**July 22, 2024**

**The Honorable Anne Milgram**
Administrator
Drug Enforcement Agency
U.S. Department of Justice
Docket No. DEA-1362
8701 Morrissette Drive
Springfield, Virginia 22151

**RE: Public Comment on Docket No. DEA-1362**

S3 Collective, a 501(c)(3) nonprofit organization, and the Medical Cannabis Student Association (MCSA), a grassroots organization of students and alumni from The University of Maryland's Medical Cannabis Science and Therapeutics (MCST) Program, are jointly writing to submit our comments regarding docket number 2024-11137, concerning the proposed changes to the scheduling of marijuana under the Controlled Substances Act (CSA).

As concerned members of the scientific and medical communities, we believe the proposed changes are of significant importance and would like to share our additional, critical research and data to consider in support of a Schedule III classification. Numerous studies cited by HHS and other organizations have shown that marijuana has potential medical benefits for a variety of conditions, including chronic pain, nausea/vomiting, anorexia/cachexia, as well as other conditions. Supporting the HHS findings, physicians across the 38 states with medical programs recommend marijuana for medical use and recent data suggests that marijuana's abuse potential is lower compared to many other controlled substances and even unscheduled substances, such as alcohol.

Thank you for considering our comments on this important issue. We strongly support the rescheduling of marijuana from Schedule I of the CSA to Schedule III. This change will align U.S. policies with current scientific understanding and public health data. We urge the DOJ and DEA to follow the science in making a final decision on the rescheduling of marijuana.

## About S3 Collective

S3 Collective is a 501(c)(3) nonprofit accelerating the scientific collaboration necessary to develop and improve standards that will ensure consumer and patient safety. Our mission is to engage experts across different sectors, promote data-driven standards for consumer protection, bring together impartial information and data, and educate stakeholders.[1] This commitment has led S3 Collective to become the first cannabis-related nonprofit to participate in the FDA's Network of Experts (NoE) Program.[2]

## About the MCSA

MCSA's mission is to promote the highest standards in medical cannabis science and therapeutics through education, advocacy, social innovation, entrepreneurship, and cultural awareness. The MCSA was founded by students and alumni of The University of Maryland's two-year MS in MCST is the nation's first graduate program dedicated to the study of medical cannabis. The program launched in 2019 and provides students with the knowledge and skills they need to support patients and professionals in the medical cannabis industry.[3]

[1] S3 Collective. https://s3collective.org/
[2] S3 Collective Joins FDA's Network of Experts Program. https://s3collective.org/blog/news-3/s3-collective-joins-fdas-network-of-experts-program-52
[3] University of Maryland School of Pharmacy Medical Cannabis Student Association. https://studentorg.rx.umaryland.edu/medical-cannabis-student-association/

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# REPORT OF ADDITIONAL RESEARCH AND DATA TO CONSIDER

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## 1.0 INTRODUCTION

Reevaluating the classification of marijuana[4] under the Controlled Substances Act presents an unprecedented opportunity for the Drug Enforcement Agency (DEA) and the US Department of Justice (DOJ) to follow the science. There is a substantial disconnect between existing laws and the evolving scientific understanding of marijuana since the 1970s.

The S3 Collective and the Medical Cannabis Student Association (MCSA) are proud to present additional scientific evidence and data to support the proposed reclassification to Schedule III. This information builds upon the analyses performed prior by HHS and other organizations to indicate:

1. Medical Use: Peer-reviewed studies demonstrate marijuana's efficacy in managing chronic pain, nausea/vomiting, and anorexia/cachexia, as well as for several other medical conditions. Additionally, there are 38 states, three territories and the District of Columbia that allow the medical use of marijuana as recommended by physicians practicing in the U.S.

2. Lower Abuse Potential: Extensive reviews and articles show that marijuana has a comparatively narrower range of dependence-related conditions, lower risk of abuse, and adverse effects relative to other Schedule I and II substances. Further, research suggests that marijuana can play a significant role in reducing the harms associated with opioid prescriptions and overdose fatalities.

We believe HHS did a thorough job in reviewing the state of scientific knowledge and providing significant evidence to support Currently Accepted Medical Use of marijuana in the U.S. Therefore, in this report, we focus on providing more information about marijuana's potential for abuse.

## 2.0 MARIJUANA'S ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

For the first factor of the Eight-Factor Analysis, DEA stated that additional data on marijuana's actual or relative potential for abuse, cannabis-related Emergency Department (ED) visits, and updated epidemiological survey data since 2022 may be appropriate for consideration. Below we evaluate recent evidence showing that marijuana has a lower relative potential for abuse showcased by less harmful possible health effects, less significant withdrawal symptoms, lower rates of ED visits, and a lower risk of fatality from overdose or poisoning than other substances such as alcohol and opioids.

### 2.1 Relative Potential for Abuse

The National Institutes of Health's (NIH) National Institute on Drug Abuse (NIDA) lists the possible health effects, effects when combined with alcohol, withdrawal symptoms, and treatment options of commonly used drugs on its website. The information from this website for marijuana, heroin, cocaine, prescription opioids, prescription stimulants, ketamine, and central nervous system depressants is displayed in Table 2.1.1.

According to NIDA, the possible health effects of marijuana are milder and have a lower harm potential than every other substance in Table 2.1.1. For example, the possible long-term effects of marijuana include mental health problems, chronic cough, and frequent respiratory infections, while the possible long-term effects of substances currently scheduled lower than marijuana (cocaine, opioids, and stimulants) include loss of sense of smell, nasal damage, infection and death of bowel tissue, poor nutrition and weight loss, increased risk of overdose or addiction, heart problems, psychosis, anger, and paranoia.[5]

In a study that analyzed data from the U.S. National Survey on Drug Use and Health from 1979 – 2022, it was reported that for the first time on record, more Americans are using cannabis daily or near daily than they use

[4] Note: In this public comment, the term "cannabis" is synonymous with "marijuana," unless otherwise indicated. However, in many public datasets (e.g., hospitalizations, emergency visits, adverse events, use reports), there are cases where the substance in question was not actually marijuana. Rather, it may have been other substances similar to marijuana, such as intoxicating hemp or synthetic marijuana, as there is consumer, healthcare provider, and law enforcement confusion on the differences between these substances.
[5] NIH-NIDA Commonly Used Drugs Charts. https://nida.nih.gov/research-topics/commonly-used-drugs-charts

alcohol at that same rate.[6] Thus, it is important to note that when marijuana is combined with alcohol it leads to less harmful outcomes (e.g., increased heart rate, slower reaction times) when compared to other substances combined with alcohol (e.g., death, coma, respiratory depression, slowed heart rate) according to NIDA's information on possible effects. Further, based on NIDA's report of withdrawal symptoms across different drugs, those associated with marijuana are typically milder and shorter in duration compared to other substances, which may include severe physical and psychological distress and even seizures. Overall, marijuana's profile of abuse is generally less severe than that of other controlled drugs and uncontrolled substances, such as alcohol and opioids.

[6] Caulkins, J.P. (2024) Changes in self-reported cannabis use in the United States from 1979 to 2022. https://onlinelibrary.wiley.com/doi/full/10.1111/add.16519

**Table 2.1.1.** Possible Health Effects, Effects When Combined with Alcohol, Withdrawal Symptoms, and Treatment Options of Commonly Used Drugs[7]

| Substance | Schedule I | | Schedule II | | | Schedule III | Schedule IV |
|---|---|---|---|---|---|---|---|
| | **Marijuana** | **Heroin** | **Cocaine** | **Prescription Opioids** (e.g., Fentanyl, Hydrocodone, Oxycodone) | **Prescription Stimulants** (e.g., Amphetamine, Methylphenidate) | **Ketamine** | **Central Nervous System Depressants** (e.g., Benzodiazepines, Sleep Medications) |
| **Short-term Possible Health Effects** | Enhanced sensory perception and euphoria followed by drowsiness/relaxation; slowed reaction time; problems with balance and coordination; increased heart rate and appetite; problems with learning and memory; anxiety. | Euphoria; dry mouth; itching; nausea; vomiting; analgesia; slowed breathing and heart rate. | Narrowed blood vessels; enlarged pupils; increased body temperature, heart rate, and blood pressure; headache; abdominal pain and nausea; euphoria; increased energy, alertness; insomnia, restlessness; anxiety; erratic and violent behavior, panic attacks, paranoia, psychosis; heart rhythm problems, heart attack; stroke, seizure, coma. | Pain relief, drowsiness, nausea, constipation, euphoria, slowed breathing, death. | Increased alertness, attention, energy; increased blood pressure and heart rate; narrowed blood vessels; increased blood sugar; opened-up breathing passages. High doses: dangerously high body temperature and irregular heartbeat; heart disease; seizures. | Problems with attention, learning, and memory; dreamlike states, hallucinations; sedation; confusion; loss of memory; raised blood pressure; unconsciousness; dangerously slowed breathing. | Drowsiness, slurred speech, poor concentration, confusion, dizziness, problems with movement and memory, lowered blood pressure, slowed breathing. |
| **Long-term Possible Health Effects** | Mental health problems, chronic cough, frequent respiratory infections. | Collapsed veins; abscesses (swollen tissue with pus); infection of the lining and valves in the heart; constipation and stomach cramps; liver or kidney disease; pneumonia. | Loss of sense of smell, nosebleeds, nasal damage and trouble swallowing from snorting; infection and death of bowel tissue from decreased blood flow; poor nutrition and weight loss; lung damage from smoking. | Increased risk of overdose or addiction if misused. | Heart problems, psychosis, anger, paranoia. | Ulcers and pain in the bladder; kidney problems; stomach pain; depression; poor memory. | Unknown. |
| **Other Health-related Issues** | Tetrahydrocannabinol (THC) vaping products mixed with the filler Vitamin E acetate (and possibly other chemicals) has led to serious lung illnesses and deaths. Pregnancy: babies born with problems with attention, memory, and problem solving. | Pregnancy: miscarriage, low birth weight, neonatal abstinence syndrome. Risk of HIV, hepatitis, and other infectious diseases from shared needles. | Pregnancy: premature delivery, low birth weight, deficits in self-regulation and attention in school-aged children prenatally exposed. Risk of HIV, hepatitis, and other infectious diseases from shared needles. | Pregnancy: Miscarriage, low birth weight, neonatal abstinence syndrome. Older adults: higher risk of accidental misuse because many older adults have multiple prescriptions, increasing the risk of drug-drug interactions, and breakdown of drugs slows with age; also, many older adults are treated with prescription medications for pain. Risk of HIV, hepatitis, and other infectious diseases from shared needles. | Risk of HIV, hepatitis, and other infectious diseases from shared needles. | Sometimes used as a date rape drug. Risk of HIV, hepatitis, and other infectious diseases from shared needles. | Sleep medications are sometimes used as date rape drugs. Risk of HIV, hepatitis, and other infectious diseases from shared needles. |

[7] NIH-NIDA Commonly Used Drugs Charts. https://nida.nih.gov/research-topics/commonly-used-drugs-charts

| Substance | Schedule I | | Schedule II | | | Schedule III | Schedule IV |
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| | **Marijuana** | **Heroin** | **Cocaine** | **Prescription Opioids** (e.g., Fentanyl, Hydrocodone, Oxycodone) | **Prescription Stimulants** (e.g., Amphetamine, Methylphenidate) | **Ketamine** | **Central Nervous System Depressants** (e.g., Benzodiazepines, Sleep Medications) |
| **In Combination with Alcohol** | Increased heart rate, blood pressure; further slowing of mental processing and reaction time. | Dangerous slowdown of heart rate and breathing, coma, death. | Greater risk of cardiac toxicity than from either drug alone. | Dangerous slowing of heart rate and breathing leading to coma or death. | Masks the depressant action of alcohol, increasing risk of alcohol overdose; may increase blood pressure. | Increased risk of adverse effects. | Further slows heart rate and breathing, which can lead to death. |
| **Withdrawal Symptoms** | Irritability, trouble sleeping, decreased appetite, anxiety. | Restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goosebumps ("cold turkey"). | Depression, tiredness, increased appetite, insomnia, vivid unpleasant dreams, slowed thinking and movement, restlessness. | Restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goosebumps ("cold turkey"), leg movements. | Depression, tiredness, sleep problems. | Unknown. | Must be discussed with a health care provider; barbiturate withdrawal can cause a serious abstinence syndrome that may even include seizures. |
| **Medications to Treat Addiction** | There are no FDA-approved medications to treat marijuana addiction. | Methadone; Buprenorphine; Naltrexone (short- and long-acting forms) | There are no FDA-approved medications to treat cocaine addiction. | Methadone; Buprenorphine; Naltrexone (short- and long-acting forms) | There are no FDA-approved medications to treat stimulant addiction. | There are no FDA-approved medications to treat addiction to ketamine or other dissociative drugs. | There are no FDA-approved medications to treat addiction to prescription sedatives; lowering the dose over time must be done with the help of a healthcare provider. |
| **Behavioral Therapies to Treat Addiction** | Cognitive-behavioral therapy (CBT); Contingency management, or motivational incentives; Motivational Enhancement Therapy (MET); Behavioral treatments geared to adolescents; Mobile medical application: reSET® | Contingency management, or motivational incentives; 12-Step facilitation therapy; Mobile medical application: reSET-O™ used in conjunction with treatment that includes buprenorphine and contingency management | Cognitive-behavioral therapy (CBT); Contingency management, or motivational incentives, including vouchers; The Matrix Model; Community-based recovery groups, such as 12-Step programs; Mobile medical application: reSET® | Contingency management, or motivational incentives; 12-Step facilitation therapy; Mobile medical application: reSET-O™ used in conjunction with treatment that includes buprenorphine and contingency management | Behavioral therapies that have helped treat addiction to cocaine or methamphetamine may be useful in treating prescription stimulant addiction; Mobile medical application: reSET® | More research is needed to find out if behavioral therapies can be used to treat addiction to dissociative drugs. | More research is needed to find out if behavioral therapies can be used to treat addiction to prescription sedatives. |

## 2.2 ED Visits

ED visits can indicate a substance's abuse potential because they often reflect acute health crises like overdoses, severe intoxication, and other serious issues. High rates of ED visits for a substance suggest frequent severe health problems requiring immediate medical intervention, highlighting its danger and potential for abuse.

According to the 2022 Drug Abuse Warning Network's Findings from Drug-Related Emergency Department Visits Report, alcohol accounted for 45.0% of drug-related ED visits, which is four times the number of visits associated with opioids (12.7%) and cannabis (11.9%). Alcohol-related ED visits were highest among people ages 26 to 44 (1,526 per 100,000) and 45 to 64 (1,507 per 100,000), males (1,358 per 100,000), Black or African American individuals (1,498 per 100,000), those who are Not Hispanic or Latino (963 per 100,000), and in the Northeast region (1,519 per 100,000). In contrast, cannabis-related ED visits were highest among people ages 18 to 25 (597 per 100,000), males (313 per 100,000), Black or African American individuals (660 per 100,000), and those who are Not Hispanic or Latino (257 per 100,000).[8]

High rates of alcohol-related ED visits indicate frequent severe intoxication, alcohol poisoning, and related injuries, showing its high abuse potential. Similarly, high rates of opioid-related ED visits indicate frequent overdoses and severe health complications, demonstrating their high abuse potential. Lower rates of cannabis-related ED visits suggest a lower potential for causing acute health emergencies, implying a lower abuse potential.

The CDC's July 2023 Morbidity and Mortality Weekly Report analyzed nearly 540,000 ED visit cases nationwide from 2019 to 2022, where people under 25 went to the hospital due to cannabis complications. Researchers found an increase in cannabis-related ED visits among this younger group.[9] However, it is important to note that this increase coincided with the enactment of the 2018 Farm Bill in December 2018, which led to a rampant increase in hemp products containing intoxicating, chemically synthesized cannabinoids flooding the market in easily accessible places like gas stations, smoke shops, and on the internet. Additionally, some cases were due to unintentional ingestion of unregulated, counterfeit products that likely do not meet the definition of "marijuana" that looked like other popular consumer food products.[10] These products are especially concerning, even prompting the FDA to issue alerts to companies[11], however, the data resulting from their use should not be commingled with that of marijuana for the purposes of rescheduling considerations.

Although there is concern about the increased risk of cannabis abuse among younger people, this can be addressed through establishing strong health and safety standards for the retail sale of marijuana-containing products, including standardized packaging and labeling requirements that protect consumers. These types of standards and controls are common in the 38 state legal markets. For example, Virginia introduced a new law to standardize aspects of production and sale of THC and hemp-based products on July 1, 2023 to make products less appealing to youth. When cannabis-related pediatric visits in Q3-Q4 of 2022 were compared to that in 2023, they dropped 14.2%, indicating effective regulation through the use of standards can address cannabis ED visit related-concerns for younger populations.[12]

The National Hospital Care Survey (NHCS), conducted by the National Center for Health Statistics (NCHS), collects data on patient care in hospital-based settings to describe patterns of health care delivery and use in the United States (U.S.). Settings include inpatient facilities and EDs. Drug use-associated hospital encounters are taken

[8] Drug Abuse Warning Network (DAWN); Findings from Drug-Related Emergency Department Visits Report, June 20, 2023, https://store.samhsa.gov/sites/default/files/pep23-07-03-001.pdf

[9] Roehler DR, Smith H IV, Radhakrishnan L, et al. Cannabis-Involved Emergency Department Visits Among Persons Aged <25 Years Before and During the COVID-19 Pandemic — United States, 2019–2022. MMWR Morb Mortal Wkly Rep 2023;72:758–765. DOI: http://dx.doi.org/10.15585/mmwr.mm7228a1.

[10] Danielle C. Ompad, Kyle M. Snyder, Simon Sandh, Daniel Hagen, Kewanda J. Collier, Emily Goldmann, Melody S. Goodman, Andy S.L. Tan, Copycat and lookalike edible cannabis product packaging in the United States, Drug and Alcohol Dependence, Volume 235, 2022, 109409, ISSN 0376-8716, https://doi.org/10.1016/j.drugalcdep.2022.109409

[11] FDA Warns Consumers About the Accidental Ingestion by Children of Food Products Containing THC. https://www.fda.gov/food/alerts-advisories-safety-information/fda-warns-consumers-about-accidental-ingestion-children-food-products-containing-thc

[12] Kennedy, D., Fewer kids in Virginia visiting the hospital for cannabis exposure, data shows, 13NewsNow, May 15, 2024, https://www.13newsnow.com/article/news/local/virginia/pediatric-hospital-visits-cannabis-marijuana-exposure-virginia/291-3d3b94a9-5867-47bc-b2bb-81e29bae32ec

from administrative claims data from January 1, 2020, through September 30, 2023, from 23 hospitals that submitted inpatient data and 23 hospitals that submitted ED data.[13] Figure 2.1.1 below shows the percentage of ED encounters by various drugs.

