

Missouri Medicine

The Journal of the Missouri State Medical Association

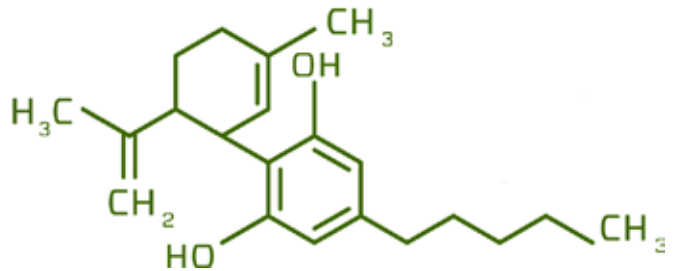
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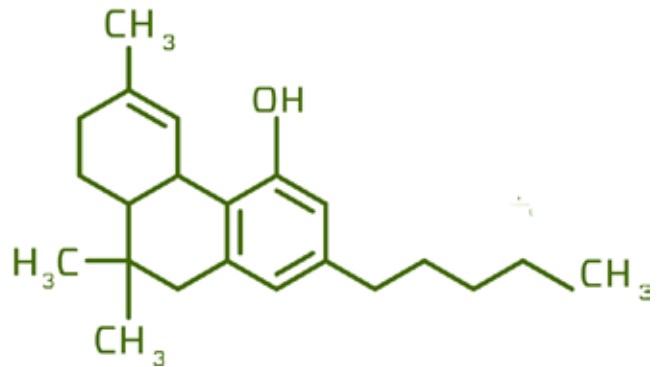
National Cannabis Review: Are CBD & THC Valid Medicines?



CBD
CANNABIDIOL

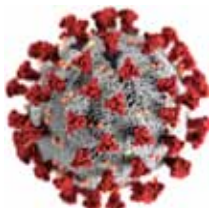


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COVID-19 REPORT: Testing & Physician Wellness



Medical Fraud, Mislabeling, Contamination: All Common in CBD Products

by David G. Evans, JD

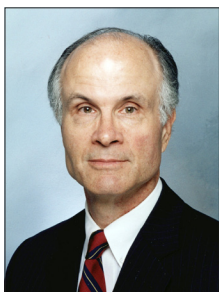
Cannabidiol (CBD) is an oil derived from the cannabis plant. It is touted as a “wonder drug.” Advertisements claim it is perfectly safe and legal and can be used for all that ails you or makes you uncomfortable mentally or physically. People are consuming it under the misapprehension that it is safe, however, CBD has negative side effects and may interfere with the functioning of other medications and may be contaminated.

Consumer demand for CBD has increased due to aggressive marketing and fraudulent health claims. In the rush to market CBD, there has been little consideration of the concerns that must be addressed before CBD is given full acceptance. This article will explore those concerns.



Is CBD Legal?

There are claims that CBD from hemp used as a medicine or food is always legal. This is not accurate. The Agriculture Improvement Act of 2018 changed federal law regarding the production and marketing of hemp. Hemp is defined as cannabis and its derivatives with extremely low (less than 0.3% a dry weight basis) concentration of the THC. These changes removed hemp from the federal Controlled Substances Act, which means that it will no longer be an illegal substance under federal law. However, Congress explicitly preserved the FDA's authority to regulate these products under the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act. These compounds are subject to the same requirements as FDA-regulated products containing any other substance regardless of the source of the substance. Cannabis products claiming in their marketing materials that they're intended for use in the diagnosis, cure, mitigation, treatment, or prevention of



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diseases must go through the FDA drug approval process for human or animal use before they are legally marketed.¹

As stated by the FDA Commissioner:

“Selling unapproved products with unsubstantiated therapeutic claims is not only a violation of the law, but also can put patients at risk, as these products have not been proven to be safe or effective. This deceptive marketing of unproven treatments raises significant public health concerns, as it may keep some patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases.”²

CBD products that are not approved by the FDA and are sold as medicines, or as food, or cosmetics are “black-market” and are illegally trafficked and sold. This includes those sold in reputable stores, restaurants, and other places that don’t have FDA approval to do so. Black-market CBD products have not been evaluated by the FDA to determine if they are safe as foods or effective or safe for any medical use, and if safe, what the proper dosage would be. In addition, they are not administered with any federally approved medical protocols as are prescription drugs and there may be no warnings for how they interact with other drugs, or whether they have dangerous side effects.³

A pure form of CBD is approved by the FDA as a medicine for two rare seizure disorders. Its approval was based on well-controlled FDA clinical trials. This is a purified form of CBD in a reliable dosage form and a reproducible route of delivery. Since it is manufactured according to FDA standards by a reliable company that has followed the rules, we can assume it is free from adulterants and contaminants. Its side effects and other clinical data are publicly available. This type of data is not provided by the black-market CBD products.⁴

There are a number of papers discussing the pros and cons of CBD as a medicine that can be viewed on the National Library of Medicine website at www.nlm.nih.gov. Some studies, notwithstanding their many deficiencies, provide some support for the hypothesis that CBD may exert some beneficial effects, but it has yet to be proven to be both effective and safe. FDA quality studies with purified CBD are warranted. However, clinical data does not support some

claimed uses of CBD for Parkinson’s disease, schizophrenia, cancer palliation and treatment, chronic pain and spasticity, depression, anxiety disorder, insomnia, and inflammation. There is insufficient evidence to rate effectiveness of CBD for Bipolar disorder, Crohn’s disease, diabetes, dystonia, Huntington’s disease, multiple sclerosis (and its muscle spasms, tiredness, bladder control, the ability to move around, or well-being and quality of life), schizophrenia, nerve damage in the hands and feet (peripheral neuropathy) and other conditions.⁵

CBD Mislabeling and Contamination

Studies suggest that black-market CBD is not very reliable or safe. In 2020, the FDA did a study on products that claimed to have a specific amount of CBD and those claimed amounts were compared to the FDA testing results. Of the 102 products that indicated a specific amount of CBD, 18 products (18%) contained less than 80% of the amount of CBD indicated, 46 products (45%) contained CBD within 20 percent of the amount indicated, and 38 products (37%) contained more than 120 percent of the amount of CBD indicated. Of great concern is that 49% of the products tested contained THC.⁶

The *Journal of the American Medical Association* published a letter demonstrating the results of “undercover” purchases of CBD. Of 84 samples tested, THC was detected in 21%. There were other defects in the mislabeled products. Only 30.95% were accurately labeled. Accuracy of labeling depended on product type, with vaporization liquid most frequently mislabeled (87.50%) and oil most frequently labeled accurately (45.0 %). THC was detected (up to 6.43 mg/mL) in 18 of the 84 samples tested (21.43%).⁷

A Johns Hopkins researcher tested CBD products. Testing showed 44 products (59%) had detectible levels of CBD, but the average ratio of THC to CBD was 36-to-1. Only one product had a 1-to-1 ratio, which some research suggests is associated with fewer side effects and improved clinical benefit compared with higher ratios of THC to CBD. The testing indicated the edible cannabis products may have very little CBD.⁸

A study published by the National Institute of Health showed that products were mislabeled



with 26% containing less CBD than labeled and 43% containing more, indicating a high degree of variability and poor standardization of online products. Notably, the oil-based products were more likely to be accurate (45% compared to 25% for tincture and 12.5% for vaporization liquid) and had a smaller percentage of deviation. Oil based products also had a higher range of concentration. In addition to CBD mislabeling, THC was detected in 21% of samples. This study also notes that products containing THC could have sufficient enough concentrations to produce intoxication in children.⁹

In a recent federal lawsuit, the plaintiff bought CBD products relying on advertising that the products had “No Heavy Metals or Insecticides.” The products failed laboratory testing for heavy metals, including copper, nickel, and lead and also for total yeast and mold. Lead can cause poisoning, speech, and language problems, neurologic toxicity, and reproductive problems. Mold can cause allergic and respiratory problems, and yeasts can cause infection in people with compromised immune systems.¹⁰ On July 28, 2020, another CBD product was recalled due to lead contamination. The recall noted that acute lead poisoning could cause pain, muscle weakness, paresthesia, abdominal pain, nausea, vomiting, diarrhea, constipation, poor appetite, weight loss, symptoms associated with encephalitis, metallic taste in the mouth, shock, hemolysis, and kidney damage.¹¹

