporized, or smoked (Figure 3). Of importance, these products lack federal regulation in the United States, resulting in a lack of standardization in dose, concentrations of cannabinoids, packaging, and labeling. For example, products purchased in a cannabis dispensary that claim pure CBD may still contain some amount of THC.

Health Policy/Regulation

Over the past 30 years, attitudes toward the recreational and medical use of cannabis have rapidly evolved in the United States from illicit to decriminalized to legalized at the state level. Figure 4, Panel A summarizes the major health policy changes that have shaped cannabis use. With the passage of the Controlled Substances Act of 1970, cannabis became classified as a schedule I substance, meaning no valid medical uses with a high potential for misuse, which significantly

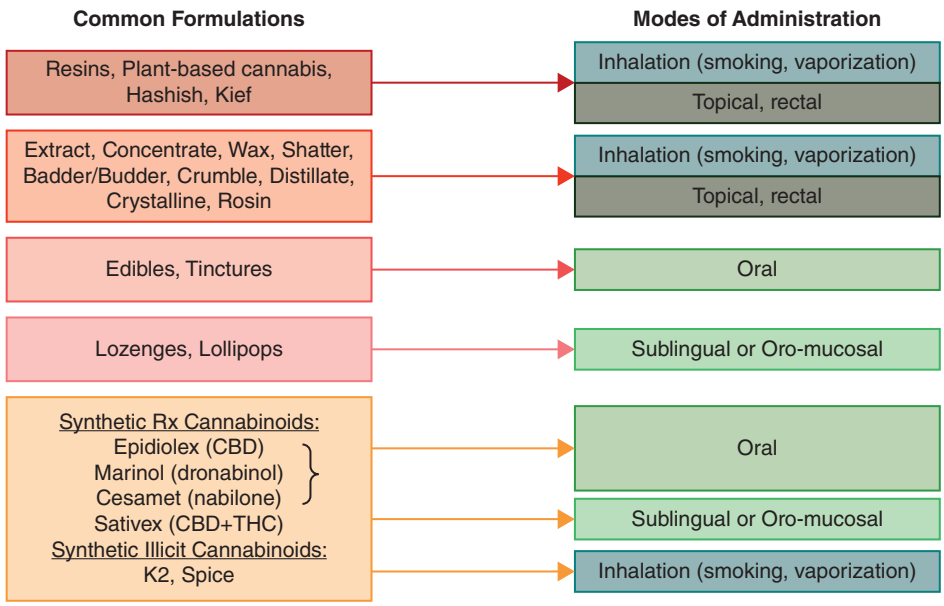


Figure 3. Modes of administration and common formulations of cannabis.

Terminology: Badder/budder: cannabis concentrate whipped under heat to create a cake-like batter. Concentrate: products made from the cannabis plant that have been processed to keep only the most desirable plant compounds (primarily the cannabinoids and terpenes) while removing excess plant material and other impurities. Crumble: dried cannabis oil with a honeycomb-like consistency. Concentrates made without the use of solvents are produced with mechanical or physical means to remove and gather trichomes. Crystalline: isolated cannabinoids in their pure crystal structure. Distillate: refined cannabinoid oil that is typically free of taste, smell, and flavor. It is the base of most edibles and vaporization cartridges. Edibles: also known as a cannabis-containing food product, varying in concentrations of THC, CBD, or both. Examples include baked goods, powders, candies, popcorn, and drinks. Extract: a cannabis concentrate created from solvents (e.g., alcohol, CO_2) that essentially washes the trichomes off the cannabis plant. Hash or hashish: the dried flower and buds from *Cannabis sativa* that are filtered and crushed into a power and molded into a sticky ball or brick. Kief: the most basic of the THC concentrate that is a powder-like substance found on cannabis flowers. Resins: the trichomes from the cannabis flower or plant used to create hash. Rosin: end product of the cannabis flower that is squeezed under heat and pressure. Shatter: a translucent, brittle, and often golden to amber concentrate used to make a solvent. Tinctures (also known as green or golden dragon): alcohol-based cannabis extracts used to make edibles.

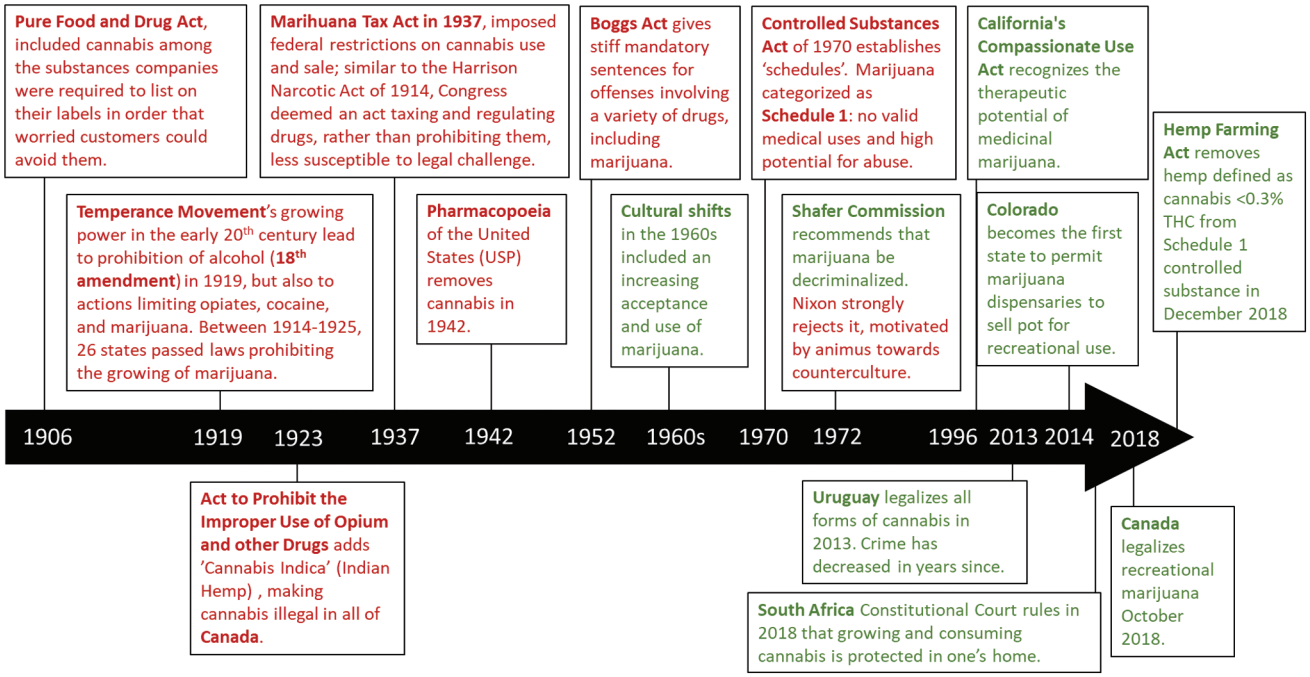
CBD = cannabidiol; THC = Δ-9-tetrahydrocannabinol.

Reprinted with permission from: Page RL II, Allen LA, Kloner RA, et al. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2020;142:e131-e52.

limited its ability to be studied clinically. However, in 2018, the Hemp Farming Act defined hemp as cannabis with less than 0.3% THC, thereby removing it from schedule I status. The Hemp Farming Act allowed the sale of CBD products outside cannabis dispensaries; however, manufacturers cannot make any claims for therapeutic or medical uses, although they have not been approved by the FDA. In 2014, Colorado was the first state to allow cannabis to be sold within a dispensary. Since then, several states have legalized, allowed for only medical use, decriminalized, or made cannabis fully legal (Figure 4, Panel B). Of importance, state policies on cannabis are specific to the state. States can define medical use, labeling and packaging, possession and age limits, and medical versus recreational cannabis on the basis of THC content. Although these laws are rapidly changing and evolving, up-to-date websites are available that offer good information sources on current state laws and regulations and approved medical indications. Regardless of state law, cannabis is still regulated under the Drug Enforcement Act under schedule I of the Controlled Substances Act, meaning interstate commerce of cannabis products is still considered a federal crime.

Cannabis and cannabis-derived products are subject to the same authorities and requirements as FDA-regulated products containing any other substance. This allows hemp to serve as a source of cannabis and cannabis-derived compounds for drug development without Controlled Substances Act controls, with the understanding that the investigational drug does not contain THC exceeding 0.3% by dry weight. According to the FDA statute, CBD and THC cannot be added to foods and are excluded from the definition of dietary supplements under the Federal Food, Drug, and Cosmetic Act.

A.



B.

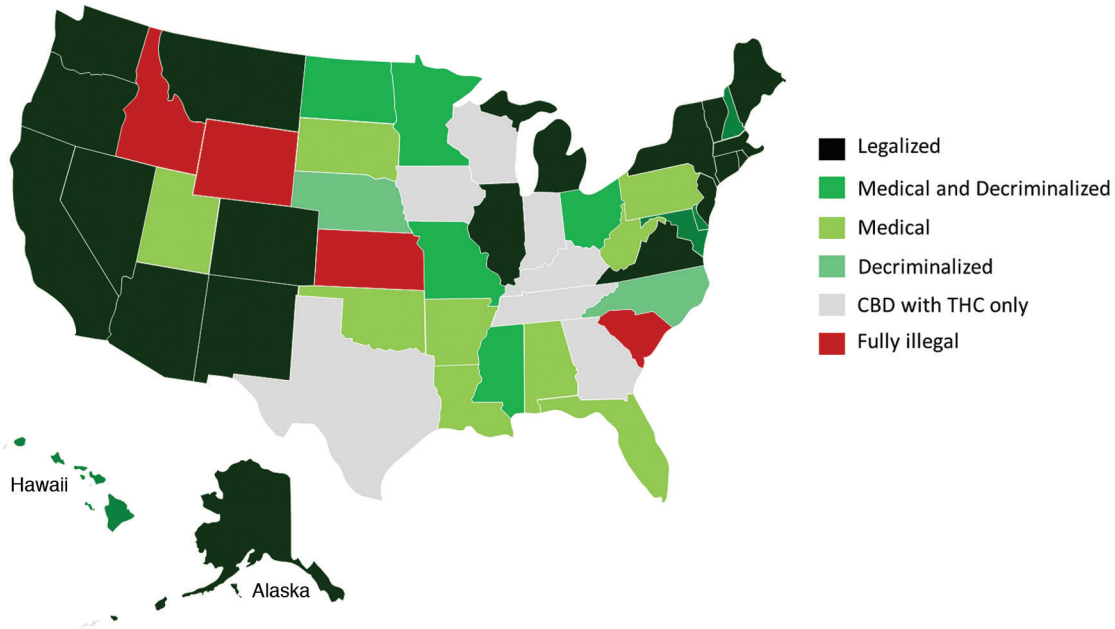


Figure 4. A, Evolution of cannabis policies worldwide. B, Medical and recreational cannabis laws by state as of July 2022.

CBD = cannabidiol; THC = Δ-9-tetrahydrocannabinol; USP = Pharmacopoeia of the United States.

A is reprinted with permission from: Page RL II, Allen LA, Kloner RA, et al. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2020;142:e131-e152; information for B from: DISA Global Solutions. Map of Marijuana Legality by State.

Patient Care Scenario

A patient who is following up for blood pressure medication titration at the University of Colorado Hospital Heart and Vascular Center admits that he has significant posttraumatic stress disorder. He was a student at Columbine High School during the shootings, and now relieves his symptoms by vaping cannabis. He asks your opinion about obtaining a medical cannabis card. Which one of the following is the best information to share with the patient.?

A. Posttraumatic stress disorder is an approved medical indication for cannabis in Colorado. Your primary care provider will need to evaluate you for an official diagnosis.

B. Posttraumatic stress disorder is not an approved medical indication for cannabis in Colorado. Let us discuss prescription options for this condition.

C. You need to stop vaping cannabis immediately and follow up with your primary care provider.

D. Posttraumatic stress disorder is an approved medical indication for cannabis in Colorado; however, I would recommend stopping cannabis use immediately.

