



# Marijuana Use in the Era of Changing Cannabis Laws: What Are the Risks? Who is Most at Risk?

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## Abstract

We review recent findings on medical aspects of marijuana use in order to identify those who are at greatest risk of marijuana-related medical problems. We analyze the impact of medical marijuana laws on health, in particular the disproportionate effects on adolescents and children. Chronic marijuana use predominantly affects certain areas of the brain that overlap the default mode network, linked hubs in the brain that play a supervisory role in critical thought processes such as attention, memory, and social interactions. Disruption of the default mode network areas has been documented in schizophrenia and Alzheimer's disease, illnesses with symptoms and brain changes that parallel findings in marijuana abusers. These findings counter the claim that marijuana is a harmless drug and are a cause for alarm in persons with cannabis dependence.

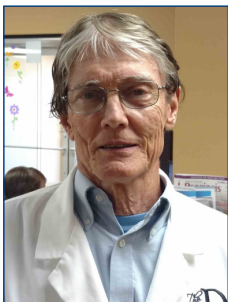
## Introduction

As the November general election nears with three ill-conceived referenda which would legalize 'medical' marijuana, physicians should carefully consider the many medical, social, educational and law enforcement problems that other states, notably Colorado, have encountered after enacting similar legislation. If legalization occurs, physicians should think how they will respond to demands for

marijuana prescriptions and the potential liability for adverse marijuana caused side effects, illnesses or accidents.

Consider this statement from the Colorado Medical Association: "Other states facing legislative efforts to legalize marijuana should consider Colorado's experience as a cautionary tale. Approving medical treatments by ballot initiatives sets a dangerous precedent for public health. This will be one of the great social experiments of the century." Source: <http://www.cms.org/articles/marijuana-legalization>.

In this article, we review properties of marijuana, to identify who may be at increased risk of problems if marijuana becomes widely available. We review the general impact of putative medical marijuana laws, including changes in marijuana use and diversion to non-medical and underage users. Finally, we identify adverse changes in the brain that can occur in chronic marijuana users. Here marijuana or equivalently "cannabis" refers to all parts of the plant in the genus *Cannabis*, including stems seeds, stalks, and any extracts derived from the plant. We consider all forms of administration including ingestion by vaporization or smoking, ingestion by eating or drinking or by contact with the skin of any cannabis products or chemicals, whether natural or synthesized, collectively referred to as "cannabinoids." The cannabinoids we discuss include 'high/mood-altering' delta-9-tetrahydrocannabinol, commonly referred to as THC, which is used in the recreational use products and the 'non-high/mood-altering' cannabidiol, or CBD, which is the form in which medicinal properties reside.



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## Medical Marijuana Laws and Marijuana Use after Legislation

Thirty-one states and the District of Columbia have passed medical marijuana laws (MML) as of September 2018. Few of these states maintain medical marijuana registries, so the National Academy of Sciences report on therapeutic marijuana relied on patients reporting qualifying illness(es) in Oregon and Colorado to obtain information

**Table 1.** Medical indications for marijuana and level of evidence<sup>1</sup>

Indication	Level of Evidence
Anxiety (individuals with social anxiety disorders)	Limited
Chemotherapy-induced nausea, vomiting	Substantial
Chronic pain	Substantial
Glaucoma	Limited
Improving clinician-measured multiple sclerosis spasticity symptoms	Limited
Improving clinician-measured multiple sclerosis spasticity symptoms	Limited
Improving symptoms of Tourette syndrome	Limited
Increasing appetite/decreasing weight loss with HIV/AIDS	Limited
Insomnia (improving short-term sleep outcomes)	Moderate
PTSD	Limited

on the proportion of patients reporting qualifying illnesses of medical marijuana users.<sup>1</sup> By far the largest proportion of these users (90-93%) reported severe pain. Other conditions reported by 2% or more of medical marijuana users are muscle spasms and multiple sclerosis (25-29%), nausea (12-13%), PTSD (8%), cancer (4-6%) and seizures (3%).<sup>1</sup> (More than one condition may be reported). Only 1% of medical marijuana users listed glaucoma as the medical qualifying condition.

The level of evidence (quality of studies available) for marijuana therapy for these indications is moderate or substantial for only three indications: chronic pain, chemotherapy-induced nausea and vomiting and insomnia (improving short-term sleep outcomes) (Table 1).<sup>1</sup> For these conditions, alternate therapies are either more effective or have fewer adverse effects. For example, marijuana alleviates chemotherapy-induced nausea, yet it can induce the cannabis hyperemesis syndrome.<sup>2-5</sup>

### Marijuana Laws, Marijuana Use and Adolescents

A large proportion of youth in the US are exposed to marijuana. For US youth 15 to 16 years old, 35.8% are said to have used marijuana.<sup>6,7</sup> One critical question is whether adolescent use of marijuana increases after marijuana laws are passed. Here we consider both medical marijuana laws as well as recreational marijuana laws.

