

## AHA SCIENTIFIC STATEMENT

# Medical Marijuana, Recreational Cannabis, and Cardiovascular Health

## A Scientific Statement From the American Heart Association

**ABSTRACT:** Cannabis, or marijuana, has potential therapeutic and medicinal properties related to multiple compounds, particularly  $\Delta$ -9-tetrahydrocannabinol and cannabidiol. Over the past 25 years, attitudes toward cannabis have evolved rapidly, with expanding legalization of medical and recreational use at the state level in the United States and recreational use nationally in Canada and Uruguay. As a result, the consumption of cannabis products is increasing considerably, particularly among youth. Our understanding of the safety and efficacy of cannabis has been limited by decades of worldwide illegality and continues to be limited in the United States by the ongoing classification of cannabis as a Schedule 1 controlled substance. These shifts in cannabis use require clinicians to understand conflicting laws, health implications, and therapeutic possibilities. Cannabis may have therapeutic benefits, but few are cardiovascular in nature. Conversely, many of the concerning health implications of cannabis include cardiovascular diseases, although they may be mediated by mechanisms of delivery. This statement critically reviews the use of medicinal and recreational cannabis from a clinical but also a policy and public health perspective by evaluating its safety and efficacy profile, particularly in relationship to cardiovascular health.

Cannabis has been used since as early as 100 CE for its potential therapeutic and medicinal properties from its multiple compounds, particularly  $\Delta$ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Over the past 25 years, attitudes toward the recreational and medicinal use of cannabis have rapidly evolved in the United States from illicit to decriminalized to legalized at the state level (Figure 1A and 1B).<sup>1-4</sup> In addition to national legalization in Uruguay and Canada, other countries have followed suit. In 2019, Thailand became the first nation in Southeast Asia to legalize medical cannabis and removed low-level cannabis and hemp extracts from its list of banned narcotic substances. Mexico has drafted legislation for cannabis legalization currently under review. Other countries that are considering legal changes to cannabis include Colombia, Argentina, Peru, Ecuador, Thailand, the United States, Australia, New Zealand, and Chile (Figure 1A). By 2025, legal cannabis sales are projected to generate \$23 billion in the United States. In the United States, cannabis use has risen particularly among those 18 to 25 years of age (Figure 2).<sup>1</sup> This massive shift in policy and use has forced clinicians to critically evaluate the safety and efficacy of cannabis. However, our understanding of the health effects of cannabis has been limited by decades of worldwide illegality and continues to

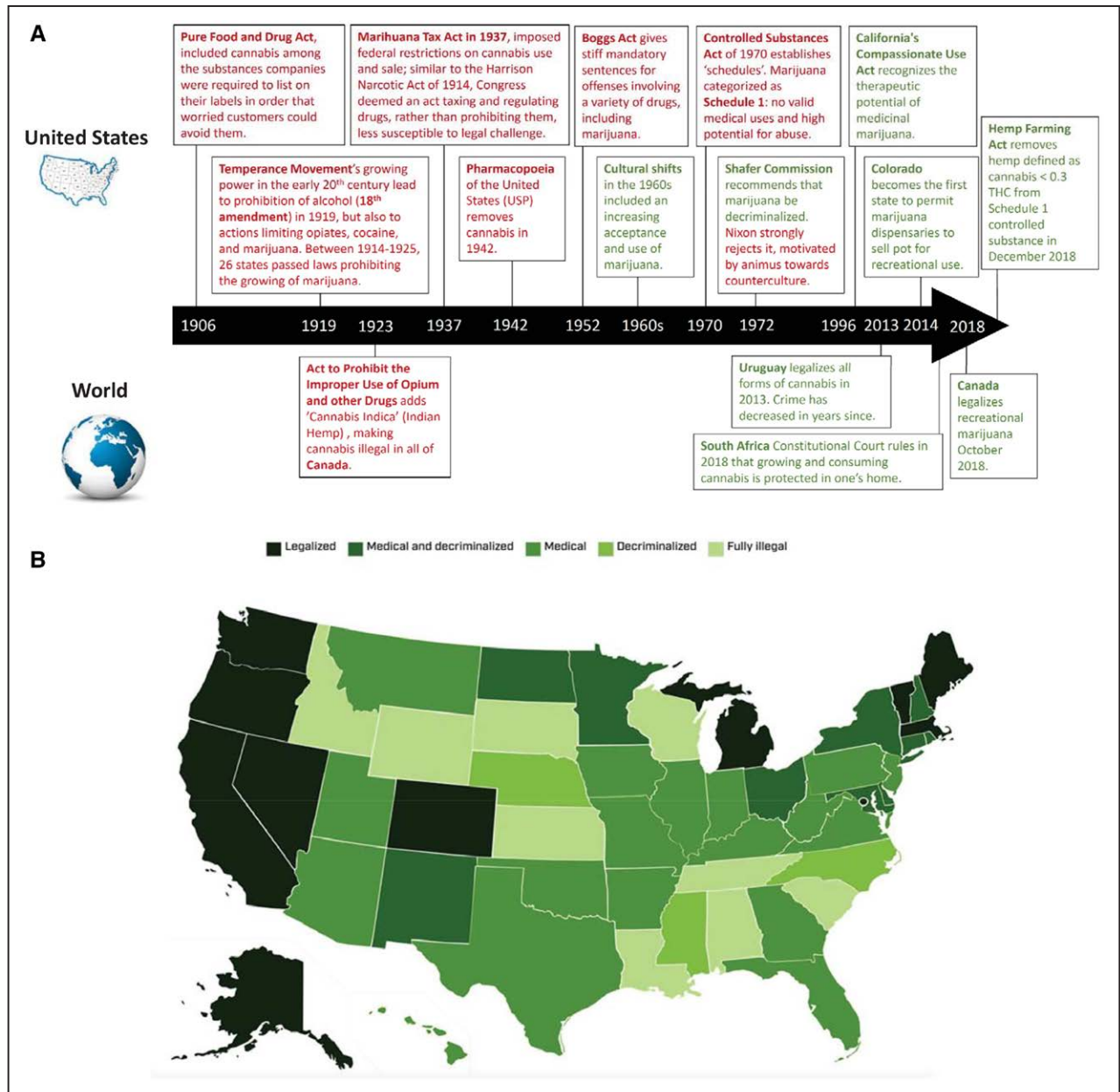
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■ cannabinoids ■ cannabis ■ medical marijuana ■ public health

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**Figure 1.** Summary of the evolution of cannabis policy (A) and by state (B).\*

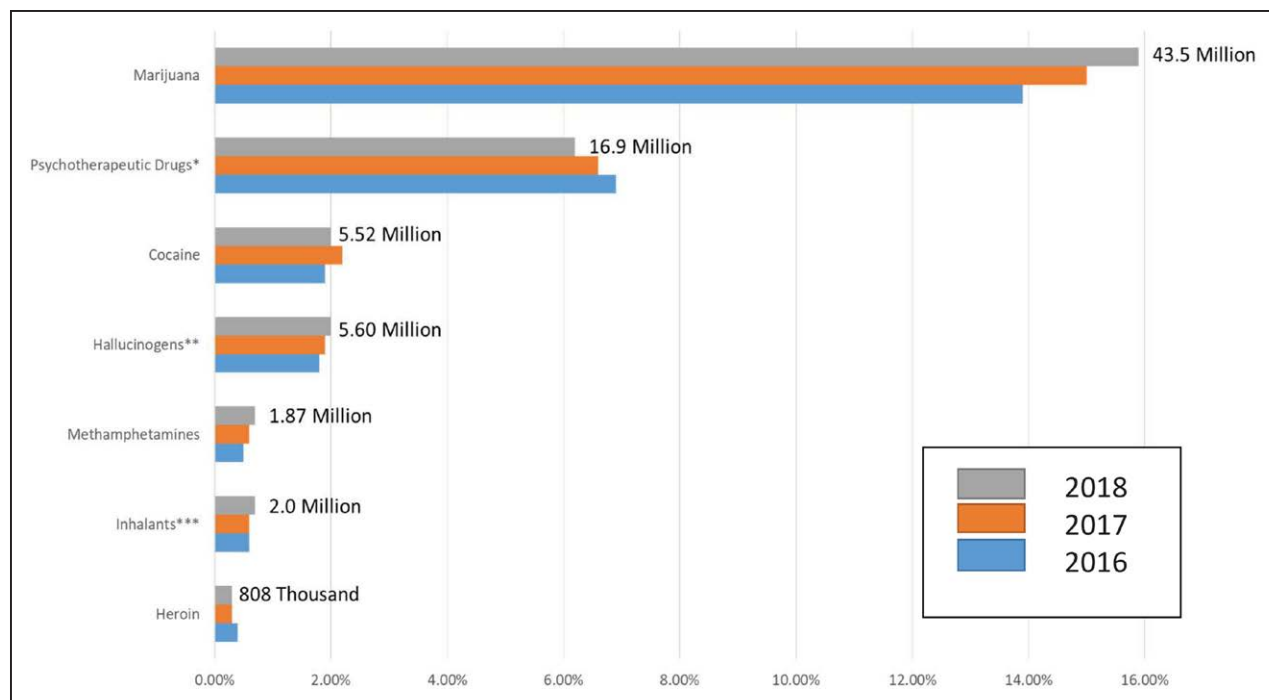
THC indicates Δ-9-tetrahydrocannabinol. \*As of November 2019. Data derived from Adrian,<sup>2</sup> Haffajee et al,<sup>3</sup> and DISA Global Solutions.<sup>4</sup>

be limited in the United States by restrictions of federal law because cannabis remains a Schedule 1 controlled substance, deeming no accepted medical use, a high potential for abuse, and an unacceptable safety profile.<sup>2,3</sup> In this document, we critically review the use of medicinal and recreational cannabis from a clinical but also a policy and public health perspective by evaluating its safety and efficacy profile as it pertains to cardiovascular health.

