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Cardiovascular effects of marijuana ☆

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ABSTRACT

More than four decades ago, the United States Surgeon General issued a warning regarding the medical problems of marijuana smoking, including cardiac toxicity. Since then, many reports have described atrial fibrillation, ventricular tachycardia, acute coronary syndromes, and cardiac arrest temporally related to marijuana use. The subjects were quite young, with no significant cardiovascular risk factors, with the only obvious trigger being marijuana use. Despite these strong signals, the drug is now legalized for recreational use in many states. We believe the time has come to conduct definitive studies about the safety of marijuana before this trend moves to the rest of the nation.

Contents

Introduction

Cannabis and cannabinoids are being utilized as therapeutic agents for a variety of medical conditions [1]. Cannabinoids are a group of drugs that exert their effects on the cannabinoid receptors. They include chemicals such as those extracted from cannabis plants, also known as marijuana, and synthetic cannabinoids. In this report, cannabis and marijuana will be used interchangeably. As a medication, cannabis (marijuana) has both benefits and side effects, and both need to be examined by clinicians prior to being prescribed. Its use by the public for recreational purposes, however, is a quite different story. The safety of marijuana needs to be established prior to its legalization, so public health can be protected. The current push to legalize its use raises many questions. Is it safe to use? What happens when people drive while under the influence? Will it lead to other addictions, or is it associated with any other health concerns? This article will focus on the various cardiovascular effects of marijuana use.

Pharmacologic effects of marijuana

Beaconsfield et al. [2] examined the cardiovascular effects of smoking marijuana in normal healthy volunteers, none of whom had previously smoked marijuana. Subjects smoked tobacco cigarettes, and this was compared to marijuana cigarettes. Smoking marijuana was associated with an increase in pulse rate to about 90 beats per minute (bpm), compared to 66 bpm in the control

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group. Pretreatment with beta-blockers blocked the heart rate increase, suggesting that it is mediated via beta-adrenergic stimulation. Electrocardiogram of the subjects did show P-wave abnormalities and inversion of the T-waves following marijuana smoking.

More recently, it was found that the drug exerts its effects mainly on two specific receptors: Cannabinoid (CB) receptor type 1, located in the central nervous system and CB2 receptors located in the periphery. CB2 was detected in cardiac myocyte and in the smooth muscles of blood vessels. The exact mechanism of the various vascular effect of marijuana is not clear, likely due to the paucity of laboratory data and to the complexity of the drug. It contains over 60 active substances, and the intensity of the effects differs among various species of the plant [3].

Perhaps the best way to have a better understanding of the effect of marijuana on the cardiovascular system is to study the various clinical studies reported in the literature. This paper will review the effect of marijuana use on cardiac arrhythmias, coronary artery diseases, stroke, and other vascular effects.

Cardiac arrhythmias

Atrial fibrillation

In the initial study reported by Beaconfield et al. [2], volunteers who smoked marijuana had electrocardiographic monitoring. It showed a decreased amplitude of the P-waves following consumption, suggesting atrial abnormality. Later, Miller et al. [4] investigated the effects of parenteral administration of delta-9-tetrahydrocannabinol on patients. Mean sinoatrial conduction time significantly decreased following drug administration. Mean A-H interval (atrioventricular node conduction time) significantly decreased. Mean atrioventricular nodal refractory periods were significantly decreased as well. Thus, marijuana has clear electrophysiologic effects on the heart. It is not surprising that cases of atrial fibrillation have been reported. Korantzopoulos et al. [5] reported atrial fibrillation following marijuana consumption, with an average age of 24-years. The youngest patient was 14-years-old, hardly an age in which atrial fibrillation is typically encountered. It was suggested that enhanced sympathetic activity could be the precipitating factor. With concomitant postural hypotension and depressed mentation, some patients were highly symptomatic, and these episodes were associated with reported falls. It is possible that the frequency of atrial fibrillation is underestimated, because it could be asymptomatic, and also patients may be reluctant to seek medical care while under the influence of the drug. Synthetic cannabinoids were also associated with atrial fibrillation, and the effect of those drugs appears to be more potent than naturally occurring plants [6]. A recent study suggests that atrial fibrillation is less frequent in cannabis users compared to non-users in patients with congestive heart failure. Interestingly, patients that reported cannabis use were significantly younger than non-users [7]. However, propensity matched analysis was done to adjust for the age difference between the two groups, which concluded this phenomenon was independent from age.