ANSWER

With the legality of cannabis both medically and recreationally increasing across the U.S., pharmacists will be asked questions regarding their respective state laws. Using the online resources provided in this chapter, this patient's posttraumatic stress disorder is covered as an approved medical indication for cannabis in Colorado; however, he will need to receive an appropriate diagnosis from a physician, making Answer A correct and Answer B incorrect. As with all psychotropic agents, abrupt cessation can lead to withdrawal and is not recommended. Additionally, the American Heart Association strongly recommends against smoking or vaping. Thus, Answers C and D are incorrect.

1. NORML. Medical marijuana laws. 2022.
2. DISA Global Solutions. Map of marijuana legality by state. April 2022.
3. Page RL2, Allen LA, Kloner RA, et al. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2020;142:e131-e152.

Since 2015, the FDA has issued several warning letters to manufacturers of cannabis products regarding misbranding and illegally marketed food and dietary supplements (FDA 2021, Congressional Research Service 2020).

Pharmacology of Cannabinoids

The physiologic effects of cannabis are derived from cannabinoids because of engagement with the endocannabinoid system, which is responsible for maintaining overall homeostasis. Cannabinoids act through G protein–coupled receptors: cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R). The CB1R is abundant in the mammalian brain and is primarily responsible for the psychotropic effects of cannabis. The CB1R is also expressed in the myocardium, vascular endothelial, smooth muscle cells, and vagal afferents, whereas the CB2R is predominantly found within the macrophage-derived immune cells. THC is the primary psychoactive component of cannabis and is a partial agonist to CB1R and CB2R. However, CBD acts as a negative allosteric modulator of the CB1R, which in animal models has shown antioxidant and anti-inflammatory properties with limited psychoactive effect. Table 1 summarizes the pharmacology and pharmacokinetics of THC and CBD. Of note, the mode of administration is exceedingly important with respect to onset, bioavailability, and duration of effect, with the shortest onset and duration being inhalation (minutes, 2–3 hours, respectively) and the longest being oral consumption (½–2 hours, 5–8 hours, respectively).

CV Drug-Drug Interactions

Cannabis-related drug interactions can be challenging, given the wide variability in products, potencies, ratios of THC and CBD, doses, routes of administration, and populations using cannabinoids. However, many interactions can be predicted by the pharmacokinetics of the cannabinoid and potential concomitant drug. In vitro experiments suggest that THC can inhibit CYP3A4, CYP2C9, CYP2C19, and CYP2D6, whereas CBD also has the potential to inhibit CYP3A4/5, CYP2C9, CYP2C19, CYP2D6, and CYP1A2. THC can induce CYP1A2, particularly with smoked cannabis. In addition, these cannabinoids can inhibit systemic transport proteins such as breast cancer resistance protein and P-glycoprotein (P-gp) activity, decrease protein expression of P-gp, and increase protein expression of breast cancer resistance protein. Whether these effects on CYP isoenzymes and transport proteins depend on chronicity and amount of cannabis used or mode of administration remains unknown. Table 2 summarizes potential drug-drug interactions between cannabinoids and CV medications.

CV Complications

When considering the CV complications associated with cannabis use, much of the available published data are short term, observational, and retrospective; lack exposure determination; have recall bias; include minimal or variable cannabis exposure with no dose or product standardization; and typically evaluate low-risk cohorts. In addition, the effect

Table 1. Summary of Pharmacology and Pharmacokinetics of Phytocannabinoids

Mechanism of Action	Absorption	Metabolism	Distribution	Elimination
CBD				
Activates CB1R and CB2R Anandamide uptake inhibitor; TRPV1, TRPV2, TRPA1, GPR55, serotinin-1a, and PPARγ receptor activation Inhibits adenosine uptake Inhibits FAAH and release of proinflammatory cytokines and expression of transcription factors (IL-1β, IL-2, IL-6, IL-8, TNFα, IFN-γ, CCL3, CCL4, NF-κB) Allosterically modulates other receptors: α_1-adrenoceptors, dopamine D_2, $GABA_A$, mu-and δ-opioid receptors (weak) Inhibits calcium, potassium, and sodium channels by noncompetitive antagonism Free radical scavenger	Inhalation: Onset: 3–5 min Bioavailability:11%–45% Duration: 2–3 hr Oral: Onset: Hours Bioavailability: 6%–33% Duration: 2–6 hr Transdermal: Not known Transrectal: Not known	Hepatic, by CYP 1A1, 1A2, 2C8, 2C9, 2C19, 3A4, 2D6; UGT1A9, UGT2B7; undergoes hydroxylation	Time-dependent, fatty tissues and highly perfused organs such as brain, heart, lung, and liver	Feces and urine; depends on administration; half-life: 18–32 hr Preclinical and animal data suggest CBD is a substrate and inhibitor of P-gp
THC				
Activates CB1R	Inhalation: Onset: Seconds to minutes Bioavailability: 2%–56% Onset: 30 min Duration: 2–3 hr Oral: Onset: 30 min to 2 hr Bioavailability: 4%–20% Duration: 5–8 hr Transmucosal: Onset: 15–40 min Bioavailability: Not known Duration: 45 min to 2 hr Transdermal: Not known Transrectal: Not known	Hepatic, by CYP 2C9, 2C19, 2D6, 3A4; UGT1A9, UGT2B7; undergoes glucuronidation	Time-dependent, fatty tissues and highly perfused organs Protein binding: 97%	Renal: 20% Feces: 65% Half-life: 20–30 hr THC may be a weak substrate and inhibitor of P-gp

CBD = cannabidiol; CB1R = cannabinoid receptor 1; CB2R = cannabinoid receptor 2; CCL = chemokine ligand; FAAH = fatty acid amide hydrolase; GABA = γ-aminobutyric acid; GPR55 = G protein–coupled receptor 55; IFN = interferon; IL = interleukin; NK = nuclear factor; P-gp = P-glycoprotein; PPAR = peroxisome proliferator-activated receptor; THC = Δ-9-tetrahydrocannabinol; TNF = tumor necrosis factor; TRPA = transient receptor potential ankyrin; TRPV = transient receptor potential vanilloid; UGT = uridine 5′-diphospho-glucuronosyltransferase.

Information from: Page RL II, Allen LA, Kloner RA, et al. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2020;142:e131-e152.

Table 2. Potential Drug-Drug Interactions Between Cannabinoids and Selective Cardiovascular Medications Stratified by Effect on Major CYP Enzymes and P-gp

Mechanism	Medication/Substrate	Effect
CBD		
Inhibits CYP3A4	Apixaban Amiodarone Atorvastatin CCBs Cilostazol Dronedarone Ivabradine Eplerenone Gemfibrozil Lidocaine Lovastatin Prasugrel Quinidine Ranolazine Rivaroxaban Sildenafil Simvastatin Ticagrelor Tolvaptan Vorapaxar	Potential increase in substrate concentrations leading to possible supratherapeutic effect
Inhibits CYP2D6	β-Blockers Carvedilol Flecainide Mexiletine Propafenone Sotalol	Potential increase in substrate concentrations leading to possible supratherapeutic effect
Inhibits CYP2C9	Candesartan Fluvastatin Irbesartan Losartan Warfarin	Potential increase in substrate concentrations leading to possible supratherapeutic effect
Inhibits CYP2C19	Clopidogrel	Potential decrease in active metabolite leading to possible therapeutic failure
Inhibits P-gp	Amiodarone Apixaban CCBs Colchicine Dabigatran Digoxin Dipyridamole Dronedarone Edoxaban Propafenone Quinidine Ranolazine Rivaroxaban Ticagrelor Tolvaptan	Potential increase in substrate concentrations leading to possible supratherapeutic effect

(*continued*)

Table 2. Potential Drug-Drug Interactions Between Cannabinoids and Selective Cardiovascular Medications Stratified by Effect on Major CYP Enzymes and P-gp (*continued*)

Mechanism	Medication/Substrate	Effect
THC[a]		
Induces CYP1A2	Clonidine Flecainide Lidocaine Mexiletine Nifedipine Pentoxifylline Propafenone	Potential decrease in substrate concentrations leading to possible therapeutic failure
Inhibits CYP2C9	See substrates above	See effect above
Inhibits CYP2C19	See substrate above	See effect above
Inhibits CYP2D6	See substrates above	See effect above
Inhibits CYP3A4	See substrates above	See effect above

[a]Note that THC may be a substrate and potentially a weak inhibitor of P-gp.

CBD = cannabidiol; CCB = calcium channel blocker; P-gp = P-glycoprotein; THC = Δ-9-tetrahydrocannabinol.

modification of mode of administration, dose, and chronicity of use of these CV complications is scant. Nonetheless, given the effects of exogenous cannabinoids at the receptor level and the differential expression of these receptors in certain tissues (e.g., myocyte, endothelium), potential CV complications can be postulated (Figure 5). The main health concern is whether cannabis triggers or potentiates major adverse CV events such as myocardial infarction (MI), arrhythmias, and stroke, as well as serves as a CV risk factor similar to smoking.

Although conflicting case series, observational studies, and epidemiologic studies suggest a temporal association with cannabis use and MI, particularly in younger males without ischemic disease, two large observational studies have addressed these issues (Reis 2017, Rezkalla 2019). Using the American Behavioral Risk Factor Surveillance System survey of U.S. adults, investigators evaluated the association between any recent cannabis use and MI history using a weighted logistic regression model that adjusted for demographic factors, socioeconomic factors, health-related behaviors, concomitant substance use, and other comorbidities (Ladha 2021). Among 33,173 young adults (18–44 years of age), 4610 respondents reported recent cannabis use. Compared with nonusers, cannabis users had a higher risk of MI (adjusted OR 2.07; 95% CI, 1.12–3.82). This association was similar in magnitude to associations with current tobacco smoking (adjusted OR 2.56; 95% CI, 1.56–4.21) and smokeless tobacco use (adjusted OR 1.88; 95% CI, 1.00–3.50). Chronic cannabis use (more than four times per month) and smoking cannabis as mode of administration were associated with a higher odds of MI (adjusted OR 2.31; 95% CI, 1.18–4.50; adjusted OR 2.01; 95% CI, 1.02–3.98, respectively) in those using cannabis than in nonusers. Although a higher odds of MI was associated with vaporization (adjusted OR 2.26; 95% CI, 0.58–8.82) and edible consumption (adjusted OR 2.36; 95% CI, 0.81–6.88) than in nonusers, these findings were not statistically significant.

In a cross-sectional analysis using the 2014–2015 nationwide Veterans Affairs Healthcare database and the Veterans with Premature Atherosclerosis registry, investigators categorized patients as having premature (n=135,703), extremely premature (n=7716), or nonpremature atherosclerotic CVD (ASCVD) (n=1112, 455); stratified each cohort on the basis of recreational substance use (e.g., tobacco, alcohol, cocaine, amphetamine, and cannabis); and evaluated the association (Mahtta 2021). Compared with patients with nonpremature ASCVD, patients with premature ASCVD had a higher use of cannabis (12.5% vs. 2.7%, p<0.01), and in adjusted models, cannabis use was independently associated with premature ASCVD (OR 2.65; 95% CI, 2.59–2.7), in which the association was stronger in women than in men.

