

High-Potency THC Concentrated Cannabis Products are Not Medicine and are Not Safe

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In November 2000, Colorado voters passed Amendment 20, which legalized medical use of marijuana for debilitating medical conditions, effective June 2001. Initially, use remained somewhat limited until 2009 when the US Department of Justice issued the 2009 Ogden memo¹, and the Colorado Legislature established the Colorado Medical Marijuana Code in 2010 allowing for the legal licensing of medical marijuana businesses. Concentrated marijuana products began to appear in the market in 2010. In 2009 there were 5,000 people on the medical marijuana registry, by 2011 there were 119,000 people. Then, in November 2012, Colorado passed Amendment 64, which legalized retail sales of marijuana. Personal use was legalized on December 10, 2012, after the Governor certified the election results. Dispensary doors opened in 2014.

Increasing THC Potency

In the two decades since Colorado legalized medical marijuana, tetrahydrocannabinol (THC) potency, the most psychoactive component in cannabis, significantly increased in marijuana products. While the marijuana available in the 1960s and 1970s had an average THC content of less than 2%, a study of the changes in cannabis potency from 1995-2014 by the University of Mississippi, found that the THC percentage in illicit cannabis products seized by the DEA, averaged 4% in 1995 and 12% in 2014.² As the earliest state to legalize marijuana, Colorado could have led policy development in this area in order to best protect public health, but sadly that has not happened.

In 2023, in Colorado, the average potency in the plant is around 20% THC with strains that are much higher and concentrated hash oil products such as wax, shatter, dab, average 69% THC but can reach upward of 99.9% pure THC. Currently in Colorado 18-20-year-olds with a medical marijuana card can purchase 2 grams of concentrate every day. Adults 21 and older can purchase 8 grams of concentrates every day. Prior to the passage of HB21-1317, which passed almost unanimously with bipartisan support, anyone could purchase 40 grams of concentrates per day, even those 18-20 with a medical card. Consider this, if a one-gram bag of shatter is 80% THC, then that is 800 mg of THC, or 1,600 mg THC per day for 18-20-year-olds and 6,400 mg THC for adults. Compare this with the FDA approved THC based medication dronabinol (Marinol) where the maximum recommended dose is 20 mg per day.

Research on Medical Cannabis

Research on the benefits of marijuana for medical conditions from the United States and around the world is limited to THC potency of less than 10%. This can be in part because research is difficult since it is a Schedule 1 drug, but also because levels of THC higher than this put people at risk for possible consequences, including psychosis. As a result, Institutional Review Boards (IRBs) may not approve randomized, double-blind, placebo-controlled trials of high potency THC marijuana, even if the DEA scheduling were to change.

Several large systematic reviews and meta-analyses of peer reviewed studies of cannabis for medical conditions done to date used THC percentages at or below 10%.³⁻⁵ There are no controlled studies of the highly concentrated cannabis products such as vaping hash oil, smoking shatter, wax, or dab for any medical condition. To put this in perspective, several of the pain studies in the systematic reviews demonstrating benefits utilized the pharmaceutical drug Sativex which is an oral mucosal spray with 2.7 mg THC and 2.5 mg CBD per dose. A typical marijuana joint weighs 0.5 g. If the product is 12 – 23% THC then a typical joint contains 60 – 115 mg of THC which is 20 – 40 times the medicinal dose.

A recent analysis of cannabis potency in medical and recreational programs in the United States found the average concentration of THC in all states was two to three times the THC content known to be efficacious in the treatment of pain (i.e. >5–10%) and that a vast majority of products in all states, including medical-only programs, contained THC designed for recreational use (i.e. > 15%).⁶ In Colorado, they found that most products available in medical dispensaries have greater than 15% THC.

The authors point out that patients who find this information in their online searches may subsequently believe high potency products are suitable for medical purposes, placing themselves at higher risk of cannabis intoxication. This is especially concerning considering the systematic review and meta-analysis of 15 studies of psychiatric symptoms caused by cannabis constituents.⁷ The authors found that acute administration of THC induces significant increases in positive, negative, and other symptoms associated

with schizophrenia and other mental disorders with large effect sizes in adults with no history of psychotic or other major psychiatric disorders.

In the early studies of smoked cannabis for pain, a cannabis naïve participant had a psychotic response to the study cigarette which was 3.56% THC.⁸ As a result, subsequent cannabis studies have excluded participants without prior experience smoking cannabis which makes it difficult to have double-blinded studies. There have been several studies that support the use of smoked cannabis for neuropathic pain, however the dose of THC in all these studies has been under 10%.⁸⁻¹⁰ In fact, a study in healthy volunteers on the effects of cannabis on capsaicin-induced pain found that there is a window of modest analgesia for smoked cannabis, with 2% THC providing no benefit, 4% THC providing significant decrease in pain but 8% THC resulting in an increase in pain or hyperalgesia.¹¹

This has been further supported by a recent study of 989 adults who used cannabis every day for chronic pain.¹² The authors found that high frequency medical marijuana use, especially the higher potency THC products, was associated with worse pain among individuals with chronic pain while those who used less frequently and primarily cannabidiol (CBD) and non-inhalation administration routes had better outcomes. This is important because the primary reason people report purchasing medical marijuana in Colorado is for severe pain issues.¹³ It is also important because, without any regulation on the THC content, medical marijuana products available in Colorado are no different than recreational products where there has yet to be any limits placed on THC potency or any meaningful limits on product types permitted to be sold.

