

CANNABIS AND LEGALITY – AN INVESTIGATION INTO THE  
MEDICAL APPLICATIONS OF CANNABIS, FEDERAL  
SCHEDULING, AND SCHEDULE I RESEARCH

by

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Cannabis has been used in medicine for thousands of years, and today, many self-prescribe cannabis for a variety of ailments. However, in many states, cannabis is legal at the state level but illegal at the federal level. This thesis attempts to answer why this difference exists, how it may be harmful, and if there is a scientific basis to the use of cannabis in traditional medicine. The social, political, and medical histories of cannabis in the United States are explored, and the findings of novel applications of cannabis in medicine are summarized. Through a literature review of randomized controlled trials, systematic reviews, expert opinions, and government documents, it was found that although substantial literature suggests a range of novel therapeutic applications for cannabis, the existing research is not rigorous enough to draw any accurate conclusions. Finally, this research has found that the restrictions on Schedule I drugs, particularly in conducting research, immensely hinders the ability to conduct future therapeutic cannabis research.

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## Background

Since the 1970s, the scientific and medical communities in the United States have been searching for empirical evidence to evaluate the use of medicinal cannabis in traditional and folk medicine. A stark contrast in legality is observed across the states, even though it remains illegal at the federal level. Cannabis is considered a Schedule I drug by the federal government, meaning that it has high safety risks, a high potential for dependence and abuse, and no currently accepted medical use (CAMU). Despite this, cannabis is both a common inebriant and traditional medicine in the U.S. today. The limited research on cannabis' function within the human body over the last few decades suggests that there might be a wide range of therapeutic applications of cannabis. Additional research might help both governmental and medical communities come to a proper and accurate consensus, but its classification as a Schedule I drug likely restricts ease of research.

### Cannabis Physiology

*Cannabis* as a genus has very high genetic diversity due to a long history of human intervention, creating confusion in taxonomy and classification. While many researchers have accepted the two-species theory (*C. sativa* and *C. indica*), others believe there are three or more distinct species, or even only one. The two-species theory places origins of *C. sativa* in current day Kazakhstan, and *C. indica* in the Western Himalayas (Hillig & Mahlberg, 2004). Importantly, the colloquial terms “indica” and “sativa” do not generally refer to the species *C. sativa* and *C. indica*, but rather describe recreational-use plants and the ratios of their psychoactive compounds (Balant et al., 2021).

Phytocannabinoids (cannabinoids) are naturally occurring chemicals that are produced by the cannabis plant by the trichomes, which are hair-like projections on the surfaces of leaves.

There are over 100 unique cannabinoids, but cannabidiol (CBD),  $\Delta^9$ -tetrahydrocannabinol (commonly referred to as THC), cannabidivarin (CBDV), and  $\Delta^9$ -cannabivarin (THCV) are the most produced. THC is psychoactive, meaning it affects behavior, mood, and cognition, and is responsible for the classic marijuana high: euphoria, loss of time sense, discoordination, difficult cognition, introspection, dreaminess, anxiety, and distorted senses (Table 1). While CBD is less psychoactive, it is believed to interact with behavior and perception in unclear ways. The effect of interactions between different cannabinoids in the body is not yet understood.

<b>Mood effects</b>	<b>Physical effects</b>	<b>Cognition effects</b>
Euphoria, pleasantness	Increased heart rate	Increased reaction time
Anxiety or panic	Decreased blood pressure	Poor working memory
Dreaminess	Dry mouth	Decreased attention span
	Nausea	Time distortion
	Increased appetite	
	Dizziness	

Table 1 – Summary of the effects of cannabis on the body.

Information from Cohen et al., 2019.

### **Pharmacokinetics**

The wide range of medical applications that are often self-treated with cannabis is thought to be a result of the varied biochemical interactions of cannabinoids within the body. The endocannabinoid system of the human body is comprised of endocannabinoids, cannabinoid receptors, and various related enzymes. Endocannabinoids are the endogenous neurotransmitters that cannabinoids like THC and CBD mimic structurally, allowing them to bind to the body's cannabinoid receptors and cause various effects. There are two primary cannabinoid receptors found in many places throughout the body: CB1, which is abundant in the brain, and CB2, which is found mostly in immune cells and tissue including the spleen, tonsils, and thymus (Simard et

al., 2022). Cannabinoid receptors are G-protein coupled receptors (GPCRs), a family of receptors that allows the binding of exterior molecules to cause internal cellular effects. GPCRs are incredibly abundant in the body and are the target of 30% of all drugs (Rehman et al., 2023). It is theorized that the range of effects caused by cannabis is due to the abundance of CB receptors and their various locations throughout the body.

Cannabinoids are able to affect the brain because of their unique structure and their interactions within the nervous system. The blood-brain barrier (BBB) is a lining of endothelial cells where blood vessels meet nervous tissue, particularly in the brain and spinal cord. The BBB allows some molecules from the blood to enter the tissue, particularly smaller and hydrophobic molecules, like nutrients. Large molecules, pathogens and foreign particles, and hydrophilic molecules are restricted from passing through the BBB. THC is hydrophobic, and since the structure mimics the body's own endocannabinoids, it passes through the BBB and affects the brain very easily (Figure 1). It is still mostly unclear how CBD interacts with the nervous system.

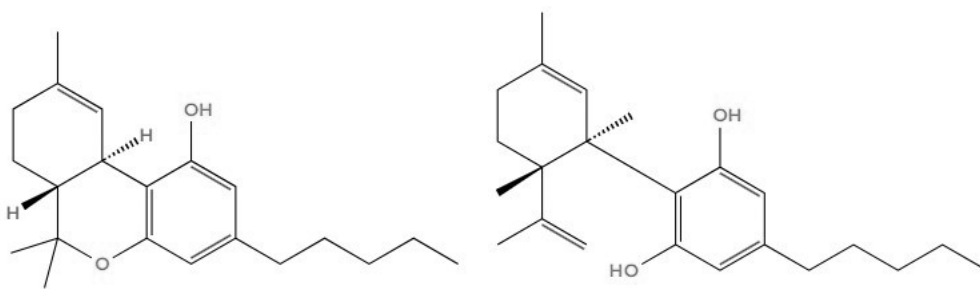


Figure 1 - The chemical structures of THC and CBD.

$\Delta^9$ -tetrahydrocannabinol (THC) on the left; cannabidiol (CBD) on the right. Benzene rings, hydrocarbon tails, and alkanes all contribute to the hydrophobic nature of the molecules.

Inhalation (smoking, vaping) and intravenous methods of delivery have similar pharmacokinetics, and peak THC and CBD levels are reached in the blood within minutes. These methods offer higher maximum blood concentrations than oral delivery. Oral delivery takes

roughly two hours to reach peak blood concentration but remains effective for longer. In oromucosal delivery (sprays, dissolvable tablets), absorption occurs via the mucous membranes of the mouth, and the absorption time is similar to inhalation (Lucas et al., 2018). Transdermal application (ointments, patches) is most common with CBD-based cannabis products. Cannabinoid blood concentration reaches a peak within a few hours, and after some amount of decay, remains at a steady level for up to 72 hours (Mahmoudinoodezh et al., 2022).