Ventricular arrhythmias

A 34-year-old man reported near syncope hours after smoking marijuana. In the emergency department, the patient presented with ventricular tachycardia at a rate of 200 bpm [8]. Emergency angiography showed normal coronary arteries, with slow coronary flow that responded to intra-coronary verapamil infusion. In the electrophysiologic laboratory, the clinical ventricular tachycardia was inducible. Following oral verapamil and abstinence from marijuana smoking, repeat angiogram showed normal coronary flow. In repeat electrophysiologic study, the ventricular tachycardia was no longer inducible. Since the report of this case, other reports of non-sustained ventricular tachycardia, temporarily related to marijuana smoking, were reported [9–11]. What is intriguing is that all cases were also associated with coronary slow-flow. A fatal case of ventricular fibrillation was reported in a young man who presented to the emergency department with ventricular fibrillation [12]. Urine toxicology screen was positive for tetrahydrocannabinol and negative for other drugs, including cocaine.

Some autopsy studies suggested a link between marijuana and sudden death [13]. In another report by Hartung et al. [14], it was very clear that only marijuana may be linked to sudden death. A comprehensive autopsy was performed in two cases where there was no cause of death identified. Both had a normal structural heart; yet cannabis was the only substance identified during comprehensive toxicological examination. Furthermore, genetic analysis was conducted to rule out other possible genetic defects that may be associated with sudden death, such as long QT syndrome. Thus, marijuana use was associated with ventricular arrhythmias, sustained, and non-sustained ventricular tachycardia; it may even be linked to sudden death.

Data from the United States National Vital Statistics between the years 1990–2014 were analyzed [15]. Cardiovascular-related mortality rates in states with liberal rules for dispensing marijuana were compared with other states. In those states where marijuana use was legal, there was an increase in cardiac mortality of 2.3% in men and 1.3% in women. A major limitation of this study was lack of data on whether those with cardiac death were actually marijuana users. The report, however, suggests an important signal regarding cardiac mortality and marijuana use that requires further investigation.

Coronary artery disease

Marijuana use is associated with acute cardiac ischemia, ST-elevation myocardial infarction (STEMI), and non-STEMI. In a study by Draz et al. [16], from 2014 to 2015 all patients with acute coronary syndromes were tested for illicit drugs. There were 138 patients who tested positive for drugs, with 23 patients positive for marijuana only. The clinical picture ranged from temporary cardiac ischemia to STEMI [16].

It has been reported that among various triggers of myocardial infarctions in the last two decades, marijuana smoking is increasingly a trigger [17]. In a study by Mittleman et al. [18], which included 3882 patients presenting with myocardial infarction, 3.2% of patients reported smoking marijuana prior to the onset of symptoms. In the first hour after drug use, the risk of developing myocardial infarction is elevated five times compared to non-users. Patients were more likely to be male, obese, and tobacco users. They were less likely to have a previous history of angina. In a large scale study by Desai et al. [19], the odds of developing myocardial infarction increased by 8% in patients with recreational marijuana use.

In France, it is mandatory to report all cases related to drug abuse presenting to hospitals to the French Addictovigilance Network [20,21]. In this national database, there is an increase in the incidence of cardiovascular complications associated with marijuana use. Furthermore, the severity of cardiac events and the mortality rate appear to be higher in marijuana use. However, in post-discharge follow-up, in a study by Frost et al. [22], long-term mortality was not statistically different between users and non-users.

