

**UNITED STATES DEPARTMENT OF JUSTICE  
Drug Enforcement Administration**

In the Matter of

**Schedules of Controlled Substances:  
Proposed Rescheduling of Marijuana**

**DEA Docket No. 1362  
Hearing Docket No. 26-96**

**STATEMENT OF AVAILABILITY FOR IN-PERSON ATTENDEES AND WITNESSES  
OF SMART APPROACHES TO MARIJUANA**

Pursuant to the Preliminary Order of June 18, 2026, Designated Party SAM Inc. (d/b/a Smart Approaches to Marijuana, hereinafter “SAM”) hereby submits this Statement in advance of the hearing in the above-captioned matter currently scheduled to commence on June 29, 2026.

**I. IN-PERSON ATTENDEES AND WITNESSES OF SMART APPROACHES TO MARIJUANA**

SAM is a Virginia non-profit corporation whose mission is to combat marijuana abuse and addiction. SAM will have the following **four (4) in person attendees**:

- Patrick F. Philbin
- John M. McNichols
- Chase T. Harrington
- Luke Dean Niforatos

SAM will also have the following **two (2) witnesses**

- Dr. Bertha K. Madras (attending **in person**)
- Dr. Luli R. Akinfiresoye (attending **in person, by DEA subpoena**)

Dr. Akinfiresoye is a DEA employee who was previously disclosed as the Government’s expert witness for Hearing 24-44, in support of which she submitted a Declaration and report which “reflects DEA’s current scientific knowledge regarding marijuana.” *See* Ex. A ¶ 13. In response to SAM’s inquiry concerning her availability for Hearing 26-96, *see* Ex. B, the Government did

not provide her availability, but instead asserted that a *Tuohy* request would be required to secure her appearance, despite having already identified her as a witness and disclosed the subject matter of her expert testimony, *see* Ex. C. Given this response, SAM is presently unable to inform the Tribunal of Dr. Akinfiresoye's availability, but will provide the Court with a completed DEA subpoena consistent with June 18 Preliminary Order.

## **II. SAM AVAILABILITY**

SAM's counsel and witness Dr. Madras are available to present SAM's case between July 6 and July 15, and they respectfully request that SAM be permitted to present its case between July 6 and July 10 (i.e., the second week) to accommodate preexisting travel plans that conflict with the third scheduled week. As noted above, however, SAM is unable to inform the Court as to the availability or convenience of Dr. Akinfiresoye.

June 23, 2026

Respectfully submitted,

/s/ Patrick F. Philbin

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*Counsel for Smart Approaches to Marijuana*

## CERTIFICATE OF SERVICE

I hereby certify that, on June 23, 2026, I caused a copy of the foregoing document to be delivered by email to the following recipients:

1. The Tribunal, by email to ECF-NPRM@dea.gov;
2. The Government, by email to
  - a. The DEA Government Mailbox at dea.registration.litigation@dea.gov;
  - b. James J. Schwartz, Esq., at James.J.Schwartz@dea.gov;
  - c. Jarrett T. Lonich, Esq., at Jarrett.T.Lonich@dea.gov;
  - d. Alexis B. Attanasio, Esq., at Alexis.B.Attanasio@dea.gov;
  - e. Kayla L. Kreinheder, Esq., at Kayla.L.Kreinheder@dea.gov;
  - f. David C. Maley, Esq., at David.C.Maley@dea.gov;
  - g. Lisa K. Man, Esq., at Lisa.K.Man@dea.gov;
  - h. Stacy M. Race, Esq., at Stacy.M.Race@dea.gov;
  - i. Mack J. Swan, Esq., at Mack.J.Swan@dea.gov
3. National Drug & Alcohol Screening Association;
  - a. M. Jo McGuire at jomcguire@ndasa.com;
  - b. David Evans, Esq. at thinkon908@aol.com;
4. Tennessee Bureau of Investigation, by email to
  - a. Jacob Durst, Esq., at jacob.durst@ag.tn.gov;
5. Smart Approaches to Marijuana, by email to
  - a. Patrick F. Philbin, Esq., at pphilbin@torridonlaw.com;
  - b. John M. McNichols, Esq., at jmcnichols@torridonlaw.com;
  - c. Chase T. Harrington, Esq., at charrington@torridonlaw.com;
6. The States of Nebraska, Idaho, Indiana, and Louisiana, by email to
  - a. Zachary Pohlman, Esq., at zachary.pohlman@nebraska.gov;

- b. Michael Zarian, Esq., at Michael.Zarian@ag.idaho.gov;
  - c. Blake Lanning, Esq., at Blake.Lanning@atg.in.gov;
  - d. Zachary Faircloth, Esq., at FairclothZ@ag.louisiana.gov;
7. DUID Victim Voices, by email to
- a. Ed Wood, at edwood27@icloud.com;
  - b. Patrick D. Kenneally, at patrick.kenneally@burkegroup.law
  - c. Connor Mighell, at connor.mighell@burkegroup.law
8. Kenneth Finn, M.D., by email to
- a. Patrick D. Kenneally, at patrick.kenneally@burkegroup.law
  - b. Connor Mighell, at connor.mighell@burkegroup.law
9. Phillip A. Drum, PharmD, *pro se*, by email at phillipdrum@comcast.net

June 23, 2026

Patrick F. Philbin  
Patrick F. Philbin

**Exhibit A**  
to SAM Statement of Availability

UNITED STATES DEPARTMENT OF JUSTICE  
DRUG ENFORCEMENT ADMINISTRATION

In the Matter of

**Scheduling of Controlled Substances:  
Proposed Rescheduling of Marijuana**

**DEA Docket No. 1362  
Hearing Docket No. 24-44**

CHIEF ADMINISTRATIVE LAW JUDGE

JOHN J. MULROONEY, II

**DECLARATION OF LULI R. AKINFIRESOYE**

I, Luli R. Akinfiresoye, under penalty of perjury, declare and state as follows:

1. I am an employee of the U.S. Drug Enforcement Administration (DEA) and have been so employed since December 2015. I currently serve as a pharmacologist with the Drug and Chemical Evaluation Section (DOE) of the DEA's Diversion Control Division and have held this role since 2017. From December 2015 until March 2017, I served in the capacity of a contract Pharmacologist with DEA.

2. I received a Bachelor of Science in biochemistry from Temple University in 2007. I then received a Master of Arts in Clinical Chemistry from the University of Scranton in 2009. Finally, I earned my Ph.D. in Pharmacology from Howard University College of Medicine in 2013. Pharmacology can be defined as the science of drugs and it deals with history, source, physical and chemical properties, compounding, biochemical and physiological effects, mechanism of action, absorption, distribution, biotransformation and excretion, and therapeutic and other uses of drugs.

3. I completed a Postdoctoral Fellowship at Georgetown University Medical Center from 2013 to 2015, where I studied the molecular mechanisms of neuronal hyperexcitability following alcohol withdrawal.

4. I served as a Scientific Research Program Manager at Howard University College of Medicine from April to December 2015, where I collaborated with other scientists to investigate the neurobiological substrates of mental disorders including depression.

5. I have served as an Assistant Professor (Adjunct) at Northern Virginia Community College, Medical Education Campus since 2011, where I teach pharmacology. I have also authored or co-authored at least 17 scientific publications.

6. I have testified in United States Federal District Court, where I was recognized as an expert in pharmacology.

7. My attached CV includes additional details regarding my education, training, research, publications, and professional experience.

8. I have been employed by the Drug Enforcement Administration since December 2015. In my capacity as a pharmacologist, I evaluate drugs of abuse and other substances for regulatory control under the Federal Controlled Substances Act (CSA). My primary duties include collecting and evaluating scientific and other relevant information to prepare scientific technical reports in support of scheduling drugs under the CSA. I provide scientific expertise on pharmacology and related biological sciences as applied to the implementation of the CSA.

9. I am aware that on May 21, 2024, DOJ through the DEA issued a Notice of Proposed Rulemaking (NPRM) in the Federal Register proposing to transfer marijuana from schedule I of the Controlled Substances Act (CSA) to schedule III of the CSA.

10. I am aware that the Department of Health and Human Services (HHS) submitted an 8-Factor Analysis (8FA) to the DEA in support of the proposed scheduling change. I have reviewed the HHS 8FA and am familiar with its content and scheduling recommendation. This document was provided to DEA pursuant to 21 U.S.C. § 811(b) and it contained the medical and scientific findings of HHS.

11. I am also aware that the NPRM seeks DEA's current state of knowledge regarding marijuana, including data, studies, and other information on the following topics: (1) marijuana's actual or relative potential for abuse, including DEA's collection of data regarding seizures of marijuana by law enforcement, additional data related to cannabis-related emergency department visits, updated epidemiological survey data since 2022, and additional data on diversion from State programs and DEA-registered manufacturers; (2) scientific evidence of marijuana's pharmacological effects; (3) the state of current scientific knowledge regarding marijuana, specifically including additional data on other marijuana constituents, routes of administration of marijuana, and the impact on delta-9-tetrahydrocannabinol ( $\Delta$ 9-THC) potency; (4) marijuana's history and current pattern of abuse; (5) the scope, duration, and significance of abuse; (6) what, if any, risk there is to the public health, including additional data on public safety risks, risks from acute and chronic marijuana use via oral and inhaled administration routes, and the impact of  $\Delta$ 9-THC potency; and (7) marijuana's psychic or physiological dependence liability.

12. Pursuant to my role in the DOE, and in the course of my official duties, I have conducted a search of the published scientific literature on marijuana related to abuse potential, pharmacology, chemistry, and medical use. I have also reviewed, analyzed, and interpreted the

data from a number of national and other databases regarding the drug distribution, drug diversion, drug abuse, mortality, and toxic exposures involving marijuana.

13. The attached document titled “Marijuana Scientific Knowledge” serves to provide the information sought by the NPRM. My colleagues and I in DOE maintain an ongoing review of the relevant scientific literature and this document reflects DEA’s current scientific knowledge regarding marijuana.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on December 23, 2024, in Arlington, Virginia.

LULI  
AKINFIRESO  
YE

Digitally signed by  
LULI AKINFIRESOYE  
Date: 2024.12.23  
10:50:41 -05'00'

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Luli R. Akinfiresoye

### **ATTACHED DOCUMENTS**

1. Curriculum Vitae for Luli Akinfiresoye (6 pages)
2. “Marijuana Scientific Knowledge” (96 pages)

**Luli Akinfiresoye, Ph.D.**

**Position: Pharmacologist (DEA)**

**PROFILE:**

- Dr. Akinfiresoye currently serves as a pharmacologist with the Diversion Control Division of the Drug Enforcement Administration.
- Dr. Akinfiresoye evaluates drugs of abuse and other substances for regulatory control under the Federal Controlled Substances Act. Provides scientific support to federal, state, and local public health and law enforcement officials related to these substances. Evaluates relevant scientific and drug abuse data on drugs of abuse and provides appropriate advice pertaining to DEA policy and regulation, legislative, and drug scheduling actions related to these drugs.
- Dr. Akinfiresoye, a senior scientific expert in drug addiction and abuse. Participates in international meetings, federal policy exchange, and scientific committees focused on drug control.
- Dr. Akinfiresoye has extensive experience in federal governmental contracts and administration.
- Dr. Akinfiresoye has published in peer-reviewed scientific journals and served as a scientific expert reviewing research grants and manuscripts.

**KEY EXPERTISE**

- Opioid and illicit substance use disorders
- Neuroscience of drug addiction and misuse
- Federal regulatory science and research administration
- US and International drug control.

**EDUCATION:**

2013- Doctor of Philosophy, Pharmacology, Howard University College of Medicine, Department of Pharmacology, Washington, DC,

2009- Master of Arts, Clinical Chemistry, University of Scranton, Department of Chemistry Scranton, PA,

2007- Bachelor of Science, Biochemistry, Temple University, Faculty of Arts and Sciences, Philadelphia, PA

**PROFESSIONAL EXPERIENCE**

***Pharmacologist, Drug Enforcement Administration- Diversion Control Division, Drug and Chemical Evaluation Section: December 2015 – Present***

**Key Project 1**

- Provides advisory services in pharmacology and related biological and physical sciences as applied to the implementation of the Controlled Substances Act (CSA) and recommends, after consideration and evaluation of relevant scientific and drug abuse data, appropriate DEA policy and regulatory, legislative, drug scheduling and other responses relating to the diversion, trafficking and/or abuse of drugs, chemicals and precursors.
- Collects and shares information that defends DEA's drug control policies to other government agencies, industry, scientific community, domestic drug control bodies and in court proceedings. Assist prosecutors and law enforcement personnel in criminal and regulatory investigations and court proceedings by providing scientific guidance.
- Lead and participate in bilateral data sharing meeting for 1): US-DEA- United Nation/WHO Expert Committee on Drug Dependence; 2): US-DEA – Health-Canada Working Group; 3): DEA-NIDA Data Working Group; 4): US- European Union Drugs Agency.
- Prepares relevant scientific and technical reviews and regulatory documents for drug control (more than 20 FDA-approved new drugs and non-medical addictive substances) for publication in the Federal Register.
- Serve as a mentor to junior level drug science specialists, pharmacologists, chemists, and program analyst regarding scientific and research topics of drug addiction and control.

## **Key Projects 2**

- Serves as scientific program manager to lead and coordinate DEA-pharmacological testing program. Evaluates applications, proposals, and adherence to DEA's policies and procedures for research contract applications in behavioral pharmacology (drug addiction and abuse).
- Provides technical advisement and administrative coordination for the planning, market research, drafting and execution of initial scientific and technical research proposal [RFI, RFQ or Statement of the Work (SOW) documents, etc.], for collecting data on emerging psychoactive substances including new synthetic opioids and cannabinoids.
- Serves as a certified FAC-COR II and scientific technical lead staff, creating and drafting detailed research contract/acquisition plans including project aims, testing options, responsibilities, deliverable schedules, scope, overall costs, oversight/monitoring, contingencies etc.
- Manages the scientific analysis and review of the technical and scientific data produced by research contractors.
- Conducts regular virtual or on-site in-person meetings for oversight, monitoring and evaluating the post-award status of progress with written evaluation summary and progress reports.
- Review and approves scientific findings to guide DEA's science-based drug control policy. Additionally, the research program has generated dataset that has advanced

knowledge and contributed to multiple peer-reviewed articles and presentations at prominent scientific conferences.

### **Other Projects**

- Serve as pharmacology instructor on emerging drug trends to international partners and the International Law Enforcement Academy.

*Assistant Professor (Adjunct), Northern Virginia Community College, Medical Education Campus: May 2011- present*

### **Summary of duties and responsibilities**

- Preparing and leading lectures for pharmacology and medical terminology courses to various health professional students to include pre-med, nursing, emergency responders, respiratory and radiology technology majors through an online course platform.
- Collaborating with other faculty members on curriculum design, course improvement design.
- Updating and maintain student records and grades.

*Scientific Research Program Manager, Howard University College of Medicine, Dept. of Pharmacology: April 2015- December 2015*

### **Summary of duties and responsibilities**

- As a program manager, I established successful independent innovative research on neurobehavioral diseases using several pre-clinical models focused on mood disorder (depression) and Alzheimer's disease. My research programs were extensively supported by multiple competitively independent research grants from the NIH and other foundation funds.
- Supervised, coached and mentored many junior researchers including two pre-doctoral, three post-doctoral trainee fellows and two technicians, and trained graduate level students in medical, dentistry, and pharmacy schools.
- Collaborated with scientists in the translation of innovative neuroscience research into pre-clinical study design with a major focus on neurobehavioral pharmacology.
- Participated in multi- and transdisciplinary collaborations and in national and professional associations and conferences.
- Planned and monitored team activities as it relates to research project plans and analyzing scientific research gaps.

*Postdoctoral Fellow, Georgetown University Medical Center, Dept. of Pediatrics: August 2013- March 2015*

Summary of duties and responsibilities

- Evaluated the molecular mechanisms underlying the enhancement of P-type Calcium Channel (PTCC) current density in inferior colliculi neurons following alcohol withdrawal.
- Evaluated the extent to which PTCCs contribute to alcohol withdrawal seizure (AWS) generation. This work involved probing the role of R-type calcium channel in epileptogenesis occurrence in neonates exposed to alcohol. Several techniques were used to elucidate the mechanism of action of phosphorylation in the alcohol withdrawal seizure in vivo pharmacological approach combined with molecular genetics and short interference RNA (siRNA) strategies to determine the extent to which blockade of P-type Ca<sup>2+</sup> channels using  $\omega$ -agatoxin TK and anti-CaV2.1a1 subunits siRNA within rat IC suppresses AWS.
- Published research findings in original articles in peer- reviewed journals.
- Developed novel scientific initiatives and stayed current in area of novel research direction through reviews of the relevant literature; educate self about the latest methods and evidence related to innovative research.

*Associate Scientist Quality control, Teva Pharmaceuticals: April 2007 – Oct 2007*

Summary of duties and responsibilities

- Performed analytical testing of finished dosage pharmaceutical products following analytical methodology.
- Assisted with data audits of standards, reagents, and other analytical instrumentation
- Assisted in ensuring testing was in adherence to schedules cGMP and cGLP requirements

**PUBLICATIONS:**

1. Wiley, J. L., Marusich, J. A., Blough, B. E., Namjoshi, O., Brackeen, M., **Akinfiresoye, L. R.**, Walker, T. D., Prioleau, C., Barrus, D. G., & Gamage, T. F. Evaluation of cannabimimetic effects of selected minor cannabinoids and Terpenoids in mice. *Progress in neuro-psychopharmacology & biological psychiatry*. 2024.
2. Patel, M., Zheng, X., **Akinfiresoye, L. R.**, Prioleau, C., Walker, T. D., Glass, M., & Marusich, J. A. (2024). Pharmacological evaluation of new generation OXIZID synthetic cannabinoid receptor agonists. *European journal of pharmacology*. 2024.
3. **Akinfiresoye LR**, Newton J, Suman S, Datta K, N'Gouemo P. Targeted Inhibition of Upregulated Sodium-Calcium Exchanger in Rat Inferior Colliculus Suppresses Alcohol Withdrawal Seizures. *Mol Neurobiology*. 2023.
4. Varshneya NB, Walentiny DM, Stevens DL, Walker TD, **Akinfiresoye LR**, Beardsley PM. Structurally diverse fentanyl analogs yield differential locomotor activities. *Neuropharmacology*. 2024.

- Pharmacol Biochem Behav. 2023.
5. Marusich JA, Gamage TF, Zhang Y, **Akinfiresoye LR**, Wiley JL. In vitro and in vivo pharmacology of nine novel synthetic cannabinoid receptor agonists. *Pharmacol Biochem Behav.* 2022.
  6. Varshneya NB, Walentiny DM, Moisa LT, Walker TD, **Akinfiresoye LR**, Beardsley PM. Fentanyl-related substances elicit antinociception and hyperlocomotion in mice via opioid receptors. *Pharmacol Biochem Behav.* 2021.
  7. Newton J, **Akinfiresoye LR**, N'Gouemo P. Inhibition of the Sodium Calcium Exchanger Suppresses Alcohol Withdrawal-Induced Seizure Susceptibility. *Brain Sci* 2021.
  8. Varshneya NB, Walentiny DM, Moisa LT, Walker TD, **Akinfiresoye LR**, Beardsley PM. Opioid-like antinociceptive and locomotor effects of emerging fentanyl-related substances. *Neuropharmacology* 2019.
  9. Newton J, Suman S, **Akinfiresoye LR**, Datta K, Lovinger DM, N'Gouemo P. Alcohol withdrawal upregulates mRNA encoding for Ca<sub>v</sub> 2.1- $\alpha$ 1 subunit in the rat inferior colliculus. *Alcohol* 2018.
  10. **Akinfiresoye LR**, Miranda C, Lovinger DM, N'Gouemo P. Alcohol Withdrawal Increases Protein Kinase A Activity in the Rat Inferior Colliculus. *Alcohol Clin Exp Res.* 2016.
  11. P. N'Gouemo, **L. Akinfiresoye**, J. Allard, D. Lovinger. Alcohol withdrawal-induced seizure susceptibility is associated with an upregulation of CaV1.3 channels in the rat inferior colliculus. *The International Journal of Neuropsychopharmacology*, 2015.
  12. Yousef Tizabi; Laura L. Hurley; Zakiya Qualls; **Luli Akinfiresoye**. Relevance of the Anti-Inflammatory Properties of Curcumin in Neurodegenerative Diseases and Depression. *Molecules* 2014.
  13. Hurley LL, **Akinfiresoye L**, Kalejaiye O, Tizabi Y. Antidepressant Effects of Resveratrol in an Animal Model of Depression. *Brain Behavior Research*, 2014.
  14. **Luli Akinfiresoye** and Yousef Tizabi. Antidepressant Effects of AMPA and Ketamine Combination: Role of Hippocampal BDNF, Synapsin and mTOR. *Psychopharmacology*, 2013.
  15. Hurley LL, **Akinfiresoye L**, Nwulia E, Kamiya A, Kulkarni AA, Tizabi Y. Antidepressant effect of curcumin in WKY rat model of depression is associated with an increase in hippocampal BDNF. *Behav Brain Research*, 2012.
  16. Tizabi Y, Bhatti BH, Manaye KF, Das JR, **Akinfiresoye L**. Antidepressant-like effects of low ketamine dose is associated with increased hippocampal AMPA/NMDA receptor density in female Wistar-Kyoto rats. *Neuroscience*, 2012.
  17. Gabriel A. Agbor, **Luli Akinfiresoye**, Julianne Sortino, Robert Johnson, Joe A. Winsor

Piper species protect cardiac, hepatic and renal antioxidant status of atherogenic diet fed hamsters. Food Chemistry, 2012.

### **SELECTED US AND INTERNATIONAL MEETINGS.**

- Workshop Presenter: Are we in the post-fentanyl era” Society of Forensic Toxicologist, October 2024.
- Emerging Trends in Illicit Drug and Production Workshop, The International Law Enforcement Academy, Rabat, Morocco, September 2024.
- Poster Presentation at The International Society for the Study of Drug Policy, June 2024.
- Emerging Trends in Illicit Drug and Production Workshop, Bosnia and Herzegovina, April 2024.
- Emerging Trends in Illicit Drug and Production Workshop, The International Law Enforcement Academy, Thailand, Bangkok, May 2023.
- Early Warning Systems are Critical to Drug Control Strategies to Protect Public Health and Safety. Lisbon Addictions, Portugal, Lisbon, November 2022.