Consequently, people are using high potency THC marijuana that may increase their level of pain. Research from other countries provides the best source of information on the consequences of high potency THC. There is an increasing body of literature that indicates psychotic symptoms can result from the use of high potency THC products. Other literature exposes the link between addiction, depression, anxiety, violence, and suicide and regular cannabis use. Cannabis use can impair the ability to make an accurate psychiatric diagnosis and can affect the medications often used for treatment.

Cannabis and Addiction

Increasing the potency of any drug increases the risk for addiction. A study in the UK in 2015 found that frequent use of Skunk (THC content around 15%) predicted a greater severity of dependence, this effect becoming stronger as age decreased. Whereby in contrast, the use of low potency cannabis (5%) was not associated with dependence.¹⁴ A 16-year observational study in the Netherlands found a positive time dependent association with increased THC potency and increased first-time admissions to drug treatment for cannabis use disorder.¹⁵

After observing the negative impacts from rising THC potencies, a team of health experts in the Netherlands concluded that THC potencies above 15% should be considered a hard drug.¹⁶

Data obtained in the United States from the Wave 2 NESARC survey 2004-2005, when THC potency was less than 10 %, indicated that 8.9% of those who experiment with cannabis will become addicted.¹⁷ Then in the Wave 3 survey 2012-2013 this went up to 30% will become addicted.¹⁸ People who begin using cannabis before the age of 18 are 4-7 times more likely to develop a cannabis use disorder than adults.

Veteran Health Administration electronic health records from 2005 to 2019 (range of Ns per year, 4,403,027–5,797,240) were used to identify the percentage of VHA patients seen each year with a

cannabis use disorder diagnosis.¹⁹ Trends in cannabis use disorder diagnoses were examined by age and by race/ ethnicity and sex within age groups <35, 35–64, and ≥65 year. Authors discovered that since 2005, diagnoses of cannabis use disorder have increased substantially among VHA patients, especially in those younger than 35. Black patients had a consistently higher prevalence of cannabis use disorder than other racial/ethnic groups, and increases were greater among Black than White patients in the <35-year group.

It used to be thought that marijuana was not addicting and was referred to as a hallucinogen because hallucinogens do not have a withdrawal syndrome associated with their use.²⁰ We now see a definite withdrawal syndrome from the higher potency cannabis, and it is a criterion for the diagnosis of cannabis use disorder.²¹ Cannabis withdrawal syndrome is recognized by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and requires the presence of at least 3 of the following symptoms developing within 7 days of reduced cannabis use: (1) irritability, anger, or aggression; (2) nervousness or anxiety; (3) sleep disturbance; (4) appetite or weight disturbance; (5) restlessness; (6) depressed mood; and (7) somatic symptoms, such as headaches, sweating, nausea, vomiting, or abdominal pain.²²

Cannabis and Psychosis

There is increasingly strong evidence that higher potency cannabis use contributes to increased risk of psychosis. Numerous studies have demonstrated that using cannabis prior to the age of 15-18 significantly increases the risk of developing psychotic symptoms.²³ A landmark study out of the UK analyzed 780 adults, ages 18-65, 410 with their first psychotic episode versus 370 matched healthy controls. It was found that the use of high potency THC >15% resulted in a three times increased risk of psychosis, and if the use was daily there was a five times increased risk. Those using < 5% THC did not exhibit psychotic symptoms.²⁴

This study was replicated in multiple sites in Europe and one site in Brazil and found the same outcomes, except this was for cannabis with 10% or more THC.²⁵ Using 10% or more THC resulted in three times increased risk for psychotic symptoms and using daily resulted in a five times increased risk. In a recent systematic review and meta-analysis of 15 studies of psychiatric symptoms caused by cannabis constituents, the authors found that acute administration of THC induces significant increases in positive, negative, and other symptoms associated with schizophrenia and other mental disorders with large effect sizes in adults with no history of psychotic or other major psychiatric disorders.²⁶

A very large longitudinal, population-based study of 7,186, 834 individuals in Denmark was done to answer the question: has the population-attributable risk fraction for cannabis use disorder in schizophrenia increased over time, as would be expected with increasing use and potency of cannabis?²⁷ Researchers found that the population-attributable risk fraction for cannabis use disorder in schizophrenia increased from approximately 2% in the period to 1995 to approximately 6% to 8% since 2010, mirroring the increase in THC potency. This study challenges the often-cited argument against causality that an expected increase in cases of schizophrenia attributable to cannabis use has not been observed.

A study was done to assess rates and correlates of cannabis-associated psychotic symptoms (CAPS) requiring emergency medical treatment, by analyzing data from an international sample of people who use cannabis (PWUC) (n = 233,475).²⁸ Looking at the lifetime occurrence of CAPS (hallucinations and/or

paranoia) that required emergency medical treatment following the use of cannabis, they found acute self-limiting psychotic symptoms in the context of cannabis use may occur in about 1 in 200 PWUC's lifetime. Factors associated with an elevated risk of CAPS include young age, mental health vulnerabilities, particularly psychosis-liability, and the use of high-potency resin. The highest rates among PWUC were found residing in Denmark, where resin was the most popular type of cannabis with a THC concentration of 23% or higher since 2014, one of most potent forms of cannabis in Europe.