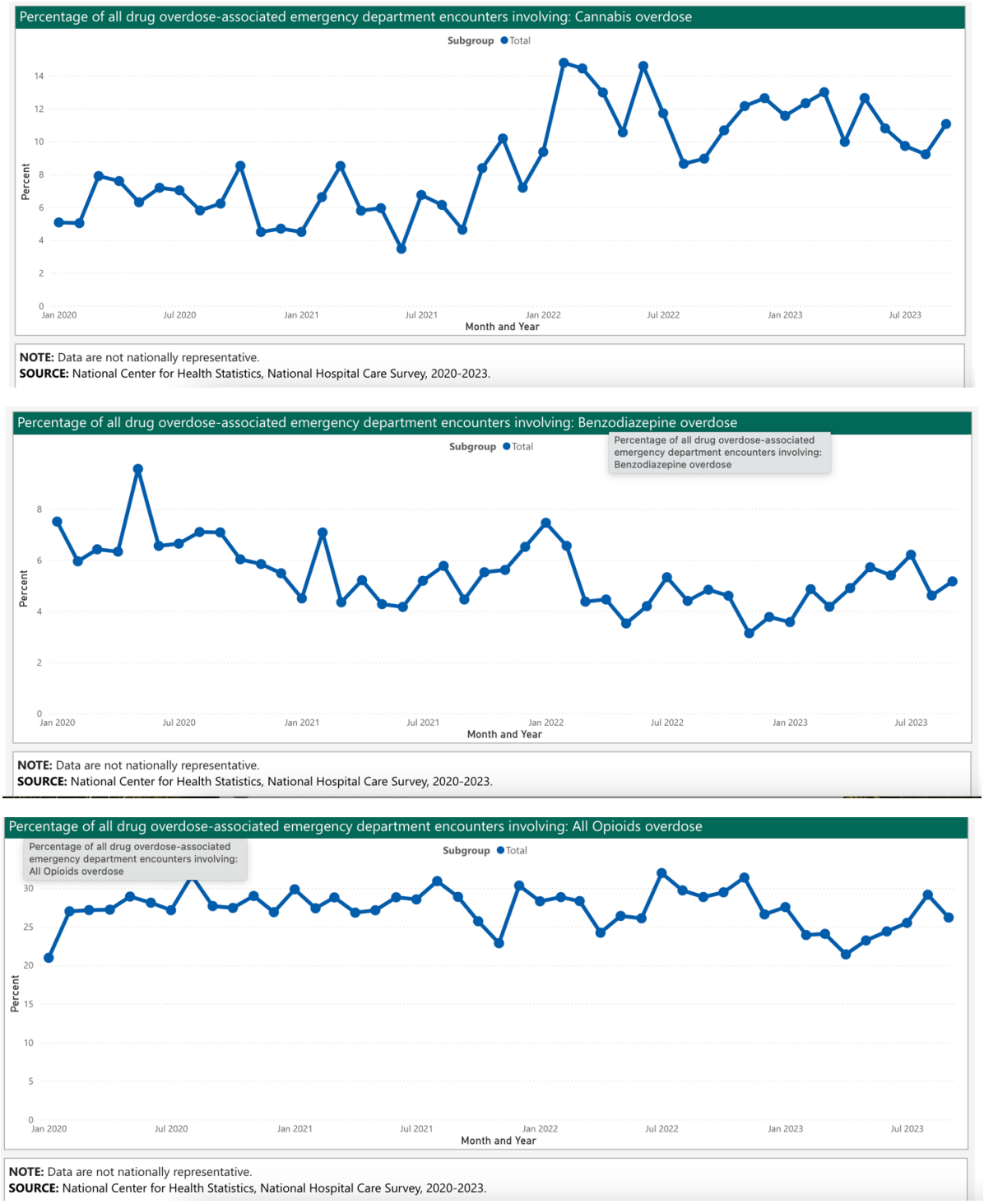


**Figure 2.2.1. Top:** Percentage of all drug overdose-associated ED encounters involving cannabis. **Middle:**

[13] Drug Overdose-Associated Hospital Encounters Involving Selected Drugs by Month from Selected Hospitals-2023 https://www.cdc.gov/nchs/dhcs/drug-use/drug-overdose.htm#print accessed 7/02/2024)

Percentage of all drug overdose-associated ED encounters involving benzodiazepine. **Bottom:** Percentage of all drug overdose-associated ED encounters involving all opioids.

In these datasets, marijuana overdose (undefined) ranged from approximately 3 - 14% of all ED visits for drug overdose. In comparison, overdose from all opioids ranged from 21 - 32% in the ED setting and 3.1 - 9.6% for benzodiazepine overdose encounters over the same period. The term "overdose" differs significantly between opioids or benzodiazepines and marijuana. With opioids or benzodiazepines, an overdose typically involves life-threatening symptoms such as respiratory depression or arrest, unconsciousness, coma, permanent brain damage, and potentially death due to the high toxicity of these substances at elevated doses.[14,15] In contrast, an "overdose" on marijuana generally refers to consuming more than intended, leading to non-lethal effects such as anxiety, paranoia, and delusions.[16] Unlike opioids and benzodiazepines, marijuana overdose is not associated with fatal outcomes or severe respiratory or physiological impairment.

It is stated the data may not be representative of the entire nation. Additionally, symptoms and severity of overdose was not captured; and in the case of marijuana, form, route of administration and medical vs. recreational use was not discussed.

In a meta-analysis of safety studies of medical cannabinoids published over the past 40 years, 23 randomized controlled studies were identified for analysis. A total of 4,779 adverse events were reported with 96.6% defined as non-serious. Of the 164 serious adverse events, the most common was relapse of multiple sclerosis (12.8%), vomiting (9.8%) and urinary tract infection (9.1%). While the rate of non-serious adverse events was higher in the cannabinoids group vs. controls (rate ratio [RR] 1.86, 95% confidence interval [CI] 1.57–2.21); the rates of serious adverse events did not differ significantly between these two groups (RR 1.04, 95% CI 0.78–1.39). Dizziness was the most reported non-serious adverse event (15.5%) among people exposed to cannabinoids.[17]

Most other marijuana-associated conditions are likely due to coexisting psychiatric disorders and substance use, rather than to marijuana itself. Marijuana use was associated with an estimated 10% of drug-related emergency department visits in the United States in 2021.[18]

### 2.3 Toxicity and Lethal Dosing

Examining poison control data shows that marijuana has a lower risk of abuse compared to other drugs and substances. According to the 2022 Annual Report of the American Poison Centers' National Poison Data System (NPDS), there were 2,622 exposure-related fatalities reported in 2022. Pharmaceutical drugs were the first-ranked substance in 2,250 of those fatalities (85.8%), with the breakdown of the two most common pharmaceutical categories, analgesics and stimulants/street drugs in Table 2.3.1.[19]

[14] National Institute on drug abuse. (2021, June 1). Prescription Opioids DrugFacts. National Institute on Drug Abuse. https://nida.nih.gov/publications/drugfacts/prescription-opioids
[15] Thomas, S. (2019). Overdose Symptoms | What Happens When You Overdose. American Addiction Centers. https://americanaddictioncenters.org/overdose
[16] National Institute on Drug Abuse. (2019, December). Cannabis (Marijuana) DrugFacts. National Institute on Drug Abuse; NIDA. https://nida.nih.gov/publications/drugfacts/cannabis-marijuana
[17] Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008 Jun 17;178(13):1669-78. doi: 10.1503/cmaj.071178. PMID: 18559804; PMCID: PMC2413308.
[18] Gorelick D, Cannabis-Related Disorders and Toxic Effects. NEJM 2023; 2267-2275
[19] Gummin, D. D., Mowry, J. B., Beuhler, M. C., Spyker, D. A., Rivers, L. J., Feldman, R., Brown, K., Pham, N. P. T., Bronstein, A. C., & DesLauriers, C. (2023). 2022 Annual Report of the National Poison Data System® (NPDS) from America's Poison Centers®: 40th Annual Report. *Clinical toxicology (Philadelphia, Pa.), 61*(10), 717–939 (page 739). https://doi.org/10.1080/15563650.2023.2268981

**Table 2.3.1.** NPDS Report 2022 Pharmaceutical Drug Fatality Data

| Primary Substance Documented in Fatality | Number of Fatalities | CSA Schedule |
|---|---|---|
| Fentanyl | 576* | II |
| Acetaminophen | 221 | None |
| Methamphetamine | 215 | II |
| Heroin | 53 | I |
| Cocaine | 51 | II |
| Oxycodone | 30** | II |
| Salicylate | 20 | II |
| Acetaminophen/hydrocodone | 19 | II |
| Morphine | 16 | II |
| Methadone | 13 | II |
| Amphetamines | 10 | II |
| Acetaminophen/oxycodone | 8 | II |
| Colchicine | 7 | None |
| Acetaminophen/diphenhydramine | 6 | None |
| Tramadol | 6 | IV |
| Amphetamines (hallucinogenic), 3,4-methylenedioxyethylamphetamine (MDA or ecstasy) | 6 | I |
| Hydrocodone | 4 | II |
| Hydromorphone | 4 | II |
| Amphetamine/dextroamphetamine | 2 | II |
| Marijuana | 2 | I |
| *Mitragyna speciosa korthals* (source of kratom) | 2 | None |
| Phentermine | 2 | IV |

*541 from non-prescription fentanyl and 35 from prescription fentanyl. **5 from the ER.

Lower poison control center fatality data for marijuana compared to other drugs demonstrates its lower potential for abuse and fatal harm. In 2022, there were only 2 fatalities related to marijuana; while fentanyl, a Schedule II drug, had 576 fatalities, and acetaminophen – an uncontrolled over-the-counter drug – had 221 fatalities. These figures suggest that marijuana poses a significantly lower risk of fatal overdose or poisoning compared to these substances, indicating a lower potential for abuse and serious harm.

America's Poison Centers is currently tracking delta-8 THC (Δ8-THC) poisoning cases as an emerging hazard. While Δ8-THC is found in the cannabis plant at trace levels, it is more commonly synthesized by converting the cannabidiol (CBD) molecule. The byproducts of this chemical synthesis are largely unknown and are not listed on the product's label. From 2021 to 2024, Poison Centers have tracked 8,985 Δ8-THC-related exposure cases, which is nearly four times the total number of cases reported for synthetic marijuana such as K2 and Spice in the same period.[20]

It is important to note that most of these data points likely come from Δ8-THC products that do not meet the definition of marijuana. These synthetic products are chemically distinct and often unregulated, leading to a higher incidence of adverse reactions from impurities and byproducts with unknown pharmacology. Therefore, data from the use of Δ8-THC products that do not meet the definition of marijuana should not be considered when evaluating

[20] National Poison Data System, America's Poison Centers. (2024, May 31). *Delta-8 THC.* https://poisoncenters.org/track/delta-8-THC

the rescheduling of marijuana. Unfortunately, many times, epidemiological data can be conflated with the risks associated with synthetic cannabinoids.

Studies have shown that marijuana is considered to be less toxic and have a lower risk of fatal overdose than other substances due to its non-lethal overdose threshold and lower physical dependence potential. Its psychoactive effects are generally milder, leading to fewer acute toxicological crises.

## 3.0 SCIENTIFIC EVIDENCE OF MARIJUANA'S PHARMACOLOGICAL EFFECTS

For the second factor of the Eight-Factor Analysis, DEA stated that additional data on marijuana's pharmacological effects may be appropriate for consideration. Below we evaluate recent research related to marijuana's pharmacology.

### 3.1 Endocannabinoid System and Receptors

The endocannabinoid system (ECS) is a complex neuromodulatory system that consists of cannabinoid receptors, endocannabinoids, and enzymes that regulate the system. The ECS plays a critical role in the central nervous system and many physiological processes, such as neural development, pain perception, appetite, memory, immune function, and cardiovascular function. Stimulating the cannabinoid receptors triggers the physiological processes. The CB1 cannabinoid receptors (CB1 receptor) are the most prevalent receptors in the brain and CNS, while the CB2 receptors are primarily located in the immune system.[21,22]

Marijuana produces cannabinoids that interact with cannabinoid receptors or otherwise affect the ECS through non-receptor mediated pathways. The major cannabinoid delta-9 THC (Δ9-THC) binds well to CB1 receptors, which triggers a cascade of cellular events, some of which have therapeutic potential.[14] THC's binding to the CB1 receptors also explains the characteristic psychoactive effects of marijuana, including euphoria, relaxation, and altered sensory perception.

Unlike Schedule I drugs like heroin and cocaine, which primarily target dopamine reward pathways in the brain, leading to intense feelings of pleasure and a high risk of addiction, marijuana's effects on the ECS are more complex and diverse.[23,24,25] THC's interaction with CB1 receptors produces a broader range of effects. Additionally, marijuana exhibits a lower dependence potential compared to Schedule II stimulants and opioids.[26]

### 3.2 Chronic Effects and Neurotoxicity

Studies investigating the long-term cognitive effects of chronic marijuana use have yielded mixed results. While some research suggests a possibility of mild, reversible impairments in memory, attention, and learning, others indicate minimal or no long-term cognitive effects.[20,27] Importantly, emerging evidence suggests that cannabinoids may possess neuroprotective properties, potentially mitigating neurodegenerative processes.[28] This stands in stark contrast to the well-established neurotoxic effects of many Schedule II drugs, such as cocaine and

[21] Toyang, N., Steele, B., Bryant, J., & Ngwa, W. (2021). The Endocannabinoid System: A Potential Target for the Treatment of Various Diseases. International journal of molecular sciences, 22(17), 9472. https://doi.org/10.3390/ijms22179472
[22] Rezende, B., Alencar, A. K. N., de Bem, G. F., Fontes-Dantas, F. L., & Montes, G. C. (2023). Endocannabinoid System: Chemical Characteristics and Biological Activity. Pharmaceuticals (Basel, Switzerland), 16(2), 148. https://doi.org/10.3390/ph16020148
[23] Kosten, T. R., & George, T. P. (2002). The Neurobiology of Opioid Dependence: Implications for Treatment. *Science & Practice Perspectives*, *1*(1), 13–20.
[24] Reddy, V., Grogan, D., Ahluwalia, M., Salles, É. L., Ahluwalia, P., Khodadadi, H., Alverson, K., Nguyen, A., Raju, S. P., Gaur, P., Braun, M., Vale, F. L., Costigliola, V., Dhandapani, K., Baban, B., & Vaibhav, K. (2020). Targeting the endocannabinoid system: A predictive, preventive, and personalized medicine-directed approach to the management of brain pathologies. *The EPMA Journal*, *11*(2), 217–250. https://doi.org/10.1007/s13167-020-00203-4
[25] Uhl, G. R., Koob, G. F., & Cable, J. (2019). The neurobiology of addiction. *Annals of the New York Academy of Sciences*, *1451*(1), 5–28. https://doi.org/10.1111/nyas.13989
[26] Solowij, N., Broyd, S., Greenwood, L.-M., van Hell, H., Martelozzo, D., Rueb, K., Todd, J., Liu, Z., Galettis, P., Martin, J., Murray, R., Jones, A., Michie, P. T., & Croft, R. (2019). A randomised controlled trial of vaporised Δ9-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: Acute intoxication effects. European Archives of Psychiatry and Clinical Neuroscience, 269(1), 17–35. https://doi.org/10.1007/s00406-019-00978-2
[27] Meier, M. H., Caspi, A., Knodt, A., Hall, W., Ambler, A., Harrington, H., Hogan, S., Houts, R., Poulton, R., Ramrakha, S., Hariri, A., & Moffitt, T. E. (2022). Long-term Cannabis Users Show Lower Cognitive Reserves and Smaller Hippocampal Volume in Midlife. The American Journal of Psychiatry, 179(5), 362–374. https://doi.org/10.1176/appi.ajp.2021.21060664
[28] Bhunia, S., Kolishetti, N., Arias, A. Y., Vashist, A., & Nair, M. (2022). Cannabidiol for neurodegenerative disorders: A comprehensive review. Frontiers in Pharmacology, 13, 989717. https://doi.org/10.3389/fphar.2022.989717

methamphetamine, which can cause permanent damage to brain structures and cognitive function.[29]

### 3.3 Cardiovascular and Autonomic Effects

Marijuana interacts with the autonomic nervous system, which regulates involuntary bodily functions like heart rate and digestion. Some of these effects are mild and can include dry mouth and red eyes. Marijuana use can have transient effects on cardiovascular function, including a slight increase in heart rate and blood pressure.[30,31] In comparison, Schedule II stimulants like cocaine can cause much more significant increases in heart rate and blood pressure, to the point of increasing the risk of heart attack and stroke.[32]

### 3.4 Endocrine System

Marijuana interacts with various hormonal systems, potentially influencing appetite, sleep regulation, and pain perception.[33] THC is known to stimulate the endocannabinoid system in the hypothalamus, a region of the brain involved in appetite regulation, leading to the characteristic "munchies" associated with marijuana use.[34] Cannabinoids may modulate sleep-wake cycles and influence pain perception through interactions with the ECS in various brain regions. These effects are generally less dramatic and pose lower risks compared to the significant hormonal disruptions caused by Schedule III steroids, which can have serious health consequences with long-term use.[35]

### 3.5 Pharmacological Effects of Cannabinoids and Dosage

Different cannabinoids, such as THC and CBD, have distinct pharmacological profiles. THC produces the psychoactive effects associated with marijuana, including euphoria, relaxation, and altered sensory perception. CBD, on the other hand, exhibits a range of therapeutic properties, including anti-inflammatory, anti-anxiety, and antipsychotic effects.[36] The effects of cannabinoids have been shown to be biphasic or bidirectional, meaning the low and high doses can have different effects, as exemplified by low CBD doses shown to produce stimulating effects whilst high CBD doses typically have a relaxing effect. [37,38] This highlights the importance of dose control and personalized treatment approaches for maximizing therapeutic benefits and minimizing potential side effects.

## 4.0 The State of Current Scientific Knowledge Regarding Marijuana

For the third factor of the Eight-Factor Analysis, DEA stated that additional data on marijuana's constituents, routes of administration, and impact of Δ9-THC may be appropriate for consideration. Below we evaluate recent research related to these topics.

