

Implications of Legalized Cannabis in Colorado Emergency Departments:

Review of the Literature of Health and Safety Effects

Abstract: Colorado legalized recreational marijuana in 2012 with legal sales beginning January 2014. This has led to unique presentations to Emergency Departments across the state. Cannabis legalization has led to significant health consequences. The most concerning of these are psychosis, suicide, and other substance abuse. Research shows deleterious effects on the brain including complex decision making processes, which may not be reversible with abstinence. Other significant health effects include increases in fatal motor vehicle collisions, adverse effects on cardiovascular and pulmonary systems, and inadvertent pediatric exposures. Cannabis dispensary workers not trained in medicine are giving medical advice which may be harmful to patients.

Cannabis research may offer unique opportunities for novel treatment of seizures, chronic pain, spasticity from multiple sclerosis, nausea and vomiting from chemotherapy, and sleep disorders. This has been difficult to navigate due to poor differentiation of the chemical composition of cannabis products.

Future research should maximize therapeutic potential by differentiating which chemical composition and at what dose may result in the best therapeutic benefit. Significant caution is advised given adverse outcomes in Colorado after legalization.

Full Text:

As of January 2018 in the United States, nine states have legalized cannabis for recreational use, with another twenty nine states legalizing it for medical use. This has created broad interest in understanding the effects on numerous public institutions including the healthcare system.

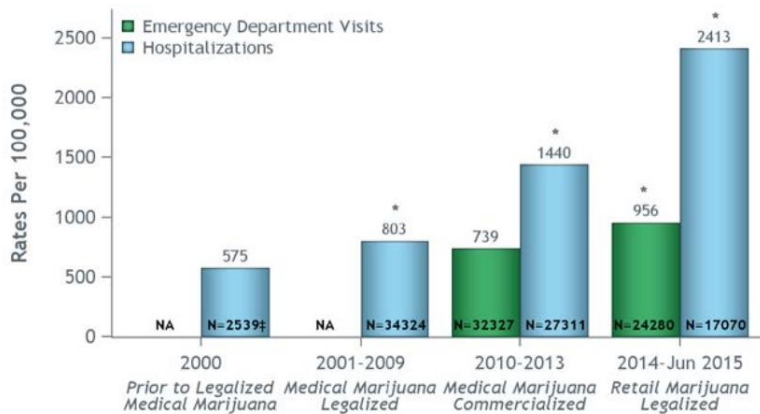
Colorado initially legalized medical marijuana in 2000 by constitutional amendment with commercialization of medical marijuana increasing in 2010. That year the US Attorney General issued the Ogden Memorandum stating that the Federal government would not prosecute individuals for medical marijuana legal at the state level. Recreational marijuana was legalized in 2012 with legal sales beginning January 2014. This has led to cannabis related presentations to Emergency Departments (EDs) and cannabis related hospitalizations across the state.

Cannabis Effects on Healthcare Resources in Colorado

Emergency Department visits and hospitalizations with marijuana related billing codes have been increasing following legalization. Mental illness represents a concerning large number of these visits. A retrospective review by Wang et al. reported Colorado Hospital Association hospitalizations and ED visits with marijuana-related billing codes and found that from 2000 to 2015, hospitalization rates increased from 274 per 100,000 hospitalizations to 593. The prevalence of mental illness among ED visits with marijuana-related codes was five-fold higher (5.07, 95% CI: 5.0, 5.1) than the prevalence of mental illness without marijuana-related codes.¹

Subsequent data by the Colorado Department of Public Health and Environment (CDPHE) show significant increases in hospitalizations in each phase of marijuana legalization, increasing from 575 per 100,000 hospitalizations in 2000 to 2413 per 100,000 hospitalizations in 2014- June 2015 as displayed in Figure 1.² The differences in numbers between the Wang study and the CDPHE report are due to the Wang study only including marijuana codes in the first 3 diagnostic codes while the CDPHE study included marijuana diagnostic codes in up to 30 listed codes.