## DEFINITIONS AND CANNABIS FORMULATIONS

Marijuana and hemp plants are cultivars of the genus *Cannabis*. The physiological effects of cannabis are

derived primarily from its cannabinoids. To date, CBD and tetrahydrocannabinolic acid, which is hepatically decarboxylated to THC, have been the best studied cannabinoids. More than 100 different phytocannabinoids have been identified, including minor cannabinoids such as cannabigerol, cannabichromene, cannabinol, and tetrahydrocannabivarin. Three commonly recognized strains of cannabis used recreationally and medicinally are *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis vendors 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. Sativa appears to provide more stimulating, uplifting, and energizing effects, whereas indica is more



**Figure 2. 2016-2018 trends in cannabis use compared with other substances in the United States.**

\*Psychotherapeutic drugs: barbiturates, benzodiazepines and nonbenzodiazepine sedatives (ie, zolpidem, eszopiclone, zaleplon), opiates, muscle relaxants, and stimulants. \*\*Hallucinogens: dimethyltryptamine, ecstasy, ketamine, lysergic acid diethylamide, mescaline, peyote, phencyclidine, psilocybin, and *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; and computer keyboard cleaner. Adapted from the National Survey on Drug Use and Health.<sup>1</sup>

relaxing, sedating, and pain reducing. However, these terminologies are rudimentary and often inaccurate.<sup>5,6</sup> Cannabis plants are also 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 ( $>>1.0$ ); chemotype 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 is  $<0.30\%$ , which is below the level of detectability.<sup>6</sup>

From a US policy perspective, cannabis is considered either medical or recreational. With the legalization of recreational cannabis and the advent of cannabis dispensaries, many formulations have entered onto the US and Canadian markets that are consumed orally, sublingually, or rectally; are vaporized; or are smoked (Figure 3).<sup>7-12</sup> These products lack federal regulation in the United States, resulting in a lack of standardization in dose, concentrations of cannabinoids, packaging, and labeling. Compared with first-generation cannabis products (eg, black market before 1996), these newer commercial products (eg, state-permitted/nonprosecuted products) have a significantly higher average THC content: 3.8% in the 1990s versus 12.2% in 2014.<sup>13,14</sup>

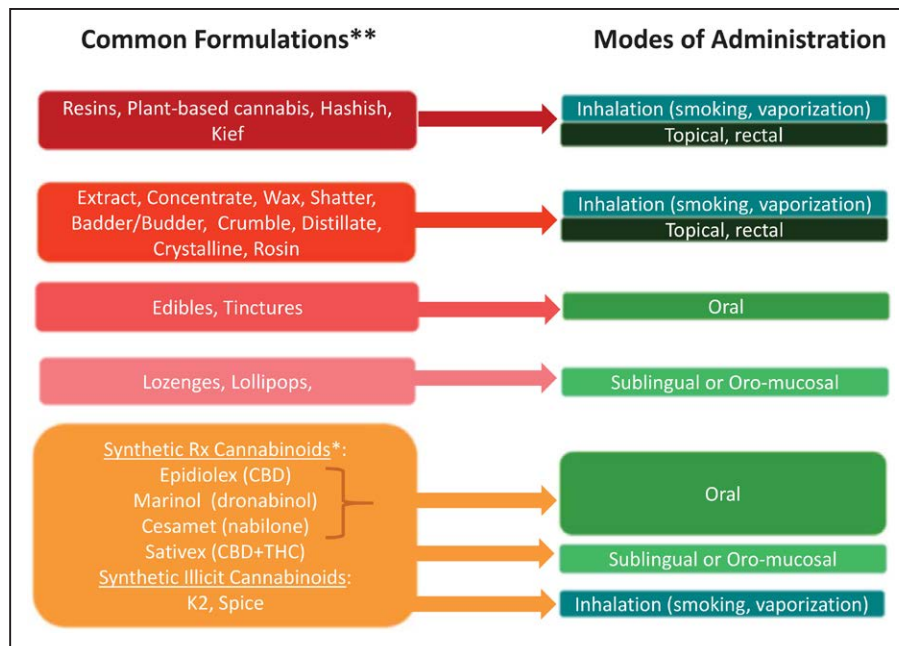
Synthetic cannabinoids are a class of molecules that can be arbitrarily divided into prescription and illicit. Initially developed to serve as pharmacological probes of the endogenous cannabinoid system, these synthetic illicit cannabinoids are now classified as new psychoactive drugs. On

the black market, many of these compounds have been developed and marketed under various brand names such as K2 and Spice and may be adulterated.<sup>15</sup> 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+THC) in Canada (Table 1).<sup>5,8</sup>

## PHARMACOLOGY, PHARMACOKINETICS, AND PHARMACODYNAMICS

The endogenous endocannabinoid system is extensive and complex, consisting of 2 naturally produced, on-demand cannabinoids (anandamide and 2-arachidonoylglycerol) and 2 CBD receptors ( $CB_1$  and  $CB_2$ ; Figure 4).<sup>5,7,8</sup> These receptors are G protein coupled to affect the conversion of AMP to cAMP. The distribution of  $CB_1$  receptors is primarily within the central nervous system along presynaptic neurons in the brain and spinal cord, as well as within the peripheral nervous system.  $CB_2$  receptors are concentrated mainly in immune cells and tissues. Through interaction with these receptors, the endocannabinoid system regulates overall homeostasis (Figure 4).<sup>5,7,8</sup>

Exogenous cannabinoids demonstrate variable affinity to  $CB_1$  and  $CB_2$  receptors. Tetrahydrocannabinol is a partial agonist with equal affinity for both CB receptors;



**Figure 3. Summary of common formulations and modes of administration of cannabinoids.**

CBD indicates cannabidiol; and THC,  $\Delta$ -9-tetrahydrocannabinol. \*Synthetic prescription cannabinoids: Epidiolex (CBD): Available in the United States; marketed by Greenwich Biosciences as an oral solution. Epidiolex is the first and only purified plant-derived CBD prescription drug approved for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients  $\geq 2$  years of age. Marinol (dronabinol): Available in the United States and Canada; marketed by AbbVie Pharmaceuticals and as a generic capsule; and labeled as a Schedule III controlled substance in the United States. Marinol (dronabinol) mimics THC and is indicated for anorexia associated with weight loss in adults patients with AIDS and nausea and vomiting associated with chemotherapy in adults who have failed conventional therapy. Cesamet (nabilone): Available in the United States and Canada; marketed by Valeant Pharmaceuticals as a capsule; and is a Schedule II controlled substance in the United States. Cesamet (nabilone) mimics THC and is indicated for the management of severe nausea and vomiting associated with cancer chemotherapy in adults  $\geq 18$  years of age. Sativex (CBD +THC): Available in Canada; marketed by GW Pharmaceuticals as an oromucosal spray. Sativex is a 1:1 ratio of CBD to THC and is a formulated extract from *Cannabis sativa*. It is approved for spasticity resulting from multiple sclerosis. \*\*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 (alcohol, carbon dioxide, etc) that essentially wash the trichomes off the cannabis plant. Hash or hashish: the dried flower and buds from *Cannabis sativa* that is 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. Data derived Health Canada,<sup>5</sup> VanDolah et al,<sup>7</sup> Ebbert et al,<sup>8</sup> Grotenhermen,<sup>9</sup> Foster et al,<sup>10</sup> and Millar et al.<sup>11</sup>

the synthetic cannabinoids are highly selective agonists or antagonists to either receptor types. CBD does not appear to bind to either CB<sub>1</sub> or CB<sub>2</sub> receptors at physiologically meaningful concentrations but may act as a modulator of CB<sub>1</sub> receptors, thus affecting the affinity of endogenous cannabinoids at the receptor level.<sup>5,7</sup>

The pharmacokinetics of cannabis and its compounds are greatly dependent on the route of administration, the specific cannabinoid, and the physical characteristics of the cannabis user. Table 1 summarizes the mechanism of action and pharmacokinetics for both THC and CBD, as well as the synthetic prescription cannabinoids.<sup>5,7-11</sup>

## FORMULATIONS

Cannabis products can contain pure THC or CBD or their combination. Products can vary in formulation and administration (Figure 3).<sup>5</sup> Products can be purchased in a dispensary for medical and recreational use, depending

on state law. With the passage of the Farm Bill, topical pure CBD products can be marketed and bought over the counter in pharmacies.<sup>16</sup> However, these topical products cannot claim to prevent, diagnose, treat, or cure diseases; thus, they are not subject to the US Food and Drug Administration drug approval process like other over-the-counter products. The US Food and Drug Administration has tested the CBD content in some of these topical products, and many were found not to contain the CBD concentrations that they claim on the label.<sup>16</sup>

## DOSING

For smoked/vaporized cannabis, the dose required to achieve therapeutic effects and to avoid adverse effects is influenced by the potency of the product, its processing, and the different smoking and vaporizing techniques.<sup>5</sup> Dosing should begin at the lowest possible dose, be increased gradually with caution (with

**Table 1. Summary of Pharmacology and Pharmacokinetics of Phytocannabinoids and Synthetic Prescription Cannabinoids**

Cannabinoid	Mechanism of Action	Absorption	Metabolism	Distribution	Elimination	
Phytocannabinoids (plant derived)						
CBD	Anandamide uptake inhibitor; TRPV1, TRPV2, TRPA1, GPR55, 5-HT <sub>1A</sub> , and PPAR $\gamma$ receptor activation	Inhalation:	Hepatic, via CYP1A1, 1A2, 2C8, 2C9, 2C19, 3A4, and 2D6; UGT1A9 and UGT2B7; undergoes hydroxylation	Time dependent, fatty tissues and highly perfused organs such as brain, heart, lung, and liver	Feces and urine; dependent on administration	
		Onset: 3–5 min				t <sub>1/2</sub> : 18–32 h
		Bioavailability: 11%–45%				
	Duration: 2–3 h	Preclinical and animal data suggest CBD may be a substrate and inhibitor of P-glycoprotein				
	Inhibits adenosine uptake				Oral:	
					Onset: hours	
	Inhibits FAAH and release of proinflammatory cytokines and expression of transcription factors (IL-1 $\beta$ , IL-2, IL-6, IL-8, TNF- $\alpha$ , IFN- $\gamma$ , CCL3, CCL4, NF- $\kappa$ B)				Bioavailability: 6%–33%	
					Duration: 12–24 h	
Allosterically modulates other receptors: $\alpha$ 1-adrenoceptors, dopamine D2, GABA <sub>A</sub> , $\mu$ - and $\delta$ -opioid receptors	Transdermal: not known					
	Transrectal: not known					
Inhibits calcium, potassium, and sodium channels by noncompetitive antagonism						
Free radical scavenger						
THC	Binds to CB <sub>1</sub> receptors	Inhalation:	Hepatic, via CYP2C9, 2C19, 2D6, and 3A4; UGT1A9 and UGT2B7; undergoes glucuronidation	Time dependent, fatty tissues and highly perfused organs such as brain, heart, lung, and liver	Renal: 20%	
		Onset: seconds–minutes				Feces: 65%
		Bioavailability: 2%–56%				
		Duration: 2–3 h			THC may be a substrate and inhibitor of the cell membrane protein, P-glycoprotein	
		Oral:				
		Onset: 30 min–2 h				
		Bioavailability: 4%–20%				
		Duration: 5–8 h				
		Transmucosal:				
		Onset: 15–40 min				
		Bioavailability: not known				
		Duration: 45 min–2 h				
		Transdermal: not known				
		Transrectal: not known				
Protein binding: 97%						
Synthetic cannabinoids (laboratory derived)						
Cesamet (nabilone)	Chemically similar to THC, binds to CB <sub>1</sub> receptor	Oral:	Hepatic, via CYP1A2, 2A6, 2C8, 2C9, 2C19, 2E1, 3A4	Similar to THC	Renal: 20%–24%	
		Bioavailability: 95%–100%				Feces: 60%–65%
		Onset: 1–1.5 h			t <sub>1/2</sub> : 35 h	
		Peak: 3–4 h				
Duration: 8–12 h	Enzymatic pathways: direct enzymatic oxidation and stereo-specific reduction					
Epidiolex (CBD)	Unknown but thought to act like CBD	Oral:	Hepatic, via CYP1A2, 2C8, 2C9, 2C19, 3A4, and 2D6; UGT1A9 and UGT2B7; undergoes hydroxylation	Similar to CBD	Renal: minor	
		Onset: not known				Protein binding: 94%
		Bioavailability: not known				
Duration: 12–24 h	t <sub>1/2</sub> : 56–61 h					
FDA indication: seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients $\geq$ 2 y of age	7-COOH-CBD (inactive metabolite) is a substrate of P-glycoprotein					