Keyes et al. and Sarvet et al. found no overall increase in adolescent use of marijuana after the passage of MMLs.<sup>8,9</sup> Chu commented on the Sarvet study, “MMLs could encourage existing casual users to become regular or heavy users. As the majority of social costs are incurred by a small number of heavy users, the effects of MMLs on the intensive margin [heavy users of marijuana] must be evaluated carefully, as this is a significant policy implication.<sup>10</sup> Chu further cited five studies that all showed an increase in adult use of marijuana after passage of MMLs. Chu asked, “Why do MMLs affect adolescents differently from adults? For

example, could MMLs reduce the black-market supply and so limit adolescents’ access to marijuana? Or could making a substance legal or semi-legal reduce teenagers’ preference for it?”

In another study, Chu analyzed marijuana arrests among adult males following the passage of MMLs and found an increase in marijuana arrests among adult males by about 15-20%.<sup>11</sup> Admissions to rehabilitation facilities for marijuana treatments similarly increased after the passage of MMLs. There is some concern that the perception of harmfulness of marijuana, possibly a key factor in lowering rates of adolescent marijuana use, may fall after MML passage. A fall in perceived harmfulness of marijuana in the general population has been noted<sup>8</sup> and confirmed by Cerdá et al. in Washington but not Colorado.<sup>12</sup>

Hasin et al. analyzed US national survey data collected in three periods from 1991 to 2013 from 118,497 participants. They determined that the risk for cannabis use and cannabis use disorders increased at a significantly greater rate in states that passed MMLs than in states that did not.<sup>13</sup>

After recreational marijuana use was legalized in the state of Washington, both eighth and tenth graders in that state perceived marijuana use as more harmless.<sup>12</sup> Marijuana use increased in both grades following the passage of recreational marijuana laws. In Oregon, following similar legislation, rates of undergraduate marijuana use increased from pre- to post-2015, at a rate that was similar to the increase that was also observed at other universities in states where marijuana was still illegal.<sup>14</sup> Increases in rates of undergraduate marijuana use were significantly greater in Oregon than in comparison institutions, but only among students reporting recent heavy alcohol use, an indication of co-morbidities in students with substance abuse.

In contrast, Colorado did not exhibit any differential change in perceived harmfulness or past-month adolescent marijuana use following legalization. Yet Jones et al. found the frequency of marijuana use in Colorado college students

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is much higher than the national average, especially the percentage of daily or almost daily users.<sup>15</sup> The same study found significant differences between the marijuana non-users and the once a week or more marijuana users in grade point average.<sup>15</sup> Cerdá suggests investment in evidence-based adolescent substance use prevention programs in any additional states that may legalize recreational marijuana use.<sup>12</sup>

### Marijuana Laws, Children, Emergency Rooms, and Schools

Calls to Poison Control Centers have reported an increase in marijuana exposure among younger children.<sup>1</sup> Accidental ingestion of marijuana edibles has resulted in respiratory failure and coma.<sup>16,17</sup> An increase in overall pediatric exposures has followed MML enactment. From 2000 to 2013, the annual rate of Poison Control Center calls for marijuana exposure for children younger than six was 2.82 times higher in states that had MMLs prior to 2000, than in states where marijuana remained illegal as of 2013.<sup>18</sup> Sergeant P Bret Hinkle of the Marijuana Unit of the Denver Police Department cited instances of parents that grow marijuana and make it available to children.<sup>19</sup>

Emergency rooms are seeing a relatively new syndrome, the marijuana hyperemesis syndrome.<sup>2,5</sup> Persistent vomiting is observed in cannabis users, at a rate that has increased significantly in states where marijuana has been legalized.<sup>2</sup> The number of emergency room visits for cyclic vomiting, including cannabis-induced vomiting, doubled since legalization in Colorado.<sup>3</sup> Although hot showers are often recommended for cannabis hyperemesis, these are of variable effectiveness, as marijuana cessation appears to be the best remedy.<sup>4</sup> Phelps County Regional Medical Center ER physician Dr. Francina Hoffman has seen her first cases in recent years. She said, “They [marijuana users] come in because they can’t stop vomiting. We prescribe Phenergan or Zofran, but they are often noncompliant. On the third ER visit, they get admitted.”<sup>5</sup>

