REVIEW

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Cardiovascular Effects of Medical Marijuana: A Systematic Review

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ABSTRACT

Utilization of marijuana as a medicinal agent is becoming increasingly popular, and so far, 25 states have legalized it for medical purposes. However, there is emerging evidence that marijuana use can result in cardiovascular side effects, such as rhythm abnormalities, syncope/dizziness, and myocardial infarction, among others. Further, there are currently no stringent national standards or approval processes, like Food and Drug Administration (FDA) evaluation, in place to assess medical marijuana products. This review includes the largest up-to-date pooled population of patients with exposure to marijuana and reported cardiovascular effects. Although purported as benign by many seeking to advance the use of marijuana as an adjunctive medical therapy across the country, marijuana is associated with its own set of cardiovascular risks and deserves further definitive study and the same level of scrutiny we apply in research of all other types of medications. When used as a medicinal agent, marijuana should be regarded accordingly, and both clinical providers and patients must be aware of potential adverse effects associated with its use for early recognition and management.

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INTRODUCTION

Marijuana (cannabis) is the most widely produced and most commonly abused drug in the United States.[1] Marijuana use is legalized in 8 states for recreational use and in 25 states for medicinal use.[2] With nationwide momentum of medical marijuana legalization affecting multiple states across the country, health care providers need to understand the complications associated with cannabis use, especially in elderly populations and patients with cardiovascular diseases.[3] As cardiovascular disease remains among the leading causes of death in men and women in the United States,[4] physicians need to be aware of the cardiovascular risks of medicinal use of marijuana that may impact patient safety.[5]

Currently, marijuana is not defined as a risk factor for cardiovascular disease despite evidence of some associated adverse cardiovascular effects.[6] In a recent survey, about 10% of US adults older than 18 years reported using marijuana once a month.[7] A national survey on drug use and health reveals that marijuana smoking is on the rise compared with tobacco smoking.[8]

We must emphasize that there is no standard or common understanding of medical marijuana. The term *medical marijuana* can apply to any cannabis product regardless of purity, processing, dose, or route of administration.

The likely mechanism behind marijuana's effects on the cardiovascular system is via its main ingredient, tetrahydrocannabinol (THC).[9] THC causes a rise in heart rate, affects blood pressure via vasovagal mechanisms, and increases myocardial oxygen demand. An additional risk is added

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when marijuana is used in combination with tobacco or illicit substances such as stimulants and opioids. No specific body of literature has focused on the use of medical marijuana in patients with established cardiovascular conditions. Furthermore, little is known regarding potential effects of medical marijuana in patients who are currently using cardiovascular medications (vasodilators, statins, beta-blockers). Little is known about the safety of medical marijuana use in a population already at heightened risk for cardiovascular disease. Using existing published evidence, we compiled a review of the medical literature looking directly at cases of marijuana-associated cardiovascular outcomes.

We made every effort to assess the evidence regarding cardiovascular effects and medical-grade marijuana but because evidence is scarce, we had to expand our literature review search to medical cannabinoid use in general. Even in this case, the data are scant and the evidence in majority of published papers were case reports or case series. We were able to identify 67 publications describing the cardiovascular effects of marijuana (Table 1) in a pooled population of more than 2 million patients. Medline/PubMed databases were searched for English-language studies from January 1, 1996, to June 30, 2019. We searched articles that evaluated cardiovascular events of marijuana either as case reports/case series or original studies. Because of heterogeneity, different methodologies used, and most studies being case reports/series, we were not able to perform a standard meta-analysis.

CLINICAL SIGNIFICANCE

- Medical and recreational marijuana use may be associated with significant cardiac side effects; careful assessment of all medications warrants special attention.
- Myocardial infarction and arrythmias are commonly reported cardiovascular adverse effects with marijuana use.
- The exact mechanism by which marijuana exerts its cardiovascular effects is not well-defined.
- The possibility of adverse cardiovascular effects should be discussed with patients using medical marijuana, especially those with significant cardiac comorbidities.

