Health Effects of Cannabis and Cannabinoids and Barriers to Research

Report to Congress Pursuant to Requirements of the Medical Marijuana and Cannabidiol Research Expansion Act

Executive Summary

The Medical Marijuana and Cannabidiol Research Expansion Act (MMCREA; Public Law No.:117-215) requires the Department of Health and Human Services, in coordination with the National Institutes of Health and other relevant federal agencies, to report the health effects of cannabis and cannabinoids and barriers to research on these compounds. Specifically, under Section 401, the report must address (1) the potential therapeutic effects of cannabis or cannabidiol on serious medical conditions including intractable epilepsy; (2) the potential effects of cannabis on the human body and developing brain, including cognitive abilities relevant to driving and operating heavy machinery; and (3) barriers associated with research on cannabis or cannabidiol in states that have legalized such substances, including recommendations as to how such barriers might be overcome and safeguards that would need to be in place to ensure product quality and safety. The following report, which synthesizes the current state of the science and research regulations, fulfills these requirements. For the purposes of this report, the terms "cannabis" and "marijuana" are generally used interchangeably. Where appropriate, the terminology used in this report reflects that of the source and is footnoted in the document.

The FDA has approved some medications that contain or are based on the primary cannabinoids in the *Cannabis sativa* L plant, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ^9-THC). Epidiolex, a prescription medication containing CBD, is used to treat certain rare seizure disorders. Marinol and Syndros (dronabinol) and Cesamet (nabilone) are Δ^9-THC-based medications that help with nausea, vomiting, and weight loss associated with specific medical conditions. Yet, as states increasingly legalize cannabis, people report using it for many purposes, both medicinal and non-medicinal, despite mixed findings from research. While there is some credible evidence that cannabis has therapeutic potential for chronic pain, there is less support for its effectiveness in other conditions. There are also acute and chronic adverse effects of cannabis, especially among certain populations. Although research advances on the effects of cannabis have been made, regulatory barriers that emanate from the Schedule I control status of cannabis at the federal level can hinder progress.

Introduction

Cannabis is one of the most commonly used substances in the United States. Results from the 2022 National Survey on Drug Use and Health (NSDUH) show that 22 percent of people aged 12 and older reported cannabis use in the past year.[1] As in prior years, this number was highest among adults aged 18 to 25 (38.2 percent of people in this age group), followed by those aged 26 to 29 (37.9 percent). Data from the Monitoring the Future (MTF) survey, supported by the National Institute on Drug Abuse (NIDA), show that past-year cannabis use among adolescents *decreased* during the COVID-19 pandemic and has remained stable and below pre-pandemic levels.[2] Yet, in 2023, more than 8 percent of eighth graders, nearly 18 percent of 10th graders, and almost 30 percent of 12th graders reported past-year cannabis use. Previous MTF analyses

[1] https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases

[2] https://monitoringthefuture.org/wp-content/uploads/2022/12/mtf2022.pdf

showed that past-year cannabis use reached record highs among adults aged 19-30[3] and 35-50[4] in recent years. Other studies indicate that adults aged 65 and older represent the fastest-growing age group of people who use cannabis.[5,6] Cannabis use among pregnant women is also on the rise,[7,8] and there are reports of increased accidental cannabis exposure among preschool-age children,[9,10] Observed increases in cannabis exposure may be due in part to rising perceptions of the drug as low-risk, [11,12,13,14,15] concomitant with the rapid legalization of medicinal and non-medicinal cannabis use in states.

This report broadly summarizes the available scientific literature on therapeutic and adverse effects of cannabis, as well as research barriers that limit our knowledge. The conclusions about therapeutic potential and adverse effects are consistent with those in the recommendation from HHS[16] to the Drug Enforcement Agency (DEA) regarding scheduling of botanical cannabis (Cannabis sativa L.) that is within the definition "marihuana" or "marijuana" under the Controlled Substances Act (CSA). However, this report includes some data that post-date that HHS recommendation and addresses some substances that are not within the definition of marijuana under the CSA and thus contains information broader than the scope of the scheduling recommendation. The findings pertaining to adverse effects for specific populations should not be generalized to the overall population; and for those who are using cannabis for medical purposes, there may be additional considerations related to the risk/benefit ratio for patients.

Therapeutic Potential of Cannabis and Cannabinoids

Cannabis sativa L is a complex plant containing over 550 compounds, including more than 100 cannabinoids, the most abundant and well-studied of which are Δ^9-THC and CBD.[17,18,19] Both of these cannabinoids interact with the body's natural endocannabinoid system (ECS), but in

[3] https://nida.nih.gov/news-events/news-releases/2022/08/marijuana-and-hallucinogen-use-among-young-adults-reached-all-time-high-in-2021
[4] https://news.umich.edu/marijuana-and-hallucinogen-use-binge-drinking-reach-historic-highs-among-adults-35-50/
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6024284/
[6] https://pubmed.ncbi.nlm.nih.gov/32091531/
[7] https://pubmed.ncbi.nlm.nih.gov/31211824/
[8] https://pubmed.ncbi.nlm.nih.gov/34570168/
[9] https://pubmed.ncbi.nlm.nih.gov/36594224/
[10] https://www.cdc.gov/mmwr/volumes/72/wr/mm7228a1.htm#:~:text=Cannabis%2Dinvolved%20ED%20visits%20among,than%20they%20did%20among%20males
[11] https://pubmed.ncbi.nlm.nih.gov/35311986/#:~:text=This%20study%20aimed%20to%20examine%20perceptions%20of%20the,and%202019%20International%20Cannabis%20Policy%20Study%20online%20surveys.
[12] https://pubmed.ncbi.nlm.nih.gov/32754880/
[13] https://pubmed.ncbi.nlm.nih.gov/37484055/
[14] https://pubmed.ncbi.nlm.nih.gov/34037250/
[15] https://nida.nih.gov/news-events/news-releases/2022/12/most-reported-substance-use-among-adolescents-held-steady-in-2022
[16] https://www.hhs.gov/sites/default/files/scheduling-recommendation.pdf
[17] https://link.springer.com/chapter/10.1007/978-3-030-57369-0_1
[18] https://www.mdpi.com/1420-3049/26/9/2774
[19] https://pubmed.ncbi.nlm.nih.gov/33302574/

