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Under the Influence: Cognitive Effects of Medical Marijuana on Developing Minds

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Cannabis is a highly discussed topic in medicine today. From therapeutic applications in conditions such as chronic pain, multiple sclerosis, epilepsy, chemotherapy-induced nausea and vomiting, and inflammatory bowel disease to the growing prevalence of recreational use, cannabis remains at the forefront of medical and societal conversations. In this review, we will explore the history of marijuana use in medicine, examine the current evidence supporting its pharmacological benefits, and delve into its impact on the developing brain. Additionally, we will highlight the pivotal role pharmacists play in this evolving landscape and guide you through the latest research findings.

ABBREVIATIONS 5-HT, serotonin; AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists; AMA, American Medical Association; ASCO, American Society of Clinical Oncology; CB1, cannabinoid-1; CB2, cannabinoid-2; CBD, cannabidiol; CD, Crohn disease; CDC, Centers for Disease Control and Prevention; CINV, chemotherapy-induced nausea and vomiting; CSA, Controlled Substances Act; DEA, Drug Enforcement Administration; DOJ, US Department of Justice; FAAH, fatty acid amide hydrolase; FDA, US Food and Drug Administration; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GPR55, G-protein coupled receptor 55; HCP, health care provider; HEC, highly emetogenic chemotherapy; HHS, US Department of Health and Human Services; IASP, International Association for the Study of Pain; IBD, irritable bowel disease; IQ, intelligence quotient; JAMA, Journal of the American Medical Association; MEC, moderately emetogenic chemotherapy; M/P, milk-to-plasma ratio; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSCA, McCarthy Scales of Children's Abilities; NICU, neonatal intensive care unit; THC, delta-9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid 1; TSC, tuberous sclerosis complex, USP, US Pharmacopeia; WHO, World Health Organization.

KEYWORDS cannabinoids; cannabis; epilepsy; fetal development; marijuana

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Introduction

In May 2024, the US Department of Health and Human Services (HHS) and Department of Justice (DOJ) requested that the Drug Enforcement Administration (DEA) reschedule marijuana to schedule III from schedule I under the Controlled Substances Act (CSA). According to the CSA, a drug in schedule I is a drug with a high potential for abuse, no currently accepted medical use, and a lack of accepted safety for use under medical supervision. Drugs in schedule III on the other hand, have a lower potential for abuse, have accepted medical use, and moderate or low propensity for physical dependence or high psychological dependence.[1] Rescheduling marijuana to schedule III will not only decriminalize it, but it will open the doors to facilitating research on pharmaceutical cannabinoids.

Brief History of Use

The earliest documented consumption for medicinal purposes is 4000 BC, when cannabis was used as medicine by the Chinese for a range of women's health conditions including dysmenorrhea, dysuria, and hyperemesis gravidarum.[2,3] In 2000 BC, cannabis plants were used as food, medicine, and clothing all over the world. Flash forward to the Victorian era, where Indian cannabis was used by neurologists for the treatment of epilepsy. Later in 1851, the US Pharmacopeia (USP) classified marijuana as a treatment for epilepsy, chronic migraines, and pain. The Great Depression also brought a great shift in perspective with marijuana use. Marijuana use was perceived to promote crime and adverse social consequences. At this point, medical marijuana did not require a prescription. The Marihuana Tax Act of 1937 imposed tax on the sale of cannabis, hemp, or marijuana. In 1941, despite opposition from the American Medical Association (AMA) and physicians who believed in the medical efficacy of marijuana, all cannabis preparations were removed from the USP and National Formulary. The Controlled Substances Act (CSA) was passed in 1970 and classified cannabis as a schedule I drug, making it illegal for any use.[4]