While all addictive drugs have the potential to cause psychotic symptoms, not everyone who experiences a drug-induced psychosis goes on to develop schizophrenia. Using the Danish Civil Registration System and the Psychiatric Central Research Register, all persons who received a diagnosis of substance-induced psychosis between 1994 and 2014 (N=6,788) were followed until first occurrence of schizophrenia or bipolar disorder or until death, emigration, or until August 2014.²⁹ Overall, 32.2% (95% CI 29.7–34.9) of patients with a substance-induced psychosis converted to either bipolar or schizophrenia-spectrum disorders. The highest conversion rate was found for cannabis-induced psychosis, with 47.4% (95% CI 42.7–52.3) converting to either schizophrenia or bipolar disorder. This was higher than that for alcohol or stimulants. Young age was associated with a higher risk of converting to schizophrenia. Self-harm after a substance induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder. Half the cases of conversion to schizophrenia occurred within 3.1 years after a substance-induced psychosis, and half the cases of conversion to bipolar disorder occurred within 4.4 years.

Cannabis and Violence

There is some evidence to suggest an association between persistent cannabis use and risk of violent behavior in individuals with serious psychiatric disorders. In one study 1,136 recently discharged psychiatric patients were followed at 4 10-week time intervals and evaluated for marijuana, alcohol and cocaine use as well as episodes of violence during the period 1992-1995.³⁰ Persistent cannabis use was associated with an increased risk of subsequent violence, significantly more so than with alcohol or cocaine.

In another study, 265 patients with early psychosis were followed prospectively for 36 months and dichotomized based on presence or absence of violent behavior.³¹ Cannabis use disorder (CUD) was the strongest risk factor of violent behavior with 61% of those with CUD versus 23% with no CUD exhibiting violent behavior. The age of onset of cannabis use was 15 in violent patients versus 17 in non-violent patients. The use of cannabis was linked to impulsivity and lack of insight.

Persistent cannabis use has been found to be an independent risk factor for violent behaviors in patients with schizophrenia. A study of 1460 patients with schizophrenia (NIHM-funded CATIE trial), 965 followed longitudinally, found that persistent cannabis use predicted subsequent violence.³² Violence did not predict cannabis use. The relationship was unidirectional and persisted when controlling for stimulants and alcohol use. While patients with schizophrenia are not inherently violent this study indicates cannabis use is an important potential risk factor for violence in the schizophrenia population and its consumption should be considered separately from that of other drugs when assessing and managing risks in clinical and in legal settings.

A 2021 study of 3028 Iraq/Afghanistan-era veterans found that current Cannabis Use Disorder (CUD) was significantly positively associated with difficulty managing anger (OR = 2.93, p < .05), aggressive

impulses/urges (OR = 2.74, $p < .05$), and problems controlling violence in past 30 days (OR = 2.71, $p < .05$), compared to those without CUD, even accounting for demographic variables, comorbid symptoms of depression and PTSD, and co-morbid alcohol and substance use disorders.³³

A large meta-analysis of 30 studies (296,815 adolescents and young adults) looking at the association between the use of cannabis and physical violence in youth found a moderate association between cannabis use and physical violence, which remained significant regardless of study design and adjustment for confounding factors (i.e., socioeconomic factors, other substance use).³⁴ The authors determined that cannabis use in this population is a risk factor for violence.

Data from the Texas 2020 child fatality and near fatality annual report demonstrates that 180 of the 251 child fatalities caused by abuse or neglect involved a parent or caregiver actively using a substance and/or under the influence of at least one substance that affected the ability to care for the child.³⁵ Marijuana was, by far, the substance most often identified as an active substance in child abuse and neglect related fatalities and was identified as prior use in 107 of the cases.

A 2020 focused review of the research looking at the association between cannabis use and violence found that evidence from meta-analytical studies in youths, intimate partners, and individuals with severe mental disorders have shown that there is a global moderate association between cannabis use and violence, which is stronger in the more at-risk populations.³⁶ These at-risk populations include samples from forensic and carceral settings. The authors point out it is noteworthy that in comparison to other drugs, lifetime and regular cannabis use remains the highest drug of use in inmates and the highest drug used at the time of offence. They conclude that interventions should ultimately aim to decrease post-release risky behavior (e.g. cannabis use) among inmates or forensic patients returning to the community and until a secure exposure pattern (e.g. quantity of cannabis, potency level) is determined by research, withholding from regularly using cannabis may be a better option in these at-risk and vulnerable populations. The authors further provide an overview of possible mechanisms relating cannabis use to violence. These include the fact that cannabis use can impair neurocognitive domains (e.g. executive functioning) and create perceptual distortions (e.g. interpreting neutral actions as aggressive); impair a user's ability to suppress aggressiveness; and heighten physiological arousal making users feel paranoid, anxious or panicky. Withdrawal symptoms, which are reported by up to a third of regular users are of clinical significance as they can be impairing and associated with trouble ceasing use. These symptoms typically onset within 24 to 48 h following abrupt cessation in frequent users and contribute to irritability, restlessness, and anxiety that may likewise be associated with aggression.

Cannabis and Suicide

There is also increasing evidence that cannabis use is associated with violence towards oneself in the form of suicide. Multiple studies have documented a relationship between cannabis use and suicidality. A large longitudinal study in Australia and New Zealand of over 2000 adolescents and maximum frequency of marijuana use found almost a seven-fold increase in suicide attempts in daily marijuana users compared with non-users.³⁷ A 2017 cross-sectional multi-site VA study of 3233 Veterans found that cannabis use disorder was significantly associated with both current suicidal ideation ($p < .0001$) and lifetime history of suicide attempts ($p < .0001$) compared to Veterans with no lifetime history of cannabis use disorder.³⁸ The significance difference continued even after adjusting for sex, PTSD, depression,

alcohol use disorder, non-cannabis drug use disorder, history of childhood sexual abuse and combat exposure.