False Medical Claims

Examples of false claims for CBD can be taken from FDA and Federal Trade Commission (FTC) warning letters to CBD companies. In order to make claims of treatment or medical use, products must obtain approval from the FDA after submitting their data. False claims include using CBD to treat: alcoholism, Alzheimer’s disease, arthritis, autism, blood pressure and heart rate, cancer, chronic traumatic encephalopathy, cardiovascular disease, chemotherapy-induced hearing loss, colitis, concussions, depression, diabetes, leukemia, liver inflammation, lupus, Lyme disease, neurological damage, Parkinson’s disease, stroke, schizophrenia, traumatic brain injury (TBI), and tumors.¹²

CBD Negative Side Effects and Drug Contraindications

There may be interactions between CBD and immunosuppressive drugs used in transplants or

chemotherapy and with warfarin as there may be the potentiation of anticoagulant effects with marijuana, including CBD. CBD may interact with other medicines, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any cannabis-based products. CBD may affect the way other medicines work, and other medicines may affect how CBD works.

CBD may decrease how fast the liver metabolizes the drug. This may possibly increase the effects and side effects. CBD may potentially interact in a negative way with anti-epileptic drugs such as: carbamazepine (Tegretol), phenytoin (Dilantin), phenobarbital (Luminal, Solfoton, Tedral), primidone (anti-seizure). Users should be cautious before taking CBD with: sedatives, herbs, and supplements that cause drowsiness, seizure medications, drugs that are broken down and changed by the liver. People should be cautious with using Brivaracetam (Briviact), Eslicarbazepine (Aptiom), and Everolimus (Zostress).¹³ Consumers should not take CBD with Clobazam for seizures.¹⁴ The use of CBD along with these drugs might increase the effects and side effects of the drugs.

Adverse Reactions

The adverse reactions to CBD include: hepatocellular injury, somnolence and sedation, suicidal behavior and ideation, hypersensitivity reactions—allergic reactions, negative interaction with anti-epilepsy drugs (such as Tegretol, Dilantin, luminal, Solfoton, Tedral, primidone), interactions with immunosuppressive drugs used in transplants or chemotherapy and with warfarin. CBD use can impair kidney function and cause anemia.¹⁵ Black market CBD is generally sold without warnings about adverse reactions.

The side effects of CBD can include: drowsiness, decreased appetite, diarrhea, transaminase elevations, fatigue, feeling unwell (malaise), rash, difficulty sleeping (insomnia, disordered sleep, and poor-quality sleep), infections, somnolence, decreased appetite, diarrhea, and asthenia.¹⁶

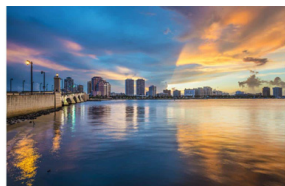
Research shows that more than 40% of children with epilepsy who were given CBD orally had adverse events that included THC like symptoms. The research challenged the widely accepted premise that CBD is not intoxicating.¹⁷



Glaucoma Made Worse by Marijuana, THC, and CBD

by John C. Hagan III, Ophthalmologist Eye, MD

Normal Vision



Early Glaucoma



Advanced Glaucoma



End Stage Glaucoma



Source: <https://www.graceandvision.com.au/eye-conditions/glaucoma/>

Although glaucoma is a listed indication for issuing sham medical marijuana cards, the most recent evidence is that cannabis in either tetrahydrocannabinol (THC) or cannabidiol (CBD) are both harmful to the eye and have a deleterious effect on glaucoma.¹⁻⁵ CBD has been shown to increase intra-ocular pressure (IOP) the fundamental problem with most forms of glaucoma; while THC lowers IOP but the effect is transient and therapeutically worthless. Chronic cannabis use causes damage and loss of retina ganglion cells as does the disease glaucoma. Moreover, ganglion cells are central nervous system tissue, like the cells of the brain, and may serve as a surrogate marker for brain cell loss. This might account for neurological problems associated with heavy cannabis use such as memory loss, lethargy and poor motivation, permanent IQ loss in youthful users, aggression, psychosis, etc. Half a century of research has found no benefit to any cannabis products in ophthalmology. Use of sham medical marijuana, CBD or any form of cannabis is not recommended for glaucoma or any other eye condition by the American Academy of Ophthalmology or the Glaucoma Society. No physician should ever recommend cannabis use for any of the many forms of glaucoma.

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Glaucoma

A recent study suggests that CBD doesn't lower eye pressure but instead raises it. High eye pressure is the primary risk factor for glaucoma, a leading cause of blindness.¹⁸ [Editor's Note: see sidebar.]

Warnings

Black Market CBD may be sold without warnings being provided. People should be warned about the known adverse reactions to CBD. People should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that CBD does not affect them adversely (e.g., impaired judgment, thinking, or motor skills). Use of

CBD may increase the risk of suicidal thoughts and behavior. Hypersensitivity reactions can occur with use of CBD. It is not known if CBD is safe and effective in children under two years of age. FDA clinical trials of CBD did not include any patients aged above 55 years. CBD for elderly persons could be dangerous due to the greater frequency of decreased liver or cardiac function, and of concomitant disease or other drug therapy.¹⁹

Vehicle Operation

A recent FDA report states that CBD can cause sleepiness, sedation, and that may make operating a motor vehicle or machinery dangerous after consuming CBD products.²⁰



CBD and Pregnancy

The FDA strongly advises that during pregnancy and while breastfeeding, women should not use CBD or THC. They may put themselves or their baby at serious risk by using these marijuana products. CBD products may also be contaminated with substances that may pose a risk to the fetus or breastfed baby such as pesticides, heavy metals, bacteria, and fungus. Studies in laboratory animals show male reproductive toxicity, including in the male offspring of CBD-treated pregnant females. This includes decrease in testicular size, inhibition of sperm development, and decreased testosterone.²¹ The CDC also notes that marijuana use by a pregnant woman can have teratogenic effects causing birth defects.²²

Drug Tests

CBD may affect drug test results. A truck driver lost his job when he tested positive for THC on a drug test after being told by the manufacturer that a CBD product had no THC.²³

Recent CBD Lawsuits

There are many recent lawsuits filed against CBD manufacturers and more are on the way. They were filed after the FDA issued a series of warning letters that such products, unless approved by the FDA, are neither safe or effective for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or because they are intended to affect the structure or any function of the body. Some of the cases allege that the manufacturers' CBD products made false medical claims or were mislabeled as dietary supplements or there were false claims as to the amount of CBD present in the product. A California case claims that the company engaged in false and deceptive practices and that their products could not be sold legally. A Massachusetts case claimed that many of the defendant's products had significantly lower levels of CBD than advertised. A California case claimed that the defendant company made false claims that CBD could help the symptoms of autism and that could treat illnesses such as hepatitis, cancer, and Tourette syndrome. A New York case alleges false medical claims for marijuana and for violations of the federal securities laws. A Florida case alleged that CBD has "been touted as having numerous

positive health effects." CBD has been used to treat conditions such as "anxiety, sleep disorders, and chronic pain." In selling the products with significantly less CBD, plaintiff claimed the Defendants "are cheating every consumer who buys the products by that amount." The Federal Trade Commission recently petitioned to enjoin a CBD company from disseminating false or unsubstantiated advertisement claims in connection sale of a product that purportedly treats, prevents or reduces the risk of COVID-19 and products that purportedly treat cancer.²⁴

Government Bans on CBD Use

The federal Department of Transportation has issued a warning that CBD use can show up as a positive THC result on a drug test.²⁵ The U.S. military has banned the use of hemp/CBD products for military personnel.²⁶

The Future of CBD and the FDA

The FDA is currently undertaking a large long-term study of black-market CBD products to understand the characteristics of CBD products in order to make informed decisions about how best to protect public health. The FDA will report again on the results from both the near and long-term studies when complete data sets are available.²⁷ On July 21, 2020, the FDA stated that in regard to CBD and other cannabinoids:

"The FDA believes the drug approval process represents the best way to ensure that safe and effective new medicines, including any drugs that contain cannabis or cannabis-derived compounds, are available to patients in need of appropriate medical therapy."²⁸

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Cannabis use should be discouraged during pregnancy and lactation.