(Continued)

Table 1. Continued

Cannabinoid	Mechanism of Action	Absorption	Metabolism	Distribution	Elimination
Marinol (dronabinol)	Chemically similar to THC, binds to CB <sub>1</sub> receptor	Oral:	Hepatic via CYP2C9, 3A4; undergoes hydroxylation	Similar to THC	Renal: 10%–20% Feces: 50% Bile: >50% t <sub>1/2</sub> : 25–36 h
FDA indication: anorexia associated with weight loss in adults patients with AIDS and nausea and vomiting associated with chemotherapy in adults who have failed conventional therapy		Onset: 0.5–1 h			
		Bioavailability: 10%–20%			
		Peak: 2–4 h			
	Duration: 4–6 h				
Sativex (CBD+THC)	Similar to CBD and THC	Oral:	Similar to CBD and THC	Similar to THC and CBD	Renal and feces t <sub>1/2</sub> : 24–36 h
HPFB indication: spasticity caused by multiple sclerosis		Onset: 5–30 min			
		Bioavailability: not known			
		Duration: 12–24 h			

CB<sub>1</sub> indicates cannabinoid receptor subtype 1; CBD, cannabinoid; CCL, chemokine ligand; CYP, cytochrome P450; FAAH, fatty acid amide hydrolase; FDA, US Food and Drug Administration; GABA,  $\gamma$ -aminobutyric acid; GPR55, G-protein coupled receptor 55; HPFB, Health Products and Food Branch of Health Canada; 5-HT, 5-hydroxytryptamine; IL, interleukin; IFN, interferon; NF- $\kappa$ B, nuclear factor- $\kappa$ B; PPAR $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; THC,  $\Delta$ -9-tetrahydrocannabinol; TNF, tumor necrosis factor; TRPA, transient receptor potential ankyrin; TRPV, transient receptor potential vanilloid; and UGT, uridine 5'-diphospho-glucuronosyltransferase.

See Figures 4 and 5 for clinical effects of the cannabinoids.

Data derived from Health Canada,<sup>5</sup> VanDolah et al,<sup>7</sup> Ebbert et al,<sup>8</sup> Grotenhermen,<sup>9</sup> Foster et al,<sup>10</sup> and Millar et al.<sup>11</sup>

sufficient time between puffs/inhalations to gauge effects,  $\approx$ 30 minutes), and cease with the onset of any of the following effects: disorientation, dizziness, ataxia, agitation, anxiety, tachycardia and orthostatic hypotension, depression, hallucinations, or psychosis.<sup>5,7,8</sup>

Oral administration of cannabis is less well characterized; however, a dose of 0.15 to 0.30 mg/kg THC (ie, an individual oral dose of 10–20 mg THC) appears to

be sufficient to achieve psychotropic effects, and a dose of 0.45 to 0.6 mg/kg of THC (ie, an individual oral dose of 30–40 mg of THC) should produce marked intoxication.<sup>5</sup> Patients must be made aware that the onset of effects begins within 30 minutes to  $\geq$ 1 hour after ingestion with a peak effect within 3 to 4 hours; thus, they should be particularly careful about stacking oral doses. Consumption of edibles should proceed slowly and in

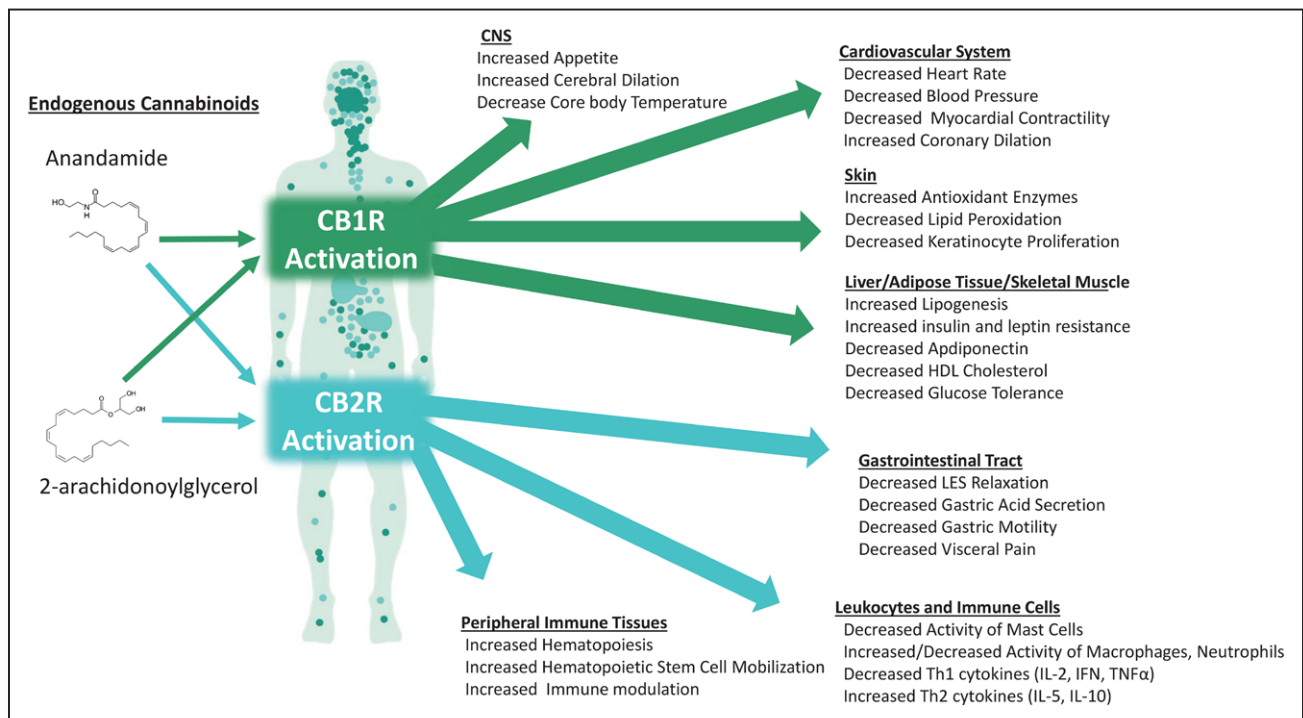


Figure 4. Effects of the endogenous cannabinoids.

CB<sub>1</sub>R indicates cannabinoid receptor subtype 1; CB<sub>2</sub>R, cannabinoid receptor subtype 2; CNS, central nervous system; HDL, high-density lipoprotein; IL, interleukin; IFN, interferon; LES, lower esophageal sphincter; Th, type; and TNF $\alpha$ , tumor necrosis factor- $\alpha$ . Data derived from Health Canada,<sup>5</sup> VanDolah et al,<sup>7</sup> and Ebbert et al.<sup>8</sup>

**Table 2. Known, Purported, and Possible Medical Benefits Associated With Cannabis Use**

Known (conclusive or substantial evidence)	
Pain	Improvements in neuropathic pain with smoked cannabis, dronabinol, and cannabis-based medicine vs placebo.
	Improvements in fibromyalgia pain with nabilone vs placebo.
	The limited available clinical evidence with certain cannabinoids (dronabinol) suggests a modest analgesic effect of dronabinol on cancer pain.
Cachexia	The anorexia/cachexia syndrome is the result of weight loss (caused by changes in taste, lack of hunger) and increased energy metabolism; cannabis use has been associated with an increase in appetite and weight gain, leading to examination of its therapeutic effect on cancer and HIV-associated anorexia/cachexia.
	Results from systematic review indicate low efficacy for the use of cannabis for enhancing appetite and weight gain in HIV and cancer.
Nausea and vomiting	Results from a systematic review indicate that in the setting of chemotherapy-induced nausea and vomiting, oral cannabinoids (nabilone and dronabinol) are effective antiemetics.
	Long-term ( $\approx 6$ –7 y) daily and weekly cannabis use has been associated with hyperemesis (ie, cannabis hyperemesis syndrome). Mechanisms may include downregulation of CB <sub>1</sub> receptors and a decrease in gastric emptying.
Multiple sclerosis spasticity	Improvements in central pain with cannabis-based medicine and dronabinol vs placebo.
	Reductions in spasticity with cannabis-based medicines vs placebo.
Epilepsy (Dravet syndrome and Lennox-Gastaut syndrome)	Improvements in monthly motor seizures in an open-label, multicenter expanded-access program in subjects with severe childhood-onset, drug-resistant epilepsy.
	Double-blind, placebo-controlled RCT showed significant reduction in the frequency of convulsive seizures in the CBD group vs placebo in pediatric and young adult subjects with treatment-resistant Dravet syndrome.
	Double-blind, placebo-controlled RCT showed a significant reduction in the frequency of drop seizures in pediatric and adult subjects with treatment-resistant Lennox-Gastaut syndrome randomized to CBD as add-on therapy vs placebo.
	Meta-analysis of observational clinical studies on the treatment of refractory epilepsy with reported improvement in the frequency of seizures in subjects treated with CBD-rich extracts and purified CBD.
Possible (moderate evidence)	
Reduction in long-term use of opioids and opiate withdrawal	Although preclinical and case studies suggest an opioid-sparing effect of certain cannabinoids, epidemiological and clinical studies with oral THC are mixed.
	Observational studies suggest an association between US states with laws permitting access to cannabis (for medical and nonmedical purposes) and lowered rates of prescribed opioids and opioid-associated mortality.
	Evidence from observational studies suggests that cannabis use could help alleviate opioid withdrawal symptoms, but there is insufficient clinical evidence from which to draw any reliable conclusions.
Dystonia	Evidence from limited preclinical studies suggests that a synthetic CB <sub>1</sub> and CB <sub>2</sub> receptor agonist may alleviate dystonia-like symptoms and that CBD delays dystonia progression.
	Evidence from a limited number of case studies and small placebo-controlled or open-label clinical trials suggests improvement in symptoms of dystonia with inhaled cannabis, mixed effects of oral THC, improvement in symptoms of dystonia with oral CBD, and lack of effect of nabilone on symptoms of dystonia.
Glaucoma	Limited evidence from small clinical studies suggests that oral administration of THC reduces intraocular pressure and that oral administration of CBD may, in contrast, cause an increase in intraocular pressure.
	The American Glaucoma Society does not recommend.
Inconclusive evidence (no RCTs)	
Alzheimer disease	Preclinical studies suggest that THC and CBD may protect against excitotoxicity, oxidative stress, and inflammation in animal models of Alzheimer disease.
	Limited case, clinical, and observational studies suggest that oral THC and nabilone are associated with improvement in a number of symptoms associated with Alzheimer disease (eg, nocturnal motor activity, disturbed behavior, sleep, agitation, and restiveness).
Anxiety and depression	A systematic review and meta-analysis of patient-reported medical cannabis use indicated that $\approx 50\%$ of patients report anxiety as a reason for using medical cannabis and 35% report depression as the reason.
	Small studies with adjunct functional neuroimaging in healthy individuals have demonstrated that CBD and dronabinol reduce anxiety related to its effects on activity in limbic and paralimbic brain areas.
	In data from a nationally representative sample of US adults (age $\geq 18$ y), cannabis use (ie, some use but less than once per month over the last 12 mo) was not significantly associated with the new occurrence of social anxiety disorder. However, more frequent use ( $\geq 1$ times per month) was associated with significantly increased odds of incident social anxiety disorder.