Suicide is the number one cause of death in Colorado for individuals between the ages of 10 and 24 and cannabis is by far the most frequently encountered drug on toxicology screens of suicides among adolescents ages 10-19 and has been increasing over the last eight years according to the Colorado Department of Public Health and Environment.³⁹ A large systematic review and meta-analysis of 11 studies of 23,327 adolescents found that cannabis use in adolescence significantly increased the risk of depression, anxiety and suicidality in young adulthood with an odds ratio of 3.5 for suicide attempts.⁴⁰ A 2022 report on 2015–2019 data from the National Survey on Drug Use and Health (NSDUH), looked at adolescents age 12 to 17 (n = 73,986) and compared any suicidal ideation, plan, or attempt in the previous year with no use of marijuana, non-weekly use, and weekly-plus use.⁴¹ They found that positive associations between marijuana use and suicide ideation/behaviors persisted among males and females as well as White, Black, and Latinx adolescents (all $p < 0.05$) with no real difference between gender or race/ethnicity.

Cannabis and PTSD

Many people with post-traumatic stress disorder (PTSD) use cannabis to alleviate their symptoms and Colorado has approved PTSD as a condition for medical marijuana. However, this does not cure PTSD any more than alcohol or benzodiazepines cure PTSD. These substances can “numb” the person, so the symptoms are not bothersome but require the person to continue daily use to alleviate the symptoms, putting them at risk for addiction. There is strong evidence that persistent use of cannabis can make the PTSD symptoms worse and increase the risk of violence and suicidal ideation.^{42,43}

An observational study of 2276 veterans treated in PTSD treatment programs of the Veterans Administration around the country found that 4 months after participating in a month-long inpatient treatment program for PTSD, those who never used marijuana had significantly lower symptom severity, those who stopped using marijuana had the lowest level of PTSD symptoms 4 months after treatment and those who started to use marijuana had the highest levels of violent behavior and PTSD symptoms 4 months after treatment.⁴⁴

Recently the 2019–2020 National Health and Resilience in Veterans Study (NHRVS) followed 4,069 U.S. military veterans and found that frequent cannabis use worsens PTSD symptoms in military Veterans.⁴⁵ Compared with veterans who did not use cannabis or used it infrequently, those who used cannabis frequently were roughly twice as likely to screen positive for co-occurring Major Depressive Disorder, Generalized Anxiety Disorder, and Suicidal Ideation; showed small-to-moderate decrements in cognitive functioning; and were 2–6 times more likely to endorse using avoidance strategies as a primary means of managing their PTSD symptoms.

Interestingly, a 2020 review of peer reviewed studies and randomized controlled trials in humans 1974-2020 of THC or THC and CBD in PTSD found that low doses of THC (7.5 mg THC) potentiate fear memory extinction in healthy volunteers and reduce anxiety responses in anxious and PTSD patients without inducing a psychotic effect. While high doses of THC (greater than or equal to 10% THC) do not facilitate fear memory extinction and are related to clinically relevant anxiogenic and psychotic effects in healthy volunteers.⁴⁶

Cannabis and the Developing Brain – Prenatal Cannabis Exposure

The negative effects of cannabis on the developing brain, both in utero and during puberty have been well documented. Prenatal cannabis use has been well documented to increase the likelihood of preterm birth, low birth weight, small-for gestational age, and major congenital anomalies, with prenatally exposed female infants showing evidence of increased susceptibility.⁴⁷ Despite this, a study of recommendations from cannabis dispensaries in Colorado found that nearly 70% of the dispensaries contacted for advice for a woman who was 8 weeks pregnant and experiencing morning sickness, recommended cannabis products to treat nausea in the first trimester.⁴⁸ Few dispensaries encouraged a discussion with a healthcare provider without prompting. A 2022 study found In Colorado, there was more than a two-fold increase in cannabis involved pregnancy hospitalizations between 2011 and 2018.⁴⁹ This increase was highest after sale of recreational cannabis began in 2014.

A very large cross-sectional study of 20,914,591 female individuals in 35 US states found that the proportion of prenatal hospitalizations involving cannabis use disorder increased substantially between 2010 and 2018.⁵⁰ The proportion of prenatal hospitalizations involving CUD increased from 0.008 in 2010 to 0.02 in 2018. There was a higher prevalence of depression, anxiety, and nausea disorders in prenatal hospitalizations with CUD compared with those without CUD, regardless of concomitant substance use disorders.

In California 99,127 pregnancies were screened for prenatal cannabis use via urine toxicology testing before (January 2019 to March 2020) and during the COVID-19 pandemic (April 2020 to December 2020).⁵¹ Larger absolute increases in prenatal cannabis use were associated with living within versus more than a 10-minute drive of a cannabis retailer. A smaller qualitative study of 53 pregnant individuals who used cannabis was performed and found consistent beliefs that legalization led to easier cannabis access (via retailers and delivery), greater acceptance (including reduced stigma), more patient-clinician discussions about prenatal cannabis use, fewer concerns about Child Protective Services involvement, and trust in cannabis retailers (including safety and effectiveness of diverse products sold and perceptions of employees as knowledgeable, nonjudgmental, and caring).⁵²

This is very concerning, given research that demonstrates prenatal cannabis exposure can lead to an increased risk of autism⁵³ as well as greater psychopathology during middle childhood.⁵⁴ Subsequent information from the large Adolescent Brain Cognitive Development (ABCD) study finds that prenatal cannabis exposure is associated with persisting vulnerability to broad-spectrum psychopathology as children progress through early adolescence.⁵⁵ These findings suggest increased psychopathology may lead to greater risk for psychiatric disorders, such as conduct disorder and aggressive behavior/rule breaking, and problematic substance use as children enter peak periods of vulnerability in later adolescence. The Surgeon General of the United States, Jerome Adams, MD issued a warning in 2019⁵⁶ that no amount of marijuana use during pregnancy or adolescence is known to be safe, supporting a 2018 recommendation from the American Academy of Pediatrics against marijuana use during pregnancy based on concerns for its potential impact on the developing fetus. This is true for all marijuana and especially true for high potency THC marijuana.