The clinical presentation of acute myocardial infarction associated with marijuana use is variable. Casier et al. [23], reported three cases who presented with myocardial infarction and collapse requiring cardiopulmonary resuscitation (CPR). Cause of arrest was

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different in every patient, ranging from asystole to ventricular fibrillation. The pertinent angiogram showed intense coronary vasospasm, atherosclerotic coronary artery disease requiring stenting, and coronary thrombus. In the majority of reported cases of marijuana-associated myocardial infarction, angiograms were normal, and either coronary thrombosis or intense coronary spasm was noted [24–28].

In our review of various reports of myocardial infarction following recent or chronic cocaine use [29–31], some cases had coronary thrombosis, and in many, exhaustive work-up for hypercoagulative states were negative, with the only associated finding being marijuana use. Coronary spasm was occasionally noted in the myocardial coronary arteries, but more commonly in the smaller arterioles, presenting as coronary no-reflow or slow reflow. While these effects may be induced by the drug effects on the cannabis receptors, other factors may contribute, such as concomitant drug use, smoking and tobacco us, or acute metabolic syndrome (since chronic marijuana users may be overweight.)

In addition to the naturally occurring marijuana plant, a variety of new, synthetic cannabis is available. These are known under different names such as spice, cloud 9, and many others. In addition to reports of myocardial infarction associated with them, the cardiac events are often more severe and associated with higher complication rates [32].

Utilizing a national database for hospital inpatients, Kalla et al. [33] identified 31,397 patients who used cannabis during the years 2009–2010, Cannabis users were predominantly men, with higher incidence of coronary artery disease, sudden cardiac death, and congestive heart failure. Adjusting for risk factors including tobacco use, the use of cannabis (marijuana) remained as an independent predictor of congestive heart failure and other cardiovascular events. This study is the main study showing that cannabis is an independent risk for cardiovascular events. Combining that with other reports, concomitant tobacco use clearly increases the risk for cardiovascular events.

In a similar report by Lorenz et al. [34], who studied 558 male patients with HIV-infection, heavy marijuana users had a 19.7% rate of cardiovascular events. That rate was significantly higher than the rate for HIV-infected men with occasional or no marijuana use. The increase in cardiac events was independent from tobacco use.

More recently, De Filippis et al. [35] conducted a retrospective study in adults younger than 50-years-of-age who suffered their first heart attack. Among 2,097 patients who had STEMI, 224 had recently used cocaine or marijuana. The patients who had used either of these drugs were associated with worse all-cause mortality and greater morbidity compared to patients who denied drug use. Furthermore, out-of-hospital cardiac arrest during initial presentation was more common in patients who admitted marijuana use prior to myocardial infarction. In this group of young patients, it appears that either cocaine or marijuana was the trigger for the infarction, since they did not have significant risk factors, such as diabetes or dyslipidemia. This study also suggests that myocardial infarction and marijuana use are linked. Various studies showing the effect of marijuana use and cardiovascular effects are depicted in Table 1 (Fig. 1).

Despite the clear link between marijuana use and the development of myocardial infarction, some studies suggest that its use may be protective for some risk factors for atherosclerosis. Some human studies report a lower prevalence of diabetes mellitus in marijuana users [36,37]. Reports from those studies could not have clear data on the frequency or dose of the drug on that effect on diabetes. An animal study reported by Montecucco et al [38] even concluded that a cannabinoid agonist in a mouse model of coronary occlusion, reperfusion resulted in a protective effect from coronary ischemia. Treated animals had a smaller infarction size.