Rhythm Abnormalities

Although much interindividual variability exists, the most consistent physiologic finding associated with marijuana administration relates to variations in heart rate. Fant et al[39] found the effect of marijuana exposure produced significantly increased heart rates over placebo controls that were found immediately after ingestion or inhalation and lasted up to an hour. Epidemiologic data suggest that marijuana users are most likely to experience a level of dose-related tachycardia as an adverse effect of exposure, with multiple studies indicating that low to moderate doses of THC increase sympathetic activity, resulting in tachycardia.[77,78] Cannabis-induced vasodilatation is thought to mediate reflex tachycardia.[79] Among reviewed case reports, sinus tachycardia was the third-most commonly occurring rhythm abnormality after marijuana exposure, with 8 of 54 patients indicating some form of elevated heart rate within the study parameters.

Atrial arrhythmias occurred in 5 of the 54 patients reviewed, with the most common being atrial fibrillation. One purported mechanism for overactivation of the atria may be related to vagal stimulation that reduces action potential durations and shortens atrial refractory periods to produce cellular hyperpolarization resulting in a predisposition to reentrant pathways.[1,23] In 2 separate case reports by Charbonney et al[41] and Singh et al,[30] marijuana appeared to be the only identifiable inciting factor for atrial fibrillation in young adults (ages 22 and 18, respectively) with structurally normal hearts, perhaps lending further support to the effect of vagal stimulation.[30,41]

Ventricular tachycardia was described in 2 separate case reports by Diffley et al[15] and Rezkalla et al,[32] respectively. In Diffley, the patient presented to the emergency department in ventricular tachycardia immediately after smoking marijuana, which ultimately resulted in the detection of ryanodine receptor-2 mutation causing catecholaminergic polymorphic ventricular tachycardia.[15] In the case of Rezkalla et al, coronary angiogram did not show any evidence of coronary artery disease.[32]

Syncope and Dizziness

Syncope and dizziness associated with marijuana exposure are reported as symptoms across various studies. Two types of cannabinoid receptors exist: cannabinoid receptor 1 (brain/liver/muscle/fat) and cannabinoid receptor 2 (immune system).[23,80] Cannabinoid receptor 1 is responsible for heart rate and blood pressure responses via heart regulatory centers and the peripheral autonomic system.[41] Gorelick et al suspect that THC levels in the blood lead to acute hypotension secondarily to activation of cannabinoid receptors in the arterial wall causing vasodilatation.[46] Vasodilatation may result in hypotension, leading to the perception of dizziness and further progression to presyncope or syncope. Casier et al suspected that levels of cannabinoids in the blood lead to inhibition of sympathetic activity leading to a compensatory parasympathetic surge resulting in hypotension.[10] Matthew et al found that exposure to marijuana/THC leads to a loss of cerebral autoregulation ultimately causing postural syncope via unclear mechanisms.[81] Four out of 54 patients had dizziness or syncope as a presenting complaint in our review.

Coronary Events

There have been case reports and case series published that demonstrate that patients who consume marijuana, even if