(Continued)

Table 2. Continued

Inconclusive evidence (no RCTs) Continued	
Antitumor effect	Preclinical studies suggest that certain cannabinoids (THC, CBD, CBG, CBC) often, but not always, block the growth of cancer cells in vitro and display a variety of antineoplastic effects in vivo, but typically at very high doses that would not be seen clinically.
	Although limited evidence from 1 observational study suggests that patients with cancer use cannabis to alleviate symptoms associated with cancer (eg, chemosensory alterations, weight loss, depression, pain), there has been only 1 limited clinical study in patients with glioblastoma multiforme, which reported that intratumor injection of high doses of THC did not improve patient survival beyond that seen with conventional chemotherapeutic agents.
Inflammatory bowel diseases (Crohn disease, ulcerative colitis)	Preclinical studies in animal models of inflammatory bowel disease suggest that certain cannabinoids (synthetic CB <sub>1</sub> and CB <sub>2</sub> receptor agonists, THC, CBD, CBG, CBC, whole-plant cannabis extract) may limit intestinal inflammation and disease severity to varying degrees.
	A very limited number of small clinical studies of patients with inflammatory bowel disease who failed conventional treatments reported improvement in a number of inflammatory bowel disease–associated symptoms with smoked cannabis.
Heart failure	In retrospective propensity-matched analysis of 161 000 patients with heart failure, cannabis use was associated with a lower risk for death while the patient was hospitalized with acute heart failure (OR, 0.197 [95% CI, 0.046–0.833]), shorter mean hospital stay (4.2 vs 4.8 d, respectively; <i>P</i> =0.004), and lower mean hospital costs (\$43,800 vs \$50,900, respectively; <i>P</i> =0.039) compared with nonusers. However, these data are retrospective and observational and have not been peer reviewed.
Hepatitis C	Preclinical studies suggest that CB <sub>1</sub> receptor activation is detrimental in liver diseases (eg, promotes steatosis, fibrosis), whereas CB <sub>2</sub> receptor activation appears to have some beneficial effects.
	In patients with ongoing chronic hepatitis C, daily cannabis use has been shown to be a predictor of steatosis severity.
	Survey and case reports suggest improvement in symptoms of nausea and reduced weight loss.
Ischemia/reperfusion injury	Preclinical studies suggest that CBD, THCV, and ultralow doses of THC may have some protective effects against ischemia/reperfusion injury related to the anti-inflammatory properties mediated by the CB <sub>2</sub> receptor.
Huntington disease	Preclinical studies report mixed results with THC on Huntington disease–like symptoms.
	Limited evidence from case studies and small clinical trials is mixed and suggests a lack of effect with CBD and a limited improvement in Huntington disease symptoms with smoked cannabis.
Metabolic syndrome, obesity, diabetes mellitus	Preclinical studies suggest that acute CB <sub>1</sub> receptor activation results in increased fat synthesis and storage, whereas chronic CB <sub>1</sub> receptor activation (or CB <sub>1</sub> receptor antagonism) results in weight loss and improvement in a variety of metabolic indicators.
	Observational studies suggest an association between long-term cannabis use and an improved metabolic profile, and preclinical and very limited clinical evidence suggests a potential beneficial effect of THCV on glycemic control (in patients with type 2 diabetes mellitus).
Parkinson disease	Limited preclinical, case, clinical, and observational studies of certain cannabinoids for symptoms of Parkinson disease are mixed.
	One observational study suggests improvement in symptoms with smoked cannabis; another clinical study of an oral cannabis extract (THC/CBD) and a clinical study of CBD suggest no improvement in symptoms.
Sleep	Human experimental data suggest that cannabis and THC have a dose-dependent effect on sleep: Low doses appear to decrease sleep-onset latency and increase slow-wave sleep and total sleep time, whereas high doses appear to cause sleep disturbances.
	Clinical studies suggest that cannabis, nabilone, and dronabinol may improve sleep in patients with disturbances in sleep associated with certain chronic disease states.

CB indicates cannabinoid; CB<sub>1</sub>, cannabinoid receptor subtype 1; CB<sub>2</sub>, cannabinoid receptor subtype 2; CBC, cannabichromene; CBD, cannabidiol; CBG, cannabigerol; OR, odds ratio; RCT, randomized controlled trial; THC, Δ-9-tetrahydrocannabinol; and THCV, tetrahydrocannabivarin.

Data derived from Health Canada,<sup>5</sup> National Academies of Sciences, Engineering, and Medicine,<sup>12</sup> Volko et al,<sup>13</sup> Segura et al,<sup>17</sup> and Wu et al.<sup>18</sup>

small quantities at a time with sufficient time between doses. Administration with a high-fat meal significantly increases the absorption of oral cannabinoid and may exacerbate these effects.<sup>5,7,8</sup>

## POTENTIAL AND KNOWN BENEFITS

Table 2 summarizes the potential and known effects of cannabis use, which include modulation of the

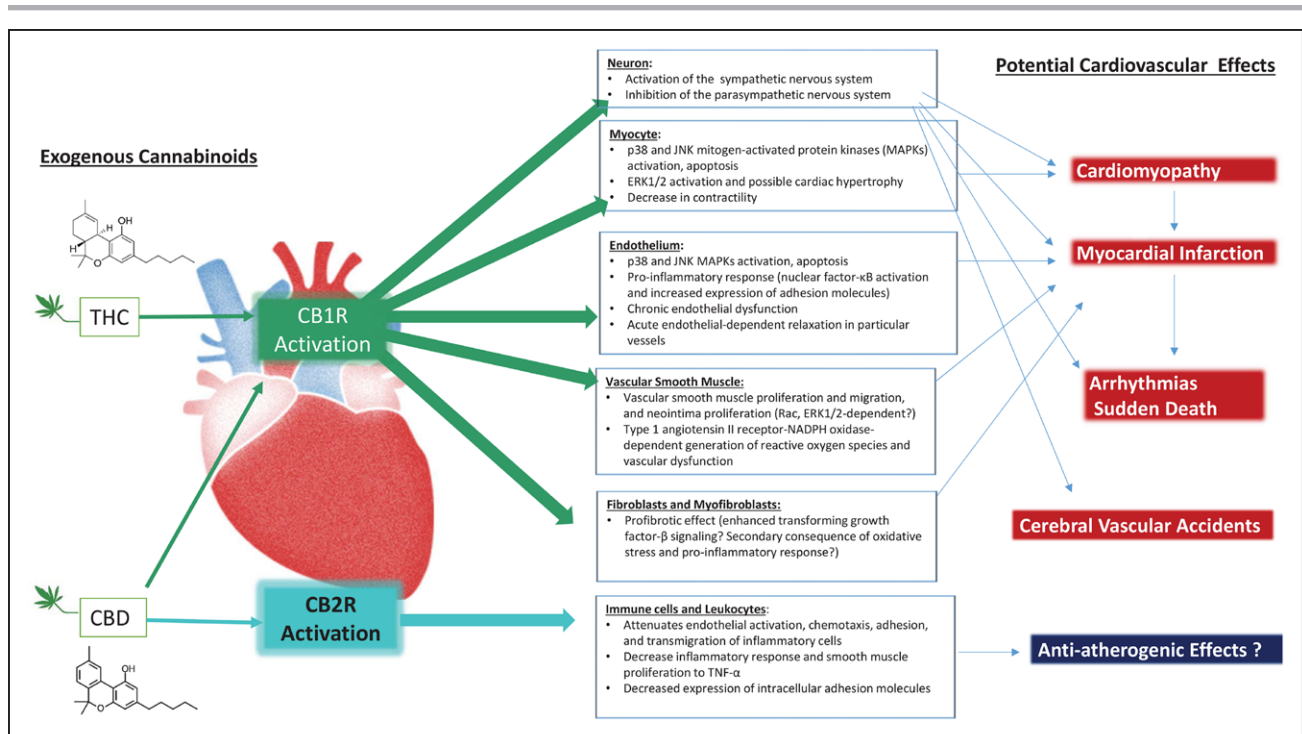
processes of pain, cachexia, nausea/vomiting, and spasticity. There are no well-documented cardiovascular benefits of cannabis.<sup>5,12,13,17,18</sup>

## SAFETY CONSIDERATIONS

### Acute Effects

In the short term, cannabis consumption has been associated with euphoria, as well as cardiovascular (eg,





**Figure 5.** Effects of exogenous cannabinoids on the cardiovascular system.

CB<sub>1</sub>R indicates cannabinoid receptor subtype 1; CB<sub>2</sub>R, cannabinoid receptor subtype 2; CBD, cannabinoid; ERK, extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; THC,  $\Delta$ -9-tetrahydrocannabinol; TNF $\alpha$ , tumor necrosis factor- $\alpha$ ; and ?, questionable. Data derived from DeFilippis et al,<sup>20</sup> Pacher et al,<sup>21</sup> and Rezkalla and Kloner.<sup>22</sup>

tachycardia, premature ventricular contractions, atrial fibrillation, and ventricular arrhythmia), bronchopulmonary (bronchitis), ocular (blurred vision), psychological (altered judgment, dysphoria, and anxiety; paranoia and psychosis with higher doses), and psychomotor (impaired motor coordination) effects.<sup>5,12,13,19</sup> Because of the increased systemic absorption, slower time to onset, and peak effect compared with smoked cannabis, edible consumption appears more likely to result in adverse effects, particularly psychiatric and cardiovascular, prompting acute medical care.<sup>5</sup>