Some metabolites of THC are psychoactive themselves and concentrate in fatty deposits in the body for long periods of time. THC metabolites are excreted through urine and feces, but even after 5 days, 10%-20% of an initial THC dose will remain in the body (Huestis, 2005). CBD pharmacokinetics are still poorly understood, but its metabolites remain in the body for a similar amount of time (Mahmoudinoodezh et al., 2022).

## **History in the U.S.**

Cannabis' history, both in medicine and policy, undoubtedly affects resting opinions that are held in the United States today. Historically, cannabis was used for many purposes, including fiber, food, oil, medicine, and inebriant (Hillig & Mahlberg, 2004). Cannabis as a medical treatment has been mentioned in texts from ancient Chinese, Greek, Roman, and Indian culture, with the oldest mention being from a 2700 B.C. Chinese pharmacopeia (Rafei et al., 2023). The United States Pharmacopeia of 1850 introduced "extract of hemp," an alcohol-based extract of the tops of the cannabis plant, to the compendium for the first time (National Medical Convention, 1851). Until the early 1900s, cannabis was an accepted medicine in the United States, commonly prescribed for pain and nausea relief (Bridgeman & Abazia, 2017). Legislation eventually tightened restrictions, however, and a shift in its public perception began.

Federal control of cannabis in the United States started in 1906 with the Pure Food and Drug Act, which ordered that any alcohol, opiates, cocaine, or cannabis sold to the public was clearly marked. Cannabis abuse was not a national concern until the 1920s, when fear grew in response to increased Mexican immigration into the southern United States (Mustro, 1999).

The narcotic content in marihuana decreases the rate of heart beat and causes irregularity of the pulse. Death may result from the effect upon the heart. Prolonged use of marihuana frequently develops a delirious rage which sometimes leads to high crimes, such as assault and murder. Hence marihuana has been called the "killer drug." The habitual use of this narcotic poison always causes a very marked mental deterioration and sometimes produces insanity. Hence marihuana is frequently called "loco weed." (Loco is the Spanish word for crazy.) While the marihuana habit leads to physical wreckage and mental decay, its effects upon character and morality are even more devastating. The victim frequently undergoes such degeneracy that he will lie and steal without scruple; he becomes utterly untrustworthy and often drifts into the underworld where, with his degenerate companions, he commits high crimes and misdemeanors. Marihuana sometimes gives man the lust to kill unreasonably and without motive. Many cases of assault, rape, robbery, and murder are traced to the use of marihuana. (The Narcotic Educational Foundation of America, 1937, pages 6-7)

The Marihuana Tax Act of 1937 essentially criminalized cannabis used for recreational purposes.

It set a heavy tax on marihuana, which was opposed by many physicians who prescribed it.

Much of the American public supported cannabis becoming illegal, believing it to be addictive, deadly, and tempting to children. The Tax Act essentially halted most American cannabis research (Patton, 2020). In a hearing regarding the formation of the bill, Presiding Chairman

Robert L. Doughton quoted a recent editorial from the Washington Times, saying:

The marijuana cigarette is one of the most insidious of all forms of dope, largely because of the failure of the public to understand its fatal qualities. The nation is almost defenseless against it, having no federal laws to cope with it, and virtually no organized campaign for combating it. The result is tragic. School children are prey to peddlers who infest school neighborhoods. High school boys and girls buy the destructive weed without knowledge of its capacity for harm, and conscienceless dealers sell it with impunity. This is a national problem and it must have national attention. The fatal marijuana cigarette must be recognized as a deadly drug, and the American children must be protected against it. (*Taxation of Marihuana*, 1937)

Not everyone agreed, however, and some scientists still worked to change public perception. A report conducted in 1944 studying cannabis use in New York City found that cannabis use was not common among young people and was not often used to the point of “addiction.” They also found that cannabis use did not lead to use of other drugs, contrary to the popular belief of cannabis being a “gateway drug”, and that it was not a contributing factor to crimes (LaGuardia, 1944).

A shift occurred in the 1960s in response to social movements like the Civil Rights Movement, climate activism, and anti-war protesting. Cannabis, previously used by people of color and those of low socioeconomic standing, was now used by young and white people, and even the rich and high-profile. Professionals and veterans began to use cannabis recreationally, and eventually less severe sentences and criminal penalties were issued in response to cannabis crimes (Patton, 2020). Public perception shifted back in the 70s, however, with President Richard Nixon’s infamous War on Drugs. Nixon vehemently opposed cannabis legalization, and while the War on Drugs was framed as a social health concern, interviews and recordings from inner government personnel suggest ulterior motives.

The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. We knew we couldn’t make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did. (John Ehrlichman White in 1994, as recorded by Patton, 2020, p.17)

While some have doubted the integrity of the above statement, the history of cannabis use and control in the United States proves that it is impossible to separate cannabis legality from racial politics. The policies and public fervor created by the War on Drugs lasted throughout the following Ford, Carter, Reagan, Bush, and Clinton administrations. Since the 90s, anti-cannabis

sentiments have decayed, due to many factors including media framing and religious affiliation (Felson et al., 2019).

### **Legality and Scheduling**

Currently, there is no global consensus on the legality of cannabis. It is largely legal for prescription or medical use but illegal for recreational use across Europe (France, U.K., Sweden, Greece), with some countries having recreational use simply decriminalized (Portugal, Beligum, Italy). This same pattern is seen across South America, Southern Africa, and Eastern Asia, with use in the Middle East and most of Africa remaining largely illegal in all capacities. Canada became the second country in the world, after Uruguay, to completely legalize cannabis in 2018, but the legality of cannabis in the United States remains very divided. Importantly, cannabis use is federally illegal, but states have set their own permissions regarding medical and recreational use. About half of the states legally allow recreational use, mostly in the West and Northeast, while most other states allow only medicinal use (Figure 2). Finally, remaining states have classified cannabis as either fully illegal, decriminalized but not legal, or CBD-only legal (Breen & Johnston, 2024).