### 4.1 Routes of Administration

In the U.S., there are many different forms and formulations of marijuana available, with a variety of delivery

[29] Dietrich J. B. (2009). Alteration of blood-brain barrier function by methamphetamine and cocaine. Cell and tissue research, 336(3), 385–392. https://doi.org/10.1007/s00441-009-0777-y
[30] Grotenhermen, F., & Müller-Vahl, K. (2012). The Therapeutic Potential of Cannabis and Cannabinoids. *Deutsches Ärzteblatt International*, *109*(29–30), 495–501. https://doi.org/10.3238/arztebl.2012.0495
[31] Page, R. et al. (2020). Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement from the American Heart Association. Circulation, 142(10). ahajournals.org/doi/10.1161/CIR.0000000000000883.
[32] Roque Bravo, R., Faria, A. C., Brito-da-Costa, A. M., Carmo, H., Mladěnka, P., Dias da Silva, D., & Remião, F. (2022). Cocaine: An Updated Overview on Chemistry, Detection, Biokinetics, and Pharmacotoxicological Aspects including Abuse Pattern. *Toxins*, *14*(4), 278. https://doi.org/10.3390/toxins14040278
[33] Leweke, F. M., Mueller, J. K., Lange, B., Fritze, S., Topor, C. E., Koethe, D., & Rohleder, C. (2018). Role of the Endocannabinoid System in the Pathophysiology of Schizophrenia: Implications for Pharmacological Intervention. *CNS Drugs*, *32*(7), 605–619. https://doi.org/10.1007/s40263-018-0539-z
[34] Williams, C. M., & Kirkham, T. C. (1999). Anandamide induces overeating: Mediation by central cannabinoid (CB1) receptors. *Psychopharmacology*, *143*(3), 315–317. https://doi.org/10.1007/s002130050953
[35] Sagoe, D., Molde, H., Andreassen, C. S., Torsheim, T., & Pallesen, S. (2014). The global epidemiology of anabolic-androgenic steroid use: A meta-analysis and meta-regression analysis. *Annals of Epidemiology*, *24*(5), 383–398. https://doi.org/10.1016/j.annepidem.2014.01.009
[36] Blessing, E. M., Steenkamp, M. M., Manzanares, J., & Marmar, C. R. (2015). Cannabidiol as a Potential Treatment for Anxiety Disorders. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *12*(4), 825–836. https://doi.org/10.1007/s13311-015-0387-1
[37] Rey, A. A., Purrio, M., Viveros, M. P., & Lutz, B. (2012). Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 37(12), 2624–2634. https://doi.org/10.1038/npp.2012.123
[38] Zuardi A. W. (2008). Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Revista brasileira de psiquiatria (Sao Paulo, Brazil: 1999), 30(3), 271–280. https://doi.org/10.1590/s1516-44462008000300015

methods. When it comes to current routes of administration, marijuana delivery methods can be split into five main categories: Inhalable, Ingestible, Transmucosal, Transdermal/Topical, and Ocular.[39] See Table 4.1.1 for a summary.

### 4.1.1 Inhalable Delivery

When it comes to inhaling marijuana, THC is rapidly absorbed into the bloodstream, avoiding the metabolic process in the liver and accelerating the effects of the active cannabinoids. Inhaled marijuana has an immediate onset of effect due to this quick absorption. Bioavailability can also differ amongst consumers based on certain conditions.[40] This differs from other substances like alcohol and nicotine, which undergo significant first-pass metabolism in the liver, resulting in a slower onset of effects and variable bioavailability depending on individual metabolic rates and other factors.

Smoking or vaping is the most common way to consume marijuana through inhalation. Smoking involves inhaling the smoke from the combustion of dried cannabis flowers (i.e., inflorescence), often using pipes, joints, or blunts. This method allows for rapid absorption of cannabinoids through the lungs, leading to quick onset of effects. Vaping, on the other hand, heats cannabis to a temperature that releases cannabinoids in vapor form without combustion, often through the use of rigs or vaporizer devices. This method is considered to produce fewer harmful byproducts than smoking, offering a potentially safer alternative while still providing fast-acting effects. Both methods allow users to control titration and experience immediate symptom relief.

Metered Dose Inhalers (MDIs) are another way marijuana may be consumed through inhalation. MDIs are made up of 3 primary parts: propellant, cosolvent, and cutting agent. Terpenes are often added to them as well. MDIs deliver marijuana through a high velocity spray. MDIs allow patients to receive a discreet combustion-less dose of marijuana which makes it safer than vaping and ideal for acute pain.[41,42]

An example of a metered dose inhalation containing medical marijuana is the Syqe Inhaler. In a retrospective analysis of the long-term effectiveness and safety of medical marijuana administered through the Syqe Inhaler, data from 143 patients (mean age 62) revealed significant pain reduction and improved quality of life (QoL). Most patients (72%) suffered from chronic neuropathic pain and achieved a stable daily dose of 1,500 µg of aerosolized Δ9-THC after a 26-day titration period. Pain intensity decreased by 22.8% in the intent-to-treat population and 28.4% among those with severe baseline pain. Additionally, 92% of patients reported enhanced QoL. Adverse events primarily occurred during titration, with only 4% of patients experiencing adverse events during long-term use. The study concluded that the Syqe Inhaler offers precise dosing, substantial pain relief, and fewer adverse events compared to conventional medical marijuana administration methods, warranting further investigation in larger populations.[43,44]

Nebulizers are similar to MDIs in the way that they can provide discreet, combustion-free doses of marijuana to a patient. Nebulizers push compressed air through a tube full of oil, which then turns into an aerosol that a patient can inhale.[45] This delivery method can include cosolvents, cutting agents, and terpenes, as well. An example of a

[39] Muheriwa-Matemba, S. R., Baral, A., Abdshah, A., Diggs, B. A., Collazos, K. S. G., Morris, K. B., Messiah, S. E., & Vidot, D. C. (2024). Cardiovascular and Respiratory Effects of cannabis use by route of Administration: a Systematic review. Substance Use & Misuse, 59(9), 1331–1351. https://doi.org/10.1080/10826084.2024.2341317
[40] Murphy, S. E. (2021). Biochemistry of nicotine metabolism and its relevance to lung cancer. *Journal of Biological Chemistry/the Journal of Biological Chemistry*, *296*, 100722. https://doi.org/10.1016/j.jbc.2021.100722
[41] Agnihotri, V. V., Pardeshi, C. V., & Surana, S. J. (2021). A current update on advanced drug delivery devices for nasal and pulmonary administration. In Elsevier eBooks (pp. 213–245). https://doi.org/10.1016/b978-0-12-819838-4.00003-1
[42] Authors, Palylyk-Colwell, E., & Farrah, K. (2022). Metered-Dose Inhalers for Medical Cannabis Use: CADTH Health Technology Review. Canadian Agency for Drugs and Technologies in Health. https://canjhealthtechnol.ca/index.php/cjht/article/view/rc1417/630
[43] Aviram, J., Atzmony, D., & Eisenberg, E. (2022). Long-term effectiveness and safety of medical cannabis administered through the metered-dose Syqe Inhaler. Pain reports, 7(3), e1011. https://doi.org/10.1097/PR9.0000000000001011
[44] Vulfsons, S., Ognitz, M., Bar-Sela, G., Raz-Pasteur, A., & Eisenberg, E. (2020). Cannabis treatment in hospitalized patients using the SYQE inhaler: Results of a pilot open-label study. Palliative & supportive care, 18(1), 12–17. https://doi.org/10.1017/S147895151900021X
[45] U.S. National Library of Medicine. (n.d.). How to use a nebulizer: Medlineplus medical encyclopedia. MedlinePlus. https://medlineplus.gov/ency/patientinstructions/000006.htm

marijuana-containing nebulizer is the Pearl$_2$O Nebulizer[46] and an example of a marijuana-containing nebulizer device available in Europe is the Volcano Medic 2 Cannabis Nebulizer.[47]

### 4.1.2 Ingestible Delivery

Ingestible marijuana comes in many different forms and formulations, all of which undergo first-pass metabolism. First-pass metabolism for marijuana includes the conversion of ∆9-THC into 11-hydroxy-THC (11-OH-THC). From there, 11-OH-THC is metabolized into the non-psychoactive compound 11-COOH-THC. This metabolism of ∆9-THC occurs in the liver following the oral ingestion of the marijuana product. Onset of effect occurs 60-120 minutes after ingestion with a duration typically lasting between 4-12 hours making it ideal for patients dealing with chronic pain.

Oral ingestion of THC, such as through edibles or capsules, results in lower bioavailability (4% to 12%) due to first-pass metabolism in the liver.[48,49] This delayed onset and variability in absorption necessitates careful dosing to achieve desired therapeutic effects.

### 4.1.3 Transmucosal Delivery

Transmucosal delivery is a more modern route of administration for marijuana that avoids the first-pass metabolism through the liver. Marijuana cannabinoids are delivered through the mucous membrane. Transmucosal marijuana is typically received through oral, nasal, vaginal/penile, or rectal application. While oral application is the primary method used for transmucosal delivery, nasal, vaginal/penile, and rectal application may be ideal for patients that are unable to take medication orally. Bioavailability of transmucosal delivery varies based on its form and formulation. Buccal/sublingual delivery has been shown to have a 10-25% bioavailability and nasal delivery resulting in 34-46%.[50]

Transmucosal delivery of marijuana via the oral route is received either buccally or sublingually. Buccal application includes absorption through the inner lining of the cheek and lips which is ⅓ of the oral cavity surface area. Buccal formulations should include mucoadhesive agents, penetration enhancers, enzyme inhibitors, and pH modifiers to ensure proper stability, absorption and anti-irritation. Sublingual application is done under the tongue where marijuana is absorbed through the capillaries into the bloodstream. Bioavailability for these oral transmucosal delivery methods is approximately 10-25% but more research should be conducted. Peak blood levels are reached within 1 hour of administration resulting in an ~4-hour duration.[51,52,53]

Intranasal delivery is another route of administration of marijuana. The nasal cavity is highly vascularized and covered by thin mucosa which makes it ideal for rapid absorption and onset of effect. This non-invasive, pain-free method avoids first-pass metabolism and allows for discreet administration.[54]

### 4.1.4 Transdermal and Topical Delivery

Topical applications of THC primarily target localized pain or inflammation with minimal systemic absorption, avoiding psychoactive effects associated with systemic exposure.[55]

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[46] Pearl$_2$O nebulizer. Pearl$_2$O. (n.d.). http://pearl2o.com/nebulizer/
[47] Volcano Medic 2. VAPORMED. (n.d.). https://www.vapormed.com/en/volcano-medic2
[48] Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics*, 42(4), 327-360. doi:10.2165/00003088-200342040-00003
[49] Hazekamp, A., Ruhaak, R., Zuurman, L., van Gerven, J., & Verpoorte, R. (2006). Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. Journal of pharmaceutical sciences, 95(6), 1308–1317. https://doi.org/10.1002/jps.20574
[50] Mahmoudinoodezh, H., Telukutla, S. R., Bhangu, S. K., Bachari, A., Cavalieri, F., & Mantri, N. (2022). The Transdermal Delivery of Therapeutic Cannabinoids. Pharmaceutics, 14(2), 438. https://doi.org/10.3390/pharmaceutics14020438
[51] Priest, A. (2023, November 1). The bioavailability of cannabis through various delivery methods. Cannabis Central. https://www.veriheal.com/blog/the-bioavailability-of-cannabis-through-various-delivery-methods/#references
[52] Belcosta Labs. (2022, October 24). Different routes of administration: A guide to cannabis products. https://belcostalabs.com/different-routes-of-administration-a-guide-to-cannabis-products/
[53] Macedo, A. S., Castro, P. M., Roque, L., Thomé, N. G., Reis, C. P., Pintado, M. E., & Fonte, P. (2020). Novel and revisited approaches in nanoparticle systems for buccal drug delivery. Journal of Controlled Release, 320, 125–141. https://doi.org/10.1016/j.jconrel.2020.01.006
[54] Eydelman, I., Zehavi, N., Feinshtein, V., Kumar, D., Ben-Shabat, S., & Sintov, A. C. (2023). Cannabidiol-Loaded Nanoparticles Based on Crosslinked Starch: Anti-Inflammatory Activity and Improved Nose-to-Brain Delivery. Pharmaceutics, 15(7), 1803. https://doi.org/10.3390/pharmaceutics15071803
[55] Mahmoudinoodezh, H., Telukutla, S. R., Bhangu, S. K., Bachari, A., Cavalieri, F., & Mantri, N. (2022). The Transdermal Delivery of Therapeutic Cannabinoids. Pharmaceutics, 14(2), 438. https://doi.org/10.3390/pharmaceutics14020438

This route of administration includes administering marijuana by applying it through the skin. Transdermal and topical marijuana products come in a variety of application forms. The skin is our largest organ and is made up of 3 layers: epidermis, dermis, and hypodermis. Transdermal products are designed to penetrate the basal layer and dermis where THC can be absorbed into the blood vessels through systemic circulation. Topical products work similarly but only penetrate the epidermis and do not enter systemic circulation. This non-invasive method allows for a steady infusion of marijuana and can be rapidly terminated by removing the transdermal/topical device. This delivery method is ideal for addressing local symptoms like arthritis and avoids first-pass metabolism, which results in improved bioavailability. Onset of effect can vary based on different sites of the skin.

### 4.1.5 Ocular Delivery

Ocular delivery involves applying marijuana through ophthalmic application to the eye. This route bypasses the first-pass metabolism and modulates intraocular pressure as a topical solution. This delivery method may be recommended for patients dealing with glaucoma. More research and development into this area could yield ideal solutions.[56]

**Table 4.1.1.** Metabolism and Absorption Information by Route of Administration[57,58,59]

| Route of Administration | Formulations | Metabolism | Absorption |
|---|---|---|---|
| Inhalable | Inflorescence, pre-rolls, vaporizers, inhalable concentrates and oils, metered dose inhalers, nebulizers | No First-Pass Metabolism (i.e., through the liver) | Immediate Onset<br>10-35% Bioavailability (Varies) |
| Ingestible | Infused foods, beverages, tinctures | First Pass Metabolism<br>Δ9-THC → 11-OH-THC → 11-COOH-THC | Delayed Onset<br>5-20% Bioavailability (Varies) |
| Transmucosal | Tinctures, oral sprays, dissolvable films, lozenges, intranasal solutions, suppositories | Mixed Absorption and/or No First-Pass Metabolism | Rapid Onset<br>10-25% Bioavailability (Varies) |
| Transdermal and Topical | Gels, paste, patches, creams, ointments, lotions, sprays, foams | First Pass Metabolism<br>Δ9-THC → 11-OH-THC → 11-COOH-THC | Steady Onset (Varies)<br>Bioavailability (Varies) |
| Ocular | Eye drops and aqueous solutions | No First Pass Metabolism | Onset Varies<br>Bioavailability Varies |

### 4.1.6 Potency Across Administration Routes

Potency variations of Δ9-THC further distinguish medical marijuana across different administration routes. Inhalation methods provide rapid and potent effects due to direct absorption into the bloodstream through the lungs. Conversely, oral ingestion leads to slower onset, but potentially stronger effects due to the conversion of Δ9-THC to 11-OH-THC in the liver.

Comparatively, substances like opioids and benzodiazepines also exhibit potency differences based on administration routes. Opioids administered intravenously bypass first-pass metabolism, resulting in rapid and potent effects compared to oral ingestion.[60] Similarly, benzodiazepines administered intravenously or intranasally

[56] Saraiva, S. M., Martín-Banderas, L., & Durán-Lobato, M. (2023). Cannabinoid-Based Ocular Therapies and Formulations. Pharmaceutics, 15(4), 1077. https://doi.org/10.3390/pharmaceutics15041077
[57] Levine, R., ADM, USPHS & U.S. Public Health Service. (2023). Basis For the Recommendation to Reschedule Marijuana into Schedule III of The Controlled Substances Act. https://www.hhs.gov/sites/default/files/scheduling-recommendation.pdf
[58] Mahmoudinoodezh, H., Telukutla, S. R., Bhangu, S. K., Bachari, A., Cavalieri, F., & Mantri, N. (2022). The transdermal delivery of therapeutic cannabinoids. Pharmaceutics, 14(2), 438. https://doi.org/10.3390/pharmaceutics14020438
[59] Saraiva, S. M., Martín-Banderas, L., & Durán-Lobato, M. (2023). Cannabinoid-Based ocular therapies and formulations. Pharmaceutics, 15(4), 1077. https://doi.org/10.3390/pharmaceutics15041077
[60] Lugo, R. A., Satterfield, K. L., & Kern, S. E. (2005). Pharmacokinetics of methadone. Journal of pain & palliative care pharmacotherapy, 19(4), 13–24.

may have faster and more potent effects than oral administration.[61] It is important to note, in the comparison to opioids and benzodiazepines, that intravenous administration is not a route of consumption for marijuana.

### 4.1.7 Dose-Response Relationship for Δ9-THC

Understanding the dose-response relationship for Δ9-THC is crucial for optimizing therapeutic outcomes and minimizing adverse effects. Inhalation allows for more controlled titration due to rapid onset and short duration of effects, facilitating self-regulation based on immediate symptom relief.[62]

In contrast, oral ingestion requires cautious titration to manage prolonged effects and potential for less predictable responses, particularly in inexperienced users. Topical applications require specific formulations to ensure consistent dosing for localized therapeutic benefits.[63]

## 4.2 Marijuana's Constituents

The marijuana plant is an extraordinarily complex combination of phytocannabinoids, terpenes, flavonoids, amino acids, proteins, sugars, enzymes, fatty acids, alcohols, ketones, lactones, steroids, glycosides, and esters.[64] There are over five hundred active compounds in the marijuana plant, highlighting how dynamic the plant is. The cannabinoids found in the plant are referred to as phytocannabinoids, which can mimic the body's own chemicals known as endocannabinoids. As described earlier, the body's ECS consists of two major receptors known as $CB_1$ and $CB_2$ receptors, as well as several minor receptors that are involved in other bodily systems. The ECS plays a crucial role in maintaining homeostasis and cognitive processes by regulating various physiological processes, including pain, mood, appetite, and immune response. The ECS facilitates communication within the body to maintain balance and health.[65]

### 4.2.1 Phytocannabinoids

There are over one hundred phytocannabinoids found in the marijuana plant.[66] These phytocannabinoids can be found throughout the plant, with the highest concentration in the trichomes, which are gland-like structures on the flower of the *Cannabis sativa* plant. The main cannabinoids frequently researched are CBD and Δ9-THC. In addition to CBD and Δ9-THC, the marijuana plant has many more important cannabinoids that can play a pivotal role in the human endocannabinoid system (ECS).

There are several other natural phytocannabinoids: cannabichromene (CBC), cannabielsoin (CBE), cannabigerol (CBG), cannabicyclol (CBL), cannabinol (CBN), cannabinodiol (CBND), cannabitriol (CBT), Δ8-THC, and other miscellaneous-type cannabinoids.[67] The most discussed naturally occurring phytocannabinoids and their beneficial pharmacological effects are listed in Table 4.2.1. However, there are 129 phytocannabinoids known to naturally occur in the marijuana plant.

[61] Mendelson, J., Jones, R. T., Welm, S., Baggott, M., Fernandez, I., Melby, A. K., & Nath, R. P. (1999). Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. Psychopharmacology, 141(1), 37–46. https://doi.org/10.1007/s002130050804

[62] Ramaekers, J. G., Kauert, G., Theunissen, E. L., Toennes, S. W., & Moeller, M. R. (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Journal of psychopharmacology (Oxford, England), 23(3), 266–277. https://doi.org/10.1177/0269881108092393

[63] Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics*, 42(4), 327-360. doi:10.2165/00003088-200342040-00003

[64] Sulak, Dustin DO. (2021). *Handbook of Cannabis for Clinicians: Principles and Practice*. W. W. Norton & Company.