Table 1 Summary of Cardiovascular Effects Associated with Marijuana Use

Study, year	Study type	No. of patients (age/sex)[a]	Hemodynamic effects	Other CV effects	Comments
Casier et al, 2014[10]	Case series	Case 1 (52/M)	Asystole	STEMI, coronary vasospasm, no coronary occlusion	Hx of alcohol, nicotine abuse, HTN, died
		Case 2 (23/M)	Cardiogenic shock	STEMI, showed total occlusion of ostial LAD, proximal RCA, LVEF 12%	Self-reported chronic marijuana user, no other illicit drug use, normal lipid panel
		Case 3 (28/M)	Hypotension	VFib, STEMI, occlusion at the ostium of proximal LAD, ostium of IMA and RCA, EF 26%	Athlete, smoked marijuana occasionally, elevated level of homocysteine, low HDL, died
Deharo et al, 2013[11]	Case report	1 (24/M)	Not reported	STEMI, inferior and basal hypokinesis, LVEF 55%; RCA thrombosis	Heavy marijuana user STEMI occurred during a soccer match
Daisley et al, 1998[12]	Case report	1 (18/M)	Not reported	Autopsy revealed LAD thrombosis	Chronic use of marijuana, autopsy revealed multiple comorbidities, positive for alcohol and cocaine positive
Caldicott et al, 2005[13]	Case report	1 (21/M)	Not reported	STEMI, LAD thrombosis	Alcohol and marijuana use, recovered well after stent placement
Sanchez Lazaro et al, 2009[14]	Case report	1 (29/M)	Sinus tachycardia VT for 45 sec	LAD occlusion, coronary vasospasm	Heart transplant recipient; graft vascular disease; Hx of dyslipidemia and HTN
Diffley et al, 2012[15]	Case report	1 (15/M)	Wide complex VT vs accelerated idioventricular rhythm	STEMI, normal coronary arteries	MDMA use; found to have RYR2; catecholaminergic polymorphic VT
Cappelli et al, 2008[16]	Case report	1 (30/M)	VFib	STEMI, proximal LAD thrombosis	Risk factors: obesity, tobacco user, normal clotting factors and lipid panel
Bailly et al, 2010[17]	Case report	1 (36/F)	None	STEMI, anterior interventricular artery thrombosis	Chronic daily marijuana user
Arora et al, 2012[18]	Case report	1 (37/M)	Tachycardia	STEMI, coronary angiography showed normal coronaries, normal LVEF	Hx of HTN, had used Viagra, BMI 34
Karabulut & Cakmak, 2010[19]	Case report	1 (35/M)	HTN	STEMI, normal coronaries, slowed coronary flow and delayed washout RCA	Chronic marijuana user 30 pack-years smoking Hx
Dwivedi et al, 2008[20]	Case series	Case 1 (50/M)	Not reported	NSTEMI	HTN, alcohol abuse, Hx of tobacco use
		Case 2 (50/M)	Not reported	STEMI	Tobacco use, chronic marijuana use
Ting, 2007[21]	Case report	1 (31/F)	Not reported	NSTEMI, cardiomyopathy (LVEF 29%), mildly dilated LV	Large quantity of marijuana use
Frost et al, 2013[22]	Multicenter cohort study	2097 patients	Not reported	Higher rate of mortality after acute MI in marijuana users (participants followed for 18 years)	Compared to nonusers, the mortality rate was 29% higher in those reporting any marijuana use within a year prior to MI
Pratap & Korniyenko, 2012[23]	Case report	1 (19/M)	Normal BP and pulse	3-mm ST elevation in V1, V2, and incomplete RBBB	5-min duration syncope 1 h after a large measure of marijuana inhalation; normal cardiac structure and LVEF on echo

Table 1 (*Continued*)

Study, year	Study type	No. of patients (age/sex)[a]	Hemodynamic effects	Other CV effects	Comments
Mittleman et al, 2001[24]	Case-crossover study design	3882 patients	Not reported	Acute MI	Risk of MI onset elevated 4.8 times over baseline (periods of non-use) within 60 min of marijuana use
McLeod et al, 2002[25]	Case report	1 (41/M)	None	ECG demonstrated an evolving non-Q-wave; inferior MI, elevated cardiac enzymes	Hx of coronary disease; smoked marijuana the previous evening; took 1 tablet of Viagra
Kocabay et al, 2009[26]	Case report	1 (32/M)	None	Acute inferior MI, RCA: 100%, left thrombotic lesion, ventricular inferoseptum and posterior segments, EF 40%	Habitual marijuana and tobacco smoking
Bachs & Morland, 2001[27]	Case series	6 reports	Patients found deceased	Autopsy revealed MI, cardiac hypertrophy, coronary atheromatosis enlarged heart	Autopsy findings of deceased patients, toxicology revealed THC in all cases
Mukamal et al, 2008[28]	Cohort study	1913 patients	1 died of sudden cardiac death from VFib	2 died of coronary heart disease	Use of marijuana preceding a year of MI was associated with 3-fold higher mortality, 7 patients who used marijuana died during follow-up
Kosior et al, 2000[29]	Case report	1 (24/F)	Not reported	Paroxysmal atrial fibrillation	Received IV hydration and IV metoprolol to slow HR, sinus rhythm was restored after 12 h; symptoms appeared several minutes after smoking a marijuana cigarette
Singh et al, 2014[30]	Case report	1 (18/M)	None	Atrial fibrillation	Presented with new onset seizure, occasional alcohol and cigarette use
Fisher et al, 2005[31]	Case report	1 (35/F)	HTN	Atrial flutter	Tobacco user, infrequent marijuana use
Rezkalla et al, 2003[32]	Case report	1 (34/M)	Heart fluttering near syncope, clinical tachycardia inducible in the EP lab	RBBB, VT, angiography showed slow coronary blood flow	Symptoms after smoking marijuana
Cooper et al, 2013[33]	Placebo-controlled, double-blind study	30 patients	Tachycardia	None	Assessing pain control with dronabinol and marijuana volunteers
Cooper & Haney, 2010[34]	Placebo-controlled, double-blind study	29 patients	Tachycardia	None	Daily marijuana user is a compared with inactive marijuana volunteers
Cooper & Haney, 2009[35]	Placebo-controlled, double-blind study	24 patients	Tachycardia	None	Naltrexone was administered before active or inactive marijuana use and cardiovascular effects of marijuana monitored
Ramesh et al, 2013[36]	Double-blind study	18 patients	Tachycardia	None	Active marijuana use caused a dose-dependent increase in HR and CO excretion
Brody & Preut, 2002[37]	Experimental study	108 participants	Increased systolic BP	None	Compared the effect of ascorbic acid in marijuana, tobacco and caffeine users