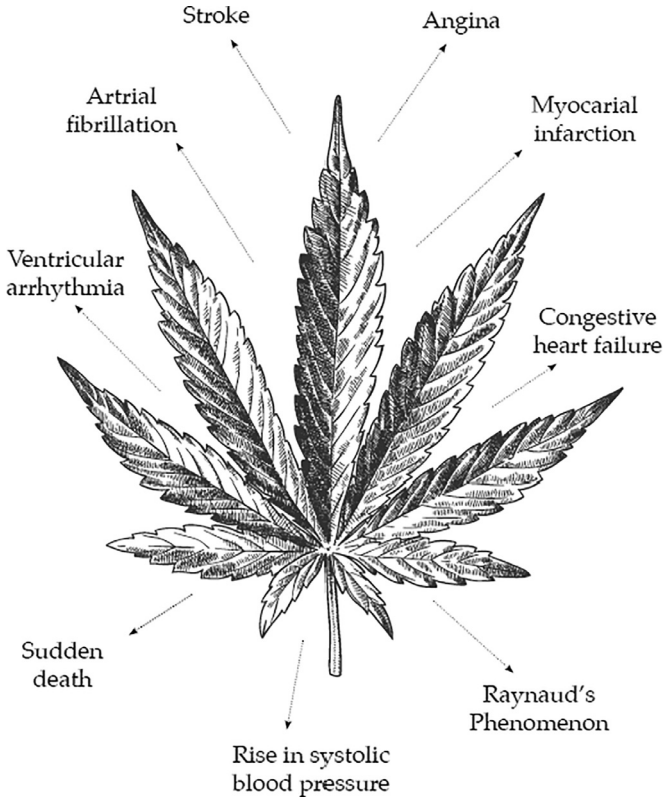

Fig. 1. Various vascular complications following marijuana use.

These reports enforce the need to have definitive studies to clarify the exact relation between various cannabis products, including marijuana, and the incidence of myocardial infarction.

Stroke

Cannabis, with its various forms, was linked to stroke development [39]. A majority of cases are non-hemorrhagic, but occasional reports were hemorrhagic strokes as well. In addition to the probable effect on cerebral blood vessels, cannabis may unfavorably affect brain mitochondria and oxidative stress; both have a detrimental effect on the pathophysiology of stroke [40,41].

Whether it is only marijuana use or whether associated tobacco use is the culprit is not clear. Barber et al. [42] investigated 25 young patients who presented with stroke, whose blood screens were positive for cannabis. With regression analysis, cannabis use was associated with increased stroke risk. When the risk was adjusted to tobacco use, no association with stroke development was found. A study by Rumalla et al. [43] investigated the relationship between acute ischemic stroke and marijuana use. Using a national inpatient sample, between the years 2004–2011, patients with stroke were stratified according to marijuana use. Among young adults presenting with stroke, smoking marijuana was associated with a 17% increase in stroke hospitalization. That increase was lost when adjusted for tobacco use. While some patients smoke pure marijuana using certain devices, many mix it with tobacco in a cigarette, and then smoke it. It is thus still unclear whether marijuana use alone or its combination with tobacco use may be implicated in the development of stroke.

Other vascular effects

Peripheral arteritis was also reported following acute and chronic marijuana use [44,45]. Subjects were mostly men who

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Table 1
Studies that examined the relationship between marijuana use and cardiovascular effects.

Author	Year	Type of study	Number of patients	Results
Mittleman et al. [18]	2001	Prospective, multi-center	3,882 with AMI	3.2% smoke marijuana Risk of AMI was elevated 4–8 times in the 60 minutes after drug use
Frost et al. [22]	2013	Multi-center inception cohort followed by NDI	1,935 with AMI followed for 12.7 years	Mortality rate was 29% higher among patients reporting marijuana use
Jouanjus et al. [20]	2014	Marijuana users presented with cardiac events reported in a national database	35	• Number of cases reported increased in more recent years • Death rated reported in these cases was 25.6%
Alshaarawy & Elbaz [48]	2016	Epidemiologic by National Center for Health Statistics	12,426	• Modest rise in systolic blood pressure in marijuana users • No effect on diastolic blood pressure
Lorenzo et al. [34]	2017	Prospective, multi-center study among AIDS patients	558	• Heavy marijuana use increased cardiovascular events • The effect is independent of tobacco use and other risk factors
Desai et al. [19]	2017	Epidemiologic from NIS	2,451,933	Lifetime of developing AMI increased in recreational marijuana users
Abouk & Adams [15]	2017	Epidemiologic from NVSS	617,466 patients with cardiac death	Cardiac death rate was higher by 2.3% in men and 1.3% in women in states (in the U.S.) with liberal marijuana laws
Kalla et al. [33]	2017	Epidemiologic from NIS	20,815,612	• Cannabis use increased heart failure and cerebrovascular accidents • Increase in sudden cardiac death
DeFilippis et al. [35]	2018	Retrospective analysis of AMI patients	2,097	Marijuana use increased all cause and cardiovascular mortality.

