Mini Review
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# Current data raises toxicity and safety concerns about today's high thc content cannabis

## Abstract

The marijuana industry has become one of the most rapidly growing industries in the US. Itâ€™s become highly visible, drawing the attention of ultra-wealthy investors such as Warren Buffet. However, todayâ€™s marijuana is engineered to contain very highly concentrated levels of THC, the psychoactive ingredient that contributes to the â€œmarijuana highâ€ that so many enthusiasts seek. THC is also a central player in many of the health concerns and adverse reactions experienced by many. Now physicians are seeing some of the reactions associated with the old, more dilute THC marijuana of the past but they are seeing new, previously unobserved reactions to the new concentrated THC-containing cannabis, included stroke, overdoses, particularly from the edible cannabis candies, brownies and cookies, there are documented suicides associated with adverse reactions while taking the new marijuana. Potential gateway effects and addiction seem on the rise. There is a lot of concern about the effect this potent marijuana has on adolescents, who are particularly sensitive to development influences of drugs including marijuana. In this mini-review I discuss current research, explain suspected mechanisms of action, and review clinical research and observations. I also point out some similarities to the growth of the tobacco industry and possible solutions to the problems that are on the rise. Cannabis enthusiasts and the expanding marijuana industry are clearly pleased with new medical and recreational marijuana laws, as well as the changing landscape in general. With regard to medical marijuana, time will tell whether that enthusiasm is warranted. However data from numerous research labs continue raising troubling issues. Most concerns revolve around the following questions:

Does cannabis use because any physical harm to either adolescents or adults?

Can cannabis use impair either adolescent or adult cognition, or both? (Attention, memory, reasoning, judgment, and intellectual function)

Can moderate to heavy cannabis use cause or exacerbate mental illness?

Does cannabis use harm cardiovascular and respiratory health and does cannabis use cause stroke?

New data suggests cannabis can act as a gateway drug. Does cannabis use lead to drugs such as heroin?

Are there risks to children if the parents conceive when they are regular marijuana users?

The purpose of this review is to present data from preclinical research, human research, individual case studies and observational studies in order to address these concerns. Specifically, I will discuss areas relating to cognition, brain function and connectivity, mental health, addiction, stroke, cardiovascular effects, health and behavioral effects cannabis use may have on kids. In some of these areas, there has been substantial research; other areas have not been thoroughly explored. In all cases, I have tried to discuss data coming from the most credible sources possible.

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Rick Brucato
Cascade Chemical Biology, USA

**Correspondence:** Rick Brucato, Cascade Chemical Biology, Princeton Corporate Plaza 9 Deer Park Dr., Suite K8 Monmouth Junction, NJ 08852, USA, Tel 914 275 8419, Email rickbrucato@rocketmail.com

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## Introduction

### Mechanisms of cannabis and its major components

There are over 70 phytocannabinoinds in cannabis, with the three major components being Δ(9) tetrahydrocannabinol (THC), cannabidiol (CBD) cannabinol (CBN). The pharmacokinetics of these components vary dramatically depending upon whether cannabis is smoked, vaped, taken orally in the form of a cannabis candy, or as a brownie or cookie. In addition drug-drug interactions with substances such as tobacco, smoking cessation products are important to consider. Marijuana and tobacco smoke both induce cytochrome P450 (CYP) 1A2 by activating the aromatic hydrocarbon receptor. This effect is additive. Smoking cessation results in rapid down regulation of CYP1A enzymes.[1] One study showed THC maximum concentrations ($C_{max}$) in blood were higher in frequent smokers [mean (range) 17.7 (8.036.1)µg/L] compared to occasional [8.2 (3.2 14.3)µg/L] smokers, suggesting frequent smoking changes the pharmacodynamics.[2] Cannabis exerts its effect via cannabinoid receptors $CB_1$ and $CB_2$. C $B_1$ receptors are distributed in the CNS and are particularly dense in limbic and learning areas such as hippocampus amygdala prefrontal cortex and striatum. $CB_1$ receptors are also found in the basal ganglia. They are also found in the cerebellum and in both male and female reproductive systems. $CB_1$ is also found in the human anterior eye and retina.[3] $CB_2$ receptors are predominantly found in the immune system or immune-derived cells with the greatest density in the