**U.S. Department of Justice  
Drug Enforcement Administration**



**Marijuana  
Scientific Data Review as it Relates to the Controlled Substances Act**

**Prepared by**

**Drug and Chemical Evaluation Section,  
Diversion Control Division, Drug Enforcement Administration**

**Washington, DC 20537**

## I. Introduction

Marijuana (*Cannabis sativa* L.) is the most used illicit drug in the United States. According to the World Health Organization (WHO), cannabis is globally the most widely cultivated, trafficked, and abused illicit drug.<sup>1</sup> The major psychoactive constituent in cannabis (marijuana) is delta-9-tetrahydrocannabinol (delta-9-THC). WHO notes that cannabis use is associated with acute and chronic health effects. Acutely, cannabis impairs a wide range of psychomotor skills, including motor coordination, divided attention, and complex task performance. Even small doses of delta-9-THC, as little as 20 mg, from cannabis smoking can impair human performance on machinery for up to 24 hours. This impairment also increases the risk of motor vehicle accidents among drivers under the influence of cannabis.<sup>2</sup> Furthermore, chronic use of cannabis can impair cognitive functioning, affecting the organization and integration of complex information, as well as impair attention and memory processes. Prolonged use may lead to greater and potentially irreversible impairment, which could impact daily life functions. Chronic users may develop a dependence syndrome characterized by a loss of control over cannabis use. Long-term cannabis smoking can also cause epithelial injury to the trachea and major bronchi, leading to airway inflammation, impaired pulmonary defenses, and a higher prevalence of chronic and acute bronchitis symptoms. Additionally, cannabis use can exacerbate schizophrenia in affected individuals. Moreover, the use of cannabis during pregnancy is associated with impaired fetal development and reduced birth weight.<sup>3</sup>

State programs have legalized cannabis for a variety of medical conditions, such as (but not limited to) chronic pain, glaucoma, anxiety, and as an antiemetic in the treatment of chemotherapy-induced nausea. However, according to the U.S. Food and Drug Administration (FDA),<sup>4</sup> the use of unapproved cannabis and/or unapproved cannabis-derived products to treat a number of medical conditions including, AIDS wasting, epilepsy, neuropathic pain, spasticity associated with multiple sclerosis, and cancer and chemotherapy-induced nausea is of great concern. FDA notes that its drug approval process involves a careful evaluation for safety, efficacy, quality, and monitoring once approved for marketing. The use of unapproved cannabis and cannabis-derived products can have unpredictable and unintended consequences, including serious safety risks. Furthermore, there has been no FDA review of data from rigorous clinical trials to support safety and efficacy of the unapproved products for the various therapeutic uses for which they are being used.

This document contains DEA's gathered and updated data, including scientific, public health, and law enforcement information, on marijuana. These data are presented according to the eight factors for consideration under 21 U.S.C. 811(c). This data includes law enforcement data, pharmacological effects, health risks such as the development of cannabis use disorder

<sup>1</sup>[Alcohol, Drugs and Addictive Behaviours](#)

<sup>2</sup> *Id*

<sup>3</sup> *Id*

<sup>4</sup> [FDA and Cannabis: Research and Drug Approval Process | FDA](#)

(CUD) and psychosis, as well as public health survey data. This document does not attempt to comprehensively summarize or recapitulate HHS' 2023 analysis, which is available in the rulemaking docket in its entirety. This review summarizes DEA's current scientific knowledge of marijuana as it relates to the Controlled Substances Act (CSA).

## **II. Eight Factors Determinative of Control**

### **Factor 1. The Drug's Actual or Relative Potential for Abuse**

#### **A. Indicators of Abuse Potential**

Data from national databases on the actual abuse of marijuana show that a large number of individuals use marijuana. According to recent data from the 2023 National Survey on Drug Use and Health (NSDUH) of the Substance Abuse and Mental Health Services Administration (SAMHSA), marijuana is the most used illicit drug. Among Americans aged 12 years and older, an estimated 21.8% (or 61.8 million people) used marijuana in the past year; smoking (77.0% or 47.6 million people) was the most common mode of use, and 38.3% (or 23.7 million people) vaped marijuana during the survey period. Additionally, the 2023 NSDUH report noted that 3.5 million Americans (aged 12 or older) initiated marijuana use in any way in the past year, with more than half (54.5% or 1.9 million people) of this group initiating marijuana use before the age of 21.

Furthermore, data from the 2023 Monitoring the Future (MTF)<sup>5</sup> survey—which tracked drug use trends among 8th, 10th, and 12th grade students nationwide—showed that 36.5% of 12th grade students reported lifetime marijuana use. The prevalence of lifetime marijuana use was 11.5% and 22.5% in 8th and 10th graders, respectively. Additionally, the prevalence of lifetime marijuana vaping was 8.4%, 16.8%, and 25.5% in 8th graders, 10th graders, and 12th grade students, respectively, indicating the vaping was a popular mode of use. Annual prevalence of marijuana use among all students surveyed was 8.3%, 17.8%, and 29.0% in 8th grade students, 10th grade students, and 12th grade students. The prevalence of vaping marijuana annually was 6.5%, 13.1%, and 19.6% in 8th graders, 10th graders, and 12th graders, respectively. Thirty-day prevalence of marijuana use was reported as 4.7%, 10.3%, and 18.4% of 8th graders, 10th graders, and 12th graders, respectively. The percentage of students reporting thirty-day prevalence of vaping marijuana was 4.2% of 8th grade respondents, 8.5% of 10th grade respondents, and 13.7% of 12th grade respondents. MTF data also show that marijuana remains one of the most consistently available drugs, with 73% of 12th grade students surveyed in 2023 reported that it would be fairly or very easy to access. Young adults (ages 19 to 30), especially individuals aged 23–24, had a higher prevalence of use than high school respondents.

<sup>5</sup> Miech, R. A., Johnston, L. D., Patrick, M. E., O'Malley, P. M. (2024). Monitoring the Future national survey results on drug use, 1975–2023: Overview and detailed results for secondary school students (PDF). Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan.

According to 2023 MTF data<sup>6</sup>, cannabis use in the past 12 months was reported by 42.4% of young adults and individuals aged 23–24 had the highest prevalence (45.6%). Similarly, cannabis use in the past 30-days was reported by 28.7 % of young adults and highest levels of use was reported for ages 23–24 at 32.2%. Daily cannabis use, characterized as consumption on 20 or more occasions within the past 30-days, was reported by 10.4% of young adults.

According to data from the Treatment Episode Data Set (TEDS) annual report, among admissions to substance use treatment services in 2021, 10.2% of admissions were for marijuana/hashish use.<sup>7</sup> The rates per 100,000 population of admissions to substance use treatment services was 47 for marijuana/hashish use. The percentage of discharge from substance use treatment was 9.7% (n =116,785) for marijuana/hashish use and the rate of discharge was 42 per 100,000 population. In addition, TEDS 2021 data show that the counts of marijuana/hashish admissions to substance use treatment services accounted for 55.9% of admissions where marijuana/hashish was listed as the primary substance in ten states (New York, California, Georgia, North Carolina, New Jersey, Texas, Minnesota, South Carolina, Florida, and Connecticut) and was the primary factor for admission in 10.2% of non-private substance abuse treatment facility admissions.<sup>8</sup> The 2020 TEDS annual report indicated that marijuana use was the primary factor in 9.8% of non-private substance abuse treatment facility admissions overall. Interestingly, the 2020 report indicated that 70.8% of admissions of those aged 15 to 17 years were for primary marijuana/hashish use.<sup>9</sup> In fact, in the 2020 report, marijuana/hashish was the primary substance reported for treatment admission for those aged 12 to 24 years. Eighty-seven percent of those admitted for marijuana/hashish abuse received ambulatory treatment services, according to the 2020 annual report. Concordantly, data from SAMHSA’s Drug Abuse Warning Network (DAWN), which provides nationally representative data on key findings from drug-related emergency department visits, reported that cannabis was one of the three leading causes

<sup>6</sup> Patrick, M. E., Miech, R. A., Johnston, L. D., & O’Malley, P. M. (2024). Monitoring the Future Panel Study annual report: National data on substance use among adults ages 19 to 65, 1976–2023 (PDF). Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan.

<sup>7</sup> [Treatment Episode Data Set \(TEDS\) 2021: Admissions to and Discharges from Substance Use Treatment Services Reported by Single State Agencies](#)

<sup>8</sup> [https://www.samhsa.gov/data/sites/default/files/reports/rpt35314/2019\\_TEDS\\_3-1-22.pdf](https://www.samhsa.gov/data/sites/default/files/reports/rpt35314/2019_TEDS_3-1-22.pdf); Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2019. Admissions to and Discharges from Publicly Funded Substance Use Treatment. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2021.

<sup>9</sup> [https://www.samhsa.gov/data/sites/default/files/reports/rpt38665/2020\\_TEDS%20Annual%20Report-508%20compliant\\_1182023\\_FINAL.pdf](https://www.samhsa.gov/data/sites/default/files/reports/rpt38665/2020_TEDS%20Annual%20Report-508%20compliant_1182023_FINAL.pdf); Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2020. Admissions to and Discharges from Publicly Funded Substance Use Treatment Facilities. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2022.

of drug-related emergency department visits (11.9%) in 2022, a slight increase from the previous year's (2021) rate of 11.19%.<sup>10</sup>

Individuals have reported that a primary source for marijuana is through other individuals with access to state medical and recreational programs. In a study of survey data, Terry-McElrath and colleagues (2020) found that approximately 73% of 35-year-old and 64% of 55-year-old marijuana users in the United States reported using marijuana intended for someone else. Additional studies have been published from different perspectives in the scientific literature that analyze marijuana diversion and concluded that individuals are using someone else's marijuana sourced under a state program (Ne'eman-Haviv and Rozman, 2023; Nussbaum et al., 2015; Olsavasky et al., 2024; Reed et al., 2020; Sznitman et al., 2020; Thurstone et al., 2013; Van Gerpen et al., 2015).

Diversion of substances from legitimate channels has been commonly used as an indication that the substance has a potential for abuse. DEA has located no national statistics on dispensary thefts; however, a Google search for news articles related to burglaries at retail marijuana shops show that cannabis products have been stolen from these businesses and provides additional information. For example, the Los Angeles Police Department reported that from January to September 2023, there were 151 reported crimes at medical and recreational cannabis dispensaries.<sup>11</sup> Of those, 92 were burglary and attempted burglary incidents and 20 were robbery and attempted robbery. Cannabis products and cash were among the items taken. In 2020, one of Colorado's largest dispensary chains experienced 15 break-ins.<sup>12</sup> In Washington, cannabis businesses reported 67 armed robberies in just the first few months of 2022.<sup>13</sup> In addition, in 2024, the King County Sheriff's Office reported an "unknown amount" of cannabis products were stolen.<sup>14</sup>

The Food and Drug Administration (FDA) has not evaluated or approved a New Drug application (NDA) for marijuana for any therapeutic indication. However, as mentioned previously, several states and the District of Columbia have passed laws allowing for individuals to use marijuana for medical use under certain circumstances; minimal data is available to determine the number of individuals using marijuana under these state laws. Nonetheless, according to 2023 NSDUH data, marijuana remains the most used illicit drug: 61.8 million

<sup>10</sup> <https://store.samhsa.gov/sites/default/files/pep23-07-03-001.pdf>; Substance Abuse and Mental Health Services Administration. (2023). Drug Abuse Warning Network: Findings from Drug-Related Emergency Department Visits, 2022 (HHS Publication No. PEP23-07-03-001). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data/>.

<sup>11</sup> Accessed May 29, 2024; <https://www.kcrw.com/news/shows/greater-la/weed-gaza-hammer/cannabis-robberies>

<sup>12</sup> Accessed May 30, 2024; <https://www.deepsentinel.com/blogs/cannabis/how-common-is-dispensary-theft/>

<sup>13</sup> id.

<sup>14</sup> Accessed May 30, 2024; <https://komonews.com/news/local/burien-pot-shop-burglary-crime-crisis-washington-seattle-12-twelve-suspects-caught-camera-surveillance-video-cannabis-marijuana-stolen-theft-vehicles-search-ambaum-blvd-south-investigation>

Americans (aged 12 or older) reported using marijuana in the past year, and 43.6 million Americans (aged 12 or older) reported using marijuana in the past month, 5.6% (or 15.8 million people) of whom vaped marijuana in that past month (SAMHSA, 2024). The 2023 NSDUH also reported that 3.5 million Americans (aged 12 or older) initiated marijuana use in any way in the past year, with more than half (54.5% or 1.9 million people) of this group initiating marijuana use in the past year before the age of 21.<sup>15</sup> Overall, these survey data indicate that many individuals are using marijuana.

## **B. Abuse Liability Studies**

Preclinical measures of a drug's subjective and rewarding effects can provide an accurate prediction of human abuse liability. Preclinical testing using drug discrimination, self-administration, and conditioned place preference methods are thought to provide information regarding the subjective and rewarding effects of a drug, respectively. Such preclinical data is commonly used to predict the abuse liability of a given test drug in humans.

Preclinical studies using marijuana and constituents of marijuana such as delta-9-THC were reviewed to evaluate the abuse liability of marijuana. While marijuana is related in its action to synthetic dronabinol, the ingredient in Marinol® and Syndros®, marijuana is a more complex and diverse substance than synthetic dronabinol, as further discussed in Factors 2 and 3. Moreover, marijuana is self-administered in a wide variety of dosage forms and dosages.

### ***Drug Discrimination***

Drug discrimination is one of the most selective animal assessment models used to identify whether the test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by a reference drug with known abuse potential and related pharmacological properties. In the drug discrimination paradigm, if a test drug or substance has discriminative stimulus effects similar to a known drug of abuse, this test drug or substance is highly likely to produce pharmacological and subjective effects in humans similar to the known drug of abuse and would be similarly abused by humans (Balster and Bigelow, 2003). Delta-9-THC, the primary compound in marijuana responsible for its abuse potential, is used extensively as the training drug in animal drug discrimination studies to demonstrate whether a novel compound produces cannabinoid effects. Studies have shown that, in addition to humans (Lile et al., 2009; 2011; 2012), animals including monkeys (McMahon, 2009) and rodents (McMahon et al., 2008) can discriminate cannabinoids from other drugs or placebo.

### ***Self-Administration***

Self-administration studies are used to identify the ability of a drug to be a positive reinforcer (i.e., produce a rewarding effect) and provides a means for studying abuse potential under controlled laboratory conditions. Results from animal drug self-administration studies

<sup>15</sup> [https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021\\_NNR\\_figure\\_slides.pdf](https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021_NNR_figure_slides.pdf)

have revealed that drugs can serve as positive reinforcers and highlight a positive correlation between humans and animals regarding drugs that are self-administered. For example, drugs that are abused by humans generally maintain responding in animals (Panlilio and Goldberg, 2007; Lynch et al., 2010). In the context of marijuana, it is well-known that marijuana elicits subjective reports of pleasurable effects in humans.

Data from a study conducted by Justinova et al. (2003) showed delta-9-THC at doses of 2, 4, and 8 ug/kg/injection maintained significant high numbers of self-administered injections per sessions and 2 and 4 ug/kg/injection produced higher rates of responding when compared to vehicle (i.e., no drug) in monkeys with no prior history of exposures to other drugs. The authors concluded that delta-9-THC acts as an effective reinforcer of drug-seeking behavior in animals with no prior exposure of other drugs; an indication that self-administration of delta-9-THC models human marijuana abuse (Justinova et al., 2003).

### ***Conditioned Place Preference (CPP)***

CPP is another behavioral method in which a subject learns to prefer one place more than others, because the preferred location has been paired previously with rewarding events. In this procedure, a test drug is administered to an animal and is paired with a distinct environment, while vehicle (i.e., no drug) administration is paired with a separate, distinct environment. Increases in time spent on the test drug-paired side (i.e., preference) indicates conditioned rewarding effects of the test drug and decreases in time spent on the drug-paired side (i.e., more time on the vehicle side) indicates conditioned aversive effects of the drug (Prus et al., 2009).

There are limited studies using CPP with cannabis. A study evaluated CPP in male and female Sprague-Dawley rats that were exposed to delta-9-THC or vehicle (propylene glycol) vapor at a low dose of 5 puffs of 100 mg/ml, medium dose of 5 puffs of 200 mg/ml, or high dose of 10 puffs of 200 mg/ml. Results showed that delta-9-THC vapor elicited CPP in an exposure dependent manner and some sex differences were seen. Data showed that low delta-9-THC vapor exposure did not produce CPP in males or females. Medium delta-9-THC vapor produced CPP in males, but not in females. High delta-9-THC vapor exposure produced CPP in both male and female rats. Delta-9-THC vapor re-exposure (i.e., drug-prime) after extinction did not result in reinstatement of CPP in either sex (Moore et al., 2024).

### **C. Forensic Laboratory Data**

Data from forensic databases can be used as an indicator of illicit activity with drugs and abuse<sup>16</sup> within the United States. The National Forensic Laboratory Information System

<sup>16</sup> While law enforcement data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011.

(NFLIS) Drug<sup>17</sup> database collects scientifically verified data on drug items and cases submitted to and analyzed by participating federal, state, and local forensic drug laboratories. According to NFLIS-Drug, cannabis/THC has been reported in all 50 states, as well as the District of Columbia, Guam, American Samoa, U.S. Virgin Islands, and Puerto Rico. State and local forensic drug laboratories reported cannabis/THC more frequently than any other reported drug each year from 2001 through 2016. In 2017, cannabis/THC became the second most frequently reported drug (the first being methamphetamine) to NFLIS-Drug by state and local forensic drug laboratories, accounting for 21.76% (344,167) of all drug reports that year. Cannabis/THC remained the second most frequently reported drug until 2022 when it became the fourth most frequently reported drug (behind methamphetamine, cocaine, and fentanyl) and accounted for 12.41% (146,631) of all drug reports that year. It is estimated that there were over 2 million exhibits of cannabis/THC submitted to and analyzed by state and local forensic drug laboratories between January 2016 and December 2023 (see Factor 5, Table 2).

The U.S. Customs and Border Protection Drug Seizures reported seizing approximately 175,000 pounds of marijuana in Fiscal Year (FY) 2024, which accounted for the largest drug seizure weight when compared to other drug types. In FY 2023 and 2022, marijuana drug seizure weight was about 150,000 pounds and 155,000 pounds, respectively.<sup>18</sup>

## **Factor 2: Scientific Evidence of its Pharmacological Effects, if Known**

A scientific evaluation of marijuana's pharmacological effects, based on the effects of its primary psychoactive component, delta-9-THC, is presented below.

### **Neurochemistry**

Marijuana contains numerous constituents, such as cannabinoids, that have a variety of pharmacological actions. Different marijuana samples derived from various cultivated strains (also referred to as chemovars) may differ in their chemical constituent concentrations, including delta-9-THC and other cannabinoids. Therefore, marijuana products from different strains may have different biological and pharmacological effects. The chemical constituents of marijuana are discussed further in Factor 3.

The primary sites of action for cannabinoids, including exogenous cannabinoids like delta-9-THC, are at the cannabinoid receptors. These cannabinoid receptors are part of the endocannabinoid system. The endocannabinoid system regulates and controls many of the most critical physiological functions and pathological conditions in the body (Zou and Kumar, 2018).

<sup>17</sup> NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of the Nation's estimated 1.2 million annual drug cases. NFLIS-Drug includes drug identification results from completed analyses only. While NFLIS-Drug data are not direct evidence of abuse, they can lead to an inference that a drug has been diverted and/or abused. See 76 FR 77330, 77332, Dec. 12, 2011.

<sup>18</sup> [Drug Seizure Statistics | U.S. Customs and Border Protection](#)

Two cannabinoid receptors, CB1 and CB2, have been identified and characterized as seven transmembrane domain G-protein-coupled receptors (Battista et al., 2012; Piomelli, 2005). Activation of these inhibitory G-protein-coupled receptors inhibits adenylate cyclase activity, which prevents the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which decreases cAMP levels. CB1 receptor activation also results in the inhibition of N- and P/Q-type calcium channels and activates inwardly rectifying potassium channels (Zou and Kumar, 2018; Mackie et al., 1995; Twitchell et al., 1997).

Cannabinoid receptors are expressed in high density in areas of the brain that are involved in executive function and memory. These receptors are involved in the regulation of brain development, memory and cognition, movement coordination, pain regulation, immune function, appetite, and motivational reward (Zou and Kumar, 2018). CB1 receptors are primarily found in the central nervous system (CNS) and are located mainly in the basal ganglia, hippocampus, and cerebellum of the brain (Howlett et al., 2004). CB1 receptors are not limited to the CNS; they are also located in peripheral tissues and the immune system (De Petrocellis and Di Marzo, 2009), but the concentration of CB1 receptors in these areas is considerably lower than in the CNS (Herkenham et al., 1990; 1992). CB2 receptors are found primarily in the immune system, predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). CB2 receptors are also found in the CNS, predominantly in the cerebellum and hippocampus (Gong et al., 2006).

Two endogenous ligands to the cannabinoid receptors, anandamide and arachidonyl glycerol (2-AG), were identified in 1992 (Devane et al., 1992) and 1995 (Mechoulam et al., 1995), respectively. These endogenous ligands are present in both the CNS and in the periphery (Zou and Kumar, 2018). Delta-9-THC and cannabidiol (CBD) are two of the major cannabinoids in marijuana. Delta-9-THC has affinity for both CB1 and CB2 receptors and acts as a partial agonist at CB1 receptors and a weak agonist at CB2 receptors. Activation of CB1 receptors mediates psychotropic effects of cannabinoids and is responsible for the abuse potential of marijuana, whereas CBD has low affinity for both CB1 and CB2 receptors (Mackie, 2006; Thomas et al., 2007).

### **Brain Structure and Function**

Marijuana exposure during neurodevelopment has the potential to alter the endocannabinoid system. Animal studies demonstrate that marijuana's constituent (i.e., delta-9-THC) directly impacts brain development via activation of endogenous endocannabinoid systems. Delta-9-THC binds to endocannabinoid receptors. Marijuana-induced activation of the endocannabinoid system causes alterations in the release of neurotransmitters and the modulation of brain plasticity in neural pathways that underlie cognition, motivation, and behavior regulation (De Genna et al., 2022). Data from preclinical studies demonstrate that in regions of the brain associated with cognition and behavior, cannabinoid receptors are highly expressed. In addition, animal studies highlight structural connectivity dysfunction and a dose-dependent relationship

for marijuana toxicity in specific brain regions (Jenkins and Khokhar, 2021; Rubino and Parolaro, 2016; Stringfield and Torregrossa, 2021). Such dysfunction and other alterations in brain morphology are associated with cognitive and behavioral abnormalities, which include impacts on critical thinking, analysis, and creativity. These are evidenced by both localized and whole brain imaging studies, which have served as valuable tools in understanding acute and chronic marijuana use and outcomes (Delvecchio et al., 2020; Fischer et al., 2014; Hirjak et al., 2022; Lorenzetti et al., 2020; Ramaekers et al., 2022; Soleimani et al., 2023).

