



Office of the Assistant Secretary for Health
Washington, D.C. 20201

August 29, 2023

The Honorable Anne Milgram
Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morrisette Drive
Springfield, VA 22152

Dear Anne Milgram:

Pursuant to the Controlled Substances Act (CSA), 21 U.S.C. 811(b) and (c), I, the Assistant Secretary for Health, am recommending that marijuana, referring to botanical cannabis (*Cannabis sativa L.*) that is within the definition “marihuana” or “marijuana” in the CSA, be controlled in Schedule III of the CSA.

Upon consideration of the eight factors determinative of control of a substance under 21 U.S.C. 811(c), the Food and Drug Administration (FDA) recommends that marijuana be placed in Schedule III of the CSA. The National Institute on Drug Abuse has reviewed the enclosed documents (which were prepared by FDA’s Controlled Substance Staff and are the basis for FDA’s recommendation) and concurs with FDA’s recommendation. Marijuana meets the findings for control in Schedule III set forth in 21 U.S.C. 812(b)(3).

Based on my review of the evidence and FDA’s recommendation, it is my recommendation as the Assistant Secretary for Health that marijuana should be placed in Schedule III of the CSA.

Should you have any questions regarding this recommendation, please contact FDA’s Center for Drug Evaluation and Research, Office of Executive Programs (cderecsec@cder.fda.gov), at (301) 796-3200.

Sincerely,

A handwritten signature in black ink, appearing to read "Q22 MD", is written over the typed name.

Rachel L. Levine, M.D.
ADM, USPHS
Assistant Secretary for Health

Enclosure

BASIS FOR THE RECOMMENDATION TO RESCHEDULE MARIJUANA INTO SCHEDULE III OF THE CONTROLLED SUBSTANCES ACT

I. Introduction

Background

On October 6, 2022, President Joseph R. Biden released a statement asking the Secretary of the Department of Health and Human Services (HHS) and the Attorney General “to initiate the administrative process to review expeditiously how marijuana is scheduled under federal law.”¹ This Presidential request led HHS to initiate a scientific and medical evaluation for botanical cannabis (*Cannabis sativa* L.) that is within the definition “marihuana” or “marijuana” in the federal Controlled Substances Act (CSA),² currently controlled under Schedule I of the CSA. As with prior evaluations conducted to reconsider the control status of marijuana under the CSA, the Food and Drug Administration (FDA) is conducting this evaluation and providing input and a scheduling recommendation to the Drug Enforcement Administration (DEA) in the form of an Eight Factor Analysis (8FA), pursuant to paragraphs (a) through (c) of section 201 and paragraph (b) of section 202 of the CSA (21 U.S.C. 811 (a-c) and 21 U.S.C. 812(b)).³

Since 2000, HHS (through the FDA and the National Institute on Drug Abuse (NIDA)) has conducted four scientific and medical evaluations of marijuana for drug scheduling purposes, in the form of 8FAs. (The process for developing an 8FA is elaborated below under *Considerations for Scheduling of Marijuana*.) The two most recent HHS 8FAs for marijuana were conducted in 2015 at the request of the DEA to enable them to respond to two petitions requesting removal of marijuana from Schedule I and placement in another schedule of the CSA. After reviewing the 8FAs conducted by HHS, DEA denied both petitions and maintained marijuana in Schedule I of the CSA.⁴

At the conclusion of an 8FA, three findings need to be made to determine the scheduling recommendation for a substance: its relative abuse potential compared to other drugs, whether it has a currently accepted medical use (CAMU) in treatment in the United States (or a currently

¹ Statement from President Biden on Marijuana Reform; <https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/>.

² Under 21 U.S.C. 802(16): “(16)(A) Subject to subparagraph (B), the terms “marihuana” and “marijuana” mean all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.

(B) The terms “marihuana” and “marijuana” do not include—

(i) hemp, as defined in section 1639o of title 7; or

(ii) the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom)

³ We acknowledge that the DEA, acting on behalf of the Attorney General, may ultimately implement any changes in the federal control status of marijuana pursuant to section 201(d)(1) of the CSA (21 U.S.C. 811(d)(1)), due to the control of cannabis and cannabis preparations internationally in Schedule I of the Single Convention on Narcotic Drugs of 1961 (hereafter, the Single Convention), and the requirement for the United States to be compliant with control measures stipulated for drugs controlled under the Single Convention.

⁴ Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 81 FR 53688 (Aug. 12, 2016); Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 81 FR 53767 (Aug. 12, 2016).

accepted medical use with severe restrictions (21 U.S.C. 812(b)(2)(B)), and its relative safety or ability to produce physical dependence compared to other drugs, as provided under 21 U.S.C. 812(b). After the Presidential request in October 2022, HHS (through FDA and NIDA) applied a two-part test to evaluate CAMU (hereinafter, “CAMU test”); this test takes into account the current widespread medical use of marijuana under the supervision of licensed health care practitioners (HCPs) under state-authorized programs.

Under Part 1 of the CAMU test, the Office of the Assistant Secretary for Health (OASH) considered whether there is widespread current experience with medical use of marijuana in the United States by licensed HCPs operating in accordance with implemented state-authorized programs, where such medical use is recognized by entities that regulate the practice of medicine under these state jurisdictions. Part 2 of the CAMU test, performed by the FDA, evaluated whether there exists some credible scientific support for at least one of the medical conditions for which the Part 1 test is satisfied.

An important difference in the present scientific and medical evaluation relative to the HHS 8FAs for marijuana from 2015 is that Congress amended the definition of “marijuana” in the CSA in 2018. This action narrowed the scope of what is considered marijuana under the CSA by removing “hemp” and chemical derivatives of “hemp”, as discussed below. When the CSA was enacted in 1970, the term “marijuana” covered all varieties of *Cannabis sativa* L., including chemovars and preparations with high concentrations of cannabinoid compounds with intoxicating effects, such as delta-9-tetrahydrocannabinol (Δ 9-THC), as well as chemovars and preparations with lower concentrations of Δ 9-THC and other cannabinoid compounds, which could include “industrial hemp.” Specifically, the 1970 definition of “marihuana” under section 102(16) of the CSA (21 U.S.C. 802(16)) stated that:

The term ‘marihuana’ means all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

In December 2018, the Agriculture Improvement Act (also known as the 2018 Farm Bill), was signed into law, which defined “hemp” as “a plant species *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a total Δ 9-THC concentration of not more than 0.3 percent on a dry weight basis” (revising Section 297A of the Agricultural Marketing Act of 1946 (specifically, 7 U.S.C. 1639o). The 2018 Farm Bill explicitly removed “hemp” categorically from the definition of marijuana in the CSA, which removed it from control under any drug schedule of the CSA. Based on the provisions of the 2018 Farm Bill, the current definition of marijuana under 21 U.S.C. 802(16) is as follows:

(16)(A) Subject to subparagraph (B), the terms “marihuana” and “marijuana” mean all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin

extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.

(B) The terms “marihuana” and “marijuana” do not include—

- (i) hemp, as defined in section 1639o of title 7; or
- (ii) the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

In implementing the hemp provisions from the 2018 Farm Bill, DEA clarified that the definition of “Tetrahydrocannabinols” under 21 CFR 1308.11(d)(31) does not include “any material, compound, mixture, or preparation that falls within the definition of hemp set forth in 7 U.S.C. 1639o.”⁵

The 2018 Farm Bill additionally had the effect of decontrolling many products containing predominantly cannabidiol (CBD) derived from hemp and containing no more than 0.3 percent Δ^9 -THC on a dry weight basis. This included the FDA-approved product Epidiolex, which contains plant-derived, highly purified CBD as its active ingredient and was approved by FDA in June 2018, just prior to the enactment of the Farm Bill. Prior to FDA approval of Epidiolex, CBD was a Schedule I substance, based on its derivation from marijuana. To address the Epidiolex approval, DEA placed “approved cannabidiol drugs” into Schedule V of the CSA in September 2018, under 21 CFR 1308.15(f),⁶ and asserted that the placement was necessary to carry out United States obligations under the Single Convention. Notably, though, FDA’s review of the NDA for Epidiolex, as well as the subsequent HHS 8FA, found that, “Based on the totality of the available scientific data, CBD does not have meaningful abuse potential. In support of this finding, the evidence for any abuse potential is also substantially less than that of all substances currently in Schedule V.” Thus, the decontrol of FDA-approved drugs that contain CBD derived from cannabis with no more than 0.1 percent Δ^9 -THC on a dry weight basis is scientifically supported by preclinical and clinical study data. Products containing predominantly plant-derived CBD or marketed with the intent of offering consumers a plant-derived, CBD-containing product, will not be addressed in this scientific and medical evaluation of marijuana. It should be noted some hemp-derived CBD products may contain Δ^9 -THC or other cannabinoids in amounts sufficient to produce drug effects more associated with marijuana, and may or may not be legally within the definition of marijuana. It is acknowledged that their widespread use may contribute to the epidemiological data on marijuana use that is discussed in Factors 4, 5, and 6 of this scientific and medical evaluation.

It is important to note that, to date, FDA has not approved an NDA for a drug product containing botanical marijuana. However, two drug products containing Δ^9 -THC (as dronabinol, which is specifically the (-)-*trans*- Δ^9 -THC stereoisomer), the primary compound in marijuana that is

⁵ 85 FR 51639, 51639-51645, August 21, 2020

⁶ Under 21 CFR 1308.15(f): “Approved cannabidiol drugs. (1) A drug product in finished dosage formulation that has been approved by the United States Food and Drug Administration that contains cannabidiol (2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol) derived from cannabis and no more than 0.1 percent (w/w) residual tetrahydrocannabinols.”

responsible for its abuse potential, have received FDA approval: Marinol and Syndros. Dronabinol is a Schedule I substance under the CSA unless it is contained in an FDA-approved drug product, as described below.

Marinol (dronabinol) capsules, 2.5, 5, and 10 mg, received FDA approval in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional anti-emetic treatments. In 1992, FDA approved an additional indication for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Following the 1985 Marinol approval, DEA conducted a product-specific rescheduling in 1986 for “synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules,” moving it from Schedule I into Schedule II. In 1999, DEA rescheduled “synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules” again, from Schedule II into Schedule III, based on low numbers of reports of abuse of Marinol relative to marijuana.

Syndros (dronabinol) oral solution 5 mg/ml received FDA approval in 2016 for the same indications as those approved for Marinol: nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS. Following FDA approval, DEA conducted a product-specific rescheduling in 2017 for “FDA-approved products containing dronabinol in an oral solution” from Schedule I into Schedule II.

Considerations for Scheduling of Marijuana

In considering the scheduling of marijuana in response to President Biden’s request, the Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA, pursuant to 21 U.S.C. 811(b). The eight factors are the following:

1. Its actual or relative potential for abuse;
2. Scientific evidence of its pharmacological effect, if known;
3. The state of current scientific knowledge regarding the drug or other substance;
4. Its history and current pattern of abuse;
5. The scope, duration, and significance of abuse;
6. What, if any, risk there is to the public health;
7. Its psychic or physiological dependence liability; and
8. Whether the substance is an immediate precursor of a substance already controlled.

Following consideration of the eight factors, three findings need to be made to determine the schedule for a drug or substance under the CSA. The three required findings relate to a substance’s abuse potential, CAMU in the United States, and safety or dependence potential (21 U.S.C. 812(b)).

In this document, the term “marijuana” will be used to refer to *Cannabis sativa L.*, to be responsive to language of the CSA definition of “marihuana” or “marijuana” and its listing as the Schedule I drug class that is subject of this evaluation. The present evaluation of marijuana discusses the scientific and medical information relative to each of the eight factors, presents

findings in the three required areas (abuse potential, CAMU, and safety or dependence liability) and makes a recommendation regarding the scheduling of marijuana.

It is important to note that this evaluation is necessarily limited in scope and depth to those preclinical, clinical, and epidemiological data that are directly related to determining the abuse potential, physical dependence, and CAMU of marijuana in response to the eight factors described in the CSA. As such, this assessment is comprehensive, but is not exhaustive or encyclopedic. Extensive reviews of marijuana and cannabinoids are publicly available in papers published in the scientific and medical literature, as well as from federal entities such as NIDA and the Congressional Research Service, from professional medical associations, and from the National Academies of Science, Engineering and Medicine (NASEM). The current review is largely focused on modern scientific considerations on whether marijuana has a CAMU and on new epidemiological data related to abuse of marijuana in the years since the 2015 HHS 8FAs on marijuana.

In the epidemiological analyses below regarding prevalence of marijuana abuse and associated harms, evaluations included comparators such as heroin (Schedule I), fentanyl (Schedule II), oxycodone (Schedule II), hydrocodone (Schedule II), cocaine (Schedule II), ketamine (Schedule III), benzodiazepines (Schedule IV), zolpidem (Schedule IV), tramadol (Schedule IV), and alcohol (FDA Office of Surveillance and Epidemiology, 2023). Each individual epidemiological database evaluated a specific group of drugs and not every comparator was evaluated under each database.

It should be noted that although alcohol is well known to be abused, it was explicitly exempted from control under the CSA when it was enacted. Typically, substances that are not controlled under the CSA are not utilized as comparator drugs for scheduling placement considerations because they may not have been formally evaluated for abuse potential in standard preclinical and clinical abuse-related studies. However, alcohol is included in the analyses because of its extensive availability and use in the United States, which is also observed for nonmedical use of marijuana (also known as recreational use of marijuana).

After assessing all available preclinical, clinical, and epidemiological data, FDA recommends that marijuana be rescheduled from Schedule I into Schedule III of the CSA. Schedule III drugs are classified as having a potential for abuse less than the drugs or other substances in schedules I and II, a currently accepted medical use in treatment in the United States, and moderate or low physical dependence or high psychological dependence that may result from their use. NIDA concurs with this recommendation.

II. Evaluating Marijuana Under the Eight Factors

Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of marijuana are considered below.

FACTOR 1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

Under the first factor, the Secretary must consider actual or relative potential for abuse of marijuana. The CSA does not define the term “abuse.” However, the CSA’s legislative history suggests using the following criteria in determining whether a particular drug or substance has a potential for abuse⁷:

- a. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.
- b. There is a significant diversion of the drug or drugs containing such a substance from legitimate drug channels.
- c. Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.
- d. The drug or drugs containing such a substance so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

In the development of this scientific and medical evaluation for the purpose of scheduling, the Secretary analyzed considerable data related to the abuse potential of marijuana. Determining the abuse potential of a substance is complex with many dimensions, and no single test or assessment provides a complete characterization. Thus, no single measure of abuse potential is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a substance can include consideration of the following elements: chemistry, receptor binding, behavioral effects indicating that the substance is rewarding or is similar to another substance controlled under the CSA, pharmacokinetics, behavioral effects indicating that the substance produces physical or psychic dependence, and epidemiological data related to abuse of the substance regarding its pattern and duration of use, as well as the risk it presents to the public health.

- a. **There is evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.**

Evidence shows that some individuals are taking marijuana in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community. However,

⁷ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.A.N. 4566, 4603.

evidence also exists showing that the vast majority of individuals who use marijuana are doing so in a manner that does not lead to dangerous outcomes to themselves or others.

The data supportive of this conclusion are found in Factor 4 (below), “Its History and Current Pattern of Abuse” (citing data from National Survey on Drug Use and Health (NSDUH), the Behavioral Risk Factor Surveillance System (BRFSS), the Research Abuse, Diversion and Addiction-Related Surveillance (RADARS) System’s Nonmedical Use of Prescription Drugs (NMURx) Program, Monitoring the Future (MTF), the Youth Risk Behavior Surveillance System (YRBSS), and the International Cannabis Policy Survey (ICPS)), in Factor 5, “The Scope, Duration, and Significance of Abuse” (citing data from National Poison Data System (NPDS), NSDUH, the Treatment Episode Data Set (TEDS), National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), the Nationwide Emergency Department Sample (NEDS), and the National Inpatient Sample (NIS)), and Factor 6, “What, if any, Risk There is to the Public Health” (citing data from NSDUH, TEDS, NEDS, NIS, ToxIC Core Registry, FDA Adverse Event Reporting System (FAERS), FDA’s Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS), National Vital Statistics System-Mortality and Drug-Involved Mortality (NVSS-M and DIM), the Drug Abuse Warning Network (DAWN), FDA’s Sentinel Distributed Database System, and Centers for Medicare and Medicaid Services (CMS)).

To provide context, from 2015 to 2019, the prevalence of past-year use of alcohol was 5-6 times greater than that of past-year nonmedical use of marijuana. In contrast, the prevalence of past-year nonmedical use of heroin, cocaine, oxycodone, hydrocodone, tramadol, benzodiazepines, and zolpidem was 4-5 times less than that for marijuana.

In NSDUH, among people with past-year marijuana nonmedical use, approximately half of individuals reported nonmedical marijuana use an average of less than 5 days/month while another 30% reported nonmedical marijuana use for an average of more than 20 days/month. In the BRFSS population of people with past-30-day marijuana use, near-daily use was more likely if the individual was using marijuana for medical reasons. However, medical-only use of marijuana was less common (25% for medical-only use, compared to 39% for medical and nonmedical use, and 36% for nonmedical use only). Additionally, in NSDUH, past-year use of marijuana was predictive of past-month use for 60-80% of respondents, similar to alcohol use (approximately 80% of those who used alcohol in the past year also did so in the past month).

The most notable conclusion from an evaluation of various epidemiological databases of adverse outcomes involving marijuana or comparator drugs that are used nonmedically, occurring over 2015 to 2021, is that the utilization-adjusted rate of adverse outcomes involving marijuana was consistently lower than the respective utilization-adjusted rates of adverse outcomes involving heroin, cocaine, and, for certain outcomes, other comparators. Also, the rank order of the comparators in terms of adverse outcome counts typically placed alcohol or heroin in the first or immediately subsequent positions, with marijuana in a lower place in that ranking. This pattern was also observed for serious medical outcomes, including death, observed in Poison Center data, where marijuana was in the lowest ranking group. This suggests consistency across databases, across drugs, and over time, and although abuse of marijuana produces clear evidence of harmful consequences, these appear to be relatively less common and less severe than some

other comparator drugs. Importantly, these comparisons of prevalence of adverse outcomes were from descriptive analyses only. Thus, underlying differences in the populations being compared (e.g., age or pre-existing medical conditions) may have contributed to observed differences in outcome frequency and severity, and the ranked order across comparators. In addition, because individuals using marijuana and/or the selected comparators may have been monitored differently, there may have been differences between the populations in outcome ascertainment.

The risks to the public health posed by marijuana are lower compared to other drugs of abuse (e.g., heroin, oxycodone, cocaine), based on an evaluation of various epidemiological databases for emergency department (ED) visits, hospitalizations, unintentional exposures, and most importantly, for overdose deaths. The rank order of the comparators in terms of greatest adverse consequences typically places heroin, benzodiazepines and/or cocaine in the first or immediately subsequent positions, with marijuana in a lower place in the ranking, especially when a utilization adjustment is calculated. For overdose deaths, marijuana is always in the lowest ranking among comparator drugs. These evaluations demonstrate that there is consistency across databases, across substances, and over time that although abuse of marijuana produces clear evidence of a risk to public health, that risk is relatively lower than that posed by most other comparator drugs.

b. There is significant diversion of the substance from legitimate drug channels.

