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Reevaluating America's Latest Pharmaceutical Trend: The Cardiovascular Risk of Cannabis

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For the first time in the history of the modern era smoking tobacco is not the most popular inhaled product. After a flurry of legislature, cannabis has come to the forefront of both medicinal and recreational drug use. A confluence of evidence suggests, however, that marijuana consumption may confer a particularly worrisome cardiovascular risk profile. While combustible forms still contain many of the same harmful chemicals found in tobacco such as aromatic amines, polycyclic aromatic hydrocarbons (PAHs), and nitric oxide, some in even greater concentrations than tobacco, edible preparations have been evidenced to cause more cardiovascular-related emergency department visits. Importantly, this body of evidence suggests that cannabis use may be placing a younger, healthier population at risk of suffering major cardiovascular accidents particularly in the moments immediately following consumption. With males in their 30's apparently bearing the brunt of this burden, cannabis consumption has been associated with an increase in ischemic stroke—a blockage in the cerebral or cerebellar vasculature—and almost a fivefold increase in myocardial infarction. THC containing compounds have also been linked to vascular complications ranging from mild plaques to total arterial occlusion resulting in claudication, rest pain, ischemic ulceration and gangrene—recently termed cannabis arteritis. While this research remains in a nascent stage, marijuana consumption seems to be predisposing a youthful, traditionally low health risk cohort to a variety of major adverse cardiovascular events.

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Introduction

The year is 1996, and the state of California ushers in the modern era of cannabis employment with the first approval of a medical marijuana proposition. Since then, recent demographic data has reported a steady upward trend in usage with more Americans now estimated to be smoking marijuana than tobacco—39 million versus 34.3 million, respectively (Table 1) [1••]. Within the last decade, 11 states in addition to Washington D.C. have gone as far as to approve it for recreational use, 33 states have passed medical marijuana legislature and many others will have revised cannabis laws appearing on upcoming ballots [2]. Furthermore, Statistic Canada claims that their populace now contains around 400,000 adults over the age of 65 who have used marijuana in the previous three months, as opposed to a mere 40,000 in 2012, which at that point was less than 1% of the senior population [3]. Cannabis colloquially has garnered favor for being the safe, nontoxic alternative to other substances of abuse and more conventional pharmaceutical agents, and this is clearly being reflected in usage statistics. Yet, many researchers have raised concerns over drug safety citing a significant cardiovascular (CV) risk profile that is often overlooked.

Cannabis contains over 500 substances, and for purposes of research and pharmaceutical production the medical field has chosen to focus on the two most abundant—tetrahydrocannabinol (THC), the main psychoactive ingredient, and cannabidiol (CBD). The body's endocannabinoid system mediates the effects of these chemicals through interaction with cannabinoid receptors 1 (CB1) and 2 (CB2) [4]. CB1 receptors are the main target of THC and are located in skeletal muscle, platelets, the liver, pancreas, peripheral nervous system, a wide array of CV tissue and are thought to be the most abundant G protein-coupled receptors in the mammalian brain. CB2 receptors are present principally on immune cells some neurons [4,5].

In addition to marijuana in its natural form, currently there are three United States Food and Drug Administration-approved cannabinoids available for medical use in America. First is a CBD-based oral medication used in the treatment of two rare yet severe forms of childhood epilepsy—Lennox-Gastaut syndrome and Dravet syndrome. Nabilone and dronabinol are the two other

Table 1

Comparison of use patterns, substance composition, legal status, and CV toxicity of cannabis versus tobacco smoking. (Information from *Marijuana Use in Patients With Cardiovascular Disease* published in Journal of the American College of Cardiology 2020)

	Marijuana Smoking	Tobacco Smoking
Estimated current use	>39 million*	34.3 million†
Recent trends in use	Rising	Declining
Psychoactive substance	Tetrahydrocannabinol	Nicotine
Composition	Similar particular matter and chemical toxin profile	Similar particular matter and chemical toxin profile
Typical use pattern	Larger puffs and inhaled volume, longer breath-hold	More frequent puffs
FDA – approved products for medicinal use	Cannabidiol (seizures); dronabinol and nabilone (nausea, anorexia, weight loss)	None
DEA controlled substance	Yes (Schedule I)	No
Current level of epidemiological evidence of CV toxicity	+	+++
Endothelial impairment after secondhand smoke	≥90 minutes	<90 minutes
Safe dose / level	?	None

CV = cardiovascular; DEA = Drug Enforcement Administration; FDA = US Food and Drug Administration.
* People reporting use in the past year according to the 2016 to 2017 National Survey on Drug Use and Health.
† Current smokers defined as people who reported smoking at least 100 cigarettes during their lifetime and who, at the time they participated in a survey about this topic, reported smoking every day or some days—according to the US Department of Health and Human Services.