Cannabis in Pregnancy and Lactation – A Review

by Joseph, Polcaro, DO & Ivana M Vettraino, MD, MBA

Abstract

Cannabis (marijuana) is now legal for either medicinal use or recreational use in 33 states with more states considering legalization for medicinal and/or recreational use. More women planning pregnancy, pregnant, or breastfeeding will present with exposure to marijuana. A familiarity with the pharmacology and potential effects for pregnancy and lactation is important for the obstetrical care provider to permit optimal counseling for the gravida. This paper provides a pertinent review of cannabis for the obstetrical care provider. The literature available for review concludes that no amount of marijuana and associated product use in pregnancy and lactation is safe. Cannabis and associated product use has the potential for adverse maternal, fetal, and long-term childhood development and its use should be discouraged during pregnancy and lactation.

Introduction

Marijuana or cannabis is also known by many slang terms including weed, herb, pot, grass, bud, ganja, and Mary Jane. Cannabis has a long history with evidence of use for medicinal, spiritual, and recreational use dating at least 5000 years ago.^{1,2} Historical texts show most ancient civilizations utilized cannabis for medicinal and spiritual properties.³ Cannabis use as a medicinal has been reported in the United States during the 19th and early 20th centuries.⁴ Medical marijuana was first described in the United States in 1850. The various modes of use include smoking, dabbing, eating, and most recently vaping.

As of June 2019, 11 states have adopted laws legalizing recreational use of marijuana. Another 22 states allow for the use of medical marijuana.⁵ The federal government does not recognize cannabis as a legal drug. Cannabis is the most commonly used illegal drug in the United States of America (USA). Approximately 22.2 million individuals use marijuana each month. One in 10 individuals will become addicted if over the age of 18 years and 1 in 6 will become addicted if use occurs under the age of 18 years.⁶ Long term and frequent use have been associated with increased risk for psychosis and schizophrenia.

As legalization of marijuana has spread across the USA, the perception of safety in pregnancy has also increased.^{7,8,9} Approximately 1 in 25 pregnant women are estimated to use marijuana during pregnancy.¹⁰ In a research letter using data from the National Surveys of Drug Use and Health from 2005 to 2012 reported that the



Joseph Polcaro, DO, (left), and Ivana M Vettraino, MD, MBA, are in the Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Mercy Hospital – St Louis, St. Louis, Missouri.



percentage of women who reported “no risk” of harm rose from 25.8 % in 2005 to 65.4 % in 2012.¹¹ This paper will review the pharmacology and the potential effects of marijuana use in pregnancy and lactation.

Pharmacology

Marijuana is composed of the leaves and flowers of the Indian hemp plant. The potency varies based on location of origin, method of cultivation, and method of storage. The active ingredient tetrahydrocannabinol (THC) is present in all parts of the plant. However, the most concentrated and strongest marijuana comes from the resin in the flowering tops of the female plants. The plant contains greater than 400 other chemicals including approximately 60 compounds chemically related to THC known as cannabinoids. Additionally, there are over 2000 compounds produced by thermal decomposition during smoking.¹²

The psychoactive metabolite of cannabis is delta-9-tetrahydrocannabinol (THC) that acts on cannabinoid receptors within the central nervous system (CNS) and peripheral tissues.¹³ THC acts on cannabinoid receptors – CB1 found in CNS and CB2 found in peripheral tissues.¹⁴ THC is similar in chemical structure to the human brain chemical anandamide. Anandamide is an endogenous cannabinoid which functions as a neurotransmitter within the endocannabinoid system.^{13,15} This system plays a critical role in the normal functioning of the nervous system and homeostasis. The endocannabinoid system is involved in a wide variety of processes including pain, memory, mood, appetite, stress, sleep, metabolism, immune function, and reproductive function. Therefore, interfering with this system can have profound effects. For example, THC can alter functioning of the hippocampus affecting memory and focus. THC also can disrupt functioning of the cerebellum and basal ganglia resulting in loss of balance, coordination, and a decrease in reaction time.¹⁶ This similarity in structure between THC and anandamide allows the brain to recognize THC in a manner like anandamide.

Psychological effects include euphoria as THC can increase the release of dopamine. This effect may lead to psychological habituation noted below. Effects of THC can vary amongst individuals. Some will experience visual disturbance, laughter, increase in appetite, and distortion in judgment, time, and

space. Visual hallucinations, anxiety, depression, psychosis, mood disturbance can also occur. If marijuana is used as an edible or beverage, the effects can be delayed by approximately 30 minutes to an hour due to tablets and within the digestive tract. Eating or drinking marijuana results in significantly less THC in the bloodstream when compared to smoking an equivalent amount. Because of these delayed effects, increased consumption of THC can lead to toxicity.¹⁷

The physical effects of cannabis use include but are not limited to red eyes, dryness of the mouth, increase in heart rate, chest tightness when smoked, drowsiness, and unsteadiness with decreased muscle coordination.

Chronic use does not appear to lead to physical dependence. Therefore, withdrawal is not a known effect of cannabis use when discontinued. However, this drug can be psychologically habituating. THC remains in the body for approximately 48 hours after smoking. Therefore, the residual effects on cognitive function including memory can last up to 48 hours.¹⁸

THC is metabolized within the liver, brain, lung, and intestine to hydroxylated and carboxylated metabolites. These metabolites are stored within the peripheral tissues and eventually excreted in the urine or feces dependent upon mode of use, inhalation or edible, respectively. Within a 5 day window, approximately 80 to 90 percent of THC is eliminated.¹⁹

Indirect exposure can occur during passive smoking of cannabis. Fifty percent of THC survives pyrolysis during smoking with 6 to 53 % released in the air. Therefore, passive inhalation can occur if the individual is within proximity of the smoker. A positive drug screen is possible following passive exposure.²⁰

Marijuana Exposure in Pregnancy

The incidence of marijuana use in pregnancy has increased. According to Centers for Disease Control (CDC) estimates, approximately 1 in 20 women self-reports the use of marijuana in pregnancy.^{21, 22} As with most self-reporting, this likely underestimates the number of women utilizing marijuana in pregnancy. A recent study found that this number has increased to approximately 18% or approximately 1 in 6 women. These numbers are likely to further increase as more states legalize recreational use of marijuana, resulting in the perception that marijuana use is safe. A research letter using data from the National Surveys of Drug



Use and Health from 2005 to 2012 reported that the number of women who recently used marijuana and believed the drug to be safe in pregnancy increased over this time frame from 25.8 % to 65.4 %.⁷ Women prior to pregnancy and during pregnancy utilize cannabis by many different routes including but not limited to smoking, edibles, vaping, lotions and other.²³

Maternal Effects

The maternal risks of marijuana use are related to method of ingestion, associated risk behaviors, polysubstance abuse, and associated mental health complications. Cannabis use disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition by impaired control, social difficulties, risky use, tolerance, and withdrawal.²⁴

Multiple studies have shown an association with depression, anxiety and other psychiatric conditions.^{25, 26} Such associated mental health conditions can lead to addiction as the marijuana is used to treat the underlying psychiatric illness. Screening for and referral for management of co-existent psychiatric conditions is imperative to decrease the use of marijuana in pregnancy.