Current State

Marijuana has become a hot topic over the last few years, and increasingly popular in use for medicinal and non-medicinal reasons. Its medicinal use affects nearly all body systems. There are over 100 phytocannabinoids derived from the genus Cannabis plant. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the 2 most common and work on cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors. It is a partial agonist in both CB1 and CB2 receptors and achieves its psychoactive properties through modulation of gamma-aminobutyric acid (GABA) and glutamate. Unlike CBD, THC is a proconvulsant while CBD is an anticonvulsant. CBD does not appear to bind to either CB1 or CB2 but does possess neuroprotective and anti-inflammatory effects. Although both have the same chemical formula, $C_{21}H_{30}O_2$, THC has a cyclic ring while CBD has a hydroxyl group.[5] CB1 receptors are located throughout the wall of the gut and peripheral nervous system. Acute stimulation of CB1 receptors causes a reduction of motility and secretion of the gastrointestinal (GI) system, mediated by motor, secretory, and sensory afferent neurons. Located on immune cells and other neurons in the epithelium and gut wall, CB2 receptors are upregulated in inflammatory states. Stimulation of CB2 receptors is anti-inflammatory and activates the immune system.[6] THC is known for supplying the user with the traditional "high" as it has more psychotropic effects.

In December of 2018, the 2018 Farm Bill was signed into law. It removed hemp, defined as cannabis (*Cannabis sativa* L.) and derivatives of cannabis with no more than 0.3% THC on a dry weight basis, from the definition of marijuana in the CSA. This meant that CBD and THC can be sold over the counter in all dosage forms including gummy candies, dabs, vapes, tinctures, oils, and more as long as the products contained no more than 0.3% of THC. Over the counter, delta-8-tetrahydrocannabinol, synthetic variations, and other blends have gained popularity. Little research has been done on the long-term effects, efficacy, and dosing of these products. Behind the counter, prescription-only US Food and Drug Administration (FDA) approved products include dronabinol and nabilone, which are both THC derived products and cannabidiol, which is a CBD-derived product.[7] The body of literature for the efficacy of medical marijuana for various disease states increase on a daily basis. As of April 2024, over 70% of the United States has legalized marijuana for recreational and medical use.[8] What does that mean? Marijuana use may increase both recreationally and medically. What else does that mean? More research needs to be done to assess its effects on the pediatric brain, from in utero to adolescence. In this review, we will review the history of marijuana use in medicine, discuss the current evidence supporting its pharmacological use in chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis (MS), irritable bowel disease (IBD), epilepsy, and chronic pain, and outline the effects marijuana has on the developing brain.

Cannabinoids, Cannabis, and Marijuana

Before we delve in, we should focus on some key definitions.

Cannabis: all products derived from the plant *Cannabis sativa*.

Cannabinoids: group of substances found in the cannabis plant. The 2 main cannabinoids are CBD and THC.

Marijuana: parts of or products from the plant *Cannabis sativa* that contain substantial amounts of THC.[9]

All 3 of these words will be used in this review; however, they cannot be used interchangeably (Table).

Pharmacotherapeutic Uses

Pain. Chronic pain, characterized by persistent or recurrent discomfort lasting more than 3 months, is a prevalent issue among children. A systematic review from The Journal of International Association for the Study of Pain (IASP) assessed the prevalence of chronic pain in children and adolescents. These authors reported a rate of 20.8%, signifying approximately 1 in 5 young individuals experiencing persistent pain.[11] Children with chronic pain often report significant physical disability, emotional distress, anxiety and depression, and sleep disturbances, compared with peers without this condition.[12,13] The World Health Organization (WHO) guidelines on the management of chronic pain highlight that an interdisciplinary and multimodal approach should be tailored to the unique needs of the child and caregivers. This strategy incorporates multiple modalities to effectively

Table. Pharmacokinetics of Inhaled vs Enteral Cannabis[6,10]

Parameter	Inhaled Cannabis	Enteral Cannabis
Onset	Seconds to minutes	2 hr
Duration	1–2 hr	2–4 hr
Bioavailability	Readily absorbed	THC: 5%–20% CBD: 6%–19%
Half life	THC: 30 hr; CBD: 9–32 hr	
Metabolism	Metabolized by and potent inhibitor of CYP2C19 and CYP3A4	
Tolerance	Downregulation of CB1 receptors	
Plasma protein binding	Highly protein bound	

CB1, cannabinoid-1; CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol

address chronic pain management including physical, psychological, or pharmacological interventions.[14] Several case reports highlight pediatric patients with conditions such as neuropathic pain, cancer pain, spasticity-related pain, and chronic pain syndromes, where traditional treatments were insufficient, leading to the consideration of medical marijuana as an alternative option for symptom relief.