Cannabis and Cognition

The negative effects of cannabis use on cognitive abilities, not only while the brain is still developing, but throughout the life span, are well documented. In a prospective study of 648 children and exposure to cannabis in-utero, women were interviewed about the amount and frequency of cannabis use at 4, and 7 months of pregnancy and at delivery.⁵⁷ Their offspring were administered an IQ test at age 6 and examiners were blinded to exposure. They found that in-utero exposure to light to moderate cannabis

use approximately three times a week had a significant negative effect on school age intellectual development.

In another prospective study 1,037 individuals were followed for 20 years and were administered neuropsychological testing at age 13 before initiation of cannabis and again at age 38.⁵⁸ Those with early persistent teen use of cannabis had an average decrease in IQ by 8 points compared with no change over time by those who never used cannabis. This same research group has continued to follow these individuals and recently reported results at age 45.⁵⁹ They found that long-term cannabis users showed IQ decline from childhood to midlife (mean -5.5 IQ points), poorer learning and processing speed relative to their childhood IQ, and informant-reported memory and attention problems. This was a greater drop than found for those who were long term tobacco users (mean -1.5 IQ points) or long term alcohol users (mean -0.5 IQ points). There was less of a decline but still significant relative to non-cannabis users, for midlife recreational cannabis users (mean -3.5 IQ Points) and for cannabis quitters (mean -3.3 IQ points).

A 2019 study evaluated 3,826 teens starting from seventh grade from 31 Montreal-area schools over the course of four years.⁶⁰ They found that teens who used cannabis more often than others had cognitive function changes that appeared to be more pronounced than those observed for alcohol. Cannabis use, but not alcohol consumption, showed lagged (neurotoxic) effects on inhibitory control and working memory and concurrent effects on delayed memory recall and perceptual reasoning (with some evidence of developmental sensitivity). Cannabis effects were independent of any alcohol effects.

There is evidence that persistent cannabis use can negatively affect neurogenesis in the hippocampus, causing it to shrink, affecting learning and memory and making it difficult to learn new things. A study of 40 male and 34 female long-term (15 years) cannabis users versus 37 non-users, healthy controls divided the marijuana users into three groups; those that smoked predominantly THC in the previous three months, those who smoked a combination of THC and CBD in the previous three months and former users with a sustained abstinence of 29 months. They found that cannabis users had smaller hippocampal volumes compared to controls but the users not exposed to CBD had greater (11%) reduced volumes (CBD appears to be somewhat protective).⁶¹ In the former users, the hippocampal integrity was comparable to controls. The conclusion was ongoing cannabis use is associated with harm to brain health, underpinned by chronic exposure to THC. However, such harm was minimized by CBD, and recovery was thought to be possible with extended periods of abstinence. Currently most of the marijuana products available in Colorado dispensaries have significant amounts of THC and negligible amounts of CBD.⁶

Cannabis and Adolescents

Although national survey data indicate that use of marijuana by youth has remained stable, there has been a significant increase in dabbing and use of edibles as the usual method of marijuana use among high school students who reported past 30-day marijuana use in Colorado between 2015 and 2017.^{62,63} These products are higher in THC potency and can result in more behavioral health consequences. A retrospective cohort study of intentional misuse and abuse exposures in school-aged children and adolescents reported to the National Poison Data System (NPDS) from January 1, 2000, through December 31, 2020, found adolescent cannabis abuse in the United States has increased drastically, by about 245%, since 2000, as alcohol abuse among teens has steadily declined.⁶⁴

A 2019 study from the UK of 1087 participants age 24, who started using cannabis between the ages of 14 and 16, found that those using the higher THC products ($\geq 10\%$ THC) reported significant increased frequency of cannabis use, cannabis problems and increased likelihood of anxiety disorder compared to those using the products with $< 10\%$ THC.⁶⁵ There has been a significant 10-year increase in adolescent marijuana-associated emergency department and urgent care visits in Colorado with a significant increase in behavioral health evaluations, most notably in the years following commercialization of medical (2009) and recreational marijuana (2014).⁶⁶

The use of electronic cigarettes (e-cigarettes) and vape devices by youth has rapidly increased, driven in large part by marketing and advertising by e-cigarette companies.⁶⁷ In 2017 Colorado was leading the nation in use of nicotine-containing vapor products or vaping among young people under the age of 18 and this use was associated with a number of other risk behaviors including significantly more reports of marijuana use in the past 30 days.⁶⁸ Among adolescents reporting use of electronic vapor products, 50.1% reported using marijuana in the past 30 days versus 7.6% of those not using vape products.