Endocannabinoids modulate several neurodevelopmental processes that begin in the fetal brain and continue through adolescence and young adulthood (Benevenuto et al., 2022; Meyer et al., 2020). Dysregulation of this endocannabinoid neurotransmitter system may result in long-term neurodevelopmental alterations. Thus, the rising use of cannabis in adolescence and early adulthood raises concerns because brain development continues through these age periods (Burggren et al., 2019). During brain development, overall brain volume remains relatively constant with slight increase through the teenage years, and brain white matter volume increases linearly with age until adulthood. Meanwhile brain gray matter volume decreases through adolescence and continues to decline well into adulthood (Gilmore et al., 2018). These changes can be studied using magnetic resonance imaging (MRI). MRI studies examining differences in the measures of brain structure, volumes of specific brain regions, thicknesses of the cerebral cortex, and densities of brain gray matter in marijuana users and nonusers have been extensively reported in the scientific literature (Burggren et al., 2019; Scott, 2023; Nader and Sanchez, 2018; Brumback et al., 2016; Subramaniam and Yurgelun-Todd, 2020). These studies demonstrated that marijuana exposure modifies brain structure, function and cognition (Burggren et al., 2019; Scott, 2023; Nader and Sanchez, 2018; Brumback et al., 2016; Subramaniam and Yurgelun-Todd, 2020).

### **Animal Behavioral Effects**

Animal abuse potential studies (drug discrimination, self-administration, conditioned place preference [CPP]) are discussed below (these studies have also been discussed in Factor 1). Briefly, studies consistently demonstrated that delta-9-THC, the primary psychoactive component in marijuana, has a distinct drug discriminative profile. In addition, animals self-administer delta-9-THC, and delta-9-THC in low doses produces CPP.

### ***Drug Discrimination***

Drug discrimination is one of the most selective animal assessment models used to identify whether the test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by a reference drug with known abuse potential and related pharmacological properties. In the drug discrimination paradigm, if a test drug or substance has discriminative stimulus effects similar to a known drug of abuse, this test drug or substance is highly likely to produce pharmacological and subjective effects in humans similar to the known drug of abuse and would be similarly abused by humans (Balster and Bigelow, 2003).

In drug discrimination studies, animals are trained to distinguish the stimulus effects of a training drug from that of a vehicle (saline) by pressing the appropriate lever. Lever presses on the drug-designated lever produce reinforcement on days the training drug was administered. In other training sessions, saline is administered (i.e., vehicle sessions) and responses on the (alternate) saline-designated lever produce reinforcement. Once training is stable for the training drug and vehicle, animals are administered the test drug. A test drug is said to have discriminatory stimulus effects (i.e., full generalization) similar to the training drug if the animals respond to the drug-designated lever on test drug days (Solinas et al., 2006).

Delta-9-THC, the primary compound in marijuana responsible for its abuse potential, is used extensively as the training drug in animal drug discrimination studies to demonstrate whether a novel compound produces cannabinoid effects. Studies have shown that, in addition to humans (Lile et al., 2009; Lile et al., 2011), animals including monkeys (McMahon, 2009) and rodents (Gold et al., 1992; McMahon et al., 2008) can discriminate cannabinoids from other drugs or placebo. These studies have shown that the major active metabolite of delta-9-THC, 11-hydroxy-delta-9-THC, and other cannabinoids found in marijuana fully generalizes to delta-9-THC stimulus cues (Browne and Weissman, 1981). However, CBD does not substitute for delta-9-THC in rats (Vann et al., 2008). In addition, marijuana containing cannabinoids are pharmacologically specific in their discriminative stimulus effects as other class of drugs do not fully substitute for delta-9-THC (Balster and Prescott, 1992; Barrett et al., 1995; Wiley et al., 1993, 1995; Jabre et al., 2001).

### ***Self-Administration***

Self-administration studies are used to identify the ability of a drug to be a positive reinforcer (i.e., produce a rewarding effect) and provides a means for studying abuse potential under controlled laboratory conditions. Results from animal drug self-administration studies have revealed that drugs can serve as positive reinforcers and highlight a positive correlation between humans and animals regarding drugs that are self-administered. For example, drugs that are abused by humans generally maintain responding in animals (Panlilio and Goldberg, 2007; Lynch et al., 2010). In the context of marijuana, it is well-known that marijuana elicits subjective reports of pleasurable effects in human.

The traditional model of animal self-administration study entails training an animal to self-administer a drug during a short daily session, typically 1 to 3 hours. Rodents are most often used in these studies; however, dogs, cats, and nonhuman primates have also been used. The most common routes of administration are intravenous and oral, but other routes (i.e., intracerebroventricular, intracranial, inhalation, intragastric) have also been used. Generally, animal self-administration studies use the route of administration that is most similar to the route used in humans for the particular drug in question (Lynch et al., 2010). These studies can also examine the primary active constituent to evaluate the substance. For marijuana, because delta-9-THC is the primary substance that confers abuse potential to delta-9-THC's ability to induce

self-administration can serve as an indicator of the abuse potential of marijuana. Four related studies are described below.

First, data from a study conducted by Justinova et al (2003) showed delta-9-THC at doses of 2, 4, and 8 ug/kg/injection maintained significant high numbers of self-administered injections per sessions and 2 and 4ug/kg/injection produced higher rates of responding when compared to vehicle in monkeys with no prior history of exposures to other drugs. The authors concluded that delta-9-THC acts as an effective reinforcer of drug-seeking behavior in animals with no prior exposure of other drugs; an indication that self-administration of delta-9-THC provides reliable animal model of human marijuana abuse (Justinova et al, 2003).

Next, a self-administration study evaluated the possibility that CBD use might influence delta-9-THC intravenous self-administration in rodents. Accordingly, male and female Long-Evans rats were trained to self-administer delta-9-THC over a 3-week period. After that period, the rats were assessed for the effects of CBD infusion on responding for delta-9-THC at 1:1 and 1:10 dose ratios. As a positive control, the establishment of cocaine self-administration was used. Results indicated that delta-9-THC self-administration was modest and only evident in a subset of animals with no sex differences, CBD pretreatment had no effect on delta-9-THC intravenous self-administration at either CBD:delta-9-THC dose ratio. Cocaine self-administration was high and evident in the majority of animals tested, indicating that the study design was sensitive to drug reinforcement (Wakeford et al., 2017).

In another study, a model of edible delta-9-THC self-administration was developed and assessed its impact on CB1 receptor-mediated behaviors in female and male mice. Mice were given limited access to a palatable dough, which occasionally contained delta-9-THC in doses ranging from 1 to 10 mg/kg in three experimental designs lasting 9, 32, or 33 days. The authors noted that the dough was well-consumed throughout each of the experiments and across the dose range. Additionally, many mice consumed all the dough in each condition, but a significant decrease in consumption in some conditions occurred. In the 32- and 33-day experiments, delta-9-THC concentration in the dough were increased in a fade-in versus a non-fade-in approach. In a fade-in approach, 1 mg/kg (given days 8 and 10), 2 mg/kg (given days 12 and 16), 5 mg/kg (given days 18 and 22 [32-day experiment] or 18, 22, and 24 [33-day experiment]), and 10 mg/kg (given day 32 or 33) of delta-9-THC was included in the dough. In the non-fade-in approach, 5 and 10 mg/kg were included on days 24 and the last day (day 32 or 33), respectively. Dough containing no delta-9-THC was provided on the rest of the study days. Dough consumption was significantly reduced in both male and female mice on days that 5 mg/kg and 10 mg/kg delta-9-THC was incorporated into the dough in the fade-in approach, and when 10 mg/kg was included in the non-fade-in design. In the non-fade-in design, even though dough consumption of the 5 mg/kg delta-9-THC was no different to control dough, consumption trended lower the next two days in male mice. Following dough consumption, mice were assessed for home cage locomotor activity (in conjunction with the CB1 receptor antagonist SR141716A), body temperature, and analgesia. Edible delta-9-THC produced dose-dependent

decreases in locomotor activity and body temperature in both sexes, with effects more pronounced in male mice. Hypolocomotion induced by edible delta-9-THC was attenuated by SR141716A, indicating mediation by CB1 receptor activation. Edible delta-9-THC had no effect on analgesia (Smoker et al., 2019).

Lastly, a more recent study published in 2020 developed a novel method of cannabis self-administration. This study used “e-cigarette” technology to deliver discrete puffs of vaporized whole-plant cannabis extracts predominantly containing delta-9-THC or CBD (and trace amounts of other phytocannabinoids found naturally in the plant) to rodents in a response-contingent manner (Freels et al., 2020). Male Sprague-Dawley rats were trained to nose-poke for puffs of delta-9-THC, CBD, or vehicle in daily 1-hour sessions. The study measured anxiety-like behavior in the elevated plus maze after acute forced abstinence from cannabis vapor, whether vaporized cannabis maintains drug seeking in the drug-predictive context (i.e., under extinction conditions) or upon response-contingent presentation of a cannabis-paired light stimulus (i.e., cue-induced reinstatement), and hippocampal CB1 receptor binding. Results indicated that cannabis vapor reinforcement leads to strong discrimination between active and inactive phases. During self-administration sessions, delta-9-THC predominant cannabis produced significantly higher responses and higher break points relative to vehicle or CBD predominant cannabis. In addition, the number of vapor deliveries were positively correlated with plasma delta-9-THC concentrations. There was a lack of force abstinence anxiety-like behavior in either group; however, the authors note that biologically relevant concentrations of delta-9-THC and CBD were present in brain tissue 24 hours after the final session. Removal of delta-9-THC-rich reinforcement (but not CBD-rich) resulted in an increase in cue-induced cannabis-seeking behavior relative to vehicle. Lastly, results showed that self-administration of delta-9-THC-rich vapor significantly reduced CB1 receptor maximal binding site density without altering CB1 receptor binding affinity compared to vehicle. Self-administration of CBD-rich vapor did not significantly alter CB1 receptor binding site density or binding affinity (Freels et al., 2020).

### ***Conditioned Place Preference (CPP)***

CPP is another behavioral method in which a subject learns to prefer one place more than others, because the preferred location has been paired previously with rewarding events. In this procedure, a test drug is administered to an animal and is paired with a distinct environment, while vehicle (i.e., no drug) administration is paired with a separate, distinct environment. Increases in time spent on the test drug-paired side (i.e., preference) indicates conditioned rewarding effects of the test drug and decreases in time spent on the drug-paired side (i.e., more time on the vehicle side) indicates conditioned aversive effects of the drug (Prus et al., 2009).

There are limited studies using CPP with cannabis. A study evaluated CPP in male and female Sprague-Dawley rats that were exposed to delta-9-THC or vehicle (propylene glycol) vapor at a low dose of 5 puffs of 100 mg/ml, medium dose of 5 puffs of 200 mg/ml, or high dose

of 10 puffs of 200 mg/ml. Results showed that delta-9-THC vapor elicited CPP in an exposure dependent manner and some sex differences were seen. Data showed that low delta-9-THC vapor exposure did not produce CPP in males or females. Medium delta-9-THC vapor produced CPP in males, but not in females. High delta-9-THC vapor exposure produced CPP in both male and female rats. Delta-9-THC vapor re-exposure (i.e., drug-prime) after extinction did not result in reinstatement of CPP in either sex (Moore et al., 2024).

In another study, Sprague-Dawley rats received intraperitoneal injections of delta-9-THC (0.05 or 2 mg/kg), a marijuana tea extract (1.0 ml/kg of a 150 mg/ml solution consisting of dried leaves and stems of the marijuana plant), or vehicle (coconut oil). Results indicated that rats that were administered 0.05 mg/kg of delta-9-THC exhibited CPP. However, rats treated with 2.0 mg/kg of delta-9-THC exhibited negligible effect, indicative of possible aversion effect. Aversion also occurred with the marijuana tea extract. There were no observed hypomotility effects with the low dose of delta-9-THC, but the effects were seen with the marijuana tea extract. The study authors suggested that the marijuana tea extract may contain higher levels of delta-9-THC, especially given that the extract was prepared from plants grown for recreational use, and that this higher dose may have contributed to the aversion effect (Young and Chin-Quee, 2017).

### **Human Physiological and Behavioral Effects**

Several clinical, epidemiological, and case studies have been published related to marijuana's physiological and behavior effects in humans, including abuse potential. It is well established that marijuana use in humans produce subjective responses. The psychoactive effects from marijuana use are considered pleasurable and associated with drug-seeking or drug-taking (Maldonado, 2002). Data show that repeated cannabis use results in alterations in behavioral, physiological, and biochemical responses.

#### ***Subjective Effects***

Subjective effects that indicate potential for drug abuse (e.g., “drug effect”, “drug liking”, “pleasant drug effects”) and impairment (e.g., trouble with memory, difficulty with routine tasks) have been evaluated in controlled research studies in humans using acute oral and vaporized marijuana products with various concentrations of delta-9-THC. Data from human abuse potential studies show that delta-9-THC or in form of marijuana produces rewarding effect, indicative of abuse potential. Other subjective, adverse effects (e.g., “paranoia”, “anxious/nervous”, “irritable”, “unpleasant drug effect”, “sick”, “dry mouth”) are further discussed in Factor 6. Common subjective effects of marijuana include the following:

- A. Euphoria, happiness, exhilaration, increased merriment, and pleasure
- B. Sedation, relaxation, and drowsiness.
- C. Increased merriment and appetite, and even exhilaration at high doses.
- D. Nausea, tachycardia, facial flushing, dry mouth, increased appetite, and tremor.

- E. Disorganized thinking, inability to converse logically, time distortions, and short-term memory impairment.
- F. Ataxia and impaired judgment, which can impede driving ability or lead to an increase in risk-tasking behavior.
- G. Illusions, delusions, heightened imagination and hallucinations that intensify with higher doses.
- H. Emotional lability, incongruity of affect, dysphoria, agitation, paranoia, confusion, drowsiness, and panic attacks, which are more common in inexperienced or high-dosed users.

In one study by Spindle et al. (2021), participants who use cannabis infrequently (n=20, 10 females/10 males) reported a perceptible drug effect after consuming marijuana at low concentrations of delta-9-THC, tested in both oral (marijuana-containing brownies with 10 mg delta-9-THC) and vaporized (marijuana containing 5 mg delta-9-THC) routes of administration. Reports of drug-liking were higher in the lower delta-9-THC marijuana products, whereas reports of impairment were higher with increasing concentrations of delta-9-THC. The authors noted that these data are in contrast with those previously published on individuals who use marijuana products frequently (Cooper and Haney, 2014; Newmeyer et al., 2017). This suggests that infrequent users of marijuana may be more likely to experience impairment and other adverse drug effects for a longer duration and of greater magnitude relative to chronic users.

### ***Effect on Organ System***

#### *Cardiovascular System*

Marijuana products with a higher concentration of delta-9-THC acutely increase heart rate after oral (marijuana-containing brownies with 25 mg delta-9-THC) and vaporized (marijuana with 5 or 20 mg delta-9-THC) administration. Oral consumption slowly increased heart rate and peaked at hour 2 relative to baseline (peak effects on average 10 beats per minute [bpm] increase) and returned to baseline levels after 3–8 hours post ingestion. Vaporized marijuana increased heart rate rapidly after administration, and heart rate was significantly higher between hours 0–1 relative to baseline (peak effects on average ~12 bpm and 25 bpm increase for 5 mg, 25 mg delta-9-THC conditions, respectively) and returned to baseline levels for hours 1–8 (Spindle et al., 2021). Recent studies have reported cardiac risks associated with marijuana use and heavier use is associated with increased risks for adverse cardiac outcomes (Bhaji et al., 2023; Jeffers et al., 2024; Mondal et al., 2024; Subramaniam et al., 2019).

Cannabis use is associated with adverse cardiovascular outcomes, with heavier use (more days per month) associated with higher odds of adverse effects (Jeffers et al., 2024). The American Heart Association provided a scientific statement as to marijuana and cardiovascular health and the concerns remain with increases in marijuana associated adverse events (Minhas et al., 2024; Page et al., 2020; Rezkalla and Kloner, 2024). Associations between marijuana use and cardiovascular complications remain concerning and high potency marijuana is associated with

vascular inflammation (Wei et al., 2022). Studies have shown a dose-dependent effect of cannabis use on cardiovascular system. Use of cannabis in naïve population causes an increase in parasympathetic tone that causes a dose-dependent baroreflexes dysregulation characterized as bradycardia and hypotension (Echeverria-Villalobos et al., 2019). Severe vascular complications associated with cannabis exposure may include malignant arrhythmias, coronary spasm, sudden death, cerebral hypoperfusion, and stroke. A study funded by the National Heart, Lung and Blood Institute found daily use of marijuana was associated with 25% increased likelihood of heart attack and 42% likelihood of stroke when compared to non-users of the marijuana (Jeffers et al., 2024). Additionally, an analysis of healthcare database indicated that those with a cannabis use disorder had an approximately 60% higher risk of experiencing adverse cardiovascular disease events than those without cannabis use disorder (Bahij et al., 2023).

Several studies in humans have analyzed the incidence of myocardial infarction and its association with cannabis use. One report assessed discharge records from the National Inpatient Sample database from years 2007–2014 and examined national trends in hospitalizations for major cardiovascular events, including acute myocardial infarction, arrhythmia, stroke, and venous thromboembolic events. The report included cases among young cannabis users (18–39 years), excluding cases with concomitant substance abuse with alcohol, tobacco, cocaine, and amphetamine (Desai et al., 2019). Results indicated the frequency of admissions for myocardial infarction, arrhythmia, and stroke was higher in cannabis users as compared to nonusers. However, the frequency of admissions for venous thromboembolic events was lower among cannabis users as compared with nonusers (Desai et al., 2019).

In a similar report by Ladha et al. (2021), study authors performed a cross-sectional study using pooled data from the 2017 and 2018 cohorts of the American Behavioral Risk Factor Surveillance System survey of US adults aged 18–44 years old. This review analyzed the association between any recent cannabis use and history of myocardial infarction, adjusting for demographic factors, socioeconomic factors, health-related behaviors, concomitant substance use, and other comorbidities. Similar to the first study, myocardial infarction was more frequent among recent cannabis users than nonusers. Smoking was the primary method among cannabis users (Ladha et al., 2021). In a study by Chami et al. (2019), study authors performed a retrospective cohort analysis on patients with cannabis encounters between October 2011 and September 2016 with the primary outcome of a 3-year cumulative incidence of myocardial infarction. Results from this study also indicated that the cannabis use group had a higher 3-year cumulative incidence of myocardial infarction and a higher prevalence of cardiovascular risk factors, such as hypertension, coronary artery disease, dyslipidemia, diabetes, and obesity. In addition, cannabis users had a greater predilection for substance abuse (including tobacco, cocaine, and alcohol) [Chami et al., 2019]. DeFilippis et al. (2018) retrospectively examined patients less than 50 years old with myocardial infarction at two academic hospitals, of whom 125 had used marijuana. In this study, cannabis appeared to confer a significant increase in all-cause and cardiovascular mortality (DeFilippis et al., 2018).

## *Central Nervous System Toxicities – Including Brain Structure and Function, and Associated Cognitive Impairments*

Several papers explore the effects of acute administration and chronic marijuana administration on cognitive abilities such as memory, attention, and learning. Testai and colleagues provide a discussion on the clinical outcomes of marijuana use on brain health (Testai et al., 2022). Acute cannabis administration affects verbal learning and memory as well as working memory (Zhornitsky et al., 2021) and varies by route of administration (Spindle et al., 2021). In infrequent marijuana users, oral ingestion of marijuana (i.e., marijuana-containing brownies) produced cognitive and psychomotor impairments that were delayed for several hours, whereas vaporized marijuana produced immediate impairments (Schlenz et al., 2020; Spindle et al., 2018, 2021).

Individuals with cannabis use disorder also show an effect on working memory (Sweeny et al., 2021). In a study by Petker et al. (2019), recent cannabis users (using delta-9-THC as an indicator) exhibited poor episodic memory and slower processing speeds (Petker et al., 2019). In people with cannabis use disorder, fluid intelligence was the only neurocognitive domain significantly predicted (Petker et al., 2019). Similarly, in another publication, daily cannabis users with a confirmed diagnosis of cannabis use disorder performed significantly poorer on tasks of visual and episodic memory compared with healthy controls (Selamoglu et al., 2021). Existing data continue to link cannabis use to adverse brain health outcomes; of particular note is the associated neurocognitive deterioration, confirmed by loss of brain volume and density (Urts et al, 2021).

Alterations of certain brain biomarkers in early age onset of cannabis use, frequent users, or having cannabis use disorder were also related to lower cognitive function. The work of D'Souza and colleagues demonstrated a lower hippocampal density in individuals with cannabis use disorders (D'Souza et al., 2021). The researchers also noted that alterations in density have consequences for network organization and function in cannabis users. Decreased brain white matter growth is attributed to functional impairment and decreased cognitive function in cannabis users with an onset of cannabis use prior to age 17 (Becker et al., 2015). Additionally, a reduction in brain volume and an increase in grey matter have been observed in marijuana users (Lorenzetti et al., 2016; Penzel et al., 2021) and in adolescents with low levels of marijuana consumption (Orr et al., 2019). Changes in grey matter volume are associated with neuropsychological deficits which include reduced performance on a perceptual reasoning, generalized anxiety symptoms, psychosis, and schizophrenia (Orr et al., 2019; Shah et al., 2022).

In a longitudinal study, brain functional resting connectivity, which has been found to be directly associated with quality of behavioral performance, was examined in cannabis adolescent users with cannabis use disorder (Camchong et al., 2017). Participants with cannabis use disorder had a decrease in functional connectivity. In this same paper, high amounts of cannabis use over an 18-month period predicted lower intelligence quotient and slower cognitive function

(Camchong et al., 2017). A meta-analysis of cannabis use on neurocognition indicated that chronic cannabis use is associated with impairment of memory function, cognitive impulsivity, cognitive flexibility and attention (Figueiredo et al., 2020).

Marijuana exposure during adolescence delays maturation of the prefrontal cortex, critical to complex behaviors and decision making (Cass et al., 2014; Camchong et al., 2017; Jacobus et al., 2016; Peters and Naneix, 2022; Renard et al., 2018; Shollenbarger et al., 2015). Marijuana exposure is also associated with prefrontal cortical thinning during adolescence (Albaugh et al., 2021; Owens et al., 2022). Similarly, structural differences in white and gray matter were also observed in another study of chronic cannabis users (Manza et al., 2020). A New Zealand cohort study, following individuals from childhood to 45 years, revealed that individuals who used cannabis starting at age 18 (considered long-term cannabis users) also have smaller hippocampal volume (Meier et al., 2022). In addition, long-term cannabis users presented with a decline in IQ from childhood to midlife and other cognitive deficits, such as poorer learning and processing relative to their childhood IQ, as well as problems with attention and informant-reported memory (Meier et al., 2022). These same cognitive deficits are seen in individuals with epilepsy and regular cannabis use (Roberts-West and Baxendale, 2023). Monoacylglycerol lipase (MAGL) and fatty-acid amid hydrolase are two enzymes critical to regulating the endocannabinoid system. High MAGL expression observed in marijuana dependence has been associated with cortical alterations in thickness (Manza et al. 2020). Furthermore, lack of cortical maturation is a liability for schizophrenia (French et al., 2015).