The American Academy of Pediatrics (AAP) opposes the use of medical marijuana outside the regulatory framework of the FDA.[15] However, there is acknowledgement that marijuana may be considered an option for children with life-limiting or severely debilitating conditions when current therapies are unable to provide sufficient relief. Medical marijuana plays a promising role in pediatric palliative care, particularly in its potential to alleviate symptoms and maximize quality of life for children with unpleasant or intolerable pain. Compared with opioid regimens, marijuana possibly offers benefits by supporting refractory pain management and reducing polypharmacy, often with fewer or milder adverse effects.[16]

A 15-year-old with hypoxic brain injury and spastic quadriplegia used medical marijuana to manage refractory spasticity and pain unresponsive to baclofen, botulinum toxin injections, and nerve blocks. After starting 3 times daily 1:1 THC:CBD regimen (unknown formulation and dose), she experienced significant pain relief, improved facial muscle function, and progress in therapy. Following spinal fusion and an oxycodone wean, her marijuana use became irregular due to increased drowsiness and limited product availability. When her supply ran out, a noticeable decline in quality of life occurred, which improved upon resumption of therapy.[17]

An 11-year-old with relapsed rhabdomyosarcoma was prescribed an oil-based tincture in a 1:1 THC:CBD ratio (dose in milligrams is not specified). Drops were administered 3 times daily to manage treatment-resistant nausea, appetite loss, anxiety, and pain. The regimen resulted in significant symptom improvement, allowing discontinuation of multiple medications, including acetaminophen and gabapentin. After 8 months, the THC:CBD was temporarily discontinued to investigate a fever, which was later determined to be caused by typhlitis rather than the THC:CBD tincture. During the pause, the patient experienced increased anxiety and pain, which resolved upon reinitiating both marijuana and gabapentin.[17]

Epilepsy. According to the Centers for Disease Control and Prevention (CDC), 1% of children have epilepsy in the United States and it is the most frequent chronic neurologic condition in childhood.[18] While the precise mechanisms by which CBD exerts its anticonvulsant effects in epilepsy are not yet fully elucidated, growing evidence suggests that it works by decreasing neuronal hyperexcitability through a combination of actions. CBD appears to antagonize G-protein coupled receptor 55 (GPR55) receptors at excitatory synapses, desensitize transient receptor potential vanilloid 1 (TRPV1) channel, and inhibit adenosine reuptake, all of which may contribute to its ability to control seizures.[19]

The largest clinical trials to date examining plant-derived, highly purified cannabidiol use in children with epilepsy were trial 1/NCT02224560, trial 2/NCT02224690, trial 3/NCT02091375, and trial 4/NCT02091375, which collectively involved 550 patients ranging in age from 2 to 55 years old with Lennox-Gastaut or Dravet syndromes and were conducted at 58 sites across Europe and the United States. These trials provided critical evidence supporting the efficacy and safety of cannabidiol (Epidiolex), contributing to its status as one of the most well-researched and widely used CBD treatments for pediatric epilepsy.[20] Key findings from trials 1 and 2 included a 44% reduction ($p = 0.01$) in drop seizures and in trial 3 a 39% reduction ($p = 0.01$) in convulsive seizures in at a dose of 20 mg/kg/day of Epidiolex.[21–23] Although these studies only looked at seizures associated with Dravet syndrome and Lennox-Gastaut syndrome, its efficacy has been widespread throughout many epilepsy syndromes, with the newest FDA approval in 2020 for seizures associated with tuberous sclerosis complex (TSC). Key findings from the study in TSC patients aged 1 to 56 years old included a 30.1% reduction from baseline seizures in the 25 mg/kg/day group and a 28.5% reduction in the 50 mg/kg/day group. The most common side effects across all studies included diarrhea, appetite suppression, and somnolence.[24]