There is a lack of evidence of significant diversion of marijuana from legitimate drug channels (i.e., marijuana that is legally marketed under United States federal law), due to the fact that an NDA for a drug product containing botanical marijuana has not been approved for marketing in the United States. Marijuana is used by researchers for clinical research under investigational new drug (IND) applications, and there are multiple DEA-registrants who have applied and are approved to produce marijuana and derived formulations for use in DEA-authorized nonclinical and clinical research. These research and manufacturing authorizations represent the only legitimate federally sanctioned drug channels in the United States, and there is a lack of data indicating diversion occurring from these entities or activities. However, there are significant additional sources of marijuana in the United States, both from illicit cultivation and production, illicit importation from other countries, and from state programs that permit dispensing of marijuana for medical use and, in some states, recreational adult use.

c. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.

FDA has not approved an NDA for a drug product containing botanical marijuana for any therapeutic indication. Thus, at the federal level, the only way an individual can use marijuana on the basis of medical advice through legitimate channels under federal law is by participating in research under an IND. However, 38 states and the District of Columbia have passed state-level medical marijuana laws allowing for individuals to use marijuana under certain circumstances for medical purposes. Outside of the federal- and state-sanctioned medical use of marijuana, individuals are using marijuana on their own initiative for medical as well as nonmedical, purposes. Epidemiological data related to nonmedical use of marijuana is detailed in Factor 4, “Its History and Current Pattern of Abuse.”

- d. The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.**

Marijuana has been a Schedule I substance under the CSA since it was enacted in 1970. The primary compound in marijuana that is responsible for its abuse potential is Δ 9-THC (also known as dronabinol, when specifically referring to the (-)-*trans*- Δ 9-THC stereoisomer), which has agonist activity at cannabinoid CB₁ receptors. As discussed under Factor 2, there are extensive nonclinical and clinical studies that establish that marijuana, due to the CB₁ agonist activity of its main cannabinoid constituent Δ 9-THC, produces rewarding effects that would be consistent with observed long-term patterns of nonmedical use and abuse, both before and in years since enactment of the CSA (see Factor 4). Additionally, FDA has approved two drug products containing dronabinol: Marinol (in 1985; Schedule III) and Syndros (in 2016; Schedule II). When these products were being developed, they underwent a systematic evaluation of their abuse potential based on animal and human behavioral studies, which showed that dronabinol has abuse potential. The abuse-related studies for Marinol and Syndros confirmed the abuse potential of Δ 9-THC, the primary compound responsible for the abuse of marijuana. These findings suggest that marijuana will continue to be used nonmedically, diverted from legitimate channels, and trafficked in illicit channels as a potential source for continued nonmedical use in the United States (see Factor 5).

Epidemiological data indicate that marijuana has the potential for creating hazards to the health of the user and to the safety of the community. However, as a relative finding on abuse liability, when comparing marijuana to heroin, oxycodone, hydrocodone, fentanyl, cocaine, ketamine, benzodiazepines, zolpidem, tramadol, and alcohol in various epidemiological databases that allow for some or all of these comparisons, marijuana is not typically among the substances producing the most frequent incidence of adverse outcomes or severity of substance use disorder (see Factors 4, 5, and 6). However, as noted above in Factor 1a, there are limitations in comparing descriptive data on adverse outcomes across drugs.

FACTOR 2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN.

Under the second factor, the Secretary must consider the scientific evidence of the pharmacological effects of marijuana, based on the effects of Δ 9-THC, the primary compound responsible for the abuse potential of marijuana. This section includes a scientific evaluation of the neurochemistry, receptor pharmacology, animal abuse-related behavioral effects, and human behavioral and physiological effects of marijuana. The overview presented below relies upon the current scientific information available in the public domain.

Neurochemistry and Receptor Pharmacology of Marijuana

Cannabis is the genus of a plant that contains numerous natural constituents, including cannabinoids (see Factor 3, below). Marijuana samples derived from various cultivated chemovars may vary with respect to their composition and concentration of various chemical constituents, including whether they contain significant amounts of Δ^9 -THC or other cannabinoids (Appendino et al., 2011; Smith et al., 2022). As a consequence, marijuana products from different strains will have differing biological and pharmacological profiles.

Marijuana contains at least 560 identified natural constituents, including 125 compounds classified as cannabinoids (Appendino et al., 2011; Elsohly & Slade, 2005; Radwan et al., 2021). Most major cannabinoid compounds occurring naturally in *Cannabis* have been identified chemically, but new and minor compounds are continuously being characterized (Pollastro et al., 2011; Radwan et al., 2021). The chemistry of marijuana is described in more detail in Factor 3, “The State of Current Scientific Knowledge Regarding the Drug or Other Substance.”

The two most abundant cannabinoids present in marijuana are Δ^9 -THC and CBD (Lewis et al., 2018). Mechoulam and Gaoni first described the structure and function of Δ^9 -THC in 1965, while Mechoulam and Shvo first described the structure of CBD in 1963 (Mechoulam & Gaoni, 1965; Mechoulam & Shvo, 1963). Δ^9 -THC is the major psychoactive intoxicating cannabinoid in marijuana (Wachtel et al., 2002) and is the component of marijuana that is primarily responsible for its abuse potential. In contrast, CBD has negligible abuse potential, as assessed by FDA during the NDA review for Epidiolex, an FDA-approved drug product containing plant-derived, highly-purified CBD (Epidiolex drug label, 2022).

There are two cannabinoid receptors: CB₁ and CB₂. The identification and cloning of CB₁ receptors from rat brain tissue (Devane et al., 1988) and then from human brain tissue (Gerard et al., 1991) was followed by identification and cloning of CB₂ receptors in the periphery (Munro et al., 1993).

CB₁ and CB₂ receptors belong to the family of G-protein-coupled receptors and present a typical seven transmembrane-spanning domain structure. Cannabinoid receptors primarily link to an inhibitory G-protein (G_{i/o}), such that adenylate cyclase activity is inhibited when a cannabinoid ligand binds to the receptor. This, in turn, prevents the conversion of adenosine triphosphate (ATP) to the second messenger, cyclic AMP (cAMP), which decreases cAMP levels (Eldeeb et al., 2020; Howlett et al., 2004). Kesner et al. (Kesner & Lovinger, 2021) have summarized the second messenger functioning in more depth, noting that G proteins also contain beta/gamma G protein units that are also liberated following ligand binding, which then bind to and alter ion channel function, including inhibition of voltage-gated ion channels and activation of potassium channels. Ligand binding can also activate some subforms of phospholipase C as well as beta-arrestin protein. All of these second messenger routes amplify the neural signal following cannabinoid binding at CB₁ and CB₂ receptors.

CB₁ receptors are found primarily in the central nervous system (CNS), but are also present in peripheral tissues, such as liver, heart, and lungs (Howlett & Abood, 2017). In the brain, CB₁ receptors are expressed with highest density in cortical regions, hippocampus, basal ganglia, and

cerebellum (Herkenham et al., 1991; Howlett et al., 2004; Marsicano & Kuner, 2008) and lowest density in brainstem and hypothalamic areas (Howlett et al., 2004; Busquets-Garcia et al., 2018). The localization of these receptors may explain cannabinoid effects on movement coordination, memory, and cognition. Additionally, CB₁ receptors are found in glial cells (Breivogel & Sim-Selley, 2009) as well as in the immune system (Klein et al., 2003). However, the concentration of CB₁ receptors is considerably lower in peripheral tissues than in the CNS (Herkenham, 1992; Herkenham et al., 1990).

CB₂ receptors are found primarily in the immune system (Klein et al., 2003; Mackie & Stella, 2006), including numerous leukocyte cell types (Bouaboula et al., 1993; Turcotte et al., 2016), as well as in activated CNS microglia (Mackie, 2008). Additionally, CB₂ receptors have been localized in the brain, primarily in the cerebellum and hippocampus (Gong et al., 2006). The distribution of CB₂ receptors throughout the body is less extensive than the distribution of CB₁ receptors (De Petrocellis & Di Marzo, 2009).

There are two endogenous cannabinoid receptor agonists, anandamide (identified in 1992) and arachidonyl glycerol (2-AG; identified in 1995) (Di Marzo, 2006). At CB₁ receptors, anandamide is a partial agonist with low intrinsic efficacy (Mackie, 2008) while 2-AG is a full agonist with high intrinsic efficacy (Gonsiorek et al., 2000). These endogenous cannabinoid ligands are present in central as well as peripheral tissues. A combination of uptake and hydrolysis terminate the action of anandamide and 2-AG. The endogenous cannabinoid system is a locally active signaling system, activated “on demand” in response to changes to the local conditions to help restore homeostasis (Medeiros et al., 2020). The endogenous cannabinoid system, including the endogenous cannabinoids and the cannabinoid receptors, demonstrate substantial plasticity in response to several physiological and pathological stimuli (Augustin & Lovinger, 2018; De Petrocellis & Di Marzo, 2009). This plasticity is particularly evident in the CNS.

Δ9-THC and CBD have varying affinity and effects at the cannabinoid receptors. Δ9-THC is a partial agonist at both CB₁ (K_i = 18-218 nM) and CB₂ receptors (K_i = 36-309 nM) (Tagen and Klumpers, 2022). However, CB₁ receptors are the main pharmacological site of action for Δ9-THC, making CB₁ receptors the site that is responsible for the abuse potential of marijuana (Zimmer et al., 1999). The other CNS site where Δ9-THC may have activity is the 5HT₃ receptor, where it functions as an antagonist (Barann et al., 2002; Shi et al., 2012). In contrast, CBD has low affinity for both CB₁ and CB₂ receptors (McPartland et al., 2007; Mechoulam et al., 2007) and may act as a negative allosteric modulator and/or weak antagonist at these sites (Morales et al., 2017; Thomas et al., 2007). CBD has additional CNS effects as a serotonin 5HT_{1A} agonist and a serotonin 5HT_{2A} weak partial agonist (Russo et al., 2005), and well as a serotonin 5HT_{3A} antagonist (Yang et al., 2010).

In the past 30 years, the potency of marijuana with regard to Δ9-THC has increased dramatically. As reported in 2021 by ElSohly et al., the concentration Δ9-THC in marijuana samples in the United States increased from 3% in 1991 to 4.47% in 1997, from 3.4% in 1993 to 8.8% in 2008, from 4% in 1995 to 12% in 2014, and from 8.9% in 2008 to 17.1% in 2017. These increases were attributed by ElSohly et al. to an increase in the number of high potency samples (i.e., sinsemilla) in the overall samples tested. In contrast, there was a decrease initially in the

concentration of CBD in the same samples, from 0.40% in 2009 to 0.14% in 2017, but this rose to 0.60% in 2019. Based on an evaluation of marijuana seized by DEA, the majority of samples contained high concentrations of Δ 9-THC and low concentrations of CBD (ElSohly et al., 2021).

Animal Abuse-Related Behavioral Effects

Self-Administration

Self-administration is a method that assesses the ability of a drug to produce rewarding effects. The presence of rewarding effects increases the likelihood of behavioral responses to obtain additional drug. Animal self-administration of a drug is often useful in suggesting whether humans will experience that a particular substance will have rewarding effects, which is indicative of abuse potential. A good correlation is often observed between those drugs that rhesus monkeys self-administer and those drugs that humans abuse (Balster & Bigelow, 2003).

Since self-administration is a methodology in which the test drug is typically administered intravenously to rats, it is not possible to evaluate botanical marijuana through self-administration. However, given that Δ 9-THC is the primary substance that confers abuse potential to marijuana, its ability to induce self-administration can serve as an indicator of the abuse potential of marijuana.

For many decades, researchers had difficulty producing consistent self-administration of Δ 9-THC in animals (Harris et al., 1974; Kaymakcalan, 1973; Mansbach et al., 1994; Pickens et al., 1973; van Ree et al., 1978). When novel training paradigms were developed, intravenous self-administration of Δ 9-THC was eventually established in a variety of animal models (Braida et al., 2004; Justinova et al., 2005; Justinova et al., 2004; Justinova et al., 2003; Tanda et al., 2000).

In the past 20 years, investigators have continued to experiment with Δ 9-THC self-administration in animal investigations by varying the methodology, testing differences in animal species and sex, route of administration (intravenous, oral, or inhalation of vaporized or combusted Δ 9-THC), dose of Δ 9-THC, and the schedule of reinforcement (fixed ratio and/or fixed interval). Based on the specific methods used, laboratories have had variable success in producing self-administration of Δ 9-THC.

Some studies showed successful animal self-administration of Δ 9-THC following intravenous administration (John et al., 2017; Justinova et al., 2003; Spencer et al., 2018; Stringfield & Torregrossa, 2021) administration of inhaled vapor (Freels et al., 2020), oral administration (Abraham et al., 2020; Nelson et al., 2019; Smoker, Hernandez, et al., 2019; Smoker, Mackie, et al., 2019), and intracerebroventricular administration (Braida et al., 2001; Zangen et al., 2006). The repeated self-administration in these studies show that Δ 9-THC produces rewarding effects that lead an animal to repeatedly seek out the substance, which demonstrates that Δ 9-THC is reinforcing.

In contrast, there are other recent animal studies that have not been able to produce Δ 9-THC self-administration following intravenous administration (Lefever et al., 2014; Wakeford et al., 2017) and oral administration (Barrus et al., 2018). However, these negative data demonstrate how the

specific methodology used in a study can limit a behavioral response, and thus do not negate the positive results from the studies in which $\Delta 9$ -THC was actively self-administered by animals.

Typically, animal self-administration is used primarily to predict whether a novel substance is likely to be used by humans for its rewarding properties, as an indication of its abuse potential. However, it is well-known from epidemiological data that humans self-administer substances that contain $\Delta 9$ -THC, including botanical marijuana (see Factors 4, 5, and 6), for their ability to produce positive subjective responses, including euphoria. Thus, a comprehensive deconstruction of which animal methodology is optimum for producing preclinical self-administration of $\Delta 9$ -THC is not necessary for an evaluation of the abuse potential of marijuana in humans, since it is already clear that humans utilize marijuana for its rewarding properties.

Conditioned Place Preference

Conditioned place preference (CPP) is a less rigorous method than self-administration of determining whether drugs have rewarding properties. In this behavioral test, animals are given the opportunity to spend time in two distinct environments: one where they previously received a drug and one where they received a placebo. If the drug has rewarding properties, animals will choose to spend more time in the environment paired with the drug than the one paired with the placebo, when both options are presented simultaneously.

Many attempts to produce animal CPP with $\Delta 9$ -THC were unsuccessful, producing either no CPP (Parker & Gillies, 1995; Vlachou et al., 2007) or a conditioned place aversion (where an animal avoids the side of the cage where the drug was given, suggesting the drug was experienced as unpleasant) (Cheer et al., 2000; Hutcheson et al., 1998; Quinn et al., 2008; Sanudo-Pena et al., 1997; Schramm-Sapota et al., 2007). This is similar to the experimental difficulties reported in producing animal self-administration of $\Delta 9$ -THC.

In 1995, CPP was first shown to be elicited from exposure to $\Delta 9$ -THC (Lepore et al., 1995), followed by success by other investigators in producing CPP associated with $\Delta 9$ -THC (Braidia et al., 2004; Castane et al., 2003; Ghosland et al., 2002; Le Foll et al., 2006; Soria et al., 2004; Valjent & Maldonado, 2000; Valjent et al., 2002).

The studies in which $\Delta 9$ -THC successfully produced CPP occurred under very specific experimental conditions, similar to the $\Delta 9$ -THC self-administration studies in animals. Experimental manipulations in CPP studies with $\Delta 9$ -THC have included varying animal species, sex, dose, route of administration, introduction of flavors to obscure unpleasant taste, and the drug history of the animals tested. However, as with animal self-administration, the use of CPP is typically to determine if a new drug produces rewarding sensations, which would suggest that a drug has abuse potential. Since it is clear that humans self-administer substances that contain $\Delta 9$ -THC, including botanical marijuana, it is not necessary to interrogate which CPP methods are optimal for demonstrating that $\Delta 9$ -THC has rewarding properties in animals.

Drug Discrimination Studies

Drug discrimination is a method in which animals indicate whether a test drug produces sensations similar to those produced by a training drug with a known pharmacological mechanism of action. In this test, an animal learns to press one bar in a test cage when it receives the training drug and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug produces effects that are similar to the training drug. Drug discrimination is only considered to be an abuse-related study when the training drug is a known drug of abuse that is scheduled under the CSA and the test drug may have abusable effects similar to the training drug, based on having a similar mechanism of action to the training drug.

Δ 9-THC, the primary compound in marijuana that is responsible for its abuse potential, is used extensively as the training drug in animal drug discrimination studies to demonstrate whether a novel compound produces cannabinoid effects. Since Δ 9-THC is already considered to be the standard for establishing if new drugs have classic marijuana-like pharmacological activity in drug discrimination, the application of this method in evaluating the abuse potential of Δ 9-THC will not be discussed further.

Human Behavioral and Physiological Effects

Subjective Effects of Δ 9-THC

The psychological, behavioral, and subjective responses to marijuana in humans have been known and characterized since antiquity (Chaachouay et al., 2023; Russo, 2016). In the modern period, data on the psychological, behavioral, and subjective responses to marijuana are available from the drug label of FDA-approved drug products, from prospective human abuse potential (HAP) studies, from accounts published in the scientific and medical literature, and from an evaluation published in 2017 by the NASEM.

FDA-Approved Drug Products Containing Δ 9-THC

Clinical scientific studies have investigated the effects of Δ 9-THC, the primary compound responsible for the abuse potential of marijuana, on humans during the drug development of the FDA-approved drug product Marinol, which contains 2.5, 5, and 10 mg dronabinol ((-)-trans- Δ 9-THC of synthetic origin in sesame seed oil). Section 6.1 (Clinical Trials Experience) of drug labels for Marinol and Syndros (which relied on the safety data from Marinol during drug development) lists the following AEs as occurring in controlled clinical studies during drug development.

Incidence > 1%:

- *CNS:* amnesia, anxiety/nervousness, ataxia, confusion, depersonalization, hallucination
- *General:* asthenia
- *Cardiovascular:* palpitations, tachycardia, vasodilation/facial flush

Incidence 3% to 10%

- *CNS:* euphoria, paranoid reaction, somnolence, thinking abnormal, dizziness
- *Gastrointestinal:* Abdominal pain, nausea, vomiting

Human Abuse Potential Studies

HAP studies evaluate whether a test drug produces positive subjective responses, compared to placebo and a known drug of abuse that is scheduled under the CSA that serves as the positive control. If the test drug produces rewarding effects that are statistically significantly greater than placebo, and beyond the acceptable placebo range of response, it is an indication that the drug may have abuse potential. The relative abuse potential is suggested by the responses from the positive control on these measures, in comparison to the test drug.