### Cardiac- and Vascular-Specific Effects

Cannabis has multiple effects on the cardiovascular system (Figure 5).<sup>20–22</sup> Tetrahydrocannabinol stimulates the sympathetic nervous system while inhibiting the parasympathetic nervous system; increases heart rate, myocardial oxygen demand, supine blood pressure, and platelet activation; and is associated with endothelial dysfunction and oxidative stress. In contrast, CBD may reduce heart rate and blood pressure, improves vasodilation in models of endothelial dysfunction, and reduces inflammation and vascular hyperpermeability in diabetic models.<sup>20–22</sup> Compared with smoking tobacco, smoking and inhaling cannabis regardless of THC content has been shown to increase the concentrations of blood carboxyhemoglobin 5-fold with a 3-fold increase in tar.<sup>23</sup> Carbon monoxide intoxication, which varies depending on the mode of

administration, depth of inspiration, and length of breath holding, has been associated with endothelial dysfunction, increased oxidation of lipoproteins, and impaired oxygen binding, as well as various cardiac clinical presentations such as cardiomyopathy, angina, acute myocardial infarction (AMI), arrhythmia, cardiac failure, pulmonary edema, cardiogenic shock, and sudden death.<sup>24</sup>

A key concern is whether cannabis triggers or potentiates major adverse cardiovascular events such as AMI and arrhythmias, as well as its impact on cardiovascular risk factors.<sup>20</sup> Unfortunately, most of the available data are short term, observational, and retrospective in nature; lack exposure determination; exhibit recall bias; include minimal cannabis exposure with no dose or product standardization; and typically evaluate low-risk cohorts. In addition, many epidemiological studies may be confounded by factors associated with access to health care and other adverse health behaviors such as tobacco use.<sup>20</sup> Finally, because the concentration of THC in cannabis has been increasing over the past several years, earlier studies may not be relevant to the present experience.<sup>25</sup>

In the current literature, summarized in Table 3, few data from rigorous prospective cohort studies have been published.<sup>19,26–49</sup> In the CARDIA study (Coronary Risk Development in Young Adults), which included adults 18 to 30 years of age followed up for >25 years, 84% reported history of cannabis use.<sup>29</sup> Cumulative lifetime and recent cannabis use did not show an association with incidence of cardiovascular disease,

coronary heart disease, or cardiac mortality. However, several studies have shown signals for adverse cardiac outcomes, mostly for hospitalized patients with inherent selection bias.<sup>28,31–36,40,41,43,45,49</sup> In the case of studies including only participants who were hospitalized, only a fraction of the overall population who experienced a health outcome were analyzed. Of note, when hospitalized patients with cannabis use serve as cases and those without cannabis use serve as controls, a high probability of selection bias exists. Thus, uncertainty exists for cannabis use as a cause for hospitalization.

In states where cannabis has been legalized, an increase in hospitalizations and emergency department visits for AMI and cannabis-associated adverse effects has been observed.<sup>26,48</sup> Case reports and observational studies also support a temporal relationship between cannabis use and atrial fibrillation, although conflicting, as well as AMI occurring mostly in young men without ischemic disease.<sup>20,22,36</sup> In a recent analysis of the National Inpatient Sample database from 2010 to 2014, Desai et al<sup>36</sup> identified 2 459 856 hospitalized cannabis users, of whom 66 179 (2.7%) experienced arrhythmias, mostly commonly atrial fibrillation. There is also the matter of concomitant use of tobacco or other drugs among marijuana users, which is inadequately accounted for in data collection and statistical adjustment. Among ever tobacco users, cannabis use was associated with an increase in abdominal and coronary artery calcification.<sup>46</sup>

Cannabis exposure has been associated with an increased risk for cerebrovascular accidents.<sup>20</sup> In an retrospective evaluation of the Personality and Total Health Through Life study, which included participants 20 to 24 years of age (n=2404), 40 to 44 years of age (n=2530), and 60 to 64 years of age (n=2551) in 1999 to 2000, 2000 to 2001, and 2001 to 2002, respectively, Hemachandra et al<sup>38</sup> found a 3.3-fold risk of stroke/transient ischemic attack in cannabis users within the past year. However, this elevated risk was specific only to participants who used cannabis weekly or more often, not those who used cannabis less often.

Although controversial, smoking cannabis has also been associated with peripheral arteriopathy or cannabis arteritis resembling thromboangiitis obliterans (eg, Buerger disease). More than 20% of lower extremity arteriopathy in young adults may be caused by such vasculitis; however, these estimates may be confounded because 97% of those who smoke cannabis also smoke tobacco.<sup>50</sup> Although the pathogenesis is poorly understood, a synergistic interaction between tobacco smoke and cannabis may exist, contributing to some patients developing a peripheral nonatheromatous arteriopathy.<sup>50,51</sup> Nonetheless, cannabis arteritis should be considered in young adults <50 years of age presenting with peripheral vascular disease.

Overall, evidence is still inconclusive for cannabis use and adverse cardiovascular outcomes, resulting in an urgent need for carefully designed, prospective short- and long-term studies. Ideally, controlled trials of various forms and routes of administration would be tested, but rigorous study of recreational drugs remains a challenge.

## Smoking and Vaping Administration Concerns

Cannabis smoke contains many of the same carcinogens and mutagens as tobacco smoke.<sup>5,12,20</sup> In addition, cannabis smoking is associated with a variety of histopathological changes in respiratory tissues, similar to those in tobacco smokers. However, limited and conflicting evidence from epidemiological studies has not shown a robust and consistent association between cannabis use and various types of cancer.<sup>52</sup> Low-strength evidence suggests that smoking marijuana long term may be associated with the development of testicular cancer. Findings for lung cancer are mixed and confounded by few marijuana-only smokers, poor exposure assessment, and inadequate adjustment within studies.<sup>52</sup> The association between long-term heavy cannabis smoking (without tobacco) and chronic obstructive pulmonary disease remains unclear; however, chronic bronchitis has been reported.<sup>5,12</sup>

Finally, with the worldwide pandemic of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2, tobacco smokers appear to be more likely than nonsmokers to have severe symptoms of COVID-19 (relative risk, 1.4 [95% CI, 0.98–2.00]) and much more likely to be admitted to an intensive care unit, to need mechanical ventilation, or to die (relative risk, 2.4 [95% CI, 1.43–4.04]).<sup>53</sup> Whether this risk also extends to smoking or vaping cannabis is not known.

## Impurities

In June 2018, the US Food and Drug Administration issued a warning about health emergencies associated with the consumption of synthetic illicit products laced with brodifacoum, an anticoagulant compound found in rat poison.<sup>54</sup> As of February 18, 2020, a total of 2807 hospitalized patients with e-cigarette or vaping use-associated lung injuries or deaths have been reported to the Centers for Disease Control and Prevention from all 50 states, the District of Columbia, and 2 US territories (Puerto Rico and US Virgin Islands). Sixty-eight deaths have been confirmed in 29 states and the District of Columbia.<sup>55</sup> Most patients attest to a history of using THC-containing products. On the basis of national and state findings, the Centers for Disease Control and Prevention suggests that products containing THC, particularly those on the black market or from other informal sources (eg, friends, family members,

**Table 3. Seminal Studies on the Impact of Cannabis on Cardiovascular Health**

Author	Year	Type of Study	No. of Patients	Results
Aboutk and Adams <sup>26</sup>	2018	US National Vital Statistics System for 1990–2014	Millions	Cardiac death rates increased 2.3% in men and 1.3% in women since legalization of medical cannabis.
Adegbalet al <sup>27</sup>	2018	Healthcare Cost and Utilization Project–National Inpatient Sample	≈4 million patients with heart failure	Cannabis users were less likely to have atrial fibrillation (19% vs 21%) compared with nonusers.
Alshaarawy et al <sup>28</sup>	2016	US National Health and Nutrition Examination Surveys (2005–2012)	12 426	Cannabis use was associated with an increase in systolic but not diastolic blood pressure ( $\beta=1.6$ [95% CI, 0.6–2.7]).
Auer et al <sup>29</sup>	2018	US-based CARDIA	3498	Among ever tobacco smokers, marijuana exposure increased AAC and CAC scores, whereas among those who never smoked tobacco, marijuana exposure was not associated with changes in AAC or CAC scores.
Bancks et al <sup>30</sup>	2015	CARDIA	>3000	Cannabis use in young adults is associated with increased risk of prediabetes (but not diabetes mellitus) by middle adulthood.
Chami and Kim <sup>31</sup>	2019	Aggregate multi-institutional database (Explorys, Inc) 2011–2016	292 770 patients with history of cannabis use; >10 million control subjects	3-y cumulative incidence of AMI was higher in cannabis abuse group vs controls (1.37% vs 0.54%; RR, 2.53 [95% CI, 2.45–2.61]).
DeFilippis et al <sup>32</sup>	2018	Young adults with MI from 2 academic hospitals (2000–2016)	2097	Adjusted HR for all-cause mortality was 1.99 and 2.22 for cardiovascular mortality among cocaine and marijuana users. Patients using cocaine or marijuana had lower rates of diabetes mellitus and hyperglycemia compared with nonusers but higher tobacco use.
Desai et al <sup>33</sup>	2019	National Inpatient Sample (2007–2014)	>52 million hospitalizations including cannabis (but not other substance abuse) users	Frequency of admissions in young adults for AMI was greater in cannabis users vs nonusers (0.23% vs 0.14%); frequency of arrhythmia and stroke was greater in cannabis users; and frequency of venous thromboembolic events was lower in cannabis users.
Desai et al <sup>34</sup>	2017	National Inpatient Sample (2010–2014) in patients with AMI	>2.4 million patients with AMI	35 771 patients had a history of cannabis use. Patients with AMI using cannabis tended to be younger, male, and black and had lower mortality rates. Cannabis use was a significant independent risk factor for AMI (adjusted OR, 1.079 [95% CI, 1.065–1.093]). Increase in AMI prevalence and mortality was seen in marijuana users from 2010–2014.
Desai et al <sup>35</sup>	2018	National Inpatient Sample (2010–2014)	465 959 patients hospitalized with history of recreational cannabis use	Among hospitalizations of patients with history of cannabis use, 1.2% were for AMI, 1% were for congestive heart failure, and 0.8% were for arrhythmias. Independent predictors of death included coagulopathy, AMI, coronary atherosclerosis, peripheral vascular disease, and others. Increasing rates of cardiovascular and cerebrovascular events from 2010–2014 included AMI (1.4%–1.8%), congestive heart failure, and arrhythmia.
Desai et al <sup>36</sup>	2018	National Inpatient Sample (2010–2014)	2 459 856 hospitalized marijuana users	2.7% of recreational marijuana users developed arrhythmia with a steadily increasing trend from 2010 through 2014; all-cause in-hospital mortality in marijuana users with arrhythmias increased from 3.7% in 2010 to 4.4% in 2014.
Frost et al <sup>37</sup>	2013	Determinants of MI Onset Study, National Death Index	3886 patients with MI	Compared with nonusers, the mortality rate was 29% higher among cannabis users, but this did not reach statistical significance (95% CI, 0.81–2.05; $P=0.28$ ).