Table 1 (*Continued*)

Study, year	Study type	No. of patients (age/sex)[a]	Hemodynamic effects	Other CV effects	Comments
Alvaro et al, 2002[38]	Case report	1 (33/M)	Elevated systolic BP	None	Chronic marijuana user, former alcoholic, right occipital infarct
Fant et al, 1998[39]	Experimental study	10 patients	Tachycardia, elevated systolic BP	None	Acute and residual effects of marijuana
Fox et al, 2013[40]	Experimental study	59 patients	Tachycardia, elevated systolic BP	None	Marijuana-dependent group compared to alcohol and cocaine when exposed to stress showed up-regulation of cardiovascular basal drive, reduced cardiovascular output
Charbonney et al, 2005[41]	Case report	1 (22/F)	Tachycardia, orthostatic hypotension, paroxysmal atrial fibrillation	None	On oral contraception, daily marijuana user
Schneider et al, 1999[42]	Case report	1 (38/M)	None	Peripheral vascular disease	Hx of epilepsy, tobacco use
Rodondi et al, 2006[43]	Longitudinal study	1365 patients	Elevated systolic BP	None	15 years longitudinal data, increased BP in unadjusted analysis
Ponto et al, 2004[44]	Prospective	36 patients	Tachycardia, increased BP	None	Increased CV effects were noted in occasional marijuana users when compared to regular users
Zuurman et al, 2008[45]	Double-blind placebo-controlled crossover study	12 patients	Increased HR	None	Change in HR was dependent on THC dose
Gorelick et al, 2006[46]	Random controlled placebo study	63 patients	7 patients with symptomatic hypotension	None	7 patients with symptoms had higher THC concentrations
Huestis et al, 2001[47]	Random controlled placebo study	63 patients	Tachycardia	None	Dose-related increase in HR, findings confirm CB1 receptors mediated CV effects
Huestis et al 2007[48]	Random double-blind controlled study	42 patients	Tachycardia	None	Study shows that antagonizing CB1 receptors decreased physiologic effects of marijuana
Akinlonu et al, 2018[49]	Case report	1 (49/M)	Brugada pattern	None	Patient presented for detox, otherwise asymptomatic
Aydin Sunbul et, 2016[50]	Observational study	72 patients	None	P wave dispersion	Study to investigate the effect of synthetic CBs on P wave dispersion
Desai et al, 2017[51]	Retrospective cohort study	2,419,739 patients	Acute MI	Congestive heart failure, cardiogenic shock, dysrhythmias	National inpatient sample analysis of patients with MI who consumed marijuana
Elsheshtawy et al, 2016[52]	Case report	1 (50/M)	Shortness of breath, tachycardia	LV dysfunction	Marijuana causing nonischemic LV dysfunction
Jehangir et al, 2015[53]	Case report	1 (27/F)	Chest pain	STEMI	Marijuana use associated with STEMI