Similar associations have been documented between cannabis exposure and risk of atrial fibrillation and cerebrovascular accidents. Using the National Inpatient Sample database from 2010 to 2014, investigators identified 2,459,856 hospitalized cannabis users, of whom 66,179 (2.7%) experienced arrhythmias, most commonly atrial fibrillation (Desai 2018). Using the 2016 Kids' Inpatient Database, investigators identified 68,793 cases of cannabis use, dependence, and misuse in individuals 13–19 years of age (Ramphul 2019). From this cohort, 26 patients had ventricular fibrillation (37.8 per 100,000 cases), and 96 reported palpitations (139.5 per

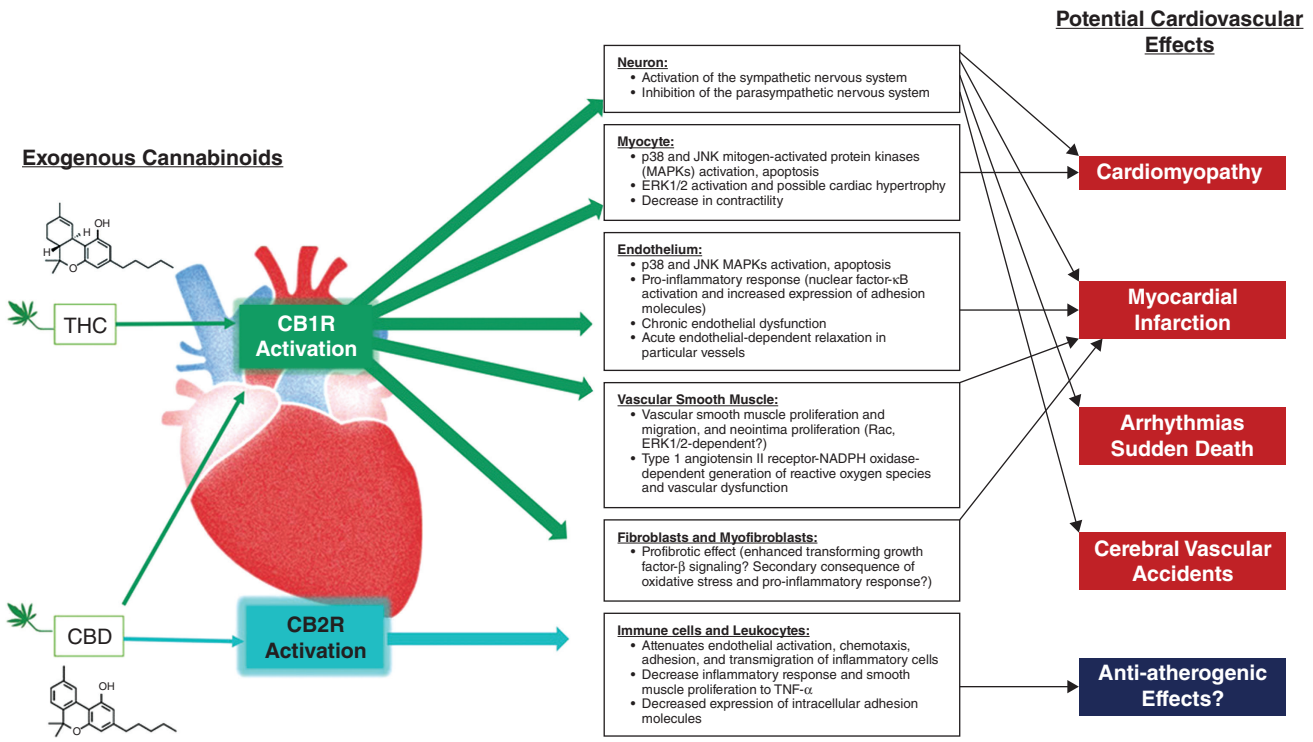


Figure 5. Cardiovascular complications of exogenous cannabinoids.

CBD = cannabidiol; CB1R = cannabinoid receptor 1; CB2R = cannabinoid receptor 2; ERK = extracellular signal-regulated kinase; MAPK = mitogen-activated protein kinase; THC = Δ-9-tetrahydrocannabinol; ? = Questionable.

Reprinted with permission from: Page RL II, Allen LA, Kloner RA, et al. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2020;142:e131-e152.

100,000 cases), whereas 57 had preexcitation syndrome (82.3 per 100,000 cases), 353 had long QT syndrome (513.1 per 100,000 cases), and 25 had atrial fibrillation (116.3 per 100,000 cases). The possible mechanism lies in increased cannabis-related adrenergic stimulation and atrial ischemia, which in turn leads to atrial arrhythmias, whereas catecholamine surges have been linked to ventricular fibrillation. Long QT syndrome may be the result of the blocking of the human ether-à-go-go–related gene (hERG) channel.

In a retrospective evaluation of the Personality and Total Health Through Life study, which included participants 20–24 years of age (n=2383), 40–44 years of age (n=2532), and 60–64 years of age (n=2547) from 1999 to 2000, 2000 to 2001, and 2001 to 2002, respectively, investigators found a 3.3-fold increased risk of stroke/transient ischemic attack (TIA) in cannabis users within the past year. However, this elevated risk was specific only to participants who used cannabis weekly or more often as opposed to those who used cannabis less often (Hemachandra 2016). Finally, using weighted data from the National Inpatient Sample (2015–2017), investigators identified hospitalizations among young (18–44 years) patients with a history of stroke/TIA grouped into those with CUD (n=4690) and those without CUD (n=156,700) and evaluated the risk of recurrent stroke (Desai 2018). Compared with those without CUD, those with CUD had a higher odds of recurrent stroke (adjusted OR 1.48; 95% CI, 1.28–1.71). Several potential mechanisms for stroke have consisted of reversible cerebral vasoconstriction triggered by acute cannabis use; impaired cerebrovascular function and cannabis-related angiopathy with chronic, heavy use; and increased procoagulant effects because THC increases the expression of glycoprotein IIb and IIIa and P-selectin on human platelets in a concentration-dependent manner according to in vitro data (Testai 2022).

Although the association between new-onset heart failure (HF) and cannabis use has been reported in one observational database analyses, the study had significant confounding, and the sample size was too small to truly elucidate a potential effect modification (Kalla 2018).

Finally, investigators estimated that 2 million of the 89.6 million adults (2.3%) who reported marijuana use had existing CVD, according to the 2005–2016 National Health and Nutrition Examination Survey (DeFilippis 2020). Given this, cross-sectional data suggest that long-term (e.g., years), continual cannabis use is associated with an increased risk of metabolic syndrome compared with no use (Yankey 2016).

However, conflicting studies have suggested that, compared with nonusers, those who use cannabis have a similar or reduced incidence of hyperglycemia, elevated fasting blood glucose, and diabetes, as well as lower BMI, TC, and LDL (Vazquez-Bourgon 2019, Alshaarawy 2015, Matthews 2019, Le Strat 2011, Penner 2013, Rajavashisth 2012).

Nonetheless, the evidence is still inconclusive for cannabis use and adverse CV outcomes; however, recent data suggest a signal for an association, as well as the potential for cannabis use to be an ASCVD risk factor.

OPIATES

The Opioid Pandemic

The evolution of the opioid epidemic in the United States began as early as 1980, when the Boston Collaborative Drug Surveillance Program at the Boston University Medical Center published its now-infamous report in the *New England Journal of Medicine* that "despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction." (Porter 1980). This statement, together with additional reassurance from pharmaceutical companies that patients would not misuse opioid pain relievers, gave the medical community a false sense of security, leading health care providers to prescribe opioids at greater rates. However, such actions led to a flooding of prescription opiates into local communities, causing an increase in addiction. Because patients could not refill their narcotics indefinitely, many turned to the gray market. As both demand and price for opiates on the gray market began to surge, heroin use began to increase by 2010 because it was a cheaper alternative (Chow 2021). By 2013, overdose deaths involving synthetic opioids, particularly those related to illicitly manufactured fentanyl, began to increase and still continue into 2022. In 2017, the Department of Health & Human Services declared opiate misuse a public health emergency. In 2019, the CDC estimated that a total of 49,860 (70.6%) drug overdose deaths involved opioids, of which 36,359 (51.5%) involved synthetic opioids (Mattson 2021). In 2020, 3.2 million Americans 12 years and older had an OUD related to opioid analgesics, and 691,000 had a heroin-related OUD (see Figure 1, Panel B; see Box 1 for diagnosis).

By early 2020, the COVID-19 pandemic intersected with the opioid pandemic. Because of lockdowns and extremely limited access to medical care and treatment, COVID-19 worsened economic and social factors, which in turn fueled an increase in opioid use and overdose deaths. From May 1, 2019, to May 31, 2020, the CDC reported over 81,000 drug overdose deaths, which appeared to be driven by synthetic opioid use. This is the most overdose deaths ever recorded in a 12-month period (CDC 2020). To this end, the CDC recently updated its 2016 Clinical Practice Guideline for Prescribing Opiates, which is currently out for public comment, to improve communication between providers and patients and empower them to make informed, patient-centered decisions related to safe and effective pain care (CDC 2022). In addition, the FDA has fast-tracked nonaddictive alternatives to opioids for acute pain management (FDA 2022).

Ironically, despite an overall reduction in opioid prescription rates, opioid-associated deaths continue to rise. This phenomenon may be related to the emergence of "street fentanyl" and heroin as nonprescription alternatives when access to prescription opioids was restricted. As of 2019, many fentanyl analogs had been increasingly controlled by class-wide scheduling; however, many non–fentanyl-related opioids are now emerging on the recreational opioid market. These emerging synthetic opioids, also known as "research chemicals," are being pirated from early patent literature and/or research papers, synthesized, and sold online through various channels (Blanckaert 2020). By the time these substances can be controlled by legislative measures, illicit drug markets have already adapted and diversified to avoid restriction. Ultimately, these new synthetic opioids end up in the street opioid supply, which was previously dominated by heroin, and sold as bundles, zip bags, or glassine bags. Of the various non-fentanyl opioids that have emerged over the past 2 years, isotonitazene ("etonitazene" and "ISO") and brorphine ("blue heroin") have become popular among drug users (Blanckaert 2020, Verougstraete 2021). Although data are limited, deaths associated with these synthetic opioids have been observed in Canada, the United States, and Europe. As of 2020, the Drug Enforcement Administration had made a temporary placement of isotonitazene as a schedule I substance and similarly for brorphine in 2021 (Drug Enforcement Administration 2020).

Pharmacology of Opiates

As a class, opiates can be classified as natural (morphine, codeine); semisynthetic (heroin, oxycodone, hydrocodone, hydromorphone, oxymorphone); synthetic (methadone, levacetylmethadol [taken off the U.S. market in 2013], propoxyphene [taken off the U.S. market in 2009], buprenorphine, fentanyl, tramadol); and opioid-like (loperamide, dextromethorphan). These opiates vary with respect to potency for the opiate receptor, half-life, pharmacokinetics, and mode of administration. Opioids do not exert their effect by inhibiting the transmission of pain; rather, they alter the perception of pain, which can be subjective. Opioid receptors are present in many regions of the nervous system, including the primary afferent neurons, spinal cord, midbrain, and thalamus. Analgesia is believed to result from inhibition of neurotransmitter release from the primary afferent terminals in the spinal cord and activation of descending inhibitory controls in the midbrain (Brownstein 1993). In the CV and cerebrovascular systems, opioids and endogenous opioid peptides such as endorphins, enkephalins, and dynorphins wield potent effects within the central and peripheral nervous systems to regulate blood pressure, heart rate, and thermogenesis.

Opiates exert their effects on the CV system primarily through on-target mu-opioid receptor–mediated effects and only secondarily through unexpected off-target receptor properties as kappa (κ), delta (δ), and nociceptin/orphanin FQ peptide receptors (Feng 2012). Figure 6, Panel A provides a mechanistic framework for the CV complications associated with natural and synthetic opioids and the interplay between opiate receptor agonism and effects on the heart and vasculature. Synthetic opiates such as methadone, levacetylmethadol, and buprenorphine and OTC opioid-like compounds such as loperamide all contain dual aromatic rings within their structure that facilitate blockade of the cardiac hERG channel. This channel is responsible for encoding the delayed-rectifier potassium ion current. Blockade of the hERG channel leads to a prolongation in action potential duration manifesting as QTc interval prolongation (see Figure 6, Panel A). In addition, these agents can block sodium and calcium channels and have anticholinesterase activity, which facilitates a negative inotropy and bradycardia, resulting in pause-dependent triggering of torsades de pointes (TdP) when combined with QTc interval prolongation.

Potency for the opioid receptor is critical and translates to potential overdose, toxicity, or death. Compared with prescription opiates and heroin, fentanyl is 50 and 100 times more potent, in which only 2 mg can be lethal, whereas methadone is 5–10 times more potent. Compared with morphine, isotonitazene and brorphine are estimated to be 500 times more potent (European Monitoring Centre for Drugs and Drug Addiction 2012). Regarding misuse, heroin is often injected intravenously or subcutaneously or smoked; morphine is injected; oxycodone tablets are crushed and then snorted; hydromorphone is typically administered intravenously or rectally because of its low oral bioavailability; and fentanyl can be injected, snorted, smoked, or spiked onto blotter paper.