(Continued)

Table 3. Continued

Author	Year	Type of Study	No. of Patients	Results
Hemachandra et al <sup>38</sup>	2016	Population survey from the PATH Through Life study (1999–2002)	20–24 y (n=2383), 40–44 y (n=2525), and 60–64 y (n=2547)	Cannabis users (n=1043) with use in the past year had 3.3 times the rate of stroke/TIA (95% CI, 1.8–6.3; $P<0.001$ ); after adjustment for covariates related to stroke, including tobacco smoking, the IRR dropped to 2.3 (95% CI, 1.1–4.5); stroke/TIA was found in those who used cannabis weekly or more often (IRR, 4.7 [95% CI, 2.1–10.7]) with no elevation among participants who used cannabis less often.
Jouanjus et al <sup>39</sup>	2014	French Addictovigilance Network (2006–2010)	1979 adverse reports related to cannabis use	35 adverse reports were cardiovascular. The percent of cannabis-related cardiovascular events rose from 1.1% in 2006 to 3.6% in 2010 of all cannabis-related reports.
Johnson-Sasso et al <sup>40</sup>	2018	Hospital records from 8 states (1994–2013)	>1.2 million patients with AMI	3854 patients with AMI reported cannabis use ( $\approx 0.3\%$ ). Incidence of AMI was higher in the cannabis group <50 y old vs nonusers (54% vs 20%; $P<0.001$ ). Primary outcome (death, intra-aortic balloon pump placement, mechanical ventilation, cardiac arrest, shock) was not associated with cannabis use. Lower mortality rate was seen among cannabis users (OR, 0.79).
Kalla et al <sup>41</sup>	2018	National Inpatient Sample (2009–2010)	>316 000, 18–55 y of age	With multivariate regression analysis, cannabis use was an independent predictor of heart failure (OR, 1.1) and stroke (OR, 1.24).
Lorenz et al <sup>42</sup>	2017	Multicenter AIDS Cohort Study (1990–2010)	558 HIV-positive men	Long-term heavy cannabis use was independently associated with increased cardiovascular events in men 40–60 y of age.
Mittleman et al <sup>43</sup>	2001	Determinants of Myocardial Infarction Onset Study (case-crossover study design)	3882 patients with AMI	Risk of MI onset was increased 4.8 times over baseline in the 60 min after use of cannabis. Cannabis users more likely to be men, cigarette smokers, and obese.
Monte et al <sup>19</sup>	2019	Large urban academic hospital in Colorado (2012–2016)	9973 adult ED visits for cannabis use	Patients using edible cannabis who visited the ED were more likely to show cardiovascular symptoms (8%) vs those who inhaled cannabis (3%). Edibles also more likely to be associated with acute psychiatric symptoms and intoxication. Inhaled cannabis was more frequently associated with cannabinoid hyperemesis syndrome. Cannabis-related visits increased from 2012–2016.
Patel et al <sup>44</sup>	2019	Systematic review of case reports, case series	62 patients with AMI and cannabis use	Mean age of 28 y. Male predominance. Onset of AMI within 5 h of last use. Normal coronary angiograms in 37% of cases. Left anterior descending coronary was occluded in 42% of angiograms.
Patel et al <sup>45</sup>	2018	Nationwide Inpatient Sample (2010–2014)	379 843 patients with primary diagnosis of AMI	3.3% of patients had a codiagnosis of cannabis-use disorder. Admissions for AMI among cannabis users increased by 32% ( $P=0.001$ ) over 5 y. Average age of cannabis users with AMI was 41 y. AMI was predominant in male cannabis users, but a 38% increase in prevalence was seen in female users from 2010–2014.
Reis et al <sup>46</sup>	2017	CARDIA study, 1985–1986 baseline	5113 adults 18–30 y of age followed up for >25 y	84% reported history of cannabis use. Cumulative lifetime and recent cannabis use did not show an association with incidence of cardiovascular disease, stroke or TIA, coronary heart disease, or cardiac mortality.
Richards et al <sup>47</sup>	2019	Systematic review of 85 studies, case reports, case series	541 581 adults	Of 33 studies evaluated, 28 suggested an increased risk of both acute coronary syndrome and chronic cardiovascular disease from cannabis use; of the 51 case series/reports with 62 subjects, 21 cases (34%) had concomitant cardiomyopathy and 14 deaths (23%) were attributed to acute coronary syndrome associated with cannabis use.

(Continued)

Table 3. Continued

Author	Year	Type of Study	No. of Patients	Results
Rodondi et al <sup>48</sup>	2006	CARDIA study	3617 with 15 y of longitudinal data	38% reported ever using cannabis. Cannabis use was associated with male sex, tobacco use, illicit drug use, higher caloric intake, alcohol intake, systolic blood pressure (113–117 mmHg), and higher triglyceride levels. Cannabis use was not associated with higher BMI or lipid or glucose levels. However, in multivariate analysis, cannabis use was not associated with higher systolic blood pressure or triglycerides.
Wang et al <sup>49</sup>	2017	Colorado Hospital Association hospitalizations and ED visits (2000–2015) and regional Poison Center data (2000–2015)	>7 million	0.3% of hospitalizations had cannabis-related billing codes. Billing codes for cannabis-related hospitalizations increased from 274/100 000 hospitalizations in 2000 to 593/100 000 in 2015 (2 y after cannabis legalization); ED visits for cannabis increased from 313/100 000 in 2011 to 478/100 000 in 2015. Calls to Poison Centers increased after medical and recreational cannabis legalization.

AAC indicates abdominal aortic calcium; AMI, acute myocardial infarction; BMI, body mass index; CAC, Coronary Artery Calcium; CARDIA, Coronary Risk Development in Young Adults; ED, emergency department; HR, hazard ratio; IRR, incidence rate ratio; MI, myocardial infarction; OR, odds ratio; PATH, Personality and Total Health; RR, relative risk; and TIA, transient ischemic attack.

illicit dealers), are linked to most of the cases and play a major role; however, the role of nicotine-containing products cannot be excluded.<sup>56</sup> Recently, the Centers for Disease Control and Prevention identified vitamin E acetate, often used as an oil-based solvent in THC and other vaping products, as a possible cause for e-cigarette, or vaping, product use–associated lung injury.<sup>56</sup> However, these findings are based on a relatively small number of tissue samples. Nonetheless, on the basis of these findings, cannabis vaping should be avoided.

In addition, over-the-counter topical CBD products sold in pharmacies do not fall under the US Food and Drug Administration regulatory oversight guidance, review, and inspection and, within that, the Good Manufacturing Practice regulations. Thus, the potential exists for these products to contain impurities such as heavy metals, herbicides, pesticides, and fungicides.<sup>56</sup>

### Chronic Side Effects

With continued long-term use, tolerance will develop as a result of reduced availability of the cannabinoid receptors, principally the CB<sub>1</sub> receptor.<sup>20</sup> Long-term users may experience a withdrawal syndrome when cannabis is suddenly stopped, the dose is decreased, or the formulation is changed. Signs and symptoms consist of anger, anxiety, restlessness, irritability, depressed mood, disturbed sleep, strange dreams, decreased appetite, weight loss, headache, and night sweats. These symptoms typically begin a few days after cannabis cessation or a reduction in use or dose, with symptoms peaking after ≈10 days and ending after 30 days.<sup>5,12</sup> Long-term, heavy (THC-predominant) cannabis use is associated with an increased risk of hyperemesis syndrome characterized by prodromal symptoms of abdominal

discomfort and nausea leading to intractable vomiting. Significant evidence from preclinical, clinical, and epidemiological studies supports an association between cannabis (especially THC-predominant cannabis) and an increased risk of psychosis and schizophrenia, particularly in individuals with a predisposition to such disorders and those with initial use early in adolescence.<sup>5,12</sup>

### Addiction Considerations

Cannabis use has addictive potential and is associated with the development of cannabis use disorder (CUD).<sup>57,58</sup> Addiction to cannabis has been reported in ≈9% of users, 17% of those who begin use in adolescence, and 25% to 50% of those who are daily users. Similar to other substance use disorders, individuals with CUD display symptoms related to impaired control over consumption and physical dependence. Using data from the National Epidemiological Survey on Alcohol and Related Conditions, Hasin et al<sup>58</sup> reported that 3 of 10 past-year cannabis users met the criteria for CUD and that the 30% prevalence of CUD was greater than that for alcohol use disorder (17.5%). According to epidemiological studies, risk factors for CUD include higher rates of edible consumption and vaping, higher THC potency and lower CBD content, and younger age at initiation.<sup>59,60</sup> However, the prevalence of CUD may be higher because the current estimates are based on self-reported survey and interview data and may use the older *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. Hence, the CUD definition used may not include cravings or cannabis withdrawal.<sup>60</sup> Although limited data exist, regular cannabis use, especially in adolescence, may serve as a gateway to the use of illicit drugs, harmful alcohol consumption,

and nicotine dependence in young adulthood.<sup>61–63</sup> Furthermore, this relationship may be bidirectional, particularly in adolescents and young adults.<sup>63</sup>

## Drug-Drug Interactions

Drug interactions with cannabis can be expected to vary considerably in clinical significance 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 predicated by the pharmacokinetics of the cannabinoid and potential concomitant drug (Table 1).<sup>5,20,64,65</sup> In vitro experiments suggest that THC has the potential to inhibit CYP (cytochrome P450) 3A4/4, CYP2C9, CYP2C19, and CYP2D6, whereas CBD also has the potential to inhibit CYP3A4/5, CYP2C19, CYP2D6, and CYP1A2.<sup>5</sup> Tetrahydrocannabinol can induce CYP1A2, particularly with smoked cannabis. Preclinical and animal data suggest that cannabinoids can inhibit systemic transport proteins such as BCRP (breast cancer-resistant protein) and p-glycoprotein activity, decrease protein expression of P-glycoprotein, and increase protein expression of BCRP.<sup>5,64,65</sup> However, the concentrations used greatly exceeded systemic concentrations likely observed in humans, suggesting that systemic transporter-mediated drug interaction with cannabinoids is unlikely.<sup>5</sup> Pharmacokinetic studies with Epidiolex suggest that CBD is not a substrate or inhibitor of P-glycoprotein or OATPs (organic anion transport proteins) such as OATP1B1 or OATP1B2 but is an inhibitor of UDP-glucuronosyltransferase 1A9 and 2B7.<sup>5</sup> Table 4 summarizes known and potential drug-drug interactions with both phytocannabinoids and synthetic cannabinoids.<sup>5,20,64,65</sup>

