Review Article
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Recreational cannabis: toxicity, stroke, aneurism and cardiovascular events

Abstract

There has been an alarming increase in incidence of cannabis associated stroke, aneurisms and cardiovascular events reported in the literature recently. These have been reported as case studies, research studies and through discussion by the scientific and medical community. Young, healthy individuals with no apparent risk factors, are apparently becoming vulnerable to stroke due to use of cannabis which contains delta 9- tetrahydrocannabinol or THC. THC may increase oxidative stress, and induce cerebral mitochondrial dysfunction. THC appears to dose-dependently inhibit brain mitochondrial respiration, thus raising the risk for ischemic stroke. Cannabis appears to also affect cerebral regulation and vascular tone, causing vasoconstriction and acute ischemic stroke. Additionally, cannabis use is associated with an 18% increased likelihood of aneurysmal subarachnoid hemorrhage (aSAH). Cardiovascular toxicity along with arterial stiffness associated with cannabis use, which in turn is associated with acceleration of cardiovascular age, which determines to a degree, biological age. These and other factors related to cannabis use, stroke, aneurism and cardiovascular health are discussed.

Volume 5 Issue 3 - 2019

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Received: April 05, 2019 | **Published:** May 24, 2019

Introduction

This review represents a small percentage of cannabis toxicity and stroke studies in the literature. However, there is a surprising amount of agreement across these major themes. Traditionally, concerns about cannabis use and abuse focused on cognition, memory, attention, motivation, altered mental states, and impaired driving, potential to induce serious mental illness such as psychosis and schizophrenia. There is a long-standing debate about gateway drug effects of cannabis. The association between moderate to heavy cannabis use and stroke, aneurism, and cardiovascular events has not been observed until recently. However, recent evidence should bring these aspects of cannabis use into focus. The proposed mechanisms by which stroke, aneurism, and cardiovascular events occur as a result of cannabis use are quite plausible. Any review of cannabis effects and mechanism of action must first make two distinctions. Do the data discussed pertain to recreational cannabis or medicinal cannabis? Recreational cannabis tends to be high in delta (9) tetrahydrocannabinol (THC) content. Some strains, such as Ghost OG, have tested at 28% THC.[1] Medicinal cannabis tends to have lower concentrations of THC (with exceptions) and higher concentrations of cannabidiol (CBD) and cannabinol (CBN). In addition to the THC vs CBD distinction, the distinction between adults and adolescents, with respect to drug effects also varies dramatically. While there are a few references to THC toxicology in infants and adolescents, this review will focus primarily on the effects of recreational cannabis on adults. All data, information and commentary in this review was obtained via research/case studies or reviews found in PubMed or Google.

Pharmacodynamic toxicity

While the major components of cannabis include delta (9) THC and CDB, there are in fact at least 70 phytocannabinoids in cannabis. The pharmacokinetics of THC and CBD vary widely depending upon route of administration; smoking, vaping, or taken orally in the form of a cannabis candy or brownie. The lethal dose at which 50% of the sample population dies or LD50 is relatively low for cannabis compared to other abuse drugs. Determined orally (PO) in Fisher rats, this value ranges from 800-1270mg/ml.[2] Compare this to a drug which contributes frequently to overdoses, such as cocaine, that has an LD50 of 95.1mg/kg I.P. in swiss mice.[3] THC is highly lipophilic and has a half-life of at least 7 days and can be detected for up to 30 days.[4] THC reaches peak blood concentrations in 1.5-3.5 hrs. The average THC content in a cannabis plant has increased from 4% to 16% over the last several decades. The mean bioavailability of THC after inhalation of a cannabis cigarette containing 3.55% THC is about 25% and the peak plasma level of 160ng/mL occurs approximately 10 min after smoking.[6] THC is quickly cleared from plasma in a multiphasic manner and is distributed to many tissues. Body fat is a long-term storage site for THC.[6] This pharmacodynamic fact complicates understanding the relationship between THC blood level and clinical effects and makes intoxication determination difficult. This is in contrast to alcohol, which obeys zero order, concentration independent kinetics, determining intoxication is relatively straightforward.