THC-containing compounds directed at treating the nausea, vomiting and anorexia associated with chemotherapy and HIV/AIDS. Still, the utility of cannabis remains a divisive topic amongst healthcare providers due in large part to adverse effects on the CV system (CVS).

Inherent Toxicity

In comparison to tobacco, the chemical composition of marijuana smoke is infrequently discussed, but when the particulate matter from both sources is analyzed, marijuana contains many of the same cytotoxic chemicals. While public health officials disparage tobacco for consisting in part of aromatic amines, polycyclic aromatic hydrocarbons (PAHs), and nitric oxide (NO), all of those are too present in marijuana [6]. Compared to tobacco, the presence of hydrogen cyanide has been detected in marijuana cigarettes, and NO, NO_x and aromatic amines have been found at 3-5 fold greater concentrations [6]. The levels of ammonia were 20 times greater, and while mainstream marijuana smoke contains select PAHs at reduced concentrations, the smoke emitted into the air—sidestream smoke—contains those same PAHs in higher concentrations in comparison to tobacco [6]. Remarkably, marijuana inhalation is associated with three times more tar than tobacco cigarettes, and ultimately deposits a third more tar. It also has the potential to confer harmful levels of heavy metals into the body, such as aluminum [7,8]. Particulate matter <2.5 μm, even at low doses, has long been known to augment all-cause mortality and CV morbidity and mortality—at 0.3-0.5 μm, combustible formulations of cannabis fit well within this range [9,10]. Emergency department visits have risen dramatically since the turn of the century (Table 2); yet, despite these mutagenic and cytotoxic compounds underlining this inherent toxicity associated with smoking, edible formulations of cannabis were responsible for a greater number of CV-related emergency room presentations(8.0% vs. 3.1%, $P < 0.001$) along with a higher proportion of severe CV events, such as myocardial infarction (MI) and ventricular dysrhythmias [11].

Table 2

The weighted annual estimates of presentations to the emergency department due to illicit drug overdose—according to the National Institute on Drug Abuse. (Information from *The Cardiovascular Effects of Marijuana: Are the Potential Adverse Effects Worth the High?* published in Missouri Medicine 2019)