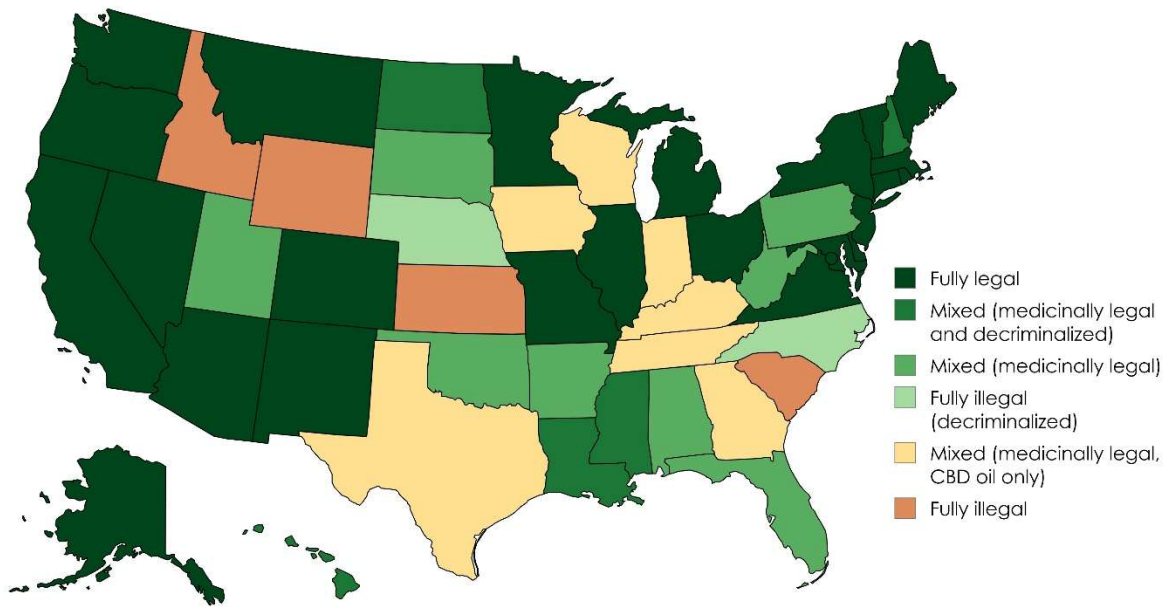


Figure 2 – Map of cannabis legality in the United States.

Information from Breen & Johnston, 2024.

The Controlled Substances Act (CSA) of 1971 is responsible for cannabis’ classification as a federally illegal, Schedule I drug. The CSA was created and is managed by the United States Drug Enforcement Administration (DEA), a branch of the Department of Justice. The CSA does not cover all drugs, for example alcohol and nicotine, but rather ones chosen by congress for federal control. Drugs are placed into categories called “schedules” based on medical use, abuse risk, and dependence potential. A drug’s general “danger” decreases down the schedule list, with Schedule I the most severe and Schedule V is the least. The CSA regulates manufacturing, distribution, and prescription of scheduled drugs. Schedule I drugs are subject to the highest federal controls, and researchers of such substances must comply with the highest level of restrictions (Lopez et al., 2023).

Confusion around cannabis’ legality is common. The cannabis plant and THC, a product of the plant, are separate substances on the DEA’s list of Controlled Substances, with both

currently sitting at Schedule I. CBD, another product of the cannabis plant, is not scheduled at all. Notably, there are four cannabis-derived products that are approved by the United States Food and Drug Administration (FDA) and are commonly prescribed by physicians. Epidiolex, an anti-seizure pharmaceutical, is CBD purified from the plant and has been descheduled, meaning that it has been removed from the CSA entirely. Marinol, a Schedule III a capsule medication, and Syndros, a Schedule II oral solution, use the active ingredient dronabinol which is a synthetic form of THC (Levine, 2023). Cesamet, a Schedule II capsule medication, uses another synthetic form of THC called nabilone. Marinol, Syndros, and Cesamet are all prescribed as antiemetics and appetite-inducers. Hemp, a product of the cannabis plant, is also descheduled.

## **Purpose**

“Federal illegality” has confusing implications to many in the United States where the state and federal legalities often conflict. The consequences of this disparity are necessary to understand for both citizens and researchers alike. Furthermore, it is vital that the ease of research into potentially beneficial medical treatments is increased in order to boost the rate of research, discover novel medical applications, and increase accessibility to those applications. This thesis aims to explore the potential disparity between cannabis’ current federal scheduling and the existing research findings on cannabis’ application for medical purposes, as well as examine how federal scheduling affects the world of drug research and outline future steps for cannabis research.

## **Methods**

Google Scholar and PubMed were searched, using “cannabis” as a consistent key term. The types of sources involved in this research include randomized controlled trials, systematic reviews, government documents, interviews, books, and transcripts.

## **Novel Medical Applications of Cannabis and Cannabis-Based Medicines**

Cannabis has an undeniable role in traditional and folk medicine. In the U.S. today, there is a large community of medicinal cannabis users that self-prescribe for a variety of conditions (Balant et al., 2021). In exploring cannabis' potential future in modern medicine, there is a need for a critical evaluation of these colloquially reported benefits.

Many included studies use the generalized term “cannabis”, likely meaning the plant form that includes both CBD and THC. Some recent papers specify the specific cannabinoid studied, and the distinction is made in the following section when possible. The term “cannabis-based medicine” (CBM) is often used to refer to cannabis medical products, which can include THC, CBD, or both. CBMs are standardized and produced specifically for medical use.

Dronabinol, the active ingredient in Marinol and Syndros, and Cesamet, is a synthetic THC medication that is prescribed to combat nausea and vomiting in patients with HIV/AIDS or undergoing chemotherapy. Epidiolex, made from purified CBD, is used to treat seizures. All of the above are FDA approved, Schedule II or higher, have a commonly acknowledged medical use, and are actively prescribed in medical practice. Therefore, their medical applications will not be investigated in the following section. Topics were chosen based on their current prevalence in the literature.

### **Sleep**

Over 25% of Americans do not meet the American Academy of Sleep Medicine's recommendations for a full 7 hours of sleep a night, and over 15% struggle to fall asleep, stay asleep, or both (Adjaye-Gbewonyo et al., 2022). The rate of sleep problems increases with age, and about 10% of the adult population is estimated to have insomnia. Insomnia is only one type of sleep disorder, which is a broad category of conditions that include sleep apneas, parasomnia,

narcolepsy, and nightmares. While daytime drowsiness is the most obvious result of disordered sleep, there is an association between sleep disorders and poor sleep quality with a range of other diseases. Those suffering from sleep disorders can receive pharmacological treatment, often through the form of benzodiazepines, or non-pharmacological treatment like cognitive behavioral therapy (Karna et al., 2025).

THC and CBD share the property of inducing drowsiness in many individuals. A survey conducted of women with breast cancer at the University of Michigan's cancer center found that almost half of the 141 surveyed patients had self-administered CBD at some point in their treatments, finding that it improved their insomnia, pain, and anxiety. The biggest increase in self-reported improvement was in sleep quality (Fleege et al., 2025). A review of randomized controlled trials (RCTs) on cannabis and sleep quality, sleep disorders, and insomnia found that many studies did indeed see an increase in reported sleep quality and a decrease in sleep disturbances, sleep onset duration, and nightmare frequency on CBMs (Kuhathasan et al., 2019).

Post-traumatic stress disorder (PTSD) is known to greatly affect sleep, particularly through nightmares and restlessness. A 2015 RCT used nabilone capsules, ranging from 0.5 – 3 mg depending on individual response, on 10 male veterans with PTSD and poor sleep due to nightmares. 70% of the treatment group had very decreased nightmare frequency, compared to 20% of the placebo capsule group (Jetly et al., 2015). Due to the very small sample size, the researchers suggest that this application is explored more before drawing any conclusions.

Cannabis is being explored as a novel treatment for obstructive sleep apnea. Sleep apneas are a range of sleep problems in which air flow is reduced during sleep. They can be caused by “central” factors, which is a reduction in brain stem respiratory motor output that tells your body to breathe, or “obstructive” factors, a collapse of upper respiratory tissue and blockage of airflow

called obstructive sleep apnea (Dempsey et al., 2010). Daytime drowsiness is a common symptom, and obstructive sleep apnea causes increased likelihood of many respiratory and cardiovascular conditions, including hypertension, cardiovascular disease, and arrhythmias. While obstructive sleep apnea is usually treated with positive airway pressure (PAP) devices, many users fail to adhere to the correct usage regimen. A review of RCTs examining pharmacological treatments, rather than PAP, for obstructive sleep apnea found evidence that dronabinol significantly reduces the apnea-hypopnea index, a measure of apnea severity, in both rats and small test populations of humans (Schutz et al., 2021).