For many decades, HAP studies have been conducted with marijuana and Δ 9-THC in subjects who had nonmedical experience with cannabinoids (Fogel et al., 2017; Hunault et al., 2014; Karschner et al., 2011; Kaufmann et al., 2010; Ramesh et al., 2013; Ranganathan et al., 2012; Schindler et al., 2020; Spindle et al., 2021; Wachtel & de Wit, 2000; Wachtel et al., 2002). In these studies, doses of Δ 9-THC ranging from 1.79 to 69 mg were administered to subjects using marijuana and/or isolated Δ 9-THC. Most of these studies used smoking or oral administration, with some studies using the intravenous route of administration.

There were commonalities in results among all of these HAP studies, despite the differences in dose of Δ 9-THC, the route of administration, or whether the Δ 9-THC was provided in the form of marijuana or isolated compound. Following administration of the study drug, there were increases on such positive subjective responses as visual analog scales (VAS) for Drug Liking, Overall Drug Liking, Good or Pleasant Drug Effects, High, Stoned, Stimulated, Enjoyment, Take Drug Again, Want More Drug, and Willing to Pay. There were also increases on the Addiction Research Center Inventory (ARCI) scales for Morphine Benzodrine Group (euphoria), Marijuana, and Amphetamine. These data consistently demonstrate that Δ 9-THC, in the form of marijuana or isolated compound, when administered under controlled experimental conditions, produces rewarding effects that are indicative of abuse potential.

Following administration of marijuana or Δ 9-THC, there were also increases on subjective responses assessing various negative drug effects and sedation, often delayed in onset from when the positive subjective effects began. These assessments included VAS for Bad Drug Effect, Sick, Dizzy, Hungry, Suspicious, Paranoid, Anxious, Sedated, Calm, Drowsy, Tired, Forgetful, Impaired Memory, Dry Mouth, and Dry/Red Eyes, as well as ARCI scales for Lysergic Acid Diethylamide (dysphoria), Benzodrine Group (stimulant), and Pentobarbital-Chlorpromazine-Alcohol Group (sedation).

Given the wide range of doses tested in HAP studies, these positive and negative subjective responses following administration of marijuana or Δ 9-THC were often dose-dependent. There were typically few differences between the responses between marijuana and Δ 9-THC, or between responses based on route of administration of the study drug.

Common Responses to Marijuana in Humans

The responses to dronabinol reported during drug development and in HAP studies parallel the common responses to marijuana that have been described by other medical scientists (Adams & Martin, 1996; Agrawal et al., 2014; American Psychiatric Association, 2013; Earleywine, 2002; Hollister, 1986, 1988), which include:

Positive Subjective Responses

- Euphoria
- Pleasurable “rush” or “buzz”
- Merriment
- Happiness
- Exhilaration

Sedative Responses

- Sedation
- Drowsiness
- Relaxation
- Changes in sleep

Anxiety and Negative Responses

- Anxiety
- Panic attack
- Fearfulness
- Agitation
- Paranoia
- Restlessness
- Dysphoria

Perceptual Changes

- Hallucinations
- Feelings seem stronger
- Sexual enhancement
- Spiritual enhancement
- Changes in time perception
- Changes in perception (sight, sound, taste, smell, touch)

Psychiatric, Social, and Cognitive Changes

- Drug abuse
- Illusions
- Delusions
- Depersonalization
- Heightened imagination
- Disinhibition
- Emotional lability

- Memory and concentration impairment
- Disorganized thinking
- Impaired judgment
- Confusion
- Increased sociability
- Talkativeness

Physiological Responses

- Nausea
- Tachycardia
- Facial flushing
- Dry mouth
- Tremor
- Dizziness
- Increased appetite, especially for sweet and fatty foods
- Reduced coordination
- Ataxia
- Hyperemesis

The positive changes that occur following use of marijuana are pleasurable to many humans and are associated with drug-seeking and drug-taking. These effects are typically dose-dependent, with higher doses and routes of administration that produce faster onset producing more intense responses and the likelihood of more negative subjective effects (Kesner & Lovinger, 2021).

National Academies of Science, Engineering, and Medicine

In 2017, NASEM published a book-length evaluation entitled *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* (National Academies of Sciences & Medicine, 2017). In this evaluation, NASEM provided a brief summary of the clinical features of marijuana intoxication, as follows:

During acute cannabis intoxication, the user's sociability and sensitivity to certain stimuli (e.g., colors, music) may be enhanced, the perception of time is altered, and the appetite for sweet and fatty foods is heightened. Some users report feeling relaxed or experiencing a pleasurable "rush" or "buzz" after smoking cannabis (Agrawal et al., 2014). These subjective effects are often associated with decreased short-term memory, dry mouth, and impaired perception and motor skills. When very high blood levels of Δ^9 -THC are attained, the person may experience panic attacks, paranoid thoughts, and hallucinations [...] Furthermore, as legalized medical and nonmedical cannabis availability increase nationwide, the impairment of driving abilities during acute intoxication has become a public safety issue.

In addition to Δ^9 -THC dosage, two main factors influence the intensity and duration of acute intoxication: individual differences in the rate of absorption and metabolism of Δ^9 -THC, and the loss of sensitivity to its pharmacological actions. Prolonged CB₁ receptor

occupation as a consequence of the sustained use of cannabis can trigger a process of desensitization, rendering subjects tolerant to the central and peripheral effects of Δ^9 -THC and other cannabinoid agonists (Gonzalez et al., 2005). Animals exposed repeatedly to Δ^9 -THC display decreased CB₁ receptor levels as well as impaired coupling between CB₁ and its transducing G-proteins (Gonzalez et al., 2005). Similarly, in humans, imaging studies have shown that chronic cannabis use leads to a down-regulation of CB₁ receptors in the cortical regions of the brain and that this effect can be reversed by abstinence (Hirvonen et al., 2012).

In conclusion, Δ^9 -THC, the substance largely responsible for the abuse potential of marijuana, is an agonist at the cannabinoid CB₁ receptor. When Δ^9 -THC is administered to animals, it produces rewarding responses, as evidenced by its ability to induce self-administration and conditioned place preference. This is consistent with the data from human studies and from clinical observations, where administration of Δ^9 -THC or use of marijuana produces euphoria and other pleasurable responses, as well as sedation and anxiety responses. Psychiatric, social, and cognitive responses, which are often experienced as negative, are also reported, as are physiological responses such as dry mouth, ataxia, and increased hunger. As described in Factor 4, the rewarding responses observed in humans are consistent with the prevalence of nonmedical use of marijuana, which includes abuse of the substance. Abuse of marijuana by individuals can lead to other negative consequences, including addiction and the need to seek medical attention through calls to poison centers or visits to an ED, as described in Factor 5.

FACTOR 3. THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE

Under the third factor, the Secretary must consider the state of current scientific knowledge regarding marijuana. Thus, this section discusses the chemistry and human pharmacokinetics of marijuana, as well as whether marijuana has a CAMU in the United States.

Chemistry

Cannabis is a genus of annual flowering plant with digitate leaves in the family *Cannabaceae* Martinov (United States Department of Agriculture Natural Resources Conservation Service, 2023; WorldFloraOnline, 2023). Many scholars have studied diverse datasets and models to estimate the origins of *Cannabis*. It likely originated in Central or Southeast Asia over 10,000 years ago and was first cultivated in China for fiber and seed production (Bonini et al., 2018; Russo et al., 2008), with cultivation spreading across Asia, Africa, and Europe and eventually to the Americas (Pisanti & Bifulco, 2019). A long-standing and significant historical debate by botanists and taxonomists continues today regarding the number of species in the *Cannabis* genus (Clarke & Watson, 2007; Hillig, 2005; Russo, 2004; Schultes et al., 1974; Small & Cronquist, 1976). It is generally treated as a single, highly polymorphic species known as *Cannabis sativa* L., with the other two previously reported species listed as *Cannabis indica* Lam. and *Cannabis ruderalis* Janisch (United States Department of Agriculture Agricultural Research Service, 2023). Plants previously believed part of the latter two species are generally recognized as varieties (or subspecies) of *Cannabis sativa* L. (*C. sativa*), which are commonly

referred to as var. *indica* and var. *ruderalis*. *Cannabis sativa* and var. *indica* plants are widely cultivated for their size, branching, and cannabinoid content, while *ruderalis* is rarely cultivated alone as it is shorter, often unbranched, and has very low cannabinoid content (Thomas & ElSohly, 2016a). Worldwide *Cannabis* varieties are separated into hundreds of different cultivars and strains. Plants selected for cultivation are known as cultivated varieties or cultivars, whereas plants reproduced asexually from a cultivar through clonal propagation are known as strains (Procaccia et al., 2022). These practices have resulted in significantly different chemical profiles for *Cannabis* cultivars and the classification term to account for these chemical profile differences has evolved. The term ‘chemovar’ accounts for the plant’s chemical profile and is a more meaningful classification for clinical researchers studying the plant’s potential drug effects (Hazekamp & Fisdick, 2012).

Cannabis is a dioecious plant (WorldFloraOnline, 2023), meaning female and male flowers occur on separate plants, and rarely occurs as a monoecious plant (single plant containing male and female flowers). The glandular trichomes found on the female plant’s unfertilized flower heads and bracts contain the highest concentrations of cannabinoids. For this reason, unfertilized female chemovars are favored to harvest large inflorescences (i.e., complete flower head) for their rich cannabinoid and terpene content. **Error! Bookmark not defined.** Consequently, marijuana products developed from diverse chemovars will have different safety, biological, pharmacological, and toxicological profiles.

The *C. sativa* plant naturally contains many different compounds and more than 550 have been identified, such as: cannabinoids, terpenoids, flavonoids, stilbenoids, steroids, polysaccharides, benzoquinone, phenanthrenes, spiroindans, lignans, fatty acids, sugars, hydrocarbons, amino acids, and proteins (Liu et al., 2022; Rock & Parker, 2021). Cannabinoids are mainly found in living *C. sativa* plants in their non-psychoactive carboxylated forms (i.e., acid form), which require drying, heating, combustion, or aging to decarboxylate to their neutral forms, (Thomas & ElSohly, 2016b) and are primarily composed of C₂₁ terpenophenolic compounds (Brenneisen, 2007). The most abundant neutral form cannabinoids are Δ⁹-THC and CBD, but nearly 200 have been identified (ElSohly et al., 2017; Johnson et al., 2020) in the plant and are divided into subclasses: cannabigerols (CBGs), cannabichromenes (CBCs), cannabidiols (CBDs), (-)-Δ⁹-trans-tetrahydrocannabinols (Δ⁹-THCs), (-)-Δ⁸-trans-tetrahydrocannabinols (Δ⁸-THCs), cannabicyclols (CBLs), cannabielsoins (CBEs), cannabinols (CBNs), cannabinodiols (CBNDs), cannabitrils (CBTs), and the miscellaneous cannabinoids (Thomas & ElSohly, 2016a).

Like any other botanical substance, marijuana plants are heterogeneous in nature and contain a complex chemical profile. Moreover, variable organic plant material, as well as manufactured preparations, result in a variety of product forms that dictate different routes of administration, associated risks, and differences in quality of the product used, which may also influence risk for users. The potential for high variability of marijuana and marijuana-derived products, both in product composition and impurity profile, are major considerations for the potential variability of drug effects and safety. This variability may derive from:

- Different botanical raw material and controls which may influence or be influenced by the following (e.g., good agricultural and collection practices) (World Health Organization, 2003).

- Harvest location (including global positioning system (GPS) coordinates), growth conditions, stage of plant harvest, and harvest time/season – as these all impact the chemical profile.
- Post-harvest processing (e.g., washing, drying, and grinding processes), including control of foreign matter (i.e., inorganic and organic contaminants like soil, insects, and algae/fungi); preservation procedures; handling, transportation, and storage conditions; tests for elemental impurities; microbial limits; tests for residual pesticides, including parent pesticides and their major toxic metabolites; and tests for adventitious toxins (e.g., aflatoxins), foreign materials, and adulterants.

Processing of marijuana and its use in further manufacturing can lead to a range of forms that individuals may use or consume, including crude mixtures and highly purified substances of botanical origin, many of which may be cannabinoid compounds. Among known cannabinoids in the cannabis plant, both Δ^9 -THC (National Center for Biotechnology Information, 2023a) and Δ^8 -THC (National Center for Biotechnology Information, 2023e) produce marijuana's psychoactive effects. Because Δ^9 -THC is significantly more abundant than Δ^8 -THC, marijuana's intoxicating effects are largely attributed to the former. Only small quantities of Δ^8 -THC acid (Krejčí & Šantavý, 1975) and Δ^8 -THC (Hively et al., 1966) have been identified in plants (Thomas & ElSohly, 2016a). Δ^9 -THC is a resinous substance, essentially insoluble in water and extremely lipophilic, that is also photolabile and volatilized when exposed to heat (ElSohly, 2007). Furthermore, Δ^9 -THC is an optically active substance with two chiral centers at C-6a and C-10a and thus has four diastereomers (Schafroth et al., 2021), which are:

- (6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol
 - alternate name: (-)-*trans*- Δ^9 -THC (National Center for Biotechnology Information, 2023b)
- (6aS,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol
 - alternate name: (-)-*cis*- Δ^9 -THC (National Center for Biotechnology Information, 2023f)
- (6aS,10aS)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol
 - alternate name: (+)-*trans*- Δ^9 -THC (National Center for Biotechnology Information, 2023d)
- (6aR,10aS)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol
 - alternate names: (+)-*cis*- Δ^9 -THC; (+)- Δ^9 -*cis*-THC (6aR, 10aS)-3 (National Center for Biotechnology Information, 2023c)

The formation of the (-)-*trans* isomer is favored in the plant and this isomer is 6–100 times more potent pharmacologically than the (+)-*trans* isomer (Brenneisen, 2007; Dewey et al., 1984).

As discussed in Section I, Background, the 2018 Farm Bill changed how the cannabis plant is scheduled under the CSA and removes hemp from the definition of marijuana. However, the term 'cannabis' is still often broadly used to refer to a wide variety of products manufactured from the *C. sativa* plant regardless of control status. These products may include the dried inflorescences (flowers), leaves, seeds, and stems and may be used in the manufacturing of concentrates, edibles, and topicals. Thus, marijuana or derived products can generally be categorized as one of four types:

- Flowers – includes dried herb that is smoked or vaped, and pre-rolls

- Concentrates – includes products for inhalation referred to as shatter, wax, butter, sugar, hash, resin, and rosin via vaping (use of an electronic vaporizer) or via dabbing (use of other paraphernalia such as a pipe or “dab rigs”) (Colorado Department of Revenue, 2021; Drug Enforcement Administration, 2023)
- Edibles – includes infused food, beverage, and tincture products (e.g., baked goods, chocolate, drinks, candies, and snacks)
- Topicals – includes infused ointments, lotions, creams, or transdermal products

As a result of the 2018 Farm Bill, a large “hemp marketplace” exists,⁸ containing a wide variety of products representing the above product categories and involving various routes of administration. Aside from products purporting to meet the definition of hemp, the public also has access to cannabis products within the CSA definition of marijuana through state-authorized adult-use (i.e., nonmedical use) and medical-use programs, as well as via the illicit marketplace (see Factor 4 for additional details).

Based on these diverse sources of marijuana, there is a lack of unified controls on cultivation and manufacturing, which raises concerns related to the safety, quality, and consistency of botanical substances (e.g., botanical raw materials, extracts, and intermediates) and final product formulations that are currently accessed for medical and nonmedical use. Products sourced from state-authorized adult-use and medical-use programs are subject to a patchwork of inconsistent product standards and safety requirements. While each state program generally has a set of standards (for example, on manufacturing, testing, labeling, and packaging), each program’s controls are different, leading to wide variation of products across state-authorized programs. Additionally, the illicit marketplace is not subject to any standards or oversight. Thus, the range of products within the CSA’s definition of marijuana encompasses a large degree of variation in forms for consumption, composition of biologically relevant constituents, potency, and contaminants.

In conclusion, marijuana has hundreds of chemovars containing variable concentrations of Δ 9-THC, cannabinoids, and other compounds. Thus, marijuana is not a single chemical with a consistent and reproducible chemical profile or predictable and consistent clinical effects. This current evaluation of marijuana will focus to greatest extent possible on wide-ranging cannabis plant-derived substances that are vehicles for the self-administration of Δ 9-THC as the key biologically active substance on which the CSA’s current definition of marijuana is based.

Human Pharmacokinetics of Δ 9-THC

The pharmacokinetics of Δ 9-THC in humans have been evaluated following inhaled administration of marijuana and oral administration of marijuana. These are the most frequently used routes of administration for marijuana or isolated Δ 9-THC (Vinette et al., 2022), as confirmed by the United States Poison Centers National Poison Data System (NPDS), which showed that ingestion (57%) and inhalation (41%) were the most common routes of administration for marijuana, while other routes of abuse were not common (<0.2%).

⁸ Additionally, hemp products with industrial applications, such as textiles, plastics, and other building materials, exist in the marketplace. However, these products are not relevant to this analysis.

Absorption of Δ 9-THC Following Inhaled Administration of Marijuana

Marijuana is commonly administered by humans via inhalation through smoking and, more recently, through vaping (e.g., heating and inhalation of botanical matter or other volatile substances containing Δ 9-THC) (Miech et al., 2019; Miech et al., 2020). Characterization of the pharmacokinetics of Δ 9-THC from smoked and vaped marijuana is difficult under naturalistic conditions because the pace of drug inhalation varies widely among individuals (Agurell et al., 1986; Herning et al., 1986; Huestis, Sampson, et al., 1992). For example, experienced marijuana smokers will titrate their Δ 9-THC dose to obtain the desired acute psychological effects and minimize undesired effects. Nonmedical marijuana users will also often hold marijuana smoke in their lungs for an extended period of time in an attempt to increase absorption and subsequent psychoactive effects despite data showing that this technique has minimal effects on Δ 9-THC plasma levels and subjective ratings of “high” (Azorlosa et al., 1995; Zacny & Chait, 1989, 1991). Thus, in order to standardize drug administration in scientific studies in humans, investigators will often use a Paced Inhalation Procedure (Foltin et al., 1987). Using this method, subjects take 5 seconds to prepare for inhalation, 5 seconds to inhale, 10 seconds to hold smoke or vapor in the lungs, followed by exhalation, and a 40 second interval prior to the next prepare/inhale/hold cycle.