CV Complications

Effects of opioid receptor agonism on the CV system are multifactorial and highly dependent on the circumstances of patient exposure. Acute and chronic opioid misuse, overdose, and withdrawal are each associated with unique complications, including vascular, valvular, and arrhythmic sequelae.

Acute opioid receptor–mediated CV effects are well documented and include hypotension, orthostasis, syncope, and bradycardia. Hypotension is primarily mediated through mu-opioid receptor vasodilatation, which is in turn linked to peripheral edema, flushing, and palpitations. Peripherally, opioids can cause a decrease in GI motility. For acute coronary syndrome, this slowing of gut can cause a delayed onset or therapeutic failure of oral $P2Y_{12}$ receptor antagonists. This particular interaction is of greatest concern in the acute setting because a delay in antiplatelet effect can lead to poor outcomes. To this end, a more cautious approach should be taken when balancing the risk-benefit of morphine in the CV setting, including prescribing the lowest possible opioid dose, considering alternative non-opioid analgesics, and even using parenteral instead of oral antiplatelet agents when coadministration of opioids is warranted (Chow 2021, Li 2013).

In contrast, the effect of chronic opioid use on the CV system continues to evolve (Doshi 2019, Qureshi 2015). One nested case-control study using the UK General Practice Research Database found an increase in MI among 1.7 million opioid users (OR 1.28; 95% CI, 1.19–1.37) compared with nonusers. A substantially larger retrospective claims analysis assessed incidence rate ratios for MI and coronary revascularization among 148,657 individuals taking chronic opioids, 122,810 using chronic cyclooxygenase-2 inhibitors, and 148,657 age- and sex-matched controls not receiving analgesics (Carman 2011). After adjustment, chronic opioid users had a 2.7 times higher rate of MI and a 2.4 times higher rate of MI and/or cardiac revascularization compared with the general population. A similar but lower rate was seen in those using chronic cyclooxygenase-2 inhibitors. Although limiting or avoiding long-term NSAIDs in patients with CVD has long been an accepted dogma, such recommendations do not hold true for chronic opiate use.

Another chronic sequela is valvular endocarditis among injection drug users because of particulate microbial or fungal contamination, which leads to bloodborne bacterial and occasionally fungal infection. With the spike in intravenous heroin and fentanyl misuse, a dramatic absolute increase (+20.3%; 95% CI, 10.5–30.9) in cardioembolic stroke from endocarditis has occurred. In fact, over the 5 years of the opioid epidemic, the rate of bacterial endocarditis has almost doubled from 15.2% to 29.1% (Omran 2019, Rudasill 2019).

Finally, synthetic opiates have been associated with proarrhythmic effects, which have been well documented with methadone. Using data from the Adverse Event Reporting System database between 1997 and 2011, the FDA found that the proportional reporting ratio for QTc prolongation and TdP associated with methadone was 11.2 (95% CI, 10.2–12.4) compared with sotalol, amiodarone, and dofetilide. This effect was not seen with natural opioids (Kao 2013). As a follow-up, the FDA evaluated a total of 4,418,215 adverse events (7283 with buprenorphine and 14,915 with methadone) from 1969 to 2011 (Kao 2015). Compared with buprenorphine, the proportional reporting ratio for TdP was 21-fold higher for methadone users. Of importance, methadone-associated TdP results from a confluence of other risk factors such as female sex, structural heart disease, electrolyte derangement (e.g., hypokalemia), concurrent use of QTc-prolonging drugs, genetic polymorphisms in methadone CYP2D6 metabolism, and variable expression of cardiac ion channel activity. Nonetheless, several opioids (e.g., fentanyl, tramadol, oxycodone) are considered intermediate-risk drugs for developing long QT interval, with TdP occurring particularly in high doses, whereas other opioids (e.g., morphine, buprenorphine) are low-risk drugs that do not produce QTc interval prolongation and TdP, or at least not with routine doses.

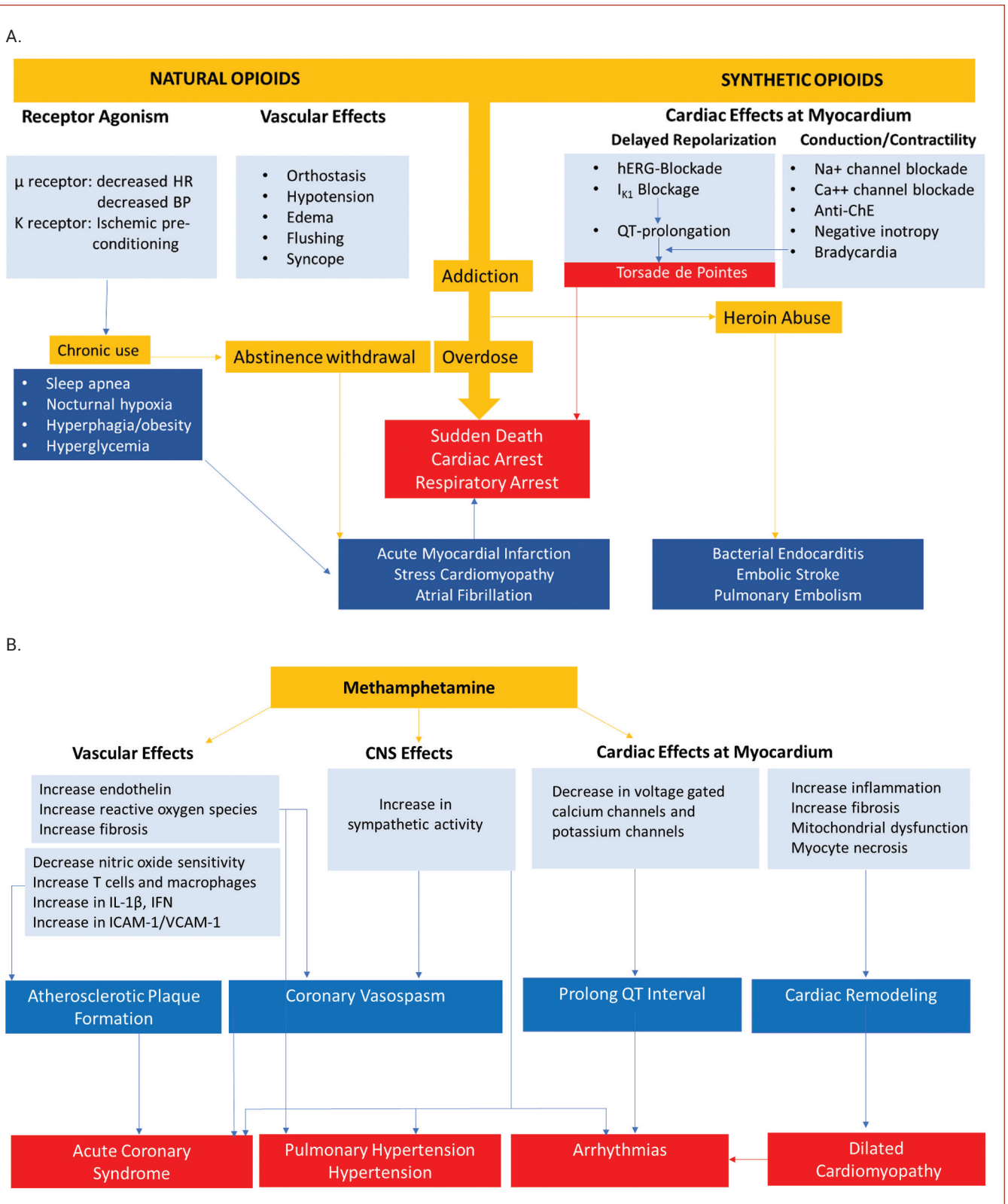


Figure 6. Cardiovascular complications with (A) natural and synthetic opioids; and (B) methamphetamine.

Ca^{++} = calcium; ChE = cholinesterase; ICAM-1 = intercellular adhesion molecule-1; IFN = interferon; IL = interleukin; Na^{+} = sodium; VCAM-1 = vascular cell adhesion molecule-1.

Information from: Krantz MJ, Palmer RB, Haigney MCP. Cardiovascular complications of opioid use. J Am Coll Cardiol 2021;77:205-23.

With respect to OTC products, loperamide, which also blocks the hERG channel, has become known as the poor man's methadone during the opioid epidemic. As a mu-opioid receptor agonist, loperamide is 50 times more potent than morphine. Because of its affinity for P-gp, loperamide has poor CNS penetration. However, when used concomitantly with large quantities of OTC P-gp inhibitors (e.g., cimetidine, quinine), this combination can cause a euphoric high. Nonetheless, several case reports of bradycardia, QTc prolongation, TdP, ventricular arrhythmias, and cardiac arrest have been reported (Marzec 2015, Swank 2017, Klein 2016).

In opiate withdrawal, the CV effects are opposite from those in intoxication. With an increase in catecholaminergic tone, an abrupt, significant increase in the rate-pressure product and myocardial oxygen consumption occurs, which can potentially destabilize patients at high risk such as those with tenuous coronary arterial perfusion from high-grade epicardial coronary artery disease (CAD), severely stenotic valvular heart disease, and advanced HF with reduced ejection fraction. Furthermore, this rapid, unrestricted catecholamine surge has been associated with both stress-induced cardiomyopathy and acute pulmonary edema (Spadotto 2013). With respect to treatment of overdose and withdrawal, the American Heart Association recently published a scientific statement regarding opioid-associated out-of-hospital cardiac arrest, which specifically addresses the emergency management of opioid poisoning, recognition of the clinical signs and symptoms of opioid overdose by the lay public or emergency dispatchers, prompt emergency response, effective ventilation together with compressions, acute administration of naloxone, and secondary prevention with take-home naloxone (see Additional Readings).

STIMULANTS

Types of Stimulants

Stimulants can arbitrarily be characterized as prescription (e.g., amphetamine salts, methylphenidate), OTC (e.g., ephedrine, pseudoephedrine), or illicit (e.g., cocaine, methamphetamine, methcathinone, and synthetic cathinones [e.g., "khat" or bath salts]). According to the Substance Abuse and Mental Health Services Administration, 5.2 million Americans 12 years and older have tried cocaine in the past year, followed by 5.1 million for prescription stimulant misuse and 2.5 million for methamphetamine (see Figure 1, Panel A). As of 2020, 1.5 million Americans 12 years and older had reported a methamphetamine use disorder, 1.3 million a cocaine use disorder, and 758,000 a stimulant use disorder (see Figure 1, Panel B; see Box 1 for diagnosis).

Pharmacology of Stimulants

As a class, all stimulants are associated with an increase in chronic excessive sympathetic nervous system activation, which not only increases cardiac workload but can also lead to a predisposition for hypertension, endothelial dysfunction, left ventricular hypertrophy, and episodes of arrhythmia. For prescription stimulants, such as those used to treat attention-deficit/hyperactivity disorder (ADHD), these sympathomimetic amines exert their stimulant effects on the CNS by increasing noradrenaline and dopamine concentrations in the prefrontal cortex and stimulate adrenergic receptors in the heart and vasculature, leading to small increases in resting heart rate and blood pressure.

Methamphetamine's pharmacology is more complex and continues to evolve (see Figure 6, Panel B). Acutely, methamphetamine has been associated with acute vascular constriction and coronary vasospasm, whereas chronic methamphetamine use leads to vasoconstriction and persistent cerebral hypoperfusion driven by neurovascular damage and an imbalance of circulating vasoregulatory substances. Although the mechanisms of methamphetamine-induced vasoconstriction remain poorly described, current evidence suggests that exposure increases the endothelial release of endothelin-1 with enhanced reactive oxygen species production and reduced sensitivity to endothelial nitric oxide. Over time, enhanced atherosclerotic plaque formation after methamphetamine use correlates with enhanced inflammation because of endothelial activation and increased T-cell and macrophage-driven proinflammatory signaling. Within the myocardium, these proinflammatory processes also drive fibrotic structural heart disease and electrical remodeling, leading to dilated cardiomyopathy and QTc prolongation, respectively. Autopsy data in methamphetamine-related deaths suggest that the route of administration does not influence rates of cardiomegaly, left ventricular hypertrophy, CAD, cardiomyopathy, or fibrosis. The onset of these CV complications is highly variable but can range from less than 7 months to 15 years of methamphetamine use (Yeo 2007, Kevil 2019).