### **Chronic Pain**

Chronic pain affects almost 15% of the population globally. Long-term pain is associated with a loss of everyday productivity, decreased ability to attend work, and increased spending on pain relief, which often leads to an overall decrease in economic prosperity (Maharajan et al., 2020). Neuropathic pain is a type of chronic pain due to damaged or malfunctioning nerves sending pain signals to the brain. It can be caused by a range of medical conditions like diabetes, HIV, and shingles, or as a result of medical treatment like radiation therapy, various drug treatments, or surgery (Cleveland Clinic, 2023). Intense pain is often managed with prescription drugs that limit neurotransmitter activity, like antidepressants, anti-convulsants, and topical sodium channel blockers. High levels of pain are also often treated with opioids, which carry a high risk of dependence, addiction, and overdose. Due to this, many providers have become hesitant to prescribe opioids and even other pain management pharmaceuticals, and subsequently, chronic pain patients are finding difficulty in getting medicine to properly manage their pain (Owens, 2019).

A retrospective patient chart review done on New York's elderly population that were prescribed CBMs found that 70% of patients reported an overall benefit on the medication. 50% reported a decrease in overall pain, 15% reported a decrease in neuropathic pain specifically, and 18% reported an increase in sleep quality. 30% of patients discontinued opioid usage after switching to CBMs (Bargnes et al., 2015). A 2025 systematic review examined 22 RCTs that studied CBMs as a treatment for neuropathic pain specifically. The make-up of CBMs included THC or nabilone only, CBD only, a mix, or CBDV. Dosages were flexible based on individual need, and administration routes included oral, sublingual, and topical. 15 RCTs found significant pain relief in a majority of subjects suffering from a wide range of conditions, including spinal cord injury, multiple sclerosis, peripheral neuropathy, and post-surgical neuropathy. However, a high rate of adverse events (AEs) was noted (Almuntashiri et al., 2025). Another review on cannabis and pain found an overall 30% rate of pain relief across 36 studies, and a 50% rate of AEs (Fisher et al., 2021).

## **Glaucoma**

Intraocular pressure (IOP) rises due to aqueous humor failing to properly drain from the eye, resulting in high pressure that causes damage to the optic nerve over time (Turbert & Gudgel, 2023). As damage to the nerve increases, more vision is lost. Glaucoma damage is permanent, but its progression can be halted. Current treatments for glaucoma work by lowering IOP. Eyedrops are common but may come with side effects like stinging and itching, heartbeat changes, breathing problems, and blurred vision. Surgery to allow fluid drainage is an alternative option (Boyd et al., 2024).

Cannabis's ocular interactions are not fully understood. Cannabis first showed scientific promise in the 1970s and 80s, where it was seen to lower IOP after inhalation (Hepler & Frank,

1971). Notably, the lowered IOP only lasted a few hours. Subsequent THC products have replicated those findings through multiple methods of administration, but CBD products have not. A study in 2022 confirmed the peak low IOP was 7% to 16% below baseline in a small sample of 11 healthy adults after 60 minutes. IOP remained low for only four hours (Mosaed et al., 2022). Interestingly, in some individuals, peak reduced IOP occurred before the subject felt “high,” meaning that some individuals might benefit from IOP reduction through cannabis without psychoactive effects. Researchers recently discovered CB1 receptors in the eye, but the exact mechanisms through which cannabis lowers IOP are still unclear. Some theorize that cannabis’ hypotensive properties lowers the blood pressure of the eye, and by extension the IOP. There is also novel evidence that cannabis interacts with the ciliary muscle, which focuses the eye, and Schlemm’s canal, which drains aqueous fluid from the eye – these structures are thought to play key roles in IOP regulation (Wang & Danesh-Meyer, 2021).

The American Academy of Ophthalmology does not currently recommend cannabis as a treatment for glaucoma. Glaucoma is a condition that requires constant treatment to keep IOP low and prevent further damage, and such high consumption of cannabis would likely have detrimental effects. The details of glaucoma’s physiology are still unclear, and some theorize that glaucoma might be worsened by low blood pressure to the optic nerve; cannabis lowers both IOP and overall blood pressure, so consistent cannabis use might exacerbate the existing problem (Turbert & Gudgel, 2023). However, research is being explored on eye drops which contain THC in various vehicle fluids; this is thought to increase ocular absorption and minimize THC’s effects elsewhere in the body (Järvinen et al., 2002).

## **Anxiety**

19% of American adults have experienced an anxiety disorder in the last year, and 31% have at some point in their lives (National Institute of Mental Health, n.d.). Anxiety disorders include post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), agoraphobia, panic disorder, and social anxiety disorder (SAD). Anxiety disorders are the most prevalent mental illness among adolescents and young adults, and the global rate for youth has risen 54% since 1990 (Bie et al., 2024). Depending on the specific condition, anxiety disorders may be treated with cognitive behavioral therapy, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and beta blockers (Curaleaf Clinic, n.d.). Some countries have already begun prescribing cannabis for anxiety where conventional therapies have failed, including the UK and Australia (Berger et al., 2022).

Cannabis's interactions with anxiety have been increasingly studied in the last 20 years. Evidence seems to suggest that CBD has anxiolytic properties, but that THC can be either anxiogenic or anxiolytic depending on the individual, dosage amount, and mental state (Sharpe et al., 2020). A 2025 review of cannabis and anxiety disorders RCTs found a wide range of results, even amongst the highest quality, lowest bias empirical studies. Among these higher quality studies, 70% found that medicinal cannabis improved GAD, PTSD, and SAD symptoms, while 90% of all studies found improvement (Roberts et al., 2025). No significant improvement was noted for specific anxiety disorders such as obsessive compulsive disorder, anticipatory anxiety, and trichotillomania. The review mentioned high AE rates, including dry mouth, drowsiness, and agitation, but severe AEs were uncommon.

Cannabis, but more specifically THC, is known to sometimes be anxiogenic, causing exacerbated anxiety symptoms in certain individuals (Berger et al., 2022). Preliminary evidence

suggests that cannabis consumption is not linked to the onset of anxiety disorders, excluding PTSD – odds of PTSD development after a traumatic event might be raised with consistent cannabis use (Botsford et al., 2020).

### **Overall Research Quality**

Experts have been unhappy with the current state of cannabis research. An important factor in high-quality or rigorous research is double-blindness; in double-blind clinical trials, both participant and researcher are unaware as to which group the participant has been assigned. This allows conclusions to be drawn from data alone, uninfluenced by either party's expectations. In cannabis research, participant blindness is difficult to maintain due to experienced psychoactive effects. Another important factor is study size; the more participants, the more accurate interpretations of results can be made (Warner & Mahan, 2022). Due to federally imposed restrictions, small sample size (<20) is a nearly universal trait of Schedule I substance RCTs.