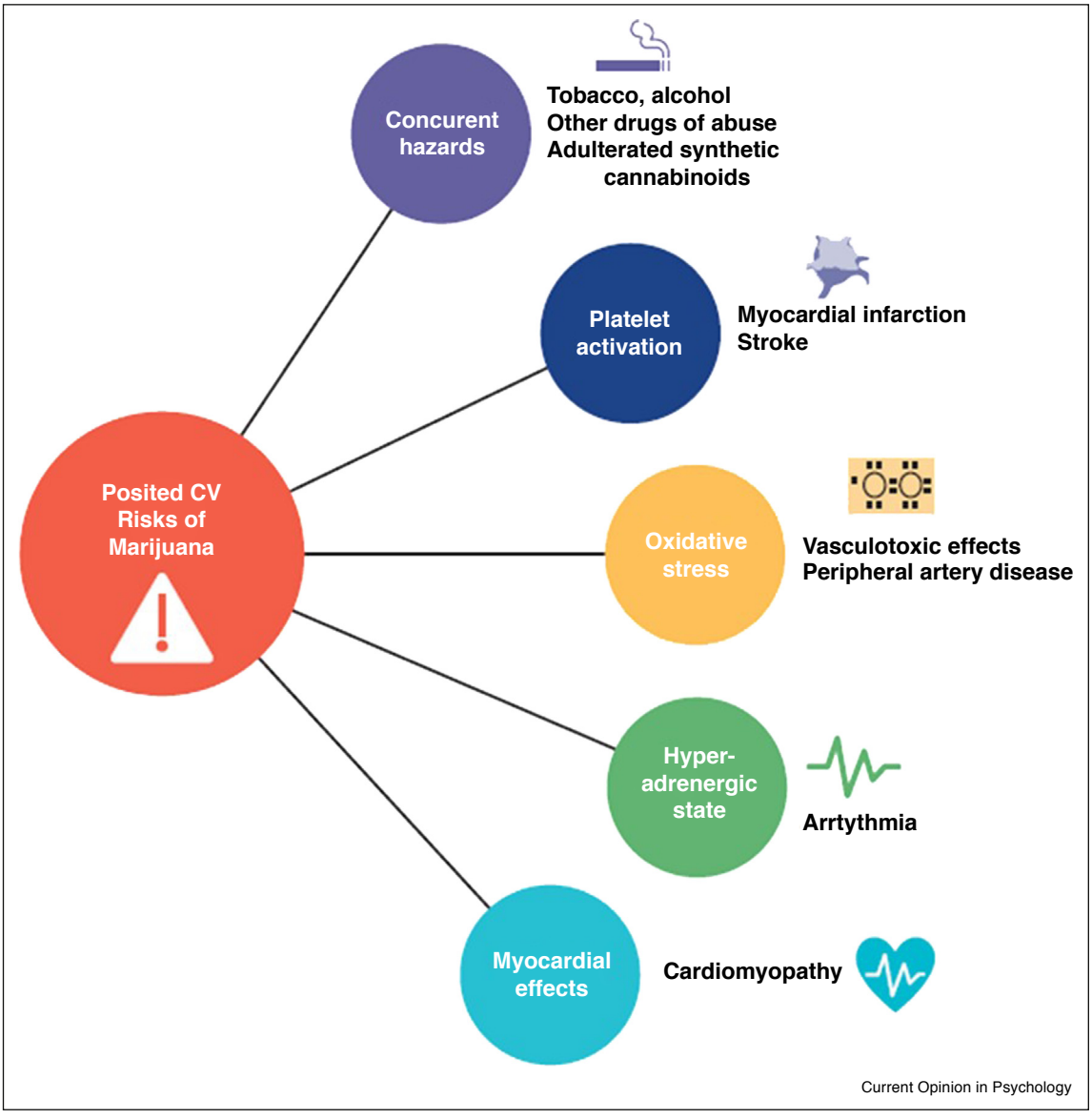
	Weighted Annual Estimates							
	Estimates 2004	Estimates 2005	Estimates 2006	Estimates 2007	Estimates 2008	Estimates 2009	Estimates 2010	Estimates 2011
Non-alcohol illicits	991,640	922,108	958,866	974,852	994,583	974,392	1,172,276	1,252,500
Cocaine	475,425	483,865	548,608	553,535	482,188	433,902	488,101	505,224
Heroin	214,432	187,493	189,787	188,162	200,666	213,118	224,706	258,482
Cannabinoids	281,619	279,668	290,568	308,547	374,443	376,492	461,028	455,668
Stimulants	162,435	137,806	107,586	85,043	91,945	93,564	138,632	159,840
Amphetamine	34,085	35,083	32,251	21,545	31,534	37,431	52,388	70,831
Methamphetamine	132,576	109,655	79,924	67,954	66,308	64,117	94,929	102,961

Major Adverse CV Events

CB1 receptors do not only reside in the myocardium, but are also located in the central nervous system, vascular endothelium, aorta smooth muscle, circulating red blood cells and platelets [12]. This widespread distribution of cannabinoid receptors has not surprisingly been associated with a number of CV events, including acute MI, stroke and sudden cardiac death (SCD), arrhythmias, cardiomyopathies, vasculopathies and concomitant drug use (Figure 1). Indeed, acute increases in blood pressure and heart rate (HR) are well described side effects, and a small trial from Aronow and Cassidy indicated cannabis inhalation could aggravate coronary ischemia, but the evidence that it's a substantial contributor to coronary atherosclerotic disease is lacking [13••,14•]. Conversely, as discussed below, there is a growing body of non-consensus evidence suggesting that cannabis use may be placing a younger, healthier populations, traditionally at lower risk for conventional coronary artery disease (CAD), at increased risk for MI.

Mittleman et al. showed that patients had 4.8 times (95% CI 2.9-9.5, $P < 0.001$) the risk of experiencing an acute MI within the hour following cannabis use [13••]. The relative risk declined, however, to 1.7 in the second hour after use and continue to plummet thereafter [13••]. The acute CVS strain of cannabis is known to be short-lived with

Figure 1



CV risk profile and pathophysiology associated with exposure to cannabis. (Information from *Marijuana Use in Patients With Cardiovascular Disease* published in Journal of the American College of Cardiology 2020).