Overall, the yearly rate of emergency department visits related to marijuana increased 35 percent after the legalization of recreational marijuana in Colorado.<sup>20</sup> The number of hospitalizations related to marijuana also increased steadily during this period, nearly doubling from 2011 to 2014.<sup>20</sup>

The superintendent of Rolla schools, Dr. Aaron Zalis, said that medical marijuana laws add work for school administrators.<sup>21</sup> “There is more to unwind,” said Dr. Zalis. “Alcohol, opiates and marijuana, right now, all are illegal for juveniles ... The schools are required to check out all the drugs that students have ... The distinction of medical

marijuana makes it a lot more complicated ... There will be more documentation and compliance with new regulations. Additionally, any legislation that makes marijuana available could lead to other substance abuse. I’ve always viewed marijuana as a gateway. Based on the counselors that we work with, over a 34-year period ... [marijuana] leads to other things.”<sup>21</sup>

### Groups at Increased Risk of Adverse Effects of Marijuana

Epidemiologic evidence shows strong correlation between heavy marijuana use during adolescence and schizophrenia.<sup>22</sup> Other evidence shows increased risk for schizophrenia with early use of marijuana in males. Onset of marijuana use in early adolescence (before age 16) has been associated with more severe psychosis.<sup>7,23-26</sup> Recent findings using a polygenic risk score for schizophrenia and cerebral cortical thickness obtained from MRI imaging showed progressive thinning of the cerebral cortex in males with a high genetic risk for schizophrenia and early marijuana use.<sup>7</sup> The researchers found no increased risk for females. Two factors may be responsible for increased vulnerability of males to schizophrenia with marijuana use: earlier onset of schizophrenia in males and sex differences in dynamics of brain development, with greater changes in male white and gray matter volumes in male adolescents compared to females.<sup>27,28</sup> The anatomic locations in the brain for both schizophrenia and brain alterations with chronic use of marijuana are similar, involving especially the hippocampus and pre-frontal cortex.<sup>29</sup>

### Users of High-Potency Weed: “Skunk”

There has been a general increase in the potency of available marijuana, with available marijuana quadrupling in strength from the 1980s to 2012.<sup>29,30</sup> Sometimes called “skunk,” a name apparently generated by users’ comments about odor, the high-potency weed has higher levels of active cannabinoids. Marijuana potency is usually judged according to concentrations of THC, the primary psychoactive constituent in marijuana. Marijuana also contains other cannabinoids such as CBD, which has been thought to lack most of the psychoactive effects of THC and even to moderate the effect of THC.<sup>31</sup> Uncertainty about the ameliorative effect of CBD on THC was raised by recent animal studies showing an increased THC level mediated by cannabidiol and cannabidiol inhibits the metabolism of THC.<sup>32,33</sup> There is no limit on the potency of marijuana in the US, as there is for example in some nations, e.g. Uruguay.<sup>31,34</sup> Fifteen states do have limits on THC content for a different purpose—to allow access to what are considered “non-psychoactive” products such as cannabidiol oil.<sup>1</sup>

Volkow et al. noted in a review in the *New England Journal of Medicine* that higher marijuana potency raises concerns that the “consequences of marijuana use may be worse now than in the past,” and “may account for the significant increases in emergency department visits by persons reporting marijuana use and the increases in fatal motor-vehicle accidents.”<sup>29,35,36</sup> The Volkow group also said, “This increase in THC potency over time also raises questions about the current relevance of the findings in older studies on the effects of marijuana use, especially studies that assessed long-term outcomes.”

Freeman and Winstock showed that high-potency skunk marijuana resulted in greater memory impairment and likelihood of paranoia.<sup>31</sup> Eighty-two percent of skunk users had memory impairment as opposed to 4% of users of “other types of grass.” Skunk was also more likely to induce a feeling of paranoia than other types (78% vs. 7%), yet it remained by far the most preferred type of marijuana, giving the “best high” and was the most available type of marijuana.<sup>31</sup>