[65] Rezende, B., Alencar, A. K. N., de Bem, G. F., Fontes-Dantas, F. L., & Montes, G. C. (2023). Endocannabinoid System: Chemical Characteristics and Biological Activity. Pharmaceuticals (Basel, Switzerland), 16(2), 148. https://doi.org/10.3390/ph16020148

[66] Nahar, L., Guo, M., & Sarker, S. D. (2020). Gas chromatographic analysis of naturally occurring cannabinoids: A review of literature published during the past decade. Phytochemical analysis : PCA, 31(2), 135–146. https://doi.org/10.1002/pca.2886

[67] Radwan MM, Chandra S, Gul S, ElSohly MA. Cannabinoids, Phenolics, Terpenes and Alkaloids of *Cannabis*. *Molecules*. 2021; 26(9):2774. https://doi.org/10.3390/molecules26092774

**Table 4.2.1.** List of Phytocannabinoids, Adapted from Clark (2021)

| Phytocannabinoids | Pharmacological Effects |
|---|---|
| Cannabidiol (CBD) | Anticonvulsive, anti-inflammatory, analgesic, anxiolytic, antipsychotic, antioxidant, neuroprotective |
| Δ9-Tetrahydrocannabinol (Δ9-THC) | Analgesic, antipruritic, antiemetic, anti-inflammatory, anxiolytic, neuroprotective, psychoactive |
| Δ9-Tetrahydrocannabinolic Acid (Δ9-THCA) | Immunomodulatory, anti-inflammatory, antiemetic, neuroprotective |
| Δ9-Tetrahydrocannabivarin (THCV) | Appetite suppressant, increase energy |
| Δ8-Tetrahydrocannabinol (Δ8-THC) | Analgesic, antiemetic |
| Cannabidiolic Acid (CBDA) | Antiemetic, anxiolytic, comparable properties to CBD |
| Cannabinol (CBN) | Sedative, anticonvulsant, anti-inflammatory, antibiotic |
| Cannabigerolic Acid (CBGA) | Parent phytocannabinoid |
| Cannabigerol (CBG) | Antineoplastic, antifungal |
| Cannabichromene (CBC) | Neuroprotective, anti-inflammatory, analgesic |
| Cannabidvarin (CBDV) | Anticonvulsant, antiemetic |

**Table 4.2.1.** Common natural phytocannabinoids

In addition to the changing field of marijuana chemistry, there is a trend of the marijuana plant becoming more potent in the average percentage of THC.[68] As is the case with most botanical products, this is a result of genetically crossed plants, as well as improved farming and growing practices. The appropriate processing and testing of marijuana products are necessary at any potency and does not present a risk to the public with appropriate education and labeling.

### 4.2.2 Terpenes

Terpenes, also referred to as terpenoids once the marijuana flower is dried,[69] are natural aromatic compounds responsible for the variety of smells produced by the marijuana plant. There have been over two hundred terpenes identified within the plant, mainly in the trichomes. Terpene combinations can vary depending on each marijuana strain or chemovar which can be responsible for the different pharmacological experiences per person. Chemovar is the term most frequently used to describe the chemical profile of a specific marijuana plant variety because of the large amount of diversity due to genetic and environmental factors. Terpenes are not unique to marijuana and have been shown to have powerful properties of their own (see Table 4.2.2), directly acting on receptors and impacting neurotransmitter uptake.[70] They interact with the rest of the plant compounds to produce a more therapeutic effect, improving health outcomes.

Many terpenes that can be derived from the *Cannabis Sativa L.* plant (i.e., marijuana) are on the Generally Regarded as Safe (GRAS) list from the FDA as acceptable food additives used as flavor or nutrient supplements.[71] The table

[68] ElSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S., & Church, J. C. (2016). Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. Biological psychiatry, 79(7), 613–619. https://doi.org/10.1016/j.biopsych.2016.01.004

[69] Byars, T. (2021). *Introduction to Cannabis Science: A Primer for Healthcare Professionals, Students, and the Cannabis Curious*. Amazon Kindle.

[70] Holland, J. (2010). *The pot book: a complete guide to cannabis: its role in medicine, politics, science, and culture*. Park Street Press.

[71] Chen, C., & Pan, Z. (2021). Cannabidiol and terpenes from hemp – ingredients for future foods and processing technologies. Journal of Future Foods, 1(2), 113–127. https://doi.org/10.1016/j.jfutfo.2022.01.001

below outlines the main terpenes and their effects on the ECS, as well as other plants containing the same terpenes.[72]

**Table 4.2.2.** List of Terpenes, Adapted from Clark (2021)

| Terpene | Properties | Occurrence in Other Plants |
|---|---|---|
| Myrcene | Analgesic, anti-inflammatory, antibacterial, antifungal, antioxidant, neuroprotective, sedative and relaxing effects | Pine juniper, citrus fruits, hops, eucalyptus, mango, thyme |
| Limonene | Antioxidant, anxiolytic, antibacterial, antifungal, antacid, stress reducer, mood elevator, | Citrus rind, pine, mint, rosemary, juniper |
| Pinene | Anti-inflammatory, bronchodilator, expectorant, antibiotic, analgesic, anticonvulsant, may increase energy and alertness, α and β monoterpenes, most abundant in nature | Pine Trees, rosemary, basil, eucalyptus |
| β-caryophyllene | Anti-inflammatory, mood elevation, anticancer, antibacterial, analgesic; only terpene that binds weakly to CB2, making it a cannabinoid and terpene, most common sesquiterpene, primary scent that police dogs are trained for | Cedarwood, black pepper, rosemary, cloves, basil, oregano, lavender, cinnamon, hops |
| Humulene | Anorectic, anti-inflammatory, antibacterial, antineoplastic, analgesic, a sesquiterpene, also known as α-humulene and α-caryophyllene | Clove, sage, ginseng, black pepper, and hops |
| Linalool | Anti-inflammatory, antianxiety, antidepressant, antiepileptic, immune booster, calming and sedative effects | Cinnamon, lavender, mint, rosewood, birch trees |
| Terpinolene | Antianxiety, anticancer, sedation and cognitive clarity effects, monoterpenoid | Juniper, allspice, rosemary, sage, tea tree |
| Camphene | Potential to reduce cholesterol and triglycerides; becomes a powerful antioxidant when combined with Vitamin C | Cypress trees, valerian, holy basil, nutmeg, sage, ginger, neroli, and rosemary |
| Terpineol | Antibacterial, antioxidant, calming and sedative effects | Pine Trees, rosemary, basil, eucalyptus |
| α-Bisabolol | Analgesic, antibacterial | Chamomile flower, candeia tree |
| Borneol | Insect repellant, anticancer | Rosemary, mint, camphor |
| Carene | Analgesic, improves memory | Rosemary, basil, bell peppers, cedar, pine |
| Eucalyptol | Analgesic, antibacterial, antifungal | Eucalyptus |
| Geraniol | Neuroprotectant, antioxidant | Lemons, tobacco |
| Guaiol | Antibacterial, antioxidant | Guaiacum, cypress pine |

[72] Clark, C. S. (2021). *CANNABIS: a handbook for nurses.* Wolters Kluwer Medical. https://shop.lww.com/Cannabis--A-Handbook-for-Nurses/p/9781975144265

| Terpene | Properties | Occurrence in Other Plants |
|---|---|---|
| Ocimene | Anti-inflammatory, antiviral, antifungal | Mint, mangoes, basil, orchids |
| Nerolidol | Antifungal, antioxidant, antimicrobial, anti-inflammatory | Jasmine, ginger, lavender |
| Phellandrene | Antifungal | Cinnamon, garlic, dill, ginger, parsley, turmeric, eucalyptus oil |
| Pulegone | Sedative, antipyretic | Rosemary |
| Sabinene | Antioxidant, anti-inflammatory | Black pepper, basil |
| Trans-nerolidol | Antiparasitic, antioxidant, antifungal, anticancer, antimicrobial | Jasmine, lemongrass, and tea tree oil |
| Valencene | Insect repellant | Valencia oranges |

### 4.2.3 Flavonoids

Marijuana contains flavonoids in addition to the more well known phytocannabinoids and terpenoids. Flavonoids are phenolic compounds, a class of chemical compounds that contain one or more hydroxyl groups attached to an aromatic hydrocarbon group. Flavonoids are frequently found in fruits, vegetables, tea, wine, bark, and flowers. They are the natural protectors of the plant by supporting growth, antimicrobial properties, natural colorants, UV light protection and defending from plant stressors.

There have been over twenty flavonoids detected in the marijuana plant. Cannflavins are flavonoids specific to the marijuana plant, such as Cannflavin A, B and C.[73] These cannflavins work synergistically with the other components of the plant to produce anti-inflammatory, antioxidant, antimutagenic, and anticarcinogenic-enzyme inhibition effects.

**Table 4.2.3.** List of Flavonoids, Adapted from Clark (2021) [74]

| Cannabis Flavonoids | Potential Benefits |
|---|---|
| Cannflavins A, B, C | Anti-inflammatory |
| Vitexin and isovitexin | Inhibit thyroid peroxidase, support healing from gout |
| Kaempferol | Antidepressant, may reduce risks of cancer and heart disease |
| Apigenin | Stimulates monoamine transporter, acts as an anxiolytic |
| Quercetin | Antiviral effects, anti-inflammatory, MAO inhibitor |
| Luteolin and orientin | Antioxidant, anti-inflammatory, antibiotic, anticancer |

### 4.2.4 Entourage Effect

In 1998, Raphael Mechoulam and Shimon Ben-Shabat discovered the “entourage effect." They found that two

[73] Desaulniers Brousseau, V., Wu, B.-S., MacPherson, S., Morello, V., & Lefsrud, M. (2021). Cannabinoids and Terpenes: How Production of Photo-Protectants Can Be Manipulated to Enhance Cannabis sativa L. Phytochemistry. *Frontiers in Plant Science*, *12*. https://doi.org/10.3389/fpls.2021.620021

[74] Clark, C. S. (2021). *CANNABIS: a handbook for nurses.* Wolters Kluwer Medical. https://shop.lww.com/Cannabis--A-Handbook-for-Nurses/p/9781975144265

compounds with no binding affinity to cannabinoid receptors worked synergistically to potentiate the binding affinity for the body's endocannabinoids. This concept has been adopted by those engaged in the cultivation, production, and research of marijuana to show that the multiple compounds within the plant work harmoniously to produce therapeutic effects.[75,76]

### 4.2.5 Origin of Cannabinoids and Synthetically Derived Cannabinoids

It is imperative that DEA recognize the difference between synthetic cannabinoids produced by the pharmaceutical industrial, hemp industry, and illicit manufacturers and naturally-derived phytocannabinoids.

Synthetically derived cannabinoids have been developed and used as a diagnostic tool to see how specific cannabinoids interact with the endocannabinoid system.[77] During the creation of these synthetics, there have been some beneficial derivatives, such as the FDA approved drugs, Syndros and Marinol. These are mono-molecular structures including only a single cannabinoid, shown to have efficacy for appetite stimulation and as an antiemetic.

However, not all synthetics are created to mimic the natural cannabinoids found in the marijuana plant. For example, Δ9-THC is a partial agonist of the $CB_1$ receptor, and many unregulated, synthetic marijuana, i.e., K2 and Spice, are created to be a full agonist of the CB receptors. This leads to a higher affinity receptor relationship causing a more intense feeling of being "high" or euphoric, potentially causing a level of abuse not seen with the phytocannabinoids in marijuana. Synthetic cannabinoids are full agonists of the CB1 receptor, meaning they have a higher affinity and are much more potent than THC, thus increasing their toxicity.[78]

These unregulated, synthetic cannabinoids are frequently a liquid that is sprayed onto plant material and smoked, further emphasizing this is not a natural product of the marijuana plant. Similarly, synthetics like the popularized HHC, HXC, THC-O, THC-P, and THC-JD[79] can be derived and put into a liquid cartridge to be vaped giving the consumer the wrongful impression they are using a marijuana product. Furthermore, synthetic cannabinoids are not metabolized in the same way as marijuana. Further, synthetic cannabinoids have a pharmacological and toxicological profile that is distinct from Δ9-THC found in natural marijuana, giving further evidence to support the differentiation between compounds.[80,81]

There are also chemical synthesis processes occurring to chemically convert CBD to THC and other molecules using harsh solvents and metal catalysts. This process is commonly used in the hemp industry to produce intoxicating products with THC concentrations higher than can be naturally found in hemp-marijuana. Depending on the reaction conditions and purification processes, synthetic Δ8-THC may contain unknown impurities, different degradants, and synthetic cannabinoid analogs not naturally produced in marijuana or hemp plants. These compounds may lack comprehensive safety or toxicity data, raising potential concerns about their use.[82,83]

While we understand that the definition of marijuana used by the DOJ and DEA relates to the natural marijuana plant (i.e., *Cannabis sativa L.*), we wanted to note the several different manufacturing methods, summarized below,

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[75] Ben-Shabat, S., Fride, E., Sheskin, T., Tamiri, T., Rhee, M., Vogel, Z., Bisogno, T., De Petrocellis, L., Di Marzo, V., & Mechoulam, R. (1998). An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. European Journal of Pharmacology, 353(1), 23–31. https://doi.org/10.1016/s0014-2999(98)00392-6

[76] Russo, E. B. (2019). The case for the entourage effect and conventional breeding of clinical cannabis: No "Strain," no gain. Frontiers in Plant Science, 9. https://doi.org/10.3389/fpls.2018.01969

[77] Le Boisselier, R., Alexandre, J., Lelong-Boulouard, V. and Debruyne, D. (2017), Focus on cannabinoids and synthetic cannabinoids. Clin. Pharmacol. Ther., 101: 220-229. https://doi-org.proxy-hs.researchport.umd.edu/10.1002/cpt.563

[78] Zagzoog, A., Brandt, A. L., Black, T., Kim, E. D., Burkart, R., Patel, M., Jin, Z., Nikolaeva, M., & Laprairie, R. B. (2021). Assessment of select synthetic cannabinoid receptor agonist bias and selectivity between the type 1 and type 2 cannabinoid receptor. Scientific reports, 11(1), 10611. https://doi.org/10.1038/s41598-021-90167-w

[79] *Synthetic cannabinoids*. (2023, September). CT.gov. https://portal.ct.gov/cannabis/knowledge-base/articles/synthetic-cannabinoids?language=en_US

[80] Fantegrossi, W. E., Moran, J. H., Radominska-Pandya, A., & Prather, P. L. (2014). Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Δ(9)-THC: mechanism underlying greater toxicity?. Life sciences, 97(1), 45–54. https://doi.org/10.1016/j.lfs.2013.09.017

[81] Tai, S., & Fantegrossi, W. E. (2017). Pharmacological and Toxicological Effects of Synthetic Cannabinoids and Their Metabolites. Current topics in behavioral neurosciences, 32, 249–262. https://doi.org/10.1007/7854_2016_60

[82] Ray, C. L., Bylo, M. P., Pescaglia, J., Gawenis, J. A., & Greenlief, C. M. (2022). Delta-8 Tetrahydrocannabinol Product Impurities. Molecules (Basel, Switzerland), 27(20), 6924. https://doi.org/10.3390/molecules27206924

[83] Gul, W., Shahzadi, I., Sarma, N., Kim, N. C., & ElSohly, M. A. (2024). Development and Validation of a GC-FID Method for the Quantitation of Δ 8-Tetrahydrocannabinol and Impurities Found in Synthetic Δ 8-Tetrahydrocannabinol and Vaping Products. Planta medica, 90(4), 316–332. https://doi.org/10.1055/a-2249-7824

that are used to create cannabinoids.[84] It is important to note that in many public datasets (e.g., hospitalizations, emergency visits, adverse events, use reports), there are cases where the substance in question was not actually marijuana. Rather, it may have been other substances similar to marijuana, such as intoxicating hemp or synthetic marijuana. This misreporting is often the result of confusion by consumer, healthcare provider, and law enforcement, on the differences between these substances. This confusion is further compounded by limitations in medical education and options for recording marijuana-use in software used by emergency departments and hospitals.

- **Cultivation and extraction:** The traditional method of producing cannabinoids, primarily THC and CBD, by growing the marijuana plant and then extracting cannabinoids most commonly through using solvents, heat, and/or pressure.

- **Chemical synthesis:** A lab-based process by which a starting molecule, usually CBD, is treated with a variety of chemicals to convert into another molecule through a series of chemical reactions. This method is prone to creating several byproducts and impurities of unknown toxicology and is used widely by the hemp industry to create intoxicating hemp products marketed as "plant derived."[85] See Figure 4.2.5.

- **Biosynthesis:** This approach produces naturally occurring chemical compounds through enzyme-catalyzed reactions. Advances in bioengineering have enabled the conversion of microorganisms, such as *E. coli* and *S. cerevisiae*, into cost-effective 'microbial cell factories' for producing cannabinoids by inserting specific enzymes and modifying their genetics, followed by extraction and purification of the target molecules.[86]

- **Combined fermentation and chemical synthesis:** This method involves bioengineering and fermenting microorganisms, such as baker's yeast, to biosynthesize cannabinoids, which are then isolated and purified. This process can be complemented with chemical synthesis to produce specific cannabinoids.

- **Biotransformation by enzymes:** This method, which is a proprietary process by InMed Pharmaceuticals, involves fermenting bioengineered *E. coli* to produce specific enzymes, which then modify chemical substrates to create rare cannabinoids.