## CONSIDERATIONS IN SPECIAL POPULATIONS

### Young Adults

Excluding nicotine, cannabis is the most commonly used drug of abuse by adolescents worldwide. Early-onset use, typically defined as use starting before 16 to 18 years of age, has been associated with reports of poorer sustained attention, reduced overall or verbal intelligence quotient, and worse executive functioning.<sup>5,12,13</sup> Multiple studies using neuroimaging suggest that regular cannabis use during adolescence may lead to structural changes such as altered cortical gray matter development and reduced white matter myelination.<sup>5,12,13</sup> Although small observational studies in older adults have reported improvement in affective symptoms such as depression and anxiety with cannabis use, the effects in adolescents and young adults are less clear. A recent meta-analysis of 11 studies including 23317 individuals assessed cannabis use and depression at different time points from adolescence to

young adulthood.<sup>66</sup> The odds of developing depression (odds ratio [OR], 1.37 [95% CI, 1.16–1.62]), suicidal ideation (OR, 1.5 [95% CI, 1.11–2.03]), and suicide attempt (OR, 3.46 [95% CI, 1.53–7.84]) were higher for cannabis users compared with nonusers. In a European case-control study, daily cannabis use has been associated with increased odds of psychotic disorder compared with never users (adjusted OR, 3.2 [95% CI, 2.2–4.1]), increasing to nearly 5 times increased odds for daily use of high-potency types of cannabis (THC  $\geq$ 10%) compared with low-potency cannabis (THC  $<$ 10%; adjusted OR, 3.2 [95% CI, 3.0–16.1]). However, this study did not account for genetic and environmental factors.<sup>67</sup> Finally, in an analysis from the Behavioral Risk Factor Surveillance System, Parekh et al<sup>68</sup> found a significantly higher odds of stroke in young marijuana users (age, 18–44 years; adjusted OR, 1.82 [95% CI, 1.08–3.10]) compared with nonusers, with even greater odds among frequent users ( $>$ 10 d/mo; adjusted OR, 2.45 [95% CI, 1.31–4.60]).

### Pregnant Women

Tetrahydrocannabinol can enter the fetal brain through the maternal blood flow, leading to disruption in the endogenous endocannabinoid system in both the fetus and the mother.<sup>69</sup> A study that evaluated state-level prevalence estimates of prenatal and early postnatal cannabis use in a state with legalized medical and recreational cannabis showed that the self-reported prevalence of cannabis use at any time during pregnancy was 5.7 $\pm$ 0.5% and the prevalence of early postnatal cannabis use among women who breastfed was 5.0% (95% CI, 4.1–6.2). Prenatal cannabis use was associated with a 50% increased likelihood of low birth weight independently of maternal age, race/ethnicity, level of education, and tobacco use during pregnancy (OR, 1.5 [95% CI, 1.1–2.1];  $P=0.02$ ).<sup>70</sup> A systematic review and meta-analysis of prenatal exposure to cannabis and maternal and child health outcomes demonstrated that women who used cannabis during pregnancy had an increased odds of anemia (OR, 1.36 [95% CI, 1.10–1.69]) compared with women who did not use cannabis during pregnancy. Similarly, compared with infants whose mothers did not use cannabis during pregnancy, infants exposed to cannabis in utero had a higher risk for low birth weight (OR, 1.77 [95% CI, 1.04–3.01]; pooled mean difference for birth weight, 109.42 g [95% CI, 38.72–180.12, respectively]).<sup>71</sup> Tetrahydrocannabinol has also been found in breast milk for up to 6 days after the last recorded use, potentially affecting the newborn's brain development and resulting in hyperactivity, poor cognitive function, and other long-term consequences.<sup>69</sup>

According to a National Academies of Science report, a lack of definitive evidence has resulted in insufficient information on the health implications of cannabis use,

**Table 4. Summary of Potential Drug-Drug Interactions With Cannabis**

	CBD Effects	THC Effects	Clinical Intervention	Examples of Potentially Interacting Drugs/Substrates
Phase 1 metabolism				
CYP1A2				
Substrate	↑ Substrate concentration	↓ Substrate concentration	Monitor for signs of either therapeutic failure or adverse effects; consider modifying substrate dose on the basis of cannabis preparation	Chlorpromazine, clozapine, cyclobenzaprine, duloxetine, haloperidol, naproxen, olanzapine, propafenone,* theophylline, tricyclic antidepressants
CYP2C9				
Substrates	↑ Substrate concentration	Conflicting data (↓ Substrate concentration)	Consider decreasing dose of substrate; monitor INR for warfarin within 3 d; monitor free phenytoin levels	Buprenorphine, fluvastatin,* celecoxib, losartan,* naproxen, phenobarbital, montelukast, phenytoin, rosiglitazone, rosuvastatin,* sulfonyleureas, valsartan,* warfarin*
CYP2D6				
Substrates	↑ Substrate concentration	↑ Substrate concentration	Consider decreasing dose of substrate; monitor for adverse reactions; monitor QTc for antidepressants and antiarrhythmics; monitor free valproate levels	Antidepressants (eg, amitriptyline, citalopram, nortriptyline), antipsychotics (eg, clozapine, haloperidol, risperidone), antiarrhythmic* (eg, amiodarone,* dronedarone,* flecainide,* propafenone*), β-blockers* (eg, carvedilol,* metoprolol*), opioids (eg, codeine, morphine, tramadol), valproate†
Inhibitors	↑ CBD concentration	↑ THC concentration	Consider decreasing dose of cannabis product	Desipramine, paroxetine, quinidine,* ritonavir, sertraline
CYP3A4				
Substrates	↑ Substrate concentration	↑ Substrate concentration	Consider decreasing dose of substrate	Benzodiazepines, dihydropyridine calcium channel blockers* (eg, amlodipine,* felodipine*), CNIs* (eg, cyclosporine,*† tacrolimus*†), PDE5 inhibitors* (eg, sildenafil*), propafenone,* statins* (except pravastatin* and rosuvastatin*), zaleplon, zopiclone, zolpidem
Inhibitors	↑ CBD concentration	↑ THC concentration	Consider decreasing dose of cannabis product	Antiarrhythmic* (eg, amiodarone,* dronedarone,* quinidine*), azole antifungals (eg, ketoconazole, itraconazole, posaconazole), nondihydropyridine* (eg, diltiazem,* verapamil*), macrolides (eg, clarithromycin, erythromycin), protease inhibitors (eg, ritonavir, indinavir, nelfinavir, saquinavir, telaprevir, atazanavir, boceprevir, lopinavir), tyrosine kinase inhibitors, valproate†
Inducers	↓ CBD concentration	↓ THC concentration	Consider increasing dose of cannabis product	Carbamazepine, cimetidine, phenytoin, phenobarbital, pioglitazone, rifampin, St. John's wort, topiramate
CYP2C19				
Substrates	↑ Substrate concentration	↑ Substrate concentration	Consider decreasing dose of substrate; monitor for adverse effects; for clopidogrel, consider using alternative antiplatelet; monitor free phenytoin levels	Antidepressants (eg, amitriptyline, citalopram, bupropion), antiseizure (eg, clobazam,‡ diazepam, phenytoin, phenobarbital, clopidogrel*), proton pump inhibitors (eg, omeprazole, pantoprazole)

(Continued)

Table 4. Continued

	CBD Effects	THC Effects	Clinical Intervention	Examples of Potentially Interacting Drugs/Substrates
(CYP2C19 Continued)				
Inhibitors	↑ CBD concentration	↑ THC concentration	Consider decreasing dose of cannabis product; monitor for adverse effects	Chloramphenicol, felbamate, fluoxetine, fluvoxamine, isoniazid, protease inhibitors (eg, ritonavir, indinavir, nelfinavir, saquinavir, telaprevir, atazanavir, boceprevir, lopinavir)
Inducers	↓ CBD concentration	↓ THC concentration	Consider increasing dose of cannabis product; monitor for adverse effects	Carbamazepine, ketoconazole,† phenytoin, phenobarbital, rifampin, rifampicin,‡ St. John's wort
Phase 2 metabolism				
UGT1A9				
Substrates	↑ Substrate concentration	No data	Consider decreasing dose of substrate; monitor for adverse effects	Acetaminophen, canagliflozin,* dabigatran,* dapagliflozin,* haloperidol, ibuprofen, irinotecan, mycophenolate mofetil,* propofol, regorafenib, sorafenib, valproic acid‡
UGT2B7				
Substrates	↑ Substrate concentration	No data	Consider decreasing dose of substrate; monitor for adverse effects	Carbamazepine, hydromorphone, ezetimibe,* ibuprofen, losartan,* lovastatin,* naproxen, simvastatin,* valproate‡

CBD indicates cannabidiol; CNI, calcineurin inhibitor; CYP, cytochrome P450; INR, international normalized ratio; PDE5, phosphodiesterase type 5; THC, Δ-9-tetrahydrocannabinol; and UGT, uridine 5'-diphospho-glucuronosyltransferase.

\*Cardiovascular medications.

†Based on observation studies or case reports.

‡Based on clinical studies or in vivo data.

Data derived from Health Canada,<sup>5</sup> DeFilippis et al,<sup>20</sup> Weinberger et al,<sup>62</sup> and Kristman-Valente et al.<sup>63</sup>

especially in vulnerable populations such as pregnant women.<sup>12</sup> The American College of Obstetricians and Gynecologists holds that women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use. Women reporting marijuana use should be counseled about concerns for potential adverse health consequences of continued use during pregnancy.<sup>72</sup> In 2018, the American Academy of Pediatrics recommended advising all adolescents and young women that if they become pregnant, marijuana should not be used during pregnancy.<sup>73</sup> In addition, because data are insufficient to assess the effects of exposure of infants to maternal cannabis use during breastfeeding, maternal cannabis use while breastfeeding is discouraged.