Figure 1: Rates of hospitalizations (HD) and emergency department (ED) visits with possible marijuana exposures, diagnoses, or billing codes per 100,000 HD and ED visits, by legalization eras in Colorado



*Rate significantly increased from previous time period with a p-value <0.001.
 †ICD-9-CM codes 305.2, 304.3, 969.6, and E854.1 were used to determine HD and ED visits with possible marijuana exposure, diagnoses, or billing codes.
 ‡The Ns are the total number of HD or ED visits with possible marijuana exposures, diagnoses, or billing codes in the specified time period.

Source: Data provided by Colorado Hospital Association with analysis provided by CDPHE.

Note: Data for 2015 covers January 1, 2015, through June 30, 2015. NA = Data not available. An individual can be represented more than once in the data; therefore, the rate is HD or ED visits with marijuana codes per 100,000 total HD or ED visits.

Marijuana related visits to emergency departments for teenagers and young adults have had a large increase since legalization and the majority of these require behavioral health evaluation. A subsequent retrospective review of 2005 to 2015 by Wang of 4,202 marijuana visits of all types for patients 13-21 years old found that, behavioral health evaluation was obtained for 2,813 (67%) and a psychiatric diagnosis was made for the majority (71%) of these. Marijuana-related visits of all types increased from 1.8 per 1,000 visits in 2009 to 4.9 in 2015. This suggests that, despite national survey data suggesting no appreciable difference in adolescent marijuana use, there has been a significant increase in adolescent marijuana-associated ED and urgent care visits in Colorado.³

Cannabis Effects on Mental Health in General

Psychosis and Schizophrenia

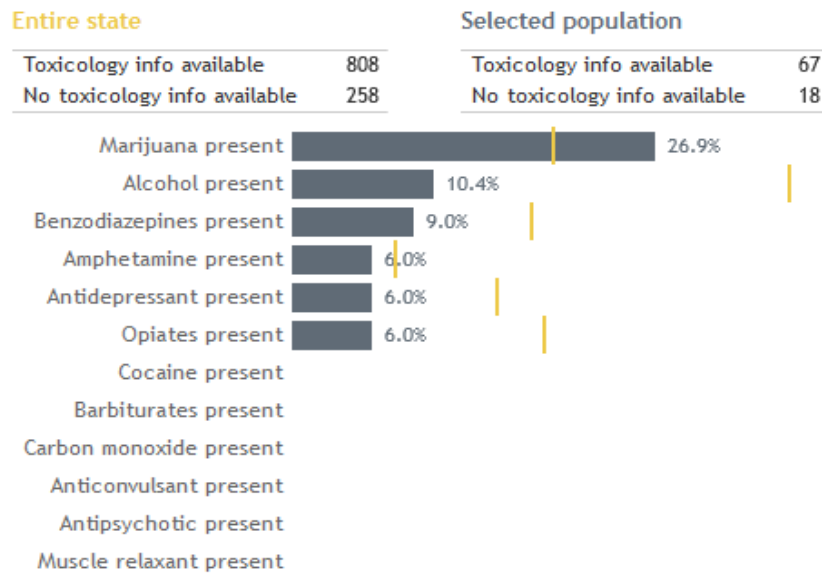
Cannabis use is strongly associated with psychoses and the development of schizophrenia. Previous studies, including large reviews by the World Health Organization (WHO) and the National Academies of Sciences, Engineering, and Medicine (NASEM) have found substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.^{4,5} In a study of 50,465 Swedish mandatory military enlisted males, the authors found that the men who had tried cannabis by age 18 were 2.4 times more likely to have schizophrenia over the next 15 years than those who had not.⁶ A follow up study found a dose–response relationship between frequency of cannabis use at the age of 18 and the risk of schizophrenia. This effect persisted after controlling for confounding factors. The researchers estimated that 13% of cases of schizophrenia could have been averted if no one in the cohort had used cannabis.⁷ These findings have been reproduced repeatedly and across the world.⁸⁻¹⁵