Endocannabinoid System

One positive benefit of research on cannabis has been an increasing understanding of the endocannabinoid system in the brain. It was named as such because it was discovered that THC fit into a receptor in the brain in the 1960s, well before there was any understanding of why we might have such a receptor in the brain.⁶⁹ The same lab that discovered this, discovered why we have these receptors. In the 1990s they discovered the brain makes a substance, they named anandamides (which is a Sanskrit word for extreme joy or bliss) which fit into these cannabis receptors (CB1) in the brain.

Experimental evidence shows that the cannabinoid system activity is neuroprotective, regulating critical homeostatic processes in the brain.⁷⁰ The brain produces anandamides when needed; they are used locally and destroyed when no longer needed. CB1 receptors regulate the balance between excitatory and inhibitory neuronal activity. CB1 receptors play a particularly important role during adolescent brain development. THC fits into the CB1 receptors blocking anandamides and is slow to disappear.

Adolescent/young adult exposure to cannabis can disrupt excitatory glutamate functioning in the brain.⁷¹ Glutamate plays an important role in normal brain development by facilitating synaptic pruning in the prefrontal motor cortex during adolescence and young adulthood. This process is not complete until the mid-20s when the brain is considered fully developed. As such the use of marijuana during development can cause long-term or possibly permanent adverse changes in the brain.

Cannabis and Children

Edible cannabis products are another area of concern in that these can contain very high concentrations of THC. In Colorado, edibles in the recreational market are limited to 10 mg THC per piece and 100 mg per package. There is no similar limit in the medical market, where there can be cookies with 1000 mg of THC in one cookie. The products are often packaged to resemble similar products on the market that do not have cannabis in them and this can be very confusing, especially to young children. In Colorado, since 2009, there has been a steady rise in the number of children, nine and younger, being reported to the Poison Control Center or showing up in emergency rooms after ingesting an edible.⁷² A retrospective analysis of the National Poison Data System data for pediatric exposures to edible cannabis products in children < 6 years of age from 2017 to 2021 found that in 2017 there were 207 reported cases and in 2021 there were 3054 cases, an increase of 1375.0%.⁷³ Seventy percent of the cases followed to a known

outcome were reported to have central nervous system depression and of all reported cases, 22.7% patients were admitted to the hospital.

A 2022 report from Canada indicated there has been an 800 % increase in cannabis poisonings among children in Ontario after the legalization of recreational cannabis in 2018, with a sharp rise after full legalization of edible cannabis products in January 2020.⁷⁴ Increases in ED visit frequency and severity occurred despite strict regulations that largely exceed US regulations (eg, a maximum of 10 mg of THC per entire edible package, child-resistant packaging, and marketing restrictions). In a study comparing the different provinces in Canada, a significant rise in the rates of hospitalization for unintentional cannabis poisonings in children ages 0 to 9 occurred in Ontario, Alberta, and British Columbia where edibles were permitted but not in Quebec where edibles were restricted.⁷⁵ This is strong evidence that stricter regulations and restrictions can help decrease the negative public health impact of high THC.

Cannabis and the Elderly

On the opposite end of the age spectrum, more and more elderly people are using cannabis products, often with detrimental outcomes. A retrospective cohort study of adults aged ≥ 65 , 2005 through 2019, from all non-federal acute care hospitals across the state of California found the cannabis-related ED visit rate increased significantly for adults aged ≥ 65 and all subgroups ($p < 0.001$).⁷⁶ There was a 1804% relative increase with 20.7 per 100,000 visits in 2005 to 395.0 per 100,000 ED visits in 2019. Adults aged 75–84 had the largest relative percent change with a 2208.3% increase. Older Black adults had the highest ED visit rate in 2019 and the largest absolute increase while older males had a higher ED visit rate in 2019 and a greater absolute increase than older women.

A scoping review of the literature on the effects of cannabis use in adults ≥ 50 years of age found medical cannabis had inconsistent therapeutic effects in specific patient conditions (e.g., end-stage cancer, dementia), with some studies suggesting possible benefits while others found no benefit.⁷⁷ For medical cannabis, harmful associations outnumbered beneficial, and randomized controlled trials reported more negative effects than non-randomized/observational studies. Cannabis use was associated with greater frequencies of depression, anxiety, cognitive impairment, substance use and problematic substance use, accidents/injuries, and acute healthcare use. Studies often were small, did not consistently assess harms, and did not adjust for confounding.

Cannabinoid Hyperemesis Syndrome

An increasing reason for hospitalizations related to cannabis use in all age groups is cannabinoid hyperemesis syndrome (CHS). Once thought to be rare, it is now being seen almost daily in emergency departments around the state in Colorado.⁷⁸ This is an idiosyncratic reaction to cannabis that is supposed to help with nausea and vomiting but some experience severe abdominal pain and uncontrolled cyclic vomiting that often requires emergency treatment to stop vomiting and rehydrate. Most common medications used for nausea and vomiting do not help and individuals often require much stronger medication such as intravenous haloperidol (which has many known side effects).

CHS is typically seen in people between the ages of 18-40 who use cannabis at least weekly, are under 50 years of age at onset, and started using cannabis in their teenage years.⁷⁹ Symptoms include cyclical nausea and vomiting, abdominal pain, compulsive hot water bathing to temporarily ease symptoms, and resolution of symptoms only by stopping cannabis. Although CHS has been documented in medical

journals, some medical providers and most consumers of cannabis are unaware of it. Deficient medical information causes confusion and serious repercussions. Patients are skeptical that the cause of their symptoms is cannabis and are reluctant to stop using. They typically undergo multiple costly and time-consuming investigations before diagnosis, while continuing to suffer and accumulate emergency medical bills due to CHS.