Each of the aforementioned reviews identified a variety of problems in their respective study areas. Many sleep studies use self-reported and subjective measures of sleep quality, rather than objective measurements, making unbiased results unlikely. Additionally, in many of these studies, sleep quality is a secondary focus to a primary condition that researchers are observing (Kuhathasan et al., 2019). CBMs seem to be a promising sleep aid for a range of conditions, but more objective and focused research is needed. The cited chronic pain reviews commented on overall poor study design, including small study sizes, limited study duration, high risk of bias, lack of washout periods, and reporting bias (Almuntashiri et al., 2025; Fisher et al., 2021). The review of cannabis used to treat anxiety disorders found that over 77% of included studies had a moderate to high risk of bias and noted high heterogeneity across studies and overall poor

quality. The review also found a very high rate of AEs across all studies, including dry mouth and headache (Roberts et al., 2025).

Due to this, limited conclusions can be drawn from existing cannabis research, but the results seem to point in a promising direction. Although there is a considerable amount of empirical evidence that has found positive results, these quality issues mean that no accurate, concrete conclusions can yet be drawn. Additionally, due to high AE rates and how differently CBMs can affect different individuals, CBMs might not be a good treatment for many. More research is necessary to solidify if CBMs could be effective for sleep, pain, and anxiety.

## **Evaluation of Schedule I Standing**

Cannabis and its cannabinoids are already confirmed to have anti-emetic, anti-seizure, and appetite-inducing properties. Marinol, Syndros, Cesamet, and Epidiolex are FDA approved and are actively prescribed by physicians. Based on current research, it appears that CBMs could also have effective applications for various sleep problems (quality, sleep onset duration, PTSD nightmare frequency), chronic pain relief, and some anxiety disorders in certain individuals. Of course, no drug comes without risks, and the federal scheduling system attempts to balance those risks with the potential benefits.

### **Federal Drug Schedules**

The Controlled Substances Act (CSA) of 1971 is the origin of drug schedules, and cannabis has been a Schedule I substance since the CSA's creation. Drugs on the schedule list are subject to regulations from the federal government. Pharmacies that prescribe scheduled drugs must be registered with the DEA (Gabay, 2013). This affects medical providers and how they prescribe certain drugs, citizens who may be subject to federal law, and researchers and the accessibility of novel controlled-substance research.

The CSA places substances in five schedules based on abuse potential, dependence and withdrawal, and currently accepted medical use (CAMU). Schedule I drugs are defined as substances with a high abuse potential, high likelihood of dependence, and no CAMU – some well-known Schedule I drugs are cannabis, heroin, and LSD. Schedule II has a high abuse potential but some CAMU; Vicodin, cocaine, methamphetamine, fentanyl, Adderall, and oxycodone are in this schedule. The schedules decrease in severity until Schedule V, which involves an identified medical utility and low abuse potential like cough syrups and

antidiarrheals. It is important to note that drug scheduling is based on abuse potential, dependence and withdrawal, and CAMU in comparison to other drugs already on the CSA.

Schedule	Example Substances
I	Heroin, LSD, MDMA, cannabis
II	Cocaine, methamphetamine, fentanyl, oxycodone, Adderall, Vicodin, <b>Marinol</b>
III	Ketamine, anabolic steroids, Tylenol with codeine, <b>Syndros, Cesamet</b>
IV	Xanax, Valium
V	Cough syrups, antidiarrheals

Table 2 – Substances included in the Controlled Substances Act and their respective schedules.

Names in green are cannabis-based pharmaceuticals.

The DEA, Department of Health and Human Services (HHS), drug manufacturers, medical societies, governmental bodies, and even individual citizens can request the addition, removal, or rescheduling of drugs on the schedule list. When evaluating a rescheduling or descheduling petition, the DEA must consider 8 factors laid out in Section 201 of the CSA (Table 3). To mirror the methods used by the DEA, this thesis aims to evaluate the position of cannabis in Schedule I of the CSA using these factors. Factors 2 and 3, regarding pharmacological effect and existing scientific knowledge, have been discussed in the previous section. Factors 1, 5, 6, and 7, which cover health risks, abuse potential, and dependency, will be evaluated in the following section.

1	Actual or relative potential for abuse
2	Scientific evidence of pharmacological effect, if known
3	State of current scientific knowledge
4	History and current pattern of abuse
5	Scope, duration, and significance of abuse
6	Risk, if any, to public health
7	Psychic or physiological dependence liability
8	Whether substance is a precursor of another already controlled substance

Table 3 – 8 factors for consideration in the DEA’s rescheduling process.

Listed in Section 201 of the CSA. Information from United States Office of Diversion Control, Drug and Chemical Evaluation Section, n.d.

**Health Risks (Factor 6)**

Most pharmaceuticals have side effects and health concerns to be weighed with the benefits they provide. The harms of cannabis vary depending on the method of delivery. Inhalation, the most common method of cannabis delivery for recreational purposes, has been the method of delivery in many studies due to the ease of access, quick onset of effects, and limited duration. In 2025, it is relatively common knowledge that smoking, of any substance, has detrimental health effects. Based on the relatively scarce literature that accounts for concurrent tobacco smoking, smoking cannabis seems less harmful than tobacco, but heavy use can induce chronic cough and bronchitis due to exposure to carcinogens and other toxins (Tashkin & Roth, 2019). Vaporization, a recent alternative to smoking, uses heat rather than combustion to avoid the release of toxic compounds. An RCT done in 2018 suggests that vaping cannabis may lead to higher levels of THC and stronger effects (Spindle et al., 2018). However, considering the very limited data on the long-term risks of vaping, many experts warn that vaping could be just as harmful as smoking (Solowij, 2018).

Cannabinoid receptors are found within heart tissue, and cannabis undoubtedly affects the cardiovascular system. With acute use, it raises heart rate and lowers blood pressure, while the opposite is true with long-term use. Based on an analysis of the Behavioral Risk Factor Surveillance Survey from 2016-2020, an association was found between heavy cannabis use and heart attacks, heart disease, and stroke, even when controlling for substance use, lifestyle, health conditions, and demographic information (Jeffers et al., 2024).

Both CB1s and CB2s are found in the reproductive system. Chronic use of THC decreases the production of Gonadotropin-releasing hormone (GnRH), which is responsible for a wide range of reproductive functions. In females, GnRH induces production of progesterone and estrogen, which affect the menstrual cycle. Consequently, frequent cannabis use is associated with menstrual irregularity. In males, GnRH stimulates release of luteinizing hormone, which stimulates testosterone and androgen production, and follicle-stimulating hormone, which increases sperm production. The consequences of these interactions are not yet understood. Novel research suggests a connection between CB1s and reproductive disorders, including polycystic ovarian syndrome and endometriotic lesions (Fonseca & Rebelo, 2022).

In the brain, the amygdala and hippocampus are rich in CB receptors. A magnetic resonance imaging study of 15 heavy-dose, long-term male cannabis users found bilaterally reduce volumes of both brain structures (Yucel et al., 2008). Other neural interactions have been suggested, like increased activation of the prefrontal region during attention tasks and hypoactivity of the anterior cingulate cortex, with both structures being responsible for high order cognition. Notably, many of these papers did not find a difference in functional tests (attention, working memory, etc.) between users and control tests, so the implications of these findings are still unclear (Cohen et al., 2019).