It is crucial for health care providers (HCPs) to emphasize the difference between Epidiolex and other cannabidiol products when counseling caregivers. A recent guideline on optimizing Epidiolex treatment highlights the importance of discussing the varying concentrations found in non-FDA-approved cannabidiol products, as these can differ significantly from the standardized formulation of Epidiolex. Another misconception is the belief that Epidiolex, due to its clinical trials and documented side effects, has more adverse effects than non-FDA-approved cannabidiol products. Non-FDA approved CBD products have not undergone the same rigorous testing, meaning their side effect profiles are less well understood and most likely are not as well characterized, thoroughly evaluated or documented than FDA-approved products.[25]

Multiple Sclerosis. Although relatively rare in pediatrics, approximately 2% to 10% of individuals with MS are diagnosed before their 18th birthday. MS is an immune disease that leads to neurodegeneration, chronic inflammation, and demyelination of the central nervous system.[26] In Canada and multiple European countries, nabiximols, an oromucosal spray containing an ~1:1 ratio of THC to CBD, is a medication

approved for the treatment of adult patients with spasticity from MS. Nabiximols are in phase 3 of FDA trials in the United States for adults, with no clinical studies in pediatric patients.[27]

The American Academy of Neurology recently published guidelines on the use of cannabinoids for MS, citing numerous studies that demonstrate its effectiveness in alleviating symptoms such as spasticity, muscle spasms, pain, and bladder retention. It is hypothesized that cannabinoids inhibit the progression of MS and provide neuroprotection in animal models through the reduction in the proliferation and number of T cells, which impacted and reduced the degree of demyelination of neurons.[28,29] However, it is important to note that these studies have not included pediatric populations, and therefore the safety and efficacy of cannabinoids for children with MS remain unclear.[30,31] Additionally, several small studies have reported impaired cognition in pediatric patients with MS after long-term cannabinoid use, which correlated with reduced tissue volume in subcortical, medial temporal, and prefrontal regions.[32] Although some of the research in adults has shown promising results, more studies in pediatric patients need to be done in order to assess long-term effects of cannabinoids.[33]

Chemotherapy-Induced Nausea/Vomiting. Nausea and vomiting are among the most challenging complications of chemotherapy, severely affecting a patient's overall well-being and jeopardizing adherence to life-saving treatment regimens. It is estimated that CINV occurs in up to 70% of the pediatric population undergoing intensive chemotherapy.[34] Pharmacologic treatment is crucial in this indication as it prevents complications such as malnutrition, reduces physical and emotional distress, and significantly improves a child's overall quality of life during therapy. Medical marijuana has surfaced as a promising adjunctive treatment for the management of CINV, particularly for patients inadequately relieved from conventional antiemetic regimens.

The mechanism by which cannabinoids alleviate CINV is multifaceted, involving both central and peripheral pathways of attenuation. Studies highlight that cannabinoid agonists influence GI function by engaging peripheral CB1 receptors, which play a key role in slowing intestinal movement.[35] The central antiemetic effects of CBD appear to be mediated by multiple mechanisms involving serotonin (5-HT) pathways. Activation of somatodendritic auto receptors, specifically 5-HT1A receptors, leads to a decreased firing rate of serotonin neurons. This reduction in neuronal activity subsequently lowers the release of serotonin in the forebrain, a key mediator of nausea and vomiting.[36] Additionally, recent findings suggest that CBD may also function as an allosteric modulator of the 5-HT3 receptor, similarly resulting in reduced serotonin signaling.[37] Given their ability to reduce vomiting through distinct mechanisms, THC and CBD both hold potential value in effectively managing CINV.