Pulmonary administration of a drug is the route that produces the fastest rate of drug absorption, even faster than that produced by intravenous administration. Inhaled marijuana results in absorption of Δ 9-THC through the lungs in the form of an aerosol within seconds. Peak plasma levels of Δ 9-THC following inhalation occur very quickly, within 6-10 minutes (Grotenhermen, 2003). Psychoactive effects begin immediately following absorption, although peak subjective effects do not coincide with peak plasma Δ 9-THC levels and are often delayed (Singla & Block, 2022). Following administration of marijuana through inhalation, the bioavailability of Δ 9-THC is 10% to 35% (Grotenhermen, 2003; Lindgren et al., 1981). Although pulmonary administration does not involve dose loss from the hepatic first-pass effect in the liver, as would be seen with oral administration, the relatively low and variable bioavailability following inhaled marijuana results from significant loss of Δ 9-THC in side-stream smoke, cannabinoid pyrolysis, incomplete absorption of inhaled smoke or vapor, and metabolism in the lungs. An individual's experience and technique with smoking marijuana also determines the dose absorbed (Herning et al., 1986; Johansson et al., 1989).

Absorption of Δ 9-THC Following Oral Administration of Marijuana

After oral administration of Δ 9-THC, marijuana, or marijuana-infused foods (e.g., brownies) the onset of effects starts within 30 to 90 minutes, reaches its peak at 1.5 to 3 hours and remains measurable for 4 to 12 hours (Adams & Martin, 1996; Agurell, 1984; Agurell et al., 1986; Grotenhermen, 2003; Vandrey et al., 2017). Due to the delay in onset of effects after oral administration, including a slower onset of peak effects, titration of oral Δ 9-THC doses is difficult compared to inhalation of marijuana (Spindle et al., 2021). Oral bioavailability of Δ 9-THC, following ingestion of an edible containing marijuana or isolated Δ 9-THC, ranges from 5 and 20% (Agurell, 1984; Agurell et al., 1986). The low and variable oral bioavailability of Δ 9-

THC is a consequence of its first-pass hepatic elimination from blood and erratic absorption from stomach and bowel (Sharma et al., 2012). Ingestion of brownies containing marijuana also results in lower Δ^9 -THC plasma levels relative to inhalation of marijuana (Schlitz et al., 2020). Inter- and intra-subject variability occurs even with repeated dosing under controlled conditions.

Distribution, Metabolism and Excretion of Δ^9 -THC

Although there are differences in absorption of Δ^9 -THC depending on route of administration, the distribution, metabolism, and excretion of Δ^9 -THC is similar regardless of how the drug is administered.

Plasma concentrations of Δ^9 -THC decrease quickly after absorption through rapid distribution into tissues and through liver metabolism. Given that Δ^9 -THC has high lipophilicity, the apparent volume of distribution of Δ^9 -THC is high (10 L/kg) (Cerne, 2020) as it is distributed initially into organs such as lung, heart, brain, and liver that are highly perfused (Huestis, 2007). Over time with regular exposure to marijuana, Δ^9 -THC will concentrate and be retained in fat.

Metabolism of Δ^9 -THC occurs primarily via cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP3A4) (Lucas et al., 2018) via microsomal hydroxylation to both active and inactive metabolites (Agurell et al., 1986; Hollister, 1988; Lemberger, Crabtree, et al., 1972; Lemberger et al., 1970; Lemberger, Weiss, et al., 1972). The primary active metabolite of Δ^9 -THC is 11-hydroxy- Δ^9 -THC (Agurell et al., 1986; Lemberger & Rubin, 1975).

Plasma clearance of Δ^9 -THC approximates hepatic blood flow at about 950 ml/min or greater. The rapid disappearance of Δ^9 -THC from blood is largely due to redistribution to other tissues in the body, rather than to metabolism (Agurell, 1984; Agurell et al., 1986). Metabolism in most tissues is relatively slow or absent. Slow release of Δ^9 -THC and other cannabinoids from tissues and subsequent metabolism results in a long elimination half-life.

The plasma half-life of Δ^9 -THC following pulmonary administration varies based on frequency of use. Thus, in periodic users, the half-life is 1 to 3 days while in chronic users, the half-life is 5 to 13 days (Huestis, Henningfield, et al., 1992). After smoking, Δ^9 -THC venous levels decline precipitously within minutes and continue to decline to 5-10% of the peak level within an hour (Agurell et al., 1986; Huestis, Henningfield, et al., 1992; Huestis, Sampson, et al., 1992). In addition to 11-hydroxy- Δ^9 -THC, some inactive carboxy metabolites have terminal half-lives of 50 hours to 6 days or more. The latter substances serve as long-term markers in urine tests for earlier marijuana use.

The majority of the absorbed Δ^9 -THC dose is eliminated in feces, and about 33 percent in urine. Δ^9 -THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy- Δ^9 -THC. The glucuronide is excreted as the major urine metabolite along with about 18 non-conjugated metabolites. Frequent and infrequent individuals who use marijuana metabolize Δ^9 -THC similarly (Agurell et al., 1986).

In conclusion, the pharmacokinetic profile of marijuana varies greatly depending on route of administration. Inhalation of marijuana produces a rapid increase in plasma levels of $\Delta 9$ -THC and an immediate onset of psychological effects. In comparison, oral administration of marijuana produces a much slower increase in plasma levels of $\Delta 9$ -THC and onset of psychological effects. Once $\Delta 9$ -THC has been absorbed, however, the metabolism and excretion of $\Delta 9$ -THC follows a standard path, although the half-life of $\Delta 9$ -THC may vary depending on frequency of use.

Currently Accepted Medical Use of Marijuana

To inform its scheduling recommendation, HHS has conducted an evaluation of whether marijuana has a CAMU for purposes of scheduling under the CSA, 21 U.S.C. § 812(b). Such an evaluation is one of the findings relevant to the placement of a substance in one of five drug control “schedules” set forth in 21 U.S.C. § 812(b).

In evaluating CAMU when considering whether to recommend rescheduling of marijuana, HHS (acting through the FDA and NIDA) applied a two-part test (hereinafter, “CAMU test”) that takes into account the current widespread medical use of marijuana under the supervision of licensed HCPs under state-authorized programs. Under Part 1 of the CAMU test, OASH considered whether there is widespread current experience with medical use of marijuana in the United States by licensed HCPs operating in accordance with implemented state-authorized programs, where such medical use is recognized by entities that regulate the practice of medicine under these state jurisdictions. Part 2 of the CAMU test evaluated whether there exists some credible scientific support for at least one of the medical conditions for which the Part 1 test is satisfied. FDA’s evaluation in Part 2 is not meant to be, nor is it, a determination of safety and efficacy under the Federal Food, Drug, and Cosmetic Act’s (FD&C Act’s) drug approval standard for new human or animal drugs. Rather, the two-part test is to determine whether a substance, in this case marijuana, has a CAMU for purposes of drug scheduling recommendations and placement in a drug schedule consistent with criteria set forth in 21 U.S.C. 812(b).

In the evaluation and assessment under Part 1 of the CAMU test, OASH found that more than 30,000 HCPs are authorized to recommend the use of marijuana for more than six million registered patients, constituting widespread clinical experience associated with various medical conditions recognized by a substantial number of jurisdictions across the United States. For several jurisdictions, these programs have been in place for several years, and include features that actively monitor medical use and product quality characteristics of marijuana dispensed. OASH, through the Assistant Secretary for Health, concluded that, taken together, the findings from Part 1 warranted an FDA assessment under Part 2 of the CAMU test to determine if there exists credible scientific support for the use of marijuana for at least one of the medical conditions identified by OASH under Part 1.

FDA conducted Part 2 of the CAMU test for seven indications, based in part on OASH's findings under Part 1 of the CAMU test⁹ and in part on FDA's own analysis of the landscape in which marijuana is currently used medically, including information from state-authorized programs on how and to what extent marijuana is being utilized for medical purposes. The seven indications are: anorexia,¹⁰ anxiety,¹¹ epilepsy, inflammatory bowel disease (IBD), nausea and vomiting, pain, and post-traumatic stress disorder (PTSD). FDA's evaluation under Part 2 of the CAMU test was based on systematic reviews of studies investigating the safety and effectiveness of marijuana, relevant professional societies' position statements, data from state medical marijuana programs and United States national surveys, and the labeling of FDA-approved products relevant to the analysis.

In evaluating whether there exists some credible scientific support under Part 2 of the CAMU test for a particular use, factors considered in favor of a positive finding included whether: 1) favorable clinical studies of the medical use of marijuana, although not necessarily adequate and well-controlled clinical studies that would support approval of a NDA, have been published in peer-reviewed journals and/or 2) qualified expert organizations (e.g., academic groups, professional societies, or government agencies) have opined in favor of the medical use or provided guidance to HCPs on the medical use. Factors considered that weigh against a finding that Part 2 of the CAMU test is met included whether: 1) data or information indicate that medical use of the substance is associated with unacceptably high safety risks for the likely patient population, e.g., due to toxicity concerns; 2) clinical studies with negative efficacy findings for the medical use of marijuana have been published in peer reviewed journals; and/or 3) qualified expert organizations (e.g., academic or professional societies, government agencies) recommend against the medical use of marijuana (based on the available data at the time of their position statement).

Our review of the available information identified mixed findings of effectiveness across indications, ranging from data showing inconclusive findings to considerable evidence in favor of effectiveness, depending on the source. The largest evidence base for effectiveness exists for marijuana use within the pain indication (in particular, neuropathic pain). For the pain indication, a systematic review of scientific and medical literature was conducted this year by the

⁹ In Part 1 of the CAMU test, OASH identified at least 15 medical conditions where there is widespread current experience with medical use of the substance in the United States by licensed HCPs operating in accordance with implemented state-authorized programs, where the medical use is recognized by entities that regulate the practice of medicine. These conditions include amyotrophic lateral sclerosis (ALS), autism, cachexia, cancer, chronic pain, Crohn's disease, epilepsy or condition causing seizures, glaucoma, HIV/AIDs, multiple sclerosis, Parkinson's disease, persistent/severe muscle spasm, persistent/severe nausea, PTSD, and spasticity. FDA conducted Part 2 of the analysis for the medical conditions identified by OASH that were likely to have the most robust evidence available for review; because the analysis concluded that the Part 2 test has been met for at least one of the conditions identified in Part 1, there was no need to analyze all of them.

¹⁰ The anorexia indication reflects anorexia due to a medical condition (e.g., HIV/AIDS) and does not represent anorexia nervosa.

¹¹ While anxiety was not one of the specific medical conditions identified by OASH, it was included in FDA's Part 2 analysis based on a review of state-level usage data. Anxiety was considered of importance to evaluate given the reported prevalence of marijuana use in the treatment of anxiety symptoms regardless of its legal status in a given jurisdiction.

University of Florida (UF) under contract with FDA. UF epidemiologists identified some data supporting effectiveness of marijuana, including some within their own meta-analysis; however, they ultimately concluded the results are inconclusive or mixed. FDA also conducted a separate review of published scientific reviews. Several of those reviews drew conclusions similar to UF. In contrast, numerous other systematic reviews concluded that there exists some level of evidence supporting the use of marijuana for painful conditions. Other reviews, such as the (National Academies of Sciences & Medicine, 2017), concluded there was “substantial evidence”¹² supporting the use of cannabis products relevant to this review for pain. The Agency for Healthcare Research and Quality’s (AHRQ) living systematic review has concluded that there is some support for the use of marijuana-related products in the treatment of pain, but overall concluded these effects were small and the increased risk of dizziness, nausea, and sedation may limit the benefit.

UF evaluated other therapeutic conditions mentioned above, i.e., anorexia, anxiety, epilepsy, inflammatory bowel disease (IBD), nausea, and PTSD, employing a similar systematic review of scientific and medical literature. UF found that there is low- to moderate-quality evidence¹³ supporting the use of marijuana as medical treatment for outcomes in anorexia, nausea and vomiting, and PTSD. However, FDA review of systematic reviews showed mixed results for these indications. In particular, FDA found that the potential for psychiatric adverse events associated with treating PTSD with marijuana may be more substantial than any limited benefit in observational studies. Although UF did not conclude that there was evidence in support of the effectiveness of marijuana in IBD, both their review and other systematic reviews found some benefit with respect to subjective symptoms in this condition. With regard to epilepsy and anxiety, both UF’s review and FDA’s review of other systematic reviews did not find support for marijuana providing benefit in the treatment of these conditions. Where positive results on effectiveness outcome measures were found, the effects and the quality of evidence were generally in the low-to-moderate range. UF did not find high quality evidence supporting worsening of outcomes in any indication.

None of the evidence from the systematic reviews included in our CAMU Part 2 analysis identified any safety concerns that would preclude the use of marijuana in the indications for which there exists some credible scientific support for its therapeutic benefit. The clinical safety data identified in the literature from controlled trials were generally consistent between sources but limited in the rigor of safety reporting. The vast majority of the observational studies evaluated in the context of medical use were excluded from the final synthesis of evidence due to concerns regarding their quality (only one observational study for the anxiety indication and one for the PTSD indication were included). Generally, data on safety from both clinical trials and observational studies were scarce. Literature shows marijuana has more AEs when compared to a placebo or active control group, however, typically in the mild to moderate severity range. Severe AEs were uncommon.

¹² The term “substantial evidence” refers to language used within the NASEM report (2017) and is not meant to represent “substantial evidence” as defined in 21 USC 355(d).

¹³ UF determined the quality of evidence rating in accordance to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach described in the Cochrane handbook. For further details, please refer to the Section II.4.2.1 in this document.

FDA also reviewed results from state reporting data from 37 states with medical marijuana programs and surveys of patients using marijuana in Maryland and Minnesota, which had data available for review. Surveys of patients using marijuana in these two states found most patients did not report any side effects and those that did report side effects mostly described them as mild. Neither state's databases included patients who chose to stop using marijuana, which may result in an overestimation of positive experiences.

To date, real-world data sources available to FDA, in general, lack the necessary elements to identify the exposure (i.e., marijuana), to distinguish the reason for use (medical vs. recreational) and, if applicable, the condition that prompted its medical use, and/or to permit sound inferential analyses. Therefore, they were not included in this review.

Data from United States national surveys, in general, lacked details on patient characteristics and factors that prompted the use of marijuana for medical purposes, and data collection for these surveys was impacted by the coronavirus disease of 2019 (COVID-19) pandemic. Despite these limitations, these data suggested that medical use of marijuana increases as age increases. Only data from one survey provided information on the intended indication for use, suggesting that individuals often use marijuana to improve or manage conditions such as depression, anxiety, PTSD, pain, headaches or migraines, sleep disorders, nausea and vomiting, lack of appetite, and muscle spasms, but only approximately half of them reportedly had ever asked a healthcare professional for a recommendation to use medical marijuana.

Additionally, although the safety data obtained from use in a medical context are considered to be the most relevant for the CAMU analysis, FDA evaluated the safety of marijuana in the nonmedical setting to inform the potential for more severe outcomes. Specifically, FDA evaluated safety outcomes related to marijuana use in the setting of nonmedical use, use of uncertain intent, and unintentional exposure through a variety of epidemiological data sources and in relation to several comparator substances controlled under the CSA, including drugs in Schedule I: heroin (an illicit opioid drug); Schedule II: hydrocodone and oxycodone (approved opioid prescription drug products), cocaine and fentanyl (largely illicitly produced drugs in the nonmedical use setting, although there are approved prescription drugs); Schedule III: ketamine (an approved prescription drug); and Schedule IV: zolpidem, benzodiazepines, and tramadol (approved prescription drugs) (FDA Office of Surveillance and Epidemiology, 2023). The comparative data demonstrate that, even in the context of nonmedical use, marijuana has a less concerning overall safety profile relative to the comparators for a number of important outcomes (e.g., single substance use overdose death, hospitalizations). However, in young children, population-adjusted rates of ED visits and hospitalizations involving marijuana poisoning were higher than heroin, cocaine, and benzodiazepines for the periods studied. Of note, some of the comparator substances are approved for use in conditions similar to the indications for which marijuana was evaluated in the CAMU analysis (e.g., opioids for pain, benzodiazepines for anxiety-related conditions).

FDA also considered position statements from professional organizations relevant to the indications discussed. The vast majority of professional organizations did not recommend the use of marijuana in their respective specialty; however, none specifically recommended against

it, with the exception of the American Psychiatric Association (APA), which stated that marijuana is known to worsen certain psychiatric conditions.

On balance, the available data indicate that there is some credible scientific support for the use of marijuana in the treatment of pain, anorexia related to a medical condition, and nausea and vomiting, with varying degrees of support and consistency of findings. Additionally, no safety concerns were identified in our review that would indicate that medical use of marijuana poses unacceptably high safety risks for the indications where there is some credible scientific evidence supporting its therapeutic use.

Conclusions of CAMU

Based on the totality of the available data, we conclude that there exists some credible scientific support for the medical use of marijuana in at least one of the indications for which there is widespread current experience in the United States, as identified by OASH under Part 1 of the CAMU test. Seven indications were selected for evaluation under Part 2 of the CAMU test based on conclusions from Part 1 of the CAMU test as well as the FDA's analysis of the landscape of medical use of marijuana. The indications evaluated anorexia related to a medical condition, anxiety, epilepsy, inflammatory bowel disease, nausea and vomiting (e.g., chemotherapy-induced), pain, and post-traumatic stress disorder. The analysis and conclusions on the available data are not meant to imply that safety and effectiveness have been established for marijuana that would support FDA approval of a marijuana drug product for a particular indication. However, the available data do provide some level of support for the way marijuana is being used in clinical practice. Thus, based on the widespread HCP experience and the extent of medical use evaluated by OASH under the Part 1 test, and an evaluation of available credible scientific support described herein for at least some therapeutic uses identified in the Part 1 test, we find that that, for purposes of the drug scheduling criteria in 21 U.S.C. 812(b), marijuana has a CAMU in the United States for: anorexia related to a medical condition; nausea and vomiting (e.g., chemotherapy-induced); and pain.

FACTOR 4. ITS HISTORY AND CURRENT PATTERN OF ABUSE

Under the fourth factor, the Secretary must consider the history and patterns of marijuana use, including in relation to relevant comparator substances that are abused. This factor considers the federal and state-level history of marijuana control, marijuana sources for nonmedical and medical use, marijuana use in the United States since passage of the CSA, and current patterns of use and abuse of marijuana.

Federal History of Marijuana Control

The national history of marijuana in the United States includes its medical and nonmedical use, as well as legislation to control its use. Marijuana (as “an alcoholic extract of the dried tops of *Cannabis sativa*”) was described in the United States Pharmacopoeia as early as 1850 (Brinckmann et al., 2020). With the passage of the Pure Food and Drug Act in 1906, drugs such as marijuana, alcohol, heroin, morphine, and cocaine began to be characterized by the federal

government as “addictive” and/or “dangerous” (Wood, 1985). At that time, these drugs were frequently included in patent medicines, often without the consumer’s knowledge. After the new law was enacted, it required accurate reporting on a drug label about the drug substance and dose contained in the medication. This law, however, did not prohibit the sale or possession of “addictive” and/or “dangerous” drugs, including marijuana. As nonmedical use of marijuana and opioids became more popular in the United States, Congress provided funding in 1929 for two “narcotic farms” in Lexington, Kentucky, and Fort Worth, Texas, which were medical treatment centers run by the Public Health Service (PHS) for federal prisoners who were “habitual users of narcotics,” which included marijuana-derived products (Campbell, 2006). In 1931, the importation of marijuana into the United States began to be restricted under the Pure Food and Drug Act, except for medicinal purposes (Musto, 1972).