Depression, Anxiety, and Suicide

Cannabis use is associated with increased rates of suicide, depression, and anxiety. The WHO and NAESM found that there was moderate evidence of a statistical association between cannabis use and the incidence of suicidal ideation and suicide attempts, with a higher incidence among heavier users, and increased incidence of suicide completion.^{4,5} There was also moderate evidence of a statistical association between cannabis use and the incidence of social anxiety disorder.^{4,5}

In the most recent data on Colorado adolescent suicides, marijuana was the most common substance present for ages 10-19 in 2015. Of 67 suicides with toxicology data available, marijuana was present in 26.9% compared to 10.4% for alcohol, as displayed in Figure 2.¹⁶ This trend started and has been increasing since liberalization of marijuana policy in 2010. From 2004-2009 alcohol was the leading drug involved at 17.4% while marijuana was involved in 15.6% of suicides with a distinct change in 2010 where marijuana was the most common involved substance. Colorado has had an increasing trend every year since then in marijuana prevalence in suicides. This is more concerning as currently suicide is the leading cause of death in adolescents in Colorado.¹⁷

Figure 2: Toxicology Data for Adolescent Suicides (ages 10-19) in Colorado 2015



Note: Counts of less than 3 are suppressed

Cannabis Dependence/Withdrawal Symptoms

Cannabis use may result in dependence and cessation of use may result in withdrawal symptoms. Dependence rates are reported at around 1 in 10 among those who ever use cannabis, 1 in 6 among adolescent users, and 1 in 3 among daily users.^{4, 18-21} Withdrawal symptoms may include symptoms such as anxiety, insomnia, appetite disturbance, and depression. These symptoms are of sufficient severity to impair everyday functioning and are markedly attenuated by doses of an oral cannabis extract.⁴

Changes on Brain Imaging Studies in Cannabis Users

Cannabis use has been shown to lead to both functional and structural changes in the brain on neuroimaging studies. Chronic cannabis use has been shown to lead to changes in the brain in the grey/white matter in global brain measures and in connectivity studies. MRI studies demonstrate reduced hippocampal, amygdala, cerebellum, and frontal cortex volumes in chronic cannabis users. Adults who have smoked cannabis since adolescence show reduced neuronal connectivity in the prefrontal areas responsible for executive functioning and inhibitory control and in the subcortical networks that are responsible for habits and routines. The precuneous- a node involved in integration of various brain functions such as awareness and alertness- is particularly affected in frequent cannabis users. Functional MRI studies demonstrate that the areas affected include areas of the brain that control alertness, self-conscious awareness, learning, memory, spatial awareness, attention, social inhibition, mental control, habits, and routines.²²⁻³² Some studies have shown that these changes may not reverse with abstinence. The

WHO reports that marijuana use results in “selective impairment of cognitive functioning which include organization and integration of complex information involving various mechanisms of attention and memory processes. Prolonged use may lead to greater impairment which may not recover with cessation of use which could affect daily life functions”.⁴