THC C max values in frequent smokers in blood have been shown to be in the following range: [mean (range) 17.[7] (8.036.1) mg/L] and in occasional smokers [8.2 (3.2 14.30mg/L].[7] These differences imply frequent smoking alters THC pharmacodynamic. There has been quite a bit of discussion about the role of vaping and comparisons between smoking, vaping and orally ingested cannabis in terms of pharmacokinetics and pharmacodynamic. There is some controversary in the literature about the effect of vaping on THC concentration. A study from John Hopkins compared vaping vs smoking (THC) found, at the doses tested, vaping increased THC delivery.[8] Another study, using different methodology, found that vaping vs smoking cannabis provided similar THC concentrations.[9]

Detection of THC in humans is complex and prone to error. A new method that reduces sample variability holds promise. This method normalizes sample creatinine and adjusts specific gravity. More sensitive detection of THC and its major metabolites[10] occurred using this approach and may help resolve the problem of assessing roadside intoxication.

While detection of THC has focused on smoked vs vaped cannabis, determining THC levels from people who have eaten cannabis or cannabis products has lagged in progress. Roadside evaluations must be able to detect orally ingested cannabis and THC levels. Modified roadside tests have included measuring pupil size, and a series of balance and walking tests. These measures showed no effect for smoking and vaping when tested at 1.5 and 3.5 hrs. post treatment. In contrast, ingested cannabis (50.4 mg), causes significant impairment.[5] Comparing occasional to frequent smokers, we see in a number of studies, frequent smokers have muted effects implying a type of tolerance takes place. Finding a method where one can distinguish THC that is bound to lipid and has been in the system for an extensive amount of time vs THC that has been recently ingested is obviously very important. The cannabinoid metabolites 11-nor-9-carboxy-THC (THCCOOH) and THCCOOH- glucuronide concentrations CBN and CBG are known to be present shortly after vaping or smoking cannabis. Thus, these metabolites could become valuable markers of recent cannabis use.[9]

Smoking vs vaping vs ingesting cannabis show different pharmacodynamic. Smoking increases expired CO concentrations, compared to vaping.[11] Heart rates (bpm) are significantly elevated for both frequent and occasional smokers regardless of smoking, vaping or ingesting cannabis.[11] When vaping was compared to smoking 0, 10 or 25mg of THC, in subjects that had not had any cannabis for at least a month and in some cases much longer, vaped cannabis yielded higher THC in blood, caused greater subjective effects and increased incidences of adverse effects vs smoked cannabis. Occasional smokers may be much more sensitive to the effects of vaping than previously expected.[8]

Because edible cannabis products have unique pharmacodynamic, overdoses are possible. The onset of action is slow, C max is achieved much later, and inexperienced users often exceed recommended doses. This is probably because they are impatient or doubts the product they have consumed, is having the desired effect. Tragic outcomes have occurred under these circumstances. The National Poison Data System reported 430 cannabis related calls from 2013 to 2015. 91% of the calls came from states with legal medical/recreational cannabis. Some cases were so severe, intubation was necessary. Edible cannabis overdoses can lead to respiratory depression.[12] The misconception that cannabis use cannot lead to respiratory depression, may contribute to cannabis overdoses.

Edible cannabis products are a primary concern for infants, as they are much more vulnerable to toxicity in general. However, a great deal of research has been directed towards the adolescent brain and cannabis effects. Regular to heavy cannabis use during adolescence, a period when neural development is very vulnerable to drugs of abuse, including THC, can permanently alter the trajectory of some neuromodulator systems.[13] It is known that cortical oscillations are an important part of brain function. In adolescent rodents, cannabis exposure suppresses cortical oscillations and impairs working memory when animals reach adulthood. Adolescent prefrontal cortex integrity is key to normal development.[13] Pediatricians conducted a comprehensive ER study, also on children, ranging from 3 years old to late teens. These children were admitted to the ER, some with very serious symptoms and had positive cannabis urine tests. Some had seizures, some required ventilation. Physicians have expressed concern about the rising concentration of THC in cannabis, and ease of access.[14] Nora Volkow, Director of NIDA, has echoed these sentiments and stated physicians should beware of the possibility of stroke in young, apparently risk-free individuals.[15]

Stroke is becoming a major, unlikely theme with cannabis. A case study of a 58-year-old woman who was admitted to the ER with "cardiogenic shock" illustrates this point. The patient had previous hospitalizations and left ventricular dysfunction. She also had more than 300ng/ml THC in her urine and prominent cardiac markers. Despite her history and age, she was considered a woman with no established risk factors other than her cannabis habit.[16]