different ways. The ECS comprises cannabinoid receptors (CB1 and CB2); endogenous cannabinoids [anandamide and 2-arachidonoylglyerol (2-AG)]; and the enzymes responsible for their synthesis and degradation. Δ^9-THC binds directly to the ECS' CB1 and CB2 receptors, thereby regulating the release of neurotransmitters (e.g., dopamine, glutamate, GABA) and inducing intoxication and other psychoactive effects.[20,21,22] CBD acts as a noncompetitive negative allosteric modulator of the CB1 receptor and an inverse agonist of the CB2 receptor. It inhibits the reuptake of anandamide and activates serotonergic and vanilloid receptors (among others). CBD alone is not intoxicating and does not produce the same effects as Δ^9-THC on thinking and performance of complex activities.[23]

The FDA has approved one CBD human drug product and three synthetic Δ^9-THC human drug products to treat medical conditions. Epidiolex is an FDA-approved, plant-derived CBD medication for the treatment of seizures associated with Lennox-Gastaut and Dravet syndromes, or tuberous sclerosis complex in patients 1 year of age or older.[24] Marinol and Syndros (dronabinol) are synthetic forms of Δ^9-THC, and Cesamet® (nabilone) is a similar drug.[25] All three are approved to treat nausea and vomiting associated with cancer chemotherapy, and the dronabinol products are indicated for anorexia associated with HIV/AIDS.[26,27,28] Sativex, which contains an approximately equal ratio of plant-derived Δ^9-THC and CBD, has not been approved by the FDA but is approved in several countries for the treatment of spasticity in multiple sclerosis and in Canada for the treatment of pain. These products are generally well-tolerated but can have side effects. Common side effects of Δ^9-THC products include dizziness, drowsiness, dry-mouth, nausea, and euphoria,[29] and common side effects of Epidiolex (high dose CBD) include drowsiness, insomnia, gastrointestinal symptoms, and abnormal liver function tests.[30]

A variety of non-FDA-approved CBD-containing products are sold in multiple consumer markets, including popular websites, often as wellness products to promote sleep and reduce anxiety.[31] A 2017 survey of U.S. adults found that the most common conditions for which CBD was used were pain, anxiety, depression, sleep, and post-traumatic stress disorder.[32] Studies of CBD for these conditions have produced mixed results.[33] More research is needed to evaluate its safety, efficacy, optimal dose, and optimal route of administration for these conditions. It is also worth noting that these products vary greatly in concentration, purity (including contamination with Δ^9-THC or other cannabinoids, pesticides, heavy metals, bacteria, and fungus), and

[20] https://pubmed.ncbi.nlm.nih.gov/35612654/
[21] https://pubmed.ncbi.nlm.nih.gov/30770892/
[22] https://pubmed.ncbi.nlm.nih.gov/21975195/
[23] https://pubmed.ncbi.nlm.nih.gov/33332002/
[24] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/210365s020lbl.pdf
[25] https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#approved
[26] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018651s033lbl.pdf
[27] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205525s011lbl.pdf
[28] lhttps://www.accessdata.fda.gov/drugsatfda_docs/label/2022/018677Orig1s017lbl.pdf
[29] https://pubmed.ncbi.nlm.nih.gov/32483988/
[30] https://www.drugs.com/epidiolex.html
[31] https://pubmed.ncbi.nlm.nih.gov/36169594/
[32] https://pubmed.ncbi.nlm.nih.gov/32291715/
[33] https://pubmed.ncbi.nlm.nih.gov/33585159/

formulation, and generally contain lower amounts of CBD than those used in research studies or the FDA-approved medication, Epidiolex®. A 2017 study of unapproved CBD products sold through online retailers found that the concentration of CBD in commonly-used liquid extracts varied widely from 0.10 mg/mL to 655 mg/mL, which makes these products difficult to compare with CBD used in clinical studies.[34] In addition, several reports have found that the labeling of unapproved CBD products is often not accurate with respect to CBD (or THC and other cannabinoids) concentrations.[35,36,37,38]

A 2020 survey of U.S. adults found that the most frequently cited reasons for consuming cannabis for medicinal purposes were to treat anxiety, insomnia, chronic pain, and depression.[39] Research shows mixed findings on the effectiveness of cannabis for many such indications; the strongest available evidence is for its effectiveness in treating certain types of chronic pain. In 2017, the National Academies of Science, Engineering, and Medicine published an extensive expert review of the state of the science related to the potential health effects of cannabis and cannabinoids.[40] This evaluation concluded that there was "substantial evidence"[41] to suggest that cannabis may be effective for treating chronic pain in adults. Similarly, more recent reviews and meta-analyses of randomized controlled trials (RCTs) found evidence to suggest that synthetic or plant-derived Δ^9-THC may be associated with improvements in chronic pain (e.g., neuropathic pain).[42,43,44,45]

Among those who use cannabis to address mental health symptoms, observational studies show that people report improvements in quality of life, well-being, and mood.[46,47,48] Yet, meta-analyses of RCTs have found insufficient evidence to conclude that cannabis improves mental health conditions, quality of life, or well-being.[49,50] More research is needed to evaluate the therapeutic potential of cannabis and cannabinoids as a means of safely and effectively treating various indications. This includes research on the cannabinoid and other chemical constituents of the plant, how cannabis products interact with prescription medications, how brain maturity and