Changes in brain structure may also result in a predisposition for psychosis in adolescents (Patel et al., 2021). A study by Delvecchio et al. (2020) examined morphological brain differences between chronic cannabis users with cannabis-induced psychosis and non-psychotic cannabis users. The results indicated that cannabis-induced psychosis patients had extensive gray matter decreases in several areas of the brain compared to the non-psychotic cannabis users.

Overall, there is evidence on brain alterations and cognition among cannabis users. The accumulating body of evidence demonstrate marijuana-induced modifications in brain structure place individuals at an increased risk for psychiatric disorders such as psychosis and schizophrenia later in life and persist over time (Cohen et al., 2012; Colyer-Patel et al., 2024; Lorenzetti et al., 2020; Meier et al., 2022; Penzel et al., 2021; Solowij et al., 2011; Xu et al., 2024). Various uncertainties still remain as to the specifics related to the frequency of marijuana use, potency, and dose on brain impact and severity; however, the risk and harms associated with mental illness, especially psychiatric disorders, has been established (Cousijn et al., 2021; Chye et al., 2020).

### *Pulmonary Toxicity*

Cannabis can be smoked through the use of joints or blunts, or it can be vaporized with use by e-cigarettes or hookah (Khoj et al., 2024). The effects of cannabis smoking on the respiratory system depend on the mode of inhalation, temperature, and chemical composition of

the smoke. Chronic bronchitis symptoms, such as cough, dyspnea, wheezing, and increased sputum production, are seen after smoking cannabis (Khoj et al., 2024). Hancox et al. (2021) conducted a cohort study to assess the effects of cannabis and tobacco on lung function at ages 18, 21, 26, 32, 38, and 45. They reported that cumulative cannabis use was associated with lower FEV1/FVC ratios<sup>19</sup>, higher total lung capacity, functional residual capacity, residual volume, and alveolar volume, along with lower mid expiratory flow rate, airway conductance, and transfer factor. Hancox et al. (2021) concluded that cannabis use is associated with higher lung volumes, suggesting hyperinflation. Furthermore, they provided the first evidence that lifetime cannabis use may be associated with impairment of gas transfer. In a case-control study utilizing electronic health records (EHRs), it was reported that regular cannabis use was significantly associated with a 44%, 56%, and 80% greater risk for asthma, chronic obstructive pulmonary disease (COPD), and pneumonia, respectively (Winhusen et al., 2019).

The cannabis and tobacco market have evolved to include the possibility to vape nicotine and cannabis/delta-9-THC to appeal to young consumers, which has been reported to be associated with electronic cigarette vaping associated lung injury (EVALI) and other respiratory symptoms. Braymiller et al. (2020) utilized cross-sectional survey data on self-reported, 6-month, and 30-day vaping among 2,553 young adults in Southern California to investigate the association of nicotine and cannabis vaping with bronchitis symptoms, wheeze, and shortness of breath. Braymiller et al. (2020) reported that the odds of chronic bronchitis symptoms were statistically and significantly higher in individuals who vaped cannabis in their lifetime but not in the past 60 months (83%), used cannabis in the past 6 months but not in the last 30 days (58%), used cannabis 1–2 days in the past 30 days (183%), and used cannabis 3 or more days in the past 30 days (114%), when compared to those whom had never vaped cannabis. Furthermore, cannabis vaping 3 or more times in the last 30 days had a statistically significant 127% increase in odds of wheeze. A current longitudinal study used time points from December 2016 to January 2018 of the Population Assessment of Tobacco and Health (PATH) Study to explore the association between respiratory symptoms among U.S adolescents who were current users (i.e., used in the past 30 days) of cigarettes, e-cigarettes, and/or cannabis, as well as lifetime users of cannabis with electronic nicotine delivery systems (ENDS). While neither e-cigarettes nor cigarettes had a significant association with any of the respiratory symptoms, it was reported that the odds of indicating “wheezing or whistling” in chest were roughly two times higher among those who had used cannabis in an ENDS product (aOR=1.81; 95% CI=1.47–2.22) [Boyd et al., 2021]. The Centers for Disease Control and Prevention (CDC) reported that as of January 21, 2020, a total of 2,711 patients had been hospitalized with EVALI with 60 resulting in deaths in 27 states and the District of Columbia (Christiani, 2020).

<sup>19</sup> Forced expiratory volume in one second to the forced vital capacity of the lungs

## *Prenatal Exposure*

Prenatal cannabis exposure is associated with a number of adverse outcomes. In a recent prospective cohort study, Mumford et al. (2021) investigated whether cannabis use assessed via urinary metabolites and self-report during preconception were associated with fecundability, live birth, and pregnancy loss. The sampled population consisted of 1,228 women that were followed for up to six cycles while attempting pregnancy (2006 to 2012) and through pregnancy if they conceived. Among the 1,228 women, 5% reported preconception cannabis use, which was based on combined urinary metabolite measurements and self-report; 1.3% reported using cannabis during the first 8 weeks of gestation based on urinary metabolites only. Mumford et al. (2021) conveyed that woman with preconception cannabis use had reduced fecundability (Fecundability OR=0.59, 95% CI=0.38–0.92).

Paternal cannabis use also has effects on offspring. The outcome of low birthweight is seen in humans after cannabis use in pregnancy, independent of other risk factors (Bailey et al., 2020; Gunn et al., 2016; Straub et al., 2021) as well as an increase in preterm birth (Bailey et al., 2020; Corsi et al., 2019). While most studies demonstrated that maternal cannabis use is a risk factor for birth outcomes, a couple of studies conclude that after adjusting for medical comorbidities, tobacco, alcohol, or other drug abuse, there were no differences in birth outcomes (Conner et al., 2015; Mark et al., 2016). Those exposed to marijuana prenatally after maternal knowledge of pregnancy had elevated levels of psychosis proneness in middle childhood (Baranger et al., 2022; Fine et al., 2019; Paul et al., 2021) and early adulthood at 22 years (Day et al., 2015). In another study, maternal and paternal cannabis use were associated with psychotic-like experiences in offspring at 10 years of age (Bolhuis et al., 2018). In addition, maternal cannabis use is associated with increased cortisol, anxiety, aggression, and hyperactivity in young children (3 to 6 years old) [Rompala et al., 2021].

Overall, there is evidence of an association between prenatal cannabis exposure and some birth outcomes such as low birthweight, anxiety, aggression, and hyperactivity, and psychotic symptoms even through early adulthood. State-level marijuana legalization resulted in higher incidence of cannabis-involved pregnancies (Wang et al., 2022).

### ***FDA-Approved Products (Syndros® and Marinol®)***

There are two FDA-approved drugs, Marinol and Syndros, that contain synthetic delta-9-THC. As stated above, delta-9-THC is the primary psychoactive ingredient in marijuana under the CSA. Both Marinol and Syndros contain synthetic delta-9-THC (dronabinol) as the only active pharmaceutical ingredient and are approved by FDA for the same two uses: (1) the treatment of nausea and vomiting associated with cancer chemotherapy in patients who did not respond to conventional antiemetic treatments, and (2) the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Marinol is a schedule III drug product formulated in sesame oil in soft gelatin capsules at dosages of 2.5, 5, or

10 mg dronabinol.<sup>20</sup> Syndros, a schedule II drug product, is formulated in alcohol as an oral solution containing 5 mg/ml dronabinol.<sup>21</sup> According to the FDA-approved product labels for both Marinol and Syndros, the recommended daily dose is approximately 5 mg delta-9-THC, administered orally up to 4 to 6 times a day, resulting in approximately 20–30 mg delta-9-THC per day. Additionally, the product labels note that the most common adverse reactions associated with Marinol and Syndros are abdominal pain, dizziness, euphoria, nausea, paranoid reaction, somnolence, abnormal thinking, and vomiting.

The abuse-related studies for Marinol and Syndros confirmed the abuse potential of delta-9-THC, the primary compound responsible for the abuse of marijuana. While marijuana is related in its action to dronabinol (synthetic delta-9-THC), the ingredient in Marinol and Syndros, marijuana is a more complex and diverse substance than synthetic dronabinol, as further discussed in Factor 3. Moreover, marijuana is self-administered in a wide variety of dosage forms and dosages. For instance, inhalation is a common route of marijuana use (Sexton et al., 2016) that is not available for Marinol and Syndros, and users often self-administer daily doses that are several folds higher than the 30 mg of delta-9-THC per day approved by FDA for use in Marinol and Syndros (Vreeke et al., 2022). Administering delta-9-THC via inhalation and in higher doses than FDA has approved in Marinol and Syndros raises concerns of adverse effects in addition to those noted in both FDA-approved drug labels.

### **Factor 3: The State of Current Scientific Knowledge Concerning the Substance**

#### **Chemistry**

Marijuana, also known as *Cannabis sativa* L., is part of the *Cannabaceae* plant family and is one of the oldest cultivated crops. *Cannabis sativa* is the primary species of cannabis, of which two varieties or subspecies are *Cannabis indica* and *Cannabis ruderalis* (McPartland, 2017). The term “marijuana” is colloquially used to refer to a mixture of the dried flowering tops and leaves from cannabis (not to be confused with the CSA definition). Cannabis is primarily a dioecious plant, meaning female and male flowers occur on separate plants (Radwan et al., 2021). Various *Cannabis* strains contain more than 550 identified natural constituents, including cannabinoids, flavonoids, terpenes, alkaloids and other constituents (Radwan et al., 2021). To date, more than 125 cannabinoids have been characterized (ElSohly and Slade, 2005; Radwan et al., 2009; Appendino et al., 2011; Radwan et al., 2021), and most major cannabinoid compounds occurring naturally have been identified. Of the cannabinoids found in marijuana, delta-9-THC<sup>22</sup> and delta-8-tetrahydrocannabinol (delta-8-THC, delta-6-THC) have been demonstrated to produce marijuana’s psychoactive effects. Psychoactive effects from marijuana usage have been mainly attributed to delta-9-THC because delta-9-THC is present in

<sup>20</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/018651s029lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf)

<sup>21</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/205525Orig1s009bledt.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205525Orig1s009bledt.pdf)

<sup>22</sup> Delta-9-THC uses a numbering system based on a dibenzopyran numbering system; previously it was numbered using a monoterpenoid numbering system and was known as delta-1-THC.

significantly higher quantities than delta-8-THC in most marijuana cultivars. Delta-9-THC is an optically active resinous substance that is extremely lipophilic. The chemical name for delta-9-THC is (6a*R*-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo-[b,d]pyran-1-ol, or (-)-delta9-(trans)-tetrahydrocannabinol. The (-)-trans delta-9-THC isomer is pharmacologically 6 to 100 times more potent than the (+)-trans isomer (HHS, 2015). Other relatively well-characterized cannabinoids present in marijuana include CBD, cannabichromene (CBC), and cannabiol (CBN). CBD and CBC are major naturally occurring cannabinoids in marijuana and are both lipophilic. In contrast, CBN is a minor naturally occurring cannabinoid with weak psychoactivity, but it is also a major metabolite of delta-9-THC.

Different marijuana samples are produced from numerous cultivated strains and may have different chemical compositions including levels of delta-9-THC and other cannabinoids (HHS, 2015). Marijuana samples with varying chemical compositions will have significant differences in the concentrations of psychoactive substances, significantly altering the safety, biological, pharmacological, and toxicological profiles and therefore, all *Cannabis* strains cannot be considered collectively due to the variations in chemical composition (HHS, 2015). Furthermore, the concentration of delta-9-THC and other cannabinoids present in marijuana may vary due to growing conditions and processing of the plant after harvesting. For example, the various plant parts collected (e.g., flowers, leaves, and stems) can influence marijuana's potency, quality, and purity (HHS, 2015).

While inconsistent from product to product, the amount of delta-9-THC in available products has steadily increased. A publication by ElSohly et al. (2021) showed that the mean delta-9-THC concentration increased over a recent 10-year period, rising from 9.75% in 2009 to approximately 14% in 2019. Similarly, data from the University of Mississippi's Marijuana Potency Monitoring Program shows that the delta-9-THC concentration in marijuana samples increased from about 3% in 1993 to about 16% in 2022 an 81% increase compared to the levels found in marijuana in previous decades. In another study that evaluated delta-9-THC and CBD products offered in online dispensaries in the United States, the average delta-9-THC concentration, regardless of intended medicinal or recreational use, was greater than 15% delta-9-THC (Cash et al., 2020). These higher delta-9-THC products also had lower CBD concentrations (Cash et al., 2020). There is considerable variability in the cannabinoid concentrations and chemical constituents among marijuana samples. The lack of consistent concentrations of delta-9-THC and other substances in marijuana complicates the interpretation of the effects of marijuana. In addition, interactions between the cannabinoids as well as the non-cannabinoid components in marijuana may potentially modify the overall pharmacological and toxicological properties of various marijuana strains and products.

Two other major and currently illicit marijuana products derived from the cannabis plant are hashish and hash oil. Hashish is composed of the dried and compressed cannabinoid-rich resinous material of *Cannabis* and is found as balls and cakes as well as other forms. Individuals may break off pieces and place them into a pipe to smoke. Hash oil, a viscous brown or amber

colored liquid, is produced by solvent extraction of cannabinoids from *Cannabis* and contains approximately 50% cannabinoids. Examples of solvents used for extraction include ethanol and butane. Using butane as a solvent result in what is known as butane hash oil, and the use of butane hash oil is often referred to as “dabbing” (Al-Zouabi et al., 2018). One to two drops of hash oil on a cigarette have been reported to produce the equivalent of a single marijuana cigarette (HHS, 2015). In 2016, a study completed by ElSohly et al. determined that of the 814 samples of hashish and the 261 samples of hash oil submitted by DEA regional labs for analysis, the average delta-9-THC concentration (by percentage) of hashish and hash oil were 21.78% and 34.32%, respectively.

### **Human Pharmacokinetics**

The pharmacokinetics of marijuana in humans depends on the route of administration and formulation (Lucas et al., 2018; Agurell et al., 1986). Pharmacokinetic studies on marijuana focused on evaluating the absorption, metabolism, and elimination profile of delta-9-THC and other cannabinoids (Agurell et al., 1986). The most reported routes of marijuana administration are via ingestion and inhalation. Traditionally, individuals have smoked marijuana as a cigarette (weighing between 0.5 and 1 gram) or in a pipe. More recently, other aerosolized methods, such as so-called “vaporizers”, have been used as an alternative method for individuals to inhale marijuana plant material or when formulated in solutions with ethanol or other solvents. Marijuana is also ingested orally in similar liquid solutions or when marijuana plant material has been incorporated into drinks or food, such as brownies.

#### ***Absorption and Distribution of Inhaled Marijuana Smoke***

Differences in individual smoking behavior, even under controlled experimental conditions, lead to highly variable pharmacokinetics of delta-9-THC and other cannabinoids from smoked marijuana (Agurell et al., 1986; Hering et al., 1986; HHS, 2015).

Smoking marijuana results in the rapid absorption—within seconds—of delta-9-THC and its rapid and efficient distribution to the brain. Following absorption, psychoactive effects are observed immediately with measurable neurological and behavioral changes for up to 6 hours (Huestis, 2007). Bioavailability of delta-9-THC from marijuana from a cigarette or pipe ranges from 10 to 35% (Chayasirisobhon, 2020). This variable bioavailability is due to loss in side-stream smoke, variation in individual smoking behaviors and experience, incomplete absorption of inhaled smoke, and metabolism in the lungs (Hering et al., 1986; Johansson et al., 1989). After cessation of smoking, delta-9-THC venous levels decline within minutes and continue to decline to approximately 5% to 10% of the peak level within an hour (Agurell et al., 1986; Huestis, 2007).

#### ***Absorption and Distribution of Orally Administered Marijuana***

Following oral administration (e.g., edibles) of delta-9-THC or marijuana, the onset of effects starts within 30 to 90 minutes, peaks after 2 to 3 hours, and remains in effect for 4 to 12

hours (Grotenhermen, 2003; Agurell et al., 1984; Agurell et al., 1986). Oral bioavailability of delta-9-THC, either in its pure form or in marijuana, is low and variable, ranging from 5% to 20% (Agurell et al., 1984; Agurell et al., 1986). There is also inter- and intra-subject variability of orally administered delta-9-THC under experimental conditions and even under repeated dosing experiments (HHS, 2015). Delta-9-THC plasma levels following oral administration of peaked 4-6 hours after ingestion of 15-20 mg of THC in sesame oil (Huestis, 2007). This low and variable bioavailability of orally administered delta-9-THC is due to first pass hepatic elimination from blood and erratic absorption from stomach and bowel.

### ***Metabolism and Excretion of Cannabinoids from Marijuana***

Studies evaluating cannabinoid metabolism and excretion have focused on delta-9-THC due to its role as the primary psychoactive component in marijuana. Delta-9-THC is metabolized via microsomal hydroxylation and oxidation to both active and inactive metabolites (Lemberger et al., 1970; 1972a; 1972b; Agurell et al., 1986; Hollister, 1988). The primary active metabolite of delta-9-THC following oral ingestion is 11-hydroxy-delta-9-THC, which is equipotent to delta-9-THC in producing marijuana-like subjective effects (Agurell et al., 1986; Lemberger and Rubin, 1975). Metabolite levels following oral administration may be greater than delta-9-THC levels and may contribute greatly to the pharmacological effects of oral delta-9-THC or marijuana. Metabolism of delta-9-THC is consistent among frequent and infrequent marijuana users (Agurell et al., 1986).

Plasma clearance of delta-9-THC approximates hepatic blood flow at a rate of 950 ml/min or greater. Rapid clearance of delta-9-THC from blood is primarily due to redistribution to other tissues in the body rather than to metabolism (Agurell et al., 1984; Agurell et al., 1986). Outside of the liver, metabolism in most tissues is considerably slow or does not occur. The elimination half-life of delta-9-THC ranges between 20 hours and 10 to 13 days (Hunt and Jones, 1980). Lemberger et al. (1970) reported that the half-life of delta-9-THC ranged from 23 to 28 hours in heavy marijuana users and up to 60 to 70 hours in naïve users. The long elimination half-life of delta-9-THC is due to the slow release of delta-9-THC and other cannabinoids from tissues and subsequent metabolism. Inactive carboxy metabolites of delta-9-THC have terminal half-lives of 50 hours to 6 days or more and serve as long-term markers in urine tests for marijuana use.

Most of the absorbed delta-9-THC dose is eliminated in the feces and approximately 33% is eliminated in urine. The glucuronide metabolite of delta-9-THC is excreted as the major urine metabolite, along with 18 non-conjugated metabolites (Agurell et al., 1986).

### **Cannabis and Prescription Drug Interactions**

The pharmacokinetic mechanism of cannabis involves the cytochrome P450 (CYP) isoenzymes, similar to other prescription drugs. Delta-9-THC and CBD are pharmacologically active cannabinoids in cannabis, which are metabolized by CYP3A4; delta-9-THC is also

metabolized by CYP2C9, a liver enzyme (Cox et al., 2019). Therefore, the concomitant use of cannabis with prescription drugs may lead to cannabis-drug interactions and increased toxicity. Marijuana-drug interactions result in alterations to pharmacokinetic or pharmacodynamic changes potentially mediated through marijuana inhibition activities of multiple P450 enzymes (Nasrin et al., 2021; Qian et al., 2019). A review of the literature found that antidepressants are less effective for adolescents with depression/anxiety who frequently use marijuana (Hen-Shoval et al., 2022). Furthermore, the use of marijuana with anticoagulant and antiplatelet agents, antiepileptics, clobazam, warfarin, and tacrolimus can induce drug-drug interactions (Greiger et al., 2020; Ho et al., 2024). A systemic review conducted by Lopera et al. (2022) found clinical evidence and probability of interactions in humans between cannabis and prescription drugs (see Table 1).

**Table 1: Some Examples of Probable Cannabis-Drug Interactions**

Drug Name	Severity	Mechanism	Reaction Type
Warfarin	Major	CYP2C9 inhibition	As reported in four different clinical cases (one CBD and three smoked cannabis cases), co-use of CBD or inhaled cannabis may increase warfarin anticoagulant effect (Lopera et al., 2022).
Buprenorphine	Moderate	CYP3A4 inhibition	Buprenorphine is metabolized by CYP3A4 and cannabis is an inhibitor of CYP3A4. The co-use of cannabis can decrease the metabolism of buprenorphine and lead to risk of intoxications (Vierke et al., 2021).
Tacrolimus	Moderate	CYP3A4 inhibition and P-glycoprotein	Potential increase in tacrolimus level with co-use of edible marijuana gummies was reported in a patient with relapsed follicular lymphoma (Hauser et al., 2016).
Clozapine	Moderate	CYP1A2 induction	A patient that received clozapine treatment developed confusion after cannabis and tobacco cessation (Zullino et al., 2002).

Drug-drug interactions remain a serious concern for the medical community (Alsherbiny and Li, 2018; Antoniou et al., 2020; Brown, 2020; Doohan et al., 2021; Ho et al., 2024). These interactions result in pharmacokinetic and pharmacodynamic changes. Concerns related to drug-drug interactions have been discussed in the scientific literature, especially as it relates to the marijuana’s impact on the effectiveness of other medications and potential complications (Alexander and Joshi, 2019; Becker et al., 2022; Echeverria-Villalobos et al., 2019; Lynskey et al., 2024; Ponturu et al., 2023; Ripperger et al., 2023). Observations include an increased risk of perioperative morbidity and mortality after surgery for individuals with CUD (Porturu et al., 2023).

Marijuana use may impact the routine use and administration of other drugs, and its use is particularly relevant as it relates to surgery and sedation. A study reviewed the amount of sedation required in patients who had received endoscopic procedures during a 2-year period (2015 to 2017) and found that regular cannabis users (n =25) required 14% more fentanyl, 18.6% more midazolam, and 220.5% more propofol when compared to non-cannabis users (n =250) [Twardowski et al., 2019]. The finding that marijuana users require higher doses of propofol for sedation has also been confirmed in additional studies (Imasogle et al., 2021; Smith et al., 2024). Similarly, Ripperger et al. (2023) found that marijuana users required more propofol, midazolam, ketamine, and fentanyl than non-cannabis users during outpatient oral and maxillofacial surgery.