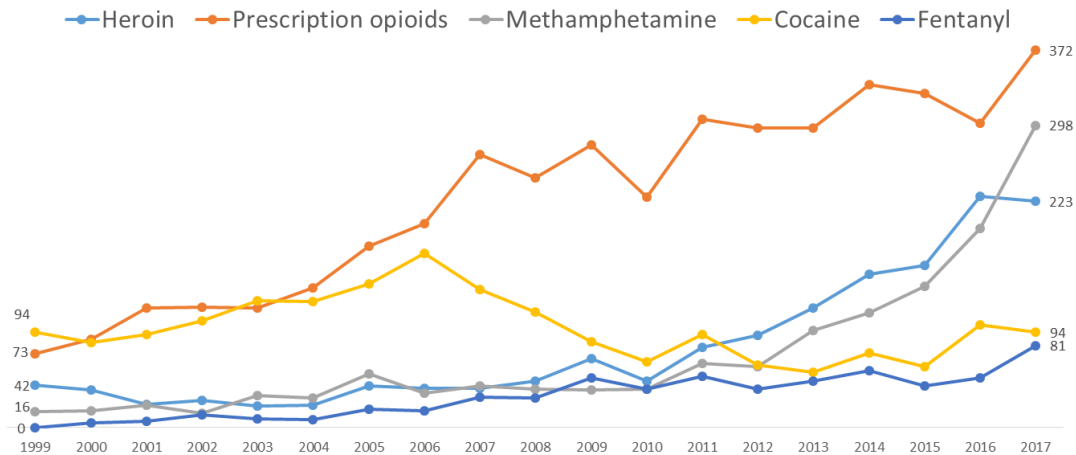
Social Outcomes

Cannabis use has been associated with adverse social outcomes which may impact emergency departments and patient health outcomes. Multiple studies demonstrate reduced IQ, reduced lifetime achievement, lower income, greater need for socioeconomic assistance, more unemployment, increased criminal behavior, and lower life satisfaction.^{30, 31, 33}

Link to Other Substance Abuse

Cannabis use has been associated with abuse of other substances. According to the NASEM report, there is moderate evidence of a statistical association between cannabis use and the development of substance dependence and/or substance abuse disorder for substances including alcohol, tobacco, and other illicit drugs.^{5,34-36} Rat studies show that after exposure to tetrahydrocannabinol (THC- the most commonly cited psychoactive molecular compound of cannabis) rats have an increased behavioral sensitization response to not only THC but also opiates and nicotine.³⁴⁻³⁶ Studies also demonstrate that these behavioral changes in rats correspond to neuronal activity changes in mesolimbic dopamine neurons in the ventral tegmental area and nucleus accumbens and that cross tolerance results with exposure to morphine, amphetamines, and cocaine.^{36, 37} Repeat morphine self-administration has been shown to be significantly lower in CB₁ knockout mice and opiate withdrawal symptoms significantly less when the knockout mice are administered naloxone.³⁸ Multiple studies in humans link marijuana use with use of other substances. Several discordant twin studies have found that the twin who used marijuana was more likely to use other substances even controlling for environmental and genetic influences.³⁹⁻⁴² Although some studies preliminarily reported that medical cannabis has resulted in improvements in opiate related deaths,^{43, 44} more recent data demonstrates that Colorado has had an increase in poisoning and deaths from opiates and methamphetamines since 2010, with the highest in 2017. This data is shown in Figure 3.¹⁷

Figure 3: Drug poisoning/overdose deaths in Colorado by involvement of specific drug type: Colorado residents, 1999-2017



Drug categories are not mutually exclusive; a death involving more than one type of specific drug will be counted in each applicable category. 'Fentanyl' is a subset of 'prescription opioid'.

Source: Vital Statistics Program, Colorado Department of Public Health and Environment

Other Relevant Physiological and Safety Concerns with Cannabis

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) has been well described in the literature.⁴⁵ The symptoms of CHS include significant nausea, vomiting, and abdominal pain in the setting of chronic cannabis use. Cardinal diagnostic characteristics associated with CHS include regular cannabis use, cyclic nausea and vomiting, and compulsive hot baths or showers with resolution of symptoms after cessation of cannabis use.⁴⁶ CHS patients present similarly to cyclic vomiting syndrome patients with the exception that cannabis use is required to make the diagnosis.⁴⁶ Following legalization, the prevalence of cyclic vomiting presentations to Denver Health and the University of Colorado Hospital increased 1.92 fold (95% confidence interval [CI] = 1.33 to 2.79). from 41 per 113,262 ED visits from a year prior to marijuana liberalization (November 1, 2008, to October 31, 2009) to 87 per 125,095 ED visits a year following marijuana liberalization (June 1, 2010, to May 31, 2011). Patients with cyclic vomiting in the postliberalization period were more likely to have marijuana use documented than patients in the preliberalization period (odds ratio = 3.59, 95% CI = 1.44 to 9.00).⁴⁷ These patients often are evaluated with multiple imaging studies, lab work, endoscopies, and admissions to the hospital as well as antiemetic treatment. These studies are often non-diagnostic and treatment often ineffective. This may also influence ED overcrowding.^{45, 48}

Motor Vehicle Collisions

Traffic fatalities attributed to driving under the influence of marijuana have sharply risen across Colorado.^{49, 50} CDPHE found substantial evidence that recent marijuana use by a driver increases their risk of a motor vehicle collision (MVC) and that the higher the blood THC level, the higher the risk of MVC. The use of alcohol and marijuana together increases risk of impairment and