Table 1 (*Continued*)

Study, year	Study type	No. of patients (age/sex)[a]	Hemodynamic effects	Other CV effects	Comments
Kariyanna et al, 2018[2]	Case report	1 (27/M)	Chest pain	Myocarditis	Marijuana consumption causing myocarditis
Kariyanna et al, 2018[54]	Case report	1 (36/M)	Chest pain	Brugada pattern	Marijuana causing Brugada pattern on ECG
Keskin et al, 2016[55]	Case report	1 (15/M)	Chest pain, hypotension	STEMI	STEMI and stroke in patient
Mcllroy et al, 2016[56]	Case report	1 (39/M)	Chest pain, syncope, cardiac arrest	STEMI, VFib	STEMI and other arrhythmias
Orsini et al, 2016[57]	Case report	1 (40/M)	Tonic-clonic seizures, cardiac arrest	VFib, STEMI	Seizures as a cause of marijuana intoxication leading to cardiac arrest
Wengrofsky et al, 2018[58]	Case report	1 (27/M)	Chest pain	STEMI (inferior wall)	None
Alshaarawy & Elbaz, 2016[59]	Retrospective cohort study	12,426 patients	Increase in systolic BP	None	Marijuana use causes mild increase in systolic BP
Brancheau et al, 2016[60]	Case report	1 (28/M)	Asystole	None	Asystole due to hypervagotonia
Davis & Boddington, 2015[61]	Case report	1 (16/F)	Cardiac arrest	None	None
DeFilippis et al, 2018[62]	Retrospective study	2097 patients	MI	None	Marijuana use a week before or urine toxicology positive for marijuana at the time of MI was associated with 2-fold increase in cardiovascular mortality
Del Buono et al, 2017[63]	Case report	1 (23/F)	VFib, tachycardia	Cardiac arrest	None
Draz et al, 2017[64]	Cross-sectional study	138 patients	Acute MI	None	87% of the patients who were positive for marijuana at the time of admission for acute coronary syndrome were found to have STEMI
Efe et al, 2016[65]	Case report	1 (23/M)	Shortness of breath, palpitations	Atrial fibrillation	Cannabis increases the risk of atrial fibrillation
Zaleta et al, 2016[66]	Case report	1 (14/M)	Chest pain, headache	Sinus tachycardia, STEMI	Very young patient with STEMI
Grieve-Eglin et al, 2018[67]	Case report	1 (54/F)	Presyncope, dizziness	Sinus arrest	None
Grigoriadis et al, 2019[68]	Case report	1 (58/F)	Tachycardia, tachypnea	Cardiogenic shock	Recurrent cardiogenic shock requiring intra-aortic balloon pump
Hayiroglu et al, 2016[69]	Case report	1 (18/M)	Chest pain	RBBB, idioventricular rhythm	Intracoronary thrombus noted on cardiac catheterization
Kumar et al, 2018[70]	Case report	1 (35/M)	Chest pain, STEMI	None	Normal coronary angiogram with resolution of symptoms with calcium channel blockers
Marchetti et al, 2016z[71]	Case report	1 (50/M)	Found unconscious	None	Autopsy revealed thrombosis of the RCA
Mithawala et al, 2019[72]	Case report	1 (51/F)	Bradycardia, intermittent dizziness	Third-degree atrioventricular block	Marijuana use associated with heart block
Tatli et al, 2007[73]	Case report	1 (24/M)	STEMI	None	Thrombosis of coronary artery

Table 1 (*Continued*)