spleen. While found manly in the peripheral nervous system, a report does indicate that $CB_2$ is expressed by a subpopulation of microglia in the human cerebellum. $CB_2$ receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis seen in animal models. $CB_2$ receptors are located in reward areas in lower density.[3] The lethal dose 50 or LD50 for THC in Fischer rats PO is 800mg/kg, 1270mg/kg depending upon vehicle.[4] This is comparatively weak compared to cocaine. The LD50 for cocaine is 95.1mg/kg, Swiss mice IP.[5] The weak marijuana LD50 is often used to argue for cannabis' comparative safely and general benign nature as a drug. We will discuss respiratory depression and the myriad of indirect ways with which cannabis can cause harm below. There is much focus on today's high THC concentration. It is common to find much more THC and much less CBD per plant.[6,7] The problem of pesticide-contaminated marijuana also requires more research.[8] Pesticide has been detected on the cannabis plant intended for commercial sale. Smoked marijuana reaches Cmax much faster than orally consumed cannabis. Smoked marijuana enters the bloodstream quickly, exerts its effects via $CB_1$ $CB_2$ receptors in the central nervous system and peripheral nervous system respectively. Marijuana constricts blood vessels, affecting the cardiovascular system, pulmonary system and brain vasculature. It also binds to $CB_1$ receptors that are in the brain, in areas central to cognitive performance such as the hippocampus, prefrontal cortex, amygdala, and striatum. It's been demonstrated that the physiology of experienced smokers differs from that of new smokers. In one study, THC maximum concentrations ($C_{max}$) in blood were higher in frequent smokers compared to occasional smokers.[3] A study reports that, because THC has a high degree of liphillicity, its half-life (T1/2) is 7 days and can be detected for up to 30 days.[9]

## Marijuana, opiates and the gateway effect

There are many new concerns regarding today's potent marijuana. Some of the old concerns that applied to less potent marijuana are being revisited. When we think back to the '70s and '80 to the days of less potent marijuana, we could not have envisioned a rampant and extensive heroin and opiate crisis among adolescents and young adults, including in suburban areas. The gateway hypothesis describes the potential for marijuana to open the door to harder drugs. It is still hotly debated.[10] However science is starting to catch up. First, there has been much work on marijuana addiction alone.[11] Scientists at NIDA have been working hard to understand marijuana's reward system. Second, credible research has shown marijuana leads to an increase in prescription drug abuse by young people, such as oxycontin.[12] We know from research[13] and accounts from heroin addicts themselves, that once hooked on oxycontin, kids will resort to less expensive heroin to achieve their opiate high. Now investigators have demonstrated that, by dosing adolescent rats with THC, allowing these $F_1$ animals to breed at maturity, the offspring's mRNA expressed an altered reward system and receptors in the striatum. Alterations in cannabinoid, dopamine, and glutamatergic receptors in dorsal striatum has implications for compulsive and goal directed behaviors such as drug seeking and drug addiction. In fact, offspring of animals exposed to THC, showed increased self-administration and lever-pressing for heroin.[14] To extrapolate to humans, this means kids who have never taken drugs, could be at greater risk for heroin addiction, if their parents were smoking marijuana when the child was conceived.

## Marijuana use, stroke and aneurysmal subarachnoid hemorrhage

Another concern unique to today's high THC cannabis comes from physicians who are seeing young healthy people coming in to the ER with stroke or aneurysm.[15,16] In the population studied, risk of non-fatal stroke or transient ischemic attack (TIA), heavy cannibus users had a significantly higher rate of stroke or TIA than non-users, approximately 3.3 times increase, adjusted for age cohort. Heavy users were defined as using at least once a week or more. One of the aged populations studied ranged from age 20-24.[16] Aneurysmal subarachnoid hemorrhage (aSAH) was also analyzed from the Nationwide Inpatient Sample (2004-2011) that drew aSAH data from hospitalized patents testing positive for cannabis that had experienced an aSAH. This study found recreational marijuana was independently associated with an 18% increase aSAH.[15] From 2004-2011, there has been a general increase in marijuana-related visits to the ER for both the use of cannabis-only and cannabis-polydrug during the studied period, particularly among young people and non-Hispanic blacks.[17]