[34] https://pubmed.ncbi.nlm.nih.gov/29114823/
[35] https://pubmed.ncbi.nlm.nih.gov/29114823/
[36] https://pubmed.ncbi.nlm.nih.gov/32431186/
[37] https://pubmed.ncbi.nlm.nih.gov/35658956/
[38] https://store.samhsa.gov/sites/default/files/pep22-06-04-003.pdf
[39] https://pubmed.ncbi.nlm.nih.gov/32291715/
[40] https://nap.nationalacademies.org/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state
[41] In its report, NASEM defined "substantial evidence" for therapeutic effects as "There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest."
[42] https://pubmed.ncbi.nlm.nih.gov/34546363/
[43] https://pubmed.ncbi.nlm.nih.gov/34497047/
[44] https://pubmed.ncbi.nlm.nih.gov/29442178/
[45] https://pubmed.ncbi.nlm.nih.gov/36129666/
[46] https://pubmed.ncbi.nlm.nih.gov/34566726/
[47] https://pubmed.ncbi.nlm.nih.gov/37159196/
[48] https://pubmed.ncbi.nlm.nih.gov/24205805/
[49] https://pubmed.ncbi.nlm.nih.gov/33530732/
[50] https://pubmed.ncbi.nlm.nih.gov/35861789/

body metabolism influence the effects of cannabis medications, how cannabis should be administered for therapeutic purposes, and at what dosages. It is also worth noting that the U.S. jurisdictions that have legalized the use of cannabis products for medicinal purposes have often done so with inadequate scientific research to support all allowable uses.

Effects of Cannabis on the Body and Developing Brain

The ECS is found throughout the body and plays a critical role in nervous system development, is present early in the prenatal period, and continues to impact the maturation of the nervous system through young adulthood.[51] The ECS is also present in the placenta and plays an important role in pregnancy maintenance and success.[52] Throughout life, the ECS is involved in emotion processing, learning and memory, sleep, temperature regulation, pain perception, immune function, and many other vital functions.[53] Exposure to cannabis during critical periods of development (e.g., prenatal, adolescence) could alter the ECS, potentially exerting lasting effects.

Acute effects during cannabis intoxication are observed on cognition and psychomotor performance (e.g., driving), mental health (e.g., high doses can produce severe anxiety or psychosis), and on some cardiovascular indices. Longer-term adverse effects are more often associated with heavy or frequent use in individuals who began cannabis use at a young age, and can include risk for psychotic disorders, other mental illnesses (including suicidal ideation and behavior) and substance use disorders (SUD), hyperemesis syndrome, and decreased academic/career achievement. These are briefly highlighted below. In general, the adverse effects of cannabis depend upon the timing of exposure, individual vulnerabilities or resilience, frequency of use, dosage, and many other variables.

Cannabis Product Characteristics

Cannabis products on the market today are vastly different that those of the past. The average Δ^9-THC concentration in cannabis products seized by law enforcement increased 3.5-fold between 1995 (4 percent) and 2021 (15 percent),[54] the average concentration in dispensary products is around 20 percent,[55] and cannabis concentrates may contain around 40 percent to over 80 percent Δ^9-THC.[56] Cannabis is also more widely available today and comes in many formulations that can be smoked, vaped, dabbed, eaten, drank, or applied under the tongue;[57] the time-course and intensity of cannabis' effects are powerfully influenced by product type/route of administration as well as potency.

[51] https://pubmed.ncbi.nlm.nih.gov/34445282/
[52] https://pubmed.ncbi.nlm.nih.gov/34220722/
[53] https://pubmed.ncbi.nlm.nih.gov/15550444/
[54] https://nida.nih.gov/research/research-data-measures-resources/cannabis-potency-data
[55] https://pubmed.ncbi.nlm.nih.gov/32214334/
[56] https://publications.aap.org/pediatrics/article/144/3/e20190338/38413/Cannabis-Concentrate-Use-in-Adolescents?autologincheck=redirected
[57] https://pubmed.ncbi.nlm.nih.gov/29770952/

There is also an emerging market for other intoxicating cannabinoids that are unregulated and widely available, with unknown public health impacts[58,59,60,61,62] While some of these products can be extracted directly from the hemp plant (e.g., THCA), most do not occur naturally but are derived semi-synthetically from CBD (e.g., Δ^8-THC) or derivatives of CBD (e.g., HHC), or manufactured synthetically from other sources. Because these products are new, research on their health effects is limited. Δ^8-THC was the first such product to emerge, and the Centers for Disease Control and Prevention (CDC) and FDA have issued advisories about Δ^8-THC citing adverse events, unsafe manufacturing processes, and other concerns.[63,64]

Cognitive Abilities and Driving

In 2020, the self-reported prevalence of driving under the influence of cannabis was 4.5 percent among U.S. adults and reached 30 percent among those who used cannabis, 57 percent among those who used cannabis daily, and 64 percent among those with symptoms of cannabis use disorder (CUD).[65] Cannabis use produces acute impairment of verbal learning and memory, executive functioning, working memory, decision-making, processing speed, motivation, and attention.[66,67,68] Such impairments can affect one's ability to perform complex tasks and studies have found a relationship between acute cannabis intoxication and impaired driving ability.[69,70,71,72] However, the strength of cannabis-induced impairment depends on a variety of factors including a person's frequency of use, tolerance, time since use, and route of administration,[73,74] so it is has been challenging to develop roadside cannabis intoxication detection methods. Research shows that plasma levels of Δ^9-THC following cannabis smoking peak at about 10 minutes and clear rapidly, but oral formulations take longer to metabolize.[75,76] Moreover, Δ^9-THC can be detected in body fluids for days or weeks after acute intoxication,