AMI, Acute Myocardial Infarction; NDI, National Death Index; NIS, Nationwide Inpatient Sample; NVSS, National Vital Statistics System.

were tobacco users. The presentations varied from Raynaud's phenomenon to venous thrombosis. Other rare vascular events reported in young patients include acute carditis [46] and spontaneous coronary dissection without any clear cause other than recent marijuana use [47].

In an epidemiologic study by the National Center for Health Statistics, 12,426 patients were examined to determine whether there was an association between blood pressure and marijuana use [48]. Patients were between the ages of 20–59 years. Assessment was done between the years 2005–2012. Marijuana use was associated with a rise in systolic blood pressure. That effect persisted even after adjustment for other risk factors such as body mass index, smoking, and other relevant co-variables. It is possible that the modest rise in systolic blood pressure plays some role in the pathogenesis of vascular complications.

Conclusion

Since 2014, marijuana use is now legal in ten states and the District of Columbia for recreational use. After initially legalizing it in the states of Colorado and Washington, few voices are questioning the effect of that action on the communities [49]. Questions raised include: What was the effect on the crime rate? Did marijuana legalization lead to an increase in traffic accidents? What was the impact on the general health of the community? More states legalized marijuana use, and others are on the way to doing so. In 1982, the surgeon general had issued a warning on recreational marijuana use [50]. It was based on scientific reviews by the World Health Organization, National Academy of Sciences, and the Canadian Addiction Research Foundation. The medical concerns, among many, included short-term memory impairment and slow learning, impaired immune response, and possible adverse effects on cardiac function. A more contemporary review published in 2014 [51], emphasized significant side effects on memory and learning ability, increased risk of motor vehicle accidents, and even increase in some forms of cancer with long-term use.

In this article, we discussed the temporal relationship between marijuana use and a variety of cardiovascular events. The events occurred in young patients with no other cardiovascular risk factors, other than recent marijuana use. The effects included atrial fibrillation, acute coronary syndromes, ventricular tachycardia, and even sudden death. The current evidence appears to be insufficient to draw a definitive conclusion on the effects of marijuana smoking on cardiovascular events and its possible mechanism [52]. There is a dire need for comprehensive definitive research on the effects of marijuana on the cardiovascular system, which might include laboratory and epidemiologic studies. The French model of compulsory reporting to a national database of acute cardiovascular events associated with marijuana use is an appealing idea, particularly in the United States where marijuana is legalized in many areas.

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Supplementary materials

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References

[1] Abrams DI. The therapeutic effects of Cannabis and cannabinoids: an update from the National Academies of Sciences, Engineering and Medicine report. Eur J Intern Med 2018;49:7–11.
[2] Beaconsfield P, Ginsburg J, Rainsbury R. Marihuana smoking. Cardiovascular effects in man and possible mechanisms. N Engl J Med 1972;287:209–12.
[3] Vettor R, Pagotto U, Pagano C, Pasquali R. Here, there and everywhere: the endocannabinoid system. J Neuroendocrinol 2008;20 Suppl 1:iv–vi.
[4] Miller RH, Dhingra RC, Kanakis C Jr, Amat-y-Leon F, Rosen KM. The electrophysiological effects of delta-9-tetrahydrocannabinol (cannabis) on cardiac conduction in man. Am Heart J 1977;94:740–7.
[5] Korantzopoulos P, Liu T, Papaioannides D, Li G, Goudevenos JA. Atrial fibrillation and marijuana smoking. Int J Clin Pract 2008:62308–13.
[6] Efe TH, Felekoglu MA, Çimen T, Doğan M. Atrial fibrillation following synthetic cannabinoid abuse. Turk Kardiyol Dern Ars 2017;45:362–4.
[7] Adegbala O, Adejumo AC, Olakanmi O, Akinjero A, Akintoye E, Alliu S, et al. Relation of cannabis use and atrial fibrillation among patients hospitalized for heart failure. Am J Cardiol 2018;122:129–34.