[84] (2022). Cannabinoid manufacturing – Innovative approaches to the production of cannabinoids. Edison Group. https://www.edisongroup.com/thematic/cannabinoid-manufacturing-innovative-approaches-to-the-production-of-cannabinoids/
[85] Capucciati, A., Casali, E., Bini, A., Doria, F., Merli, D., & Porta, A. (2024). Easy and Accessible Synthesis of Cannabinoids from CBD. *Journal of natural products*, *87*(4), 869–875. https://doi.org/10.1021/acs.jnatprod.3c01117
[86] Luo, X., Reiter, M. A., d'Espaux, L., Wong, J., Denby, C. M., Lechner, A., Zhang, Y., Grzybowski, A. T., Harth, S., Lin, W., Lee, H., Yu, C., Shin, J., Deng, K., Benites, V. T., Wang, G., Baidoo, E. E. K., Chen, Y., Dev, I., Petzold, C. J., … Keasling, J. D. (2019). Complete biosynthesis of cannabinoids and their unnatural analogues in yeast. *Nature*, *567*(7746), 123–126. https://doi.org/10.1038/s41586-019-0978-9

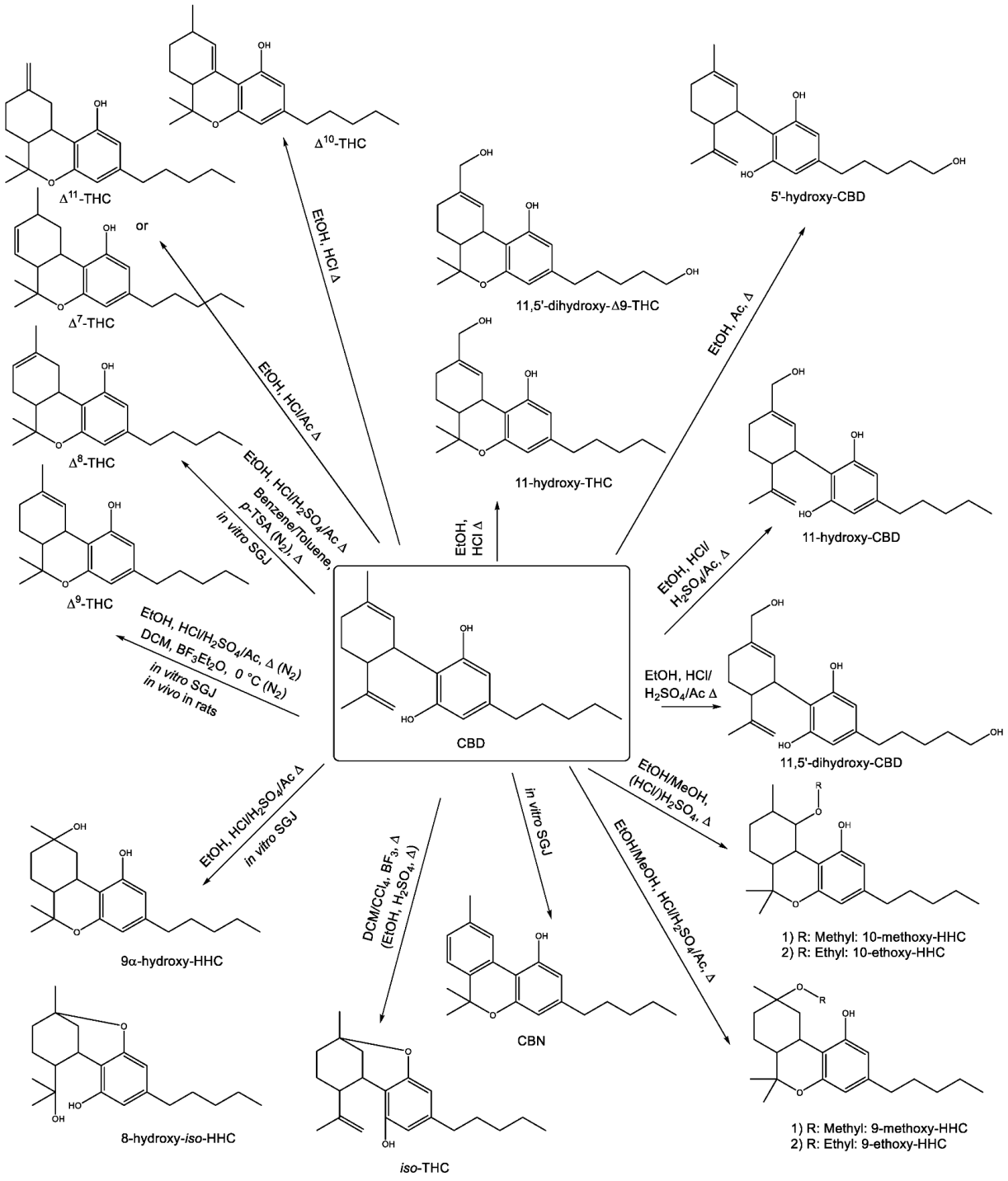


**Figure 4.2.5.** Overview of Chemical Conversions of CBD to Different Conversion Products and the Respective Conditions Reported in the Literature[87]

[87] Golombek, P., Müller, M., Barthlott, I., Sproll, C., & Lachenmeier, D. W. (2020). Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature. Toxics, 8(2), 41. https://doi.org/10.3390/toxics8020041

## 5.0 MARIJUANA'S HISTORY, CURRENT PATTERN OF ABUSE, AND SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

For the fourth and fifth factors of the Eight-Factor Analysis, DEA stated that additional data on marijuana's history, current pattern of abuse and scope, duration, and significance of marijuana abuse may further inform the findings that must be made to reschedule marijuana in regards to these factors. Below we evaluate recent research related to these topics.

### 5.1 Epidemiological Survey Data

It's important to understand usage among the different age groups, genders, socioeconomic status and even geographical locations. Since the demand of marijuana has continued to rise, research and education is necessary to inform policymakers, healthcare providers, and researchers of the therapeutic uses of marijuana.[88,89]

This data below analyzes the intricate dynamics that influence the epidemiology of medical marijuana, emphasizing the complex factors at play. It emphasizes the critical need for thorough data collection and analysis to navigate well-informed decision-making within public health and medicine. With medical marijuana increasingly recognized as a therapeutic option, continuous epidemiological studies are indispensable. They serve to track evolving trends, evaluate diverse health outcomes, and provide essential insights that support evidence-based practices. This ongoing research is pivotal in navigating the evolving landscape of medical marijuana use and its potential impacts on health and society at large.

### 5.2 Marijuana Usage Across Age Groups and Genders

Medical marijuana usage varies across different age groups. Approximately half of Americans have claimed to have used marijuana at least once in their life. Although younger age groups have traditionally shown the highest rates of recreational marijuana use, states with licensed and legal cannabis programs have actually observed a declining trend in youth use (see Section 6.6). Concurrently, the introduction of medical marijuana programs has led to increased use among older adults who seek therapeutic options for managing chronic pain and other conditions. In general, males have reported higher rates of marijuana use compared to females. However, recent studies have shown a rise in marijuana use among women.

With respect to trends over the last 50 years, marijuana use peaked in the late 1970s followed by a significant decline through the 1980s and early 1990s, only to markedly increase in the mid-1990s.[90] After a period of stagnation, there has been a steady increase year-over-year, beginning in the mid-2000s. While increases cannot be attributed entirely to any one factor, the introduction of state legal medical markets, which include safety testing and product labeling, and changes in public attitude towards marijuana have likely contributed to this trend. According to one study, individual marijuana users have reported increased intake/frequency over time, with 4.1% of Americans claiming increased use over the prior year ending in 2002 compared to 9.1% claiming increased marijuana use for the prior year ending in 2015.[91] In general, as evidenced by a series of public opinion polls, and in conjunction with the passage of medical marijuana laws in a growing number of states, a majority of Americans continue to support the use of medical marijuana.[92]

Today's regulatory environment, where marijuana continues to be illegal at the federal level but legalized by state markets, has further complicated the ability for researchers and public health officials to understand marijuana

[88] Caulkins J. P. (2024). Changes in self-reported cannabis use in the United States from 1979 to 2022. Addiction (Abingdon, England), 10.1111/add.16519. Advance online publication. https://doi.org/10.1111/add.16519

[89] Yang, K. H., Tam, R. M., Satybaldiyeva, N., Kepner, W., Han, B. H., Moore, A. A., & Palamar, J. J. (2023). Trends in past-month cannabis use among US adults across a range of disabilities and health conditions, 2015-2019. Preventive medicine, 177, 107768. https://doi.org/10.1016/j.ypmed.2023.107768

[90] National Academies of Sciences, Engineering, and Medicine; The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US); 2017 Jan 12. 3, Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425763/

[91] National Center for Drug Abuse Statistics, Marijuana Addiction: Rates & Usage Statistics, 2024https://drugabusestatistics.org/marijuana-addiction/

[92] Carliner, H., Brown, Q. L., Sarvet, A. L., & Hasin, D. S. (2017). Cannabis use, attitudes, and legal status in the U.S.: A review. Preventive medicine, 104, 13–23. https://doi.org/10.1016/j.ypmed.2017.07.008

consumption patterns as compared to other controlled substances. Other prescribed drugs such as pain relievers, tranquilizers, stimulants and prohibited drugs like cocaine, hallucinogens and heroin trail behind marijuana in terms of consumption, but these consumption patterns are difficult to compare when considering that marijuana has been legalized in one form or another across 38 states. Adding to the complexity is the availability of hemp-derived products, which have become ubiquitous across all 50 states in response to the 2018 Farm Bill and may serve to increase consumption patterns.

### 5.3 Socioeconomic Status and Marijuana Usage Patterns

The economic impact of medical marijuana legalization has been significant, with implications for disparities in its access and usage rates among different socioeconomic groups. In recent years, marijuana use increased among men and women at all income levels between 2007 and 2014.[93] This trend is particularly important when considering the historical differences in access to medical marijuana across socioeconomic groups, with higher-income individuals having greater access to healthcare resources, including medical marijuana recommendations from their healthcare providers.

Further, it is important to note that stigma, fear, and issues of access that have disproportionately impacted Black, Indigenous, and People of Color communities who have been targeted by the federal government's enforcement efforts against marijuana and other drugs. With the majority of states having legalized medical marijuana use, research from these legalized states indicate that while the overall number of marijuana-related arrests has decreased, racial disparities in these arrests persist or have even worsened.[94,95] Despite similar usage rates across racial groups, Black Americans are disproportionately targeted and arrested for marijuana-related offenses. For instance, Black people are nearly four times more likely to be arrested for marijuana possession than white people, even though usage rates are comparable across these groups.[96] This aggressive enforcement has led to significant personal and economic consequences for those arrested, including barriers to employment, housing, and education, which further entrench socioeconomic disparities.

### 5.4 Geographic Variations in Marijuana Usage Patterns

Geographic location significantly shapes medical marijuana usage patterns through differing legislation, cultural attitudes, and healthcare approaches. While, states with legalized marijuana programs report higher usage rates than those where it's illegal or restricted,[97] it is important to note that this data does not include consumption patterns of intoxicating hemp-derived products in states without legal marijuana programs, where use of these products is rising. Globally, disparities persist: some nations support medical marijuana legalization, contrasting starkly with others while maintaining stringent prohibitions. These distinctions underscore how local contexts profoundly influence the adoption and perception of medical marijuana on both national and international scales.

## 6.0 What, If Any, Risk There is to the Public Health

For the sixth factor of the Eight-Factor Analysis, DEA stated that additional data on public safety risks, risks from acute and chronic marijuana use via oral and inhaled administration routes, and the impact of Δ9-THC potency may be appropriate for consideration. Below we evaluate recent research related to these topics.

### 6.1 Driving

[93] Carliner, H., Brown, Q. L., Sarvet, A. L., & Hasin, D. S. (2017). Cannabis use, attitudes, and legal status in the U.S.: A review. Preventive medicine, 104, 13–23. https://doi.org/10.1016/j.ypmed.2017.07.008
[94] Joshi, S., Doonan, S. M., & Pamplin, J. R., 2nd (2023). A tale of two cities: Racialized arrests following decriminalization and recreational legalization of cannabis. Drug and alcohol dependence, 249, 109911. https://doi.org/10.1016/j.drugalcdep.2023.109911
[95] Gunadi, C., & Shi, Y. (2022). Cannabis decriminalization and racial disparity in arrests for cannabis possession. Social science & medicine (1982), 293, 114672. https://doi.org/10.1016/j.socscimed.2021.114672
[96] American Civil Liberties Union. (2020, April 17). A Tale of Two Countries: Racially Targeted Arrests in the Era of Marijuana Reform. American Civil Liberties Union. https://www.aclu.org/news/criminal-law-reform/a-tale-of-two-countries-racially-targeted-arrests-in-the-era-of-marijuana-reform
[97] Wkya, K., & Weinberger, A. (2022, July 19). Cannabis Use Highest in Legalized States, More So Among Cigarette Smokers. Columbia University Mailman School of Public Health. https://www.publichealth.columbia.edu/news/cannabis-use-highest-legalized-states-more-so-among-cigarette-smokers

The debate over marijuana legalization often includes concerns about public safety, particularly in relation to driving. This section reviews current research to evaluate the impact of marijuana on driving safety as compared to alcohol and other mind-altering substances.

Some limitations faced when tracking drugged driving is the fact that drugs don't impact everyone in the exact same way, there's no agreed upon limit for drug impairment, and there are limitations to current drug testing technology.[98] The problem with driving under the influence of marijuana is that it has the potential to impair psychomotor skills, lane tracking, and cognitive function.[99] As the HHS stated about 4% of drivers aged 16+ were found to drive while on marijuana.[100] Looking at the same demographic, 5% drove under the influence of alcohol while less than 1% were under the influence of cocaine or heroin.[3] Some State findings have suggested that alcohol use goes down upon medical legalization of marijuana. They have also shown an association between medical marijuana legalization and the reduction in fatal car crashes.[101]

Overall, when it comes to driving under the influence of marijuana more research needs to be conducted, particularly when looking at the effects of decriminalizing marijuana and its impact on drugged driving. However, it does seem like an increase in public health education regarding marijuana is associated with a lowered rate of individuals driving under its influence. It is also possible that marijuana labeling regulations can impact these driving rates as well; States with legalized marijuana often include mandatory labels, warning consumers about the risks of driving while using marijuana (similar to that for alcohol). These labels do vary, however, and are left to each State's own discretion.[102] One study looked at the impact of medical marijuana on car accidents and found that insurance premiums actually went down in States that legalized medically, and its effects were more strongly seen in areas near dispensaries and in areas where drunk driving had higher prevalence prior to legalization.[103]

### 6.1.1 Driving and Alcohol

The consumption of alcohol has had a significant impact on public health safety, particularly in relation to driving. Motor vehicle crashes (MVCs) are a leading cause of injury death in the U.S. In 2022, more than 13,000 MVC fatalities involved a driver with a positive blood alcohol concentration (BAC). There is a strong, graded relationship between BAC and the risk of MVCs and crash fatalities, with physiological impairment beginning well below the current legal limit of 0.08%. The risk is significantly elevated at BACs exceeding 0.02%, indicating that even low levels of alcohol consumption can impair driving ability and increase the likelihood of accidents.[104]

The National Highway Traffic Safety Administration (NHTSA) estimates that, in 2022, alcohol-induced traffic fatalities accounted for between 20% and 41% of the total traffic fatalities across various states, with a national average of 32%. On a daily basis, approximately 37 lives are lost in the U.S. due to motor vehicle accidents involving an alcohol-impaired driver, equating to a new fatality every 39 minutes. The estimated annual cost of alcohol related fatal crashes is a staggering $44 billion, encompassing lost productivity, legal, court, and medical

[98] *Drugged driving | Marijuana-Impaired driving*. (2024, June 23). https://www.ncsl.org/transportation/drugged-driving-marijuana-impaired-driving

[99] Confirmed Toxicology Results from Drug Recognition Expert Enforcement Evaluations, 2017. (2017). In Sobriety Testing Resource Center, *Sobriety Testing Resource Center*. https://www.nhtsa.gov/sites/nhtsa.gov/files/documents/13839-drugged_facts_flyer_101918_v8_002.pdf

[100] Levine, R., ADM, USPHS & U.S. Public Health Service. (2023b). *BASIS FOR THE RECOMMENDATION TO RESCHEDULE MARIJUANA INTO SCHEDULE III OF THE CONTROLLED SUBSTANCES ACT*. https://www.hhs.gov/sites/default/files/scheduling-recommendation.pdf

[101] Windle, S. B., Socha, P., Nazif-Munoz, J. I., Harper, S., & Nandi, A. (2022). The Impact of cannabis decriminalization and Legalization on road safety Outcomes: A Systematic review. *American Journal of Preventive Medicine*, *63*(6), 1037–1052. https://doi.org/10.1016/j.amepre.2022.07.012

[102] Dutra, L. M., Farrelly, M., Gourdet, C., & Bradfield, B. (2022). Cannabis legalization and driving under the influence of cannabis in a national U.S. Sample. *Preventive Medicine Reports*, *27*, 101799. https://doi.org/10.1016/j.pmedr.2022.101799

[103] Ellis, C. M., Grace, M. F., Smith, R. A., & Zhang, J. (2022). Medical cannabis and automobile accidents: Evidence from auto insurance. Health economics, 31(9), 1878–1897. https://doi.org/10.1002/hec.4553

[104] Bingham, C. R., Shope, J. T., Parow, J. E., & Lohman, M. C. (2020). Alcohol policies and motor vehicle crash deaths involving blood alcohol concentrations below 0.08%. *American Journal of Preventive Medicine*, *58*(5), 613-620. https://doi.org/10.1016/j.amepre.2019.12.015

expenses, property damage, and insurance administration.[105, 106]

The number of alcohol-related traffic accidents and fatalities has decreased over time as laws have become more stringent. However, this data underscores the profound public health implications of alcohol-impaired driving and highlights the need for stringent alcohol policies and effective interventions to further mitigate these risks.

### 6.1.2 Driving and Opioids

The impact of opioid use on public health safety, particularly in relation to driving, has become a growing concern. Opioids, both prescription and illicit, have been shown to significantly impair driving ability, leading to an increased risk of MVCs. The detrimental effects of opioids on driving skills are well-documented. The use of prescription opioids can impair crucial psychomotor and cognitive skills required for safe driving such as manual dexterity, hand-eye coordination, mental alertness, and visual information processing.