Also important for the obstetrical care provider is awareness of cannabinoid hyperemesis syndrome.^{27, 28} Cannabinoid hyperemesis syndrome (CHS) can be challenging to differentiate from hyperemesis gravidarum. CHS should be considered in patients presenting with hyperemesis gravidarum with a history of chronic marijuana use, atypical presentation, and failure to improve with the usual course of management. CHS is characterized by a history of chronic marijuana use; acute-onset nausea, vomiting, and abdominal pain; symptoms alleviated by hot showers; and episodes lasting 24 to 48 hours.^{28, 29, 30} Resolution requires discontinuation of marijuana use.^{28, 30}

Although robust studies are lacking in regard to maternal complications of marijuana use in pregnancy, the data available to date suggests that pregnant women need to be educated to the potential adverse effects on their health and encouraged to discontinue marijuana use in pregnancy.

Fetal and Long-Term Childhood Effects

Studies regarding the use of marijuana in pregnancy have provided conflicting results.³¹⁻⁴³ This is likely due to the challenges in controlling for confounding factors including but not limited to other associated drug use, challenges in quantifying the amount of drug used, difficulties in evaluating childhood development due to other familial/socioeconomic economic factors. Thus, definitive guidelines regarding marijuana use in pregnancy are challenging.

The American College of Obstetrics and Gynecology (ACOG) published a committee opinion in 2017.⁴⁴ In this opinion, the ACOG recommends that women attempting pregnancy, currently pregnant, or breastfeeding avoid marijuana use. The American Academy of Pediatrics also recommends against marijuana use in women who are breastfeeding.⁴⁵

The literature regarding marijuana use in pregnancy is varied and many of the studies have limitations as would be expected in studying a drug in pregnancy. There are recall biases for self-reporting amount and timing of use, confounding variables difficult to control, and meta-analyses with variability in study design. Taking the aforementioned in consideration, the following findings are applicable at this time pending further study.

The inherent physiologic endocannabinoid system is known to be important in human pregnancy. This system has been shown to be important for implantation and pregnancy maintenance.⁴⁶ The role of THC use in implantation and pregnancy maintenance is unclear at this time.

There has not been consistent data to date to suggest an increase in fetal anatomic abnormalities. Likewise, there is no consistent data to show an association with preterm delivery and other adverse pregnancy outcomes in patients reporting only marijuana use.^{31, 32, 33} Preterm labor and delivery can be increased in women using other substances such as tobacco.³⁴ Earlier data suggested that perinatal morbidity/intrauterine fetal demise does not appear to be increased in patients using marijuana alone in pregnancy. Like preterm delivery, use of other substances such as tobacco may slightly increase the risk of stillbirth in this patient population. A recent



retrospective cohort analysis controlling for many of the confounders that affected other studies showed newborns exposed to marijuana had increased rates of lower birth weight - 218 g less; low birth weight, deliver preterm; admitted to the neonatal intensive care unit, and have lower Apgar scores than matched newborns not exposed to marijuana.³⁵ This adds to the literature for concern regarding marijuana exposure in pregnancy.

Regarding neurobehavior development, THC crosses the placenta and enters the fetus at a level of approximately 10% maternal levels.⁴⁷ This level is likely increased with heavy and repetitive use as the half-life of THC can vary based on amount and repetition of use. Fetal brain development can therefore be impacted as the fetal brain contains cannabinoid receptors type 1 as early as 14 weeks' gestation necessary for normal brain development. The THC can preferentially bind to these cannabinoid receptors potentially resulting in abnormalities in brain development and response to endogenous neurotransmitters.^{47, 48} Newborns with in utero exposure to THC can undergo a neonatal abstinence like syndrome characterized by tremors, increased startle reflex and reduced habituation to light.⁴⁹

Children exposed *in utero* to have been found to have lower scores on tests of visual problem solving, visual-motor coordination, and visual analysis, decreased attention span, behavioral challenges than children who were not exposed to marijuana in utero.^{50, 51, 52} There have been no consistent findings regarding cognition and school performance. This is likely due to the multiple confounding variables in studies involving education and school performance. However, studies have shown these children have challenges throughout the educational milestones.

Most recently, a large retrospective analysis of live births in Ontario, Canada has shown an association between cannabis use in pregnancy and the incidence of autism spectrum disorder in their offspring. Women who reported cannabis use without associated tobacco, alcohol or opioid use had an adjusted hazard ratio of 1.51 (confidence interval of 1.17 to 1.96) for a child with a diagnosis of autism.⁵³ This study also found an increase incidence of intellectual and learning disabilities in the children of women who used cannabis in pregnancy. These results support previous studies reporting similar findings as referenced above.

Lactation

To date, most of the literature assessing the effects of marijuana exposure to the neonate through breastfeeding have studied the pharmacokinetics of THC and breast milk.^{54, 55, 56} As cannabinoids are lipophilic, cross the blood brain barrier, affects to the developing fetal brains raise significant concerns. Studies have shown that the concentration of THC in breast milk is variable based on the amount and frequency of maternal ingestion. Unlike many other drugs and medications that are excreted into breast milk but are not concentrated in breast milk, THC is excreted and concentrated in the breast milk. Breast milk can have up to eight times the concentration of maternal plasma and can be detectable for up to 6 days.⁵⁶

Additionally, THC can be found in breast milk approximately 1 hour following ingestion.⁵⁶ Therefore, pumping and dumping between feeds is not likely to significantly decrease the exposure to the neonate.

As individuals with passive inhalation of secondhand marijuana smoke have been shown to have THC present in bodily fluids, one must assume that secondhand exposure can also effect the breast milk and therefore the neonate. Passive or secondhand exposure to marijuana while breastfeeding should be avoided given the potential for harm.⁵⁷

Medical Marijuana

A review of the literature regarding the effectiveness of medical marijuana in decreasing pain and in management of chronic pain syndromes is outside the scope of this paper.

Medical marijuana is not regulated by the Food and Drug Administration. Given that maternal, fetal, and neonatal effects are present as noted above, women managed with medical marijuana should be encouraged to discontinue the medical marijuana and adopt more traditional strategies for management of their underlying medical condition(s) in pregnancy.

Cannabidiol

Cannabidiol (CBD) is a chemical obtained from the Cannabis sativa plant primarily from the hemp type.^{58, 59, 60} Hemp and marijuana are both in the Cannabis family, but hemp contains very little (less than 0.3 percent) of the psychoactive compound delta-9-tetrahydrocannabinol (THC). CBD, unlike marijuana, does not produce a psychoactive response.



The FDA has approved only one CBD product as a prescription drug indicated for the management of rare forms of seizure disorder in children.⁵⁹

The Farm Bill passed in 2018 made the sale of hemp and hemp products legal in the United States. It remains illegal to tout medicinal properties of CBD. Despite lack of scientific evidence for efficacy, CBD has gained in popularity in products such as cosmetics, creams and ointments for pain relief, dietary supplements, treatments for anxiety, management of some neurologic disorders as seizures and Parkinson's, and in edibles. The science and pharmacology of CBD is unknown. Effects on the brain is a proposed mechanism of action. There are no approved dosing regimens. The amount of CBD in these products is variable and the safety of CBD is unclear. Reported side effects include but are not limited to: dry mouth, low blood pressure, light headedness, and drowsiness. Liver injury has been reported. Possible interactions with prescription medications, alcohol, or other illicit drugs remains unknown potentially causing serious side effects.⁵⁹

The Food and Drug Administration (FDA) citing lack of data and concern from animal studies strongly advises against the use of cannabidiol (CBD) in any form during pregnancy or while breastfeeding.⁵⁹ High doses of CBD given to pregnant test animals suggest abnormalities in the reproductive system of developing male fetuses including decreased testicular size, low testosterone, and abnormalities of spermatogenesis.⁶¹ There is an extrapolation from information available to suggest that some amount of CBD will be transferred to babies through breast milk.

There are the additional concerns for CBD products to be contaminated with other potentially harmful substances to the developing fetus or neonate including but not limited to: THC, pesticides, heavy metals, bacteria, and fungus.