These observations mark a disturbing trend that seems to associate cannabis use with otherwise healthy, young people who present in the ER not only with stroke, but aneurism, transient ischemic attack (TIA), subarachnoid hemorrhage (aSAH) and cardiovascular events. Young adults who use cannabis may inadvertently be causing narrowing of the arteries in the brain, or stenosis. It is also possible a clot forms in peripheral system, releases and travels to the brain where it occludes vessel(s) and deprives the brain of oxygen, causing tissue death. Hemorrhagic stroke does not cause damage via occluding vessels via a clot or thrombus but causes damage when a brain blood vessel leaks or ruptures. Dr. Valerie Wolff states brain arterial stenosis is most common in cannabis users. Wolff continues: "THC increases oxidative stress and induces cerebral mitochondrial dysfunction. This mechanism may be involved in young cannabis users who develop ischemic stroke since THC apparently increases patient's vulnerability to stroke." She and her colleagues found THC dose-dependently inhibited maximal brain mitochondrial respiration, thus raising the risk for ischemic stroke.[17]

Those interested in stroke and cardiovascular effects of cannabis have increasingly sophisticated tools in the lab to understand how cannabis precipitates stroke. Cannabis smoking was recently proved to cause pulmonary toxicity by inducing genotoxic effects or generating reactive oxygen species.(18) Because p53, a tumor suppressor gene, plays an important role in the regulation of lung epithelial cell DNA damage responses, investigators here hypothesized that p53 may contribute to oxidative stress-mediated apoptosis induced by smoking.[18] It is known that marijuana smoke condensate (MSC) causes oxidative stress in BEAS-2B cells. Reactive oxygen species (ROS) generation increases in the presence of MSC. Antioxidant enzyme (superoxide dismutase, catalase) activity and their mRNA expressions are up-regulated by MSC. These results taken together suggest that MSC partially induces p53-mediated apoptosis through ROS generation in human lung epithelial.[18]

Former or current tobacco smoking patients, with lung disease and are chronic cannabis consumers have detectable cannabinoids in their broncholavages (BAL)s. Thus, cannabis and its metabolites can be found in the lungs of smokers with lung disease. Analysis of the BALs shows cytotoxic effect of the cannabinoids. The cannabinoids are either present with the lung disease, in an associated manner, or they are contributing to the lung disease in a causal manner (or both).[19] Ischemic and hemorrhagic strokes associated with cannabis use are reported in the literature. Cannabis appears to affect cerebral regulation and vascular tone, causing vasoconstriction and acute ischemic stroke. However, hemorrhagic strokes, often seen with sympathomimetic illicit drugs (e.g. cocaine and amphetamines), have rarely been reported due to cannabis. Many cellular mechanisms within non-ischemic tissue post stroke may be augmented by heavy cannabis use.[20,21]

Citation: Brucato R. Recreational cannabis: toxicity, stroke, aneurism and cardiovascular events. *MOJ Toxicol.* 2019;5(3):101–104.
DOI: 10.15406/mojt.2019.05.00162

In the last few years, cannabis use has been associated with an 18% increased likelihood of aneurysmal subarachnoid hemorrhage (aSAH). Rumalla and colleagues looked at the relationship between aneurysmal subarachnoid hemorrhage (aSAH) cannabis use. The Nationwide Inpatient Sample (2004-2011) was used to identify patients (age 15-54) with a primary diagnosis of aSAH and cannabis use was considered among the sample. Cannabis use was found to be an independent predictor of aSAH when adjusting for demographics, substance use, and risk factors.[22] Cardiovascular toxicity of smoked cannabis is now more frequently observed as are measures of arterial stiffness or vascular age (VA). In view of its diverse toxicology, the possibility that cannabis-exposed patients may be ageing more quickly is gaining interest. Radial arterial pulse wave tonometry (AtCor, Sphygmogram Cor, Sydney) was used on cannabis smokers, tobacco smokers, combined and non-smokers, between 2006 and 2011. Cannabis has been determined to be an interactive cardiovascular risk factor (additional to tobacco and opioids). Cannabis use does appear to be associated with an acceleration of the cardiovascular age, which determines to a degree, biological age.[23,24]

Cardiovascular events related to cannabis have led to severe outcomes. In a study of the French Addictoviggilance Network, a clinical assessment of a sample of average age 34.3 years old, mostly men are as follows: 22 cardiac complications (20 acute coronary syndromes), 10 peripheral complications (lower limb or juvenile arteriopathies and Buerger-like diseases), 3 cerebral complications (acute cerebral angiopathy, transient cortical blindness, and spasm of cerebral artery). In 9 cases, the event led to patient death.[25] Cardiovascular cases in very young subjects continue to be alarming. In one case, a 21-year-old healthy man had a myocardial infarction and was a chronic cannabis smoker with no apparent risk factors, other than he also smoked cigarettes. A large thrombus was observed in his left descending coronary artery, with no atherosclerosis.[26]