As with all stimulants, cocaine potentiates acute sympathetic effects on the CV system with consequential increased inotropic and chronotropic effects on the heart and increased peripheral vasoconstriction. These effects are driven by increased endothelin-1 activation, impaired acetylcholine-induced vasorelaxation, deranged intracellular calcium handling, and blockade of nitric oxide synthase and sodium channels, which can contribute to possible coronary vasospasm. Cocaine, like methamphetamine, induces endothelial injury and stimulates vascular fibrosis. Over time, cocaine induces vascular smooth muscle apoptosis and cystic medial necrosis with consequential vessel wall weakening. Taken together, these effects can lead to chronic hypertension; coronary, aortic, and carotid dissection; accelerated atherosclerosis; cardiomyopathy; myocarditis; and stroke (Vongpatansin 1999). With increased myocardial oxygen demand as a result of increased inotropic and chronotropic effects, accompanied by coronary vasoconstriction and a prothrombotic state, cocaine exposure can ultimately

cause myocardial ischemia and possible acute coronary syndrome and HF. Although infrequent and not well understood, cocaine-induced elevations in sympathetic tone and subsequent myocardial ischemia have been related to an increased risk of cardiac arrhythmias. With this increased sympathetic tone together with the induction of myocardial ischemia and prolonged cardiac repolarization through the blockade of sodium, potassium, and calcium channels, cocaine exposure can induce ventricular ectopy, QTc interval prolongation, TdP, ventricular fibrillation, and sudden cardiac death.

CV Complications

Controversy exists regarding the impact of prescription stimulants prescribed in childhood for ADHD but continued chronically into adulthood on CV health, particularly in those with underlying CV conditions. In a systematic review, investigators found that the prescription stimulants used to treat ADHD in children and young adults caused modest elevations in resting heart rate and blood pressure (Torres-Acosta 2020). Although arrhythmias, nonischemic cardiomyopathy, Takotsubo cardiomyopathy, and sudden death have been associated with prescription stimulant use, such reports did not imply causation. However, in an observational, cohort study from 2002 to 2017 of 6457 older adults (66 and older) initiated on a stimulant for any cause compared with 24,853 matched older adult nonusers, investigators found that prescription stimulant initiation was associated with a 40% increase in the composite end point of increased risk of ED visits or hospitalization for MI, stroke, TIA, or ventricular arrhythmias at 30 days (HR 1.4; 95% CI, 1.1–1.8), but not at 180 (HR 1.2; 95% CI, 0.9–1.6) or 365 (HR 1.0; 95% CI, 0.6–1.8) days (Tadrous 2021). In the secondary analysis, stimulant initiation was associated with an increased risk of ventricular arrhythmias (HR 3.0; 95% CI, 1.1–8.7) and stroke or TIA (HR 1.6; 95% CI, 1.1–2.1) at 30 days. Of note, about 70% of patients in both cohorts had hypertension, 30% diabetes, 14% HF, and 10% any CV event, with more than 50% receiving an antidepressant. These data suggest that in older adults, an increased risk of CV events after starting stimulant use exists, with no association for an increased risk with long-term use.

For cocaine and methamphetamine, acute CV effects highly depend on routes of administration, which affect onset and absorption. In general, the intravenous and inhaled (i.e., smoked) routes have a very rapid onset of action (seconds to minutes) and a short-lived duration (30 minutes) compared with the mucosal (e.g., oral, nasal or "snorted," rectal, vaginal) routes. Although similar in onset because of the method of administration, the euphoria associated with methamphetamine can last 4–14 hours (Kim 2019).

The acute CV effects of cocaine have been well studied and established. Studies have consistently shown ECG abnormalities, acute hypertension, arrhythmia, coronary vasospasm, and acute MI with cocaine use through multifactorial mechanisms, as discussed earlier. However, results have been mixed for chronic cocaine use. Several studies have examined whether cocaine use was associated with chronic CV conditions such as cardiomyopathy (e.g., left ventricular hypertrophy), subclinical atherosclerosis, and CAD. Although some studies found no association between cocaine use and CAD, others reported its association with subclinical coronary atherosclerosis and cardiomyopathy. These inconsistent findings may be related to the heterogeneity of ASCVD risk in the study population, as well as variable exposure. Nonetheless, populations at high risk of CAD and cocaine misuse had coronary atherosclerosis, whereas those at low risk did not, thereby suggesting that the chronic CV effects of cocaine are more likely augmented in patients with a higher ASCVD risk. As observed in a 2015 study, all-cause mortality was about 2 times higher among regular cocaine users (lifetime cocaine use greater than 100 times) than in cocaine nonusers (Qureshi 2015). However, all-cause mortality of infrequent cocaine users (lifetime cocaine use: 1–10 times) or frequent cocaine users (lifetime cocaine use greater than 10 times) was not significantly different from that of cocaine nonusers in this study. Finally, cocaine may induce sudden cardiac death through several mechanisms, including direct arrhythmogenic effect, arrhythmias occurring because of the sympathomimetic effect, coronary vasospasm, thrombosis, or aggravation of preexisting CAD (Gay 1982, Pergolizzi 2021, Schwartz 2010).

As discussed earlier, the acute CV effects of methamphetamine are caused by its sympathomimetic properties and direct cardiotoxicity manifested with an increase in heart rate, systolic blood pressure, and respiratory rate over several hours. Acute cardiac decompensation with pulmonary edema because of malignant hypertension has also been reported with acute exposure. Contaminants, which may be intermediaries of methamphetamine synthesis or deliberately added impurities to cut the drug, may exert additional toxic effects on their own such as pulmonary embolism.

Chronic misuse can lead to long-term hypertension, hypertensive cardiomyopathy, and possible idiopathic pulmonary hypertension and aortic dissection; however, uncertainty exists regarding the actual percentage of patients who develop these cardiac conditions. A retrospective analysis of ED patients found a diagnosis of HF as evidenced by elevated natriuretic peptides in around 10% of those who misused methamphetamine. In a retrospective, case-control study, investigators evaluated 107 cases and 111 matched controls discharged with a diagnosis of cardiomyopathy or HF and evaluated the association for a possible methamphetamine etiology (Yeo 2007). Both groups had similar sex distribution, length of hospital stay, rates of health insurance, and prevalence of CAD, diabetes, hypertension, cigarette smoking, alcohol misuse, and marijuana and cocaine use. Compared with nonusers, methamphetamine exposure had a 3.7-fold increased risk of cardiomyopathy (95% CI, 1.8–7.8) compared with nonusers, particularly in patients younger than 45. In a retrospective

study of patients with methamphetamine-induced cardiomyopathy, almost one-third of patients presented with a reverse Takotsubo cardiomyopathy-like pattern of hypokinesia compared with global hypokinesia (Voskoboinik 2016). These patients had a shorter duration of misuse, lower rate of ventricular fibrosis, and improved recovery of left ventricular ejection fraction during follow-up, suggesting that Takotsubo cardiomyopathy is an early, reversible form of methamphetamine-induced cardiomyopathy. Coronary artery disease is common in chronic methamphetamine misusers in which early coronary microcirculation abnormalities and reduced myocardial perfusion have been detected by echocardiography. In an Australian study of 894 methamphetamine-associated deaths, autopsy showed a high prevalence of CAD (19%), left ventricular dilatation (26.3%), left ventricular hypertrophy (19%), and myocardial scarring (19.8%), despite a younger mean age of 38 years (Darke 2017). From case reports and case series, a high prevalence of MI in the absence of CAD in methamphetamine users has been documented, possibly because of generalized microvascular coronary vasospasm. Finally, methamphetamine exposure has been linked with both hemorrhagic and ischemic strokes. In a review of case reports and case series, 80% of reported strokes in young patients taking methamphetamine were hemorrhagic, which varies for the general population, where the primary etiology is ischemic, even in younger adults. The mechanism may be provoked by methamphetamine-associated arterial hypertension, whereas ischemic stroke may be caused by vasoconstriction, vasculitis, or thromboembolism (Karila 2010, Richards 2018).

EMERGING SUBSTANCES OF ABUSE AND POLYSUBSTANCE USE

With the change in public and health policies surrounding the restriction of prescription opioids, several older prescription medications and illicit substances (e.g., street drugs) have emerged (National Institutes of Health 2020). Both gabapentin and bupropion have become known on the gray market and misused as the poor man's morphine and cocaine, respectively, because these drugs are cheap and readily available (Stall 2014, Schifano 2018). Ironically, both morphine and bupropion have been studied off-label for the use of cocaine and methamphetamine dependence (Myrick 2001). Although gabapentin is an analog of γ-aminobutyric acid (GABA), it does not bind to $GABA_A$ or $GABA_B$ receptors, nor to benzodiazepine,

Patient Care Scenario

M.T., a 51-year-old homeless woman, is admitted to the cardiology unit for new-onset acute decompensated heart failure (LVEF: 20%, NYHA class III, Stage C) following several years of smoking methamphetamine. She attests to using methamphetamine primarily to relieve the stress of losing her job and home during the COVID-19 pandemic. After being stabilized with intravenous diuresis, M.T. is initiated on guideline-directed medical therapy including aspirin 81 mg daily, lisinopril 20 mg daily, digoxin 0.125 mg daily, and spironolactone 25 mg daily. Her blood pressure is 145/80 mm Hg and heart rate of 90 beats/minute The medical team wants to initiate a β-blocker once the patient is stabilized. At discharge, the patient adamantly states that she will quit her methamphetamine use. Which one of the following is best to recommend for M.T.?

A. Metoprolol tartrate
B. Bisoprolol
C. Metoprolol succinate
D. Carvedilol

ANSWER

By stimulating the release of endogenous catecholamines (dopamine and norepinephrine), methamphetamine has both α- and β- adrenergic agonist effects that modulate heart rate, heart contractility, and vasoconstriction, resulting in adverse cardiovascular (CV) consequences that include tachycardia, hypertension, pulmonary arterial hypertension, and dilated cardiomyopathy. Like with cocaine, using an evidence-based β-1 selective β-blocker such as bisoprolol or metoprolol succinate in a patient with HF with reduced ejection fraction could lead to coronary artery vasoconstriction and hypertension exacerbation as catecholamines are shunted to the α-adrenergic receptor. Therefore, β-blockers with α activity are theoretically more appealing for use. In this case, M.T. is refusing to stop using methamphetamine, thus the choice of her β-blocker becomes paramount. Carvedilol, which is a nonselective β-blocker with α-adrenergic blockade, would be the ideal guideline directed β-blocker as this patient is still using methamphetamine, making Answer D correct and Answer B (bisoprolol) and Answer C (metoprolol succinate) incorrect. Answer A (metoprolol tartrate) is incorrect in that it is not a guideline directed β-blocker for HF with reduced ejection fraction and is also β-1 selective.

1. Page RL II, Allen LA. Cocaine, heart failure, and carvedilol: triangulating the safety of β-blocker therapy. JACC-HF 2019;7: 779-781.
2. Reddy PKV, Ng TMH, Oh EE, et al. Clinical characteristics and management of methamphetamine-associated cardiomyopathy: state-of-the-art review. JAHA 2020;9:e016704.
3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;0:10.1161/CIR.0000000000001063.

opioid, or cannabinoid receptors, but it increases GABA and decreases glutamate concentrations through an unknown mechanism. Snorting a single high dose that exceeds recommended doses can produce a feeling of euphoria but also results in hypotension and reflex tachycardia. Because of its misuse, several states have placed a schedule on gabapentin. As a selective inhibitor of catecholamine (noradrenaline and dopamine) reuptake and devoid of any serotonergic, antihistamine, or anticholinergic properties, bupropion tablets can be crushed and administered either nasally or intravenously, leading to a cocaine-like euphoria. Acutely, patients can experience sinus tachycardia; however, with a massive bupropion overdose, QRS widening, ventricular dysrhythmias, and CV collapse have been reported. Both gabapentin and bupropion misuse, particularly at doses exceeding FDA-approved doses, can exacerbate underlying or unstable CV conditions.