Study, year	Study type	No. of patients (age/sex)[a]	Hemodynamic effects	Other CV effects	Comments
Toce et al, 2019[74]	Case report	1 (16/M)	Chest pain	STEMI	Coronary angiogram showed acute coronary obstruction, cardiac biopsy revealed sub-endocardial acute MI, MRI showed dilated cardiomyopathy
Velibey et al, 2015[75]	Case report	1 (27/M)	Chest pain; bradycardia	NSTEMI	None
Total studied participants:		**N = 10,343 patients** (case reports/ series + research studies	**Most frequent CV events reported in research studies (N = 10,289):** 1. **Mortality following MI:** increase in mortality 29% to 3-fold[22,28,62] in patients positive for marijuana at the time of MI or use within preceding year 2. **Risk of MI**[24,64]: 4.8 times higher risk of MI within 1 hour of consumption of marijuana or 87% higher chance of STEMI in patients positive for marijuana when presenting for acute coronary syndrome. 3. **Tachycardia:** Increase in HR vs baseline: Range 8%-59%. Average HR increase of 27%		**Most frequently reported CV events in 54 patients/46 case report/series.** 1. MI-22 patients (41%) 2. Arrythmias 19 patients (35%) 3. Tachycardia 8 patients (15%)

BMI = body mass index; BP = blood pressure; CB = cannabinoid; CO = carbon monoxide; CV = cardiovascular; echo = echocardiogram; EF = ejection fraction; ECG = electrocardiogram; EP = electrophysiology laboratory; F = female; HDL = high-density lipoprotein; HR = heart rate; HTN = hypertension; Hx = history; IMA = intermediate artery; IV = intravenous; LAD = left anterior descending artery; LV = left ventricular; LVEF = left ventricular ejection fraction; M = male; MDMA = methylenedioxymethamphetamine ; MI = myocardial infarction; MRI = magnetic resonance imaging; NSTEMI = non-ST elevation myocardial infarction; RCA = right coronary artery; RBBB = right bundle branch block; RYR2 = Ryanodine receptor 2; STEMI = ST-elevation myocardial infarction; THC = tetrahydrocannabinol; Vfib = ventricular fibrillation; VT = ventricular tachycardia.

Table 2 Cardiovascular Effects and Possible Pathophysiology of Coronary Events in Patients Using Marijuana

Cardiovascular effects of marijuana	Pathophysiology of coronary events in patients using marijuana
• Sinus tachycardia • Atrial fibrillation • Atrial flutter • Ventricular fibrillation • Orthostatic hypotension • Syncope • Dizziness • ST segment elevation myocardial infarction • Non-ST segment elevation myocardial infarction • Myocarditis • Sudden cardiac death	• Coronary vasospasm • Plaque disruption • Procoagulant effects that increase platelet aggregation • Increased carboxyhemoglobin level, which decreases oxygen-carrying capacity of blood in midst of increase in oxygen demands

they are young and healthy, are at risk for coronary events (Table 2). Mittleman et al reported the risk of triggering a myocardial infarction was elevated almost 5-fold within 1 hour of smoking marijuana, compared with those who did not smoke.[24] Another study elucidated the risk of cardiovascular mortality was twice as high with any cannabis use and the risk increased with more frequent use of marijuana.[28] We identified[25] patients with acute coronary syndrome associated with marijuana use with majority cases being ST segment elevation myocardial infarction (Table 2).

The exact pathophysiology behind myocardial infarction in patients consuming marijuana is unknown. One proposed mechanism of these sudden coronary occlusions was likely a disruption of a coronary plaque secondary to the acute hemodynamic changes that marijuana causes on the cardiovascular system.[24] It has also been postulated that marijuana has procoagulant effects, which increase platelet aggregation and activation of factor VII. This furthers the thrombosis if there is a ruptured plaque.[82] THC may affect the endocannabinoid system (cannabinoid receptors 1 and 2), which causes an increase in both blood pressure as well as heart rate, inducing a tachycardia.[23] Marijuana also causes an increase in the carboxyhemoglobin level, therefore causing a decrease in oxygen-carrying capacity. In combination, the nature of increasing oxygen demand from the hemodynamic effects combined with a decreased oxygen-carrying capacity, worsens demand supply mismatch, hence, contributing to myocardial infarction.[13,23] Marijuana may also cause coronary vasospasm. Patients present with signs and symptoms of myocardial infarction but coronary angiogram does not demonstrate any significant obstruction.[83]