A population-based case-control study evaluating the relationship between prescription opioids, alcohol and fatal motor vehicle accidents, highlighted the compounded risk when opioids are used in conjunction with alcohol. Compared to drivers who tested negative for both substances, those who tested positive for prescription opioids had a 72% increased risk of fatal crash involvement. This risk was nearly 17-fold higher for those testing positive for alcohol alone, and about 21-fold higher for those testing positive for both opioids and alcohol. These results indicate that prescription opioid use by drivers significantly elevates the risk of fatal crash involvement, even independent of alcohol use, and the combined use of both substances together exacerbates this risk further.[107]

In summary, the evidence from these studies underscores the significant public health threat posed by opioid use in relation to driving safety. The substantial increase in risk for both injurious and fatal MVCs associated with opioid use, especially when combined with alcohol, highlights the urgent need for targeted public health interventions and policies to address this growing issue.[108]

### 6.1.3 Driving and Marijuana

The implications of marijuana use on driving performance are multifaceted. A study that examined the impact of recreational marijuana markets on MVCs found mixed results. However, a study conducted in Virginia found no significant association between testing positive for marijuana and increased crash rates. Multiple meta-analyses have concluded that marijuana intoxication is associated with low to moderate increase in crash risk, although some smaller studies found no significant association between intoxicated driving and living in states with medical or recreational legalization.[109]

A randomized clinical trial investigating the driving performance of regular marijuana consumers found that those who smoked marijuana exhibited worse driving performance compared to those who smoked a placebo, regardless of the THC content, use history, or blood concentration.[110] The complexity of marijuana's effects on driving is further highlighted in a systematic and meta-analytic review, which emphasized that while marijuana impairs aspects of driving performance, the magnitude and duration of impairment vary depending on the dose, route of administration, and frequency of use. Unlike alcohol, the relationship between blood THC concentration and impairment is not straightforward due to complex pharmacokinetics of THC. Moreover, experimental studies have shown that certain aspects of driving, such as lane position deviation, are more affected by THC than others, such as

[105] García-España, J. F., Tencer, H., & Hingson, R. W. (2021). Alcohol-related traffic laws and drunk-driving fatal accidents. *Accident Analysis & Prevention, 155*, 106358. https://doi.org/10.1016/j.aap.2021.106358
[106] National Highway Traffic Safety Administration. (n.d.). Drunk driving. U.S. Department of Transportation. Retrieved June 30, 2024, from https://www.nhtsa.gov/risky-driving/drunk-driving#driving-after-drinking-5036
[107] Chihuri, S., & Li, G. (2019). Prescription opioids, alcohol, and fatal motor vehicle crashes: A population-based case-control study. *Injury Epidemiology, 6*(1), 4. https://doi.org/10.1186/s40621-019-0187-x
[108] Tochikubo, M., & Lathrop, S. (2021). Opioids and the risk of motor vehicle collision: A systematic review. *Journal of Pharmacy Technology, 37*(1), 20-27. https://doi.org/10.1177/87551225211059926
[109] Tochikubo, M., & Lathrop, S. (2021). Opioids and the risk of motor vehicle collision: A systematic review. *Journal of Pharmacy Technology, 37*(1), 20-27. https://doi.org/10.1177/87551225211059926
[110] Marcotte, T. D., Umlauf, A., Grelotti, D. J., Sones, E. G., Sobolesky, P. M., Smith, B. E., & McCaffrey, S. (2022). Driving performance and cannabis users' perception of safety: A randomized clinical trial. *JAMA Psychiatry, 79*(1), 75-83. https://doi.org/10.1001/jamapsychiatry.2021.4037

average driving speed. This nuanced understanding underscores the need for careful consideration when developing policies and regulations related to marijuana consumption and driving.[111, 112, 113]

Participants were recruited from the EDs of the study sites in Denver, Colorado, Portland, Oregon, and Sacramento, California. Eligible cases were adult (≥18 years old) English-speaking patients who presented to the ED within 8 h of being in an MVC in which they were the driver. In total, 1,398 were enrolled into the study. An adjusted model for odds of MVC among all patients compared alcohol use, marijuana use, and combined use of both marijuana and alcohol. Marijuana alone was not associated with higher odds of MVC, while acute alcohol use alone and combined use of alcohol and marijuana were both independently associated with higher odds of MVC.[114] Some studies have also suggested that marijuana users demonstrate greater awareness that they are impaired, may overestimate their impairment (compared to drinkers, who tend to under-estimate impairment), and apply increased compensatory behaviors when driving.[115]

While driving under the influence of marijuana (like alcohol) may result in slower coordination, judgment, and reaction times, driving under the influence of cocaine and methamphetamines may make a person more aggressive and reckless.[116] Prescription drugs are also commonly linked to drugged driving crashes, with 19.7% of drivers testing positive for opioids in 2016.[117] Benzodiazepines, like Xanax and Valium, have also been shown to increase the risk of traffic accidents by 60% due to its abilities to produce sedation, relax muscles, blur vision, cause vertigo, and impair thinking.[118]

In another analysis of two-vehicle crash fatalities from 1993 - 2014 found that relative to the responsible drivers who tested negative for both alcohol and marijuana, there was 5.37 times increase in fatality for those who tested positive for alcohol and negative for marijuana.[119]

In conclusion, while marijuana use does pose some risks to driving performance, these risks are complex and influenced by multiple factors. The evidence suggests that marijuana intoxication is associated with an increased risk of MVCs, although this risk is much lower than associated with alcohol and opioids.

### 6.2 Learning Processes, Long Term Effects. Public Safety Risks, And Strategies

When it comes to learning and associative processes, marijuana has a range of impact. While our endogenous cannabinoids (anandamide, AEA and 2-arachidonoylglycerol, 2-AG) are involved in regulating memory, pre- and postsynaptic modulation and learning. The exogenous cannabinoid Δ9-THC, has been shown to impair short-term memory. CBD however, was shown to have neuroprotective activities that could counteract the adverse learning effects of Δ9-THC. This in part is due to CBD being a partial inhibitor of the CB1 receptor (the primary receptor responsible for psychoactive activity). A blockade of the CB1 receptor has also been associated with improved learning.[120] Effects of Δ9-THC on learning and associative processes seems to also increase with earlier exposure

[111] Booth, J., & Miller, P. G. (2021). Medicinal cannabis and driving: The intersection of health and road safety policy. *Drug Policy, 103*, 307. https://doi.org/10.1016/j.drugpro.2021.103307

[112] McCartney, D., Arkell, T. R., Irwin, C., & McGregor, I. S. (2021). Determining the magnitude and duration of acute Δ9-tetrahydrocannabinol (Δ9-THC)-induced driving and cognitive impairment: A systematic and meta-analytic review. *Neuroscience & Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2021.01.003

[113] Pearlson, G. D., Stevens, M. C., & D'Souza, D. C. (2021). Cannabis and Driving. *Frontiers in Psychiatry, 12.* https://doi.org/10.3389/fpsyt.2021.689444

[114] Hartman, R.L., Brown, T.L., Milavetz, G., et al., 2016. Cannabis effects on driving longitudinal control with and without alcohol. J. Appl. Toxicol. 36 (11), 1418–1429. https://doi.org/10.1002/JAT.3295

[115] Sewell, R. A., Poling, J., & Sofuoglu, M. (2009). The effect of cannabis compared with alcohol on driving. The American journal on addictions, 18(3), 185–193. https://doi.org/10.1080/10550490902786934

[116] *Drugged driving | Marijuana-Impaired driving*. (2024, June 23). https://www.ncsl.org/transportation/drugged-driving-marijuana-impaired-driving

[117] *Drugged Driving DrugFacts | National Institute on Drug Abuse*. (2024, May 27). National Institute on Drug Abuse. https://nida.nih.gov/publications/drugfacts/drugged-driving.

[118] American Addiction Centers Editorial Staff & American Addiction Centers Editorial Staff. (2023, January 19). *5 reasons driving on benzos is just a bad idea - DrugAbuse.com.* DrugAbuse.com.https://drugabuse.com/blog/5-reasons-driving-on-benzos-is-just-a-bad-idea/

[119] Li, G., Chihuri, S., & Brady, J. E. (2017). Role of alcohol and marijuana use in the initiation of fatal two-vehicle crashes. Annals of epidemiology, 27(5), 342–347.e1. https://doi.org/10.1016/j.annepidem.2017.05.003

[120] Niloy, N., Hediyal, T. A., Vichitra, C., Sonali, S., Chidambaram, S. B., Gorantla, V. R., & Mahalakshmi, A. M. (2023). Effect of cannabis on memory consolidation, learning and retrieval and its current legal status in India: a review. Biomolecules, 13(1), 162.

(before 18yrs old) and frequent use. This is similar to alcohol which also is shown to impair memory after a few drinks, with an increase of effect occurring with increased consumption.[121] Drinking has also been associated with poorer academic performance and decreased study hours. Stimulants like Adderall have also been shown to be popular amongst young adults (especially students) but they carry the risk of dependence with the potential to cause paranoia and auditory hallucinations.[122]

Overall, the main public safety risks associated with marijuana use includes driving under the influence and unintentional exposures to youth. One strategy to utilize for the prevention of drugged driving includes increasing public health information around marijuana. This could include free public health events hosted by marijuana professionals to broaden reach in the community. Enforcing packaging and warning regulations may also prove promising in regards to improved public safety. In preventing unintentional marijuana exposure to youth, strategies similar to alcohol and prescription drugs should be utilized. Marijuana products should come in child proofed packaging with warning labels for adults to keep out of kids reach. Marijuana products should also be regulated to keep companies from appealing to children (i.e., marijuana products with packaging similar to mainstream brands like Cheetos or Oreos). Canada provides an excellent example of how a regulated, legalized market with strict standards on labeling and packaging can significantly reduce accidental access by children. According to the Health Canada 2023 report, five years after legalization, accidental cannabis consumption among children was so negligible that it couldn't even be estimated, highlighting the effectiveness of these regulations.[123] Increased public health education on the effects of marijuana on children may also help decrease these unintentional exposures.

### 6.3 Pulmonary & Respiratory Considerations

Marijuana can be consumed in a multitude of ways, but the most common is inhalation via smoking. Unfortunately, the long-term effects of marijuana smoking have not been studied to the extent that tobacco and nicotine have been studied due to prohibition.[124]

In 2013, a study on pulmonary exposure to marijuana over the course of 20 years determined that “Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function.” The study found strong statistical evidence that associations between marijuana use and pulmonary function were non-linear, so that true cause and effect was not clearly evident. At low lifetime exposure levels, increasing marijuana use was associated with a steep increase in both Forced Expiratory Volume in 1 second (FEV1) and in Forced Vital Capacity (FVC). These widely accepted measures of pulmonary health surprisingly showed healthier than average function for the infrequent marijuana consumers than for those who abstained from marijuana completely.[125]

### 6.4 Harm Reduction

Marijuana is an increasingly accessible substitute for substances with higher risk profiles than marijuana (such as fentanyl, heroin, cocaine, and methamphetamine). In psychology, replacing a harmful substance with a less harmful substance is called “harm reduction”. Modalities focused on *harm reduction* have shown that one of the benefits of marijuana use is that its consumption may result in *less* dependence on riskier substances.[126,127]

If a substance that does a great deal of harm, such as an opioid, can be replaced with a substance that has *not* been

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https://doi.org/10.3390/biom13010162

[121] Editorial Staff. (2022, October 25). *The impact of drinking while studying | Alcohol.org*. Alcohol.org. https://alcohol.org/health-effects/drinking-while-studying/

[122] *Adderall for Study: Does it Really Make You Smarter?* (n.d.). Drugs.com. https://www.drugs.com/medical-answers/adderall-study-make-you-smarter-3573697/

[123] Canada, H. (2024, January 12). Canadian Cannabis Survey 2023: Summary. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/canadian-cannabis-survey-2023-summary.html

[124] Subramaniam VN, Menezes AR, DeSchutter A, Lavie CJ. The Cardiovascular Effects of Marijuana: Are the Potential Adverse Effects Worth the High?. Mo Med. 2019;116(2):146-153.

[125] Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012;307:173–81

[126] Beaugard CA, Walley AY, Amodeo M. "Everything is kind of the same except my mind is with me": exploring cannabis substitution in a sample of adults in early recovery from an opioid or stimulant addiction. Harm Reduct J. 2024;21(1):83. Published 2024 Apr 20. doi:10.1186/s12954-024-01002-0

[127] Mok J, Milloy MJ, Grant C, et al. Use of Cannabis as a Harm Reduction Strategy Among People Who Use Drugs: A Cohort Study. Cannabis Cannabinoid Res. 2023;8(4):670-678. doi:10.1089/can.2021.0229

shown to cause such high levels of risk and harm, such as marijuana, it can be a healthy step in the journey towards recovery. Research on marijuana substitution suggests it can be an effective strategy to decrease more harmful substance use, in part because it has fewer adverse side effects and less withdrawal potential than other drugs.[128,129,130] Exogenous marijuana use, via action on cannabinoid receptors, can also be a valuable tool in mitigating the effects of other medications.[131]

### 6.5 Comparison with Ketamine

Ketamine is a Schedule III drug which is consumed as both a medically prescribed and an illicit substance and shares several key similarities with marijuana. It is considered to possess a comparable risk profile, and in some respects exceeds marijuana's potential for harm.[132] Ketamine is used for a number of medically accepted purposes, including being used as a concomitant therapy for substance abuse and depression, but the potential for adverse outcomes and abuse also exist.[133] Due to its pharmacokinetic properties ketamine users can develop tolerance over time and potentially could develop Ketamine Use Disorder, though abuse of the substance remains low in the U.S.. An estimated 1% or less of the US population misuses ketamine,[134] which is considerably less than the estimated 6.7% who are considered to have Cannabis Use Disorder.[135] Although illicit use of ketamine does occur, there is no data to suggest that its classification as a Schedule III substance has had an effect on incidence of recreational use.

The difference between patterns of abuse in ketamine and marijuana may be attributed in part to the differences in their regulatory status and resulting acceptance by the medical community. Ketamine is administered in clinical settings and/or by practitioners, and in doing so individuals who are utilizing the drug for therapeutic purpose are afforded important advantages. Administering substances with potential for abuse in a clinical setting offer several benefits including monitoring for dose adherence, guidance in the event of adverse events, and oversight to reduce or mitigate risk of harm and abuse. The lack of acceptance by the medical community due to marijuana's continued status as a Schedule I substance means that individuals pursuing the substance are often doing so outside the regulatory and clinical frameworks that reduce the potential for negative outcomes, resulting in the potential for an increased risk to public health.

### 6.6 Youth Use

As the legal landscape for marijuana evolves, concerns about its impact on youth have prompted extensive research. Recent studies have examined the effects of marijuana legalization on adolescent use rates, revealing insightful trends.

#### 6.6.1 Marijuana Regulation and Teen Use Rates

Following the enactment of both medical marijuana access laws and adult-use marijuana laws, data consistently

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[128] Reiman A. Cannabis as a substitute for alcohol and other drugs. Harm Reduct J. 2009;6:35. Published 2009 Dec 3. doi:10.1186/1477-7517-6-35

[129] Siklos-Whillans J, Bacchus A, Manwell LA. A scoping review of the use of cannabis and its extracts as potential harm reduction strategies: insights from preclinical and clinical research. Int J Ment Health Addict. 2021;19(5):1527–50. doi: 10.1007/s11469-020-00244-w

[130] Hameed, M., Prasad, S., Jain, E., Dogrul, B. N., Al-Oleimat, A., Pokhrel, B., Chowdhury, S., Co, E. L., Mitra, S., Quinonez, J., Ruxmohan, S., & Stein, J. (2023). Medical Cannabis for Chronic Nonmalignant Pain Management. Current pain and headache reports, 27(4), 57–63. https://doi.org/10.1007/s11916-023-01101-w

[131] Be the Change in Mental Health - Ketamine-assisted Therapy outpatient mental health clinic - Innovative Ketamine treatments for depression anxiety. Ketamine timeline - how did it all start? ketamine clinic in Santa Rosa, CA. Be the Change in Mental Health. Accessed July 1, 2024.

[132] Bonnet, U., Specka, M., Soyka, M., Alberti, T., Bender, S., Grigoleit, T., Hermle, L., Hilger, J., Hillemacher, T., Kuhlmann, T., Kuhn, J., Luckhaus, C., Lüdecke, C., Reimer, J., Schneider, U., Schroeder, W., Stuppe, M., Wiesbeck, G. A., Wodarz, N., McAnally, H., … Scherbaum, N. (2020). Ranking the Harm of Psychoactive Drugs Including Prescription Analgesics to Users and Others-A Perspective of German Addiction Medicine Experts. Frontiers in psychiatry, 11, 592199. https://doi.org/10.3389/fpsyt.2020.592199

[133] Vines, L., Sotelo, D., Johnson, A., Dennis, E., Manza, P., Volkow, N. D., & Wang, G. J. (2022). Ketamine use disorder: preclinical, clinical, and neuroimaging evidence to support proposed mechanisms of actions. Intelligent medicine, 2(2), 61–68. https://doi.org/10.1016/j.imed.2022.03.001

[134] Vines L, Sotelo D, Johnson A, et al. Ketamine use disorder: preclinical, clinical, and neuroimaging evidence to support proposed mechanisms of actions. Intell Med. 2022;2(2):61-68. doi:10.1016/j.imed.2022.03.001

[135] Substance Abuse and Mental Health Services Administration. (2023). Key substance use and mental health indicators in the United States: Results from the 2022 National Survey on Drug Use and Health (HHS Publication No. PEP23-07-01-006, NSDUH Series H-58). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2022-nsduh-annual-national-report

show no significant rise in self-reported marijuana use by adolescents. A comprehensive study using Youth Risk Behavior Surveys from 1993 to 2021 found that recreational marijuana laws were not associated with increased current or frequent marijuana use among youth.[136] Similarly, another analysis of YRBS data from 2011 to 2021 indicated no net increases in marijuana, alcohol, or tobacco use among adolescents following the legalization and retail sales of recreational marijuana.[137] These findings indicate that the legalization and increased regulation of marijuana markets in the U.S. has not led to an increase in marijuana use among adolescents.

### 6.6.2 Regional Trends and Specific Populations

In King County, Washington, data from the Healthy Youth Survey covering 2008–2021 showed a decline in marijuana use among students in grades 8, 10, and 12 after the legalization of nonmedical marijuana, suggesting that regulation and controlled availability might reduce underage use.[138] Additionally, a study examining marijuana use in 619 high-risk young adults in Canada actually found decreases in both marijuana use frequency and marijuana-related consequences following legalization.[139] This shows an example in a country with legalized marijuana that in this age group of high-risk young individuals, providing access to marijuana does not necessarily increase use.

Furthermore, a study in California indicated that legal dispensaries effectively prevent underage access to marijuana, as 100% of the licensed dispensaries require age identification.[140] This indicates that the legal, licensed marijuana providers do not provide access to underaged minors and that minors are likely accessing similar substances through illicit, unregulated sources (e.g., intoxicating hemp, synthetic marijuana, illicit market marijuana).

### 6.6.3 Comparative Analysis with Other Substances

Analysis of data from the Illinois Youth Survey revealed that marijuana use was significantly lower among 10th and 12th graders living in ZIP codes with medical dispensaries compared to those without.[141] A study analyzing trends in alcohol, cigarette, e-cigarette, and non-prescribed pain reliever use among young adults in Washington State found that the implementation of legalized nonmedical marijuana (i.e., recreational or adult use marijuana) coincided with decreases in the use of these substances.[142] These results indicate that marijuana use among youth is not only lower in areas with regulated access through medical dispensaries but also that the legalization of nonmedical marijuana is associated with a decline in the use of other substances such as alcohol, cigarettes, e-cigarettes, and non-prescribed pain relievers.