---

58 https://static1.squarespace.com/static/5f7e577e23ad7c718c269776/t/63d1c660f373490041c463b9/1674692193920/Hemp+Regulatory+Challenges+-+Short+FINAL.pdf

59 https://static1.squarespace.com/static/5f7e577e23ad7c718c269776/t/643c5d64c5e0c73aad733bf4/1681677670844/Considerations+for+Federal+Hemp+Regulation_April+2023.pdf

60 https://pubmed.ncbi.nlm.nih.gov/38091045/

61 https://pubmed.ncbi.nlm.nih.gov/34662224/

62 https://pubmed.ncbi.nlm.nih.gov/36710464/

63 https://emergency.cdc.gov/han/2021/pdf/CDC_HAN__451.pdf

64 https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc

65 https://pubmed.ncbi.nlm.nih.gov/33726992/

66 https://pubmed.ncbi.nlm.nih.gov/34276511/

67 https://pubmed.ncbi.nlm.nih.gov/35048456/

68 https://pubmed.ncbi.nlm.nih.gov/34215784/

69 https://nap.nationalacademies.org/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state

70 https://pubmed.ncbi.nlm.nih.gov/31094805/

71 https://pubmed.ncbi.nlm.nih.gov/33839427/

72 https://www.liebertpub.com/doi/10.1089/can.2020.0048

73 https://pubmed.ncbi.nlm.nih.gov/30056176/

74 https://pubmed.ncbi.nlm.nih.gov/32585912/

75 https://pubmed.ncbi.nlm.nih.gov/18847571/

76 https://pubmed.ncbi.nlm.nih.gov/16237477/

especially among regular users.[77] This makes it challenging to attribute driving impairment to Δ^9-THC levels in bodily fluids or to determine a cut-off for use in *per se* or other driving laws. Another confounding factor is alcohol, with which cannabis is often co-consumed. A meta-analysis of research on cannabis- and alcohol-induced driving impairment shows clear evidence that each of these drugs independently impairs driving ability, while the combination of the two is significantly more detrimental than either one alone.[78]

While research is underway at NIDA to develop accurate measures for detecting cannabis driving impairment, there are no established standards. Some states have zero-tolerance laws for Δ^9-THC, some have set specific blood level limits, while others are working to determine their regulations. Public awareness of potential driving impairments is key, as driving after consuming cannabis poses increased risks of traffic accidents and the time course of this effect varies with the potency and route of administration (e.g., edible vs. smoked products), as well as individual factors, such as tolerance and frequency of use.

Emergency Department Visits

Emergency department (ED) visits related to cannabis (both acute and chronic exposures) are on the rise, likely due to various changes in the market (e.g., increased cannabis product availability, product diversity, higher Δ^9-THC concentrations, and emergence of Δ^8-THC and other intoxicating products derived from hemp)[79, 80, 81, 82, 83, 84] and the populations who are using it. Chronic cannabis use can induce a hyperemesis syndrome characterized by cyclical nausea and vomiting and severe abdominal pain requiring medical attention.[85] While various interventions may be partially effective (e.g., neuroleptics, hot showers), the condition resolves only after cessation of cannabis use.[86, 87]

There are many reports of cannabis-induced anxiety and psychosis requiring emergency medical care.[88, 89, 90] For most people, these effects on mental health are temporary and abate when cannabis is stopped, but psychosis can be long-lasting for people who are vulnerable (see *Substance Use and Mental Health Disorders* below). Increased heart-rate and other temporary

[77] https://pubmed.ncbi.nlm.nih.gov/32841811/
[78] https://pubmed.ncbi.nlm.nih.gov/35083810/
[79] https://pubmed.ncbi.nlm.nih.gov/35033959/
[80] https://nida.nih.gov/research/research-data-measures-resources/cannabis-potency-data
[81] https://pubmed.ncbi.nlm.nih.gov/34662224/
[82] https://static1.squarespace.com/static/5f7e577e23ad7c718c269776/t/64df8be73b14185feeebc368/1692371974882/CANNRA+Response+to+Hemp+RFI_FINAL_08172023.pdf
[83] https://www.fda.gov/food/alerts-advisories-safety-information/fda-warns-consumers-about-accidental-ingestion-children-food-products-containing-thc
[84] https://emergency.cdc.gov/han/2021/han00451.asp
[85] https://www.ncbi.nlm.nih.gov/books/NBK549915/
[86] https://pubmed.ncbi.nlm.nih.gov/33568074/
[87] https://www.ncbi.nlm.nih.gov/books/NBK549915/
[88] https://pubmed.ncbi.nlm.nih.gov/32726001/
[89] https://pubmed.ncbi.nlm.nih.gov/31563981/
[90] https://pubmed.ncbi.nlm.nih.gov/37252542/

cardiovascular symptoms can occur,[91] and long-term cannabis use has been linked with decreased heart rate, and secondary low blood pressure and postural hypotension.[92] Although serious cardiovascular effects have also been reported, including strokes and heart attacks,[93, 94, 95] findings are mixed and more research is needed to determine if there is a causal connection or if other factors are involved.[96,97] Similarly, the impact of cannabis on respiratory health is difficult to determine without long-term studies and because cannabis is often used along with tobacco.[98,99] Notably, in 2019, an outbreak of e-cigarette or vaping product use-associated lung injury (EVALI) was later shown to result from vitamin E acetate, a component of some illicit vaporizable Δ^9-THC products.[100]

There are also concerning reports of harmful cannabis exposures resulting in ED visits among youth and young adults. From 2017-2021, there was a sharp rise in intensive care unit (ICU) and non-ICU ED visits for unintentional exposure to cannabis edibles among children below the age of six, including admissions for central nervous system depression.[101] A study showing increased cannabis-related ED visits among youth in 2018 to 2022, found the largest increase among children under age 10, followed by those aged 11 to 14.[102] The largest number of visits were among those aged 15-24 who are also more likely to use higher potency products like vapes.[103] In 2022, the highest rate of ED visits related to cannabis use among adults was for young adults ages 18 to 25.[104] As cannabis products are increasingly available and more potent, there is a clear need for public health safety measures and research to inform such measures.