There are other considerations to make regarding regular cannabis use. THC is psychoactive, and not suitable for those who need to drive regularly. Cannabis can enhance the effect of depressants, which include alcohol, barbiturates, and benzodiazepines. There may be other interactions with existing pharmaceuticals that are not clear yet. Additionally, if CBMs do find more prevalence as regular medication, they may not be ideal for everyone due to the high rate of side effects. Finally, there is a concern that cannabis use may be linked to higher rates of cancer, but the research is currently inconclusive (Cohen et al., 2019). Although research on the harms of cannabis is more robust than research on the benefits, these studies are still restricted by federal regulations that will be discussed in the following sections, and there may be a range of health risks that are not yet understood.

### **Dependence and Abuse Potential (Factors 1, 5, and 7)**

Like any psychoactive substance, cannabis carries a risk of dependence and abuse. According to the 2012 National Survey on Drug Use and Health, 2.7 million individuals aged 12 and up met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) definition of cannabis dependence. In comparison, 5.1 million have a dependence on any illicit drug, and 8.6 million have a dependence on alcohol (Volkow et al., 2014).

Cannabis abuse disorder (CUD), as described by the DSM-V, is defined by a list of criteria that an individual must meet some number of (Table 4). As of 2022, 20% of lifetime users had CUD, and 25% of those cases were considered severe. It is important to note that not all regular cannabis users develop CUD, so cannabis use alone is not sufficient to cause abuse. Causing factors of CUD are thought to be genetic and environmental (Hasin, 2018).

Regular users who meet definitions of dependence or abuse might experience withdrawal when stopping. About 15%-40% of heavy users experience withdrawal symptoms when quitting;

the most common symptoms are irritability, insomnia, anxiety, decreased appetite, depressed mood, fever, and headache (Gorelick, 2012).

<b>Impaired Control</b>	1	More use than intended
	2	Inability to quit, despite desire to
	3	Spending significant time obtaining, using, or recovering from
	4	Intense craving
<b>Social</b>	5	Failing to fulfill role obligations (work, school, home)
	6	Social or interpersonal problems
	7	Lost social opportunities
<b>Risky Use</b>	8	Taking substance even when hazardous
	9	Continued use despite awareness of caused physical or mental health condition
<b>Pharmacological</b>	10	Tolerance
	11	Withdrawal

Table 4 – List of criteria for cannabis abuse disorder, according to the Diagnostic and Statistical Manual of Mental Disorders V.

Mild CUD is meeting 2-3 criteria, moderate is 4-5, severe is 6+ (American Psychiatric Association, 2022).

### **Comparison to Other Scheduled Drugs**

Many experts have called for a rescheduling of cannabis to a higher schedule, or removal from the CSA all together. Some argue that cannabis does indeed have valid medical properties, as explored in the previous section, or that cannabis use or abuse doesn't compare properly with those of other drugs in Schedule I or II. The DEA has stated in 2016 that if a substance has no CAMU, it goes into Schedule I regardless of its abuse, dependence, or safety risk factors (United States Office of Diversion Control, n.d.). The CAMU of a drug is usually evaluated based on

prior randomized controlled trials with clear results, which are difficult to achieve with high-scheduled drugs. Although most research points to a decent improvement in many conditions on CBMs, the previous section has demonstrated a lack of thorough, high-quality research on cannabis' medical applications.

As stated previously, scheduled drugs are often compared with one another when evaluating current placements. One measure of a drug's risk factor is its toxicity, called the median lethal dose, or  $LD_{50}$ . The  $LD_{50}$  is the amount of a substance that will kill 50% of subjects. A similar type of measurement is a drug's therapeutic effectiveness, or the median effective dose,  $ED_{50}$ . This measures how much of a substance will cause the desired effect in 50% of subjects. The  $LD_{50}:ED_{50}$  ratio is the therapeutic index (TI) of a drug, and it can be used to compare how dangerous a drug is compared to a regular dose size. Cannabis has an experimental TI of about 1000, indicating that it is relatively safe from overdose risk compared to other substances (Figure 3). There is no significant relationship between cannabis use and death, although intoxication can lead to poor decision making such as driving while under the influence. Cannabis exposure in children, however, has a much higher risk to life (National Academies of Sciences, Engineering, and Medicine, 2017).

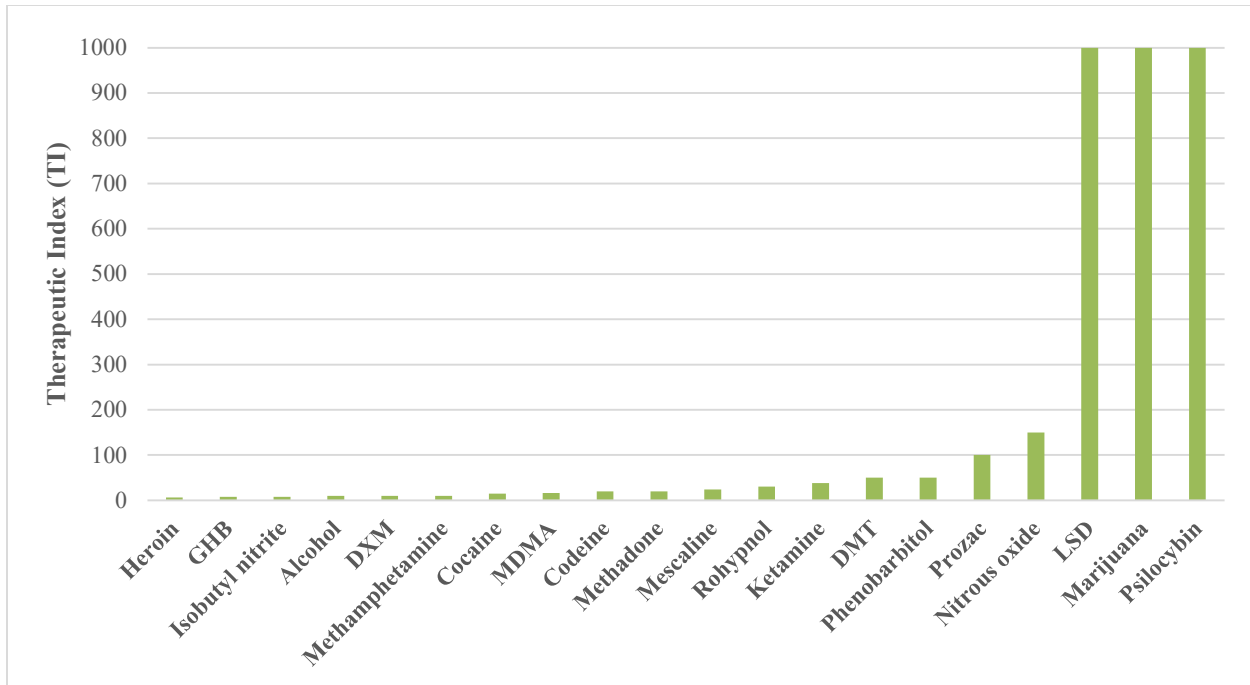


Figure 3 – Experimental TIs of common psychoactive substances, based on their average dose size.