### **Analysis of Currently Accepted Medical Use for Marijuana**

Traditionally, DEA and HHS have considered whether marijuana has a currently accepted medical use under Factor 3, State of the Current Scientific Knowledge Concerning the Substance, in addition to DEA’s evaluation of whether the drug has a currently accepted medical use as one of the findings required for schedule placement under 21 U.S.C. 812(b).

Historically, for substances that are not contained in an FDA-approved drug, DEA and HHS have applied a five-part test to determine whether the substance has a currently accepted medical use. Specifically, with respect to a drug that has not been approved by FDA, in order for that drug to have a currently accepted medical use in treatment in the United States, DEA and HHS have required that the substance demonstrate all of the five following elements: (1) The drug's chemistry must be known and reproducible, (2) there must be adequate safety studies, (3) there must be adequate and well-controlled studies proving efficacy, (4) the drug must be accepted by qualified experts, and (5) the scientific evidence must be widely available.<sup>23</sup>

On April 11, 2024, the Department of Justice’s Office of Legal Counsel (OLC) issued an opinion that, among other things, concluded that the existing five-part test is sufficient to determine that a drug has a currently accepted medical use, but that limiting the analysis to the five-part test is “impermissibly narrow.”<sup>24</sup> OLC concluded that DEA also must consider “whether, at the present time, the medical community widely understands that a drug has a ‘use in treatment in the United States.’”<sup>25</sup> OLC specified that “there is no single right answer as to *how* specifically DEA should make this determination.”<sup>26</sup>

### ***Five-Part Test***

FDA approves medical use of a drug following a submission and review of an NDA or BLA. The FDA has not approved any drug product containing marijuana for marketing.

<sup>23</sup> Marijuana Scheduling Petition; Denial of Petition; Remand, 57 FR 10499 (Mar. 26, 1992), pet. for rev. denied, *Alliance for Cannabis Therapeutics v. Drug Enforcement Admin.*, 15 F.3d 1131, 1135 (D.C. Cir. 1994).

<sup>24</sup> Office of Legal Counsel, Memorandum for Merrick B. Garland Attorney General Re: Questions Related to the Potential Rescheduling of Marijuana at 12 (April 11, 2024).

<sup>25</sup> *Id.* at 16.

<sup>26</sup> *Id.* (emphasis in original).

However, FDA approval of an NDA is not the only means through which a drug can have a currently accepted medical use in treatment in the United States. In general, a drug may have a “currently accepted medical use” in treatment in the United States if the drug meets a five-part test. Established case law (*Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131, 1135 (D.C. Cir. 1994)) upheld the Administrator of DEA's application of the five-part test to determine whether a drug has a “currently accepted medical use.” The following describes the five elements that characterize “currently accepted medical use” for a drug: <sup>27</sup>

DEA has evaluated marijuana’s currently accepted medical use using the established five-part test. Below is a summary of DEA’s findings:

1. *The drug’s chemistry must be known and reproducible:*

*"The substances' chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(g) of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient to meet this requirement."*

Chemical constituents in marijuana, including delta-9-THC and other cannabinoids, vary significantly across different marijuana strains. Marijuana has many strains with high variability in the concentrations of delta-9-THC, the main psychoactive component, as well as other cannabinoids and compounds. In addition, the concentrations of delta-9-THC and other cannabinoids may vary between strains. Due to the variation of the chemical composition in marijuana strains, it is not possible to derive a standardized dose. Marijuana is not a single chemical and does not have a consistent and reproducible chemical profile with predictable or consistent clinical effects. However, if a specific cannabis strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive standardized doses. As per the Code of Federal Regulations (CFR) in 21 CFR 314.50(d)(1)(i), “adequate information regarding the chemistry, manufacturing, and control of a drug substance includes: synthesis, purification, identity, strength, quality, and purity of the drug substance, as well as stability, sterility, particle size, and crystalline form of the drug product.” There are limited data regarding these elements for marijuana.

2. *There must be adequate safety studies:*

*"There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder."*

The considerable variation in the chemistry of marijuana results in differences in safety, biological, pharmacological, and toxicological parameters among the various marijuana samples.

<sup>27</sup> [57 FR 10499, 10504-06](#) (March 26, 1992)

Based on criteria for an adequate and well-controlled study for purposes of determining the safety and efficacy of a human drug as defined in 21 CFR 314.126, there are limited published studies in which safety or effectiveness of purified marijuana has been evaluated. One observed trend is the increased use of high delta-9-THC and low CBD material in recreational and medical marijuana markets (Urits et al., 2020; Hasin et al., 2021). Additional findings highlight that state markets are dominated by high-THC products (Cash et al., 2020; Dobbins et al., 2022; Pennypacker et al., 2022).

3. *There must be adequate and well-controlled studies proving efficacy:*

*"There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder."*

There are no adequate and well-controlled studies that determine marijuana's efficacy. In the absence of clinical trials and demonstration of efficacy, state programs have legalized marijuana for a variety of indications, such as (but not limited to) chronic pain, glaucoma, anxiety, and as an antiemetic in the treatment of chemotherapy-induced nausea. According to FDA,<sup>28</sup> "unapproved cannabis and/or unapproved cannabis-derived products are being used to treat a number of medical conditions including, AIDS wasting, epilepsy, neuropathic pain, spasticity associated with multiple sclerosis, and cancer and chemotherapy-induced nausea. Caregivers and patients can be confident that FDA-approved drugs have been carefully evaluated for safety, efficacy, and quality, and [these approved drugs] are monitored by the FDA once they are on the market. However, the use of unapproved cannabis and cannabis-derived products can have unpredictable and unintended consequences, including serious safety risks. Also, there has been no FDA review of data from rigorous clinical trials to support that these unapproved products are safe and efficacious for the various therapeutic uses for which they are being used."

4. *The drug must be accepted by qualified experts:*

*"The drug has a New Drug Application (NDA) approved by the Food and Drug Administration pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. 355. Or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus."*

Medical practitioners who are not experts in evaluating drugs are not qualified to determine whether a drug is generally recognized as safe and effective, or it meets NDA requirements (57 FR 10499-10505). Currently, there is no consensus of opinion among experts

<sup>28</sup> [FDA and Cannabis: Research and Drug Approval Process | FDA](#)

concerning the medical utility of marijuana for use in treating specific, recognized disorders. To date, FDA has not approved a marketing application for cannabis for the treatment of any disease or condition. The agency has, however, approved one cannabis-derived drug product—Epidiolex (cannabidiol)<sup>29</sup>—and three synthetic cannabis-related drug products—Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone). These approved drug products are only available with a prescription from a licensed healthcare provider. Importantly, FDA has not approved any of the other cannabis, cannabis-derived, or cannabidiol (CBD) products currently available on the market.

5. *Scientific evidence must be widely available:*

*"In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder."*

The currently available data and information on marijuana is not sufficient to address the chemistry, pharmacology, toxicology, and effectiveness. Though the chemistry, pharmacology, and, to an extent, toxicology of some of the cannabinoids (e.g., delta-9-THC and CBD) present in marijuana is known, interactions between the cannabinoids, as well as the non-cannabinoid components in marijuana, may potentially modify the overall pharmacological and toxicological properties of various marijuana strains and products. The paucity of data available on the other pytocannabinoids present in marijuana remains unknown.

### **State Programs for Marijuana**

State programs exist for both medical and recreational marijuana use. As of February 2024, 47 states, 3 territories (Guam, Puerto Rico, U.S. Virgin Islands), and the District of Columbia have allowed the use of marijuana for medical purposes. In addition, 38 states, as well as 3 territories and the District of Columbia, have allowed the use of marijuana for medical purposes through comprehensive programs. Furthermore, 14 states and 2 territories have a comprehensive medical-only program.<sup>30</sup> Although there appears to be some distinction on the administration of these programs by the states, there also appears to be an overlap of recreational and medical marijuana users (Roy-Byrne et al., 2015; Turna et al., 2020). Pacula and colleagues (2016) noted that in the United States, the degree of overlap between medicinal and recreational cannabis users is 86%. In addition, some individuals moved from state medical programs to recreational programs which have less inconveniences or limitations (Ataiants et al., 2024; Morean and Lederman, 2019; Pacula et al., 2016).

<sup>29</sup> Epidiolex is an FDA-approved drug product that contains plant derived, highly purified CBD.

<sup>30</sup> [State Medical Cannabis Laws | Cannabis and Public Health | CDC](#)

Independent researchers have noted a prevalence in state medical and recreational programs for the use of high potency delta-9-THC products (Hasin et al., 2023). Little is known regarding these marijuana products in state programs prior to their introduction; thus, research is needed (Brown, 2019; Bidwell et al., 2021; Jameson et al., 2022). According to CDC, nine states have medical programs, which only allows the use of CBD/low-THC products for certain qualifying medical conditions.<sup>31</sup>

Twenty-five states have an inventory tracking system that monitors product flows from seed or immature plant stage until the final product is sold to a customer for adult or medical use. These states use the Metrc,<sup>32</sup> a Medical Marijuana and Adult-Use (Cannabis/Marijuana) Seed-to-Sale Tracking System for the regulation of legalized marijuana market. The Metrc has the ability to track patients purchases against the control limits set by each state and to record any adverse reactions to the medicine (product).

Some states have restricted the use of certain products (e.g., high potency products) for medical products. For example, in Maryland,<sup>33</sup> dispensaries may only sell high potency products to qualifying patients and registered caregivers. Examples of these products include:

- Concentrated cannabis products with a total product weight greater than 1 gram (g)
- Edible cannabis products, capsules, and tinctures containing more than 10 milligrams (mg) tetrahydrocannabinol (THC) per serving or 100 mg THC per package

Adult consumers in the state of Maryland may purchase different products, such as:

- Cannabis vaporizing devices, of any product weight (e.g., vapes)
- Concentrated cannabis products with a total weight of 1 gram or less
- Infused pre-rolls of any product weight
- Infused non-edible cannabis products
- Home cultivation products (including clones, seeds, seedlings up to 8 inches tall and 8 inches wide, stalks, roots, and stems of the cannabis plant)
- Usable cannabis products (e.g., flower, pre-rolls)
  - o Infused pre-rolls and cannabis vaporizing devices are weighed as concentrated cannabis for purposes of adult-sales limits; however, they are exempt from the 1 g cap for adult-use consumers
  - o The combined weight of flower sold as a usable cannabis product to an individual may not exceed 1.5 oz or 42.5 g
- Edible cannabis products, capsules, and tinctures containing up to 10 mg THC per serving or 100 mg of THC per package

<sup>31</sup> *Id*

<sup>32</sup> [Metrc Partners | Leading Track-and-Trace Solutions](#)

<sup>33</sup> [6.18.24 Dispensary Guidance.pdf](#)

- Any products with greater than 10 mg of THC per serving or 100 mg of THC per package may not be sold to adult-use consumers.

### **“Medical Advice” by Dispensary Staff**

Moreover, harms associated with marijuana, such as addictiveness, were not acknowledged by dispensary staff (Bulls et al., 2023; Slawek et al., 2023). From a survey of 434 dispensary staff, less than half of the respondents believed that they had encountered CUD (49%), and over a quarter of respondents did not believe that cannabis is addictive (26%) [Slawek et al., 2023]. Dispensary staff are providing medical advice to patients that may be harmful to patients (Roberts, 2019; Nayak et al., 2023). This is particularly concerning, because dispensary staff are serving as “proxy” clinicians who cannot provide clear counseling on benefits versus harms (Calcaterra et al., 2020; Merlin et al., 2021). In a survey of users accessing material from cannabis dispensary, rates of problematic cannabis use were high, with 30% meeting the criteria (Lo et al., 2022). Only 10% of subjects reported medical cannabis use was recommended by their doctor. From a nationwide cross-sectional survey, Merlin and colleagues (2021) noted a gap in marijuana medical use perception between dispensary staff and clinicians. Their findings are consistent with other studies and suggest that dispensary staff are comfortable providing medical advice where clinicians may not, due to a lack of standardized dosing and regulatory oversight (Braun et al., 2021; Christensen et al., 2021; Merlin et al., 2021; Peiper et al., 2017; Romm et al., 2024). Particularly concerning are medical recommendations from dispensary staff that may not be informed by medical evidence, but rather personal experience, and thus contradict recommendations from primary care providers (Dickson et al., 2018).

### **Marijuana Clinical Research Studies Assessing Potential Therapeutic Effects**

Although some researchers claim that marijuana can reduce pain, there is also evidence that marijuana has no effect on chronic pain in clinical trials. In one trial, 23 participants with sickle cell disease, a condition that is often characterized by experiences of chronic pain and episodic pain bouts, inhaled marijuana with 4.4% delta-9-THC and 4.9% CBD via an aerosolization model that results in similar bioavailable concentrations of delta-9-THC relative to smoked cannabis (Model #0100; Volcano©). Marijuana was inhaled three times a day for five days and users experienced no reduction of pain compared to those consuming a placebo marijuana product from which the cannabinoids had been extracted (Abrams et al., 2020).

Another trial indicates that the relative dose of delta-9-THC is important and that some marijuana strains with either low or higher relative concentrations of delta-9-THC exacerbate pain in patients with diabetic peripheral neuropathy (Wallace et al., 2020). A review by the American Society of Pain and Neuroscience noted that both safety and efficacy data are lacking for the use of medical cannabis to treat chronic nonmalignant pain conditions (Strand et al., 2023).

Some preclinical and retrospective studies suggest that cannabinoids and marijuana may be effective in treating migraines. In one study by Schuster and colleagues (2024), participants inhaled a 6% delta-9-THC dominant cannabis strain, 11% CBD dominant cannabis strain, a combo 6% delta-9-THC dominant + 11% CBD cannabis strain, and a placebo strain in a randomized, double-blind, cross-over trial. The main endpoint was pain relief, with secondary endpoints of pain freedom and the most bothersome symptom (MBS) freedom, assessed two hours after vaporization. In total, nearly 250 migraine attacks were treated in 92 participants. The delta-9-THC dominant strain reduced pain relative to placebo (69 vs. 47%), but did not improve pain freedom or MBS freedom at two hours. The CBD-dominant strain, relative to placebo, did not improve pain relief, pain freedom, or MBS freedom, whereas the combination strain achieved pain relief (67 vs. 47%), pain freedom (35 vs. 16%), and MBS freedom (69 vs. 47%) relative to placebo. This suggests that not all marijuana products are the same and some may have little to no effect based on the actual marijuana consumed. Notably, adverse events were reported by participants one hour after inhalation in each condition. In particular, the delta-9-THC dominant strain produced sleepiness (41%), euphoria (36%), and cognitive impairment (36%).

Studies have highlighted an increase in pain intensity associated with marijuana use (Thomas et al., 2022; Zhang-James et al., 2023). The motivations associated with marijuana use for patients prescribed opioids for pain versus opioid addiction has been investigated (Clem et al., 2020). In one study, Bauer et al. (2018) found that opioid use was higher in marijuana users despite lower subjective pain scores. In another study, result showed robust associations between increased frequency of daily marijuana use and worse clinical pain and associated symptoms among medical marijuana patients with chronic pain (Boehnke et al., 2020). Additionally, marijuana users had poor outcomes for other medical procedures (Maskal et al., 2024). Furthermore, Olfson and colleagues (2018) found that marijuana use appeared to increase the risk of non-medical prescription opioid use and opioid use disorder.

### **Relationship Between Marijuana Use and Opioid Use**

The relationship between marijuana use and opioid use has been the subject of numerous recent studies. The scientific literature describes mixed results that increased access to marijuana will result in few opioid overdose deaths. Data support no effect relative to the availability of medical marijuana and opioid overdose deaths (Cano et al., 2023; Bryson et al., 2021; Fleisthler et al., 2020; Phillips and Gazmararian, 2017). These researchers noted the relationships need to be further analyzed. State activities relative to marijuana programs did not result in a reduction of opioid prescribing and adverse outcomes related to problematic opioid use (Hasin et al., 2022; Kim et al., 2022; Tormohlen et al., 2021). An analysis by Neilson and colleagues (2021) concluded that access to marijuana does not lower the use of chronic opioids for pain. A recent investigation found no evidence that state recreational or medical marijuana programs were associated with changes in opioid prescribing and overdose deaths (Nguyen et al., 2024).

Marijuana may serve as an initiator for opioid use and problematic patterns (Wilson et al., 2022). On days of marijuana use, the non-medical use of opioids nearly doubled in one study, confirming in this study that marijuana was not a substitute for opioids (Gorfinkel et al. 2021; Streck et al., 2022). Furthermore, evidence from a long-term study does not support a unidirectional or bidirectional relationship between marijuana and opioid use (Wilson et al., 2024).

Physicians have raised concerns about using marijuana as a potential treatment for Opioid Use Disorder (OUD) [Humphreys and Saltz, 2019]. Studies have found that marijuana is not an effective treatment for OUD and may have no effect and potentially increase the risk for OUD (Rosic et al., 2021; Olfson et al., 2018). Suzuki and Weiss (2021) noted that caution should be observed until more research is conducted with respect to marijuana as a treatment option for OUD. Evaluations suggest marijuana is not protective against OUD relapse (Naji et al., 2022). In contrast, Ganesh et al. (2024) reported that the co-use of cannabis and opioids among people who inject opioids resulted in reduced patterns of opioid use. Evidence for the use of cannabis-based products in the management of opioid use disorder remains heterogeneous, with numerous cases supporting and refuting the effectiveness of cannabis-based in the management of opioid use disorder (Le at al., 2024).

#### **Factor 4: History and Current Pattern of Abuse**

Marijuana continues to be a widely used substance. Survey data indicate that marijuana users are teenagers (aged 12 years and older), young adults, and older adults. According to the WHO, cannabis is globally the most used psychoactive substance under international control. Accounting for half of all drug seizures worldwide, the global annual prevalence of cannabis consumption is 2.5% or about 147 million people (WHO, n.d.).<sup>34</sup> In 2016, an estimated 28.6 million Americans aged 12 or older were current (past month) illicit drug users. Of those, 24.0 million were current (past month) marijuana users.<sup>35</sup> NSDUH 2023 data showed that approximately 61.8 million Americans aged 12 or older reported using marijuana in the past year, of which marijuana was the most commonly used illicit drug. The 2023<sup>36</sup> data showed that the percentage of use was highest among young adults aged 18 to 25 (36.5% or 12.4 million Americans) [SAMHSA, 2024].

According to 2023 NSDUH estimates, among individuals aged 12 or older who reported past year marijuana use (61.8 million people), smoking was the most common route of administration of using marijuana (77% or 47.6 million people) across all age groups. Of those who used marijuana in the past year, 84.4% of young adults (18 to 25 years), 79.3% of adolescents (12 to 17 years), and 74.9% of adults (26 or older) smoked marijuana. Other

<sup>34</sup> <https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/drugs-psychoactive/cannabis>

<sup>35</sup> <https://www.samhsa.gov/data/report/key-substance-use-and-mental-health-indicators-united-states-results-2016-national-survey>

<sup>36</sup> [Highlights for the 2023 National Survey on Drug Use and Health](#)

common routes of administration for marijuana among past year users varied across aged group. Among adolescents, 63.4% of vaped marijuana, 38.5% ate or drank marijuana, and 16.9% dabbed waxes, shatters or concentrates. Among young adults, about 52.2% vaped marijuana, 49.9% ate or drank marijuana, and 27.9% dabbed waxes, shatter, or concentrates. Among adults, 48.5% ate or drank marijuana, 33% vaped marijuana, and 12.8% dabbed waxes, shatter, or concentrates. There were other routes of administration for marijuana that were less common across all age groups. For example, 7.8% (4.8 million) applied lotion, cream, or patches to skin; 5.5% (3.4 million people) used marijuana as strips, lozenges, or sprays in the mouth or under the tongue; 3.3% (2.0 million people) took marijuana in pill form; and 0.7% (443,000 people) reported other routes.<sup>37</sup>

The 2023 MTF survey reported that the lifetime prevalence of marijuana use was 11.5% among 8th graders, 22.5% among 10th graders, and 36.5% among 12th graders (see Table 3; Miech et al., 2024). In addition, 8.3%, 17.8% and 29.0% of 8th, 10th, and 12th graders, respectively, reported using marijuana in the past year. The prevalence of vaping marijuana annually was 6.5%, 13.1%, and 19.6% in 8th graders, 10th graders, and 12th graders, respectively. Thirty-day prevalence of marijuana use was reported as 4.7%, 10.3%, and 18.4% of 8th graders, 10th graders, and 12th graders, respectively. The percentage of students reporting thirty-day prevalence of vaping marijuana was 4.2% of 8th grade respondents, 8.5% of 10th grade respondents, and 13.7% of 12th grade respondents. MTF data also show that marijuana remains one of the most consistently available drugs, with 73% of 12th grade students surveyed in 2023 reported that it would be fairly or very easy to access. According to 2023 MTF data,<sup>38</sup> cannabis use in the past 12 months was reported by 42.4% of young adults and individuals aged 23–24 had the highest prevalence (45.6 %). Cannabis use in the past 30-days was reported by 28.7 % of young adults and highest levels of use was reported for ages 23–24 at 32.2%. Of those reporting daily cannabis use (i.e., used 20 or more occasions in the past 30-days), 10.4 % young adults reported daily cannabis use.

## **Marijuana Products**

Historically, individuals would smoke dried cannabis plant material that contained delta-9-THC as the principal product constituent (Streck et al., 2019; Spindle et al., 2018, 2019a, 2019b). However, recreational marijuana legalization among states has allowed for an expansive retail marijuana marketplace with novel marijuana products and methods of administration (Dowd et al., 2023; Taylor and Pruyn, 2023). Marijuana is now available in a variety of products and forms such as dried flower, concentrates (includes oil, waxes, and shatters), edibles, cigarettes, vaping solutions, tinctures, and even topical solutions despite none of those options

<sup>37</sup> [Key Substance Use and Mental Health Indicators in the United States: Results from the 2023 National Survey on Drug Use and Health](#)

<sup>38</sup> Patrick, M. E., Miech, R. A., Johnston, L. D., & O'Malley, P. M. (2024). Monitoring the Future Panel Study annual report: National data on substance use among adults ages 19 to 65, 1976–2023 (PDF). Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan.

having an FDA-approved medical use (Steigerwald et al., 2018; Spindle et al., 2019a; Taylor and Pruyn, 2023). These forms and formulations of marijuana are widespread in Medicinal and Adult-Use states. Products containing marijuana or derived from marijuana are generally obtained from state-authorized non-medical programs, state-authorized medical-use programs, illicit drug market, and home cultivation for personal use. Edibles can be cannabis food or drink products and can be packaged as oral oils and tinctures. A survey of cannabis users show that they perceive edibles as a healthier alternative to smoking cannabis that can aid with sleep; however, negative outcomes include the unpredictable intensity of edibles (Lamy et al., 2016). Steigerwald et al. (2018) evaluated delta-9-THC concentrations in available, marketed products within states that have recreational or medical marijuana laws. That study found that some states with recreational marijuana use laws have defined potency thresholds in edibles, limiting THC doses in those products to 50 or 100 mg per package and 5 or 10 mg per serving, depending on the state. Even so, among 1,294 products that listed THC content on their packaging, THC content in edibles ranged from 5 to 7000 mg, approximately 4.2% (30) of packages exceeded the 100 mg limit, and 4.0% (28) of servings exceeded the 10 mg limit. Among all edibles, 8.1% (183) were in forms that may potentially attract children, such as a candy product (Steigerwald et al., 2018).