The current recommendation from the American Society of Clinical Oncology (ASCO) Focused Guideline highlights 2 FDA-approved cannabinoid products, dronabinol (Marinol) and nabilone (Cesamet), for the treatment of nausea and vomiting unresponsive to traditional antiemetic medications. Despite recent advancements in medical marijuana research, ASCO states that existing evidence remains insufficient to recommend medical marijuana for this indication. ASCO likely considers the evidence insufficient due to the lack of standardized dosing, robust clinical trials, and consistent outcomes in studies on medical marijuana for CINV, particularly when compared with FDA-approved treatments like dronabinol and nabilone; as such, ASCO remains cautious about recommending medical marijuana until higher-quality, large-scale, randomized controlled trials can provide more definitive and reliable evidence.[38] Although data on medical marijuana use in pediatric oncology remain limited, clinical trials have assessed the safety and efficacy of FDA-approved synthetic cannabinoids in the pediatric cohort.

To highlight the use of cannabinoids in CINV, a 10-year retrospective chart review analyzed 55 pediatric patients ranging in age from 0 to 18 years old receiving moderately or highly emetogenic chemotherapy (MEC or HEC) and at least 1 dose of dronabinol.[39] The response to dronabinol, based on the frequency of emesis events, was categorized as good, fair, or poor. Patients received a median of 3.5 doses per hospital visit (range: 1–129). Across all emetogenic risk levels, 60% of patients reported a good response, 13% had a fair response, and 27% were classified as poor responders. Tolerability, indirectly assessed by the continuation of therapy as outpatients, was noted in 62% of patients.

Irritable Bowel Disease. It is estimated that 1 in 1299 children aged 2 to 17 are affected by IBD.[40,41] Patients with IBD have been found to exhibit genetic polymorphisms in cannabinoid receptors. One example is fatty acid amide hydrolase (FAAH), which degrades endocannabinoids like anandamide and 2-arachidonoylglycerol, leading to increased activation of cannabinoid receptors (e.g., CB1), influencing GI motility. CBD inhibits FAAH, potentially raising endocannabinoid concentrations in the gut, which may improve motility and homeostasis. Additionally, CBD interacts with 5-HT1A serotonin receptors, which regulate GI function through antidepressant and antiemetic effects. Further research is needed to fully elucidate these interactions and their therapeutic potential.[42]

Between 18% and 61.2% of pediatric patients with IBD were reported to use cannabinoids for symptom control.[43–45] Patients report that marijuana improves nausea, vomiting, appetite, diarrhea, coping, pain, and delayed motility for patients with IBD. A retrospective case-control study of 615 adults with Crohn disease

(CD), which analyzed data from the Healthcare Cost and Utilization Project-National Inpatient Sample found that patients who used marijuana for symptom control had lower rates of fistulizing disease, lower total parenteral nutrition requirements, and underwent fewer colonic surgical resections.[46] To date, there has not been a randomized controlled trial studying marijuana as a treatment for pediatric IBD. The body of literature consists primarily of retrospective case studies and surveys; therefore, cannabinoid use in pediatric IBD is not widely recommended in clinical practice, and more rigorous studies are needed to determine the efficacy and safety of these treatments in children with IBD. From a clinicians perspective, for refractory patients who have exhausted all FDA-approved treatments, medical marijuana may serve as a promising alternative as long as there are no drug-drug, drug-food, drug-disease, and drug-genetic interactions.

Effects During Pregnancy. Despite the American College of Obstetricians and Gynecologists (ACOG) recommendations against marijuana use during pregnancy,[47,48] data from 2007–2012 National Surveys on Drug Use and Health, a cross-sectional nationally representative survey, found that 16.2% of pregnant women in the United States used marijuana daily. Women report using cannabinoids in pregnancy to help with common ailments such as morning sickness, sleep, stress, depression, and pain. Since this survey, marijuana legalization has expanded substantially across the United States, therefore prevalence is likely much higher. THC is found to cross the placenta. Fetal plasma THC concentrations were approximately 10% of maternal values after acute exposure and were significantly higher after repeated exposure.[49] THC binds to the cannabinoid receptors of the placenta. Binding to the cannabinoid receptors inhibits the migration of the epithelial layer of human placental amnion tissue. It disrupts endogenous cannabinoid signaling and estrogen signaling. As a result, it affects the development and function of the placenta.[50–52] What does this do to the fetus? Studies have shown that in utero exposure to marijuana disrupts normal brain development and function leading to impaired cognition, increased sensitivity to polysubstance abuse, decreased attention span, behavioral problems impaired visual problem solving, motor coordination, and analysis.[53–59] There is currently no literature to support the association between perinatal marijuana use and fetal mortality, however the risk of stillbirth is slightly increased.[60] These data strongly advise against the use of maternal marijuana during pregnancy.