Higher TIs generally correlate with lower risk of death for an average dose (Gable, 2004).

Apart from toxicity, examination of the benefits and risks of other high-scheduled drugs raises more questions about cannabis' placement in Schedule I. For example, cocaine (Schedule II) is used occasionally as a topical anesthetic, but illicitly, over 4 million Americans have used cocaine in the past year and one million are dependent (Peacock et al., 2018). Addiction potential is very high due to cocaine's interactions with the dopaminergic and serotonergic neurotransmitter systems in the body. Side effects of acute abuse are dangerous, including arrhythmia, tremors, stroke, and seizures. Regular cocaine use is very harmful to the cardiovascular system, causing hypertension, myocardial infarctions, aneurysms, cardiomyopathy, and atherosclerosis. It is the most common drug of abuse to result in hospitalization (Bravo et al., 2022). Death by overdose is a possibility due to cocaine's low LD<sub>50</sub>. Many other commonly abused drugs are more dangerous to the body and have higher rates of

addiction than cannabis, including fentanyl, methamphetamine, and opioids. Although evidence for the CAMU of cannabis is currently weak, the health and addiction risks seem less severe, leading to confusion regarding the priorities of the federal scheduling system.

### **Opinions on Rescheduling**

Expert opinions on the topic of cannabis rescheduling vary. Dr. Rachel Levine, Assistant Secretary of Health to the Department of Health and Human Services, wrote a public letter in favor of rescheduling cannabis to Schedule III in response to President Biden's petition to re-evaluate the current placement. She also included the official public support from both the FDA and National Institute on Drug Abuse to place cannabis in Schedule III (Levine, 2023). Experts at the DEA, however, review analyses and petitions regularly, and even as recently as 2016, issue a rejection every time. The most recent rescheduling efforts will be discussed later in this paper. Cannabis' toxicity and abuse potential seems less severe than many other similarly or higher scheduled drugs. Additionally, promising novel research seems to indicate many potential medical applications of cannabis, but more rigorous research is needed to meet the DEA's standards of CAMU.

## **Penalties for Citizens and Restrictions on Research**

The DEA argues that because existing cannabis research is not high-quality enough to meet CAMU standards, its placement in Schedule I is fitting. Alternatively, cannabis and its derivatives seem to show promise in improving a variety of ailments, and when comparing its abuse potential and health risks to other scheduled drugs, it is clear why many are in favor of rescheduling or descheduling. Federal control is exerted on scheduled drugs in a range of ways, and these restrictions can affect average citizens and researchers alike. What does federal illegality mean, both for regular citizens and for researchers investigating the therapeutic properties of cannabis, when it is legal in so many states? Do these restrictions hinder novel therapeutic cannabis research? Do these restrictions hinder the rescheduling process itself?

### **Impact on Citizens**

Cannabis is one of the most common controlled substances to be used recreationally, and as described earlier in this thesis, many pursue cannabis use as a self-prescribed treatment for medical conditions. In comparison to other scheduled drugs, the penalties for recreational use seem unproportional to the risks and benefits of users. The schedule placement of cannabis affects millions of citizens in the United States, and the argument for descheduling must acknowledge that fact. It is often unclear how federal illegality impacts those in states where the state and federal classifications do not match. Acts of Congress have tried to reconcile this; as a result, the Department of Justice (DOJ) is prevented from prosecuting individual states for legalizing cannabis. The DOJ is also largely hands-off on recreational cannabis businesses in states where recreational cannabis is legal, but the DOJ is not prevented from prosecuting individuals and other federally illegal activities, like cannabis consumption and possession (Lampe, 2024).

Individuals with cannabis charges are subject to countless federal penalties. Cannabis consumption is not allowed on federal land, including national parks and military bases, and on any federally funded property. Due to the Drug-Free Workplaces Act of 1988, federal employees can be at risk of losing their jobs. Immigrants have lost green card status as a result of working in the cannabis industry. The Higher Education Act of 1998 states that college students with controlled substance offenses, including cannabis, are not eligible for federal financial aid. This means that students with cannabis charges can lose their Perkins Loans, Pell Grants, and Work-Study programs. Finally, individuals with cannabis convictions can lose access to federally subsidized housing (State of Colorado, 2025).

## **Impact on Research**

### *The Schedule I Research Process*

Every researcher must follow a variety of guidelines depending on the nature of their research, like their protocol, research subjects, and any involved substances. Schedule I researchers, due to the perceived danger of those substances, are subject to the strictest regulations. To properly understand how cannabis research is affected by its schedule placement, it is necessary to examine the process of Schedule I research and discuss the ways that researchers may be dissuaded from pursuing cannabis research due to existing federal restrictions.

First, a variety of registrations and approvals must be acquired by the research team. A Schedule I research registration and site licensure must be obtained from the DEA, which requires intense review of the researcher's protocol by the DEA, FDA, and institutional review board (IRB). During the approval process, the DEA performs rigorous background checks and may perform site inspections. In some states, additional registration from a state board of

physicians or government members may be required. Research cannot start until registration is acquired, but Schedule I registration can take over a year to be processed and approved. In some cases, each investigator involved in a project must receive their own registration, and if multiple sites are involved, a registration may be required for each site. Finally, an Investigational New Drug application must be submitted to the FDA and DEA. Any changes to research protocol must be submitted and approved by the FDA and DEA (Collins, n.d.).

Researchers have reported a lack of transparent registration requirements from various administrative bodies, as well as differing interpretations of the listed requirements by different DEA agents. Ambiguity complicates the already intensive registration process, and as a result, some researchers are hesitant to perform Schedule I research (Collins, n.d.).

These restrictions continue even after research begins. In the case of cannabis research, acquisition of the substance itself can be a challenge; researchers must get their cannabis from only DEA-approved sources. Prior to 2020, the only DEA-certified grower of cannabis for research purposes was the University of Mississippi, which made the acquisition of needed materials difficult (National Institute on Drug Abuse, 2025). Schedule I substances must be stored in DEA-approved safes that are bolted to the wall, and meticulous records of their acquisition, inventory, and disposal must be kept for years after research concludes (Yale University, 2009). Disposal of damaged, out-of-date, or unwanted substances requires hiring a DEA-registered disposal service (University of North Texas, 2022).

Finally, funding is critical to all types of research, but due to the public's historical perception of cannabis, many funders are hesitant to support cannabis studies. Research institutions and universities are funded by both state and federal governments (State of Oregon, n.d.). However, of the 38 states that have legalized cannabis (recreationally or medicinally), less

than half have legislative methods in place to fund cannabis research at the state level (Balla et al., 2025). Federal spending on cannabinoid research has fortunately increased from 147 million to 217 million since 2018, but much more is allocated for alcohol, opioid, and tobacco research (Figure 4). The National Institute on Drug Abuse, a subsidiary of the NIH, is the largest federal funder of cannabis research, but as of 2015, most of their cannabis budget went towards research on health risks and cannabis abuse. Only 16% was spent on studies of the medicinal benefits (National Academies of Sciences, Engineering, and Medicine, 2017).