[8] Rezkalla SH, Sharma P, Kloner RA. Coronary no-flow and ventricular tachycardia associated with habitual marijuana use. Ann Emerg Med 2003;42:365–9.
[9] Sanchez Lazaro IJ, Bonet LA, Sancho-Tello MJ, Martinez-Dolz L. Ventricular tachycardia due to marijuana use in a heart transplant patient. Reve Esp Cardiol 2009;62:451–63.
[10] Karabulut A, Cakmak M. ST segment elevation myocardial infarction due to slow coronary flow occurring after cannabis consumption. Kardiol Pol 2010;68:1266–8.
[11] Khouzam RN, Kabra R, Soufi MK. Marijuana, bigeminal premature ventricular contractions and sluggish coronary flow: are they related? J Cardiology Cases 2013;8:121–4.
[12] Orsini J, Blaak C, Rajayer S, Gurung V, Tam E, Morante J, et al. Prolonged cardiac arrest complicating a massive ST-segment elevation myocardial infarction associated with marijuana consumption. J Community Hosp Intern Med Perspect 2016;6:31695.
[13] Tormey WP. Cannabis, possible cardiac deaths and the coroner in Ireland. Ir J Med Sci 2012;181:479–82.
[14] Hartung B, Kauferstein S, Ritz-Timme S, Daldrup T. Sudden unexpected death under acute influence of cannabis. Forensic Sci Int 2014;237:e11–13.
[15] Abouk R, Adams S. Examining the relationship between medical cannabis lawas and cardiovascular deaths in the US. Int J Drug Policy 2018;53:1–7.
[16] Draz EI, Oreby MM, Elsheikh EA, Khedr LA, Atlam SA. Marijuana use in acute coronary syndromes. Am J Drug Alcohol Abuse 2017;43:576–82.
[17] Nawrot TS, Perez L, Künzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 2011;377:732–40.
[18] Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardia infarction by marijuana. Circulation 2001;103:2805–9.
[19] Desai R, Patel U, Sharma S, Amin P, Bhuva R, Patel MS, et al. Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. Cureus 2017;9:e1816.
[20] Jouanjus E, Lapeyre-Mestre M, Micallef JFrench Association of the Regional Abuse and Dependence Monitoring Centres (CEIP-A) Working Group on Cannabis Complications*. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc. 2014;3:e000638.
[21] Rezkalla S, Kloner RA. Recreational marijuana use: is it safe for your patient? J Am Heart Assoc. 2014;3:e000904.
[22] Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman MA. Marijuana use and long-term mortality among survivors of acute myocardial infarction. Am Heart J 2013;165:170–5.
[23] Casier I, Vanduynhoven P, Haine S, Vrints C, Jorens PG. Is recent cannabis use associated with acute coronary syndromes? an illustrative case series. Acta Cardiol 2014;69:131–6.
[24] Arora S, Goyal H, Aggarwal P, Kukar A. ST-segment elevation myocardial infarction in a 37-year-old man with normal coronaries–it is not always cocaine!. Am J Emerg Med. 2012;30:2091.e3-5.
[25] Dahdouh Z, Roule V, Lognoné T, Sabatier R, Grollier G. Cannabis and coronary thrombosis: what is the role of platelets? Platelets. 2012;23(3):243–5.
[26] Shah M, Garg J, Patel B, Guthier J, Freudenberger RS. Can your heart handle the spice: a case of acute myocardial infarction and left ventricular apical thrombus. Int J Cardiol 2016;215:129–31.
[27] Hodcroft CJ, Rossiter MC, Buch AN. Cannabis-associated myocardial infarction in a young man with normal coronary arteries. J Emerg Med 2014;47:277–281.
[28] Gunawardena MD, Rajapakse S, Herath J, Amarasena N. Myocardial infarction following cannabis induced coronary vasospasm. BMJ Case Rep 2014;2014.
[29] Rezkalla S, Stankowski R, Kloner RA. Cardiovascular effects of marijuana. J Cardiovasc Pharmacol Ther 2016;21:452–5.
[30] Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014;113:187–90.