What about the pregnant woman? How does marijuana use affect her? Young-Wolff et al[61] performed a population-based retrospective cohort study of 250,221 pregnant women in California who reported prenatal marijuana use. They found that prenatal marijuana use increased the risk of gestational hypertension, preeclampsia, and placental abruption. On the other hand, there was a decreased risk of gestational diabetes. The study concluded there was no association with placenta previa, placenta accreta, or maternal morbidity.[61] Due to the potential risks to both the mother and fetus, the lack of standardized formulations, and inconsistent dosing, prenatal marijuana use is not recommended. Pharmacists play a crucial role in supporting expectant mothers by offering non-punitive, compassionate guidance to help them make informed decisions about discontinuing marijuana use and not using the drug during their pregnancy. By providing evidence-based, FDA-approved therapeutic alternatives, pharmacists can help ensure the health and safety of both the mother and the developing infant.

Effects During Lactation. The use of marijuana during lactation raises significant concerns due to the potential transfer of cannabinoids through breast milk and its subsequent effects on the lactating infant. THC is the primary psychoactive component of marijuana, driving both its effects on the mind and associated therapeutic properties. THC is a highly lipid soluble compound with rapid uptake and accumulation in adipose tissue.[62] Additionally, THC's low molecular weight further contributes to its pharmacokinetic profile, facilitating its effective transfer into human breast milk. A prospective, observational pharmacokinetic study conducted by Wymore et al[63] established a milk:plasma partition coefficient for THC of approximately 6:1. A milk-to-plasma (M/P) ratio of less than 1.0 indicates that minimal concentrations of a compound are transferred into breast milk, classifying these drugs as low risk for breastfeeding infants.[63] Therefore, an M/P ratio of 6:1 indicates significantly higher concentrations of THC in breast milk compared with maternal plasma, suggesting high risk of exposure to the infant. Furthermore, studies have shown that THC can linger in breast milk for varying durations, with detectable concentrations ranging from as little as 6 days to over 6 weeks.[64] Wymore et al[63] demonstrated that THC was detectable in the breast milk of all participants for the entire 6-week duration of their study, enrolling 25 breastfeeding mothers who reported marijuana use. Seven women participating in this study abstained from cannabis use for more than 5 weeks. Despite this termination of use, the estimated mean THC half-life in their breast milk was 17 days. This prolonged period highlights the potential for sustained infant exposure even after maternal cessation.

Data are sparse on the relationship between THC transfer into breast milk and factors such as the potency of marijuana and maternal usage frequency. Additional components such as the method of consumption (e.g., smoking, vaping, edibles), and the timing of breastfeeding relative to cannabis use may influence the amount of THC transferred through lactation. The variability in these factors complicates the ability to predict infant exposure

accurately and highlights the need for further research to better understand these dynamics and their potential impact on infant health. While THC's effects during lactation are a major consideration, CBD also warrants attention, especially regarding its presence in breast milk. A physiologically based pharmacokinetic model was developed using data from 181 mothers who donated 200 breast milk samples. Interestingly, 42% of these samples had CBD concentrations below the level of quantification. The study found that CBD levels in breast milk were higher when the mother ingested it through oil or pipe, compared to other forms such as joints, blunts, or edibles. The estimated dose for fully breastfed infants was projected to result in exposure of less than 1% of what children aged 4 to 10 years might receive if taking CBD therapeutically for seizures. Despite these findings, the FDA continues to strongly advise against the use of CBD, THC, or marijuana in any form during pregnancy and breastfeeding due to potential risks.