### 6.6.4 Systematic Reviews and Broader Impacts

A systematic review of 32 studies evaluating the impact of recreational marijuana legalization on public health metrics found no increase in adolescent marijuana use, supporting the conclusion that legalization does not necessarily lead to higher use rates among youth.[143] Additionally, longitudinal studies from Oregon, New York, and Washington showed no significant changes in the probability or frequency of adolescent marijuana use post-

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[136] Anderson, D. M., Fe, H. T., Liang, Y., & Sabia, J. J. (2024). Recreational Marijuana Laws and Teen Marijuana Use, 1993-2021. JAMA psychiatry, e240698. Advance online publication. https://doi.org/10.1001/jamapsychiatry.2024.0698

[137] Coley, R. L., Carey, N., Kruzik, C., Hawkins, S. S., & Baum, C. F. (2024). Recreational Cannabis Legalization, Retail Sales, and Adolescent Substance Use Through 2021. JAMA pediatrics, 178(6), 622–625. https://doi.org/10.1001/jamapediatrics.2024.0555

[138] Esie, P. (2024). Cannabis Use Among Students in Grades 8, 10, and 12, by Sex — King County, Washington, 2008–2021. MMWR. Morbidity and Mortality Weekly Report, 73. https://doi.org/10.15585/mmwr.mm7302a1

[139] Doggett, A., Belisario, K., McDonald, A. J., Ferro, M. A., Murphy, J. G., & MacKillop, J. (2023). Cannabis Use Frequency and Cannabis-Related Consequences in High-Risk Young Adults Across Cannabis Legalization. JAMA network open, 6(9), e2336035. https://doi.org/10.1001/jamanetworkopen.2023.36035

[140] Fell, J. C., Toomey, T., Eichelberger, A. H., Kubelka, J., Schriemer, D., & Erickson, D. (2022). What is the likelihood that underage youth can obtain marijuana from licensed recreational marijuana outlets in California, a state where recreational marijuana is legal?. Journal of safety research, 82, 102–111. https://doi.org/10.1016/j.jsr.2022.05.002

[141] Smith, D. C., Begum, S., Carrington, A. A., Campbell, C. C., Taylor, S. E., Reinhart, C. A., & Swartz, J. A. (2022). Adolescent Cannabis Use Among Youth in ZIP Codes with Medical Dispensaries. Cannabis (Albuquerque, N.M.), 5(3), 36–46. https://doi.org/10.26828/cannabis/2022.03.004

[142] Fleming, C. B., Ramirez, J. J., Rhew, I. C., Hultgren, B. A., Hanson, K. G., Larimer, M. E., Dilley, J. A., Kilmer, J. R., & Guttmannova, K. (2022). Trends in Alcohol, Cigarette, E-Cigarette, and Nonprescribed Pain Reliever Use Among Young Adults in Washington State After Legalization of Nonmedical Cannabis. The Journal of adolescent health : official publication of the Society for Adolescent Medicine, 71(1), 47–54. https://doi.org/10.1016/j.jadohealth.2022.03.006

[143] Athanassiou, M., Dumais, A., Zouaoui, I., & Potvin, S. (2023). The clouded debate: A systematic review of comparative longitudinal studies examining the impact of recreational cannabis legalization on key public health outcomes. Frontiers in psychiatry, 13, 1060656. https://doi.org/10.3389/fpsyt.2022.1060656

legalization.[144] Another study drawing on data from 24 states published in 2024 showed declines in marijuana use amongst youth from 2019 to 2021, as shown in Figure 6.6.4, and marijuana use prevalence did not differ significantly by state-of-residence marijuana legal status among the 24 participating states in 2021.[145]

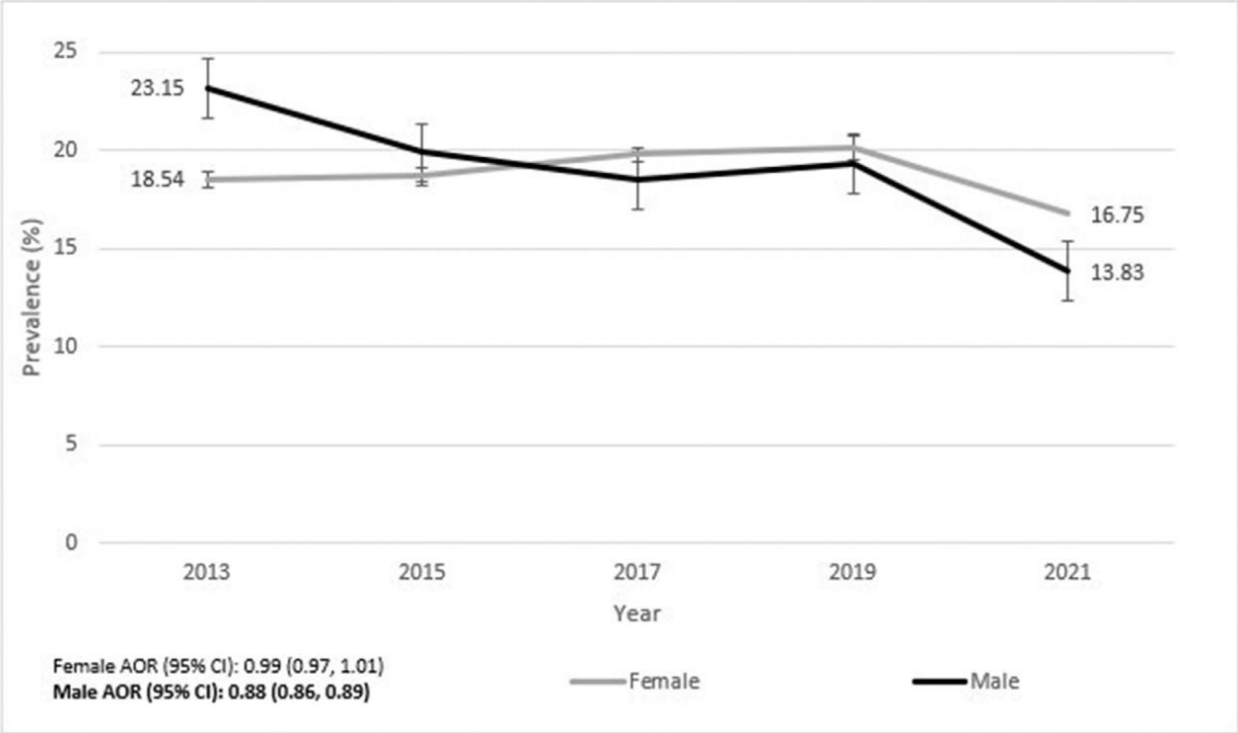


**Figure 6.6.4.** Past 30-day cannabis use prevalence among adolescents by sex, YRBSS, 2013−2021. YRBSS, Youth Risk Behavior Surveillance System

The evidence presented indicates that the enactment of marijuana laws, both medical and recreational, has not led to significant increases in marijuana use among adolescents. These findings suggest that regulated marijuana markets, coupled with effective public health strategies, can mitigate potential risks associated with youth use, supporting a reevaluation of marijuana's current scheduling.

### 6.7 Risk of Serious Adverse Events and Death

An adverse event is defined as any untoward medical occurrence which may possibly be correlated to with the administration of a particular drug. An adverse reaction is a type of adverse event which can be causally linked to a drug.

Adverse events and adverse reactions can range in severity, with a serious adverse event being one that that can result in any of the following:

- Death
- A life-threatening adverse event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect

[144] Bailey, J. A., Tiberio, S. S., Kerr, D. C. R., Epstein, M., Henry, K. L., & Capaldi, D. M. (2023). Effects of Cannabis Legalization on Adolescent Cannabis Use Across 3 Studies. American journal of preventive medicine, 64(3), 361–367. https://doi.org/10.1016/j.amepre.2022.09.019

[145] Goodwin, R. D., & Silverman, K. D. (2024). Evolving Disparities in Cannabis Use Among Youth by Demographics and Tobacco and Alcohol Use in the U.S.: 2013-2021. *American journal of preventive medicine*, *66*(6), 1035–1042. https://doi.org/10.1016/j.amepre.2024.01.012

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.[146] As indicated in the HHS Basis for Recommendation, marijuana has one of the lowest incidences of overdose deaths among comparator drugs. While there are some adverse reactions that can pose risks to marijuana consumers, the severity is less than some other Schedule I, II, and III substances.

### 6.7.1 Cannabis Hyperemesis Syndrome (CHS)

Cannabis Hyperemesis Syndrome (CHS), first described in 2004, is a form of Cyclic Vomiting Syndrome (CVS) often accompanied by abdominal pain, and occurs during or within 48 hours after frequent and heavy marijuana use. CHS accounts for about 10% of patients with CVS. CHS is distinguished from cyclic vomiting syndrome by its temporal association with marijuana use, relief with hot baths or showers, and resolution with extended abstinence from marijuana. A review of the literature has proposed that CHS is a subset of CVS in which chronic marijuana use triggers symptoms in patients who are genetically predisposed to develop CVS. [147] This symptom develops in approximately 1 out of every 200 regular, chronic marijuana consumers.[148]

Although CHS should be regarded as a serious adverse event, it is a condition that occurs only in those marijuana users who engage in heavy and/or chronic usage and should not be regarded as a widespread risk to public health. Cessation of marijuana use resolves CHS episodes in patients who suffer from the condition, shortening its duration and effect on life quality. Due to its federal status many patients do not disclose their marijuana consumption habits to their practitioners; rescheduling could change this and subsequently lead to the reduction of instances of CHS diagnosis.

### 6.7.2 Cardiovascular Events

Cardiovascular disease is the leading cause of mortality in the U.S., being responsible for 21.4% of deaths in 2022.[149] Many marijuana users opt for an inhalable dosing form and as such the possibility exists that this may have an effect on their cardiovascular system. However, available data suggests an insignificant correlation between cardiovascular events and marijuana use, including myocardial infarction, stroke, and composite cardiovascular diseases.[97]

In a meta-analysis of 20 studies with more than 183,000,000 patients found that the risk of adverse cardiovascular events, such as acute myocardial infarction and stroke, is not significantly elevated with marijuana exposure.[150] A graphical abstract of this analysis is shown in Figure 6.7.2.

[146] IND Application Reporting: Safety Reports -2021 https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports
[147] Chu F, Cascella M. Cannabinoid Hyperemesis Syndrome. [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549915/
[148] Zannese K. Clues emerging to mysterious cannabinoid hyperemesis syndrome. CMAJ. November 28, 2022. Accessed July 4, 2024. https://www.cmaj.ca/content/194/46/E1576.
[149] Centers for Disease Control and Prevention (2022). National Center for Health Statistics Brief 492. Mortality in the United States, 2022. Retrieved from https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm
[150] Theerasuwipakorn N, Prechawat S, Chokesuwattanaskul R, Siranart N, Marsukjai A, Thumtecho S, Rungpradubvong V. Cannabis and adverse cardiovascular events: A systematic review and meta-analysis of observational studies. Toxicol Rep. 2023 Apr 25;10:537-543. doi: 10.1016/j.toxrep.2023.04.011. PMID: 37168078; PMCID: PMC10165401.

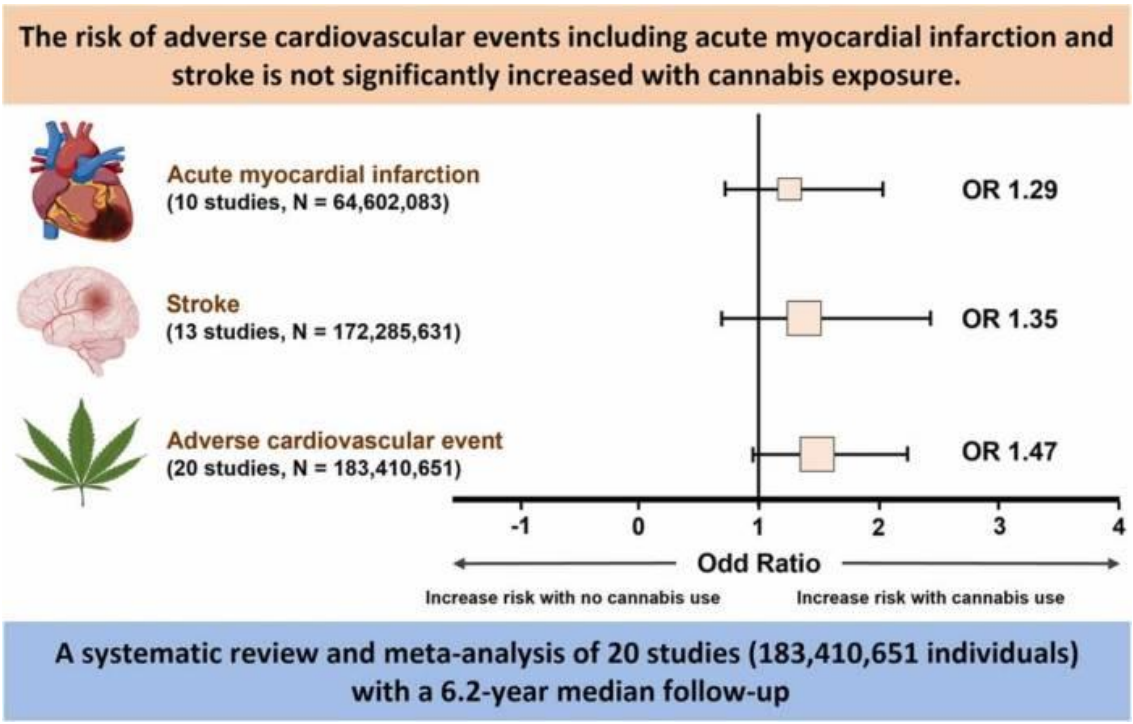


**Figure 6.7.2.** Graphical Abstract of Theerasuwipakorn, et. al. (2023)

### 6.7.3 FDA Adverse Event Reporting System (FAERS) Data

The FAERS database collects reports submitted to the FDA by manufacturers, healthcare providers (HCPs) and consumers. Submission of a safety report does not assign causality to a product and is limited by the self-reporting nature and unverified information in the database. Additionally, there may be duplicates so incidence and prevalence of an event cannot be determined. Other limitations are that all products consumed are linked to the event. For example, if a patient takes fentanyl and eye drops, both agents are linked to the event.

Since 2022, 3,171 cases including the following search terms have been reported: *Cannabis sativa* flowering top, *Cannabis sativa* seed oils/herbal, *Cannabis sativa* subspecies indica top, *Cannabis sativa* subspecies indica top/device and *Cannabis sativa* whole.[151] Of these, 203 cases resulted in death. Even though cannabis was listed as an additional active ingredient in these 203 fatal cases, the primary Suspect Product Name(s) was not listed as cannabis for a single case. Rather, deaths were primarily attributed to adverse reactions to unscheduled substances such as fluoxetine (a Selective Serotonin Reuptake Inhibitor antidepressant), ceftriaxone (an antibiotic), Schedule I substances such as heroin, and Schedule II substances such as fentanyl, methadone, dextroamphetamine.[152] This suggests cannabis has not been the cause of death in the recent adverse event cases reported to the FDA, while other uncontrolled, Schedule I, and Schedule II substances have, indicating a lower potential for serious harm.

### 6.7.4 Mortality Rates Amongst Marijuana Users

It is generally recognized that the risk of death due to direct marijuana toxicity is negligible. According to the DEA, no deaths from overdose of marijuana have ever been reported. However, there are clear harms associated with marijuana use that can prove fatal, including accidental trauma and risk of cardiac complications.[153] In a study of 3455 deaths where marijuana use was detected, use of the substance alone was rare (4% of cases, n=136/3455).

[151] FAERS Public Dashboard Search. https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis
[152] FAERS Public Dashboard Search. https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis
[153] Rock KL, Englund A, Morley S, Rice K, Copeland CS. Can cannabis kill? Characteristics of deaths following cannabis use in England (1998–2020). Journal of Psychopharmacology. 2022;36(12):1362-1370. doi:10.1177/02698811221115760

Traumatic injury was the prevalent underlying cause (62%, n =84/136), with marijuana toxicity cited in a single case. Polydrug use was evident in most cases (96%, n =3319/3455), with acute drug toxicity the prevalent underlying cause (74%, n=2458/3319). Cardiac complications were the most cited physiological underlying cause of death (4%, n=144/3455).

The National Academies of Science Committee on the Health Effects of Marijuana in a review of the primary literature concluded that there is no or insufficient evidence to support or refute a statistical association between marijuana use and all-cause mortality.[154]

## 7.0 MARIJUANA'S PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY

For the seventh factor of the Eight-Factor Analysis, DEA stated that additional data on psychic or physiological dependence liability may be appropriate for consideration. Below we evaluate recent research related to this topic.

Marijuana has a moderate potential for abuse and dependence compared to other substances listed under the Schedule III category, with about 9% of users developing dependence. A study based in Vancouver, Canada that analyzed the association between marijuana use and the management of stimulant cravings in marginalized individuals who use unregulated drugs revealed that individuals decreased their stimulant use during periods of marijuana use. This is significantly lower than benzodiazepines, which may have a higher risk for dependence and withdrawal symptoms.[155] In this study, marijuana was utilized in harm reduction by providing a safer alternative to more harmful substances. It revealed the alleviation of withdrawal symptoms and cravings, making it easier for individuals to taper off more dangerous substances. The American Addiction Center surveyed over 1,000 individuals and determined that alcohol was more addictive than marijuana. Additionally, individuals who did not consume marijuana believed alcohol was 25% more dangerous than marijuana.[156]

The marijuana plant has been used around the world in a variety of ways for centuries. In the U.S. it was used as a medicine until the early twentieth century due to the varying compound formulations that naturally occur in different varieties of the cannabis plant.[157] Despite there being an overall severe lack of research, due to marijuana's current scheduling under the CSA, there is still a substantial amount of research available to suggest that marijuana does in fact have medicinal value. The data presented here shows that when compared to other popular substances and drugs of abuse, like alcohol and tobacco, the safety profile of marijuana is superior. The dependence liability of marijuana is far lower than that of alcohol, tobacco, and other illicit substances and can even be used as an early treatment for various substance use disorders.