MVC more than either substance alone. For less than weekly marijuana users, using marijuana containing 10 mg of THC is likely to impair the ability to safely drive, bike, or perform other safety sensitive activities. A typical marijuana cigarette or joint contains 60-115 mg of THC.⁵¹

Cardiovascular Effects

Cannabis smoking may increase the risk of myocardial infarction and stroke. Second-hand cannabis smoke has been shown to have an effect on vascular endothelial function similar to second hand tobacco smoke.⁵²⁻⁵⁴

Respiratory Effects

Marijuana smoking leads to adverse pulmonary outcomes. CDPHE reports substantial evidence that marijuana smoking leads to symptoms of chronic bronchitis including chronic cough, increased sputum production, and wheezing.⁵¹ It may also lead to increased rates of pneumonia and upper respiratory infections. On histology, this is associated with a reduction in ciliated cells and subsequent increase in mucus secretion from the larger number of mucus-secreting cells.^{4, 31, 55}

Exposures to Children

Reported exposures to children less than age 10 have sharply increased in Colorado following recreational marijuana legalization. Edibles are sold as cookies, candies, and sodas with advertising that appeals to children.⁵⁶

Marijuana Shop Employees Providing Medical Advice

Marijuana shop employees not trained in medicine or pharmacology are giving medical advice that may be harmful to patients. A recent study in Colorado found that non-medically trained cannabis shop employees are giving medical advice 70% of the time to use cannabis for treatment of nausea and vomiting in pregnancy, and few dispensaries encouraged discussion with a health care provider without prompting.⁵⁷ I have personally had patients in my practice bring in products recommended by dispensary workers with a recommended potency, frequency of use, and report having been advised to stop their normal medications and instead use the cannabis product. Cannabis dispensaries provide medical advice and offer treatment without medical training, even when this may harm the patient.

Potential Medicinal Uses of Cannabis

There are potential therapeutic intervention targets for cannabinoids. In general these therapeutic targets require a high ratio of cannabidiol compounds (CBD- cited to decrease or eliminate the psychoactive effects of THC), and are from products which significantly differ from those found in commercial dispensaries. The NASEM report found substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults, effective as an antiemetic for chemotherapy induced nausea and vomiting, and for improving patient reported multiple sclerosis spasticity symptoms. They also found moderate evidence that cannabis or cannabinoids are effective for improving short-term sleep outcomes associated with obstructive sleep apnea,

fibromyalgia, chronic pain, and multiple sclerosis.⁵ Likely the most significant treatment implication has been in patients with refractory epilepsy, most commonly in patients with Dravet's Syndrome and Lennox-Gestalt Syndrome but also in other patients with refractory epilepsy. This has led to the FDA approving Epidiolex (a high CBD cannabinoid treatment) in June 2018 for the treatment of Dravet's Syndrome and Lennox-Gestalt Syndrome.⁵⁸⁻⁶⁰

Variations in Potency Confuses Consumers and Scientific Research

The potential positive health effects of cannabis depend on which of the multiple species and hybrids are studied and their ultimate chemical composition. One of the difficulties in determining the physiological effects of cannabis is that 'marijuana' or 'cannabis' can refer to numerous species of plants with widely varying chemical compounds between plants and corresponding widely varying physiological effects with use. The cannabis genus includes multiple species, most commonly *Cannabis sativa* and *Cannabis indica*, and within those are hybrids specifically developed by growers to achieve a specific effect. For example, the commonly used term, *hemp*, refers to a variety of *Cannabis sativa* which is fast growing and can be spun into usable fiber for paper, textiles, clothing, biofuel, animal feed, and other industrial uses. Hemp has low concentrations of THC (less than 0.3%) and higher concentrations of CBD.