## Marijuana use and mental illness

There have been quite a few tragic deaths since marijuana has been made legal. Most appear to result from taking much more than the recommended dose of edibles such as brownies, gummy bears etc. Some of these adverse reactions led to suicide by gunshot, suicide by leaping off the roof of a building etc. Highly potent cannabis seem to induce psychosis by disrupting Gabaergic transmission in the prefrontal cortex, at least in part.[18] Another advancement has been a greater understanding of how marijuana (THC) causes paranoia. Another disruptive and frightening adverse reaction some marijuana users can have.[19] It has also been discovered the AKT1 genotype found in some adolescents, seems to influence pscyhotominmetic effects of smoking cannabis.[20]

## Marijuana use modifies brain structure and physiology

There are quite a few studies that conclude heavy smoking during adolescence can actually modify the brain, by altering connectivity, size, structure or even change the brain's gyri profile. Most critical, emerging adults with heavy use backgrounds show size effects in brain areas that are involved in cognition, such as the prefrontal cortex and parietal region.[6–21]

**Remaining concerns:** While beyond the scope of this current review it is important to mention there is much concern about:

a. Cannibus Use Disorder (CUD)/addiction

b. Second hand smoke effects both as an irritant and as a potential psychological stressor for those who have undergone rehabilitation for CUD.

c. Sensory motor effects that may contribute to cannabis related automobile accidents and observations that some with

d. Violent tendencies may, through disinbibition, act out there violent potential.

# Summary

Current research is targeting ways to make marijuana safer. One approach is to use cannabidiol, the potentially therapeutic cannabinoid, to antagonize the toxic effects of THC. Alternatively, we could engineer strains of cannabis that have a gentler ratio of CBD to THC. In other words some of cannabis's harmful effects could be managed with less THC and more CBD.[22] It is clear that there is tremendous enthusiasm and momentum in both loosening the marijuana laws and developing an industry around legal marijuana. However current research calls into question the safety of today's highly potent marijuana Physicians are seeing increased ER traffic, OD's, greater incident of stroke and

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cardiovascular events, increased evidence that marijuana use impairs cognition and memory, even causes changes brain architecture in heavy users. It's become clear that addiction really happens and there is stronger evidence that marijuana is associated with opiate abuse, including heroin. The fear that those at risk for serious mental illness, are harmed by today's' cannabis, seems to be validated. Those at risk for developing mental illness do have more adverse reactions to marijuana than the general public. It is clear that marijuana poses the biggest threat to adolescents who are at risk socially and whose brains are dramatically affected both physiologically and structurally. The brain is slow to develop, particularly the prefrontal cortex, which is rich in $CB_1$ receptors and does not complete development until the early or mid-twenties. The PFC is involved with memory, judgment and reasoning and emotion. The medicinal potential of the non-psychoactive component of cannabis, cannabidiol, is frequently confused or equated with THC. The failure to make this distinction clear to parents and kids, has allowed the general community to make false conclusions about cannabis safety. People fail to distinguish between the actions of THC and CBD. They hear good things about medicinal cannabis, which may be low in THC, higher in CBD. This confusion has lead to overdoses and ER visits, automobile crashes, stroke and other conditions listed above. Legalization of medical marijuana has been associated with increased use of recreational marijuana in some communities. Obviously the message received by the kids is if cannabis helps make a sick person well, it has to be safe for me. This is a major problem that must be resolved. It is certainly possible that CBD medicinal potential becomes more promising over time while at the same time research continues to highlight and discover THC's negative effects. Unfortunately much of the interest in cannabis and the flourishing marijuana industry revolve around the psychoactive properties the user seeks from THC containing cannabis. Resolving this will become a matter of our culture's desire to protect our kids vs. the desire of many to experience psychoactive THC and the altered mental state it induces.

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## Conflict of interest

The author declares no conflict of interest.

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