In a 2013 international survey, the harms and benefits of various psychoactive drugs were assessed, and marijuana was found to be less harmful than most popular substances of abuse. The visual representation of the data is shown in Figure 7.1.1.[158]

[154] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US); 2017 Jan 12. Committee On The Health Effects Of Marijuana: An Evidence Review And Research Agenda. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425770/

[155] Reddon, Hudson. Socias-Eugenia, Maria. DeBeck, Kora. Hayashi, Kanna. Walsh, Zach. Milloy, M-J. (July 2023). Cannabis Used to Manage Stimulant Cravings Among People Who Use Unregulated Drugs. Addictive behaviors. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37748225/

[156] Regan, James. Editorial Staff. (March 2024). Americans' Perceptions of Alcohol vs. Marijuana. American Addiction Centers. Retrieved from: https://americanaddictioncenters.org/blog/perceptions-of-alcohol-vs-marijuana

[157] Schlag, A. K., Hindocha, C., Zafar, R., Nutt, D. J., & Curran, H. V. (2021). Cannabis based medicines and cannabis dependence: A critical review of issues and evidence. *Journal of Psychopharmacology*, *35*(7), 026988112098639. https://doi.org/10.1177/0269881120986393

[158] Morgan, C. J., Noronha, L. A., Muetzelfeldt, M., Feilding, A., & Curran, H. V. (2013). Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. *Journal of Psychopharmacology*, *27*(6), 497–506. https://doi.org/10.1177/0269881113477744

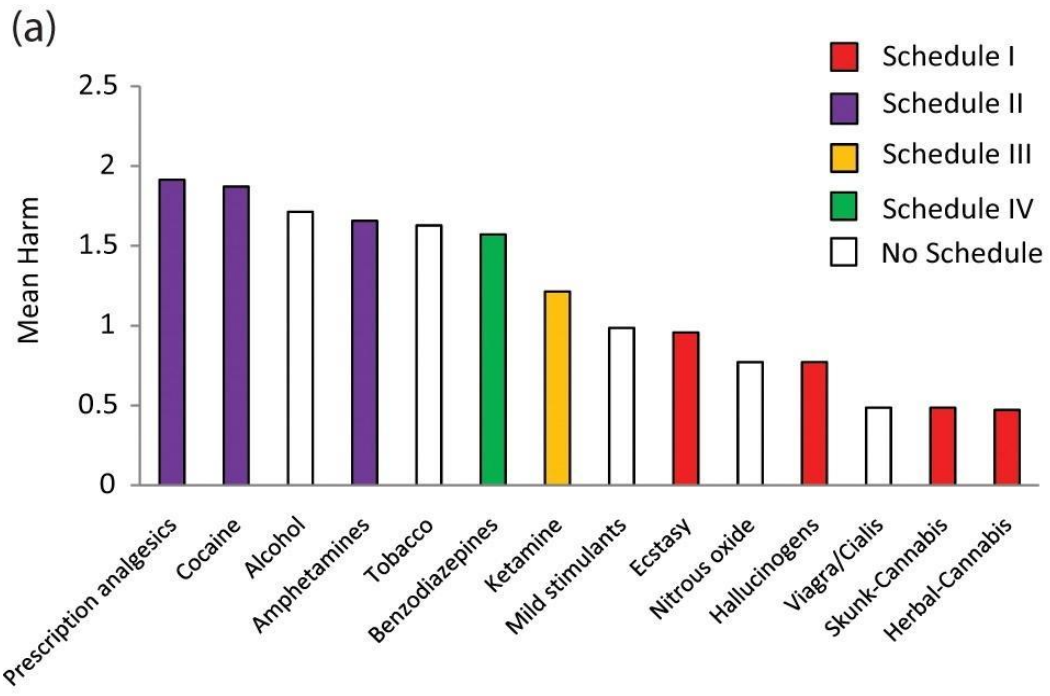


**Figure 7.1.1.** Mean Harm Ratings of Drugs Against U.S. Schedules Under The Controlled Substances Act

The same study found that participants rated marijuana as being the most beneficial drug overall, with the lowest harm rating, as seen in Figure 7.1.2. Prescription analgesics, opioids, cocaine, and alcohol have higher harm ratings due to their higher risk of reliance and craving.[159]

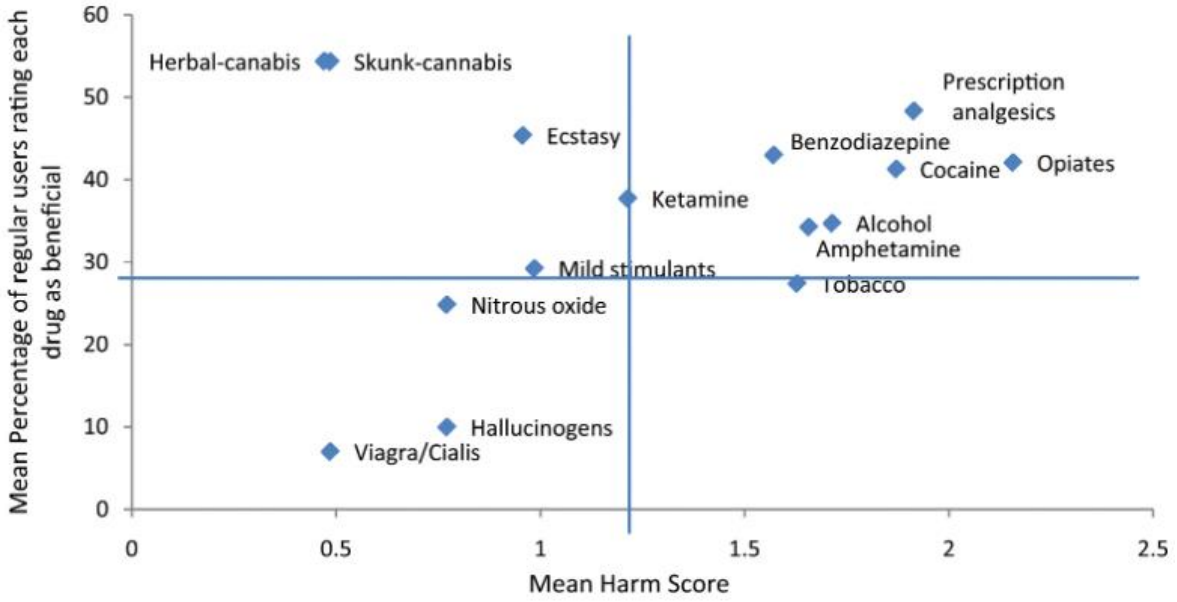


**Figure 7.1.2.** Comparison Between Mean Percentage of Participants Rating Each Drug as a Benefit and Mean Harm

[159] Morgan, C. J., Noronha, L. A., Muetzelfeldt, M., Feilding, A., & Curran, H. V. (2013). Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. *Journal of Psychopharmacology*, *27*(6), 497–506. https://doi.org/10.1177/0269881113477744

### 7.1 Cannabis Use Disorder (CUD)

One of the risks of chronic marijuana consumption is diagnostically called Cannabis Use Disorder (CUD). The Diagnostic and Statistical Manual of Mental Disorders (DSM–5) defines CUD as the presence of clinically significant impairment or distress in 12 months, manifested by at least two of the following: marijuana (or related substance such as synthetic marijuana) is taken in larger amounts or used over a longer period than intended, persistent desire to cut down with unsuccessful attempts, excessive time spent acquiring marijuana, using marijuana, or recovering from its effects, cravings for marijuana use, recurrent use resulting in neglect of social obligations, continued use despite social or interpersonal problems, important social, occupational, or recreational activities foregone to be able to use marijuana, continued use despite physical harm, continued use despite physical or psychological problems associated with marijuana use, tolerance, withdrawal symptoms when not using marijuana. The frequency of marijuana consumption is a major risk factor for the development of CUD. 9% of all marijuana consumers experience addiction.[160] This statistic considers both recreational and medical consumers.

Marijuana's current status as a Schedule I substance has limited access to education and research for medical students, as well as diagnostic categories for marijuana users in hospitals and emergency department settings. These limitations have created a scenario where it is likely that CUD is being over-reported in medical settings. Also, it is important to note that use of synthetic cannabinoids, which are not marijuana as stated earlier, can lead to CUD, because of their pharmacology and binding affinity to the CB receptors.[161] This means that data associated with CUD may be due to substances that are not legally defined as marijuana. In addition to educational limitations of healthcare providers, it is difficult to ascertain how many CUD cases are due to natural marijuana versus synthetic marijuana.

With a rescheduling to Schedule III status, more research could be conducted on the potential for developing CUD within the medical marijuana community while also segmenting the ways in which providers record regular marijuana use within electronic health records and other systems.

In a study analyzing 807,105 adolescent hospitalizations, 6.9% were diagnosed with Cannabis Use Disorder. The adolescents in this study had additional underlying etiology and factors at play, such as depression, anxiety, eating disorders, ADHD, Conduct Disorder, Alcohol Use Disorder, Nicotine Use Disorder, Cocaine Use Disorder and Stimulant Use Disorder.[162] The availability of medical marijuana has not been shown to increase adolescent use, but rather, to increase the number of adolescents who report *no* marijuana use.[163]

The World Health Organization assessed low, moderate, and high risk of problematic marijuana use. Between 2018 and 2021, 'high risk' marijuana use has remained relatively stable, between 7-9% of consumers. These are individuals who have, or could be, diagnosed with CUD. In 2021, approximately 9% of past 12-month marijuana consumers in the U.S. reported seeking medical help for an adverse event from marijuana.[164] It is crucial to understand when reading such statistics, that an increase in people seeking help does *not* indicate a rise in consumption. Instead, it indicates that more individuals feel *comfortable* seeking medical assistance as they no longer fear prosecution due to the end of marijuana prohibition in their state.

### 7.2 Dependence on Marijuana Compared to Other Substances

A person is far less likely to develop dependency to marijuana after a lifetime of exposure (only 8.9%) when compared to tobacco (67.5%), alcohol (22.7%), or cocaine (20.9%).[165] The marijuana plant produces non-

[160] J, Marwaha R. Cannabis Use Disorder. [Updated 2024 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538131/
[161] Synthetic cannabinoids. Office of Addiction Services and Supports. (n.d.-b). https://oasas.ny.gov/synthetic-cannabinoids
[162] Oladunjoye AF, Li E, Aneni K, Onigu-Otite E. Cannabis use disorder, suicide attempts, and self-harm among adolescents: A national inpatient study across the United States. PLoS One. 2023 Oct 17;18(10):e0292922. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0292922
[163] Ritchell M. Does Legalizing Cannabis Increase Adolescent Use? This Expert Found Mixed Results. New York Times. https://www.nytimes.com/2024/05/20/health/marijuana-weed-adolescents-coley.html?smid=url-share. Published May 20, 2024.
[164] 2022 NSDUH Annual National Report. SAMHSA.gov. Accessed July 4, 2024. https://www.samhsa.gov/data/report/2022-nsduh-annual-national-report.
[165] Lucas, P., Baron, E. P., & Jikomes, N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduction Journal*, *16*(1). https://doi.org/10.1186/s12954-019-0278-6

psychoactive compounds that can help alleviate dependance to marijuana, as well as other substances. CBD (cannabidiol) has zero potential for abuse, has been shown to mitigate the psychoactive effects of THC, and has shown potential for anti-addictive properties[166]. In a recently published systematic review (2024), researchers observed that CBD has the potential to assist in managing Alcohol Use Disorders (AUD) symptoms as it helps regulate activity in regions of the brain associated with reward pathways, reward anticipation, regulation of emotions, salience processing, as well as executive functioning.[167]

According to a 2019 survey and a 2024 study, marijuana can be used successfully as a harm reduction tool to help people struggling with dependance on a variety of substances. In the 2019 survey that had participants substitute other drugs/substances with marijuana, 30.9% of the 515 participants who substituted marijuana for alcohol reported total cessation of alcohol use and 36.7% reported a use reduction of 75%. 50.7% of the 406 participants who substituted marijuana for tobacco reported total cessation of tobacco use, and 59.3% of the 610 participants who substituted marijuana for opioid medications reported total cessation of opioid use.[168] In the 2024 study, marijuana was used successfully in early treatment for patients recovering from opioid and stimulant addiction. Specifically, three patients managed to resolve their addiction to methamphetamines and 11patients successfully beat their addiction to opioids with the help of marijuana use in their early treatment. It is important to note that participants found marijuana to be appealing due it's less harmful nature when compared to other substances.[169]

### 7.3 Withdrawal from Marijuana

Marijuana withdrawal is only experienced by those who have been heavily using marijuana and over a prolonged period of time. Marijuana withdrawal symptoms can take a day or two to begin and include irritability, anxiety, trouble sleeping, weight disturbance, restlessness, depression, and somatic symptoms, like headaches and nausea. It is important to note that prevalence of marijuana withdrawal was higher with individuals who had concurrent substance abuse disorders, daily marijuana consumers, and men.[170] Marijuana withdrawal symptoms typically resolve within a week or two and can also be ameliorated with the administration of CBD.[171]

When compared to withdrawal from other substances, marijuana withdrawal symptoms are on the mild end of the spectrum. Alcohol is one of the most popular recreational substances in the world; and its abuse is one of the world's leading risk factors in mortality, morbidity, and disability, as well as the first cause of hospitalization in a number of western nations. Alcohol Withdrawal Syndrome (AWS) wreaks havoc on the brain and body, and, if not managed properly, can cause alcoholic dementia or death. AWS symptoms start to begin within the first few hours of alcohol cessation and can include tremors, sweats, agitations, delusions, as well as seizures, delirium tremens and death.[172]

## 8.0 Other Information

### 8.1 2023 Canadian Cannabis Survey

Five years after the Government of Canada legalized and regulated cannabis, the findings of the 2023 Canadian Cannabis Survey highlight how a regulated market with proper public health measures can lead to better public

[166] Schlag, A. K., Hindocha, C., Zafar, R., Nutt, D. J., & Curran, H. V. (2021). Cannabis based medicines and cannabis dependence: A critical review of issues and evidence. *Journal of Psychopharmacology*, *35*(7), 026988112098639. https://doi.org/10.1177/0269881120986393

[167] Hurzeler, T., Watt, J., Logge, W., Towers, E., Suraev, A., Lintzeris, N., Haber, P., & Morley, K. C. (2024). Neuroimaging studies of cannabidiol and potential neurobiological mechanisms relevant for alcohol use disorders: a systematic review. *Journal of Cannabis Research*, *6*(1). https://doi.org/10.1186/s42238-024-00224-0

[168] Lucas, P., Baron, E. P., & Jikomes, N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduction Journal*, *16*(1). https://doi.org/10.1186/s12954-019-0278-6

[169] Beaugard, C. A., Walley, A. Y., & Amodeo, M. (2024). "Everything is kind of the same except my mind is with me": exploring cannabis substitution in a sample of adults in early recovery from an opioid or stimulant addiction. *Harm Reduction Journal*, *21*(1). https://doi.org/10.1186/s12954-024-01002-0

[170] Bahji, A., Stephenson, C., Tyo, R., Hawken, E. R., & Seitz, D. P. (2020). Prevalence of Cannabis Withdrawal Symptoms Among People With Regular or Dependent Use of Cannabinoids. *JAMA Network Open*, *3*(4), e202370. https://doi.org/10.1001/jamanetworkopen.2020.2370

[171] Shannon, S., & Opila-Lehman, J. (2015). Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. *Integrative Medicine: A Clinician's Journal*, *14*(6), 31–35. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4718203/

[172] Airagnes, G., Ducoutumany, G., Laffy-Beaufils, B., Le Faou, A.L., & Limosin, F. (2019). Alcohol withdrawal syndrome management: Is there anything new? *La Revue de Médecine Interne*, *40*(6), 373–379. https://doi.org/10.1016/j.revmed.2019.02.001

health outcomes, safer consumption practices, and reduced negative impacts associated with cannabis use. Below are key findings that suggest better health outcomes with a federally regulated marijuana market.

- A significant proportion of medical cannabis users (44%) reported a decrease in the use of other medications due to their cannabis use. This suggests that medical cannabis can serve as an alternative to riskier pharmaceuticals. The five most common medications respondents were able to reduce were non-opioid pain relievers such as acetaminophen (56%); anti-inflammatories such as ibuprofen (54%); opioid pain relievers (26%); sedatives (23%); and antidepressants (16%).
- Over half of the respondents (57%) who used cannabis reported using it three days per month or less, indicating that most users are not frequent consumers, which evidences a lower potential for abuse and dependence.
- A significant proportion of users reported that cannabis use had beneficial effects on their quality of life (50%) and mental health (43%), with minimal reported negative effects. This positive perception among users may contribute to safer usage patterns under a regulated system.
- The frequency of combining alcohol or tobacco with cannabis has significantly decreased in Canada since 2018. Moreover, the vast majority of Canadians who used cannabis in the past 12 months reported never combining it with other substances, such as opioids (96%), sedatives (96%), stimulants (93%), or hallucinogens (90%). This indicates that under a regulated cannabis market, Canadians are not increasing their substance use or mixing of substances, supporting safer consumption practices.
- The rate of accidental cannabis consumption in homes was reported to be very low, with less than 1% involving children under 13 years old. This indicates effective prevention measures such as childproof packaging and public education in place.
- The proportion of individuals driving within 2 hours of smoking or vaporizing cannabis decreased from 27% in 2018 to 17% in 2023, indicating better awareness and responsible behavior regarding cannabis use and driving.
- Over half (55%) of the respondents who saw health warnings on cannabis products reported an increased knowledge of cannabis-related harms. This reflects the effectiveness of public health messaging in a regulated market.
- Nearly 73% of respondents obtained their cannabis from legal sources, a significant increase from 2018. This shift from illicit to regulated markets ensures better quality control and reduces the risks associated with unregulated products. In comparison, about half (52%) of American consumers report purchasing from a brick-and-mortar dispensary rather than a friend, delivery service, or dealer.[173]

### 8.2 Analytical Marijuana Testing Labs in the U.S.

With the rapid expansion of state-legal marijuana markets over recent years, there are now a significant number of analytical marijuana testing laboratories in the U.S. These labs play a crucial role in ensuring the safety and accuracy of marijuana products by testing for harmful contaminants and verifying product labels. This infrastructure supports public health and safety by maintaining high standards for product quality and consistency. Currently, 39 states, D.C., Puerto Rico, and Guam have marijuana product testing regulations, with approximately 290 analytical marijuana testing labs in those states and territories.[174]

We included this information about the number of analytical marijuana testing labs currently operating in the U.S. because it highlights the existing state-run infrastructures that are dedicated to ensuring medical marijuana product safety and quality. The presence of these labs demonstrates a commitment to public health and safety. While the DEA itself may not directly oversee these labs, their existence and function provide crucial product data and

[173] Cannabis Consumers in America 2023: Part 1. (2023). New Frontier Data. https://info.newfrontierdata.com/cannabis-consumers-in-america-2023-part-1

[174] This information is gathered from Medicinal Genomics internal lists of labs as clients, marijuana regulatory agency website lists of labs, and lists provided by marijuana regulatory agencies where they were not published on their websites.

compliance support that aligns with federal regulatory standards, thereby facilitating the enforcement of controlled substance regulations and ensuring consumer protection.

## 9.0 CONCLUSION

Reclassifying marijuana to Schedule III is a crucial step that demonstrates our collective commitment to scientific integrity and public health. The compelling evidence presented by HHS, the S3 Collective and the Medical Cannabis Student Association (MCSA), and others highlights the medical utility and lower abuse potential of marijuana.

In addition to formally recognizing the therapeutic potential and reduced harms of marijuana, rescheduling would reduce the unnecessary burden on the criminal justice system and allow for more science-based approaches to marijuana use and abuse prevention. Also, facilitating more rigorous scientific research into the potential medical benefits and risks of marijuana, should be a goal in rescheduling. Current scheduling severely restricts research opportunities, hindering our understanding of its therapeutic applications and safety profiles.[175]

Rescheduling could signal to legislative and regulatory bodies the importance of allocating more resources to supporting current state-based regulatory oversight, ensuring product safety and quality through standards and testing, and to educate healthcare practitioners. This could allow for better regulation, quality control, and safer consumption practices. However, as noted by the Cannabis Regulators Association (CANNRA) in their public comment, guidance to support state and territorial regulators is essential to keep consumers and patients safe.[176]

Lastly, this change will also have positive economic impacts by fostering a regulated market that is taxed fairly, supports jobs, and generates tax revenue.

We urge you to consider the objective evidence and to act in the best interest of the public and the scientific community.

[175] Piomelli, D., Solomon, R., Abrams, D., Balla, A., Grant, I., Marcotte, T., & Yoder, J. (2019). Regulatory Barriers to research on cannabis and cannabinoids: A proposed path forward. Cannabis and Cannabinoid Research, 4(1), 21–32. https://doi.org/10.1089/can.2019.0010
[176] Comment ID DEA-2024-0059-32395 on FR Doc # 2024-11137. https://www.regulations.gov/comment/DEA-2024-0059-32395