Substance Use and Mental Health Disorders

Heavy, chronic (daily or near-daily) use, especially of high Δ^9-THC concentration cannabis products, can lead to CUD. Estimates indicate that approximately 22 to 30 percent of people who use cannabis have CUD.[105, 106] A recent study of primary care patients in a state with cannabis use laws found that 21 percent of patients who used cannabis had CUD and 6.5 percent had moderate to severe forms. CUD was highest among patients who used cannabis for both medicinal and non-medicinal purposes (7.5 percent), followed by non-medicinal use only (7.2 percent), and medicinal use only (1.3 percent).[107] For people with CUD, discontinuing cannabis use can be challenging due to withdrawal symptoms like anxiety, depression, irritability,

[91] https://pubmed.ncbi.nlm.nih.gov/32575540/
[92] https://pubmed.ncbi.nlm.nih.gov/33786179/
[93] https://pubmed.ncbi.nlm.nih.gov/28432636/
[94] https://pubmed.ncbi.nlm.nih.gov/30964363/
[95] https://www.ahajournals.org/doi/10.1161/JAHA.123.030178
[96] https://pubmed.ncbi.nlm.nih.gov/30980200/
[97] https://pubmed.ncbi.nlm.nih.gov/33208143/
[98] https://pubmed.ncbi.nlm.nih.gov/32285993/
[99] https://pubmed.ncbi.nlm.nih.gov/35942197/
[100] https://pubmed.ncbi.nlm.nih.gov/36199112/
[101] https://pubmed.ncbi.nlm.nih.gov/36594224/
[102] https://pubmed.ncbi.nlm.nih.gov/37440436/
[103] https://nida.nih.gov/research-topics/trends-statistics/monitoring-future
[104] https://store.samhsa.gov/sites/default/files/pep23-07-03-001.pdf
[105] https://pubmed.ncbi.nlm.nih.gov/26502112/
[106] https://pubmed.ncbi.nlm.nih.gov/32485547/
[107] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2808874

anger/aggression, insomnia and other sleep problems, loss of appetite, as well as other less common symptoms like chills, headaches, physical tension, sweating, and stomach pain. More frequent use of higher potency products is associated with worse withdrawal symptoms, especially poor sleep, irritability, and low mood.[108] Although withdrawal symptoms generally peak within two to six days, they can last up to three weeks or more.[109] There are effective psychosocial therapies for CUD, like cognitive-behavioral therapy and contingency management, but there are no treatment medications and achieving long-term abstinence is difficult.[110]

The link between cannabis and psychotic disorders is a major concern, especially for individuals who have genetic or other risk factors for psychosis. A 2020 review and meta-analysis of 26 other such studies concluded that psychotic disorders, and earlier first-episode psychosis, are more common among people who use cannabis relative to those who do not, and this relationship may be dose-dependent.[111] Cannabis use was also linked with increase rates of psychosis relapse, hospitalizations, and positive symptoms of psychotic illness (e.g., hallucinations). Cannabis use and cannabis-induced psychosis have also been linked with chronic psychotic disorders (e.g., schizophrenia), particularly among those with a family history of psychosis.[112,113,114] Analyses of comprehensive data from integrated healthcare systems in other countries demonstrate a connection between cannabis use and increased population-level rates of psychotic and other disorders. A longitudinal, prospective, population study in Denmark found that cases of schizophrenia associated with CUD increased 3- to 4-fold in the past two decades, a period associated with increases in the frequency of use and potency of cannabis.[115] A follow-up study showed that CUD is also associated with increased risk of non-psychotic bipolar disorder and unipolar depression.[116] A study of people with first-episode psychosis in Europe and Brazil showed that daily cannabis use substantially increased the odds of first-episode psychosis, and use of high-potency cannabis (i.e., greater than 10 percent Δ^9-THC) increased the odds 5-fold.[117] Notably, the definition of "high-potency" in this study reflects a Δ^9-THC concentration much lower than that found in many products on the market. While these data are concerning, it is important to note that a causal link has not been established. Indeed, there is evidence that people with mental illnesses may be more likely to use cannabis.[118,119] There may also be common risk

[108] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9110517/
[109] https://pubmed.ncbi.nlm.nih.gov/34791767/
[110] https://pubmed.ncbi.nlm.nih.gov/33627670/
[111] https://pubmed.ncbi.nlm.nih.gov/31563981/
[112] https://pubmed.ncbi.nlm.nih.gov/29179576/
[113] https://pubmed.ncbi.nlm.nih.gov/31055966/
[114] https://pubmed.ncbi.nlm.nih.gov/31618428/
[115] https://pubmed.ncbi.nlm.nih.gov/34287621/
[116] https://pubmed.ncbi.nlm.nih.gov/37223912/
[117] https://pubmed.ncbi.nlm.nih.gov/30902669/
[118] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1361129/
[119] https://pubmed.ncbi.nlm.nih.gov/34087766/

factors (including genetics) that account for the associations between cannabis use and psychosis.[120,121]