Further complicating understanding the physiological effects of cannabis are the varying growing techniques and end-product alteration that can occur. Cannabis growth can be altered to achieve higher growth rates, changes in potency, and ease of production. This can include use of varying soil types, fertilizers, and pesticides which can result in varying physiological effects.⁶¹ There are also changes in end product concentrations such as oils (hydrophobic components, such as THC, are commonly removed with a heated butane solvent), wax (concentrated and solidified oil), and dabs (heated wax that is inhaled off of an object such as a nail).⁶² There are also multiple methods of use including inhalation, ingestion, and topical which also lead to varying physiological effects.

The differences in composition offer different potential treatment effects. For example, the effect for pain control cited in the NASEM review was primarily found with nabiximols, (trade name Sativex), a cannabis extract mouth spray which delivers a dose of 2.7 mg of THC and 2.5 mg of CBD.⁶³ For comparison, a typical marijuana cigarette or joint contains 0.5 g of marijuana and THC content ranges from 12-23%; therefore a typical joint contains 60-115 mg of THC. The NASEM cautioned that many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States.⁵

This is further complicated in that commonly sold cannabis products are often mislabeled for CBD and THC content. One study showed only 17% of dispensary products were accurately labeled.^{64, 65} Many studies, particularly for treatment of pain, have been limited by a high degree of bias and results have varied.^{66, 67} This may help to explain why some studies demonstrate improvement in pain⁵ with coinciding decreases in opiate abuse^{5, 43, 68} while others the opposite.^{66, 67, 69, 70}

It has also been well documented that cannabis potency has increased. Current commercialized cannabis is near 20% THC while in the 1980's concentration was <2%. This 10-fold increase does not include other formulations such as oils, waxes, and dabs (as described above) which can reach 80-90% THC⁴

There are several limitations to this article. This article was not a systematic review of the literature but rather a summary of a large body of research including several large review studies such as the National Academies of Sciences, Engineering, and Medicine review as well as the review by the World Health Organization. Its purpose was to summarize a large body of research and make this accessible in a condensed version to practicing emergency physicians who are increasingly confronted with questions regarding cannabis. Although the author practices and resides in Colorado, the information extends well beyond experiences isolated to Colorado. Although I attempted to remove my own bias out of the summary, the article is certainly limited to the biases of myself, the author, which itself represents a large limitation to the article. Discussions regarding cannabis are large in spectrum as they affect not only the healthcare system but legal, business, environmental, legislative, and numerous other branches within a public health framework. This article is meant to provide information to the practicing emergency physician and does not address those other facets of cannabis. There are numerous other physiological effects of cannabis which were not addressed. Also, as noted, cannabis potency has dramatically changed since the 1980's. Many of the previous research studies have been on cannabis at a much lower THC level which limits generalizability to cannabis available at dispensaries today. Furthermore, the conflict between federal and state laws on the medical use of cannabis products, the lack of consistency among state laws, and the availability of artisanal cannabis products in dispensaries, with high variability between composition of products, has caused significant confusion for researchers and has limited the ability to fully and accurately research the true effects of commonly available dispensary cannabis products.⁷¹

The words 'marijuana' and 'cannabis' were used interchangeably throughout the article. This was done to keep wording from the studies cited consistent with the study's original language. No difference should be implied with the alternating use of these terms.

In conclusion, cannabis legalization has led to significant health consequences, particularly to ED and hospitals in Colorado. The most concerning include psychosis, suicide, and other substance abuse. There are also deleterious effects on the brain including complex decision making, some of which may not be reversible with abstinence. Other significant health effects include increases in fatal motor vehicle collisions, adverse effects on cardiovascular and pulmonary systems, and inadvertent pediatric exposures. Cannabis dispensary workers not trained in medicine are giving medical advice which may be harmful to patients.

Cannabis research may offer opportunities for novel treatment of seizures, chronic pain, spasticity from multiple sclerosis, nausea and vomiting from chemotherapy, and sleep disorders. This has been difficult to navigate secondary to absent standardization of the chemical composition of cannabis products.

Future research should strive to maximize therapeutic potential through differentiating chemical composition and dosing which may result in therapeutic benefit. Given these factors and the Colorado experience, other states should carefully evaluate whether and how to decriminalize or legalize non-medical cannabis use.

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