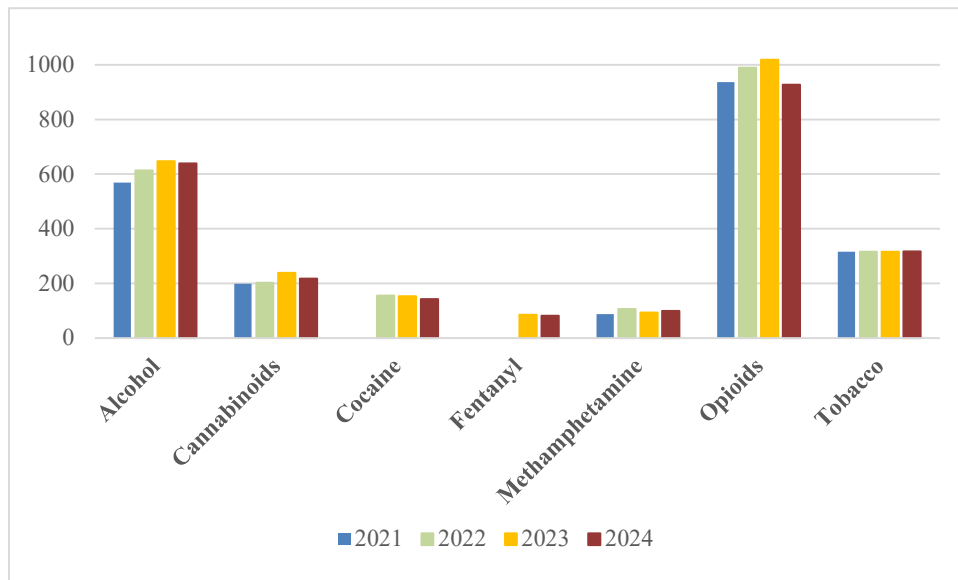


Figure 4 – NIH research funding for common drugs of abuse.

The NIH is the largest federal funder of biomedical research. Y-axis is amount per year spent on funding that area of research, in millions (National Institute of Health, 2025).

Many of these hurdles can be summarized as a type of “privilege” – researchers must have enough time, money, social connections, and motivation to perform Schedule I research. A recent article that interviewed controlled substance researchers described Schedule I research as a “closed loop” that is difficult to enter. Researchers described the importance of having mentors or friends who have successfully performed Schedule I research who helped them navigate the

confusing process. Some also reported being treated with a certain stigma due to their choice of research topic that other scientists were not (Howard et al., 2021).

### *Policy Affects Research, Affects Policy*

The previous section described how the federal penalties on cannabis use seems out of proportion in comparison to the reasons one might pursue it and the health risks it might bring. The difficulties of registering for and completing Schedule I research has been explored. It has been stated that the DEA requires a large collection of rigorous scientific evidence in order to re-evaluate a drug's CAMU. In their denial letter of a 2016 rescheduling petition, the DEA states:

There are not adequate safety studies; there are not adequate and well-controlled efficacy studies; there is not a consensus of medical opinion concerning medical applications of marijuana; and the scientific evidence regarding marijuana's safety and efficacy is not widely available. To date, scientific and medical research has not progressed to the point that marijuana has a currently accepted medical use, even under conditions where its use is severely restricted. (United States Drug Enforcement Administration, 2016, p. 3)

As evaluated previously in this paper, the existing database of cannabis research lacks enough high-quality, thorough studies to draw accurate conclusions about cannabis' therapeutic applications. The FDA agrees, stating:

There has been no FDA review of data from rigorous clinical trials to support that these unapproved products are safe and efficacious for the various therapeutic uses for which they are being used. (United States Food and Drug Administration, 2023, para. 5)

Federal policy, arising from cannabis' Schedule I placement, imposes restrictions on the process of innovative research to such an extent that researchers are dissuaded from conducting it in the first place (Collins, n.d.). There is a decent amount of evidence showing that cannabis has relatively low toxicity and abuse potential compared to a variety of other scheduled drugs, and novel research points to many potential medical uses. However, the DEA argues that the lack of abundant, clear evidence means that cannabis has no CAMU, and therefore should remain in

Schedule I. This scheduling creates unremitting restrictions on innovative research and dissuades large-scale studies on cannabis' medical applications. These restrictions, and their impact on research, prevent cannabis from being rescheduled to a higher schedule where research would be easier. A Schedule I scientist performing research on psychedelics had this to say about the current scheduling system:

It's historical. It's a complete waste of time. I mean the drugs that we're talking about are no more dangerous...in fact they're probably less dangerous, so it's all down to this fairly arbitrary scheduling process that involves whether it's a medical...it has a medical use or not. (Howard et al., 2021, p.7)

The scheduling system exists to control potentially dangerous substances, and it is a necessary system; however, many experts argue that the CSA is imperfect and that the rescheduling protocol should be amended. The scientific community has suggested incorporating medical providers into controlled substance policy making. They propose that the prescribing authority, first-hand experience with patients, and familiarity with scheduled drugs that physicians could provide would add a knowledgeable perspective that is currently unfilled by the current DEA's scheduling process (Ruheel et al., 2021).

## Conclusion

The movement to reschedule cannabis, or even de-schedule it altogether, saw a resurgence in 2024 with no conclusion as of August 2025. In early 2024, the DEA announced the intention to officially reschedule cannabis to Schedule III (Luce, 2024). During the 2-month open comment period, the DEA received around 43,000 comments from the public, a historic high for any DEA policy change. Roughly 69% of comments favored rescheduling, decriminalizing, or legalizing marijuana at the federal level (Drug Policy Alliance, 2024). The first hearing, set for January 2025, was postponed due to improperly submitted evidence on the part of the DEA. The overseeing judge called the DEA's conduct "unprecedented and astonishing...this action is clearly not a mistake borne of misunderstanding or inadvertence, but an action taken in deliberate defiance" (Herrington, 2025). The hearings seem to have been postponed indefinitely, likely due to rapid turnover in DEA administration personnel during the second Trump administration. In August 2025, President Donald Trump commented that his administration was interested in reclassifying cannabis in the following weeks but noted that "it's a very complicated subject" (Hutzler, 2025).

CBMs could prove helpful to many individuals who have not found relief via traditional therapies. The risks associated with cannabis use seem lower than many other scheduled drugs, and some evidence points to therapeutic potential in some individuals. Researchers largely agree, however, that the lack of rigorous research is hugely problematic to the argument of rescheduling. Due to the significant weight the DEA places on CAMU in their rescheduling considerations, cannabis has been repeatedly denied any rescheduling attempts. Existing federal restrictions and policies, created by the Controlled Substances Act, hinder research into both the benefits and harms of CBMs. More cannabis research must be conducted, and it must be more

rigorous than the existing literature. If properly researched, cannabis could be an accessible therapeutic for many, but progress can only be made if the federal government makes a change. A solution to this problem could be a re-evaluation of the DEA's rescheduling process and/or incorporation of medical providers into the conversation. Alternatively, incentives could be offered to those who conduct cannabis research. Finally, restrictions could be lowered for cannabis research specifically.

If cannabis research is encouraged to continue, the scientific community will hopefully find more objective results to either support or oppose the suggestion of cannabis in modern medicine.

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