## Geriatric Population

Cannabis use has been suggested to be safe and effective for older populations seeking a reduction in neuropathic pain, improved quality of life, and decreased prescription drug use (including opioids).<sup>17,74</sup> In addition, benefits for patients with age-related diseases, including Parkinson and Alzheimer disease, have been reported (Table 2). However, there is a paucity of longitudinal data specific to the effects in an elderly/geriatric patient

population.<sup>75,76</sup> Cross-sectional analysis of national data from the 2012 to 2013 National Epidemiological Survey on Alcohol and Related Conditions indicates that adults ≥65 years of age had significantly lower rates of cannabis use compared with younger age groups. However, individuals in the group ≥50 years of age who had used cannabis in the past year had the greatest rates of mental disorders (33.2%), including anxiety, manic-depressive disorder, posttraumatic stress disorder, and bipolar disorder, compared with past users (26.5%) and never users (19.4%).<sup>77</sup> These findings may be driven by the strong positive association between major depressive episodes and self-medication in the general population.<sup>78,79</sup>

Interindividual variation exists for THC pharmacokinetics, but time to reach maximal concentration in older adults is similar to that in young adults.<sup>80</sup> However, pharmacodynamics in an older cohort may be altered, with smaller observed effects from a given dose compared with a younger cohort resulting from age-related impairments in G proteins and signaling pathways.<sup>81</sup> Administration route (eg, oral versus inhalation) may affect response to a given dose; the first-pass effect and hepatic blood flow/clearance in an older cohort may affect cannabinoid efficacy greatly.<sup>82</sup> Given the pervasiveness of polypharmacy in an aging population, the



potential for drug-drug interactions could be high, particularly with regard to anticoagulants, antidepressants, antipsychotics, antiarrhythmics, and statins (Table 4).<sup>20</sup>

### Transplantation Patients

Traditionally, most solid organ transplantation programs have recommended that patients with active drug or alcohol abuse not undergo transplantation. However, legislation has passed in at least 7 US states (California, Washington, Illinois, Arizona, Delaware, New Hampshire, and Maine) that explicitly forbids denial of transplantation listing on the basis of a patient's use of medical cannabis.<sup>83,84</sup> Data from a web-based survey designed to examine practice patterns of and attitudes of heart transplantation providers in 26 countries toward cannabis use revealed that the majority of respondents (64.4%) supported transplantation listing for patients who use legal medical cannabis.<sup>84</sup> However, 68.3% of providers require a documented period of abstinence before the patient is eligible for transplantation, including respondents from those states with laws prohibiting cannabis-using patients from being denied transplantation. Significantly fewer respondents (27.5%) supported transplantation listing for patients using legal recreational cannabis. There are unique risks in an immunocompromised patient because inhaled smoked or vaporized cannabis can expose the user to life-threatening pulmonary infections (most commonly *Aspergillosis*).<sup>85</sup> In addition, significant drug-drug interaction of exogenous cannabinoids with calcineurin inhibitors may exist, potentially leading to increased calcineurin inhibitor concentrations and toxicity (Table 4).

### Comorbid Cardiovascular Disease

Because cannabis consumption increases myocardial oxygen demand and decreases myocardial oxygen supply, patients with underlying ischemic disease could see an increase in angina, particularly when cannabis is smoked. Using data from the National Health and Nutrition Examination Survey from 2005 to 2016, DeFilippis et al<sup>20</sup> estimated that 2 million (2.3%) of the 89.6 million adults who reported marijuana use had cardiovascular disease. Observational studies have suggested that cannabis may be a trigger for AMI.<sup>86,87</sup> Recent data suggest that cannabis use is present in 6% of patients  $\leq 50$  years of age who present with AMI and is associated with worse all-cause and cardiovascular mortality.<sup>32</sup> This risk may be temporally related to the timing of cannabis use. In 3882 patients with AMI, Mittleman et al<sup>43</sup> found that 3% of patients smoked cannabis in the prior year. Of these patients, 37 had smoked within the previous 24 hours and 9 within 1 hour of AMI presentation. Smaller studies have shown a signal toward increased mortality in patients with coronary artery disease who use cannabis, although many of

these findings failed to reach statistical significance.<sup>37,87</sup> In patients with chronic stable angina, smoking a single cannabis cigarette decreased exercise time to angina by 48% compared with placebo.<sup>88</sup> However, in a study in patients with coronary artery disease and angina, cannabis use was associated with a decreased end-diastolic volume, stroke index, and ejection fraction without causing any change in end-systolic volume or cardiac index.<sup>89</sup> Other studies have linked cannabis use to a higher risk of cerebrovascular accident and heart failure. However, not all of those included had known cardiovascular disease.<sup>41,90</sup>

### Patients With Cardiac Risk Factors

Cross-sectional data indicate long-term (eg, years), continual cannabis use to be associated with an increased risk of metabolic syndrome compared with no use.<sup>91</sup> However, conflicting studies have suggested that compared with nonusers, those who use cannabis had a similar or reduced incidence of hyperglycemia, elevated fasting blood glucose, and diabetes mellitus, as well as a lower body mass index, total cholesterol, and low-density lipoprotein.<sup>92–98</sup> In young adults (18–44 years of age), compared with nonusers, the risk of stroke was higher among frequent marijuana users with concomitant combustible cigarette use (adjusted OR, 3.12 [95% CI, 1.40–6.97]) and e-cigarette use (adjusted OR, 2.63 [95% CI, 1.07–6.46]).<sup>68</sup> The limited longitudinal data and nature of recall bias in cross-sectional studies highlight the need for additional research; the present evidence for a link between health outcomes and the use of cannabis, especially in patients with cardiac risk factors, is insufficient.

## PATIENT EDUCATION AND CONSIDERATIONS

The decision to use cannabis, whether medicinal or recreational, should involve shared decision-making between provider and patient, highlighting state and federal laws, possible risks and benefits for various forms of administration, and adverse effects.<sup>99</sup> Because of the risk of contamination and adulteration, all cannabis products on the black or gray market, especially synthetic illicit cannabinoids, should be avoided. As with tobacco and nicotine products, smoked or vaporized cannabis is generally not recommended, especially in patients with respiratory diseases such as asthma or chronic obstructive pulmonary disease, and should be avoided in patients with severe liver disease because of the potential risk of fibrosis or steatorrhea.<sup>5</sup> Driving a car or operating heavy machinery should be avoided because blood THC concentrations of 2 to 5 ng/mL are associated with substantial driving impairment.<sup>100</sup> Likewise, when cannabis is used in combination with opioids, alcohol, or sedative/hypnotics, cross-tolerance and potentiated central nervous system

**Table 5. Future Needs and Specific Actions**

Need	Specific Action
Legal	Harmonize international, national, and regional laws; in the United States, this should start with removal of cannabis from Schedule 1 of the US Controlled Substances Act at the federal level to allow a more nuanced approach to marijuana legislation and regulation.
	Remove legal barriers to research funding and clinical trials.
	Create a supportive, robust public health infrastructure to address critical aspects of public health response, including surveillance, prevention, countermarketing, and public safety.
	Integrate marijuana into comprehensive tobacco control and prevention policy.
	Support laws and regulation that prevent cannabis use in minors.
	Integrate equity considerations into policy development of marijuana-related laws to ensure that racial and ethnic disparities are not further exacerbated. Jurisdictions will need to consider the removal or expungement of criminal records of existing offenders, age restrictions, juvenile offenses, and other legal implications and processes that may result from legalization or decriminalization of marijuana.
	Support comprehensive FDA regulation of CBD products. Standardize manufacturing and labeling to quantify THC and CBD content; this should include over-the-counter topical CBD products.
	Require packaging to convey a meaningful unit of consumption (following alcohol ABV example), as well as clear differentiation of cannabis products from food.
	Regulate retail sales, marketing, and promotion through national guidelines paired with local control.
	Apply taxes in ways that moderate use and fund appropriate law enforcement, education, and research.
Education, clinicians	Bolster comprehensive cannabis education in existing training on substance use and abuse.
	Create knowledge and automated warnings around drug-drug interactions.
	Standardize the way cannabis use is considered in medical decision-making, including transplantation eligibility, to destigmatize use but also to recognize health consequences; apply fair and equitable testing through algorithms.
Education, public	Educate the public about different cannabis products, the various active substances they may contain, and the known health consequences of smoking and vaping.
	Expand information sources about impairment, abuse, and its consequences (eg, cannabis use disorder, hyperemesis syndrome).
	Dispel myths about cannabis, particularly concerning the lack of risk and overly exuberant claims of health benefits.
Research	Support basic and clinical research into the purported and health benefits of cannabis products, including cardiovascular health.
	Support basic and clinical research into the potential short- and long-term health consequences of cannabis products, including vascular disease and myocardial injury.
	Construct a standardized dose similar to that for alcohol (the standard drink), tobacco (a cigarette), or opioids (morphine milligram equivalents) for researchers to use in analyzing use and for users to understand their consumption.
	Establish standards for measuring cannabis intoxication and impairment, including ED and roadside testing.
	Understand the epidemiology and trends in cannabis use, particularly among youth and higher-risk populations.
	Understand cannabis use disorder and its effect on health and healthcare use.

ABV indicates alcohol by volume; CBD, cannabidiol; ED, emergency department; FDA, US Food and Drug Administration; and THC,  $\Delta$ -9-tetrahydrocannabinol.

depressant effects with cannabis may develop. The delayed onset of effect when edible cannabis is consumed should be explained to minimize potential adverse effects. Patients who are long-term, heavy cannabis users should be advised not to suddenly stop their cannabis because of the risk of cannabis withdrawal syndrome. Patients should contact their provider immediately if signs and symptoms of cannabis withdrawal and hyperemesis syndrome should arise. In addition, cannabis containing primarily THC (with little if any CBD), especially higher levels of THC, should not be used in patients with a personal history of psychiatric disorders (eg, psychosis, schizophrenia, anxiety, and mood disorders); history of substance abuse, including alcohol or concomitant psychoactive drugs; or a family history of schizophrenia because of the risk of exacerbation. Because of variations

in state laws, patients using cannabis should understand that although >30 states may have legalized cannabis for medicinal purposes, fewer than half protect patients from being fired or rejected for a job as a result of a positive cannabis test. Finally, interstate transportation of cannabis is a federal crime, even if the patient has an approved medical indication.

## POLICY CONSIDERATIONS AND FUTURE DIRECTIONS

Because of the rapidly changing landscape of cannabis laws and marijuana use, there is a pressing need for refined policy, education of clinicians and the public, and new research. Laws should be harmonized in ways that

limit confusion and better reflect the existing science behind cannabis, starting in the United States at the federal level with removal of cannabis from Schedule 1 of the US Controlled Substances Act, followed by a proactive approach to labeling that standardizes concentrations of THC and CBD content. Meanwhile, the negative health implications of cannabis should be formally and consistently emphasized in policy, including a doubling down on the American Heart Association's commitment to limiting the smoking and vaping of any products and banning cannabis use for youth. All clinicians (physicians, advanced practice providers, nurses, pharmacists, and others) need greater exposure to and education on the various cannabis products and their health implications during their initial training and continuing education, and they must be alert to the possibility that the use of cannabis or its potent synthetic analogs might be the underlying cause of severe cardiovascular events and pathologies. The public needs high-quality information about cannabis, which can help counterbalance the proliferation of rumor and false claims about the health effects of cannabis products. Furthermore, research funding must be increased proportionally to match the expansion of cannabis use, not only to clarify the potential therapeutic properties but also to better understand the cardiovascular and public health implications that now follow the decriminalization of cannabis. Table 5 summarizes the needs and specific actions that should be considered.

## Disclosures

### Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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## Reviewer Disclosures

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