Developing Brain

Exposure to cannabis during the prenatal period is associated with risks to prenatal and newborn health, including lower birth weight, preterm birth, and reduced size for gestational age.[122,123] From 2005 to 2015, perceptions of harm associated with cannabis use during pregnancy decreased,[124] and cannabis use among pregnant women increased from 2013 to 2020.[125,126] In a study of 400 dispensaries where researchers posed as pregnant women, nearly seventy percent of dispensary workers recommended cannabis to treat morning sickness.[127] The majority indicated that their guidance was based on personal opinion, demonstrating a need for evidence-based information on cannabis and health. These findings prompted some states to require that dispensaries post warnings about the use of THC products during pregnancy.[128] Analyses of NIH's Adolescent Brain Cognitive Development℠ Study, or (ABCD Study®) data suggest prenatal exposure may have lasting effects including sleep problems in middle childhood,[129,130] symptoms of psychopathology in middle childhood and adolescence,[131,132] deleterious effects on adolescent cognition and brain volume,[133] and two-fold increased odds of early cannabis initiation.[134] Prospective, longitudinal research is needed to better understand the effect of cannabis exposure on child development. NIH's HEALthy Brain and Child Development (HBCD) Study is following a large cohort of pregnant women and their children from the prenatal period through ages 9-10. This study will substantially contribute to our understanding of healthy development and the impact of early environmental exposures, including cannabis. This research, as well as public education on the potential effects of cannabis on fetal health and development, is critical.

Research shows a connection between adolescent cannabis use and a variety of adverse outcomes, including decreased cognitive performance, motivation, and school and work success later in life, and increased risk of developing CUD and other SUDs.[135,136] Recent studies also show an increased likelihood of depression and suicidality among youth and young adults who

[120] https://pubmed.ncbi.nlm.nih.gov/37208114/
[121] https://pubmed.ncbi.nlm.nih.gov/33950550/
[122] https://pubmed.ncbi.nlm.nih.gov/33887075/
[123] https://pubmed.ncbi.nlm.nih.gov/38085313/
[124] https://pubmed.ncbi.nlm.nih.gov/28843740/
[125] https://pubmed.ncbi.nlm.nih.gov/31211824/
[126] https://pubmed.ncbi.nlm.nih.gov/34570168/
[127] https://pubmed.ncbi.nlm.nih.gov/29742676/
[128] https://hightimes.com/news/colorado-cannabis-stores-will-begin-posting-warning-signs-about-thc-risks-during-pregnancy/
[129] https://pubmed.ncbi.nlm.nih.gov/32605891/
[130] https://pubmed.ncbi.nlm.nih.gov/36840387/
[131] https://pubmed.ncbi.nlm.nih.gov/32965490/
[132] https://pubmed.ncbi.nlm.nih.gov/36094599/
[133] https://pubmed.ncbi.nlm.nih.gov/36791556/
[134] https://pubmed.ncbi.nlm.nih.gov/37358866/
[135] https://pubmed.ncbi.nlm.nih.gov/37414504/
[136] https://pubmed.ncbi.nlm.nih.gov/32026735/

use cannabis during adolescence. Compared with those who do not use cannabis, adolescents who use cannabis are more likely to have depression and experience suicidal thoughts and behaviors, and to have these conditions in young adulthood[137,138] An analysis of nationally representative data from young adults without depression showed that cannabis use and CUD were associated with increased prevalence of suicidal ideation, particularly among women.[139]

These negative outcomes may be dose-related,[140] with chronic, frequent use linked to more deleterious effects.[141,142] NIDA-supported brain network modeling research shows that adolescent cannabis use may be linked with accelerated prefrontal cortical thinning, which could account for some of these findings.[143] Although causal relationships have not been established, it is possible that cannabis use may pose greater risks to the developing adolescent and young adult brain than to the fully-developed adult brain. Findings to date highlight the need for public awareness about the potential risks of cannabis exposure, especially during critical periods of development. It is encouraging that rates of cannabis use among adolescents decreased after the onset of the pandemic, leveled off in 2022, and held steady in 2023.[144] Moving forward, longitudinal research like NIH's ABCD Study® will shed light on risk and resilience factors and disentangle adverse effects of cannabis from the effects of other substance use and social determinants.

Barriers to Research on Cannabis Products

The Agriculture Improvement Act of 2018 (AIA), also known as the "2018 Farm Bill," amended the definition of "marihuana" in the CSA to exclude hemp. The AIA defined hemp as "the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis."[145] As such, research using hemp-derived products no longer requires a Schedule I registration from the DEA. However, marijuana, which refers to the plant *Cannabis sativa* L. and any part of that plant as described above with a Δ^9-THC concentration of more than 0.3 percent on a dry weight basis, remains a Schedule I controlled substance.

There is some confusion among constituents about the control status of intoxicating compounds derived from hemp (e.g., Δ^8-THC) that have emerged due to perceived loopholes in the AIA.[146] For example, the Ninth Circuit Court of Appeals ruled in 2022 that hemp-derived products

[137] https://pubmed.ncbi.nlm.nih.gov/30758486/
[138] https://pubmed.ncbi.nlm.nih.gov/32663935/
[139] https://pubmed.ncbi.nlm.nih.gov/34156452/
[140] https://pubmed.ncbi.nlm.nih.gov/26360862/
[141] https://pubmed.ncbi.nlm.nih.gov/33782115/
[142] https://pubmed.ncbi.nlm.nih.gov/37414504/
[143] https://pubmed.ncbi.nlm.nih.gov/35523763/
[144] https://nida.nih.gov/research-topics/trends-statistics/monitoring-future
[145] https://uscode.house.gov/view.xhtml?path=/prelim@title7/chapter38/subchapter7&edition=prelim
[146] https://static1.squarespace.com/static/5f7e577e23ad7c718c269776/t/643c5d64c5e0c73aad733bf4/1681677670844/Considerations+for+Federal+Hemp+Regulation_April+2023.pdf

containing Δ^8-THC are considered "hemp" and are not controlled under the CSA.[147] If so, researchers are not required to hold a Schedule I researcher registration to conduct research on non-synthetic hemp-derived compounds containing no more than 0.3% Δ^9-THC on a dry weight basis. However, when manufactured from non-hemp sources, chemically identical "synthetic equivalent cannabinoids" require a Schedule I researcher registration.[148] Thus, indistinguishable compounds may be controlled differently depending on whether they are non-synthetic hemp/CBD-derived or derived from other sources. These inconsistencies remain a source of confusion for scientists and could have a chilling effect on research by deterring scientists from conducting research on these compounds. Additional guidance from the DEA, including on how researchers can determine the source of cannabis materials (i.e., whether they are hemp-derived and thus non-controlled) would be useful.