In 2019, Colorado became the first state to decriminalize mushrooms containing psilocybin, 4-phosphoryloxy-N,N-dimethyltryptamine (e.g., magic mushrooms). City-level policies surrounding psilocybin, which is still considered a schedule I substance, continue to evolve. Psilocybin is a natural hallucinogen and the main therapeutic compound in magic mushrooms. For many years, psilocybin has been used on the gray market for depression, anxiety, and several other psychiatric conditions. Although minimal safety data exist, fatal intoxications are rare and have been associated with concomitant use of alcohol or other illicit substances (Amsterdam 2011). From a CV perspective, psilocybin has been known to cause acute tachycardia and hypotension, which could affect underlying CV conditions; however, because psilocybin activates serotonin-2B and serotonin-2A receptors, concern has emerged regarding the potential for valvular damage. This warning is extrapolated from data with similar serotonin-2B agonists such as fenfluramine and phentermine, which have been associated with new-onset valvular heart disease and have since been removed from the U.S. market.

Because limited primary literature exists with these new illicit substances, pharmacists can reference free NIH websites (Box 2), which provide good evidence for possible health and CV effects.

Finally, many of the patients diagnosed with SUD do not misuse just one illicit substance (Baily 2019). The CDC defines polysubstance use as taking two or more illicit substances together or within a short time, either intentionally or unintentionally. Among data from the State Unintentional Drug Overdose Reporting System show that around 80% of these deaths involved one or more opioids, and illicitly manufactured fentanyl was involved in three of four opioid-involved overdose deaths. About 50% of these overdose deaths involved two or more illicit drugs such as cocaine, heroin, illicitly manufactured fentanyl, or methamphetamine (O'Donnell 2020). Epidemiologic studies suggest that one in five young adults engage in polysubstance misuse and that they begin at younger ages and have more severe disease outcomes.

Growing evidence suggests that SUD accelerates vascular aging and contributes to early-onset ASCVD, especially when polysubstance misuse is present (Reece 2016). According to a study discussed earlier in the chapter, patients with premature and extremely premature ASCVD reported higher rates of polysubstance use, in which a graded risk was found according to the number of substances used – meaning the risk of extremely premature and premature ASCVD increased with each additional substance used (only 1: OR 2.05; only 2: OR 3.45; only 3: OR 6.38; 4 or more: OR 8.85) (Mahtta 2021). The substances of misuse evaluated consisted of tobacco, alcohol, and illicit drugs such as cocaine, amphetamines (e.g., methamphetamine), and cannabis. Of note, the investigators found that certain combinations of illicit substances are more risky than others. Compared with nonusers, those taking amphetamine with cocaine and cannabis had a 5.57-fold increase in premature ASCVD, whereas combining amphetamine with cocaine led to a 5.37-fold risk. In extremely premature ASCVD, those taking amphetamines with cocaine and cannabis had a 7-fold increase, whereas those taking amphetamine with either cocaine or cannabis had a 6.4- and 7.2-fold risk, respectively.

Given the growing body of literature on SUD and its CV outcomes, the need for a nationwide education campaign on the potential long-term damage being done to CV health is needed. Patients, especially those misusing several substances, should be made aware of the long-term risk of chronic debilitating ASCVD beyond just the acute risk of overdose.

Box 2. NIH Drug Resources

- National Library of Medicine (NLM). Commonly Abused Illicit, Prescription, and Over-the-Counter Drugs. 2020.
- National Institute on Drug Abuse (NIDA). Commonly Used Drug Charts. 2020.

PUBLIC HEALTH CONSIDERATIONS/ PATIENT EDUCATION

Substance use disorder has become an epidemic worldwide. From a public health perspective, education of communities at large will be necessary if this crisis is to be curtailed. Opioid users who are marginalized or vulnerable, including those who inject such substances, may also use synthetic opioid "research chemicals" in lieu of traditional opiates. However, the general public may not be aware of their high potency and potential health risks and/or that these agents are being sold on the internet as falsified oxycodone tablets. One major public health initiative to curtail the opioid epidemic has been to limit and remove the current supply of prescription opioids from the gray market and out of communities. For example, the Drug Enforcement Administration holds a national annual prescription drug takeback day to try to turn the tide against OUD (Drug Enforcement Administration 2018). Although

Patient Care Scenario

A 41-year-old woman was brought to the ED by ambulance after being found down in her apartment unconscious and unresponsive. She had pinpoint pupils and was minimally responsive to sternal rub. Two minutes after arrival, she received naloxone 0.4 mg intravenously, after which she woke up and was able to answer questions. On presentation, her blood pressure was 90/60 mm Hg, with heart rate 134 beats/minute, respiratory rate 10 breaths/minute, and Spo_2 80%. Her ECG was significant for a prolonged QTc interval. Naloxone was administered again with limited response. For 2 hours, the patient remained somnolent but was able to stay awake and speak coherently. She attested to ingesting 1 tablet of hydrocodone with acetaminophen, which was purchased on the internet. She normally has a prescription for hydrocodone/acetaminophen for chronic back pain; however, she ran out, and her physician refused to refill the prescription. Her social history includes current alcohol use, with about 3 beers consumed per day; cigarette smoking (1 pack/day); cannabis use once weekly; and a history of methamphetamine use, which she quit 10 years ago. Her medical history includes type II bipolar disorder, asthma, L3/L4 disc herniation, chronic pain, and anxiety. Her medications are bupropion, valproic acid, inhaled albuterol, ibuprofen, and as-needed hydrocodone/acetaminophen for 5–7 days. A urine toxicology screen is positive for opiates and cannabis. A serum acetaminophen concentration is undetectable. Which one of the following most likely caused this patient's CV signs and symptoms?

A. Hydrocodone/acetaminophen

B. Cannabis

C. Fentanyl-tainted opioid

D. Methamphetamine

ANSWER

This patient's presenting signs and symptoms (e.g., hypotension, tachycardia, depressed respiratory rate) are consistent with opioid overdose. However, a single hydrocodone/acetaminophen tablet should not produce such effects (Answer A is incorrect). Of note, her QTc interval is prolonged, which is key. Although cannabis use has been associated with long QT syndrome and other arrhythmias, these cases are rare, and this patient attests to infrequent use (Answer B is incorrect). The acute CV effects of methamphetamine are caused by its sympathomimetic properties and direct cardiotoxicity, manifesting with an increased heart rate, systolic blood pressure, and respiratory rate. This patient's urine drug screen was negative for amphetamines, and she reportedly has not used methamphetamines for over a decade (Answer D is incorrect). The best choice is fentanyl-laced opioid (Answer C is correct). With the restrictions placed on the prescription of opioids, many have turned to the gray web to purchase what they believe to be an opiate but what is in fact an agent tainted with fentanyl.

1. Behazdi M, Joukar S, Beik A. Opioids and cardiac arrhythmia: a literature review. Med Princ Pract 2018;27:401-14.
2. Page RL II, Allen LA, Kloner RA, et al. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2020;142:e131-e152.
3. Reddy PKV, Ng TMH, Oh EE, et al. Clinical characteristics and management of methamphetamine-associated cardiomyopathy: state-of-the-art review. JAHA 2020;9:e016704.

many national and federal organizations recommend disposing of controlled substances by mixing them in kitty litter or coffee grounds, throwing them away in the trash, or flushing down the toilet, these methods have been controversial and could affect the environment. Instead, disposal at local police stations or local pharmacies is a safer alternative in which the medications are instead incinerated (Drug Enforcement Administration 2014). The National Association of Boards of Pharmacy website can help patients identify which pharmacies near them participate in this program. However, not all pharmacies participate in such programs because incineration is extremely expensive.

As cannabis use continues to increase and become more pervasive in the United States, especially among young adults, pharmacists may encounter many questions from both providers and patients and should be well informed regarding state and federal laws, possible CV and health risks for the various forms of administration, and their adverse effects. At each patient encounter, conversations regarding cannabis should be nonjudgmental and include a shared decision-making approach. The following are a few key talking points with each patient encounter. First, all cannabis products on the gray market, especially synthetic illicit cannabinoids, should be avoided because not only can they be adulterated or contaminated with other and more dangerous illicit substances such as heroin or fentanyl, but they also are several times more toxic than typical phytocannabinoids. Second, the American Heart Association recommends against smoking or vaping cannabis because of the carcinogens and impurities produced through combustion, especially for patients with respiratory diseases such as asthma or chronic obstructive pulmonary disease. In addition, the CDC has found that vaping products containing THC are linked to cases of e-cigarette or vaping use–associated lung injuries, which is possibly because of the vitamin E acetate that is often used as an oil-based solvent for THC (CDC 2022). Third, driving a car or operating heavy machinery should be avoided because blood THC concentrations of 2–5 ng/mL are associated with substantial driving impairment. Similarly, when cannabis is used in combination with opioids, alcohol,

or sedative/hypnotics, cross-tolerance and potentiated CNS depressant effects with cannabis may develop and may also result in impaired cognition and driving impairment. Fourth, regarding edible consumption, a delayed onset of effect may occur and should be explained to minimize potential adverse effects and overconsumption. Patients must be made aware that the onset of effects may take several hours after ingestion; thus, they should be particularly careful about stacking oral doses (see Table 1). Fifth, patients who are long-term, heavy cannabis users should be advised not to abruptly or suddenly stop their cannabis use because of the risk of withdrawal. Patients should contact their provider immediately if signs and symptoms of withdrawal or hyperemesis syndrome occur – common complications associated with CUD. Finally, interstate transportation of cannabis is a federal crime, even if the patient has an approved medical indication. The pharmacist's role with respect to cannabis varies by state. Some states such as Arkansas, Connecticut, Minnesota, New York, and Pennsylvania require a pharmacist to dispense cannabis or supervise the activities within a cannabis dispensary when used medically. Although some states allow for patient education, others forbid recommending cannabis products in any form because this might be seen as drug trafficking and/or unprofessional conduct. To this end, pharmacists need to know their state laws and regulations through their state board of pharmacy regarding what they can and cannot do.

CONCLUSION

Substance and prescription medication misuse continues to dramatically increase nationwide. With changes in public and health policies at the local, national, and state levels, newer substances and prescription medication misuse will continue to increase in the U.S. market and into communities. Substances of misuse are typically not used in silo but are combined with other illicit and prescription medications, which complicates the picture when evaluating potential CV toxicities and concomitant pharmacotherapies. Because of a paucity of randomized clinical trial data, pharmacists will need to be detectives, using their pharmacologic and pharmacokinetic knowledge to possibly predict potential CV toxicities associated with these agents and appropriately adjust pharmacotherapy for concomitant CV conditions.

Practice Points

- **Attitudes toward the recreational and medical use of cannabis have rapidly evolved within the United States. With state-based legalization, pharmacists need to be knowledgeable of their respective cannabis laws.**
- **THC and CBD have direct and indirect effects on the CV system. THC may stimulate the sympathetic nervous system while inhibiting the parasympathetic nervous system, increase heart rate and supine blood pressure, cause platelet activation, and promote endothelial dysfunction and oxidative stress. Cannabidiol may reduce heart rate and blood pressure, improve vasodilation, and reduce inflammation and vascular hyperpermeability.**
- **Several safety signals have emerged from a paucity of prospective and observational studies regarding adverse CV outcomes and cannabis use, including MI, stroke, and atrial fibrillation, particularly in young adults.**
- **THC can inhibit CYP 3A4, 2C9, 2C19, and 2D6, whereas CBD can inhibit CYP 3A4/5, 2C19, 2D6, and 1A2; therefore, potential drug-drug interactions exist and should be anticipated.**
- **Opiates can be classified as natural, semisynthetic, synthetic, or opioid-like, and CV complications vary between them.**
- **Effects of opioid receptor agonism on the CV system are multifactorial and greatly depend on the circumstances of patient exposure. Acute and chronic opioid misuse, overdose, and withdrawal are each associated with unique complications, including vascular, valvular, and arrhythmic sequelae. In older adults, an increased risk of CV events after starting stimulants may exist but may not be associated with chronic use.**
- **Unlike natural opiates, synthetic opiates, particularly methadone and high-dose loperamide, have been associated with QTc prolongation as well as TdP.**
- **Prescription stimulants used to treat ADHD in children and young adults cause modest elevations in resting heart rate and blood pressure. In older adults, recent observational data suggest an initial increased risk of CV events after stimulant initiation but no association for increased risk with long-term use.**
- **Chronic methamphetamine misuse can lead to long-term hypertension and hypertensive cardiomyopathy with possible idiopathic pulmonary hypertension and aortic dissection. Other complications consist of hemorrhagic stroke, HF, and MI, even in the absence of ASCVD risk factors.**
- **Several new substances have emerged onto the market during the opioid epidemic, including misuse of prescription gabapentin and bupropion. As misuse of various substances continues to increase, many electronic resources exist to help pharmacists predict potential adverse CV toxicity and develop pharmacotherapy recommendations.**

REFERENCES

Alshaarawy O, Anthony JC. Cannabis smoking and diabetes mellitus: results from meta-analysis with eight independent replication samples. Epidemiology 2015;26:597-600.