In order to further restrict nonmedical use of marijuana, the Federal Bureau of Narcotics campaigned for passage of the Marihuana Tax Act of 1937, which stated that, “Every person who imports, manufactures, produces, compounds, sells, deals in, dispenses, prescribes, administers, or gives away marihuana” would need to be registered and pay specified taxes (Anslinger, 1951). These taxes applied equally to healthcare providers as they did to manufacturers, and were considered extremely high, especially in the middle of the Great Depression. This led the American Medical Association to oppose the Marihuana Tax Act, since it restricted medicinal access to marijuana. During deliberations on the bill, which emphasized that marijuana was a dangerous drug, Dr. Walter L. Treadway of the Division of Mental Health at PHS (the precursor to the National Institute of Mental Health) provided testimony to Congress (Musto, 1972), stating that marijuana:

... does not produce dependence as in opium addiction. In opium addiction there is a complete dependence and when it is withdrawn there is actual physical pain which is not the case with cannabis. Alcohol more nearly produces the same effect as cannabis in that there is an excitement or a general feeling of lifting of personality, followed by a delirious stage, and subsequent narcosis. There is no dependence or increased tolerance such as in opium addiction. ... As with alcohol, it may be taken a relatively long time without social or emotional breakdown. Marihuana is habit forming although not addicting in the same sense as alcohol might be with some people...

Despite these criticisms, the Marihuana Tax Act was passed. Subsequently, the taxes imposed by the Marihuana Tax Act effectively prohibited marijuana use for medical, nonmedical, scientific, or industrial purposes (U.S. Customs and Border Protection, 2019). Five years later, marijuana was removed from the United States Pharmacopoeia in 1942 (Downs, 2016). With the passage of the Boggs Act of 1951, mandatory minimums lengthened the average sentence for first time marijuana offenders to 2 to 5 years, similar to that for opioid offenses, regardless of whether the individual was a nonmedical user or a trafficker (Tallaksen, 2019). The Narcotic Control Act of 1956 increased the minimum sentence for a first offender for marijuana to 2 to 10 years (Courtwright, 2004).

Despite the legal consequences, nonmedical marijuana use increased dramatically in the 1960s, especially among youth (National Academies of Sciences & Medicine, 2017). In 1969, the United States Supreme Court determined that the Marihuana Tax Act was unconstitutional in *Leary v. United States* because the law violated the Fifth Amendment right against self-

incrimination (Carroll, 1969). The following year, in 1970, Congress passed Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, which is commonly known as the CSA. The CSA effectively repealed all previous federal drug laws, including the Marihuana Tax Act, and provided a unified framework for control of drugs with abuse potential. When the CSA was enacted, marijuana was placed into Schedule I, which prohibited use of marijuana for medicinal or nonmedical purposes. This placement was consistent with the criteria established by the CSA under Section 202(b).

State-Level History of Marijuana Control

Changes in state-level marijuana laws in the United States in the modern era began in 1996 with the passage of California's Proposition 215, the Compassionate Use Act. This law legalized the use, possession, and cultivation of marijuana for treatment of patients with cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief, as long as they had a recommendation from their physician. Under the law, marijuana could also be cultivated by patient caregivers.

Since that time, as of August 2023, state-level laws allowing medicinal use of marijuana have been passed in a total of 38 states plus the District of Columbia: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Hawaii, Illinois, Kentucky,¹⁴ Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Utah, Vermont, Virginia, Washington, and West Virginia. Legalization of medical use of marijuana occurred through the action of 20 state legislatures and by 18 ballot measures.

In 2012, state-level legalization of nonmedical use of marijuana occurred for the first time in the United States in Colorado and Washington. Since then, state-level legalization of nonmedical use of marijuana occurred in a total of 23 states and the District of Columbia: Alaska, Arizona, California, Colorado, Connecticut, Delaware, District of Columbia, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nevada, New Jersey, New Mexico, New York, Oregon, Rhode Island, Vermont, Virginia, and Washington. Nonmedical use of marijuana occurred by ballot initiatives in 13 states and by state legislatures in nine states.

Marijuana Sources for Nonmedical and Medical Use

Products containing marijuana or derived from marijuana are generally obtained by the public from four main sources:

- State-authorized adult-use (nonmedical) programs
- State-authorized medical-use programs
- Illicit marketplace – includes unregulated smoke/vape shops, gas stations, convenience stores, marijuana clubs/lounges, person to person sales, and illicit cultivation (see also Factor 5, “National Forensic Laboratory Information System” section)
- Home cultivation for personal use (either legal or illegal under state programs)

¹⁴ When the supporting documents associated with the evaluation under the CAMU test were finalized, Kentucky had not yet legalized medicinal use of marijuana.

Individuals in the United States have access to a wide variety of marijuana and marijuana-derived products for purchase that are diverse in their potency, composition, and forms that dictate use through various routes of administration. The availability of these marijuana products varies across the three main sources above. Marijuana products can generally be categorized as one of four types:

- Flowers – includes dried herb that is smoked or vaped, and pre-rolls
- Concentrates – includes products for inhalation referred to as shatter, wax, butter, sugar, hash, resin, and rosin via vaping (use of an electronic vaporizer) or via dabbing (use of other paraphernalia such as a pipe or “dab rigs”) (Colorado Department of Revenue, 2021; Drug Enforcement Administration, 2023)
- Edibles – includes infused food, beverage, and tincture products (e.g., baked goods, chocolate, drinks, candies, and snacks)
- Topicals – includes infused ointments, lotions, creams, or transdermal products

In the epidemiological data described below, the broad range of products that are marijuana or marijuana-derived may not be identified fully in terms of being from certain product categories or specific/multiple sources or being used by specific routes of administration.

Marijuana Use in the United States Since Passage of the CSA

Since 1970 when the CSA was passed, marijuana use has vacillated over time. As stated in the 2017 NASEM report *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*:

“The prevalence of cannabis use peaked in the late 1970s, when more than one-third of high school seniors (37 percent in 1976) and one in eight Americans over 12 years old (12.8 percent in 1979) reported past-month use (Johnston et al., 2016). Self-reported past-month use declined throughout the 1980s and by 1992 was just one-third of the 1970s peak, both among high school seniors (12.1 percent) and the general population (4.4 percent). The recorded decline in use did not last long. The mid-1990s saw rapid increases, with use by high school seniors nearly doubling within just the 5 years from 1992 (11.9 percent) to 1997 (23.7 percent). Throughout the late 1990s and early 2000s, the rates of use largely stagnated, with trends among youth and the general population moving roughly in parallel (Johnston et al., 2016).

“The years since 2007 have seen steady year-over-year increases in general population past-month use, rising from 5.8 percent to 8.4 percent in 2014 (a 45 percent increase). There is no single clear explanation for the post-2007 increases in use. Hypothesized causes include declining potency-adjusted prices on the illicit market; the proliferation of medical cannabis laws, especially those that allow for sale at brick-and-mortar dispensaries; and changing public perceptions about the harms of cannabis use (Sevigny et al., 2014).”

Gallup Poll data from 1969 to 2013 show a steady increase over time in response to a question regarding whether the respondent had personally tried marijuana (Saad, 2013). In 1969, there was a 4% affirmative response, which increased to 12% by 1973. By 1977, 24% of respondents

affirmed they had used marijuana, which increased to 33% in 1985. After this date, the percent of individuals who affirmed they had used marijuana was stable, with 34% in 1999 and 38% in 2013.

Current Patterns of Use and Abuse of Marijuana

In analyzing current patterns of use and abuse of marijuana and marijuana-derived products, epidemiological databases were analyzed from 2015 to the most recent years of available data (which varies among data sources). A wide variety of epidemiological databases provide necessary data for our analyses. These include the NSDUH, BRFSS, RADARS, NMURx, MTF, YRBSS, and ICPS. A description of each data source and a summary of the data from each source follows below.

These epidemiological evaluations of marijuana use were limited to products containing only botanical marijuana, including various forms of marijuana such as dried leaves rolled into cigarettes or smoked in pipes, edibles (e.g., brownies, cookies, tea), vaping oils, concentrates, and liquid marijuana extract. Cannabis-derived products with less than 0.3% Δ 9-THC (e.g., hemp, FDA-approved cannabidiol oral solution), synthetic cannabinoids that are intended to mimic Δ 9-THC, and marijuana-related FDA-approved drug products [Marinol (dronabinol), Syndros (dronabinol), Epidiolex (cannabidiol), and Cesamet (nabilone)] have been excluded from this analysis to the extent possible, although some respondents on these survey instruments could potentially conflate their use of these excluded products with “marijuana” when responding.

National Survey on Drug Use and Health

NSDUH is an annual, nationally representative, cross-sectional household survey of individuals ages 12 years and older that provides information on the use of drugs and alcohol in the United States (SAMHSA, 2022b). Since 2015, NSDUH has elicited information on any use of a drug (for nonmedical and medical uses combined), as well as on nonmedical use (called “misuse” in the database), of select prescription and illicit drugs in the past year. NSDUH defines misuse of a drug as “use in any way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told.” This definition of “misuse” includes use of a drug with therapeutic intent that is not the result of a recommendation from a health care provider, as well as intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (abuse). As a result of the public-health emergency resulting from the COVID-19 pandemic, NSDUH data collection was disrupted in 2020 and 2021, leading to trend breaks in these years. As a result, it is not possible to interpret trends on use of drugs or other substances from 2019 and years prior with 2020 and 2021 estimates, and it is not possible to combine estimates from 2020 with estimates from 2021.

Past-Year Use of Marijuana for Nonmedical and Medical Uses Combined

Based on NSDUH data, from 2015 to 2019 the past-year use of marijuana for any reason (nonmedical and medical) among people ages 12 years and older increased from 14 to 18%. This is in contrast to past-year use (nonmedical and medical) of comparator drugs that have

FDA-approved therapeutic indications, where use declined or remained relatively stable over the same timeframe, including hydrocodone (22 to 16%), benzodiazepines (12 to 11%, 2017 to 2019 only), oxycodone (11 to 9%), tramadol (7 to 6%), zolpidem (4 to 3%), and ketamine (less than 1%). The decline for hydrocodone was the largest for any comparator drug (~6%), and by 2019, the prevalence of any past-year use of marijuana exceeded that of hydrocodone (18% vs. 16%, respectively). Although there were trend breaks for the years 2020 and 2021, hydrocodone past-year use continued to decrease during these 2 years while marijuana past-year use continued to increase (13% vs. 19%, respectively, in 2021).

Past Year Use of Marijuana for Nonmedical Uses Only

Based on NSDUH data, from 2015 to 2019, the prevalence of past-year nonmedical use of marijuana (i.e., use without an HCP recommendation among people ages 12 years and older) increased. This finding is based on an increase in the prevalence of overall nonmedical use of marijuana from 12 to 15% and on an increase in nonmedical use of marijuana only, without nonmedical use of other drugs that are abused, from 8% to 11% during this period. There was a slight decrease in both categories in 2020, but the prevalence increased again in 2021 (16% and 11%, respectively) to levels that were higher than those reported in 2019.

In contrast, the prevalence of past-year nonmedical use of comparator drugs was less than 3% for each drug, including heroin cocaine oxycodone, hydrocodone, tramadol, benzodiazepines, and zolpidem, which is much less than that for marijuana, either alone or with other drugs. Over the 2015 to 2021 reporting period, the overall use of these comparator drugs declined slightly or remained fairly stable. Notably, the majority of individuals who reported nonmedical use of marijuana did not report nonmedical use of the comparator drugs.

Over the same reporting period of 2015 to 2021, the prevalence of past-year use of alcohol ranged from 62% to 65% for individuals ages 12 years and older, far exceeding the prevalence for marijuana or other comparator drugs.

These data demonstrate that alcohol has the highest prevalence of past-year only use, followed by nonmedical use of marijuana. The prevalence of the other comparators is far below that of alcohol and marijuana.

Prevalence of Past-Year Marijuana Use Without and With a Recommendation from Health Care Provider

The NSDUH data show that most individuals who used marijuana in the past year did not do so based on a recommendation from an HCP (i.e., they were using marijuana for nonmedical purposes). The yearly percentage of individuals who used marijuana but did not have an HCP recommendation ranged from 89% from 2015-2017, decreasing over time to 84% in 2020 and increasing slightly to 86% in 2021. During the same period, exclusive medical use of marijuana that was recommended by an HCP ranged from 7-8% from 2015-2019, increased to 10% in 2020, and decreased to 9% in 2021.

An evaluation of the frequency of past-year marijuana use showed that ~50% of those individuals without an HCP recommendation used marijuana for 60 or fewer days in the year. However, another 29% of those without an HCP recommendation used marijuana for more than 241 days in the year. In contrast, for those individuals whose use of marijuana was sometimes or always recommended by an HCP use, 51% and 55% (respectively) used marijuana at least 241 days in the year.

Prevalence of Past-Month Marijuana Use

The NSDUH data from 2021 show that among individuals who used any marijuana in the past year, 69% used marijuana in the past month, while 81% of those who used marijuana without nonmedical use of other drugs used marijuana in the past month. For comparator drugs, the percentage of individuals with past-year use who used each substance nonmedically in the past month was 76% for alcohol, 49% for heroin, 38% for cocaine, and 28% for ketamine.

Behavioral Risk Factor Surveillance System

BRFSS is a national, state-based, cross-sectional telephone survey by the Centers for Disease Control and Prevention (CDC) (CDC, 2021a, 2021b, 2022). The participants in the 2021 BRFSS module for marijuana included ~68 million individuals 18 years and older, residing in 24 states and territories: Alaska, Connecticut, Delaware, Hawaii, Idaho, Illinois, Indiana, Kentucky, Maine, Maryland, Minnesota, Montana, Nebraska, Nevada, New Hampshire, New York, North Dakota, Ohio, Oklahoma, Rhode Island, Utah, Vermont, Wyoming, and Guam.

The estimated prevalence of past month marijuana use for any reason in the BRFSS survey was 12%, with 88% reporting no marijuana use. Among those with past-month marijuana use, mean frequency of use was 17 days/month, with half of respondents reporting that they used marijuana 20 to 30 days/month. This pattern was consistent across all age categories and sex.

When the reason for use was evaluated, the percentage of individuals who reported use for both medical and nonmedical reasons was 39%, compared to 36% for those who reported use for nonmedical reasons only and 25% for those who reported use for medical reasons only. Those individuals who reported past-month use of marijuana for medical reasons were more likely to be adults 55 years and older, while individuals who reported past-month marijuana use for nonmedical reasons only were more likely to be younger adults aged 18 to 24 years.

Individuals who reported using marijuana in the past 30 days for both nonmedical and medical reasons were more likely (62%) to report marijuana use near daily (20-30 days/month) than individuals who reported marijuana use for nonmedical reasons only (34%). Similarly, individuals who used marijuana for medical reasons only were also more likely (57%) to report near daily use.

Researched Abuse, Diversion and Addiction-Related Surveillance System Survey of Nonmedical Use of Prescription Drugs

The RADARS System conducts the NMURx Program, a serial, cross-sectional, online survey of the general adult population (18 years and older) to elicit information on the nonmedical use of drugs (prescription, nonprescription, unapproved, and illicit) (Black et al., 2019; The Researched Abused, 2023). NMURx estimates represent measures of past-year drug use in an enriched sample of United States adults with higher-than-average nonmedical use of prescription pain relievers and illicit drugs.

Based on NMURx program, past-year use of marijuana was reported by 21% of individuals, while past-year use of comparator substances was substantially lower: benzodiazepines (4%), hydrocodone, oxycodone, tramadol (2% each), cocaine or crack (less than 2%) and illicit fentanyl, heroin, and ketamine (less than 1% each). This pattern of much greater marijuana use compared to other drugs is consistent with the patterns reported in NSDUH and BRFSS.

Monitoring the Future

MTF collects information on the use of selected prescription and illicit drugs and alcohol by conducting an annual, nationally representative, cross-sectional survey of 8th, 10th, and 12th graders in public and private schools (Miech et al., 2022; Miech et al., 2023). As a result of the COVID-19 pandemic, there is a potential trend break in the 2020 MTF data.

MTF data show that during the years 2012 to 2022, the illicit drug most frequently used by 12th grade students who reported past-year drug use was marijuana/hashish (~35% per year from 2012 to 2020, with a reduction to ~30% per year in 2021 and 2022). In contrast, in 2022, alcohol was used by 52% of 12th grade students within the last 12 months, similar to percentages in 2019 and 2020 (52% and 55%, respectively), but higher than the 2021 level of 47%. All other comparator drugs (hydrocodone, heroin, tramadol, cocaine, ketamine, and zolpidem) were each used in the past year by fewer than 5% of 12th graders from 2012 to 2022.

MTF data for past-month use showed a similar pattern. During the years 2012-2022, the illicit drug most frequently used by 12th grade students who reported past-month drug use was marijuana/hashish (~20-22% per year) compared to past-month use of cocaine (~1% per year) or heroin (less than 0.5% per year). However, past-month alcohol use by 12th grade students (28%) exceeded that of marijuana in 2022. MTF does not provide past-month use data for hydrocodone, heroin, tramadol, ketamine, or zolpidem.

MTF data show that for those 12th graders who used marijuana, cocaine or heroin in the past month, daily use of marijuana ranged from ~6-7%, compared to daily use of cocaine or heroin that was less than 1%. MTF does not provide past-month use data for hydrocodone, tramadol, ketamine, or zolpidem.

Youth Risk Behavior Surveillance System

YRBSS was established by the CDC and conducts school-based surveys every 2 years, in partnership with state, local, territorial, and tribal governments, with a focus on youth health behavior in the United States. The YRBSS high school component, the Youth Risk Behavior Survey, includes a nationally representative survey of 9th through 12th grade students (CDC, 2020, 2023; Underwood et al., 2020).

YRBSS data show that from 2009 to 2019, ~ 20% of students in 9th-12th grade reported using marijuana at least once in the past month during each year evaluated. When students 17 years and older were asked how old they were when they first used marijuana, 43% reported they initiated use between the ages of 15 to 16 years, 25% initiated use between 13 to 14 years, and 13% initiated use at 12 years of age and younger.

In contrast, past-month alcohol use by high school students (29%) in 2019 was greater than that of marijuana use, while past month prescription opioid misuse (including codeine, hydrocodone, or oxycodone) (7%) in 2019 was much lower than that of both alcohol and marijuana use.

International Cannabis Policy Study

ICPS conducted serial, cross-sectional surveys in 2019 to 2021 of individuals ages 16 to 65 years living in the United States to understand the public health impact of marijuana legalization (Hammond et al., 2022; ICPS, 2023). The present evaluation focused on respondents who reported at least some past-year marijuana nonmedical use (by indicating that they were not a medical marijuana user, defined as someone who uses marijuana only to treat a medical condition).