Effects During Infancy/Childhood. Prenatal cannabinoid use has been linked to lower birth weight, impaired cognitive functioning, and an increased risk of psychological issues in infants and children. A meta-analysis published in Journal of the American Medical Association (JAMA) in 2022 found that among 16 studies including 59,138 patients, there were significant increases in risk of birth weight less than 2500 g (RR, 2.06 [95% CI, 1.25–3.42]; $p=0.005$), small for gestational age (RR, 1.61 [95% CI, 1.44–1.79]; $p<0.001$), preterm delivery (RR, 1.28 [95% CI, 1.16–1.42]; $p<0.001$), neonatal intensive care unit (NICU) admission (RR, 1.38 [95% CI, 1.18–1.62]; $p<0.001$), decreased mean birth weight (mean difference, −112.30 [95% CI, −167.19 to −57.41] g; $p<0.001$), Apgar score at 1 minute (mean difference, −0.26 [95% CI, −0.43 to −0.09]; $p=0.002$), and infant head circumference (mean difference, −0.34 [95% CI, −0.63 to −0.06] cm; $p=0.02$).[65] Beyond the first 28 days of life, 2 studies utilized the McCarthy Scales of Children's Abilities (MSCA) to measure the cognitive functioning of infants and children who were exposed to cannabis prenatally. They found a dose-dependent relationship between frequency of cannabis use during pregnancy and infants' verbal memory, motor development and intelligence quotient (IQ) at 36 and 48 months. Interestingly, the same frequency was not found at 60 or 72 months.[66–68]

Prenatal cannabinoid use altered caudate functional connectivity with cerebellum, occipital fusiform, and anterior insula with cerebellum. These alterations contribute to deficits in motor and visual-spatial activity, integration and coordination, attention, and social-emotional stability.[65] The ABCD Study looked at 655 children aged 9 to 11 years of age who were exposed to cannabis prenatally. They found that infants exposed to cannabis before and after maternal knowledge of pregnancy were associated with a higher incidence of psychotic like experiences (internalizing, externalizing, attention, thought and, social problems), sleep problems, and body mass index, as well as lower cognition and gray matter volume in childhood.[69] Goldschmidt et al[70] found daily cannabis use in any trimester was associated with lower IQ in childhood. Daily cannabis use in the second and third trimesters predicted poor performance on tests assessing memory and quantitative reasoning among 6-year-old children. Published studies show a causal link between prenatal cannabinoid use and adverse outcomes for infants and children. As noted above and further substantiated by these later studies, cannabis use by mothers planning or anytime during pregnancy should be strongly discouraged through compassionate, non-punitive approaches from using cannabis during these susceptible phases.

Effects During Adolescence. It is estimated that 78% of first-time cannabinoid users are children 12 to 20 years old.[71] By age 18, about 45% of youth have reported using cannabis. According to the Monitoring the Future Study which looks at trends in illicit and legal drug use in adolescents found that the perceived risk of cannabis compared with other drugs has decreased substantially, resulting in increased cannabinoid use rates.[72,73] In fact, in 2022, the CDC reported 6% of 12th graders utilize cannabis daily.[74] With increased use comes increased risk as many teens choose smoking cannabis over drinking alcohol[75] recognizing alcohol abuse has its own well-defined health risks.

Since cannabis is derived from the dried flowers and leaves of the cannabis sativa plant, many adolescents perceive them as "natural" and therefore safer to use. However, research shows a very different story—cannabis can have significant and potentially harmful effects on developing adolescent brains. Adolescent brains are developing until about age 25, therefore early cannabinoid use affects the brain's ability to focus, remember, solve problems, regulate addiction and coordinate body movements.[76] Chronic cannabinoid use has been associated with the downregulation of CB1 receptors, leading to disrupted reward signaling and reduced reward sensitivity. This disruption can manifest as depressive symptoms such as anhedonia, low mood, and decreased motivation, ultimately increasing the risk for addiction, psychosis, and depression.[77] Adolescents who use cannabis daily are 4 times as likely to develop cannabis dependence within 2 years after use onset.[78] Long-lasting mental health issues associated with cannabinoid use include social anxiety and schizophrenia.[79]