maximal increases in HR occurring 10 to 30 minutes post-inhalation, and this may be reflected in the acutely elevated risk of MI [15]. Nevertheless, these MI sufferers are deviants from the norm as they were significantly less likely to have a history of angina or hypertension, and the mean age was 44 ± 8 years, compared with 62 ± 13 years for nonusers [13••]. Data from the Midi-Pyrenees region estimated serious adverse cannabis-related events to occur at an incidence rate of 1.9 (95% CI 1.4-2.3) per 1,000 recent users and 3.2 (95% CI 2.5-3.9) per 1,000 regular users. Hospital admissions for CV disorders, including MI, thrombosis and cerebral stroke composed 9.5% of those events with incidence rates of 1.5 (95% CI 1.1-1.9) and 2.6 (95% CI 1.9-3.2) per 1,000 people for recent and regular users, respectively [16].

There are now numerous case reports of CV accidents occurring in young, healthy adults and consequently being attributed to cannabis due to a paucity of alternative risk factors; more recently too, links have been drawn between cannabis and SCD in the same youthful population. Moreover, researchers have shown graded elevations in mortality rates after MI (Hazard Ratio 4.2, 95% CI 1.2-14.3) correlating with more frequent cannabis use [17]. There, however, is conflicting data. A retrospective cohort study of 62,012 patients between 15 and 49 years old, mean age of 33, demonstrated no association between current and/or previous cannabis use and acute MI. Desai et al. retrospectively analyzed 2,451,933 patients and concluded that while marijuana use did not correlate with increased mortality, it still remained a significant risk factor for acute MI (OR 1.079, 95% CI 1.065-1.093, $P < 0.001$) [18,19•]. Particularly at large doses, Jouanjus et al. aggregated 115 studies and evidenced an association between cannabis exposure and CV diseases (CVD), mainly ischemic stroke and MI, with a mean age of 31 and a heavy predominance of males (81.9%) [20].

Alternative CV Complications

Various arrhythmias have been described with marijuana use, including, atrial fibrillation (AF)/flutter, atrioventricular block/asystole, sick sinus syndrome, premature ventricular beats, ventricular tachycardia, and Brugada pattern [1••]. In Desai's patient population of almost two and a half million cannabis users, 66,179 (3%) experienced arrhythmias with AF comprising the majority of disease [19•]. The question of cannabis-induced cardiomyopathy is also being raised as case reports of stress cardiomyopathy and toxic myocarditis are appearing in the absence of CAD [21,22].

One fact that is known for certain, however, is that cannabinoids interfere with cytochrome P450 family of metabolizing enzymes. Predominately acting as an inhibitor, this means that cannabinoids have the ability to inadvertently raise blood levels of a number of pharmaceuticals including important cardiovascular drugs like antiarrhythmics, calcium-channel blockers, statins, β-blockers, and warfarin [23]. While at this time there is no quorum of research, there is substantial evidence to suggest cannabis can predispose healthy populations to serious adverse CV events, and the estimated 2 million CVD patients currently using cannabis should exercise caution [1••].

Vasculopathy

Reversible arterial vasospasm—the acute narrowing of the arteries caused by a persistent contraction of the blood vessels—is believed to be the culprit of most cannabis-related vascular events, and affected coronary circulation is postulated as the etiology in many of the case reports of MI [24]. Mendizabal et al. suggested that chronic marijuana use may result in autonomic nervous system (ANS) dysfunction; matched with inherent predilection for vascular irritation, this could explain the erroneous, THC-induced cycles of coronary vasodilation and vasoconstriction [25]. Furthermore, the resulting inflammation, oxidative damage and endothelial erosion associated with sympathetic overstimulation has been hypothesized as the origin of nonatherosclerotic dependent thrombi found in a number of cannabis-related mortalities [26•]. Large doses of cannabinoids have been shown to induce irreversible platelet aggregation [27,28]. Outside of coronary vasospasm and platelet aggregation, marijuana has been associated with a number of other potentially deleterious vascular effects including increased velocity and resistance, slowed coronary microcirculation, increased myocardial oxygen demand with decreased oxygen supply, and increased circulating levels of catecholamines [29–32]. Regardless of the mechanism, just a single minute of exposure to secondhand marijuana smoke impaired endothelial function in rats for the next 90 minutes, at least. While a similar vascular effect was elicited from a comparable dose of tobacco, recovery after marijuana exposure was significant slower than that of tobacco [33•].