Vaporization is another popular method for cannabis administration (Morean et al., 2015; Lee et al., 2016; Spindle et al., 2018, 2019a, 2019b). Cannabis vaporizers heat dried cannabis, concentrated cannabis extracts, and/or resins to create an aerosol or vapor that can be inhaled. In a study that measured the acute effects of inhaling vaporized cannabis or smoking cannabis containing 10 and 25 mg delta-9-THC, inhalation of vaporized delta-9-THC produced effects (i.e., heart racing, difficulty performing routine tasks, dry mouth) that were stronger than those from smoking delta-9-THC (Spindle et al., 2018). Consistent with these drug effects, inhaled delta-9-THC resulted in a higher delta-9-THC blood concentration than that from the same dose smoked. Other studies have found no differences in delta-9-THC blood concentration between smoking and vaporized cannabis (Abrams et al., 2007; Newmeyer et al., 2016; Swortwood et al., 2017). While bioavailability of delta-9-THC varies based on the route of administration, in general, smoking and some vaporization devices yield similarly high bioavailability levels of delta-9-THC compared to oral administration. Thus, inhaling an average 151 mg of delta-9-THC, versus the FDA-approved maximum 30 mg of oral synthetic dronabinol products, would result in much higher concentration of bioavailable delta-9-THC and may lead to higher abuse potential and adverse effects than those reported in the FDA-approved dronabinol products.

One study collected data from over 54,000 smart vaporization devices from November 2020 to May 2022 (Vreeke et al., 2022). Here, the authors found that most consumers with these specific devices were considered “less than daily users” and on average used them eight days a month. The reported average amount of delta-9-THC consumed per day, week, and month were 151 mg, 271 mg, and 452 mg, respectively. Based on the 50<sup>th</sup> (median) and 90<sup>th</sup> quartile data, ranges in device use were 5 to 19 days per month and delivered 44 to 333 mg delta-9-THC daily,

91 to 671 mg delta-9-THC weekly, and 146 to 1081 mg delta-9-THC monthly. Other studies have reported mean daily use of 64 mg delta-9-THC in users the United States (n=2000; Blinc Group, 2022), an estimated 80 mg delta-9-THC in a rolled marijuana cigarette (Meehan-Atrash et al., 2019), and self-reported median monthly use of 1000 g, with the average use of 4600mg delta-9-THC, but with wide variations (n=83; Morgan et al., 2022). Of note, the data from Vreeke et al. (2022) are limited to use of the smart delivery devices and do not consider any other cannabis products that a user might have ingested using other vaporization devices or other routes of administration, such as smoking or oral ingestion.

### **Factor 5: Scope, Duration and Significance of Abuse**

Actual abuse data demonstrate that marijuana is one of the most widely abused substances in the United States. Recently, there have been introduction of various cannabis products with varying delta-9-THC concentration. Potency data<sup>39</sup> obtained from illegal cannabis products seized by law enforcement show that between 1995 and 2022, the concentration of delta-9 THC changed from 3.96% to 16.14%, a four-fold increase. Consistently, cannabis products available in dispensaries may contain more than 35% of delta-9-THC (Cash et al., 2020). Evidence suggests that there is a likelihood that higher potency delta-9-THC may increase the risk of developing cannabis use disorder (Arterberry et al (2019). Evidence posits that use of high concentration of delta-9-THC by adolescents and young adults is linked with increase in the frequency of cannabis use and development of mental health issues (Di Forti et al., 2019; Hines at al., 2020).

### **National Survey on Drug Use and Health**

As previously noted, according to the NSDUH, in 2023, an estimated 61.8 million people (21.8%) age 12 or older had used marijuana in the past year, and 43.6 million (15.4%) had used it in the past month, including 15.8 million (5.6%) who vaped marijuana in that period (SAMHSA, 2024). Among people who used marijuana in the past year regardless of mode, young adults (36.5% or 12.4 million people) had the highest percent, followed by 20.8% of adults aged 26 or older (46.5 million), then 11.2% adolescents aged 12 to 17 (or 2.9 million people). The percentage of past month use was highest among young adults aged 18 to 25 years (25.2% or 8.6 million people), followed by 15% of adults aged 26 or older (33.5 million people), then by 6% adolescents (1.6 million people). In 2023, among those who used marijuana, 19.2 million people (6.8%) had a past year marijuana use disorder. The percentage of individuals who had a past year marijuana use disorder was highest among young adults aged 18 to 25 years (16.6% or 5.6 million people) followed by adults aged 26 or older (5.5% or 12.3 million), then by adolescents aged 12 to 17 (4.7% or 1.2 million people). Furthermore, the average percentage of delta-9-THC in seized marijuana has increased over the past two decades (The University of Mississippi Potency Monitoring Project). The increase in percentage of the population using

<sup>39</sup> [Cannabis Potency Data | National Institute on Drug Abuse \(NIDA\)](#)

marijuana and increased potency of delta-9-THC is of great concern as this can lead to problematic health consequences.

### **Treatment Episode Data Set**

TEDS data showed that in 2020, marijuana/hashish was the primary substance in 9.8% of all admissions to substance abuse treatment among patients aged 12 and older. Marijuana/hashish admissions (87.2%) received ambulatory treatment services in greater proportion than other drug-related admissions combined (53.3%). In 2021, TEDS data reported that marijuana/hashish was the primary substance of abuse in 10.2% of all admissions to substance abuse treatment among patients aged 12 and older. In 2021, TEDS data reported that New York, California, Georgia, North Carolina, New Jersey, Texas, Minnesota, South Carolina, Florida, and Connecticut accounted for 55.9% of admissions to substance use treatment services where marijuana/hashish was listed as the primary substance.

### **Drug Abuse Warning Network**

DAWN provides national survey data of emergency department visits related to substance use and misuse. According to 2021 DAWN data, marijuana-related emergency department visits were highest among White, non-Hispanic or Latino males ages 26–44. In general, White Americans accounted for 50.2% of marijuana-related emergency department visits, while Black or African American patients (24.3%) accounted for the second highest percentage of marijuana-related emergency department visits. In 2022, the rate of cannabis-related emergency department visits was higher among Black or African American (660 per 100,000) patients compared to White (153 per 100,000) patients. Rates for cannabis-related emergency department visits were highest in individuals 18–25 years (597 per 100,000). Cannabis (12%) was the third-most frequently reported substance involved in drug-related emergency department visits.

### **National Poison Data System (NPDS)**

Data from America's Poison Centers' NPDS show that in 2021, there were 18,245 case mentions<sup>40</sup> involving various marijuana products. Of those, there were 12,045 single exposure calls for varying marijuana products.<sup>41</sup> About 41% (4,990) of the single exposure calls involved young children under five years old. The majority (8,488) of these marijuana exposures were managed at a health care facility. Gummin et al. (2022) reported that 132,995 exposures to 134,772 cannabinoid products were reported to the US poison centers over the 10-year period from January 2012 to June 2022. The report showed that plant-based marijuana products (n=61,159, 45.38%) was the most common substance involved in exposure calls. Exposure calls for plant-based marijuana products increased annually from 2012 to 2017, declined between 2018 to 2019, and increased again in 2020 and 2021. Further analysis showed that in 2021, there

<sup>40</sup> Other substances were co-involved.

<sup>41</sup> Edible, e-cigarettes, plant, other unknown marijuana product.

was a shift in exposure calls from plant-based marijuana products (7,688) to edible marijuana products (7,691). For exposure calls involving edible marijuana products, young children under the age of 13 years were mostly involved (40.62%). Of note, these exposure calls involving marijuana edible mostly affected pediatric patients less than 5 years. Consistently, in 2022, single exposure calls involving edible marijuana (10,512) exceeded plant-based marijuana (3,994) cases. Of the 10,512 edible marijuana single cases, 41% (4,301) involved pediatric patients. These data suggest an emerging trend in rising edible marijuana exposure calls to poison control centers and, of particular concern, exposure in pediatric population (Gummin et al., 2022; 2023).

### **Law Enforcement Data**

DEA's National Forensic Laboratory Information System (NFLIS) Drug<sup>42</sup> database collects scientifically verified data on drug items and cases submitted to and analyzed by participating federal, state, and local forensic drug laboratories in the United States (U.S.). Reports of cannabis/THC to NFLIS-Drug include substance descriptions of cannabis, various cannabis plant materials, concentrated cannabis, cannabis oil, delta-9-tetrahydrocannabinol, tetrahydrocannabinol (organic), and tetrahydrocannabinol - non-specific.

According to NFLIS-Drug, cannabis/THC has been reported in all 50 states, as well as the District of Columbia, Guam, American Samoa, U.S. Virgin Islands, and Puerto Rico. State and local forensic drug laboratories reported cannabis/THC more frequently than any other reported drug each year from 2001 through 2016. In 2017, cannabis/THC became the second most frequently reported drug (methamphetamine being first) to NFLIS-Drug by state and local forensic drug laboratories, accounting for 21.76% (344,167) of all drug reports that year. Cannabis/THC remained the second most frequently reported drug until 2022 when it became the fourth most frequently reported drug (behind methamphetamine, cocaine, and fentanyl) and accounted for 12.41% (146,631) of all drug reports that year. It is estimated that there were over 2 million exhibits of cannabis/THC submitted to and analyzed by state and local forensic drug laboratories between January 2016 and December 2023 (see Table 2).<sup>43</sup>

<sup>42</sup> NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of the Nation's estimated 1.2 million annual drug cases. NFLIS-Drug includes drug identification results from completed analyses only. While NFLIS-Drug data are not direct evidence of abuse, they can lead to an inference that a drug has been diverted and/or abused. See 76 FR 77330, 77332, Dec. 12, 2011.

<sup>43</sup> Sources: U.S. Drug Enforcement Administration, Diversion Control Division. (2017-2023). *National Forensic Laboratory Information System: 2016-2022 Annual Reports*. Springfield, VA: U.S. Drug Enforcement Administration. <https://www.nflis.dea/diversion.usdoj.gov/publications/Redesign.xhtml>. U.S. Drug Enforcement Administration, Diversion Control Division. (2024, November 29). Reports of Cannabis/THC and All Reported Drugs submitted to and analyzed by State, Local, and Private Entities during 2023 [NFLIS-Drug Data Query System analysis]. Retrieved from <https://www.nflis.dea/diversion.usdoj.gov/>

There has been a steady decline in the NFLIS-Drug annual estimates of cannabis/THC identifications over the last decade. This decline could be due to several factors, including, but not limited to, state legalization, policies in state and local laboratory reporting, and law enforcement prioritization. Still, the continued reporting of seized drugs indicates continued, widespread trafficking and abuse of marijuana.

**Table 2: Annual Reports of Cannabis/THC to NFLIS-Drug from State and Local/Municipal Forensic Drug Laboratories by Year, Projected National Estimates for 2016–2022 and Current Raw Count Data for 2023<sup>44</sup>**

	2016	2017	2018	2019	2020	2021	2022	2023
<b>Number of Cannabis/THC reports</b>	374,712	344,167	344,489	282,679	188,735	167,669	146,631	128,440
<b>Percent of Total Drug reports</b>	24.13%	21.76%	21.54%	18.58%	14.70%	12.64%	12.41%	10.60%
<b>Total Drug Reports</b>	1,552,720	1,581,426	1,599,428	1,521,360	1,283,971	1,326,205	1,181,750	1,211,213

The U.S. Customs and Border Protection Drug Seizures reported seizing approximately 175,000 pounds of marijuana in Fiscal Year (FY) 2024, which accounted for the largest drug seizure weight when compared to other drug types. In FY 2023 and 2022, marijuana drug seizure weight was about 150,000 pounds and 155,000 pounds, respectively.<sup>45</sup>

*High Intensity Drug Trafficking Area (HIDTA)*

In the midst of expansion and increased use of marijuana, California—a High Intensity Drug Trafficking Area (HIDTA)—witnessed a 75% increase in emergency department visits and admissions for marijuana-related use from 2016 (125,418) to 2020 (219,441). Furthermore, data from this report showed a 568% increase from 2008 (2,030) to 2020 (13,568) in emergency department visits and admissions for primary marijuana use in California (California HIDTAs, 2022). Consistently, marijuana impact reports from other HIDTAs show similar emergency department-related trends and include numerous other metrics to evaluate trends and outcomes. For example, in Arizona, emergency department admissions increased by 267% due to marijuana use from 2012 (630) to 2020 (2,313) and by 165% for marijuana-induced poisonings from 2012

<sup>44</sup> NFLIS-Drug national estimates from 2016–2022 Annual Reports. Reports for 2023 are still pending and a projected national estimate is not yet available. Therefore, 2023 reports are presented as raw counts based on data available on November 29, 2024. The total number of cases submitted to and analyzed by NFLIS-Drug reporting laboratories for 2020-2022 is noticeably lower than the number reported in previous years. The decrease in cases (and subsequent drug reports) is likely due, in part, to the impacts of COVID-19 on drug availability within disrupted illicit markets and changes in law enforcement activities and laboratory caseloads, staffing, and operations. As a result, one should use caution when comparing data from 2020-2022 with data from previous years.

<sup>45</sup> [Drug Seizure Statistics | U.S. Customs and Border Protection](#)

(617) to 2020 (1,637) [Arizona HIDTA, 2022]. In the Midwest, Iowa reported a 59.4% increase in marijuana-related emergency department visits from 2016 (106) to 2021 (169); Missouri observed a 75% increase in marijuana-related hospitalizations from 2018 (174) to 2022 (305); and North Dakota witnessed 294% increase in emergency department visits due to marijuana use from 2016 (556) to 2022 (2,189) and a 73% increase in marijuana-related hospitalizations from 2016 (139) to 2022 (240) [Midwest HIDTA, 2023].

**Factor 6: What, if Any, Risk There Is to the Public Health**

Marijuana use is associated with multiple adverse health and public safety risks, is commonly used by individuals with mood disorders, and results in comorbidities (Kuhns et al., 2022). Serious adverse effects have been demonstrated in those who report an early onset of use (i.e., beginning in adolescence), occasional or intermittent use, and chronic, long-term heavy use. These effects include increased risk of addiction to marijuana and other substances, motor vehicle accidents, cardiovascular complications in otherwise young and healthy patients, chronic bronchitis, certain cancers, cognitive effects, abnormal brain development, schizophrenia, depression, and anxiety.

**High potency marijuana – flower and concentrates**

State medical and recreational programs have access to high potency marijuana (Carlini et al., 2024; Dobbins et al., 2022). High potency marijuana flower ( $\geq 20\%$  delta-9-THC) and concentrates ( $\geq 60\%$  delta-9-THC) are accessible via State dispensaries and the illicit drug market.<sup>46</sup> Acute harms associated with high potency marijuana and marijuana products are well documented in the scientific literature (Cutler et al., 2022; Hinckley and Hopfer, 2021; Matheson and Le Foll, 2020; Murray et al., 2017; Prince et al., 2019), is highly desirable to the user (Smart et al., 2017) and places the user at increased risks of adverse health effects (Pennypacker et al., 2022).

A 2020 report<sup>47</sup> of market trend and patterns in Colorado’s adult use marijuana and medical marijuana markets showed an increase in average THC potency for flower and concentrate products (see Table 3). For flower, in 2020, the average THC content increased to 19.2% potency from 18.8% in 2019. For concentrates, the average percent of THC in products varied. For concentrate products sold by the gram, there was a slight decrease in 2020 to 67.8 percent from 69.4 percent in 2019. Among the concentrate product types such as Oil, Shatter, Wax, and Resin, percent of THC content had slight increases. For vaporizer cartridge, the percent THC content increased from 69.1% in 2019 to 79.7% in 2020.

**Table 3: Colorado 2020 Average Percent THC Content in Product Type**

<b>Product</b>	<b>Average THC %</b>
Flower (g)	19.17

<sup>46</sup> [Understanding THC concentration and potency | Washington State Liquor and Cannabis Board](#)

<sup>47</sup> [2020-Regulated-Marijuana-Market-Update-Final.pdf](#)

Shake/Trim (g)	17.03
Concentrates	67.82
- 500 mg Cartridge (each)	79.67
- Oil (g)	73.60
- Resin (g)	71.60
- Shatter (g)	70.97
- Sugar (g)	70.93
- Wax (g)	70.93
- Butter (g)	67.14
- Hash (g)	61.40

### **Risks from Acute Use of Marijuana**

Acute or intermittent use of marijuana can cause a myriad of adverse effects. A review of acute marijuana effects by Wilkinson et al. (2014) reported impaired neurological function including altered perception, paranoia, delayed response time, and memory deficits. Additionally, individuals who use marijuana occasionally may experience dysphoria, prolonged anxiety, and psychological distress (Carlyle et al., 2021). Below is a brief summary of some acute effects that may occur after intermittent or occasional use of marijuana, including anxiety and the effects of marijuana on driving under the influence, in controlled clinical trial settings, and other general observations.

#### ***Driving Impairment***

Studies examining the risks associated with marijuana use and driving have been published, including data from the National Highway Traffic Safety Administration (NHTSA) and controlled research studies that utilize driving simulators, impaired driving mobile device applications, and driving on a closed track after smoking various marijuana products or consuming marijuana-infused brownies. Marijuana use is known to increase risks of collision involvement among drivers (Asbridge et al., 2012; Li et al., 2012; Voas et al., 2012; Fares et al., 2022) and is associated with reports of increased lane departures or weaving (Arkell et al., 2019; Bramness et al., 2010; Lenné et al., 2010; Micallef et al., 2018; Ramaekers et al., 2000; Ronen et al., 2008).

Younger drivers (under 21 years of age) have been characterized as both at the highest risk of involvement in a fatal motor vehicle crash and in the age group most likely to use marijuana (Whitehill et al., 2014). Furthermore, in 2013, marijuana was found in 13% of the drivers involved in automobile-related fatal accidents (McCartt, 2015). In 2014, a publication noted the potential risk of automobile accidents associated with marijuana use appeared to be increasing along with the steady increase in individuals intoxicated with marijuana over the previous 20 years (Wilson et al., 2014). The most recent study by the NHTSA in 2013–2014 reported that delta-9-THC was the most frequent drug found in randomly tested drivers, with 8.7% of daytime drivers and 12.7% of nighttime drivers testing positive. When comparing the

2013–2014 results to the same drugs tested in 2007, nighttime use of delta-9-THC increased 46% between the two reports. A general increase of 19% was also observed in all nighttime drugs tested (medical and illegal) from 16.3% in 2007 to 20.1% in the latest report (Kelley-Baker et al., 2017).

Several controlled research trials have investigated the acute effects of marijuana and driving impairment. In one study by Spindle et al. (2021), infrequent cannabis users (ten men and women) ingested cannabis-infused brownies or inhaled vaporized cannabis products. To account for different absorption rates with different delivery methods, the cannabis brownies had 0, 10, or 25 mg delta-9-THC, whereas the vaporized cannabis doses were at 0, 5, and 20 mg delta-9-THC. The authors used the Driving Under the Influence of Drugs (DRUID<sup>®</sup>) driving mobile device application using an iPad mini. Significant differences in impairments were noted between placebo and all active doses in both routes of administration, with women showing greater impairment than men at the highest vaporized marijuana condition. The highest delta-9-THC marijuana condition exhibited the highest DRUID impairment score; however, the highest oral and vaporized doses produced scores that were not significantly different. Both the high oral and vaporized marijuana conditions resulted in scores equivalent to blood-alcohol concentrations of 0.08%. Impairment after oral ingestion lasted the longest amount of time. At the 25 mg oral delta-9-THC condition, impairment was significantly higher than at baseline for hours 2–5, whereas after the highest vaporized marijuana condition, significant impairment was at hours 0–1. This demonstrates that the slower pharmacokinetics of oral marijuana can impact impairment for a longer duration.

Using a driving simulator (NADS miniSim<sup>™</sup>), driving behaviors (e.g., lane weaving) were found to be impaired after inhaling 500 mg vaporized marijuana using a Volcano<sup>©</sup> Digit Vaporizer containing 6.7% (~34 mg) delta-9-THC, compared to placebo cannabis containing 0.009% delta-9-THC, in rural straight line driving tests with no distractions (Brown et al., 2020) and in urban and rural driving (including urban curves, interstate, interstate curves, dark rural, and rural straightaways) [Brown et al., 2019]. Driving under the influence of marijuana alone using an advanced driving simulator (the University of Iowa National Advanced Driving Simulator; NADS-1), which is a full vehicle cab simulator with 360° horizontal field of view and motion base that provides realistic feedback, has been assessed and showed significant impairments in driving. Impairments were often worsened when alcohol was administered in addition to marijuana (Hartman et al., 2015a; 2015b; 2016).

Taken a step further, the same research group added divided-attention tasks into the driving simulator (Miller et al., 2020). Here, participants inhaled the same 500 mg placebo, low delta-9-THC (~14.5 mg), or high delta-9-THC (~33.5 mg) vaporized marijuana *ad libitum* using the Volcano<sup>©</sup> device. To note, the blood levels of delta-9-THC varied from person to person. In some cases, participants had higher blood levels of delta-9-THC after inhaling the low dose delta-9-THC rather the high dose delta-9-THC marijuana. As a result, data analyses were shifted to make comparisons based on blood delta-9-THC concentrations. In a music artist selection

task, as one might do while driving, delta-9-THC blood concentration was a significant predictor of incorrect responses or longer time to complete the task. During a message-reading task, participants tended to decrease speed while completing the task. Additionally, lane departures were common during task periods and after active drug consumption. Higher delta-9-THC concentrations increased the odds significantly of slower recoveries from minor lane departures during the artist selection task, meaning participants had longer-duration lane departures. This could indicate either a slower recovery ability or decreased awareness of the vehicle's lane position while engaged in the task. The authors note that extreme lane departures were rare, occurring three times in the low delta 9-THC condition, twice when the low delta-9-THC condition was combined with alcohol, and seven times when the high delta-9-THC condition was combined with alcohol. The authors noted that declines in task completion were more prominent in cognitively demanding tasks such as sign identification. These effects are similar to other research in divided-attention tasks requiring substantial cognitive load (Anderson et al. 2010; Lenné et al. 2010; Hartman and Huestis 2013). Taken together, the results are consistent with other literature supporting the decreased capacity to multi-task under the influence of cannabis, which includes the numerous diverse tasks typically involved in driving.