ICPS data show that the prevalence of past-year nonmedical use of marijuana ranged from 18% to 22% of individuals surveyed from 2019 to 2021, while the prevalence of past-month nonmedical use was lower, ranging from 12% to 14% of individuals surveyed. Individuals 26 to 34 years had the highest relative prevalence of nonmedical marijuana use, with 26% reporting past-year use and 18% reporting past-month use. This prevalence was higher than that of individuals ages 16-17, 18-25, and 35-64 years, where past-year use was 19-23% while past-month use was 12-13%.

When those individuals who reported past-year marijuana use in 2021 in ICPS were asked why they used the drug, 33% reported use for medical reasons, while 61% responded “no” to the question about past-year medical use and were classified as using marijuana for nonmedical reasons only. The percentages do not sum to 100% because of nonresponse.

When frequency of nonmedical use of marijuana was evaluated in ICPS for those individuals who used marijuana nonmedically at least once a year, individuals 16-17 years had the highest percentage of use less than once a month (~40%) compared to other age cohorts (~25-31%), while individuals 26-34 years had the highest percentage of daily use (~43%) compared to individuals in other adult cohorts (~34-37%) and to individuals 16-17 years (~24%).

Among individuals who nonmedically used marijuana in the past year, 49% never used alcohol and marijuana at the same time, while 35% sometimes used the two substances together, 9% often used them together, and 5% used alcohol every time they used marijuana.

Conclusions

When data on marijuana use from epidemiological databases are evaluated together, certain conclusions can be drawn about its current pattern of abuse.

From 2015 to 2019, NSDUH data show that the prevalence of past-year use of alcohol was 5-6 times greater than nonmedical use of marijuana. In contrast, the prevalence of past-year nonmedical use of heroin, cocaine, oxycodone, hydrocodone, tramadol, benzodiazepines, and zolpidem was 4-5 times less than that for marijuana nonmedical use. Similar past-year comparative drug use data were reported in RADARS-NMURx, in MTF, and in ICPS.

In NSDUH, among people with past-year marijuana use, approximately half of individuals reported nonmedical marijuana use an average of less than 5 days/month while another 30% reported nonmedical marijuana use for an average of more than 20 days/month. In the BRFSS population of people with past-30-day marijuana use, near-daily use was more likely if the individual was using marijuana for medical reasons in BRFSS data; however, medical-only use was less common (25% for medical use compared to 39% for medical and nonmedical use, and 36% for nonmedical use only). In NSDUH, past-month frequency of marijuana nonmedical use is less than what was reported in BRFSS for frequency of marijuana use for any reason (the mean frequency of use was 17 days and half of respondents reported that they used marijuana for any reason more than 20 days/month). Yet, the NSDUH population was younger (included people ages 12 years and older) and included people who used marijuana in the past year, not just within the past month, like in BRFSS. Additionally, in NSDUH, past-year use of marijuana was predictive of past-month use for 60-80% of respondents, similar to alcohol use (approximately 80% of those who used alcohol in the past year also did so in the past month).

These data show that use of marijuana for medical and nonmedical purposes is extensive in the United States, but that its prevalence of use is less than that of alcohol and significantly more than that of other drugs of abuse that are scheduled under the CSA.

FACTOR 5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

Under the fifth factor, the Secretary must consider the scope, duration, and significance of marijuana abuse, including in relation to relevant comparator substances that are abused. The consequences over time of marijuana abuse compared to the abuse of other substances are described based on data from the NPDS, NSDUH, TEDS, NAVIPPRO, NEDS, and NIS.

Epidemiological Data on Consequences of Marijuana Abuse

National Poison Data System

Data from America's Poison Centers' NPDS provide information on the scope of contacts with a poison center (PC) following marijuana abuse, relative to abuse of selected comparators (AAPCC, 2016; Gummin et al., 2022). (American's Poison Centers' National Poison Data System [NPDS] Data Definitions 2016 defines *moderate effect* as, "[t]he patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms" and defines *major effect* as "[t]he patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.")

In order to quantify the scope and burden of PC cases involving abuse of marijuana and selected comparator drugs, the number of PC abuse cases for a substance (either alone or in combination with another substance) was analyzed for the period of 2015 to 2021. The highest number of PC abuse cases was observed for alcohol (n=56,143), followed by heroin (n=34,083) and by benzodiazepines (n=33,688). The fourth highest number of PC abuse cases was for marijuana (n=22,731), with all other comparators showing even fewer PC abuse cases: cocaine (n=15,196), oxycodone (n=12,683), hydrocodone (n=5,575), illicit fentanyl (n=3,636), tramadol (n=2,965), zolpidem (n=2,348), and ketamine (n=832).

When the PC abuse cases for 2015 to 2021 were analyzed for cases involving a single substance only, the rank order of PC abuse cases by number was the same as the order from all PC abuse cases for substances used alone or in combination with another substance, such that the highest number was still for alcohol (n=24,022), with heroin (n=21,970) and benzodiazepines (n=10,872) in second and third place. The fourth highest number of PC abuse cases for a single substance was still for marijuana (n=10,388), with all other comparators showing even fewer PC abuse cases: oxycodone (n=5,943), cocaine (n=4,242), hydrocodone (n=2,062), tramadol (n=1,398), illicit fentanyl (n=1,233), zolpidem (n=941), and ketamine (n=382).

In order to assess the proportion of PC cases that involve abuse (either alone or in combination with another substance), the number of PC abuse case counts for a substance was divided by the total number of PC cases for that substance, for the period of 2015 to 2021. This calculation showed that abuse cases made up the largest proportion of PC cases that involved illicit fentanyl (72%), heroin (65%), cocaine (41%) and ketamine (40%). The fifth highest percentage was for cases involving marijuana (36%), followed by alcohol (15%), oxycodone (13%), benzodiazepines (8%), hydrocodone (5%), tramadol (4%), and zolpidem (3%).

When a similar calculation was made to assess the prevalence of abuse cases contacting a PC based on adverse consequences associated with a single substance only for the same period, the three substances most likely to lead to a PC call following abuse were heroin (65%), oxycodone (47%), and tramadol (47%). The fourth highest percentage was for marijuana and ketamine (46%), followed by alcohol (43%), zolpidem (40%), hydrocodone (37%), illicit fentanyl (34%), benzodiazepines (32%), and cocaine (28%).

Annual utilization-adjusted abuse case rates were then calculated by dividing the number of PC abuse case counts by the prevalence of past-year use based on NSDUH estimates from people 12 years and older, for the period of 2015 to 2019. There were two calculations for each substance, based on two denominators: one for any past-year use of the substance and one for past-year

nonmedical use of the substance. These utilization-adjusted rates convey the likelihood that use of a drug will result in PC abuse cases when considering how many people use the drug for any reason or for nonmedical reasons.

When utilization-adjusted abuse rates (PC abuse cases per one million people with any past year use for a substance alone or with another substance) were calculated using data from 2015 to 2019, the highest rate was seen for heroin (increasing from 4038 to 7201 cases per one million people). The next highest rates were seen for ketamine (decreasing from 535 to 227 cases per one million people), cocaine (relatively stable at 375 to 389 cases per one million people), and benzodiazepines (relatively stable at 171 to 139 cases per one million people, 2018 to 2019 only), but these rates were considerably lower than the rate for heroin. The rates for marijuana (relatively stable at 75 to 70 cases per one million people) and oxycodone (relatively stable at 60 to 61 cases per one million people) were similar, as were the rates for alcohol (relatively stable at 47 to 41 cases per one million), zolpidem (relatively stable at 46 to 30 cases per one million people), tramadol (relatively stable at 36 to 19 cases per one million people) and hydrocodone (relatively stable at 23 to 13 cases per one million people). A similar pattern of utilization-adjusted abuse rates was seen among cases involving a single substance only during the same time period.

The most common routes of administration for single-substance PC abuse cases from 2015 to 2021 for all substances were primarily through oral ingestion and inhalation/nasal administration, with occasional parenteral administration (including intravenous), depending on the substance. As would be expected, alcohol was almost exclusively used orally by respondents (99%). Benzodiazepines, tramadol, zolpidem and hydrocodone were also nearly always used orally by respondents (97%, 97%, 96%, and 95%, respectively), although each of them also had a small degree of use via inhalation/nasal administration (3%, 2%, 4%, and 4%, respectively). Oxycodone use by respondents was 72% oral, 22% inhalation/nasal, and 4% parenteral. Marijuana was used orally by slightly more than half of respondents (57%) and was also used through inhalation/nasal administration by 41% of respondents. Cocaine and ketamine were both used orally by 37% of respondents, with a similar frequency of use through inhalation/nasal routes (40% and 37%, respectively) and lesser frequency of use through parenteral routes (6% and 12%, respectively). Finally, illicit fentanyl use was 24% oral and 28% through inhalation/nasal use. For those drugs where the route percentages do not add up to 100%, this is attributable to cases involving more than one route of abuse, small percentages observed for other routes of administration, and by large percentages where the route is unknown.

An analysis of medical outcomes, related to exposure based on severity, timing, and assessment of clinical effects, for all single-substance PC abuse cases involving marijuana or comparator drugs show that serious medical outcomes (a combination of moderate effect, major effect, and death) were greatest with illicit fentanyl (81%) and heroin (79%), followed by oxycodone (70%), ketamine (64%), tramadol (62%), cocaine (59%), hydrocodone (44%), marijuana (41%), benzodiazepines (32%), alcohol (31%), and zolpidem (27%). When the death rate was evaluated, the highest rate was for fentanyl (25%). Cocaine, heroin, and alcohol had very low rates (3%, 2%, and 2%, respectively) compared to fentanyl, with all other comparators reporting death rates less than 1% (oxycodone, hydrocodone, tramadol, ketamine, benzodiazepines, zolpidem, marijuana). However, out-of-hospital deaths are under-captured in NPDS so these

death rates cannot be broadly extrapolated to indicate the rate of death from adverse events involving these substances.

National Survey on Drug Use and Health

Data from NSDUH provide nationally representative information on the prevalence of substance use disorder (SUD) in 2021 among individuals aged 12 years or older who reported nonmedical use of marijuana in past year, in comparison to heroin, cocaine, or alcohol use in the past year. Drug-specific data on oxycodone, hydrocodone, fentanyl, tramadol, ketamine, benzodiazepines, and zolpidem were not available in the NSDUH analyses of SUDs. A diagnosis of SUD is made when an individual endorses at least 2 of the 11 criteria for SUD, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (e.g., has at least a mild severity of the SUD). Individuals are classified with a mild SUD if they meet two to three of the criteria, a moderate SUD if they meet four to five of the criteria, and a severe SUD if they meet six or more of the criteria.

NSDUH data show that among individuals with past-year heroin use in 2021, there was an 81% prevalence of meeting the criteria for a heroin SUD (i.e., endorsing at least 2 of the 11 criteria for SUD (according to DSM-V; severity data for heroin not available). In comparison, there was a 30% prevalence of meeting the criteria for marijuana SUD among individuals who used marijuana for nonmedical reasons only, with 17% of individuals with past-year nonmedical only use having a mild SUD, 8% having a moderate SUD, and 5% having a severe SUD. Data were also available on individuals who did not use other drugs illicitly and nonmedically used only marijuana, where there was a slightly lower prevalence of 24% for marijuana SUD, with 15% of individuals with past-year marijuana use having mild SUD, 6% of these having a moderate SUD, and 3% having a severe SUD. There was also a 30% prevalence of meeting criteria for cocaine SUD among individuals who used cocaine in the past year, with 13% of those with past-year cocaine use having a mild SUD, 5% having a moderate SUD, and 12% having a severe SUD. For those individuals who used alcohol in the past year, the prevalence of alcohol SUD was 17%, with 10% of individuals with past-year alcohol use having a mild SUD, 4% having a moderate SUD, and 3% having a severe SUD.

Although the 2021 NSDUH data show that the likelihood of meeting the criteria for a SUD was highest for heroin, followed by marijuana/cocaine, and alcohol, the absolute number of individuals who met criteria for the specific drug SUD had a different rank order. Thus, alcohol had the highest estimated number of individuals who met criteria for its specific SUD (~29,544,000), followed by marijuana (~13,078,000 people with marijuana nonmedical-only use, ~7,454,000 with nonmedical-only use and no nonmedical use of other drugs), cocaine (~1,408,000), and heroin (~894,000) for their specific SUDs.

Treatment Episode Data Set

TEDS is a database run by HHS' Substance Abuse and Mental Health Services Administration (SAMHSA) that presents information on the demographic and substance use characteristics of the annual admissions to treatment for alcohol and drug abuse in facilities that are licensed or certified by the States to provide substance abuse treatment and is required by the States to

provide TEDS client-level data (SAMHSA, 2022c). Since TEDS is based only on reports from these facilities, TEDS data do not represent the total national demand for substance abuse treatment or the prevalence of substance abuse in the general population. Additionally, TEDS is an admissions-based system, not an individual-based one, which means that an individual who is admitted to treatment twice within a given year would be counted as two admissions.

Out of 1.4 million admissions documented in the 2020 TEDS dataset, the most frequently reported primary drug of admission was alcohol (31%, n=442,014 admissions), followed by heroin (21%, n=292,126 admissions), marijuana (10%, n=139,481 admissions), and cocaine (5%, n=71,725 admissions). Other comparator drugs, including oxycodone, benzodiazepines, hydrocodone, ketamine, or tramadol, were each reported as the primary drug in less than 2% of admissions.

Over the reporting period of 2015 to 2020, the proportion of admissions with alcohol reported as the primary drug declined from 33% in 2015 to 30% in 2018 but increased slightly to 31% of admissions in 2019 and 2020. In comparison, the proportion of admissions with heroin reported as the primary drug was relatively stable from 2015 to 2018 (~26% for each year), declined to 23% in 2019 and declined further to 21% of admissions in 2020. The proportion of admissions with marijuana as the primary drug declined each year from 14% in 2015 to a low of 10% in 2020, while the proportion of admissions with cocaine as the primary drug increased slightly during this time from 5% in 2015 to 6% in 2019. During this reporting period, the other comparator drugs, oxycodone, benzodiazepines, hydrocodone, ketamine, and tramadol, were each reported as the primary drug in less than 2% of admissions each year.

In 2020, marijuana and cocaine were most likely to be reported as the secondary drug at admission (25% and 24%, respectively), followed by alcohol (15%), heroin (8%), and benzodiazepines (6%), with all other comparators reported as less than 2%. For tertiary drugs at admission, marijuana (29%) was reported most frequently, followed by cocaine (18%), alcohol (16%), and heroin (5%), with all other comparators reported as less than 2%.

National Addictions Vigilance Intervention and Prevention Program

NAVIPPRO is a surveillance system for substance use and nonmedical use of prescription medication in a convenience sample of adults seeking treatment or being assessed for substance use disorder treatment at participating facilities across the United States. NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV) is a self-administered, computerized, validated clinical assessment tool that collects data on recent drug use behaviors for evaluation and treatment planning at intake (Butler et al., 2001).

From 2020 through 2021, there were a total of 76,249 NAVIPPRO ASI-MV assessments in individuals entering or being assessed for substance use disorder treatment at a center participating in the NAVIPPRO network. The drug most frequently endorsed for past-month use was marijuana (n=20,458; 27%), followed by alcohol (5 or more alcoholic drinks/day, n = 16,388; 22%), heroin (n=9,078; 16%), fentanyl (n=6,186; 8%), hydrocodone (n=3,448; 5%), oxycodone (n=3,186; 4%), cocaine and/or crack (n=5,417; 7%), tramadol (n=543, 1%), and ketamine (n=169; less than 1%).

Nationwide Emergency Department Sample

NEDS is the largest all-payer ED database in the United States, yielding national estimates of hospital-owned ED visits, as developed for HHS' AHRQ (AHRQ, 2022a, 2022c). NEDS is a sample of records from ED visits sourced from the State Emergency Department Databases, which captures discharge information on all ED visits that do not result in hospital admission, and the State Inpatient Databases, which contains information on patients first seen in the ED and then admitted to the same hospital. In 2020, the included sample of ED visits was sourced from 995 hospital-owned ED units and sourced from 41 states, accounting for 85% of the United States population. The unweighted NEDS sample in 2020 contains data from over 28 million ED visits, which resulted in a weighted estimate of 123 million ED visits. In this evaluation, ED visits that noted an alcohol, marijuana or cocaine-related disorder were compared. ED visits may not have been directly due to a specific substance-related disorder, but the patient was recorded as having had an alcohol, marijuana or cocaine-related disorder in the administrative claim associated with their ED visit. (A "substance-related disorder" refers to any one of a set of International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes that indicate abuse, dependence, or unspecified use of a specific substance (i.e., marijuana, cocaine or alcohol) or set of substances (i.e., opioids or stimulants). Since it cannot be determined if the ICD-10 code also included a substance use disorder diagnosis according to the DSM-V criteria, the term "substance-related disorders" is used in this review.

Based on NEDS data, from 2016 to 2020, the highest estimated number of annual ED visits were for an alcohol-related disorder, which rose slightly over this reporting period from ~4 million to ~4.1 million, with ~3.2 million estimated annual ED visits each year during this period that involved alcohol as a single substance. Over the 2016 to 2020 timeframe, estimated annual ED visits involving a marijuana related disorder increased from approximately 1.3 million to over 1.7 million, with the estimated annual ED visits for single substance marijuana increasing from 757,731 to 1.08 million. For cocaine, the estimated annual ED visits involving a cocaine-related disorder increased from 599,165 in 2016 to 774,737 in 2018, then declined to 664,641 in 2020, with the estimated annual ED visits for single-substance cocaine-related disorder ranging from 204,257 in 2016 to 225,566 in 2020, with an increase in estimated annual ED visits for 2017 to 2019 ranging from 261,155 to 266,614.

A utilization-adjusted rate of estimated ED visits was then calculated by dividing the estimated annual ED visits for each substance as reported in NEDS by the number of individuals reporting any past-year use of that substance as reported in NSDUH. The highest utilization-adjusted rate of estimated ED visits was observed for cocaine-related disorder, which ranged from 2016 to 2020 from 11,765 to 14,014 per 100,000 individuals, with the annual rate of single-substance ED visits ranging from 4,011 to 4,952 per 100,000 individuals. Marijuana had the second-highest utilization-adjusted rate of estimated ED visits from 2016 to 2020, where the rates for marijuana related disorder ranging from 3,472 to 3,940 per 100,000 individuals (lowest rate in 2016 and highest rate in 2018), with the annual rate of single-substance ED visits ranging from 2,017 to 2,413 per 100,000 individuals. The utilization-adjusted rate of estimated ED visits involving an alcohol disorder, the lowest of the three substances, ranged from 2,225 to 2,327 per 100,000

individuals, and ranged from 1,775 to 1,843 per 100,000 individuals for single-substance ED visits.