In summary, the use of CBD in any form should be discouraged during pregnancy and during lactation.⁵⁹

Conclusion

As states continue to legalize medical and recreational marijuana, more women planning pregnancy, pregnant, or breastfeeding will present with exposure to marijuana. In summary, the

literature available for review suggests that no amount of marijuana use in pregnancy and lactation is safe. Marijuana use has the potential for adverse maternal, fetal, and long-term childhood development. Women contemplating pregnancy or pregnant should discontinue marijuana use. Consultation with an addiction specialist and/or mental health provided may be indicated. Passive or secondhand exposure to marijuana also may have potential effects and should also be avoided. Given the concerns regarding the potential for adverse pregnancy outcome, prenatal care should be adjusted to screen for the potential adverse outcomes.

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None reported.

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Medicinal Marijuana, Stress, Anxiety, and Depression: *Primum non nocere*

by Mark Gold, MD

Medications are viewed as dangerous until proven safe and effective by science and approved by the FDA. Drugs of abuse are taken for many other purposes but often considered safe until proven unsafe.

Higher levels of stress are associated with an increased risk of substance use disorders (SUDs) and other mental health conditions like depression. Stress may exacerbate underlying medical and psychiatric conditions and weaken individual response systems that process events and build resilience. Stress can also make licit and illicit substance use more appealing as a quick self-treatment for anxiety. Stress may also cause SUD slips and relapse in patients who are in treatment for opioid and other substance use disorders. Deaths of despair,¹ including overdoses, have increased during the pandemic.²

The use of cannabis, vaping, or other tetrahydrocannabinol (THC) products may carry unique risks for those “self-medicating” and make depression worse when used as an ersatz antidepressant.³ So-called ‘medical marijuana’ shouldn’t be so lightheartedly rendered or prescribed as a relaxation tool. Short and long term changes in mood, depression, and suicidality can begin during adolescence and exacerbate by teen marijuana use according to a recent study.⁴ This longitudinal cohort study of over 30 years found that cannabis use during adolescence is not a medicine, but is associated with both depression and suicidality in adult life. Early use is the riskiest. The younger the user of regular cannabis,

the higher the risk of depression in adulthood. Recent use of marijuana for pain has also had unintended consequences, not replacing opioids but adding cannabis and even *de novo* cannabis use disorders to opioid risks.

Adults and youth with pain have heard and read claims about cannabis smoking or THC vaping for non-opioid pain relief. However, they are vulnerable to adverse cannabis outcomes, including continued opioid use and the development of additional substance use disorders.⁵ Public “medicinal” opinions on hydroxychloroquine and actual FDA- quality studies of safety and efficacy in SARS COVID 19⁶ or voting marijuana a medicine is quite different than proving in a prospective, random assignment, placebo-controlled double-blind studies. FDA standards protect us from unsafe and ineffective drugs and require that studies are specific to a particular disease at a precise dose and by a particular route and also superior to existing FDA treatments for that disease. While hopes for cannabis-derived medicines are rational, medicinal claims are premature.⁷

While not approved by the FDA for pain relief, it might have seemed logical to think and hope that medicinal marijuana would reduce opioid use. On the contrary, when studied, medical marijuana users are significantly more, rather than less, likely to use and misuse prescription drugs.⁸ Drugs of abuse are unique in that they stimulate their taking but also because they all cause euphoria, loss of self-control, and self-administration through virtually the same net effect on the brain’s dopamine systems. So even drugs initially supported by evidence of effectiveness may later prove to be more harmful than beneficial. Recommending marijuana as if it was an FDA approved and tested medication is currently a topic of great concern, debate, and consternation. *Primum non-nocere*, i.e., first do no



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harm. Medications are viewed as dangerous until proven safe and effective by science and approved by the FDA. Drugs of abuse are taken for many other purposes but often considered safe until proven unsafe. The reversal in the burden of proof means that drugs of abuse are field-tested en masse and consequences discovered over time. Vaping is a recent disastrous example.

Smoking and Vaping Marijuana and THC

The University of Michigan's Monitoring the Future reported that in 2019 (www.monitoringthefuture.org), there was a significant increase in daily cannabis use in the younger grades. Medicinal re-branding of marijuana smoking has accelerated trends in teens' perceptions of the risks of marijuana use; teens' view of risks has steadily declined over the past decade. In 2019, 11.8% of 8th graders reported marijuana use in the past year, and 6.6% were considered current users. Among 10th graders, 28.8% had used marijuana in the past year, and 18.4% were current users. Marijuana use among 12th graders is surprising since 35.7% had used marijuana during the year before the survey, and 22.3% used in the past month. An especially alarming, 6.4% of current high school seniors use marijuana daily or near-daily. Marijuana use is now at a 35-year high for college students. Daily or near-daily use of marijuana was 5.8% in 2018 for college students. It has been between 4% and 6% in the past five years. Among same-age non-college youth, it was 11.1%, nearly double the level for college youth. NIDA's Director Volkow⁹ has discussed these findings, concerns of cannabis use disorders, and likely health, memory, and performance problems caused by regular marijuana use. With the growing popularity¹⁰ of vaping, teens have increased vaping THC, with nearly 4% of 12th graders saying they vape THC daily. The use of tobacco, nicotine, and THC products is widespread among teens. Marijuana use has many adverse consequences, especially for children and teens, whose use is considered dangerous.¹¹

Rates of cannabis smoking and vaping are similar to those reported for cigarettes, and cigarette smoking is related to marijuana use. Cannabis and tobacco use and misuse

frequently co-occur,¹² and in some cases, cannabis smoking precedes tobacco smoking, and in others, tobacco smoking precedes marijuana smoking. THC use is also rising in many states that have legalized the substance, and among the young, for whom the effects of THC are different and likely more dangerous than they are for older individuals. The NIH's 2019 Monitoring the Future survey also found a spike in rates of youth vaping marijuana, concerning because of the substance and the risky delivery route. Learning to inhale drug vapors may be the gateway event worth additional study.¹³ Most of the public health attention has been focused on vaping THC and death or severe toxic effects on lung and pulmonary function. The field testing of THC vaping and e-cigarettes have led to the CDC recommending no use of all e-cigarette or vaping, THC, and nicotine products.¹⁴ Many more current and potential consequences of cannabis smoking and vaping THC are coming to light. Marijuana use has increased in teens following the reduction in perceived danger, ballot initiatives, and largely unproven medical marijuana claims.¹⁵

Whether it's logical to use alcohol or THC products for stress relief, instead of exercising or meditating or taking a walk or doing yoga or talking to a friend or therapist, is a different question from why some individuals do it. People often report anxiety as a primary motivation for using THC

Adolescent cannabis exposure results in impaired cognition, sleep, and driving ability.





products, and it isn't hard to find someone who will swear by the substance as a tranquil godsend without which life would be far less exciting and considerably more fraught. Researchers have focused more recent cannabinoid stress and anxiety efforts on inhibition of monoacylglycerol lipase (MAGL) to enhance signaling of the most abundant and efficacious endocannabinoid ligand, 2-arachidonoylglycerol (2-AG). Preclinical evidence supports a role for this system in the regulation of anxiety-related outcomes and stress and anxiety in the brain (doi:10.1016/j.biopsych.2020.01.015). Many research groups are hopeful that this work will provide us with answers to the question of why some individuals turn to marijuana for acute stress relief only to find that their stress and anxiety may make smoking cannabis or vaping THC more reinforcing.

Marcus et al. found¹⁶ that a molecule, called 2-AG, helps create and move stress-related chemicals in the brain. These chemicals move along a brain path that connects the amygdala, which handles emotion, to the prefrontal cortex, which helps us make decisions. When individuals experience more stress, this path between the amygdala and prefrontal cortex becomes more active. The molecule works to manage stress and anxiety by limiting the chemicals that pass through the connecting path. 2-AG is part of the brain's anxiety-managing endocannabinoid system, in which the effects of marijuana are also felt. The brain's anxiety-limiting molecule and marijuana operate through the same receptors. In this study, researchers made mice stressed through exposure to foot shocks and bad odors. Then they observed the mice's brains and behavior to measure the effects of 2-AG and the path connecting the amygdala and prefrontal cortex. They found that making the mice stressed inhibited the effects of the molecule's ability to limit anxiety and led to more activity in the connecting path as the mice behaved more anxiously. These new findings indicate that more substantial levels of stress interfere with 2-AG's effects on blocking anxiety, overwhelming the endocannabinoid system and allowing anxiety-related chemicals to speed through the brain.¹⁷

Why Is This New 2-AG Study So Important?