Beyond the nuances of the control status of various cannabis products, there are numerous barriers that can deter scientists from pursuing research with Schedule I drugs. Even experienced researchers have reported that requirements for obtaining a new Schedule I registration, adding new substances to an existing registration, and getting approval for research protocol changes are time-consuming. Unlike for Schedule II through V substances, new and amended Schedule I applications go through additional and often duplicative reviews to those already conducted by HHS, the FDA, Institutional Review Boards, and/or Institutional Animal Care and Use Committees. Establishing the security infrastructure needed to conduct Schedule I research can be expensive and may need to be duplicated for each registrant working within a single research department. Security measures involve expensive safes, locking refrigerators and freezers, surveillance systems, and other equipment, sometimes even requiring a remodeling of existing facilities. Researchers have also reported that there is a lack of clarity in some of the registration requirements and variability in their interpretation by local vs. federal DEA personnel, and by academic institutions, which complicates and adds time to the process.

Another barrier to cannabis research is that researchers cannot legally obtain or analyze products sold through state marijuana dispensaries. Under current regulations, the DEA must approve all sources of cannabis used in research, and no state-authorized dispensaries have been approved.[149] As such, researchers must rely on study participants' self-reported use and/or photos of dispensary products, with testing and labeling requirements that are not consistent across jurisdictions. Due to this variability—and because researchers cannot test these products—it is challenging to determine exactly what is in the products consumers are using and what characteristics of them are responsible for any reported therapeutic or adverse effects.

In 2022, the U.S. Pharmacopeia (USP) published a draft general chapter prospectus for comment, which is still under discussion, that proposes topics such as standards and analytical approaches for ensuring the quality of cannabis and cannabis-derived compounds in clinical research.[150] In 2023, FDA published final guidance on several topics relevant to clinical research related to the development of human drugs containing cannabis or cannabis-derived compounds,

[147] https://cdn.ca9.uscourts.gov/datastore/opinions/2022/05/19/21-56133.pdf
[148] https://www.federalregister.gov/documents/2020/08/21/2020-17356/implementation-of-the-agriculture-improvement-act-of-2018
[149] https://nida.nih.gov/research/resources-grants-contracts/faqs-conducting-research-with-cannabis-hemp
[150] https://www.uspnf.com/notices/gc-1568-prospectus-20220527

including information on quality considerations.[151] This timely information could be helpful in the evaluation of dispensary products for research purposes.

Until recently, NIDA's Drug Supply Program (DSP) was the only source of cannabis for research authorized by the DEA. Through a contract with the University of Mississippi, the DSP provides a wide range of cannabis plant material and products to researchers free of charge and at varying potencies and ratios of THC to CBD.[152] Due to cost barriers, the DSP is not likely to be able to reproduce the entire range of products available through state-authorized dispensaries—such as concentrates, vape pens, edibles, and other emerging products/formulations. In addition, without the ability to test products on the market, it is challenging to develop research-grade materials to match their potency and diversity. In 2021, the DEA began to authorize additional cannabis growers that are permitted to provide products directly to researchers.[153] Although this is an important step in diversifying cannabis products available for research, it is not clear how many of these growers have begun providing cannabis to researchers or how products supplied by these growers would reflect the diversity of cannabis products available in dispensaries. Ultimately, to determine the effects of cannabis and characteristics and components of cannabis that are responsible for its effects, it will be important to ensure that research-grade products reflect those that consumers are using.

Recommendations for Addressing Dispensary Product Research Barriers

In 2022, Congress passed and the President signed into law MMCREA to expand research on cannabis.[154] Although it has not yet been implemented, the law is aimed both at increasing the number and variety of manufacturers authorized to provide cannabis for research and facilitating the process of obtaining a Schedule I registration to conduct cannabis research.

The HALT Fentanyl Act,[155] which was passed by the House of Representatives on May 23, 2023, and is with the Senate as of December 26, 2023, would also address some of the barriers to conducting research on marijuana. If enacted, this bill would facilitate the process of obtaining a research registration for *all* Schedule I drugs, including cannabis. Moreover, it would clarify or amend provisions in the CSA that have been sources of confusion and administrative burden for the research community. For example, the bill makes clear that separate Schedule I research registrations are not required for every Schedule I researcher at an institution; that a single Schedule I research registration can allow research at multiple locations under the control of a single institution within the same city or county; and that Schedule I research registrants are not required to obtain a manufacturing registration to manufacture small quantities of material coincident to research, such as creating dosage formulations needed to administer cannabis and other drug products to study participants. The research provisions in the HALT Fentanyl Act

[151] https://www.fda.gov/media/164690/download
[152] https://nida.nih.gov/research/research-data-measures-resources/nida-drug-supply-program-dsp/nida-drug-supply-program-dsp-ordering-guidelines/marijuana-plant-material-available
[153] https://www.deadiversion.usdoj.gov/drugreg/marihuana.html
[154] https://www.congress.gov/bill/117th-congress/house-bill/8454/text
[155] https://www.congress.gov/bill/118th-congress/house-bill/467/text?s=1&r=1&q=%7B%22search%22%3A%5B%22HALT+Fentanyl+Act%22%5D%7D

reflect those proposed by the Biden Administration and were developed in collaboration with the White House Office of National Drug Control Policy, NIDA, FDA, and DEA.