Public Health Implications

With the growing number of individuals exposed to marijuana along with the increasing severity of the cardiovascular disease epidemic in the United States, there are some important considerations that every clinician has to be aware of to properly educate and advise their patients. In a 1997 study by Sidney et al, current marijuana smokers were twice as likely to be current tobacco cigarette smokers and nearly 2.5 times more likely to be alcohol drinkers.[76] Tobacco is widely recognized as a significant component in the progressive development of coronary artery disease and is also recognized as a correlative factor in developing thrombangitis obliterans (Buerger disease), cancer, and chronic lung diseases. Schneider et al reported on a case of progressive arteritis of the feet secondary to heavy marijuana smoking despite abstinence from tobacco.[42] Rodondi et al found that marijuana use was regularly associated with increased appetite and higher caloric intake, potentially introducing another risk factor for the progression to cardiovascular disease.[43]

Areas of Knowledge Gap

Several previous reviews have looked at the data in regard to specific cardiac outcomes; however, none of them have gathered a database of total cardiovascular outcomes associated with exposure to marijuana. As a result of our review, we identified the following areas with a noteworthy gap in knowledge:

1. There is a lack of published evidence regarding the cardiovascular effects of medical marijuana. Most of the data we reviewed was based on case reports and case series rather than original research articles. Randomized controlled trials are considered the gold standard of US pharmacologic research, and yet none exists for marijuana. If there is intent to use marijuana as a medical therapy, it needs to meet the same level of scrutiny and randomized research invested in it as is done for all other medications before they become clinically available. Currently, medical approval of marijuana is by popular vote or by the state legislature; hence, it does not follow the stringent criteria of US Food and Drug Administration.[84]
2. Few studies have looked at what is considered medical-grade marijuana and analyzed the specific effects of marijuana that has been grown and synthesized for a medical purpose, making it free from pollutants or tobacco. Accordingly, if physicians are going to

recommend marijuana use as medical therapy, the recommendation should be made that a medical-grade product be used. However, these recommendations should be based on serious evidence and prospective research focusing on the route of administration, dose of the product, safety of different product forms (inhaled vs edible vs topical), and risk profiles that prescribers need to be aware of prior to making the recommendation for this type of therapy. Oral formulation of THC, approved by the regulatory bodies, are available for cachexia of HIV/AIDS, chemotherapy-induced nausea and vomiting.[84] An oromucosal spray of THC and cannabidiol is available to treat multiple sclerosis-related spasms in Canada and Europe.[85] Recently, Vandry et al found that in 2 of the largest medical marijuana markets in the United States, greater than 50% of products (all edible) evaluated had significantly less THC than labeled on the packaging.[86] This further supports the need for serious methods of standardizing marijuana-based therapies across the United States. At a minimum, there needs to be a medical registry allowing for standardized evaluation of cannabis products causing cardiovascular effects and drug-drug interactions.

3. Even in original published research, we had difficulty interpreting individual dose responses to the amount of marijuana exposed prior to the inciting cardiovascular event. Multiple studies reinforce the idea that the dose-dependent relationship that produces effects has tremendous interpersonal variability. Importantly, confounding factors such as tobacco use, alcohol use, other substance abuse, and lifestyle modifiers (eg, physical activity, diet) were not well-identified. This further supports the need for dedicated research in the field of medical marijuana.
4. Dedicated research of medical marijuana in those with existing cardiovascular pathology is lacking, especially when it comes to understanding the effects in patients currently using cardiovascular drugs. It is unclear in the future how individuals who use both therapies may be affected. Although some data about the drug-drug interaction of marijuana with cardiovascular medication exists, there are not any quality studies evaluating this question.

Practical Considerations and Clinical Implications

Our comprehensive review provides an important collection of data regarding existing evidence of cardiovascular effects associated with marijuana. To date, there are no randomized, controlled trials regarding dose-related responses to marijuana and what potential outcomes may result. Review of the available publications identifies that cardiovascular effects of marijuana are not always benign and may include serious hemodynamic changes, such as tachycardia and hypotension, as well as clinically significant atrial and ventricular arrhythmias. Serious complications may result from these cardiovascular effects, including acute myocardial infarction, syncope, dizziness, significant arrhythmias, and death.[87] Therefore, physicians, dispensaries, and prescribers need to understand the risks associated with recommending marijuana when no current recommendation standards exist. Unfortunately, both the advocates and detractors of medical marijuana are responsible for blocking any serious studies on medical marijuana products.