Cannabis use proponents claim it is a medicine and treatment for anxiety, stress, pain, and also the opioid crisis. It is easier to make claims of safety and efficacy than to prove them. A formal study may determine safety and effectiveness, but in the meantime, cannabis has many advocates who argue that it is as good as any

medication or therapy for anxiety and stress. But, no one has provided the kind of evidence that would be presented to the FDA as part of a new drug application. These claims have not been studied in random assignment, double-blind or comparable efficacy scientific trials. In the interim, it is safer to conclude that this also is not true.

This new study¹⁷ finds specific pathways in the brain that lead to anxiety—especially the impairment of 2-AG—and suggests that new medications could be designed to work on this system to be more effective anti-anxiety medication. The authors of this study hope to do more research on how the cannabinoid system becomes impaired after stress exposure, how it repairs its anxiety-limiting function after impairment, and which molecules are involved in these processes. Well-functioning cannabinoid systems have a critical role in stopping or limiting anxiety. Genes and specific efforts to support this system like exercise,¹⁸ diet, meditation, may explain why some individuals exposed to extreme stress or trauma don't develop severe mental health conditions. This research refers to stressed-out mice, not humans. Again, only further study can prove any of this.

Risks and Concerns

Advancements in the understanding of the endogenous cannabinoid system, neuroscience, and pharmacology of cannabis have led to numerous proposed uses. Medical cannabis is now legal in a majority of states, and THC and cannabidiol (CBD), the prominent cannabinoids found in cannabis, have both been utilized in the development of FDA-approved drugs. Medicinal claims and cannabis legalization have been influential and related to the emergence, and frequency of cannabis use disorders.¹⁹ Cannabinoid exposure in rat adolescence reprograms the initial behavioral, molecular, and epigenetic response to cocaine.²⁰ Smoking marijuana for problems with pain management may result in a new substance use disorder without any change in the underlying disease or relief. As cannabis marketing, legal status and clinical studies of cannabis-related 'medications' continue, physicians are often lost without FDA guidance and will need to balance the real potential of these compounds with their limitations and adverse effects.²¹

Early exposure to cannabinoids in adolescent rodents decreases the reactivity of brain dopamine reward centers later in adulthood. To the extent that



In a recent survey, marijuana use among 12th graders is disturbing and concerning: 35.7% had used marijuana during the year before the survey, and 22.3% used in the past month.

these findings generalize to humans, this could help explain the increased vulnerability for addiction to other substances of misuse later in life that most epidemiological studies have reported for people who begin marijuana use early in life. It is also consistent with animal experiments showing THC's ability to "prime" the brain for enhanced responses to other drugs. For example, rats previously administered THC show heightened behavioral response not only when further exposed to THC but also when exposed to other drugs such as morphine—a phenomenon called cross-sensitization. Adolescent cannabis exposure results in impaired cognition, sleep, and driving ability. Cannabis Use Disorders are increasing, especially in teens and young adults, as a result of escalating use and consequences. Supportive and traditional behavioral therapies are currently the mainstay of treating cannabis misuse, with no pharmacotherapies presently approved by the FDA for cannabis use disorder in youth.²²

Medicinal Cannabis and CBDs

There are no FDA-approved cannabinoid medications approved for psychiatric disease or even for the treatment of psychiatric symptoms. But, we have learned a great deal and have more to learn about marijuana as a medicine and CBD. The FDA has recently approved Epidiolex or CBD oral solution

for the treatment of seizures associated with tuberous sclerosis and previously approved for the treatment of seizures associated with two other rare and severe forms of epilepsy, Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS). Epidiolex is the only FDA-approved drug that contains a purified drug substance derived from cannabis. That means the FDA has concluded that this particular drug product is safe and effective for its intended use. The FDA has also approved Marinol and Syndros, medications which include a synthetic delta-9-tetrahydrocannabinol (dronabinol, THC) for the treatment of anorexia associated with weight loss in AIDS patients. Some valid researchers are optimistic that pharmaceutical-grade cannabinoids may be found through additional controlled study to be a useful medication for other diseases. CBD has also been shown to have promise as a treatment for specific distressing symptoms, especially in patients with precipitated craving and anxiety.²³ This does not mean that it is safe and effective for stress management, anxiety, depression, and other problems that can and are safely treated by psychiatrists and other health providers with approved and well-studied evidence-based approaches. Developing better tools to manage stress and anxiety makes the most sense. Developing better coping mechanisms is likely to be especially beneficial for individuals using risky



substances. Research continues to suggest that smoked or vaped marijuana or THC is one of these hazardous substances. As Harvard's Kevin Hill, MD,²⁴ has said recently, "Medical cannabis may ultimately prove to be effective in treating many other medical conditions, including posttraumatic stress disorder and Tourette syndrome, but as yet, there is little evidence to show that this is the case."

The risks of marijuana smoking and THC vaping are mostly unknown, but no news is not necessarily good news. Many substances, like marijuana, without overdose death risks, are considered safe because we can not imagine all of the ways that they can be dangerous. Of course, edibles have gained in popularity because it is evident that smoking exposes everyone to second hand (SHS) and third-hand smoke risks. SHS or "second hand" designation a sanitized way to say exposure to carcinogen-polluted air or intoxication without permission (doi:10.1371/journal.pone.0153327) and second-hand tobacco smoke is a significant cause of death each year. Inhaling someone's smoke vapors is a major second-hand problem, but there are other concerns like impaired drugged driving. Traffic accidents are increasing in cities and states where cannabis is legal and widely used. A recent study found that individuals using cannabis are worse drivers.²⁵ Impaired driving ability in tested simulations included crossing the centerline, speeding, hitting pedestrians, and missing stop signs. Study participants who started using cannabis before the age of sixteen fared even worse.

Cannabis use is presented in the media as a stress-relieving substance, a mostly harmless escape from life's ups and downs. It's also portrayed as an option to alcohol for those seeking an alternative to relaxation, meditation, or exercise to unwind chemically. Scientists rarely evaluate these urban myths, and once one is evaluated, a new claim is made for a new problem of modern living in real-time. A person may initiate cannabis smoking or vaping THC, believing that they may be self-medicating stress and anxiety. But, not only has this not been proven to work, but, if anything, research suggests that it is not a treatment but a significant risk.

Many more cannabinoids are likely to be approved as medicines, but it is not clear at this time as to which cannabinoid, in what dose, by which route, and in what disease. The role of cannabis in medicine is expanding, often with claims preceding testing. Use is not without other risks. One risk identified in new

studies that cannabis and several cannabinoid-based medications may make other drugs of abuse more reinforcing.²⁶ Marijuana use is also linked to other substance use disorders, including alcohol and nicotine addiction.²⁷ Many findings are consistent with the idea of marijuana as a "gateway drug." The majority of people who use marijuana do not go on to use other "harder" substances. It may be becoming clear that current marijuana use makes cocaine and other drug use more reinforcing. New studies have suggested that parental use may cause such sensitization in their children to opioids.²⁸ Cross-sensitization is not unique to marijuana. Alcohol and nicotine also prime the brain for a heightened response to other drugs and are, like marijuana, also typically used before a person progresses to other, more harmful substances.²⁹