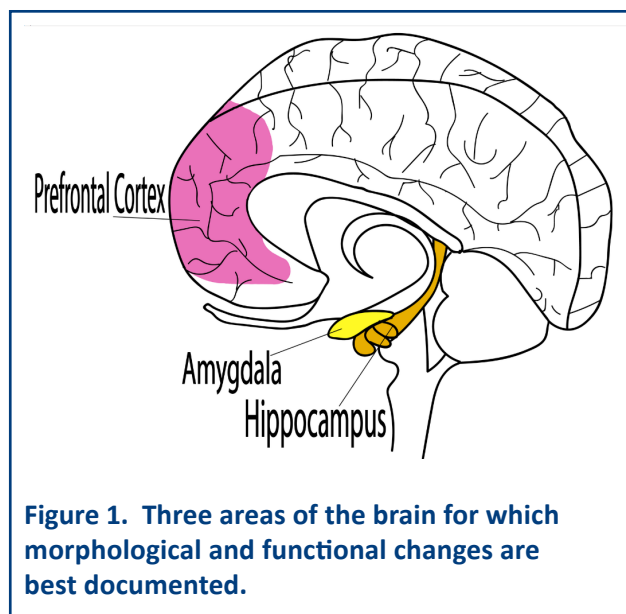
### Adverse Effects of Marijuana on the Lungs: Chronic Bronchitis Symptoms

The organ with best evidence for adverse effects from chronic marijuana use, besides the brain, is the lower respiratory system. The National Academy of Sciences report<sup>1</sup> found association between smoking marijuana on a regular basis and an increase in chronic cough and phlegm production as well as more frequent chronic bronchitis episodes.<sup>1</sup> Quitting marijuana smoking reduces these adverse effects. Tétrault et al. found a lower FEV<sub>1</sub> in long-term marijuana exposure.<sup>37</sup> Hancox et al. found higher forced vital capacity (FVC), although other studies varied in their conclusions on objective measures such as FEV<sub>1</sub> and FVC.<sup>1,38</sup>

### Brain Changes in Regular Users of Marijuana

Lorenzetti et al. reviewed anatomic brain changes in chronic marijuana users.<sup>39</sup> Chronic marijuana use was defined as exposure to marijuana on a daily or almost daily basis. Most users in the study started smoking marijuana between the ages of 15 to 17 and continued for a duration between two and 23 years. Lifetime episodes of marijuana use, typically referring to the number of joints smoked, ranged from 402 to 5,625. The brain abnormalities found were associated with higher levels of marijuana use, taking into consideration dosage, age of onset, and duration.

The review found substantial overlap between the location of the changes in the brains of marijuana users and the location of concentrated THC receptors.<sup>39,40</sup> The most



**Figure 1. Three areas of the brain for which morphological and functional changes are best documented.**

consistent alterations, in comparison to control subjects, were found in the hippocampus and pre-frontal cortex. Yucel and Ashtari found a 12-13% volume reduction in the hippocampus.<sup>41,42</sup> Additional groups found other changes in the hippocampus such as shape and gray matter content.<sup>43-46</sup> Changes in amygdala were also well documented.<sup>39</sup> Figure 1 shows the three areas of the brain for which morphological and functional changes are best documented.

The brain regions most affected in regular users of marijuana, the hippocampus and regions of the cerebral cortex (parietal cortex, inferior frontal gyrus), are “integral components of the brain reward, memory, and executive-attention systems.” This may explain the deficits that marijuana users show in these areas.<sup>39,47-51</sup> Rueda et al. cited work by Posner and Raichle showing that the regulatory effects of these executive areas “apply just as well to brain areas involved in processing the semantics of words, storing information in memory, and generating emotions such as fear and sadness.”<sup>52,53</sup>

### Risks for Psychoses

Alongside changes in major brain structures, marijuana has been repeatedly linked to an increased risk for psychosis. The review committee for the National Academy of Sciences found multiple high-quality studies that confirmed association between marijuana use and development of schizophrenia and other psychoses, including manic-depressive disorder, hypomania, depression, and suicide, as well as well as a marijuana and psychosis dose-response relationship.<sup>1</sup> In a recent review, Marconi et al. found substantial evidence for the ability of marijuana “to induce