No current US Food and Drug Administration guidelines exist to help practitioners make educated decisions regarding risk profiles to counsel patients before seeking out marijuana in addition to current therapies. Because dispensaries in many parts of the country serve the role of both prescriber and physician, potential exists for prescriber patterns to increase adverse outcomes secondarily to lack of guidelines. Based on our review, some of the potential effects of cannabis use in patients with known cardiovascular disease are now well-defined. Soon, the physicians will have to take into consideration clinical concerns related not only to the inhalation method of cannabis administration but also consider the increasing popularity of ingestible or edible forms of marijuana. It is clear that there is no standard technique in production, purity, labeling, or use of various products called *medical marijuana*. Additionally, with exception of a few states that involve poison and drug information centers, there are no standard guidelines for physicians, mid-level providers, or public education about these products.

In this regard, we would like to postulate several important clinical implications of our research:

1. The discussion with the patient to initiate medical marijuana as an adjunctive or primary therapy and should be focused on healthy behaviors as a whole, with emphasis on healthy exercise, diet, reduction of opioids used for pain, and avoidance of tobacco or illicit drugs.
2. The mechanism by which a cannabis (not cannabinoid, which are synthetic) is delivered (oral vs vaping) requires appropriate consideration for an individual's physiology as considerable differences are noted between mechanisms of inhalation versus ingestion. Dose response effects are a predominant part of the cannabinoid-receptor relationship and deserves dedicated study. If marijuana products are to be treated as a medication, then these products should be treated as any other medication, meaning their purity, dose, route of administration, and effect should be studied.
3. Although marijuana itself does not appear to be independently associated with excessive cardiovascular risk factors, it can be associated with other unhealthy behaviors such as alcohol use and tobacco smoking that can be detrimental. Use of medical marijuana is probably safe in younger and healthy individuals with no exposure to tobacco or illicit drugs, but some precautions and adverse effects have been described even among these healthy individuals. Patients need education regarding most the frequent marijuana effects (transient hypertension, tachycardia, possible syncope and dizziness, and even myocardial injury). In our understanding, administration of medical marijuana should

be regarded in the same manner as any new medication therapy with patients requiring appropriate counseling prior to initiation.
4. In patients with existing coronary artery disease or other cardiovascular pathology, more pronounced effects on cardiovascular systems are possible, and these patients should be informed of the possibility of symptoms worsening and should be encouraged to seek medical attention if symptoms last.
5. Cardiovascular effects of marijuana should always be considered when the patient is on other cardioactive medications because these effects may potentially worsen the hemodynamic effects that marijuana might cause.
6. Further research is needed to investigate cardiovascular effects of marijuana in middle aged and older patients with and without existing cardiovascular pathology, as well as what are the potential long-term effects of use of marijuana therapies.
7. Some case reports suggest a potential acceleration of cardiac effect if cannabis is used directly prior to exercise. This deserves further study as well as education for patients.

Previous Reviews

A systematic review and meta-analysis looking at cannabinoids for medical use was recently published looking at the quality of evidence associated with cannabinoid therapies. This review, however, did not focus on specific cardiovascular outcomes.[88] There have been few studies that have discussed the cardiovascular outcomes of marijuana use, but they do not have the extensive database that we have collected.[8,87,89,90]

CONCLUSION

This review includes the largest up-to-date pooled population of patients with exposure to marijuana and reported cardiovascular effects. Although purported as benign by many seeking to advance the use of marijuana as an adjunctive medical therapy across the country, marijuana is associated with its own set of cardiovascular risks and deserves further definitive study and the same level of scrutiny we apply in research of all other types of medications. When used as a medicinal agent, marijuana should be regarded accordingly, and both clinical providers and patients must be aware of potential adverse effects associated with its use for early recognition and management.

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