Finally, in another review of patients with cannabis use also appeared related to stroke. The distribution of these patients was as follows: The sample includes 85 cannabis users and 13 users of synthetic cannabinoids.[4] patients had an undetermined type of stroke, 85 had an ischemic stroke and/or a transient ischemic attack, and 9 had a hemorrhagic stroke. The mean patient age was 32.3±11.8years (range 15-63), and the majority were male. Cannabis was smoked with tobacco in 66% of cases. Most of the patients with cannabinoids-related strokes were chronic cannabis users (81%). Importantly, in many of these cases there was a recent increase of the amount of cannabis used just prior to the stroke. Although stroke prognosis was favorable or without complications in 46% of cases, 5 patients died after the stroke. The authors state: "One of the mechanisms involved in young cannabis users with stroke may be the generation of reactive oxygen species leading to an oxidative stress, which is a known mechanism in stroke in humans. It is useful to inform the young population about the real potential risk of using cannabinoids." The authors suggest to systematically ask all young adults with stroke about their drug consumption including cannabinoids.[27]

Conclusion

It is clear today's recreational cannabis presents health dangers for a variety of reasons. The fundamental differences between today's cannabis and that of the 1970's, when cannabis was already popular among many is: 1) the increase in availability either through legalization or easier illicit access, and 2) increased perception that cannabis is safe and acceptable to use, 3) financial incentives to invest, which also encourages use, 4) the substantial increase in THC content, at 28% for the most potent strains currently available 5) the younger age of cannabis consumers. All of these factors influence the prevalence of Cannabis Use Disorder, or health impairing moderate to heavy habitual cannabis use. It is true cannabis has a low LD50, compared to other abuse drugs. It is difficult for a grown adult to smoke so much cannabis, death results directly. This is partly because smoked cannabis does not have the same effect on respiratory depression as many other drugs. CB1 receptors have limited distribution and concentration in the respiratory system. However, respiratory depression can still occur with high doses of orally ingested cannabis or cannabis products. Infants that consumed available edible cannabis products, have died. That is a fact. In this review, I discussed the growing incidences of stroke, aneurism, and cardiovascular events. The numbers of healthy young people with no risk factors, ending up in the ER with stroke, aneurism and cardiovascular events is rising. There are several explanations for stroke, aneurism and cardiovascular events that are becoming plausible.

In arterial stenosis, THC increases oxidative stress and induces cerebral mitochondrial dysfunction. This mechanism may be involved in young cannabis users who develop ischemic stroke since THC apparently increases patient's vulnerability to stroke. THC dose-dependently inhibits maximal brain mitochondrial respiration, thus raising the risk for ischemic stroke [(17)]. Cannabis smoking causes pulmonary toxicity by inducing genotoxic effects or generating reactive oxygen species.[(18)] The tumor suppressor gene p53, plays an important role in the regulation of lung epithelial cell DNA damage responses. Oxidative stress-mediated apoptosis is induced by smoking cannabis.[18] Cannabis appears to affect cerebral regulation and vascular tone, causing vasoconstriction and acute ischemic stroke. Cannabis use is associated with an 18% increased likelihood of aneurysmal subarachnoid hemorrhage.[22]

Cardiovascular toxicity along with arterial stiffness and vascular age are now more frequently observed. Cannabis use does appear to be associated with an acceleration of the cardiovascular age, which determines to a degree, biological age.[23,24] Traditionally, concerns about cannabis use and abuse have focused on cognition, memory, attention, motivation, altered mental states, potential to induce serious mental illness such as psychosis and schizophrenia. There is a long-standing debate about gateway drug effects of cannabis.[28–30] The association between moderate to heavy cannabis use and stroke, aneurism, and cardiovascular events is a relatively new concern, supported by evidence. This recent evidence that shows young, healthy, otherwise risk-free individuals who present in the ER with stroke, aneurism or cardiovascular events, should be asked if they use cannabis. If so, how frequently, and the ER physician should review their tox screen closely. Furthermore physicians should alert one another, when these cases occur.

Acknowledgment

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Citation: Brucato R. Recreational cannabis: toxicity, stroke, aneurism and cardiovascular events. *MOJ Toxicol.* 2019;5(3):101–104.
DOI: 10.15406/mojt.2019.05.00162

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DOI: 10.15406/mojt.2019.05.00162