long-lasting psychotic disorders.”<sup>54</sup> Increased marijuana use was associated with a “higher risk of schizophrenia and other psychosis-related outcomes compared to nonusers.” Marijuana use has been “widely reported to induce acute psychotic experiences,<sup>55-57</sup> to affect the severity of psychotic symptoms,<sup>58-59</sup> and previous meta-analyses have reported a two-fold increase in the risk to develop a psychotic disorder in [marijuana] users compared to nonusers.”<sup>54</sup> Following this pattern, in another study where “the history of [marijuana] use and a spot urine test for cannabinoids were obtained” for 137 persons diagnosed with schizophrenia in treatment, the “subjects who were using cannabis during the six-month observation period presented with a significantly higher degree of delusional and hallucinatory activity than those who did not. Moreover, the group using cannabis made a higher average number of visits to the hospital during the same period.”<sup>61</sup> Not only does marijuana work to induce and increase severity of psychotic episodes,<sup>63</sup> but marijuana use is also linked to “increased risk of relapse,<sup>64</sup> earlier relapse,<sup>65</sup> longer inpatient stay,<sup>66</sup> and an increased risk of violence and criminal activity<sup>67</sup> as well as being associated with higher rates of transition to psychosis.<sup>68,69</sup> Substance abuse (including marijuana, amphetamines, and cocaine) leads to increased mortality from overdoses.<sup>70</sup> Rosen et al. found that substance abuse-linked illness, including overdoses, accounted for 27.6% of deaths among 169,051 male Vietnam-era veteran psychiatric patients, vs. 8.8% among psychiatric patients in the same group of veterans without substance abuse.<sup>70</sup> In summarizing the link between chronic marijuana use and psychoses, the National Academy review stated: “The higher the use, the greater the risk.”<sup>71</sup>

Persons with schizophrenia and substance abuse, including marijuana, amphetamines and cocaine, are at risk of increased risk of relapse of schizophrenia symptoms<sup>71</sup> as well as increased mortality from overdoses.<sup>70</sup> Rosen et al. found that substance abuse-linked illness, including overdoses, accounted for 27.6% of deaths among 169,051 male Vietnam-era veteran psychiatric patients, vs. 8.8% among psychiatric patients in the same group of veterans without substance abuse.<sup>70</sup>

### **Brain Regions Affected by Marijuana, Schizophrenia, and Earliest Areas of Alzheimer’s Disease Overlap and Symptoms are Similar**

Sheline, Raichle et al. studied a group of functionally normal persons with PET scans using Pittsburgh Compound B (PIB) imaging.<sup>72</sup> The PIB-positive PET scan patients were considered to have an early marker predictive of later-onset Alzheimer’s disease.<sup>73</sup> Early changes were found in and around the hippocampus, anterior and dorsal cingulate area of the prefrontal cortex and precuneus; most of these

areas are associated with abnormalities from chronic marijuana use.<sup>39,74</sup>

Further studies of preclinical Alzheimer’s disease used functional MRI for imaging with similar findings.<sup>75</sup> Studies of schizophrenia have shown abnormalities in related brain regions.<sup>76-78</sup> The clinical similarity between schizophrenia and dementia was observed in early descriptions of schizophrenia, which was termed “dementia praecox,” used to describe “a deteriorating process involving intellectual functions and behavior but no involvement of consciousness.”<sup>79</sup> Clinical descriptions of schizophrenia, early dementia, and chronic marijuana use overlap.<sup>79</sup>

### **Importance of the Default Mode Network**

The discovery of the default mode network by Raichle and other researchers at Washington University was widely cited and confirmed by other laboratories.<sup>80,81</sup> These linked hubs within the brain have been described as “orchestra conductors,” directing other specialized parts of the brain that can be compared to orchestra sections. Raichle said, “The [default mode network] is thought to behave something like an orchestra conductor, issuing timing signals, much as a conductor waves a baton, to coordinate activity among different brain regions.”<sup>82</sup>

The functioning of the default mode network, the orchestra director in the brain, was further described by Andrews-Hanna.<sup>83</sup> She surveyed new findings in psychology bolstered by imaging studies that showed the function of these midline core areas. The default mode network allows humans to “spontaneously and deliberately” engage in “introspective and adaptive mental activities,” thinking about the past and planning the future, placing high value on “personally significant information,” especially about “friends, family members, and romantic partners.”<sup>83</sup>

The areas of the brain<sup>83</sup> affected by chronic marijuana use are very closely associated with the default mode network defined originally by Raichle and colleagues. The results of chronic marijuana use are believed to negatively influence the ability to focus attention, to retain information, and to succeed in social roles.<sup>84</sup>

### **Conclusions**

In this review, we discussed the general impact of medical marijuana laws, changes in marijuana use after medical marijuana laws are passed, and groups at increased risk when restrictions on the availability of marijuana are loosened. Changes that occur in the brain with chronic use of marijuana are of primary concern, especially for males. Earlier use of marijuana, stronger marijuana, and those with schizophrenia or polygenic risk for schizophrenia are at increased risk for adverse changes in the brain. Similar

areas in the brain are affected in schizophrenia, Alzheimer's disease, and chronic marijuana use. Research findings raise critical concerns for chronic marijuana users. Marijuana should not be considered a medicine or pure drug.

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## Disclosure

None reported.

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