Conclusion

It may be useful to recall that alcohol and tobacco^{30, 31, 32} are not medicines, but medicinal uses were proposed for them. The U.S. Treasury Department, during prohibition, authorized physicians to write prescriptions for medicinal alcohol for cancer, GI distress, and depression. Of course, alcohol is not a safe and effective medicine for these problems and may cause them. The same may be true for cannabis claims and effects. Medicinal applications that are advertised or made for cannabis typically would require a pharmaceutical company to prove the treatment works for a specific illness. Physicians might wonder or ask if alcohol, tobacco, or cannabis can ever be called medicines without FDA approval? This cannabis- as-medicine process and outcome have made it easier to argue with the FDA over the definition of a medicine. Should we decide if hydroxychloroquine or cannabis is a medicine for COVID-19 by utilizing the FDA or by asking elected officials? A prescription should be tested rigorously in dose-safety – efficacy studies, successfully navigate the entirety of the FDA's new drug approval process and utilize modern science to separate therapeutic molecules from the smoke. Sure we might think about eating or smoking foxglove but is quite toxic. Digoxin was isolated from the foxglove plant, and Digitalis has become a great addition to the treatment of heart diseases recognized by the World Health Organization on its shortlist of safe, effective, and "Essential Medicines." Decriminalizing or legalizing adult recreational cannabis, like Budweiser or alcohol,³³ is one thing, but physicians and the public in short-circuiting the FDA protections are another. Short-

circuiting science from the new medicine decision-making process is a slippery slope. The 18th Amendment or National Prohibition Act enforced the ban on alcohol with a few specified exceptions. It allowed physicians to prescribe alcohol for most any ailment, farmers to produce wine for their consumption, and Clergy to provide alcohol during ceremonies. In his book on alcohol prohibition,³⁴ the author writes: “Presumably, doctors were doing examinations and diagnoses, but it was mostly bogus.” Much remains to be settled about the claims, safety, and efficacy of cannabis. The FDA has just approved CBD again, this time for the treatment of seizures associated with tuberous sclerosis. Many more clinical trials are in progress. It is logical to expect pharmaceutical companies to successfully translate cannabinoid science to make new treatments and classes of medicines. In the meantime, Physicians should insist on science and data first, FDA controlled studies, and “First do no harm.”

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Cannabis in Medicine: An Evidence-Based Approach

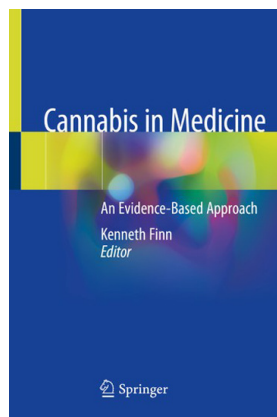
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The title of “Cannabis in Medicine: An Evidence-Based Approach” contains an irony. In chapter after chapter in this multi-authored book written predominately by providers associated with mainstream medical facilities in Colorado, the authors point out the inadequacy of the evidence we have and the absence of the evidence we need to determine how – or even if – cannabis has medical legitimacy. The foreword’s title, “Losing Ground: The Rise of Cannabis Culture,” sets the tone. David Murray, a senior fellow at the Hudson Institute, argues convincingly that “the current experiment with cannabis, underway nationwide [is] leading us towards a future of unanticipated consequences, a future already established in the patterns of use ‘seeded’ in the population but as yet unmanifested.” In other words, the cannabis horse has not only fled the barn but has been breeding prolifically to the point that we couldn’t get rid of it and its progeny if we wanted to!

The 20 chapters following the foreword are divided into basic science (three chapters) and clinical evidence (17 chapters) sections. Over and over in the clinical evidence chapters, individual authors remind the reader of the lack of quality control in production, the dearth of strong evidence from adequately designed research trials, and the intensifying potency of cannabis with attendant dangers, particularly for youth. The organization of this section lacks consistency in that some chapters focus on specialty (e.g. pulmonary medicine), others on patient groups (e.g. the pediatric and adolescent population), others on physiological implications (e.g. clinical cardiovascular effects; neuropsychiatric effects), others on specific diseases (e.g. gastrointestinal disorders; ocular conditions), and still others on public health topics (e.g. cannabis-impaired driving). While all are relevant, a specialty or organ system focus, with a separate public health section might lend the book more coherence. It would also be worth exploring how “cannabis culture” has become in essence a parallel medical system, with many of cannabis’s most ardent proponents as dropouts



from establishment medicine after its nostrums for diagnoses like chronic pain, anxiety, and depression have failed to bring them relief.

I would have liked a chapter specifically grappling with the porous boundary between federal and state jurisdictions over cannabis as medicine and marijuana as recreational substance. Lawyer David G. Evans’ admirable chapter on “The Legal Aspects of Marijuana as Medicine” moves in that direction when he writes

that, “‘medical marijuana’ is not a ‘states’ rights’ issue.” To wit, for no other drug than cannabis has the federal government ceded regulatory responsibility to states that are variably (but mostly not) equipped to handle it. The truth, complex in its contradictions and inconsistencies, is that in the United States, marijuana remains a Schedule I drug without recognized medical value; the Federal Drug Administration overseeing American pharmaceuticals throws roadblocks in the way of studying it, thereby interfering with the development of a robust evidence base; the federal government has looked the other way and even colluded with the states as one after another has legalized cannabis medically, recreationally, or both; and physicians risk their federal licenses to prescribe if they do more than recommend this drug. In a nutshell, any effort to impose logic is doomed because the American scene vis-à-vis cannabis is seemingly irretrievably illogical.

The editor of this volume, Kenneth Finn, MD, a PMR and pain management specialist in Colorado Springs, Colorado, is to be commended for encouraging individual chapter authors to develop encyclopedic bibliographies. The book can thus serve as a resource for practitioners wishing to delve into a vast and growing literature that continues to offer little that is conclusive. The book can also serve as a primer on what is known about cannabis as medicine, keeping in mind a slant throughout – not necessarily unjustified, at least from an allopathic or osteopathic perspective – that cannabis is neither legitimate as medicine nor safe, even for recreational use.

MM



No Legal Recreational Marijuana in Missouri: We Have Enough Problems with Addiction!

by John C. Hagan III, MD

Do your part to oppose any petition or referendum aimed at making high THC marijuana legal for recreational use. Only the COVID pandemic prevented legal recreational cannabis from being on the November 2020 ballot. Commercial and street level THC or CBD are not valid medications.

Big Weed (commercial interests profiting from harmful cannabis use), not satisfied with their 2018 victory passing sham medical marijuana into Missouri constitutional law, is geared up to enrich themselves further at the expense of their habituated customers. Only the intervention of the COVID pandemic prevented recreational cannabis from being on the 2020 November General Election ballot. Millions of dollars and scores of paid, mostly marijuana-using, workers were hitting Show-Me sidewalks to get legal-recreational cannabis on the November 2020 general election ballot as a referendum. You could find and smell them collecting signatures while loitering around vaping and CBD stores that are (appropriately) sprouting faster than weeds and grass.

When COVID is over, Big Weed will be back in 2021, 2022, 2023...you get the idea. With enough time, money, paid workers, and fake news about the benign effects of regularly stoning out on 95% THC cannabis products, they only need win once as with 2018 sham medical marijuana.



John C. Hagan, III, MD, FACS, FAAO, MSMA member since 1975, is a Kansas City, Missouri, ophthalmologist and *Missouri Medicine* Editor since 2000. He is a multi-year Diamond Contributor to MMPAC.

Sham medical marijuana is a social and medical disaster in Missouri as in other states before us. (Figure 1). This issue of *Missouri Medicine* and many previous articles clearly demonstrate that commercial and street level THC or CBD are not valid medications. Pharmaceutically pure, FDA tested and approved CBD drugs (Epidiolex, Marinol, Syndros, Cesamet) being the sole exception for a limited number of indications.

The Missouri recreational marijuana referendum is financed by a despicable conglomerate of entities ranging from George Soros, to the Mexican drug cartels, to mainline businesses such as the alcohol industry which considers 95% THC (the high/euphoria producing chemical of cannabis products) the next 'logical' adult beverage to accompany beer, wine, and liquor.^{1,2,3} Collectively, I refer to this unsavory and unwholesome alliance as "Big Weed." As physicians, parents, grandparents, responsible Missourians, we can't let them succeed!