[31] Singla S, Sachdeva R, Mehta JL. Cannabinoids and atherosclerotic coronary heart disease. Clin Cardiol 2012;35:329–35.
[32] Mills B, Dishner E, Velasco CE. Acute myocardial infarction triggered by use of synthetic cannabis. Proc (Bayl Univ Med Cent) 2018;31:200–2.
[33] Kalla A, Krishnamoorthy PM, Gopalakrishanan A, Figueredo VM. Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the National Inpatient Sample. J Cardiovasc Med (Hagerstown) 2018;19(9):480–4.
[34] Lorenz DR, Dutta A, Mukerji SS, Holman A, Uno H, Gabuzda D. Marijuana use impacts midlife cardiovascular events in HIV-infected men. Clin Infect Dis 2017;65:626–35.
[35] DeFilippis EM, Sing A, Divakaran S, et al. Cocaine and marijuana use among young adults with myocardial infarction. J Am Coll Cardiol 2018;71:2540–2551.
[36] Sidney S. Maijuana use and type 2 diabetes mellitus: a review. Curr Diab Rep 2016;16:117.
[37] Rajavashisth T, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open 2012;2:e000494.
[38] Montecucco F, Lenglet S, Braunersreuther V, Burger F, Pelli G, Bertolotto M, et al. CB2 cannabinoid receptor activation is cardioprotective in a mouse model of ischemia/reperfusion. J Mol Cell Cardiol 2009;46:612–20.
[39] Gomez Ochoa SA. Stroke and cannabis use in patients with no cardiovascular risk factors: a systematic review of case reports. Neurologia 2017 Dec 22 pii: S0213-4853(17)30362-6. Epub ahead of print. doi:10.1016/j.nrl.2017.09.016.
[40] Atchaneeyasakul K, Torres LF, Malik AM. Large amount of cannabis ingestion resulting in spontaneous intracerebral hemorrhage: a case report. J Stroke Cerebrovasc Dis 2017;26:e138–9.
[41] Wolff V, Schlagowski AI, Rouyer O, Charles AL, Singh F, Auger C, et al. Tetrahydrocannabinol induces brain mitochondrial respiratory chain dysfunction and increases oxidative stress: a potential mechanism involved in cannabis-related stroke. Biomed Res Int 2015;2015:323706.
[42] Barber PA, Pridmore HM, Krishnamurthy V, Roberts S, Spriggs DA, Carter KN, et al. Cannabis, ischemic stroke, and transient ischemic attack: a case-control study. Stroke 2013;44:2327–9.
[43] Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: a population-based analysis of hospitalized patients in the United States. J Neurol Sci 2016;364:191–6.
[44] El Omri N, Eljaoudi R, Mekouar F, Jira M, Sekkach Y, Amezyane T, et al. Cannabis arteritis. Pan Afr Med J 2017;26:53.
[45] Desbois AC, Cacoub P. Cannabis-associated arterial disease. Ann Vasc Surg 2013;27:996–1005.
[46] Tournebize J, Gibaja V, Puskarczyk E, Popovic B, Kahn JP. Myocarditis associated with cannabis use in a 15-year-old boy: a rare case report. Int J Cardiol. 2016;203:243–4.
[47] Schmid J, Auer J. Spontaneous coronary artery dissection in a young man - case report. J Cardiothorac Surg 2011;6:22.
[48] Alshaarawy O, Elbaz HA. Cannabis use and blood pressure levels: Unites States National Health and Nutrition Examination Survey, 2005–2012. J Hypertens 2016;34:1507–12.
[49] National Conference of State Legislatures. State Medical Marijuana Laws. 2018. Available at: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed 16 October 2018.
[50] Centers for Disease Control (CDC) The surgeon general's warning on marijuana. MMWR Morb Mortal Wkly Rep 1982;31:428–9.
[51] Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370:2219–27.
[52] Ravi D, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations between marijuana use and cardiovascular risk factors and outcomes: a systematic review. Ann Intern Med 2018:168187–94.

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