Accordingly, there are now a number of case reports linking cannabis, transient ischemic attacks (TIA) and stroke. Similarly to MI, these documented episodes typically occurred around the time of exposure and involved young males who were heavy and/or frequent users [34,35]. In a study of 15 to 54-year-olds from the Nationwide Inpatient Sample, recreational cannabis use was associated with an 18% and 17% greater likelihood of aneurysmal subarachnoid hemorrhage (OR 1.18, 95% CI 1.12-1.24) and hospitalization for acute ischemic stroke (OR 1.17, 95% CI: 1.15-1.20), respectively [36,37]. Marijuana users overall demonstrated more illicit drug use than the control group, but they had less comorbidities and fewer medical risk factors for cerebral cerebellar strokes and CVD. Individuals aged 25-34 ingesting cannabis showed the most alarming increase in risk with a more than twofold incidence of acute ischemic stroke as compared to their non-using counterparts [37].

7455 Australians responding to a general population survey uncovered a possible link between heavy cannabis use and 153 cases of stroke or TIA [38]. Indeed, after adjustment, those using cannabis at least weekly were 2.3 times more likely to suffer a TIA or non-fatal stroke as compared to non-users [38]. Westover, Mcbride and Haley bolstered that data by showing a significantly increased risk of ischemic stroke among cannabis users in 998 patients (OR 1.76, 95% CI 1.15-2.71), while also concluding that the evidence surrounding cannabis-related hemorrhagic stroke remains circumstantial and unproven [39].

Cannabis Arteritis

Cannabis Arteritis is a unique pathological sequela of marijuana use closely resembling thromboangiitis obliterans (TAO)—commonly known as Buerger's disease. TAO is an uncontrolled inflammation of small to medium sized arteries of usually the hands and legs that can lead to extensive vasculature damage and thrombi formation. While TAO is historically linked to tobacco usage, cannabis arteritis is associated with THC containing compounds. Clinically, both are known to typically affect younger males with the symptoms of claudication—pain stemming from a lack of blood flow to the extremities during physical activity—and rest pain progressing to ischemic ulceration and gangrene [40]. Importantly, TAO is often characterized by thrombophlebitis, Raynaud's phenomenon and almost invariably involvement of more than one limb. Cannabis arteritis, however, classically presents as unilateral lower limb involvement [41]. Arteriography shows atherosclerotic disease ranging from mild plaques to total arterial occlusion, and just as the most effective treatment in TAO is tobacco cessation, marijuana cessation is currently the gold standard for halting cannabis arteritis progression [42].

Peyrot et al. described a male aged 36 presenting with a six month history of a necrotic wound on the medial side of the second toe on the right foot [43]. He had no relevant past medical history, no tobacco usage, but admitted to daily intake of 10 marijuana cigarettes for over 20 years. Arteriographic evidence showed bilateral lower limb distal segmental lesions, with a 90% stenosis of the right popliteal artery. Despite medical advice, patient continued cannabis use, experienced worsening of symptoms, and eventually submitted to an amputation of the left leg and right second toe. Then in 2017, Santos et al. described a 34-year-old male smoker of 20 tobacco and two cannabis cigarettes for 14 years [44]. The gentleman had a necrotic lesion on the left hallux and submitted to revascularization and anticoagulation. Yet, the patient returned months later with a recurrence of symptoms and persistence of distal necrosis. While he assured providers he had ceased tobacco consumption, he admitted to continued cannabis use—subsequent amputation of the left hallux was required. Nevertheless, some researchers argue that until more conclusive evidence comes forth, due to the high prevalence of concomitant tobacco use among these case reports, cannabis arteritis should not be classified as a clinically separate disease from TAO at this time [45].

Conclusion

Research in this field has proven extraordinarily difficult for a multitude of reasons. Cannabis comes in a variety of formulations of widely varying concentrations. There are a number of different methods of usage, and often marijuana smokers are also concomitant tobacco smokers. The bulk of cannabis users are younger, more resilient and have not had sufficient exposure to the drug to elicit consistent pathology. Additionally, studies often have to utilize self-reporting as marijuana remains a schedule 1 drug. Nonetheless, there now exists a substantial body of evidence to assert that cannabis is not a benign substance. It has the potential to precipitate major adverse cardiovascular events in a younger population that does not show the typical constellation of risk factors. Moreover, the nearly two million CVD patients that use cannabis need to be aware that they are a particularly vulnerable group that may be jeopardizing longevity.

CRediT author statement

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

The role(s) of all authors should be listed, using the relevant above categories.

All authors have contributed to this manuscript by research and writing manuscript

Authors may have contributed in multiple roles.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Grants and conflicts of interest

None.

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