National Inpatient Sample

NIS is the largest publicly available all-payer inpatient administrative healthcare database in the United States, sponsored by AHRQ. NIS is a sample of discharges from participating community hospitals, reporting from 46 to 48 states and the District of Columbia per year. NIS data include ~7 million inpatient stays annually (unweighted), accounting for annual estimates of 35 million hospitalizations nationally after weighting (AHRQ, 2021, 2022b). In this evaluation, alcohol, marijuana, and cocaine data were compared.

Based on NIS data, from 2016 to 2020, alcohol-related disorder had the highest estimated annual number of hospitalizations, which was stable at ~1.8 million each year, with ~1.2 to 1.25 million estimated annual hospitalizations that involved alcohol-related disorder per year for single-substance alcohol. Marijuana-related disorder had the second-highest estimated annual number of hospitalizations, increasing from 795,140 in 2016 to 914,810 in 2020, with estimated annual hospitalizations that involved marijuana-related disorder per year for single-substance marijuana increasing from 373,160 to 452,985. The lowest estimated annual number of hospitalizations among these three substances was related to cocaine-related disorder, which ranged from 387,385 to 453,955 from 2016 to 2020, with estimated annual hospitalizations per year for single-substance cocaine increasing from 94,695 to 112,725, with the highest rates observed in 2018.

A utilization-adjusted rate of estimated hospitalizations was then calculated by dividing estimated annual number of hospitalizations for each substance as reported in NIS by the number of individuals reporting any past-year use of that substance as reported in NSDUH. The highest utilization-adjusted rate of estimated hospitalizations was observed for cocaine-related disorder, which ranged from 2016 to 2020 from 7,185 to 8,211 per 100,000 individuals with any past-year use, with the annual rate of single-substance hospitalizations ranging from 1,796 to 2,039 per 100,000 individuals. Marijuana-related disorder had the second-highest utilization-adjusted rate of estimated hospitalizations from 2016 to 2020, where the rates for marijuana related disorder ranging from 1,850 to 2,117 per 100,000 individuals, with the annual rate of single-substance hospitalizations ranging from 906 to 1,026 per 100,000 individuals. The utilization-adjusted rate of estimated hospitalizations involving an alcohol-related disorder was the lowest of the three substances, ranging from 987 to 1,039 per 100,000 individuals and ranging from 675 to 715 per 100,000 individuals for single-substance hospitalizations.

National Forensic Laboratory Information System

The National Forensic Laboratory Information System (NFLIS) is a program of the Diversion Control Division of DEA. Data from the NFLIS-Drug system serves as a surveillance resource to monitor drug encounters by law enforcement across the United States (Drug Enforcement Administration). Specifically, the NFLIS-Drug system collects data on drugs seized by law enforcement during a law enforcement investigation, and which are submitted to federal, state, and local forensic laboratories for analysis. Data fields include but are not limited to number of

“reports or exhibits” submitted to the laboratories, number of cases encompassing the exhibits, approximate dates of encounters, approximate location (states) of drug encounters and other drugs found in the encounters. The degree to which these and other fields are completed is dependent upon the individual laboratories.

As indicated above, NFLIS provides data on the number of “reports” or “exhibits,” consisting of drug evidence (e.g., bulk substance, cannabis resin) obtained during a law enforcement investigation (i.e., a drug “case”) that was sent and analyzed by federal, state, and local forensic laboratories. State and local forensic laboratories, and to a certain extent federal laboratories, primarily conduct qualitative analysis of drug exhibits and to a lesser extent quantitative analysis, depending upon goals and requirements of each case.

In NFLIS, a case may result in one or more reports or exhibits and that each exhibit may contain one drug or multiple drugs. Multiple drug exhibits (e.g., reports in combination) may represent exhibits in which drugs are mixed (e.g., mixed powder material) or in which drugs were found separately (e.g., individual drugs packaged separately but found in the same container). When reporting at the case level-data, all drugs identified in a drug-related incident are counted, although a small number of laboratories may choose to assign a single case number to all drugs related to an entire case.

Limitations on the NFLIS-Drug data, as noted by DEA, include that not all drugs encountered by law enforcement are sent for analysis and not all drugs sent to reporting forensic laboratories are tested. Seized drug evidence may not be sent for analysis or some forensic laboratories may have policies to not test submitted samples in drug cases that are dismissed, result in a guilty plea or a plea bargain was reached before samples are submitted for analysis or before being analyzed by the forensic laboratories (Pitts et al., 2023).

Annually and semiannually DEA publishes NFLIS-Drug national report estimates to account for nonreporting laboratories, among other things.¹⁵ An analysis of 2021 national estimates (Drug Enforcement Administration, 2021) for cannabis/THC, as reported in the published literature in comparison to other drugs seizures, is discussed below.¹⁶ The analysis of national estimates data allow us to compare the number of reports by year and reporting trends. In calculating national and regional estimates the DEA uses the National Estimates Based on All Reports approach, which uses all NFLIS-Drug reporting laboratories.

In 2021, there were a total of 1,326,205 drug reports identified by State and local forensic laboratories in the United States. This estimate represents an increase of approximately 3% from the drug reports identified in 2020. Nationally, 61% of all drug reports in NFLIS were identified

¹⁵ Detailed description of methods used in preparing national estimates is provided in the 2017 NFLIS statistical methodology publication found at: <https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-2017-StatMethodology.pdf> (Last accessed July 2023)

¹⁶ This category includes the following substances: Cannabis, Cannabis (All plant material excluding intact plants), Cannabis oil (Concentrated liquid resin extract), Cannabis plant (Intact plant), Cannabis resin (Hashish), Cannabis seed, Cannabis Stems, Concentrated cannabis, Tetrahydrocannabinol (organic) and Tetrahydrocannabinol (THC)-Non-specific (Source: DEA’s Drug and Chemical Evaluation Section Office of Diversion at DEA)

as involving methamphetamine (406,200 reports or 31%), cannabis/THC (167,669 reports or 13%), cocaine (165,162 reports or 12%) or heroin (72,315 reports or 5%).

In 2021, there were 1,027,219 drug-specific cases submitted to and analyzed by state and local laboratories, representing a 2% increase from drug specific cases in 2020. It is noted that although the total NFLIS number of drug reports increased in 2021 from 2020, the total number of cases and drugs reported continues to be noticeably lower than the number reported for the years before the COVID-19 pandemic. Nationally, in 2021, 45% of all drug cases contained one or more reports of methamphetamine, followed by cocaine and cannabis/THC which were identified in 18% and 17% of all drug cases, respectively. Heroin was identified in 8% of all drug cases.

National trends indicate that the number of cannabis/THC reports as well as the number of cases in which cannabis/THC was identified decreased from 2015 through 2021. From 2020 to 2021 the number of cannabis/THC reports decreased from 188,735 to 167,669 (Drug Enforcement Administration). It should be noted that a decrease in the number of reports of cannabis/THC does not necessarily mean that there was a decrease in the number of cannabis/THC encounters, it means that there was a decrease in the number of exhibits submitted by law enforcement for analysis or a decrease in the number of exhibits processed (analyzed) by forensic laboratories.

Conclusions

The most notable conclusion from an evaluation of various epidemiological databases related to the medical outcomes from abuse of selected drugs is that for all measures that were evaluated from 2015 to 2020, the rank order of the comparators in terms of greatest adverse consequence typically places alcohol, heroin, and/or cocaine in the first or immediately subsequent positions, with marijuana in a lower place in the ranking. This pattern was also observed for PC data with regard to serious medical outcomes, including death, where marijuana was in the lowest ranking group. This demonstrates that there is consistency across databases, across substances, and over time, and although abuse of marijuana produces clear evidence of harmful consequences, including substance use disorder, they are relatively less common and less harmful than some other comparator drugs. Additionally, the number of law enforcement encounters with marijuana decreased from 2020 to 2021, at a time when law enforcement encounters were increasing for other scheduled drugs of abuse. However, as noted above in Factor 1a, there are limitations in comparing descriptive data on adverse outcomes across drugs.

FACTOR 6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

Under the sixth factor, the Secretary must consider the risks posed to the public health by marijuana. Previous factors have provided data that contribute to an understanding of this issue. For example, Factor 2 includes a discussion of the typical psychological, behavioral, and physiological effects of marijuana that may impact public health. Factor 4 details the abuse patterns and trends of marijuana use that can affect public health, using data from NSDUH, BRFSS, RADARS-NMURx, MTF, YRBSS, and ICPS. Factor 5 includes a discussion of the risk

to the public health as measured by data from NPDS, NSDUH, TEDS, NAVIPPRO, NEDS, and NIS.

Factor 6 addresses which sectors of the public are most at risk by detailing NSDUH data related to the demographics of United States individuals meeting criteria for marijuana use disorder, TEDS data related to the demographics of admission to treatment centers for marijuana use disorder, NEDS and NIS data on admissions to EDs and hospitals related to a marijuana poisoning, ToxIC Core Registry for intentional and unintentional exposure, and NPDS data describing the risks to youth of unintentional exposure to marijuana. The risks to public health are also detailed through NSDUH data on driving under the influence of marijuana in adults and high school students. Finally, data are provided regarding the risk of serious AEs and death associated with nonmedical use/use of uncertain intent of marijuana as reported to FAERS, CAERS, NVSS-M, DIM, DAWN, FDA's Sentinel Distributed Database System, and CMS.

This review uses sources of data on overdose, healthcare encounters for poisoning, and AEs that do not specify whether the person affected was using marijuana or any of the comparator substances for medical or nonmedical reasons. As a result, overdose death, healthcare encounters for poisoning, and spontaneously reported AEs involving marijuana or other substances are described as "use of uncertain intent" when the intent of use cannot be determined.

Epidemiology of Risk Posed by Marijuana to Public Health

Demographics of Marijuana Use Disorder

NSDUH data from 2021 show that among those individuals with past-year, marijuana nonmedical-only use, the prevalence of meeting criteria for marijuana use disorder is highest for those who are age 12-17 years (44%), even among individuals who used only marijuana for nonmedical reasons (37%). The data also show that as age increases, the prevalence of marijuana use disorder coinciding with nonmedical use of marijuana decreases in a linear fashion, depending on whether nonmedical marijuana use is examined overall or as a single substance: age 18-25 years (39% and 29%, respectively), age 26-34 years (35% and 26%, respectively), age 35-64 years (23% and 20%), and age 65 years or older (13% and 11%). These data suggest that the likelihood of being diagnosed with marijuana use disorder is higher if the individual might have been using other drugs nonmedically in addition to marijuana, compared to only using marijuana for nonmedical reasons.

TEDS admission data from 2020 show that there were 139,481 admissions for substance use disorder treatment where marijuana was the primary drug for admission, which represents 10% of 1.4 million total admissions. Of these admissions for marijuana as the primary drug of admission, 69% of patients were male. An age analysis of the admissions where marijuana was the primary drug for admission shows that the age groups accounting for the highest proportion of admission were ages 35 to 64 years (25%) and 18 to 24 years (24%), followed by the groups for ages 25-29 years (19%), 12 to 17 years (17%), and 30 to 34 years (15%). There were very few admissions for those ages 65 years or older (less than 1%). When a further analysis of the treatment admissions for youth (the 12-17 age group) was conducted compared to other drugs,

the primary drug of admission was marijuana/hashish for the vast majority of admissions (69%), with alcohol as the second most frequent primary drug of admission (9%). The comparator drugs heroin, cocaine, and benzodiazepines were each the primary drug of admission in ~1% of admissions, with the category of “other drugs” as primary drug of admission accounting for 6% of admissions. A primary drug of admission was not reported in 13% of admissions.

Risk of ED Visit and Hospitalization from Marijuana Poisonings

Data from the NEDS and NIS databases for 2016 to 2020 show that marijuana poisonings in the United States resulted in ED visits ranging from 29,050 to 49,357 visits per year and hospitalizations ranging from 12,940 to 18,470 per year. Although most ED visits involving marijuana poisoning were for marijuana as a single substance, most hospitalizations involving marijuana poisoning involved at least one additional substance.

When the NEDS database is evaluated for 2020 numbers of ED visits involving poisoning from a single substance, heroin had the highest number of cases (n = 18,440), followed by benzodiazepines (n = 10,427), marijuana (n = 7,880), alcohol (n = 5,035), and cocaine (n = 2,850). When utilization-adjusted rates of ED visits involving single-substance poisoning were calculated per 100,000 individuals who reported any past-year use in NSDUH in 2020, heroin had the highest rate (n = 8,661), followed by benzodiazepines (n = 961) and cocaine (n = 240). The lowest rates were reported for marijuana (n = 79) and alcohol (n = 10).

An evaluation of NEDS 2020 data regarding the reason for poisoning involved in an ED visit with each comparator shows that accidental/unintentional poisoning was the most frequently reported reason for cocaine (n=29,563), heroin (n=108,862), benzodiazepines (n=42,339), alcohol (n=25,791), and marijuana (n=32,914). However, for benzodiazepines, poisoning classified as adverse effects of the drug (n=27,404) was often reported, along with very high numbers also reported for intentional/self-harm (n=37,389). Also, for alcohol, intentional/self-harm was also reported at a relatively high number (n=7,808). For cocaine, heroin, and marijuana, poisonings classified as intentional/self-harm, assault, and undetermined intent occurred in fewer cases (n=less than 5,000 for each substance and respective intent).

When the NIS database is evaluated for 2020 estimated numbers of hospitalizations involving poisoning from a single substance, benzodiazepines had the highest estimated number of hospitalizations as a single substance (n=19,420), followed by alcohol (n=7,380), heroin (n=7,085), cocaine (n=7,065), and marijuana (n=5,240). When utilization-adjusted rates of hospitalizations involving single-substance poisoning were calculated per 100,000 individuals who reported any past-year use in NSDUH in 2020, heroin had the highest rate (757 hospitalizations per 100,000 individuals), followed by cocaine (145 hospitalizations per 100,000 individuals), and benzodiazepines (73 hospitalizations per 100,000 individuals). The lowest rates were reported for marijuana (11 hospitalizations per 100,000 individuals) and alcohol (4 hospitalizations per 100,000 individuals).

The disposition at discharge from hospitalization after single substance drug poisoning was also evaluated, showing that the largest estimated number of hospitalizations for each comparator were “routine” (discharge to home or self-care) for benzodiazepines (n=9,345), alcohol (n=5,020), cocaine (n=4,715), marijuana (n=4,315), and heroin (n=4,140). Transfers to skilled

nursing facility, intermediate care facility was the second most frequent discharge disposition for benzodiazepines (n=5,810) and alcohol (n=955), and the third most frequent discharge disposition for cocaine (n = 630). Discharge to home health care was the third most frequent discharge disposition for marijuana (n=270) and heroin (n=145). Those cases where the individual left the hospital against medical advice were small for benzodiazepines (n = 580) and alcohol (n=690) but were the second most frequent discharge disposition for heroin (n=1,445), cocaine (n=695), and marijuana (n=365). For hospitalizations involving poisoning as a single substance that resulted in death at discharge, the largest numbers were from heroin (n=590) and cocaine (n=550), with smaller numbers for benzodiazepines (n=365) and alcohol (n=135). The number for marijuana could not be calculated because statistics representing fewer than 10 hospitalizations were suppressed. When utilization-adjusted rates per 100,000 individuals who reported any past-year use in NSDUH in 2020 were calculated for hospitalizations involving poisoning as a single substance that resulted in deaths, the highest rates were from heroin (63 hospitalizations per 100,000 individuals) and cocaine (11 hospitalizations per 100,000 individuals), with very small numbers for benzodiazepines (1 hospitalizations per 100,000 individuals) and alcohol (n=less than 1 hospitalizations per 100,000 individuals). Utilization-adjusted rates per 100,000 individuals who reported any past-year use in NSDUH in 2020 could not be calculated for marijuana because statistics representing fewer than 10 hospitalizations were suppressed.

Toxicology Investigators Consortium Core Registry

The ToxIC Core Registry comprises over 50 locations throughout the United States, with several international locations also participating. The majority of active United States medical toxicology practices and accredited medical toxicology fellowship programs are participating locations. All cases entered into the ToxIC Core Registry represent a patient that has been formally evaluated and treated by a medical toxicology physician as part of their medical care at a participating center (American College of Medical Toxicology).

A search of the ToxIC Core Registry from January 1, 2012, to July 31, 2022, yielded 829 single-substance, marijuana-containing product exposure cases. The majority of cases involved individuals ages 19 to 65 (n=277) or 6 years and younger (n=277). Intentional ingestion was described in 427 cases, of which 290 involved misuse/abuse, 17 cases involved therapeutic intent, and 120 cases had no additional information. Unintentional ingestion was described in 342 cases, of which 309 cases were in children aged 13 years or younger.

From the 829 marijuana cases in the ToxIC Core Registry, 575 involved acute exposure and 145 involved chronic exposure. A majority of cases in the ToxIC Core Registry had no major/notable vital sign abnormalities (n=552 (67%)); the most frequently reported vital sign abnormality was tachycardia (n=103). Furthermore, a majority of cases in the ToxIC Core Registry exhibited no toxidrome (n=511 (62%)), whereas the most frequently reported toxidrome was sedative-hypnotic (n=105). Of the 829 marijuana cases, 499 (60%) resulted in admission to a hospital; of the 499 hospital admissions, 202 (40%) were admitted to a critical care unit. An additional 320 cases received medical care in an ED or observation unit and were not hospitalized. Notably, ToxIC Core Registry cases represent patients who were formally evaluated and treated by a medical toxicology physician as part of their care at a participating

medical center. It is possible that patients who had formal toxicologist consultation had a more complicated or severe clinical presentation following cannabis ingestion than usually expected, which could contribute to the high rate of hospital and critical care unit admissions among ToxIC Core Registry cases.

The ToxIC Core Registry had two cases involving marijuana-containing product exposure with an outcome of death. Both fatal cases involved the inhalational route of exposure to a non-pharmaceutical product (a substance other than an approved medication) in the setting of intentional misuse/abuse. One of the two deaths involved acute exposure in a 16-year-old boy who had life support withdrawn. The other death involved chronic exposure in a 21-year-old man with vaping-induced pulmonary injury.

Risks from Unintentional-General Exposure to Marijuana

NPDS data provide information about unintentional-general exposures to a drug, out of the total number of PC cases for that drug during the period of 2015 to 2021. NPDS states that most unintentional exposures in children should be coded as “unintentional-general” (e.g., a child obtaining a drug from a grandparent’s prescription bottle). The highest numbers of unintentional-general exposure cases in relation to total PC cases were for benzodiazepines (n=40,085 out of 440,030) and alcohol (n=22,350 out of 370,118). Marijuana had the third highest number of unintentional-general exposure cases (n=15,301 out of 63,645), with all other comparator cases documenting fewer unintentional-general exposures (hydrocodone (n=10,455 out of 106,934), oxycodone (n=9,769 out of 99,534), tramadol (n=8,453 out of 67,582), zolpidem (n=5,604 out of 71,575), cocaine (n=1,298 out of 37,538), heroin (n=1,066 out of 52,713), illicit fentanyl (n=186 out of 5,085), and ketamine (n=106 out of 2,096)).