Studies using the CAMH Virage VS500M simulator found similar evidence of increased lane departures (e.g., number of subjective effects also reported alone and with alcohol, feel effect, feel high, feel drowsy) after using marijuana containing an estimated 76 mg of delta-9-THC (Fares et al., 2022). Additive effects were noted when alcohol (enough to meet the 0.08% blood alcohol level) was consumed in addition to marijuana; however, the participants seemed unaware of the increased effects when under the influence of both substances.

### ***Other Acute Observations***

Other observations (e.g., euphoria, solemnness, drug liking) have presented in clinical trial settings in which a known amount of cannabis was consumed. In one trial, a healthy male participant with a history of using marijuana experienced intense auditory and visual hallucinations, although he had not consumed marijuana in the previous 30 days. This participant inhaled vaporized cannabis containing 25 mg delta-9-THC and reported the experience to be ketamine-like. Large changes were observed in the Intensity, Somaesthesia, Perception, and Volition scale of the Hallucinogen Rating Scale, which is a scale used to measure the effects of hallucinogens (e.g., psilocybin, salvinorin A, dextromethorphan) in laboratory settings. In this case, marijuana administration yielded higher scores of Intensity and Perception subscales compared to mean scores after administration of considerably high doses of psilocybin or salvinorin A, as well as comparable scores to the Perception scores of a high dose of dextromethorphan in other trials. In the same trial, this individual smoked the same marijuana material containing 25 mg delta-9-THC and did not experience the same hallucinogenic effects. Taken together, this finding suggests that the adverse effects on perception may occur and vary each time marijuana is consumed (Barrett et al., 2018).

## **Risks Associated with Chronic Use of Marijuana**

The scientific literature extensively reports that long-term and frequent use of marijuana can lead to both negative physical and psychological outcomes. Regular, long-term marijuana use can lead to increased risk of some individuals developing cannabis use disorder, schizophrenia or other psychoses in people who are predisposed to these conditions, severe vomiting (cannabis hyperemesis syndrome), toxicities to various organ systems (e.g., cardiovascular and pulmonary), and prenatal effects when marijuana is consumed while pregnant. Furthermore, daily cannabis use is significantly more common among persons with serious psychological distress and is increasing in this group, as well as among those without (Weinberger et al., 2019).

## ***Mental Health Outcomes Associated with Marijuana Use***

Marijuana consumption leads to psychopathological disturbances. Marijuana is known to be a contributing factor and exacerbate adverse mental health outcomes (Anthanassiou et al., 2021; Baral et al., 2024). In addition to being a contributing factor, marijuana users report self-medicating to manage mental health conditions. In addition to the desire to get high, self-medication with marijuana is reported for a host of conditions to alleviate psychiatric conditions (e.g., anxiety, depression, mania, etc.) [Scherma et al., 2020]. Furthermore, patients with mental health disorders using marijuana to self-medicate are often diagnosed with cannabis use disorder (Jenkins and Kohkrar, 2021).

The recent publications in the scientific literature highlight the impact of high potency marijuana on mental health (Aterberry et al., 2019; Di Fonti et al., 2015; Hines et al., 2020; Petrilli et al., 2023). Utilization of healthcare services (EDs, treatment, etc.) as a result of marijuana use has been increasing steadily among older adults (Choi et al., 2022; Han et al., 2023). One study in the Netherlands over a 16-year time frame found positive time-dependent associations between changes in cannabis potency and first-time cannabis admissions to drug treatment (Freeman et al., 2018). High potency marijuana is associated with self-reported depression and dependence (Chan et al., 2017; Freeman and Winstock, 2015; Rup et al., 2021).

In a review by Gorelick (2023), the seven marijuana-related disorders were highlighted as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision (DSM-5-TR). As noted in that review, the marijuana-related disorders listed in DSM-5-TR are:

1. Cannabis intoxication
2. Cannabis-induced anxiety disorder
3. Cannabis-induced psychotic disorder
4. Cannabis-induced sleep disorder
5. Cannabis-induced delirium
6. Cannabis withdrawal
7. Cannabis use disorder

Cannabis use disorder is much more prevalent in individuals with mental illnesses like schizophrenia, mood and anxiety disorders, PTSD, and personality disorders (Lowe et al., 2019). Earlier age at first exposure to cannabis was associated with younger age at prodrome and psychosis onset, worse premorbid functioning, and greater severity of cannabis use disorder at admission (Fergusson, 2003; Kline et al., 2022; Wiles et al., 2006). Early consumption, before the age of 15 years, is associated with a greater risk of developing psychosis (Casadio et al., 2011; Arseneault, 2002; Stefanis et al., 2004).

### *Cannabis Use Disorder*

CUD is a chronic relapsing condition in which there is loss of control over cannabis use despite physical or psychological harm. The “high” can produce a desire for repeated use and in some users develop into CUD. Drugs of abuse can induce neuroadaptation in the midbrain of dopaminergic neurons through excessive and repeated stimulation of dopaminergic neurons (Koob and Volkow, 2016). Delta-9-THC, the main psychoactive compound in cannabis, causes changes in dopaminergic circuitry and produce reinforcing effects (Bloomfield et al., 2016). Delta-9-THC activation of CB1 receptors influences the presynaptic release of both GABA and glutamate, which then alter the mesolimbic dopaminergic system activity (Volkow et al., 2019). The reinforcing effects of cannabis produce the desire for repeated use that can lead to the development of CUD in some users.

The major risk factors for the development of CUD are the frequency and duration of cannabis use as well as the potency of cannabis (see Factor 3). Thus, of significant concern is the significant increase in the level of delta-9-THC in cannabis products (Chandra et al., 2019). Frequency of marijuana use for medical symptoms did not improve pain, anxiety, or depression symptoms but did result in the new onset of CUD in roughly 17% of the participants after 12 months of use (Cooke et al., 2023).

Ten percent of the 193 million individuals in the United States who have ever used cannabis meet the criteria for lifetime cannabis dependence (Urits et al., 2021; Connor et al., 2021). Matson et al. (2023) found CUD to be underdiagnosed and undertreated. This remains concerning as adolescent use of marijuana increases (Ladegard and Bhatia, 2023). State medical and recreational marijuana programs played a role in increasing diagnosis of CUD, especially among population with high rates of CUD risk factors (Hasin et al., 2023).

CUD is a health concern in its own right, but also has been shown to increase other health risks. Evidence demonstrates that cannabis use and CUD are associated with some psychiatric disorders (Hasin and Walsh, 2020) as mentioned above. In addition, a two sample Mendelian randomization study using secondary data analyses (n=184,765) based on the Genome-Wide Association Study and the Psychiatric Genomics Consortium aimed to assess the effect of cannabis use on cancer risk (Niu et al., 2024). After conducting analyses of cannabis use disorders and cancer risk, they reported that cannabis use disorder elevated the risk of breast cancer as well as the risk of lung cancer by 12% (OR=1.122, p-value=0.014) [Niu et al., 2024].

## *Psychosis*

There has been extensive research to determine whether marijuana usage is associated with development of schizophrenia or other psychoses. Marijuana use is associated with early onset of psychosis, symptom severity, higher rates of relapse, longer hospitalizations, and poorer health outcomes (Lowe et al., 2019). Daily use of high-potency marijuana increases the risks for admissions and interventions after first-episode psychosis and relapse in psychosis (Large and Nielsen, 2017; Schoeler et al., 2016). Marijuana has long been linked to drug-induced psychosis (with and without complete reversibility) and increased incident rates for psychotic disorders (Das, 2021; Di Gennaro and Colizzi, 2023). In general, marijuana-induced psychosis lasting at least 48 hours can occur during intoxication or withdrawal (Starzer et al., 2018).

Per Ganesh and D'Souza (2022), available evidence supports that marijuana causes psychosis and that the risk for conversion of psychosis to schizophrenia is highest when the psychosis is marijuana-induced. Studies report that up to 50 percent of cannabis users that have emergency department presentations with subsequent hospitalizations for cannabis-induced psychosis will go on to develop schizophrenia (Crocker et al., 2021). A relationship exists between age of first use, dose, and the risk of developing psychosis. Furthermore, cannabis use doubles the risk of developing psychosis in vulnerable people (Ortiz-Medina et al., 2018). A recent review reaffirmed the relationship between THC exposure and psychotic symptoms manifested by chronic marijuana use, and acute marijuana use is associated with temporary psychotomimetic symptoms (Cupo et al., 2021). Numerous factors, including genetic and environmental factors, increase the risk of developing schizophrenia, and substance use disorder, and cannabis is associated with the strongest link and evidence (Crawford and Go, 2022). Healthcare providers hypothesize, based on data from a report in South London, that between 8% and 24% of all psychotic disorders could be avoided by limiting highly potent/concentrated marijuana (Di Forti et al., 2015).

Marijuana use is known to result in and to be a contributing factor in psychosis and worsening of outcomes (Sideli et al., 2020). Risk for psychosis is influenced by age of initiation, frequency of use, potency of material, and administration (Fischer et al., 2023). Despite the well-established link between marijuana use and the increased risk for developing a psychotic disorder, the underlying mechanisms are poorly understood, as is common with other disorders (Dawes et al., 2024). Marijuana use is a major contributor to the course of psychosis and associated outcomes to include increased severity in symptoms, risk of violence, longer hospital visits, and diminished quality of life (Chesney et al., 2024). The increased potency of marijuana is directly associated with adverse outcomes. This is relevant and notable where marijuana material with upwards of 90 percent THC concentrations can be accessed (Colizzi and Murray, 2018).

Furthermore, harm reporting associated with marijuana and psychosis appear to be increasing. Emergency department presentations in the United States and Canada have increased

for marijuana-associated psychosis (Callaghan et al., 2022; Wang et al., 2022). One study found a five-fold increase in mental health diagnoses in marijuana-associated emergency department visits compared to visits without marijuana involvement in Colorado from 2012 to 2014 (Hall et al., 2018). Similarly, from 2015 to 2019, observed emergency department presentations for cannabis-induced psychosis doubled in Canada (Callaghan et al., 2022; Myran et al., 2023). From 2000 to 2016, incidence of cannabis-induced psychosis increased by 67% in Norway, 115 percent in Denmark, and 238% in Sweden, based on national patient registries (Rognli et al., 2023).

Studies have established that marijuana exposure preceded symptom development for psychosis and schizophrenia, reaffirmed by recent genetic studies (Johnson et al., 2021; Mustonen et al., 2018; Quattrone et al., 2021; Radhakrishnan et al., 2022; van Os et al., 2021). Additional research has demonstrated that marijuana exposure precedes the development of psychosis and schizophrenia and can trigger psychosis and suicidal thoughts for individuals with no previous history of mental illness (Di Forti et al., 2015; Levi et al., 2023; Marconi et al., 2016; Petrilli et al., 2022; Volkow et al., 2016). These findings are further concerning when marijuana users with mental health disorders seek-out high potency marijuana, with its increased risks for negative health outcomes.

Furthermore, a high percentage of presentations for marijuana-induced psychosis will convert to either schizophrenia or bipolar disorder (Myran et al., 2023; Niemi-Pynttari et al., 2013; Starzer et al., 2018). Crocker and colleagues (2021) found up to 50 percent of patients with marijuana-related psychotic symptoms presenting to the emergency department requiring hospitalization will go on to develop schizophrenia. When comparing various geographical locations through the US, the Pacific census division—consisting of Alaska, Washington, Oregon, California, and Hawaii—had significantly higher odds of hospital discharges for psychosis than other divisions. There was a significant correlation between the cannabis legality score and proportion of hospital discharges for psychosis associated with cannabis use. The authors concluded that there was a higher proportion of hospital discharges for psychosis associated with cannabis use in areas with more liberal cannabis legalization laws.

Delvecchio and colleagues (2020) observed selective brain reductions in a pilot study of marijuana-induced psychosis when compared to non-psychotic marijuana users. A familial predisposition has not been identified for patients who develop psychosis or schizophrenia using marijuana (Arendt et al., 2008; Di Forti et al., 2015). Cheng et al. (2023) found psychotic disorders showed a causal effect on cannabis phenotypes, and lifetime cannabis use had a causal effect on bipolar disorder. Through an analysis via DSM-5, there is a well-established association between marijuana-induced psychosis and later schizophrenia (Pearson and Berry, 2019).

## *Schizophrenia and Other Disorders*

As mentioned previously, marijuana use increases the risk of developing schizophrenia (Crawford and Go, 2022). Marijuana use and schizophrenia are closely associated, and the prevalence of schizophrenia is high among those with CUD. Epidemiological studies suggest that marijuana use has a negative impact on the expression and course of schizophrenia (D'Souza et al., 2009). Approximately one in every four individuals with schizophrenia has a concurrent diagnosis of CUD (Lowe et al., 2019). Additionally, a research study by Hamilton (2017) concluded that evidence exists of a dose-response relationship between cannabis and psychosis, and that for those individuals with schizophrenia, cannabis exacerbated their symptoms. While examining the prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings between 1990 and 2017, Hunt et al. (2018) concluded that patients with substance use disorder had an earlier age of onset of schizophrenia, however a meta-regression showed prevalence of use of all illicit drugs increased among patients with schizophrenia spectrum disorders over time in addition to marijuana. From a published review of medical charts, in a psychiatric unit over a four-month period in 2017, approximately half of the patients with schizophrenia spectrum disorder self-reported marijuana use amongst other substances (Olayinka et al., 2020). Results from longitudinal analyses highlight a 3- to 4-fold increase in schizophrenia associated with cannabis use disorder during the past 2 decades in Denmark (Hjorthøj et al., 2023). Schizophrenia patients with CUD have an increasingly challenging path. Patient histories for schizophrenic patients with cannabis use disorder compared with those without document longer and more frequent psychiatric hospital stays (Pearson and Berry, 2019).

In an analysis of longitudinal studies, adolescents between 12 and 18 years of age were found to be at an increased risk of schizophrenia with both high- and low-frequency marijuana usage (Godin and Shehata, 2022). Colizzi and colleagues (2020) pointed to the overlap of structural, functional, neurochemical, and structural connectivity brain alterations in individuals with frequent or high potency marijuana use to explain the pathophysiology of schizophrenia. Escalation in marijuana use may be predictive of an increased risk for onset of schizophrenia and early adult use may be as important as adolescent use (Hjorthøj et al., 2023; Kelley et al., 2016). Almost 50 percent of individuals who experience an initial episode of marijuana-induced psychosis are diagnosed with schizophrenia 2 to 4 years after their first psychosis experience (Starzer et al., 2018; Arendt et al., 2005). While the relationship between marijuana use and the onset of schizophrenia remain complex and dependent on many factors, early marijuana use remains a critical event (Koenders et al., 2016; Patel et al., 2021; Penzel et al., 2021). Reduced gray matter volumes were associated with patients with schizophrenia who use marijuana (Cohen et al., 2012; Ghosh et al., 2022; Shah et al., 2022; Solowij et al., 2011).

Despite distinct diagnostic criteria, schizophrenia and bipolar disorder show some degree of overlap on different aspects, especially in certain subpopulations of patients. The association between marijuana use and mood disorders is well documented (Kuhns et al., 2022; Lowe et al.,

2019; Sorkhou et al., 2024). Cannabis use disorder is associated with an increased risk of psychotic and nonpsychotic bipolar disorder (Jefsen et al., 2023). As our understanding of marijuana and bipolar disorder develops, an analysis by Maggu and colleagues (2023) proposed that marijuana use may precipitate or worsen bipolar disorder. In addition, cannabis use is associated with differences in regional brain structure among adolescents with bipolar disorder (Sultan et al., 2021).

In a review by Lucatch and colleagues (2018), patients with mood disorders including major depressive disorder and bipolar disorder have higher rates of marijuana use. Individuals with bipolar disorder may present intense patterns of marijuana use (Taub et al., 2018). The outcomes of adolescent marijuana use remain concerning relative the finding that a large number of young people could develop depression and suicidality attributable to marijuana (Borges et al., 2016; Gobbi et al., 2019; Onaemo et al., 2022). Comorbid cannabis use disorder and major depression are an independent predictor of suicide, with frequency of marijuana use being associated with increased suicide attempts (Schmidt et al., 2020).

#### *Major Depressive Disorder*

Gukasyan and Strain (2020) examined results from the NSDUH, comparing adolescents with a history of cannabis use (N=14,873) with never users (N=73,079). They reported that adolescents with any cannabis use history had significantly higher rates of major depressive disorder, although the directionality between frequency of use and major depressive disorder remains unclear. Interestingly, when comparing different marijuana groups for their frequency of use, heavy smokers, defined for this study as using marijuana on a weekly or greater basis, had significantly lower predicted prevalence of “lifetime and past year major depressive disorder”, and “past year major depressive disorder with severe role impairment” compared to light users and those who used marijuana greater than one year ago.

Agrawal et al. (2017) sought to identify associations between aspects of marijuana use and major depressive disorder as well as suicidal thoughts and behaviors in identical twins who are discordant for cannabis exposure. They used retrospective data on same-sex male and female twin pairs drawn from 3 studies that had recruited twins from the Australian Twin Registry from 1992–93, 1996–2000, and 2005–09. Their findings showed that the monozygotic twin who used cannabis frequently was more likely to report major depressive disorder and suicidal ideation compared with their identical twin who had used cannabis less frequently, even after adjustment for covariates. Carrà et al. (2019) hypothesized that heavy cannabis users are more likely to report depressive disorders but noted that the evidence was not conclusive. They examined prevalence rates of different levels of past-year cannabis use and major depressive episode, separately for young people (12–17 years) and adults (18–64 years), using data between 2006 and 2015 from the NSDUH. Their results showed that cannabis users were more likely, using both single-year and pooled survey data, to have suffered from a major depressive episode in the past year. Multiple logistic regression models, after adjusting for time period, age, and gender,

showed an association between major depressive episode and marijuana use, regardless of marijuana use levels.

Pacek et al. (2020) similarly used NSDUH data to estimate trends in the prevalence of cannabis use and risk perceptions of cannabis use from 2005–2017 among individuals in the United States with and without depression. Their findings showed that the prevalence of any, daily, and non-daily cannabis use in the past month was higher among those with depression versus those without. Any, daily, and non-daily cannabis use increased among persons with and without depression from 2005–2017, yet the increase in any and daily cannabis use, adjusted for sociodemographic characteristics, was more rapid among those with depression. Perception of great risk associated with regular cannabis use was significantly lower among those with depression and decreased significantly more rapidly over the study period among persons with depression, compared with those without. Overall, they concluded that the prevalence of cannabis use in the United States increased from 2005–2017 among persons with and without depression, was approximately twice as common among those with depression, and that persons with depression experienced a more rapid decrease in perception of the risk associated with cannabis use.

Most recently, Xu et al. (2024) examined 2016–2019 NSDUH data from 168,859 adults, among which 15,959 had experienced major depressive disorder in the past year, indicated by a major depressive episode marked by major depressive disorder symptoms. In addition, the results demonstrated that adolescent use of alcohol, marijuana, and inhalants prior to age 18 were associated with increased odds of major depressive disorder.

Feingold et al. (2017) used data from Wave 1 and Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions, which included individuals with baseline major depressive disorder (N=2,348). These individuals were compared to nonusers of marijuana using linear and logistic regression analyses controlling for sociodemographics, psychiatric disorders and substance use disorders at baseline. Their results found that the level of cannabis use was associated with significantly more depressive symptoms at follow-up, particularly anhedonia, changes in body weight, insomnia or hypersomnia and psychomotor problems.

### **Emergency Department Visits**

As noted in sections above and in other Factors, published case reports and case series highlight instances where acute and chronic marijuana use has resulted in seeking professional medical care in the emergency department. Some of the common presentations included intoxication, severe anxiety, altered mental status, suicidal ideation, and hallucinations and often result in a prolonged admittance to the hospital, rather than being released from the emergency department (Leach et al., 2022).

More research is emerging concerning marijuana-related emergency department presentations, due in part to the increasing numbers of states that have legalized marijuana

medically or recreationally. The increases in marijuana use and in cannabis potency have led to cannabis-related emergency department visits and hospitalizations across states (Tweet et al., 2023). As expected, there is a positive correlation between the location of medical cannabis dispensaries and hospitalizations due to marijuana use (Mair et al., 2021). Emergency department visits associated with marijuana only and marijuana-poly substance use increased between 2004 and 2011 (Zhu and Wu, 2016). Increasing emergency department visits and associated harms continue as detailed in the scientific literature (Shen et al., 2019; Gates and Bridgford, 2020; Gresnigt et al., 2023; Han et al., 2023; Myran et al., 2024; Roehler et al., 2022). Among the numerous adverse events for emergency department presentations, cardiovascular events have been reported (Gresnigt et al., 2023; Zongo et al., 2021). Individuals presenting to the emergency department are highly likely to have repeated visits (Gates and Bridgford, 2020; Kim et al., 2023).

In a study analyzing 2012–2013 National Epidemiologic Survey on Alcohol and Related Problems, marijuana use increased the likelihood of emergency department visits through increased injury risk. In this study, past-year emergency department visits and past-year injury rates were higher in individuals who used marijuana compared to nonusers (Choi et al., 2018). Studies report up to 50% of cannabis users that have emergency department presentations with subsequent hospitalization for marijuana-induced psychosis, will go on to develop schizophrenia (Crocker et al., 2021). Similarly, in the state of Colorado, emergency physicians have noted an increase in marijuana-associated psychiatric visits. Statewide data from Colorado demonstrated a fivefold higher incidence of mental health diagnoses in cannabis-associated emergency department visits compared to non-cannabis associated emergency department visits (Hall et al., 2018). In another study, three hospitals in Colorado were analyzed based on emergency department syndromic surveillance system data from 2016–2017. Analysis of the data (submitted through the Electronic Surveillance System for the Early Notification of Community-Based Epidemics) indicated that out of a total of 44,942 emergency department visits, 453 were identified as potential acute adverse effects of marijuana cases. After review of 422 medical records, 188 (45%) cases were true acute adverse effects of marijuana cases. Data also revealed that, compared with all other emergency department cases, cases involving acute adverse effects of marijuana were significantly more likely to be among non-Colorado residents than among Colorado residents. Among these emergency department presentations in the Colorado study, cases were significantly more likely to involve edible marijuana use than smoked marijuana use (Marx et al., 2019). Wang et al. (2018) completed a retrospective study of adolescent marijuana-related emergency department visits in Colorado, from 2005 through 2015, for patients between 13 and 21 years old. In this analysis, 4,202 marijuana-related emergency department visits were identified and 71% of these visits were associated with a psychiatric diagnosis. In addition, adolescent marijuana-related visits increased from 1.8 per 1,000 visits in 2009 to 4.9 in 2015 (Wang et al., 2018). Furthermore, in Colorado, there has been a positive association between cannabis dispensaries and rates of ED visits for psychosis with a 24% increase (Wang et al., 2022).