Do not be confused. This is not sham medical marijuana. After a decade of effort, tens of millions of dollars of advertising, promotion, and half-hearted, ineffectual opposition by the healthcare professions, no opposition by the Missouri Hospital Association and support by the *Kansas City Star* and *St. Louis Post-Dispatch* newspapers, sham medical pot was passed into constitutional law in 2018.¹



Figure 1. Both the passage of so-called ‘medical marijuana’ and legal recreational marijuana in Colorado raised domestic violence and increased homelessness and theft.

Source: *DenverPost.com*

That ship has sailed and, for better or for worse (my bet the latter), we will have to live with the consequences. At least until there is enough overwhelming scientific evidence of the harms of sham medical marijuana to roll back the tsunami of state pot laws. That has happened before. Heroin was an over the counter ‘medicine’ until 1914 when all use became illegal.¹ Eventually, the public understood that nicotine has catastrophic healthcare consequences. Cannabis is now used more than nicotine, some users believing Big Weed’s narrative about its medicinal properties, just like Big Tobacco, convinced the public and many physicians with their phony nicotine research about its medicinal properties.

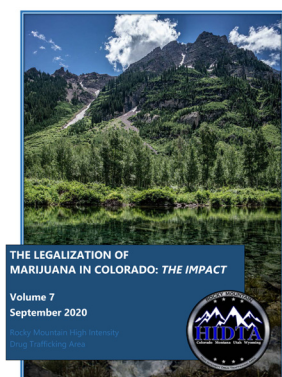
The implications of living with medical marijuana as law is very comprehensively discussed in a recent FP: Missouri Family Physician article.⁴ Recreational marijuana is not

decriminalization of marijuana. That arrow is already in the air. Missouri’s law enforcement and judicial systems are no longer prosecuting small amounts of pot for personal use; those incarcerated for same are being released and their criminal records expunged. Many states and municipalities have already decriminalized small amounts of personal use weed. Throwing their arms around the personal use pot clemency issue is deliberate obfuscation on the part of slimy and dishonest Big Weed. Widespread, easy access, high THC marijuana disproportionately works against the young, the poor, minorities, and the ill.

The Missouri State Medical Association has declared our organization against making high THC cannabis products legal in Missouri for recreational use. MSMA joins other influential Missouri physician organizations including Missouri Association of Osteopathic Physicians



Figure 2. The Legalization of Marijuana in Colorado: The Impact



The Legalization of Marijuana in Colorado: The Impact

Volume 7, September 2020

by the Rocky Mountain High Intensity Drug Trafficking Area program

Medical and recreational marijuana are destroying the health and social fabric of Colorado the Centennial State. Efforts are already underway to introduce recreational marijuana into law in Missouri via public referendum.

Executive Summary

The Rocky Mountain High Intensity Drug Trafficking Area (RMHIDTA) program has published annual reports every year since 2013 tracking the impact of legalizing recreational marijuana in Colorado. The purpose is to provide data and information so that policy makers and citizens can make informed decisions on the issue of marijuana legalization.¹

Section I: Traffic Fatalities & Impaired Driving

- Since recreational marijuana was legalized, traffic deaths in which drivers tested positive for marijuana **increased 135%** while all Colorado traffic deaths **increased 24%**.
- Since recreational marijuana was legalized, traffic deaths involving drivers who tested positive for marijuana **more than doubled** from 55 in 2013 to 129 people killed in 2019.
 - This equates to one person killed every 3.5 days in 2019 compared to one person killed every 6.5 days in 2013.
- Since recreational marijuana was legalized, the percentage of all Colorado traffic deaths that were marijuana-related **increased from 15% in 2013 to 25% in 2019**.

Section II: Marijuana Use

Since recreational marijuana was legalized in 2013:

- Past month marijuana use (ages 12 and older) **increased 30%** and is **76% higher** than the national average, currently ranked **3rd** in the nation.
- Adult marijuana use (ages 18 and older) **increased 19%** and is **73% higher** than the national average, currently ranked **3rd** in the nation.
- Past month college age marijuana use (ages 18-25) **increased 6%** and is **50% higher** than the national average, currently ranked **3rd** in the nation.
- Past month youth marijuana use (ages 12-17) **decreased 25%** and is **43% higher** than the national average, currently ranked **7th** in the nation.

Section III: Public Health

- Marijuana *only* exposures more than **quadrupled** in the seven-year average (2013-2019) since recreational marijuana was legalized compared to the seven-year average (2006-2012) prior to legalization.
- Treatment for marijuana use for all ages **decreased 21%** from 2009 to 2019.
- The percent of suicide incidents in which toxicology results were positive for marijuana has **increased** from **14%** in 2013 to **23%** in 2018.

Section IV: Black Market

- RMHIDTA Colorado Drug Task Forces (10) conducted **278 investigations** of black market marijuana in Colorado resulting in:
 - 237 felony arrests
 - 7.49 tons of marijuana seized
 - 68,600 marijuana plants seized
 - 29 different states the marijuana was destined
- Seizures of marijuana reported to the El Paso Intelligence Center in Colorado **increased 17%** from an average of 242 parcels (2009-2012) to an average of 283 parcels (2013-2019) during the time recreational marijuana has been commercialized.

Section V: Societal Impact

- Marijuana tax revenue represent approximately **0.85%** of Colorado's FY 2019 budget.
- **67%** of local jurisdictions in Colorado have banned medical and recreational marijuana businesses.

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& Surgeons, Kansas City Medical Association, Greene County (Springfield) Medical Society, Missouri Society of Eye Physicians & Surgeons, and Missouri Academy of Family Physicians. Additional medical organizations are in the process of officially opposing recreational marijuana. Make no mistake, we cannot do this alone. We desperately need the support of other healthcare professionals, nurses, dentists, and most especially the Missouri Hospital Association. Anecdotal reports from Missouri suburban hospitals and emergency rooms published in *Missouri Medicine* already indicate easy access medical marijuana is resulting in increased cannabis related ER visits and hospitalizations.⁵

Missouri Medicine has published more scientific and perspective articles on the unscientific nature of the studies of medical marijuana and the deleterious effects of moving from legal sham medical marijuana to legal recreational marijuana than any other state medical journal. The most important are open access, referenced and linked.⁶ We need a big tent and a huge coalition. We must reach out to school system administrations, teachers, PTAs. We must ask for the help of clergy, religious denominations, law enforcement, the business community, civic organizations, state, county, and local government. We need to ask questions such as: Why is Mothers Against Drug Drivers (MADD) committed to stopping death and disability due to alcohol but not cannabis DUI? Every state passing medical and recreational marijuana has had an increase in traffic accidents, deaths and disability.^{1,2} Why shouldn't we encourage more lawyers and organizations (e.g. <https://www.civel.org/>) opposing widespread cannabis to go after Big Weed via litigation as they did against Big Tobacco?

The best insights about legalizing marijuana come from studies in states like Colorado that have legalized medical marijuana then doubled down with recreational marijuana. Once among the healthiest of states, Colorado public health indices are in free fall.^{7,8,9} (Figure 1.) Colorado state leaders are so alarmed about the adverse effects of legalized marijuana that they have

appointed a commission to study and report on it annually. Named The Rocky Mountain High Intensity Drug Trafficking Area Program, the most recent, disturbing 2020 executive report is shown in Figure 2. Note that the anticipated revenues from recreational marijuana are a pitiful 0.85% of Colorado's annual budget and are dwarfed by the law enforcement, educational, medical and social costs of easy access, high potency recreational marijuana. Missouri does not need to repeat this disastrously sad social experiment.

Educate yourself. Educate your patients. Educate the medical, religious, social, educational circles you move in. Physicians once advocated and contributed to the medical problems of tobacco and shilled for Big Tobacco. Physicians once contributed to the problems of over prescribing opioids. Let's not make the same mistake with slimy Big Weed. Let's get out ahead of the problem. Do your part to oppose any petition or referendum aimed at making high THC marijuana legal for recreational use. While you are at it keep a look out for evolving problems with the sham medical marijuana law. Let's not let Missouri go to pot!

Disclosure

None. Dr. Hagan did refuse a generous financial offer from Big Weed to be a paid medical cannabis consultant (2019).

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