NIDA has recently funded a research project to develop a cannabis registry with the goal of gaining a better understanding of dispensary products that are being used by patients for medicinal purposes. It will capture information on products used, routes of administration, frequency and amount used, and health data from diverse sources, including health records, prescribing providers, and participants.[156] To facilitate comparisons among studies, the registry will measure and report THC exposures based on a 5mg standard unit, as is now required for all NIDA-supported cannabis research.[157] The researchers will also form partnerships with other organizations (e.g., the cannabis regulators association or CANNRA) to leverage ongoing data collection and harmonize measures. If this study is successful, it will provide a rich source of data on outcomes of medical use, participant characteristics, and product type and use.

Still, none of the efforts described above address the critical need for researcher access to the full range of state-authorized dispensary products; thus, there remains a substantial gap in understanding the impact of cannabis products on health. Innovative solutions to bridge this gap are needed. Licensing cannabis growers that are already providing products to state dispensaries as approved manufacturers of research-grade cannabis is one possible path through which researchers could access some of the same products sold in state-legal markets. Exploring partnerships through which the federal government could legally acquire and make available to registered researchers cannabis products from state-authorized dispensaries could also bridge this gap.

Conclusion

Cannabis sativa L. is a complex plant, and it is being manufactured and consumed in varying potencies and formulations for a wide range of medicinal and non-medicinal purposes. Although there are medical benefits associated with the use of FDA-approved cannabinoid medications and there is credible scientific support suggesting that cannabis has additional therapeutic potential, there are also risks and many unknowns. It is imperative that we learn as much as we can about the wide variety of available products and their constituents, including cannabinoids other than Δ^9-THC and CBD. By expanding the number of cannabis manufacturers and enacting legislation to make it easier to conduct cannabis research, federal policymakers have taken important steps toward advancing this work. Nevertheless, continued regulatory hurdles, including lack of access to the products the public is using, hinder our ability to fully understand cannabis' potential as a therapeutic agent and its risks when used for medicinal and non-medicinal purposes, and must be addressed.

[156] https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-23-011.html

[157] https://nida.nih.gov/about-nida/noras-blog/2021/05/establishing-5mg-thc-standard-unit-research

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

DATE: October 17, 2023

TO: Melanie Anne Egorin
Assistant Secretary for Legislation

THROUGH: Elizabeth J. Gramling, Executive Secretary

FROM: Lawrence Tabak, D.D.S., Ph.D.
Acting Director, National Institutes of Health

SUBJECT: INFORMATION ONLY – Therapeutic Potential of Cannabis and Cannabinoids, Adverse Effects of Cannabis on the Body and Developing Brain, and Barriers to Cannabis Research

KEY INFORMATION

Attached for your transmittal to Congress is a report entitled *Therapeutic Potential of Cannabis and Cannabinoids, Adverse Effects of Cannabis on the Body and Developing Brian, and Barriers to Cannabis Research* in fulfillment of a requirement set forth in the Medical Marijuana and Cannabidiol Research Expansion Act. This report was prepared by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH).

EXECUTIVE SUMMARY

The Medical Marijuana and Cannabidiol Research Expansion Act (Public Law No.:117-215) requires the Department of Health and Human Services, in coordination with the National Institutes of Health and other relevant federal agencies, to report the health effects of cannabis and cannabinoids and barriers to research on the compounds. Specifically, under Section 401, the report must address (1) the potential therapeutic effects of cannabis or cannabidiol on serious medical conditions including intractable epilepsy; (2) the potential effects of cannabis on the human body and developing brain, including cognitive abilities relevant to driving; and (3) barriers associated with research on cannabis or cannabidiol in states that have legalized such substances, including recommendations as to how barriers might be overcome and safeguards that would need to be in place to ensure product quality and safety. The following report, which synthesizes the current state of the science and research regulations, fulfills these requirements.

The U.S. Food and Drug Administration has approved some medications that contain or are based on the primary cannabinoids in the cannabis plant, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). Prescription CBD medications are used to treat certain rare seizure disorders and delta-9-THC-based medications help with nausea, vomiting, and weight loss associated with specific medical conditions. Yet, as states increasingly legalize cannabis, people

report using it for many purposes, both medicinal and adult use. While there is evidence that cannabis has therapeutic potential for some conditions for which it is not FDA-approved (e.g., neuropathic pain), there is less support for its effectiveness in addressing other conditions. Moreover, there are known acute adverse effects on cognition and psychomotor performance, and chronic use has been linked to medically serious vomiting, cannabis use disorder, and increased risk for psychosis among vulnerable people, such as those with a family history of psychosis. Additionally, because cannabis can alter the body's natural endocannabinoid system, there may be adverse, lasting effects of cannabis exposure during development.

While research advances have been made, regulatory barriers that emanate from the Schedule I control status of cannabis at the federal level can hinder progress. This report provides an overview of what is known about the therapeutic potential of cannabis and cannabinoids, the effects of cannabis on the body and developing brain and driving ability, and the barriers to research on cannabis products, including research on state-legal dispensary products.

Notable Timing Factors:
The statutory deadline for this report is December 2, 2023, one year after the date of enactment of this Act.

Key Stakeholders:
This report will be sent to 10 members of Congress, consisting of the Co-Chairs of the Caucus on International Narcotics Control; the Chair and Ranking Member of the Senate Committee on the Judiciary; the Chair and Ranking Member of the Senate Committee on Health Education, Labor, and Pensions; the Chair and Ranking Member of the House of Representatives Committee on Energy and Commerce; and the Chair and Ranking Member of the House of Representatives Committee on the Judiciary. This report is non-controversial and is not expected to garner significant attention beyond the members of Congress noted above.

Lawrence A. Tabak, D.D.S, Ph.D.

Attachments
TAB A: Transmittal letters to Congress
TAB B: Report to Congress