In a study by Han et al. (2023), trend analysis of marijuana-related emergency department visits from all acute care hospitals in California from 2005 to 2019 was conducted. In this analysis, cannabis-related emergency department visit rates increased significantly for adults aged 65 and older. The overall rate increased by 1,804%, from 20.7 per 100,000 visits in 2005 to 395.0 per 100,000 emergency department visits in 2019. When examining the data by race/ethnicity, older Black adults had the highest emergency department visit rates in 2019 and the largest absolute increase when compared to Whites, Hispanics/Latinas, Asians/Pacific Islanders, and the ethnicity listed as other. When comparing males to females, older males had a higher emergency department visit rate in 2019 and a greater absolute increase than older women (Han et al., 2023). In Michigan, Keung et al. (2023) conducted a retrospective cohort analysis of all emergency department patients with cannabis-associated diagnostic codes that presented to a hospital from November 2018 to October 2020. In this analysis, 1,135 children and adults were evaluated for acute cannabis toxicity. The study authors found 196 patients (17.3%) fit the criteria for cannabis-induced anxiety disorder. In comparison, 939 (82.7%) experienced some other form of cannabis toxicity, such as cannabis hyperemesis syndrome (Keung et al., 2023; Brown et al., 2023). Also, an ED chart audit from Michigan, post marijuana legalization in the state, found 15.8% of charts had marijuana use documented, and users were likely to have a history of cocaine use, schizophrenia, antipsychotic use, and tobacco use (Pawl et al., 2022).

Marijuana users present to emergency departments in response to acute cannabis toxicity, drugs used in combination with marijuana, and effects related to the chronic use of marijuana. Over the last decade, emergency departments in medical and recreational marijuana states have observed significant health consequences (Roberts, 2019). Marijuana related presentations add to the caseloads of already chronically overburdened emergency departments (Razban et al., 2022). Accidental marijuana ingestion and marijuana-induced anxiety disorder are common presentations. Some researchers have observed an increase in emergency department presentations for marijuana as an impact of marijuana legalization (Hinckley et al., 2024; Moran et al., 2022; Tolan et al., 2023; Wang et al., 2018, 2022).

Among primary diagnosis categories, mental illness was more prevalent in emergency department visits and hospitalizations for marijuana negative outcomes per marijuana-related billing codes (Wang et al., 2018). Examination of the role marijuana plays in mental health-driven healthcare encounters is critical given the relationship between drug use disorders and mental health disorders (Aspis et al., 2015; Hanna et al., 2016; Grant et al., 2016). From Colorado statewide data, a five-fold higher prevalence of mental health diagnoses in marijuana-associated emergency department visits was observed from 2012 to 2014 (Hall et al., 2018).

#### *Accidental Ingestion of Marijuana by Youth*

State medical and recreational programs are a major contributor to pediatric marijuana exposures and presentations at emergency departments (Dean et al., 2021; Wang et al., 2016). Analyzing data before and after legalization in Colorado, it was found legalization did affect the

incidence of exposures (Wang et al., 2016, 2018). Following the surge in individuals receiving medical cannabis in Colorado, there was a significant increase in emergency department visits for children less than 12 years old for cannabis exposure at an academic tertiary pediatric hospital in Colorado, with 57% of these cases being due to exposure to edibles (Wang et al., 2013). Additionally, Colorado regional poison center cases for pediatric marijuana exposures increased significantly and more than the national average from 2009 to 2015, with significant increases in pediatric marijuana exposures occurring in the 2 years following recreational legalization (Hinckley et al., 2024; Wang et al., 2018).

### *Cannabis Hyperemesis*

Cannabinoid hyperemesis syndrome is a syndrome of cyclic vomiting associated with chronic marijuana use. Cannabinoid hyperemesis and marijuana withdrawal have similar symptoms at presentation, notably abdominal pain and vomiting. As Razban and colleagues (2022) noted, cannabinoid hyperemesis syndrome and marijuana withdrawal are the result of two differing pathophysiological processes. Survey participants from emergency department admissions reported high rates of persistent cannabinoid hyperemesis symptoms (abdominal pain, nausea, or cyclic vomiting) in the two-week period immediately following an emergency department visit, with a median duration of 7 days (Wightman et al., 2024). As cannabis consumption steadily increases, cannabis hyperemesis syndrome has become a more common occurrence (Khattar and Routsolias, 2018).

### *Marijuana Use and Association with Self-Harm*

Marijuana use has been associated with depression and self-harm, and a recent study established phenotypic and genetic associations (Hodgson et al., 2020). Moreover, marijuana use, and the increased prevalence of self-harm have been suggested to be moderately associated with emotional regulation and impulsivity (Escelsior et al., 2021). Evidence demonstrates an association between marijuana use, cannabis use disorder, and psychiatric disorders (Hasin and Walsh, 2020). Marijuana use negatively influences the development, course, and prognosis of major depressive disorders and bipolar disorders (Sorkhou et al., 2024). Cannabis use disorder is a common comorbidity and risk marker for self-harm, all-cause mortality, and death by unintentional overdose and homicide among youths with mood disorders (Fontanella et al., 2021; Watterreus et al., 2018). Evidence from observational and experimental studies has confirmed the important role of cannabis use, the development of a cannabis use disorder, and the initiation and persistence of psychotic disorders. Moreover, marijuana use, especially heavy use, is associated with the onset and course for depression and psychosis (Kuhns et al., 2022; Sideli et al., 2020). Researchers are still trying to better understand whether marijuana use aims to regulate mood and whether use precipitates comorbid conditions. Of the many potential associations, findings have confirmed an association between marijuana use and increased suicidality among persons with bipolar disorder (Bartoli et al., 2019; Selloni et al., 2022). Bipolar disorder is characterized by alternating and fluctuating episodes of depression and mania

or hypomania, or mixtures of manic and depressive features (Bobo, 2017). Relative to bipolar disorder, some individuals may initiate marijuana after symptom onset to regulate mood, while most studies point to marijuana preceding the onset of bipolar disorders and increasing the severity of depressive, manic, and psychotic symptoms in bipolar disorder (Kuhns et al., 2022; Kvitland et al., 2015). Regarding suicide, there is a bidirectional association between marijuana use and suicide in the general population; marijuana use increases the risk for suicidal behavior and vice versa (Kuhns et al., 2022).

A recent literature review by Ricci and colleagues (2023) found that there is a positive correlation of marijuana use with increased suicide risk. The onset of cannabis use is a risk factor in suicidal ideation. Associations have been found that connect early initiation and suicidal behaviors (Ahuja et al., 2022). Results from survey analyses indicate that cannabis use and cannabis use disorder are a risk for suicidal ideation (Han et al., 2021). The impact of marijuana in adolescents presents with an increased risk for self-harm, suicidal ideation, and suicide attempts (Ahuja et al., 2022; Denissoff et al., 2022; Fresán et al., 2022; Oladunjoye et al., 2023). Marijuana use has also been found to worsen outcomes and is associated with an increased risk of transitioning from suicidal ideation toward making a suicide attempt (Mason et al., 2024). In addition to adolescents, other vulnerable populations see an increased risk of suicide associated with marijuana use. Specific studies further highlight the association of marijuana use and worsening outcomes for users. Studies have examined the link between cannabis use and suicidality, with all reporting significant associations (Halladay et al., 2020; Hinckley et al., 2023; Kelly et al., 2021; Shalit et al., 2016). Through an analysis of electronic health records, the risk of suicidality was 22 times higher for marijuana users with cannabis use disorder than for the general public (Pavarin et al., 2023). A recent study analyzing data from 2009 to 2019 found that medical marijuana legalization and recreational marijuana legalization were associated with increased suicide-related mortality in 14- to 16-year-olds (Hammond et al., 2024). Consistent across published studies, suicide rates for adolescents have increased with recreational and medical state programs (Flores et al., 2023; Hammond et al., 2024; Myran et al., 2024; Oladunjoye et al., 2023; Roberts, 2019).

Among veterans, those using marijuana with a cannabis use disorder are more likely to suffer comorbid conditions such as, psychiatric, suicidality, pain, mortality, and other substance use compared with those without cannabis use and cannabis use disorder (Livne et al., 2023). Suicidal ideation is a known risk factor for suicide attempts and completions, veterans with comorbid posttraumatic stress disorder and depression represent a vulnerable group. Heavy marijuana use has been identified as a unique risk factor for suicide attempts among veterans (Adkisson et al., 2019). With these findings, it remains of particular concern any increases in cannabis use disorder. Marijuana use is a risk factor for suicide in veterans (Grove et al., 2023). Although, marijuana has been promoted as treatment option for veterans' evidence has not demonstrate safety and efficacy and the risks continue to be communicated in the scientific literature. Current findings suggest a potentially concerning association between suicide risk and

marijuana use in veterans which should be a critical consideration (Adkisson et al., 2019; Boscarino et al., 2022; Kimbrel et al., 2017). A particular study noted an increase since 2005 in diagnosis of cannabis use disorder has increased substantially among Veteran Health Affairs patients when compared to general and other patient populations (Hasin et al., 2022). Results suggest marijuana use, especially for military personnel experiencing elevated posttraumatic stress disorders symptoms may negatively impact suicidal thoughts and behavior (Allan et al., 2019). Additionally, marijuana use may be a predictor as a risk for self-harm (Borges et al., 2016; Kimbrel et al., 2017; Grove et al., 2023; Kimbrel et al., 2023). Findings suggest screening and positive result for cannabis use disorder might be an especially strong indicator of suicide ideation and planning in veterans (Bohnert et al., 2017; Hill et al., 2021). Currently, the U.S. Department of Defense Clinical Practice Guidelines recommends against use of marijuana or marijuana-derived products for the treatment of posttraumatic stress disorder (Schnurr et al., 2024).

## **Factor 7: Its Psychic or Physiological dependence Liability**

### **Physiological (Physical) Dependence in Humans**

Physical dependence is a common effect associated with the discontinuation of chronic drug use, which can lead to the development of withdrawal symptoms when the drug is discontinued. It is well known that abrupt cessation or significant reduction in cannabis use leads to cannabis withdrawal in dependent cannabis users. In chronic users of marijuana, withdrawal symptoms occur within 24–48 hours after cessation of cannabis use. This initial phase of withdrawal is characterized by decreased appetite, irritability, insomnia, and shakiness. These symptoms observed during the early phase are expected to peak between 2–6 days and can last up to three weeks as delta-9-THC levels continue to decline. Symptoms such as anger and depression can occur at approximately 1–2 weeks into marijuana withdrawal phase. Pattern changes in sleep can continue for several weeks (Conner et al., 2022). Withdrawal symptoms commonly reported in experimental studies include irritability, insomnia, decreased appetite, depressed mood, anxiety, and restlessness. Less common physical symptoms include chills, headaches, physical tension, sweating, and stomach pain (Conner et al., 2022). A diagnosis of CUD under the DSM-5 lists cannabis withdrawal syndrome as a criterion. According to DSM-5 criteria, in order to be characterized as having marijuana withdrawal, an individual must develop at least three of the seven symptoms within one week of decreasing or stopping the heavy and prolonged use (American Psychiatric Association, 2022). These seven symptoms are (1) irritability; anger or aggression, (2) nervousness or anxiety, (3) sleep difficulty, (4) decreased appetite or weight loss, (5) restlessness, (6) decreased mood, and (7) somatic symptoms causing significant discomfort (American Psychiatric Association, 2022).

The severity and duration of withdrawal symptoms associated with marijuana cessation are greater in those diagnosed with CUD. A study by Bonnet et al. (2017), in women seeking treatment for CUD showed that women have more frequent and severe withdrawal symptoms

than men after cessation of marijuana. The severity of cannabis withdrawal and the duration can vary between individuals depending on the amount of prior marijuana use, comorbidities, social factors and/or stressors, context of cessation, and even the severity of dependence (Bonnet et al., 2017).

### **Psychological (Psychic) Dependence in Humans**

DSM-5 combined cannabis abuse and dependence into a single category capturing the behavioral disorder that can occur with chronic cannabis use, mainly CUD. Physicians in Colorado noted that CUD is underdiagnosed and undertreated in the medical setting (Matson et al., 2023). CUD needs to be better understood and characterized to better inform users and treatment professionals. According to the findings in the 2021 NSDUH survey, an estimated 13.3 million individuals aged 12 years and older used marijuana daily or almost daily (i.e., 20 or more days within the past month). In the 2022 NSDUH annual report, among the total population, an estimated 15.1 million individuals aged 12 years and older used marijuana daily or almost daily in the past year. The 2023 NSDUH annual report shows that marijuana was the most commonly used illicit drug, 61.8 million people used in the past year. In the 2022 MTF report, daily marijuana use (i.e., 20 or more days within the past 30 days) in 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> graders were 0.7%, 2.1%, and 6.3%, respectively.

The 2023 NSDUH report stated that 19.2 million individuals were classified with dependence on or abuse of marijuana in the past year (representing 6.8% of the total population age 12 or older) based on criteria specified in DSM-5. Young adults aged 18 to 25 had the highest percentage of marijuana use disorder, which was consistent with the higher percentage among this age group for marijuana use in the past year (SAMSHA, 2024). Moreover, of the admissions to licensed substance abuse facilities, as presented in TEDS, marijuana/hashish was the primary substance of abuse for 11.2% (211,484) of 2019 admissions; 9.8% (139,481) of 2020 admissions; and 8.7% (129,343) of 2021 admissions. Of the 138,381 admissions in 2020 for marijuana/hashish as the primary substance, 29.7% used marijuana/hashish daily. Among admissions to treatment for marijuana/hashish as the primary substance in 2020, 17.4% were of ages 12–17 years and 14.8% were of ages 20–24 years. Hasin noted there is a misperception CUD is rare and, in a review (Hasin, 2018), found 19.5% of lifetime users met the criteria for DSM 5 Cannabis Use Disorder, of whom 23% symptomatically severe. The review went on to report that of these individuals, 48% were not functioning (e.g., not working) in any role; and that cannabis use disorder is not a rare occurrence.

### **Factor 8: Whether the substance is an immediate precursor of a substance already controlled under this subchapter**

Marijuana is not an immediate precursor of another controlled substance.

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**Exhibit B**  
to SAM Statement of Availability

## Chase T. Harrington

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**To:** Schwartz, James J; John McNichols; Pohlman, Zachary; jomcguire@ndasa.com; thinkon908@aol.com; jacob.durst@ag.tn.gov; Patrick Philbin; Michael.Zarian@ag.idaho.gov; Blake.Lanning@atg.in.gov; FairclothZ@ag.louisiana.gov; edwood27@icloud.com; kfinn0731@gmail.com; phillipdrum; Barnett, Cody  
**Cc:** Lonich, Jarrett T  
**Subject:** RE: Proposed Marijuana Scheduling

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**From:** Schwartz, James J <James.J.Schwartz@dea.gov>

**Sent:** Tuesday, June 23, 2026 11:36 AM

**To:** John McNichols <jmchnichols@torridonlaw.com>; Pohlman, Zachary <Zachary.Pohlman@nebraska.gov>; jomcguire@ndasa.com; thinkon908@aol.com; jacob.durst@ag.tn.gov; Patrick Philbin <pphilbin@torridonlaw.com>; Chase T. Harrington <charrington@torridonlaw.com>; Michael.Zarian@ag.idaho.gov; Blake.Lanning@atg.in.gov; FairclothZ@ag.louisiana.gov; edwood27@icloud.com; kfinn0731@gmail.com; phillipdrum <phillipdrum@comcast.net>; Barnett, Cody <Cody.Barnett@nebraska.gov>

**Cc:** Lonich, Jarrett T <Jarrett.T.Lonich@dea.gov>

**Subject:** RE: Proposed Marijuana Scheduling

The Government does not intend to identify Dr. Akinfiresoye as witness for our case in chief.

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**From:** John McNichols <jmchnichols@torridonlaw.com>

**Sent:** Monday, June 22, 2026 5:37 PM

**To:** Schwartz, James J <James.J.Schwartz@dea.gov>; Pohlman, Zachary <Zachary.Pohlman@nebraska.gov>; jomcguire@ndasa.com; thinkon908@aol.com; jacob.durst@ag.tn.gov; Patrick Philbin <pphilbin@torridonlaw.com>; Chase T. Harrington <charrington@torridonlaw.com>; Michael.Zarian@ag.idaho.gov; Blake.Lanning@atg.in.gov; FairclothZ@ag.louisiana.gov; edwood27@icloud.com; kfinn0731@gmail.com; phillipdrum <phillipdrum@comcast.net>; Barnett, Cody <Cody.Barnett@nebraska.gov>

**Cc:** Lonich, Jarrett T <Jarrett.T.Lonich@dea.gov>

**Subject:** [EXTERNAL] RE: Proposed Marijuana Scheduling

James:

The government identified two DEA employees as witnesses in its pre-hearing statement for 24-44. Are you planning to identify the same witnesses tomorrow, for the new hearing (26-96)? I ask because we may want to call Dr. Akinfiresoye in our case if the government does not, and we can't comply with the court's order to disclose her identity and her availability (much less whether a subpoena will be required, for Wednesday), unless we know what the government's doing.

I realize it's after 5 right now but if we could your answer by noon tomorrow, that would certainly facilitate the next round of deliverables to the court and ensure an orderly hearing.

**John McNichols**  
**Torridon Law PLLC**

**Exhibit C**  
to SAM Statement of Availability

## Chase T. Harrington

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**From:** John McNichols  
**Sent:** Tuesday, June 23, 2026 5:32 PM  
**To:** Schwartz, James J  
**Cc:** Lee, Jonathan E; Porter, Amber M; jomcguire@ndasa.com; thinkon908@aol.com; jacob.durst@ag.tn.gov; Patrick Philbin; Chase T. Harrington; zachary.pohlman@nebraska.gov; michael.zarian@ag.idaho.gov; blake.lanning@atg.in.gov; fairclothz@ag.louisiana.gov; edwood27@icloud.com; patrick.kenneally@burkegroup.law; connor.mighell@burkegroup.law; kfinn0731@gmail.com; phillipdrum@comcast.net; Lonich, Jarrett T  
**Subject:** RE: Proposed Marijuana Scheduling

Copying all counsel of record for Hearing 26-96

James:

I received the below in response to my inquiry to you earlier today about our intent to call DEA employee Dr. Akinfiresoye as a witness for Hearing 26-96. This is not a good faith response as to a hearing commencing next week, as to a witness previously identified by the government in this same DEA Hearing Docket.

A Touhy request is not required to secure Dr. Akinfiresoye's testimony because the information in question is already in the public domain by virtue of the Government's Pre-Hearing Statement and the accompanying Declaration that Dr. Akinfiresoye submitted for Hearing 24-44. Surely you knew that. The assertions in Ms. Porter's email below that there may be some privacy interest or privilege at stake, as to information that the government has already chosen to disclose, are frivolous, and serve no apparent purpose other than keeping relevant information and testimony out of the proceeding.

SAM's statement to the Court later today concerning its witnesses will identify Dr. Akinfiresoye as our witness and our intent to secure her appearance by subpoena as the Preliminary Order permits. Because of your approach to this, we do not know, and cannot provide, her availability. SAM reserves all rights.

**John McNichols**  
**Torridon Law PLLC**

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**From:** Porter, Amber M <[REDACTED]@dea.gov>  
**Sent:** Tuesday, June 23, 2026 3:51 PM  
**To:** John McNichols <jmcnichols@torridonlaw.com>  
**Cc:** Lee, Jonathan E <[REDACTED]@dea.gov>  
**Subject:** Proposed Marijuana Scheduling

**EXTERNAL EMAIL:** Please exercise caution when opening attachments or clicking on links.

Hi John:

I was made aware of your request to call to call Dr. Akinfiresoye as a witness in the Proposed Marijuana Scheduling hearing.

Pursuant to this, we recommend that you submit a request pursuant to the *Touhy* regulations, set forth below.

As this type of disclosure request stems from a court proceeding where the agency is a party, any release of information should come from the agency pursuant to the *Touhy* regulations set forth below. If a party to a proceeding is seeking DEA-related information, they would need to provide the agency a demand pursuant to the regulations.

The U.S. Department of Justice (DOJ) has enacted regulations that govern the release of testimony by DOJ employees or documents in a legal proceeding in which the United States is a party. These regulations are commonly referred to as the *Touhy* regulations and can be found at 28 C.F.R. §§ 16.21-16.29. See *generally United States ex. rel. Touhy v. Ragen*, 340 U.S. 462 (1951). The *Touhy* regulations are an absolute condition precedent to obtaining testimony from a DOJ employee or other information, and the regulations must be complied with before DOJ or DEA may respond to any such request. See *United States v. Bizzard*, 674 F.2d 1382 (11th Cir.), *cert. denied*, 459 U.S. 973 (1982); *United States v. Allen*, 554 F.2d 398 (10th Cir.), *cert. denied*, 434 U.S. 836 (1977); *United States v. Wallace*, 32 F.3d 921 (5th Cir. 1994); *Smith v. Cromer*, 159 F.3d 875, 879-80 (4th Cir. 1998).

In order for the agency to process your request, you would need to provide an affidavit, or a statement if an affidavit is not feasible, that sets forth a summary of the testimony sought. See 28 C.F.R. § 16.23(c). The requesting party would then provide the affidavit, or statement, to the agency. For purposes of this matter, the requesting party can provide the affidavit to me at the below email address or by mail. Upon receipt, this office will consult with the Office of the United States Attorney to decide what disclosures, if any, may be appropriate under the regulations. 28 C.F.R. § 16.23(a).

Please be aware, however, that the information you seek may be protected under the Privacy Act, 5 U.S.C. § 552a, in which case the information may not be disclosed without prior written consent of those identified in documents who are protected by the Privacy Act, or pursuant to the order of a court of competent jurisdiction and signed by a Judge. Please also be aware that one or more privileges, such as the law enforcement privilege, may bar release of the information you seek.

Once an appropriate request is made to the agency, we will be able to process your request and provide an update on the next steps of the process.

Very Respectfully,

Amber Porter  
Section Chief | FOIA & Information Law Section  
U.S. Department of Justice  
Office of Chief Counsel | Drug Enforcement Administration  
(o) [REDACTED] | (c) [REDACTED]  
Email: [REDACTED]@dea.gov

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