Early onset use of cannabis has also been linked with causing more impairments in daily functioning. Studies have shown that cannabinoid use impairs attention, processing speed, verbal learning and memory, and executive functioning.[80] Even when used for a short period of time, longitudinal studies found that these effects last well into adulthood.[81] Additionally, adolescents with early onset use of cannabis had the greatest reductions in IQ (i.e., from "average"

in childhood to "low-average" in adulthood). These reductions persisted into adulthood despite early discontinuation of cannabinoids.[82] In 2021, Albaugh et al[83] analyzed 1598 magnetic resonance imaging (MRI) images from 799 adolescents aged 14to 19 years old and found that cannabis use over 5 years was associated with dose-dependent thinning of the left and right prefrontal cortices, areas critical for decision-making and impulse control. These neuroanatomical changes, linked to CB1 receptor activity, suggest that cannabis use during adolescence may alter normal brain development, particularly in regions undergoing significant age-related changes.[83] Recreational cannabinoid use is not recommended due to its potential risks to the developing adolescent brain. Pharmacists play a vital role in supporting adolescents by providing compassionate, non-judgmental guidance to help them make informed decisions about discontinuing marijuana use when it is not medically necessary. If an adolescent believes they may need marijuana for medical reasons, pharmacists can also facilitate a referral to a registered HCP for further evaluation and appropriate care. Over the counter CBD products are not as heavily regulated as medical marijuana prescribed by a HCP, therefore use is not recommended.

DEA Rescheduling: A New Era for Cannabis Innovation

On May 16, 2024, the DEA issued a notice of proposed rulemaking to explore moving cannabis from schedule I to schedule III, following a recommendation from the HHS after reviewing its medical applications and scientific evidence.[84] The investigation into rescheduling cannabis represents a pivotal moment in drug policy reform, with the potential to transform the landscape of medical cannabis research and access. By aligning policy with evolving scientific understanding, this shift could facilitate more comprehensive studies and broaden the scope of therapeutic applications. Changing cannabis to a schedule III substance could simplify the research process by reducing regulatory challenges and barriers. This transition would lower security demands, minimize storage needs, and decrease federal reporting duties, making studies more cost-effective and adaptable.

In 2023, the National Institutes of Health dedicated 74% of its $95 million in cannabis research funding to areas unrelated to therapeutic use, including its largest share (45%) to the National Institute on Drug Abuse for studying abuse potential and safety.[84] The National Institutes of Health's emphasis on funding cannabis research focused primarily on abuse potential and safety often overlooks its promising therapeutic applications. Redirecting a greater proportion of resources toward exploring the medical benefits of cannabis could pave the way for new treatments, offering significant advancements in patient care and scientific discovery. Rescheduling cannabis, alongside a balanced focus on both safety and therapeutic potential, could have significant implications for the future of clinical practice, offering new opportunities for providers and patients alike.

Conclusion

Advancements in medicine and evolving legislation have significantly highlighted the role of cannabinoids in health care. Cannabinoids have proven their utility as treatments for disease states such as CINV, MS, IBD, epilepsy, and chronic pain. While cannabinoids have proven valuable in clinical practice, the recent rescheduling from schedule I to schedule III underscores the need for further research including active compound content, health/physiologic effects, if any, from the other many components found in marijuana or other non-single-compound products, individual compound dose, and amount and duration of use supports expanded clinical trials to optimize their therapeutic potential. While cannabinoids are recommended for certain medical uses, studies have highlighted their negative impact on pregnant mothers, infants, children, and adolescents. Pharmacists play a critical role in counseling individuals seeking safer therapeutic alternatives or discontinuing cannabinoid use altogether. By providing education and raising awareness, pharmacists can help address this public health concern and promote healthier outcomes.

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