A 2019 study looked at the number of emergency department visits and costs of CHS to 17 patients who were diagnosed after extensive examinations, x-rays, and emergency treatment.⁸⁰ The average was 17.9 emergency department visits, costing an average \$76,920.92 per patient. If the public and health care providers understood that the only solution to CHS is the cessation of cannabis, these procedures, costs, and prolonged suffering could be avoided. Broader education regarding CHS is a critical need.

A 2021 study found a substantial increase in vomiting-related ED visits in Colorado after legalization of recreational cannabis.⁸¹ From January 1, 2013, through December 31, 2018, there were a total of 820,778 vomiting-related ED visits. Annual vomiting-related health care encounters increased from 119,312 in 2013 to 153,699 by 2018 (a 29% increase). A similar trend has been seen in Canada. In a study covering 2014 to 2021 there were 12,866 ED visits for CHS from 8140 individuals.⁸² The most significant increase occurred after full commercialization of cannabis and during COVID. Overall, the mean (SD) age was 27.4 (10.5) years, with 2834 individuals (34.8%) aged 19 to 24 years, 4163 (51.5%) females, and 1353 individuals (16.6%) with a mental health ED visit or hospitalization in the 2 years before their first CHS ED visit. Nearly 10% of visits (1135 visits [8.8%]) led to hospital admissions. The monthly rates of CHS ED visits increased 13-fold during the 7.5-year study period.

A 2022 mixed methods study was conducted, using an internet survey of 157 CHS sufferers in Canada and the United States, as well as administrative health databases for the province of Alberta (population 5 million) to measure emergency department (ED) visits for vomiting, with a concurrent diagnostic code for cannabis use.⁸³ The survey data found that patients with CHS almost universally suffer from a cannabis use disorder, which has significant treatment implications. Treatment prevalence in the ED has increased substantially over a very short time period, with the highest rates seen during the Covid-19 pandemic. Treatment prevalence among chronic cannabis users was as high as 6 per 1000 in the 16–24 age group.

Although many people believe cannabis is safe because people do not die from overdosing on cannabis, there have been increasing numbers of case reports of people dying from CHS.^{84,85} Treatment providers and consumers need to be aware of this potential consequence of using cannabis, especially high THC, regularly.

Cannabis and Opioids

Many states including Colorado have “in lieu of an opioid” as an indication for obtaining a medical marijuana card, in fact in Colorado it is the number 2 reason for obtaining a card, next to severe pain.⁸⁶ This is despite any real research to support this. Coloradoans have had access to medical marijuana since 2001 and recreational marijuana since 2014 and this has done nothing to decrease the opioid overdose deaths in Colorado. Colorado Department of Public Health and environment data in 2020 demonstrated a 136% increase in prescription overdose deaths and 864% increase in fentanyl deaths since 2000.⁸⁷

Earlier research seemed to suggest that expanding cannabis laws could reverse the opioid epidemic when Bachhuber et al.⁸⁸ reported in 2014 that states with medical cannabis laws had a lower-than-expected opioid overdose mortality rates from 1999-2010. They estimated a 24.8% reduction in deaths per 100,000 population. However, subsequent research by Shover et al.⁸⁹ used the same methods to expand the analysis through 2017. Between 2010 and 2017, 32 states enacted medical cannabis laws. The initial findings did not hold over the longer period but reversed direction and states with a medical cannabis law had a 22.7% increase in opioid overdose deaths.

A study using data from the 2001-2002 NESARC (wave 1) survey (81% response) and the 2004-2005 (wave 2) survey (70.2% response rate) (N=34,653) compared cannabis use at wave 1 to prescription opioid use disorder at wave 2.⁹⁰ Cannabis use at wave 1 was associated with a significant increase in the odds of having a prescription opioid use disorder at wave 2.

In a study of 1514 patients with chronic non-cancer pain prescribed opiates, 723 (60%) who were also using cannabis, there was no evidence that cannabis use improved patient outcomes.⁹¹ People who used cannabis had greater pain and lower self-efficacy in managing pain. There was no evidence that cannabis use reduced pain severity and no evidence that cannabis exerted an opioid-sparing effect.

A 2021 study of 2,334 individuals with opioid use disorder (OUD) on opioid assisted treatment medication found that half reported current cannabis use, 68% of whom reported daily use.⁹² Twenty-four percent of participants who use cannabis endorsed suicidal ideations in the past 30 days, compared to 17% of those who do not use cannabis. Cannabis use, regardless of frequency of use, is associated with a 40% increase in the odds of endorsing suicidal ideation.

Given the fact that the United States has the world's highest opioid death rate and the second highest cannabis-use-disorder prevalence, a 2022 study tested the hypothesis that marijuana availability reduces opioid mortality.⁹³ The United States opioid mortality rate was compared in states and District of Columbia that had implemented marijuana legalization with states that had not, by applying joinpoint methodology to Centers for Disease Control and Prevention data. Variables included race/ethnicity and fentanyl-type opioids (fentanyls). Researchers found that after the same rates during 2010–2012, the opioid mortality rate increased more rapidly in marijuana-legalizing than non-legalizing jurisdictions (2010–2020 annual pairwise comparison $p = 0.003$ for all opioids and $p = 0.0004$ for fentanyls). During the past decade, all four major race/ethnicities in the U.S. had evidence for a statistically significant greater increase in opioid mortality rates in legalizing than non-legalizing jurisdictions. Among legalizing jurisdictions, the greatest mortality rate increase for all opioids was in non-Hispanic blacks (27%/year, $p = 0.0001$) and for fentanyls in Hispanics (45%/year, $p = 0.0000008$). The greatest annual opioid mortality increase occurred in 2020, the first year of the COVID-19 pandemic, with non-Hispanic blacks having the greatest increase in legalizing vs. non-legalizing opioid-death-rate difference, from 32% higher in legalizing jurisdictions in 2019 to more than double in 2020. These results suggest that marijuana legalization has contributed to the U.S.'s opioid epidemic in all major races/ethnicities, and especially in blacks.