Amsterdam JGC, Opperhuizen A, van den Brink W. Harm potential of magic mushroom: a review. Regul Toxicol Pharmacol 2011;59:423-9.

Bailey AJ, Farmer EJ, Finn PR. Patterns of polysubstance use and simultaneous co-use in high risk young adults. Drug Alcohol Depend 2019;205:107656.

Blanckaert P, Cannaert A, Van Uytfanghe K, et al. Report on a novel emerging class of highly potent benzimidazole NPS opioids: chemical and in vitro functional characterization of isotonitazene. Drug Test Anal 2020;12:422-30.

Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci U S A 1993;90:5391-3.

Carman WJ, Su S, Cook SF, et al. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf 2011;20:754-62.

CDC. States Update Number of Hospitalized EVALI Cases and EVALI Deaths. 2020.

CDC. Federal Register Notice: CDC's Updated Clinical Practice Guideline for Prescribing Opioids Is Now Out for Public Comment. February 10, 2022.

CDC. Overdose Deaths Accelerating During COVID-19. December 17, 2020.

Chow SL, Sasson C, Benjamin IJ, et al. Opioid use and its relationship to cardiovascular disease and brain health: a presidential advisory from the American Heart Association. Circulation 2021;144:e218-e232.

Congressional Research Service (CRS). FDA Regulation of Cannabidiol Consumer Products: Overview and Considerations for Congress. February 2020.

Darke S, Duflou J, Kaye S. Prevalence and nature of cardiovascular disease inmethamphetamine-related death: a national study. Drug Alcohol Depend 2017;179: 174–179.

DeFilippis EM, Baja NS, Singh A, et al. Marijuana use in patients with cardiovascular disease. J Am Coll Cardiol 2020;75:320-32.

Desai R, Patel U, Deshmukh A, et al. Burden of arrhythmia in recreational marijuana users. Int J Cardiol 2018;264:91-2.

Drug Enforcement Administration (DEA). Schedules of controlled substances: Temporary placement of isotonitazene in Schedule 1. 2020.

Drug Enforcement Administration (DEA). Department of Justice. Disposal of Controlled Substances. 2014.

Drug Enforcement Administration (DEA). Department of Justice. How to Properly Dispose of Your Unused Medications. 2018.

Doshi R, Majmundar M, Kansara T, et al. Frequency of cardiovascular events and in-hospital mortality with opioid overdose hospitalizations. Am J Cardiol 2019;124:1528-33.

Dutta T, Ryan KA, Thompson O, et al. Marijuana use and risk of early ischemic stroke. Stroke 2021;52:3184-90.

European Monitoring Centre for Drugs and Drugs Addiction. Report on the Risk Assessment of N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene) in Accordance with Article 5c of Regulation (EC) No. 1920/2006 (as amended). 2020.

Feng Y, He X, Yang Y, et al. Current research on opioid receptor function. Curr Drug Targets 2012;13:230-46.

U.S. Food and Drug Administration (FDA). FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD). 2021.

U.S. Food and Drug Administration (FDA). FDA Takes Steps Aimed at Fostering Development of Non-addictive Alternatives to Opioids for Acute Pain Management. February 9, 2022.

Gay GR. Clinical management of acute and chronic cocaine poisoning. Ann Emerg Med 1982;11:562-72.

Hemachandra D, McKetin R, Cherbuin N, et al. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. Aust N Z J Public Health 2016;40:226-30.

Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in cannabis (Cannabaceae). Am J Bot 2004;91:966-75.

Kalla A, Krishnamoorthy PM, Gopalakrishnan, A, et al. Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the National Inpatient Sample. J Cardiovasc Med (Hagerstown). 2018;19:480-484

Kao D, Bucker Bartelson B, Khatri V, et al. Trends in reporting of methadone-associated cardiac arrhythmia events, 1997-2011. Ann Intern Med 2013;158:735-40.

Kao DP, Haigney MC, Mehler PS, et al. Arrhythmia associated with buprenorphine and methadone reported to the Food and Drug Administration. Addiction 2015;110:1468-75.

Karila L, Weinstein A, Aubin HJ, et al. Pharmacological approaches to methamphetamine dependence: a focused review. Br J Clin Pharmacol 2010;69:578-92.

Kevil CG, Goeders NE, Woolard MD, et al. Methamphetamine use and cardiovascular disease. Arterioscler Thromb Vasc Biol 2019;39:1739-46.

Kim ST, Park T. Acute and chronic effects of cocaine on cardiovascular health. Int J Mol Sci 2019;20:584.

Klein MG, Haigney MCP, Mehler PS, et al. Potent inhibition of hERG channels by the over-the-counter antidiarrheal agent loperamide. JACC Clin Electrophysiol 2016;2:784-9.

Ladha KS, Mistry N, Wijeysundera DN, et al. Recent cannabis use and myocardial infarction in young adults: a cross-sectional study. CMAJ 2021;193:E1377-E1384.

Le Strat Y, Le Foll B. Obesity and cannabis use: results from 2 representative national surveys. Am J Epidemiol 2011;174:929-33.

Li L, Setoguchi S, Cabral H, et al. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. J Intern Med 2013;273:511-26.

Mahtta D, Ramsey D, Krittanawong C, et al. Recreational substance use among patients with premature atherosclerotic cardiovascular disease. Heart 2021;107:650-6.

Marzec L, Katz D, Peterson P, et al. Torsade de pointes associated with high-dose loperamide ingestion. J Innov Card Rhythm Manage 2015;6:1897-9.

Matthews KA. Associations between cannabis use and cardiometabolic risk factors: a longitudinal study of men. Psychosom Med 2019;81:281-8.

Mattson CL, Tanz LJ, Quinn K, et al. Trends and geographic patterns in drug and synthetic opioid overdose deaths – United States, 2013-2019. Weekly 2021;70:202-7.

Myrick H, Henderson S, Brady KT, et al. Gabapentin in the treatment of cocaine dependence: a case series. J Clin Psychiatry 2001;62:19-23.

National Institute on Drug Abuse (NIDA). Cannabis (Marijuana) Potency. 2021.

National Institutes of Health (NIH). Appendix B: Commonly Abused Illicit, Prescription, and Over-the-Counter Drugs. 2020.

O'Donnell J, Gladden RM, Mattson CL, et al. Vital signs: characteristics of drug overdose deaths involving opioids and stimulants – 24 states and the District of Columbia, January–June 2019. MMWR 2020;69:1189-97.

Omran SS, Chatterjee A, Chen ML, et al. National trends in hospitalizations for stroke associated with infective endocarditis and opioid use between 1993 and 2015. Stroke 2019;50:577-82.

Pacher P, Steffens S, Haskó G, et al. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. Nat Rev Cardiol 2018;15:151-66.

Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med 2013;126:583-9.

Pergolizzi JV, Magnusson P, LeQuang JK, et al. Cocaine and cardiotoxicity: a literature review. Cureus 2021;13:e1459.

Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980;302:123.

Qureshi WT, O'Neal WT, Khodneva Y, et al. Association between opioid use and atrial fibrillation. The reasons for geographic and racial differences in stroke (REGARDS) study. JAMA Intern Med 2015;175:1058-60.

Rajavashisth TB, Shaheen M, Norris KC, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open 2012;2:e000494.

Ramphul K, Joynauth J. Cardiac arrhythmias among teenagers using cannabis in the United States. Am J Cardiol 2019;124:1966.

Reece AS, Norman A, Hulse GK. Cannabis exposure as an interactive cardiovascular risk factor and accelerant of organismal ageing: a longitudinal study. BMJ Open 2016;6:e011891.

Reis JP, Auer R, Bancks MP, et al. Cumulative lifetime marijuana use and incident cardiovascular disease in middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Public Health 2017;107:601-6.

Rezkalla S, Kloner RA. Cardiovascular effects of marijuana. Trends Cardiovasc Med 2019;29:403-7.

Richards JR, Harms BN, Kelly A, et al. Methamphetamine use and heart failure: prevalence, risk factors, and predictors. Am J Emerg Med 2018;36:1423-8.

Rudasill S, Yas S, Mardock AL, et al. Clinical outcomes of infective endocarditis in injection drug users. J Am Coll Cardiol 2019;73:559-70.

Schifano F, Chiappini S. Is there a potential of misuse for venlafaxine and bupropion? Front Pharmacol 2018;9:1-10.

Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. Circulation 2010;24:2558-69.

Spadotto V, Zorzi A, Elmaghawry M, et al. Heart failure due to "stress cardiomyopathy": a severe manifestation of the opioid withdrawal syndrome. Eur Heart J Acute Cardiovasc Care 2013;2:84-7.

Stall N, Godwin J, Jurrlink D. Bupropion abuse and overdose. CMAJ 2014;186:1015.

Swank KA, Wu E, Kortepeter C, et al. Adverse event detection using the FDA post-marketing drug safety surveillance system: cardiotoxicity associated with loperamide abuse and misuse. J Am Pharm Assoc 2017;57:S63-S67.

Tadrous M, Shakeri A, Chu C, et al. Assessment of stimulant use and cardiovascular event risks among older adults. AMA Netw Open 2021;4:e2130795.

Testai FD, Gorlick PB, Aparicio HJ, et al. Use of marijuana: effect on brain health: a scientific statement from the American Heart Association. Stroke 2022;53:e176-e187.

Torres-Acosta N, O'Keefe JH, O'Keefe CL, et al. Cardiovascular effects of ADHD therapies: JACC review topic of the week. J Am Coll Cardiol 2020;76:858-66.

VanDolah HJ, Bauer BA, Mauck KF. Clinicians' guide to cannabidiol and hemp oils. Mayo Clin Proc 2019;94:1840-51.

Vázquez-Bourgon J, Setién-Suero E, Pilar-Cuéllar F, et al. Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: results from a three-year longitudinal study. J Psychopharmacol 2019;33:284-94.

Verougstraete N, Vandeputte MM, Lyphout C, et al. First report on brorphine: the next opioid on the deadly new psychoactive substance horizon? J Anal Toxicol 2021;44:937-46.

Vongpatanasin W, Mansour Y, Chavoshan B, et al. Cocaine stimulates the human cardiovascular system via a central mechanism of action. Circulation 1999;100:497-502.

Voskoboinik A, Ihle JF, Bloom JE, et al. Methampetamin-associated cardiomyopathy: Patters and predictors of recovery. Intern Med J 2016; 46: 723-7.

Yankey BN, Strasser S, Okosun IS. A cross-sectional analysis of the association between marijuana and cigarette smoking with metabolic syndrome among adults in the United States. Diabetes Metab Syndr 2016;10(suppl 1):S89-S95.

Yeo KK, Wijetunga M, Ito H, et al. The association of methamphetamine use and cardiomyopathy in young patients. Am J Med 2007;120:165-71.

Self-Assessment Questions

Questions 1–5 pertain to the following case.

T.R., a 29-year-old man, presents to the ED at the University of Utah Hospital with severe dyspnea at rest associated with mild substernal nonradiating chest pain. He denies palpitations, productive cough, abnormal sounds while breathing, difficulty swallowing, history of cardiac problems, recent viral illness, or recent travel. T.R.'s medical history includes attention-deficit/hyperactivity disorder (ADHD), for which he was prescribed methylphenidate 10 mg orally twice daily. His home medications also include oxycodone 5–10 mg orally once daily as needed for a baseball injury, which he states he rarely uses. Both medications were prescribed by his primary care physician in the past month, and T.R. attests to taking them correctly. His family history is significant for his mother's death because of a myocardial infarction (MI) at age 45. T.R.'s urinary drug screening is positive for amphetamines, cannabinoids, and opioids. After losing his job, he states that he has been smoking methamphetamine once or twice per month over the past 6 months but has been smoking cannabis for more than 4 years, which he regularly obtains from a local cannabis grower. T.R. understands that using cannabis and methamphetamine is "bad for his health," and such misuses led to his recent divorce and job loss. When he does stop cannabis, he develops tremors, nightmares, and significant nausea and can smell the "skunk of pot" until he uses again. Over the past year, his cannabis consumption has increased from once at bedtime to now four times daily to help with anxiety. T.R. attests that he refuses to stop cannabis use. On physical examination, he is alert and oriented but significantly agitated. His vital signs on presentation are blood pressure 90/70 mm Hg, heart rate 120 beats/minute, and respiratory rate 26 breaths/minute. His Sao_2 is 88% on room air. Chest examination reveals bilateral diffuse crackles, most pronounced at lung bases. Chest radiography reveals pulmonary congestion and cardiomegaly. An ECG reveals sinus tachycardia and Q waves in leads II, III, and aVF suggestive of an old MI. T.R.'s cardiac troponins are within reference range; however, his BNP concentration is elevated at 800 pg/mL. All other laboratory values are in normal range. Transthoracic echocardiogram reveals severe left ventricular and atrial dilatation with a left ventricular ejection fraction of 15%, as well as a left ventricular thrombus.

1. Given his presentation and history, which one of the following best characterizes T.R.'s substance use?

   A. Methylphenidate misuse
   B. Cannabis withdrawal
   C. Methamphetamine tolerance
   D. Oxycodone misuse

2. Which one of the following best evaluates T.R.'s substance use disorder (SUD)?

   A. Mild cannabis use disorder (CUD)
   B. Severe CUD
   C. Moderate stimulant disorder
   D. Severe stimulant disorder

3. Which one of the following is most likely the cause of T.R.'s heart failure (HF) with reduced ejection fraction?

   A. Cannabis
   B. Methylphenidate
   C. Methamphetamine
   D. Oxycodone

4. T.R. is discharged on warfarin 5 mg on Mondays, Wednesdays, and Fridays and 7.5 mg on all other days in addition to his guideline-directed medical therapy for HF. His INR at discharge is stable at 2.5. Within 1 week of discharge, T.R. returns to the cardiology clinic for a follow-up. At this visit, his INR is 7.5, and he has concerns for epistaxis. He states he has not changed his diet and has been adherent to his prescription medications, including oxycodone and methylphenidate, but continues to smoke methamphetamine and cannabis. Which one of the following is most likely responsible for T.R.'s elevated INR?

   A. Cannabis
   B. Methylphenidate
   C. Methamphetamine
   D. Oxycodone

5. At the follow-up, T.R. asks about obtaining medical cannabis for his uncontrolled anxiety, in which he wants to grow three plants. Which one of the following is the best educational point to share with T.R.?

   A. Talk to your primary care physician because anxiety is an approved medical condition for cannabis in Utah.
   B. Utah state law prohibits the use of medical and recreational cannabis, and it is illegal.
   C. Talk to your primary care physician because Utah state law allows for possession of only one cannabis plant.
   D. Utah state law does not list anxiety as a prequalifying condition.

Questions 6–8 pertain to the following case.

J.S. is a 28-year-old man with no cardiac risk factors or significant medical history except for occasional migraines. He has an out-of-hospital cardiac arrest, is successfully resuscitated in the field by paramedics, and is admitted to the ICU at the University of Colorado Hospital with an initial rhythm of ventricular fibrillation. After return of spontaneous circulation,

J.S.'s surface ECG reveals slight ST-segment elevation (1 mm) in precordial leads V2 and V3 with no troponin elevations; therefore, the patient is transferred sedated and ventilated to the cardiac catheterization laboratory for primary percutaneous coronary intervention. Angiography reveals critical stenosis of around 9 mm in the proximal left circumflex coronary artery, left dominant but without any typical angiographic sign of a culprit lesion. Intracoronary nitroglycerin is administered, leading to complete disappearance of the stenosis and proving severe focal spasm. Accordingly, no coronary intervention is performed. J.S. is admitted to the ICU, where his urine toxicology test is positive for cocaine, opiates, and Δ-9-tetrahydrocannabinol (THC). The patient's wife confirms her husband's recreational cocaine use (snorting) at most once a month over the past 6 months and vaping cannabis daily for the past 2 years. He smokes 1 pack/day of cigarettes and drinks 1 beer at bedtime. She states that J.S. has hidden these habits from her. Although his cannabis use has not affected his family, work, or social life, she worries because he still drives a car while vaping weed. When questioned about opiate use, she attests that he was prescribed oxycodone 10 mg once as needed for severe migraines, which he has every 2 months. She states that he has not misused oxycodone because he fears developing an oxycodone use disorder.

6. Given his presentation and history, which one of the following best characterizes J.S.'s substance use?

   A. Opiate misuse
   B. Moderate CUD
   C. Severe stimulant use disorder
   D. Mild CUD

7. Which one of the following is most likely causing J.S.'s cardiac event?

   A. Cocaine
   B. Oxycodone
   C. Cannabis
   D. Tobacco

8. After being stabilized, J.S. is discharged to home on the following medications: lisinopril 10 mg orally daily, aspirin 81 mg orally daily, chlorthalidone 25 mg orally daily, pravastatin 40 mg orally at bedtime, isosorbide mononitrate 30 mg orally daily, and sublingual nitroglycerin as needed. He presents to the clinic for follow-up blood pressure management by the pharmacist. J.S. has agreed to stop cocaine use but continues to use cannabis to relieve anxiety. He is concerned that his medications will interact with his use of weed. Which one of the following is the best educational point to share with J.S.?

   A. An interaction could occur with lisinopril because cannabis increases its concentrations.
   B. We may need to change the statin to simvastatin because cannabis can increase pravastatin concentrations.
   C. Call the clinic if you become hypotensive because cannabis can increase isosorbide mononitrate concentrations.
   D. At this time, there are no drug-drug interactions, but chronic use could lead to another cardiac event.

Questions 9 and 10 pertain to the following case.

T.N. is a 45-year-old man whose medical history includes active intravenous heroin and methamphetamine use, hypertension, type 2 diabetes, hepatitis C, history of osteomyelitis, and cerebrovascular accident. He is brought to the ED for mental status changes, flu-like symptoms, night sweats, and dyspnea. T.N.'s physical examination is significant for temperature 39.3°C, blood pressure 150/80 mm Hg, sinus tachycardia 105 beats/minute, and respiratory rate 30 breaths/minute. His Sao_2 is 98% on nasal cannula with 35% oxygen concentration. In the ED, T.N.'s troponins are normal with a procalcitonin concentration of 0.6 ng/mL. His pupils are pinpoint. T.N. has several abscesses on the upper extremities.

9. Given his history and presentation, which one of the following is best to recommend for T.N.?

   A. Begin a heparin drip because he may have an acute coronary syndrome.
   B. Obtain blood cultures and initiate empiric antibiotics for possible endocarditis.
   C. Administer flumazenil because he may have a heroin overdose.
   D. Obtain an immediate 12-lead ECG for possible arrhythmia.

10. T.N. is admitted to the medical ICU. On questioning, he admits chewing khat before admission. The attending physician asks you, the pharmacist, whether this contributed to his cardiac issues. Which one of the following is the best educational point to share with T.N.'s provider?

    A. Khat is a schedule I substance with opioid-like activity leading to possible respiratory depression.
    B. Khat is an illegal stimulant that acutely can cause hypertension and tachycardia.
    C. Khat is a form of synthetic cannabis associated with potential arrhythmias and MI.
    D. Khat is a form of inhalant that is commonly misused and can increase atherosclerotic cardiovascular disease (ASCVD) risk.

Questions 11 and 12 pertain to the following case.

J.B. is a 25-year-old man with opioid use disorder (OUD), benzodiazepine dependence, amphetamine dependence, generalized anxiety disorder, bipolar depression, and neuropathic pain who presents to the addiction clinic. He currently takes sertraline, valproate, gabapentin, and lamotrigine. During this first visit, J.B. will begin buprenorphine for OUD. The patient's

mother accompanies him and provides collateral history. She is currently administering the medications because of her concerns of misuse by her son. J.B. began using opiates at age 16, which he obtained illegally on the streets. He reports starting heroin use at age 17, injecting intermittently. According to the patient, he was also smoking 1.5 g of methamphetamine daily and admits cocaine use. In addition, his mother expresses concern over her J.B.'s possible misuse of his current prescription medications.

11. Which one of his prescription medications has the most potential to be misused by J.B.?

    A. Sertraline
    B. Valproate
    C. Gabapentin
    D. Lamotrigine

12. Because of the potential for misuse, J.B.'s mother wants to dispose of all of her controlled substances from the house. She asks you where or how she can dispose of them. Which one of the following is best to convey to J.B.'s mother?

    A. Bring them to the clinic, and I can dispose of them.
    B. Crush all tablets, and open all capsules and flush down the toilet.
    C. Put all medications in kitty litter, and throw away in the garbage.
    D. Search the internet to locate a pharmacy that takes back prescription medications.

Questions 13–15 pertain to the following case.

K.S., a 25-year-old man whose medical history includes hypertension, familial hyperlipidemia, and ADHD, presents to his primary care provider for a follow-up of his chronic back pain. He smokes 1 pack/day of cigarettes and has a strong family history of heart disease. K.S.'s current prescription medications include oxycodone, methylphenidate, and atorvastatin. He has been taking controlled-release oxycodone 40 mg orally twice daily with as-needed immediate-release oxycodone, which has helped his pain over the past 3 years. K.S. worries he has developed an oxycodone use disorder because he has been warranting higher doses of narcotics to control the pain. He eagerly wants to come off the opioid regimen. His primary care physician wants to start a cannabis regimen and discontinue oxycodone.

13. Given the pharmacology of cannabinoids and opiates, which one of the following is best to recommend for K.S.?

    A. Discontinue oxycodone and begin an edible cannabis regimen because cannabidiol (CBD) is a full mu-agonist.
    B. Discontinue oxycodone and begin an edible cannabis regimen because CBD has several off-target effects to alleviate pain.
    C. Do not abruptly discontinue oxycodone. CBD has weak mu-agonist activity and the patient could go through opiate withdrawal.
    D. May discontinue oxycodone, but the patient will need a THC/CBD combination edible product because THC has stronger mu-agonist activity.

14. K.S.'s physician did not receive training on cannabinoid use during medical school or residency. He asks your opinion on appropriate cannabis formulations for pain. Which one of the following is best to recommend for K.S.?

    A. Smoking cannabis is preferred because it has a rapid onset and can easily titrated be for pain. The offset is also fairly rapid, so it does not impair driving.
    B. Consumption through edibles is an excellent option because the effects are seen within a few hours and they can easily be titrated. Fewer drug-drug interactions would be expected.
    C. Consumption through edibles is an excellent option, but their effects are not seen for several hours. Patients need to be aware of this so that they do not layer dosing with no immediate effect.
    D. Vaping cannabis is preferred because it has a rapid onset, can easily be titrated, and may be much safer than smoking cannabis.

15. K.S. worries about the long-term use of oxycodone, methylphenidate, and possible medical cannabis use on his heart health. Which one of the following is the best educational point to share with K.S.?

    A. Chronic opioid use has not been associated with chronic CV conditions such as MI, stroke, or arrhythmias.
    B. Cannabis use has been associated with increased ASCVD risk, especially given your strong family history of CVD and history of smoking.
    C. Long-term use of prescription methylphenidate has been associated with an increased risk of valvular heart disease and HF.
    D. Chronic opioid use has been associated with an increased risk of stroke, particularly in young men.