Opioid antagonism has been found to enhance marijuana's effects in heavy marijuana smokers. In a study of 29 heavy marijuana smokers, identified as smoking at least four times a week, the subjective, performance, and physiological effects of marijuana (0.0, 3.27% THC) under placebo and active naltrexone (12, 25, 50, and 100 mg) conditions were measured.⁹⁴ It was found that by blocking potential input from the opioid system with naltrexone, the subjective experience and cardiovascular effects of

marijuana are enhanced. This may explain results from a randomized double-blind, placebo-controlled trial of naltrexone in non-treatment seeking cannabis smokers in a laboratory setting, where those receiving the placebo had 7.6 times the odds of self-administering active cannabis compared with those receiving daily naltrexone.⁹⁵ The opioid blockade may have enhanced the effects of the marijuana and the subjects did not feel the need to smoke more.

Research by Wadeker⁹⁶ indicates that first use of marijuana before the age of 18 has the highest contribution to developing opioid use disorders (OUD), a much higher contribution compared to early initiation of alcohol.

Drug Interactions with Cannabis

Because cannabis can often cause or worsen psychiatric symptoms, it is difficult to diagnose mental health conditions and determine appropriate pharmacological interventions in a patient who is actively using cannabis products, especially the high potent THC products. Drugs are metabolized and eliminated by enzymes in the liver, specifically, the cytochrome P450 (CYP) family of enzymes. Drugs can act as either inhibitors or inducers of these enzymes and as a result, cannabis can have many drug-drug interactions with other drugs.^{97,98}

THC and CBD are both metabolized by CYP3A4 and CYP2C9. Some medications can increase cannabinoid levels. For example, drugs that are CYP3A4 inhibitors such as ketoconazole, an antifungal medication, can double THC and CBD concentrations, augmenting the psychoactive effects of THC. This is similar for drugs that inhibit CYP2C9 such as fluoxetine which could be expected to increase THC exposure and psychoactive effects. On the other hand, cannabis can affect the levels of other medications. THC induces CYP1A2 and can reduce levels of drugs metabolized by CYP1A2 such as theophylline or olanzapine. CBD inhibits CYP3A4 and CYP2D6 and can increase levels of drugs metabolized by these isoenzymes. CYP3A4 metabolizes about a quarter of all drugs.

CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin). CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone). Increased concentrations of these drugs can result in increased side effects.

Currently in Colorado, a physician can recommend that a patient have a medical marijuana card but another physician prescribing for the patient has no way to know that the patient is using medical marijuana unless the patient self-reports his/her use. Medical marijuana is not on the Prescription Drug Monitoring Program (PDMP) as are other scheduled medications. While there are now requirements (since the passage of HB21-1317⁹⁹) that prescribers recommending medical marijuana determine the type, dose, frequency and route of administration, it is not known if they are actually doing this. There are no requirements that the patients' current medications are reviewed nor requirements to document that patients are advised about possible drug-drug interactions. So even if a prescriber recommends a low THC product, there is no "prescription" and the patient can purchase any concentration, including any product the dispensary worker recommends. The patient can purchase high potency edibles, wax, shatter, or vape oil, even though there is no evidence to support their use for any medical condition.

Equally concerning is the fact that many prescribers have limited knowledge of cannabis and its uses medicinally, or possible consequences from use. A report of an on-line survey of 451 health care

professionals including neurologists, nurse practitioners/nurses and pharmacists indicated that many health care professionals are not educated enough about medical marijuana to counsel their patient and recommend specific products or dosing.¹⁰⁰ The authors reported “professional cannabinoid education nationwide is immensely needed.”

Patient care in Colorado would be improved substantially if medical marijuana was on the PDMP. This information would allow other physicians seeing the patients, who are using medical marijuana, to consider drug to drug interactions with other prescribed medicine. It could also facilitate communication between providers to discuss the best options for the patient. This way the providers would know who was making the recommendation for medical marijuana and how to contact them. Anecdotally in Colorado, very few patients can tell a primary care provider or psychiatric provider the name of the physician who signed their medical marijuana card, often because they spend only a few minutes with them on-line, so there is very little communication between providers regarding the use of medical marijuana. Because of the inherent danger in scheduled medications, they should all be on the PDMP, including medical marijuana.

Recommendations

Given that research supporting the use of cannabis for medical conditions is limited to less than 10 % THC and use of products greater than 10 % THC can contribute to a myriad of problems, a strong recommendation is to:

Limit potency of THC to under 10% in **medical** cannabis and eliminate the concentrates such as wax, shatter, oil for vaping, from **medical** cannabis since there is no research on these products for any **medical** condition.

Eliminate edibles or significantly reduce the THC in edibles and prohibit any packaging that make edibles appear like current popular food items such as candies, cookies, etc.

Recognizing that there is really no difference between medical marijuana and recreational marijuana products, require and enforce warnings of all these afore mentioned possible consequences to adults who are purchasing recreational marijuana products.

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