When a utilization-adjusted rate for 2021 was calculated by dividing the unintentional-general exposure case data from NPDS by the number of individuals ages 12 years and older with any past-year use from NSDUH, the highest rates of unintentional-general exposure per one million people were observed for benzodiazepines (rate=146 cases per one million people with any past-year use) and heroin (rate=127 cases per one million people with any past-year use), followed by marijuana (rate=98 cases per one million people with any past-year use), zolpidem (rate=66 cases per one million people with any past-year use), ketamine (rate=59 cases per one million people with any past-year use), cocaine (rate=52 cases per one million people with any past-year use), oxycodone (rate=52 cases per one million people with any past-year use), tramadol (rate=46 cases per one million people with any past-year use), hydrocodone (rate=25 cases per one million people with any past-year use), and alcohol (rate=18 cases per one million people with any past-year use).

Marijuana had the highest percent of PC unintentional-general exposure cases as a single substance (92%). Oxycodone, alcohol, hydrocodone, tramadol, zolpidem, and benzodiazepines ranged from 72-76% as the percent of unintentional-general exposure cases to that drug as a single substance, while heroin, fentanyl, ketamine, and cocaine ranged from 54-68% as the percent of unintentional-general exposure cases to that drug as a single substance.

The number of unintentional-general cases in children ≤ 12 years was greater for marijuana (n=12,757) than for most comparator substances (n=27 to 7,731), apart from alcohol (n=14,753) and benzodiazepines (n=30,021). A similar pattern was observed for children < 6 years where the number of unintentional-general cases was greater for marijuana (n=10,636) than for most comparator substances (n=25 to 7,499), apart from alcohol (n=13,971) and benzodiazepines (n=28,962).

Among single-substance unintentional-general exposure cases, ingestion was the predominant exposure route for children 6 years of age or younger, as well as for children aged 6 to 12 years, for marijuana (93% to 97%) and for the other comparators with at least 10 cases (65 to 100%).

Among United States PC cases from 2015 to 2021 involving unintentional-general exposure to marijuana as a single substance by children under 6 years old, the most frequently documented related clinical effects, based on severity, timing, and assessment of clinical effects, were CNS depression (mild/moderate) (82%), vomiting (10%), and tachycardia (10%).

Finally, the ToxIC Core Registry contains cases of unintentional exposure to marijuana-containing products in pediatric patients. Of the 829 ToxIC Core Registry cases involving single-substance, marijuana-containing product exposure with uncertain intent, 342 (41%) involved unintentional ingestion. Of the 342 cases of unintentional ingestion, 309 (90%) were in pediatric patients less than 13 years of age.

Risk of Driving Under the Influence of a Drug

NSDUH data from 2021 were examined to evaluate the prevalence of reported driving under the influence of marijuana, alcohol, cocaine, or heroin over the past year in individuals ages 16 years and older. The prevalence of driving under the influence of a drug when all individuals over the age of 16 are combined was 4% for marijuana and 5% for alcohol, with less than 1% for cocaine and for heroin.

When the NSDUH data are evaluated by age cohorts, the highest prevalence for driving under the influence of marijuana was in individuals who were age 21 to 25 (10%), followed by individuals aged 26-34 (7%), aged 16 to 20 (6%), aged 35 to 64 (3%) and aged 65 and older (1%). An age cohort analysis for alcohol showed the highest prevalence for driving under the influence in individuals aged 21 to 25 (8%), followed by individuals aged 26 to 34 (7%), aged 35 to 64 (6%) and ages 16 to 20 and 65 and older (both 3%).

Additional information about driving under the influence is provided by the YRBSS, which provided data on high school students, aged 16 years and older in 2017 (the year for which comparative data for marijuana and alcohol were available). Among individuals who reported driving in the past month and who also reported using marijuana in the past month, 53% reported driving under the influence of marijuana at least once, 21% of whom did so at least six times in the past month. In contrast, among individuals who reported driving in the past month and who also reported using alcohol in the past month, 16% reported driving under the influence of alcohol.

Adverse Events Associated with Marijuana Use Reported to FDA

FAERS is a database that contains adverse event reports, medication error reports, and product quality complaints submitted to FDA and is designed to support FDA's postmarket safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation (US Food and Drug Administration). The CAERS database contains information on adverse event and product complaint reports submitted to FDA for foods, dietary supplements, and cosmetics (US Food and Drug Administration). Separate from their purpose of supporting the safety of FDA-regulated products, the FAERS and CAERS databases contain voluntary reports involving unapproved products (e.g., marijuana) submitted to FDA directly from healthcare professionals, consumers, and other reporters. FDA does not require that a causal relationship between a product and event be proven; furthermore, reports do not always contain adequate information to assess the causal relationship between an event and a drug/substance. Because FDA does not receive reports for every adverse event or medication error that occurs with a product, FAERS/CAERS data cannot be used to calculate the incidence of an adverse event or medication error in the United States population.

A search of the FAERS and CAERS databases from January 1, 2012, to October 31, 2022, yielded 133 cases describing AEs or quality/labeling complaints involving marijuana-containing products directly reported to FDA. An additional 11 cases had an outcome of death and listed a marijuana-containing product; of these 11 death cases, 2 were attributed to another cause, 8 had insufficient information to assess the causal role of marijuana, and 1 case narrative did not describe an outcome of death (i.e., was likely miscoded). Therefore, the 11 fatal cases were not included in the separate analysis of the 133 cases involving a marijuana-containing product.

From 2012 to 2018, fewer than 10 cases per year involving marijuana were reported to FDA's FAERS/CAERS databases; similarly, in 2020, 2021, and the first 10 months of 2022, between 10 and 20 cases involving marijuana were reported each year. However, in 2019, FDA received 66 cases involving marijuana-containing products; of the 66, a total of 61 involved vape products. Notably, of 84 total cases involving vape products, 61 were received in 2019. The majority of marijuana cases (n=103) involved individuals who were ages 19 to 65 years (n=78) or 13 to 18 years (n=25).

Of 133 marijuana cases in FAERS and CAERS, 92 had one or more serious outcomes, including: hospitalization (n=54), life-threatening (n=28), required medical intervention (n=21), disability (n=15), or other serious outcome (n=35); in addition to the 54 hospitalizations, 17 cases described an ED visit.

Of the 133 marijuana cases in FAERS and CAERS, 127 described an adverse event; 10 or more of these 127 cases were coded with terms describing the following events: difficulty breathing (n=29), cough (n=14), nausea (n=14), seizure (n=13), fever (n=11), chest pain (n=10), loss of consciousness (n=10), respiratory disorder (n=10), and vomiting (n=10).

National Vital Statistics System-Mortality and Drug-Involved Mortality

NVSS-M contains information on United States death certificates that contain a single, underlying cause of death, up to twenty multiple causes, and demographic data. The underlying cause of death indicated the injury intent (e.g., accident, suicide, undetermined) and whether the cause was drug-induced (CDC, 2021c). DIM data consist of NVSS-M data linked to the literal-text fields in the death certificate containing information written by the official certifying the death, including the cause of death, manner, and circumstances. Any drug mentioned in a literal text field is assumed to be involved in the death unless contextual information indicates otherwise (CDC, 2018). DIM data provide information about drug-involved mortality at the level of the active ingredient such that the selected comparators could be evaluated, but the data have not recently been updated.

Over a 10-year period (2012 to 2021) the total number of overdose deaths involving marijuana was much lower than that of most comparators. Fentanyl had the highest total number of overdose deaths (n=258,785) followed by cocaine (n=119,208), heroin (n=118,992), and benzodiazepines (87,581). Alcohol had a much lower number of overdose deaths (n=10,484), with marijuana producing the lowest number of overdose deaths (n=5,957). Polysubstance deaths were common. Overall, 5% or less of overdose deaths involving marijuana and most comparators documented were single substance, with the exception of alcohol (13%).

A slightly different rank order of the comparators was seen when overdose deaths in NVSS-M were evaluated in the same period for single substances: fentanyl had the highest total number of overdose deaths, as a single substance (n=12,843), followed by those for heroin (n=6,078), cocaine (n=2,774), alcohol (n=1,338), and benzodiazepines (n=277), with marijuana producing the lowest number of overdose deaths as a single substance (n=160). When utilization-adjusted single-substance overdose death rates were calculated per 100,000 individuals who reported any past-year use in NSDUH in 2020 (the most recent year for which data on marijuana as a single substance in NVSS-M were not suppressed due to small death counts), the drug with the highest rate is heroin (22.22 deaths per 100,000 people who reported past-year use), followed by cocaine (4.79 deaths per 100,000 people who reported past-year use). The utilization-adjusted single-substance overdose death rates were especially low for benzodiazepines (0.14 deaths per 100,000 people who reported past-year use) and alcohol (0.08 deaths per 100,000 people who reported past-year use), with marijuana producing the lowest rate (0.04 deaths per 100,000 people who reported past-year use). Utilization-adjusted estimates of illicit fentanyl use were not available as past-year use of illicit fentanyl is not captured by NSDUH.

When DIM data from 2017 (the latest year for which data are available for comparators) are evaluated as total overdose deaths and as single-substance overdose deaths, as mentioned in the death certificate literal text as contributing to the death, fentanyl had the highest number of total and single substance overdose deaths (n=27,028 and 6,057, respectively), followed by heroin (n=15,831 and 2,660, respectively) cocaine (n=14,796 and 2,987), and benzodiazepine (n=10,375 and 512, respectively). Oxycodone (n=5,386 and 695, respectively), hydrocodone (n=2,588 and 275, respectively), and tramadol (n=1,078 and 120, respectively) had the next highest total and single substance overdose deaths reported, with zolpidem (n=434 and 13, respectively), marijuana (n=202 and 12, respectively), and ketamine (n=69 and 7, respectively)

showing the lowest rates of overdose deaths. When utilization-adjusted total overdose death rates were calculated for total single substance overdose deaths per 100,000 individuals who reported any past-year use in NSDUH in 2017, heroin had the highest rate (1733 per 100,000 individuals), followed by cocaine (249 per 100,000 individuals), benzodiazepines (179 per 100,000 individuals), oxycodone (142 per 100,000 individuals), tramadol (63 per 100,000 individuals), zolpidem (48 per 100,000 individuals), and hydrocodone (42 per 100,000 individuals). Marijuana had the lowest utilization-adjusted rate (0.5 per 100,000 individuals).

Drug Abuse Warning Network Surveillance System

DAWN is a public health surveillance system administered by SAMHSA that provides nationally representative estimates on ED visits related to recent substance use and misuse by reviewing all electronic health records from the EDs of non-federal, short-stay, general surgical and medical hospitals located in the United States. DAWN uses a hybrid design of sentinel hospital-based surveillance (i.e., large urban hospitals located in counties with high counts and rates of morbidity and mortality due to opioid, cocaine, and stimulant overdose) and probability sample-based surveillance (stratified random sampling method) to select a sample of 53 hospitals as well as a non-probability sample of 13 hospitals that were located in areas highly affected by drug overdoses (SAMHSA, 2022a).

An evaluation of the 2021 estimated number of ED visits in DAWN where the specific drug was a direct cause (e.g., overdose) or a contributing factor (e.g., injury) show a wide range of ED visits between comparator drugs, where alcohol (n = 2,996,516) represents the greatest estimated number of ED visits, followed to a much lesser degree by marijuana (n = 804,285), heroin (n = 506,355), cocaine (n = 342,770), and fentanyl (n = 123,563). The utilization-adjusted rate of 2021 ED visits in DAWN per 100,000 individuals who reported any past-year use in NSDUH in 2020 also show a different rank order between the comparators, where heroin (46,281 ED visits per 100,000 people who reported past-year use) represents the highest rate, followed to a much lesser degree by cocaine (7,119 ED visits per 100,000 people who reported past-year use) and alcohol (1,715 ED visits per 100,000 people who reported past-year use), with marijuana (1,529 ED visits per 100,000 people who reported past-year use) showing the lowest rate. Data for any past-year use of illicit fentanyl were not available in NSDUH.

When an age evaluation was conducted on DAWN data for all ED visits in 2020, the largest estimated total number and percentage of ED visits were reported for individuals aged 26-44 years for all comparators, where alcohol (n=1,213,589; 41%) had the highest numbers, followed to a much lesser degree by marijuana (n=362,250; 45%), heroin (n=290,293; 57%), cocaine (n = 155,858; 46%), and fentanyl (n=77,375; 63%). The total number and percentage of ED visits was second highest for individuals aged 45-64 years for three comparators: alcohol (n=1,168,342; 39%), heroin (n=152,160; 30%), cocaine (n=132,892; 39%), while this age group was third highest for marijuana (n=132,305; 17%) and fentanyl (n=18,127; 15%). For individuals aged 18 -25, this age group was second highest for total number and percentage of ED visits for marijuana (n=215,307; 27%) and fentanyl (n=20,722; 17%) and third highest for alcohol (n=299,951; 10%), heroin (n=40,964; 8%), cocaine (n=32,974; 10%). After adjusting for the U.S. resident population in each age group, the 18- to 25-year-old age group had the highest estimated rate of ED visits involving marijuana (626 ED visits, per 100,000 U.S. resident

population). For each comparator, the population-adjusted rate of ED visits was highest among 26- to 44-year-olds.

When an analysis was conducted on ED visits from the 13 participating hospitals from areas highly affected by drug overdoses between March to December 2021, the highest number of ED visits involved alcohol (n=31,458), with lower numbers for ED visits involving marijuana (n=6,368), cocaine (n=5,440), heroin (n=3,499), and fentanyl (n=3,064). When the proportion of these ED visits were calculated on the basis of single substance (i.e., visits in which the medical record documented only that substance as involved in the adverse event), the proportion was highest for alcohol (78%), followed by heroin (44%), with similar proportions for fentanyl (38%), marijuana (37%), and cocaine (35%).

FDA's Sentinel Distributed Database System

FDA's Sentinel System is an active surveillance system for post-marketing medical product safety that uses administrative claims data from three national health insurers (Aetna, Humana Inc., and Optum) and six regional integrated delivery systems (Health Partners, Kaiser Permanente Colorado, Kaiser Permanente Hawaii, Kaiser Permanente Northwest, Kaiser Permanente Washington, and Marshfield) that contribute to the Sentinel Distributed Database (FDA, 2023a, 2023b, 2023c, 2023d). Administrative billing ICD-10-CM codes as a result of healthcare encounters (inpatient, outpatient/ED visit, or institutional stay) that documented poisoning involving marijuana, cocaine, alcohol, heroin, or benzodiazepines were used for the evaluation.

From April 2016 to June 2022, the greatest number of healthcare encounters (i.e., inpatient, outpatient, ED, or institutional) in the Sentinel Distributed Database were for benzodiazepine poisonings that involved 63,074 encounters in a total of 39,864 unique patients (1.6 encounters per individual). The next highest number of healthcare encounters were 25,272 encounters involving heroin poisonings in a total of 15,707 unique patients (1.6 encounters per individual), 17,961 encounters involving marijuana poisonings in a total of 14,668 unique individuals, representing 1.2 encounters per individual, 15,599 encounters involving alcohol poisonings in a total of 11,891 unique individuals (1.3 encounters per individual), and 9,062 encounters involving cocaine poisonings in a total of 6,382 unique individuals (1.4 encounters per individual).

The Sentinel Distributed Database shows that for encounters involving marijuana poisonings, the mean age of the individuals was 35 years and 53% were male. Individuals with encounters involving marijuana poisoning often had prior encounters with diagnoses of chronic pain (30%), anxiety disorders (27%), depression (20%), nausea (20%), hypertension (17%), marijuana-related disorders (14%), alcohol-related disorders (6%), and opioid-related disorders (5%).

For encounters involving heroin poisonings, the mean age of the individuals was 35 years and 68% were male. Individuals with encounters involving heroin poisonings frequently had prior encounters with a diagnosis of nicotine use/vaping (43%), opioid-related disorders (47%), alcohol-related disorders (20%), marijuana-related disorders (18%), and cocaine-related disorders (15%) as well as of depression (32%), chronic pain (34%), and sleep disorders (18%).

For encounters involving alcohol poisonings, the mean age of the individuals was 40 years and 53% were male. Individuals with encounters involving alcohol poisoning frequently had prior encounters with a diagnosis of anxiety disorder (40%), chronic liver disease (10%), depression (38%), hypertension (28%), nicotine/vaping use (30%), sleep disorders (19%), alcohol-related disorders (37%), marijuana-related disorders (6%), and opioid-related disorders (8%).

For benzodiazepine encounters, the mean age of the individuals was 42 years and, 62% were female. Individuals with encounters involving benzodiazepine poisonings frequently had prior encounters with a diagnosis of chronic pain (48%), anxiety disorders (61%), depression (50%), hypertension (32%), sleep disorders (30%), alcohol-related disorders (15%), and opioid-related disorders (14%).

For cocaine encounters, the mean age was 40 years and 70% were male. Individuals with encounters involving cocaine poisonings had evidence of prior encounters with a diagnosis of nicotine use/vaping (39%), cocaine-related disorders (24%), opioid-related disorders (20%), alcohol-related disorders (19%), marijuana-related disorders (12%) as well as of depression (29%), chronic pain (38%), and sleep disorders (20%).

Individuals with encounters involving marijuana poisoning were slightly younger than those with encounters involving cocaine, alcohol, or benzodiazepine poisoning and similar in age to those with encounters involving heroin poisoning. They appeared to be less likely than individuals with encounters for poisonings involving the selected federally controlled substances or alcohol to have a diagnosis in the 6 months prior to the index event for certain psychiatric conditions (anxiety, depression, psychotic disorders, PTSD, sleep disorders), and non-acute pain. They also were less likely than individuals with encounters for poisonings involving the selected federally controlled substances or alcohol to have a diagnosis of nicotine use/vaping. However, the relatively low frequency of chronic respiratory diseases in this group might represent a biased underestimate of nicotine use/vaping, since tobacco use, which is generally not well captured in claims data, is even less likely to be captured among patients who do not have respiratory diseases. Other substance-related disorders, except for marijuana-related disorders, were also less common among individuals with encounters involving marijuana poisoning than for those with encounters for poisonings involving the selected federally controlled substances or alcohol.

CMS Medicare

Medicare is a national health insurance program administered by the CMS that provides healthcare coverage for people aged 65 years or older, as well as those who qualify because of a disability and/or end-stage renal disease (ESRD) regardless of age (CMS, 2021, 2023). The study populations were comprised of beneficiaries with continuous enrollment in Medicare Fee-For-Service (FFS) or Medicare Advantage (MA) in the 183 days prior to the first day of each calendar year and through the full calendar year or through the date of death (if they died during that year). The populations did not include beneficiaries residing in a nursing home for more than 100 days and those ages 18-64 years with ESRD in the 183 days prior to the index date. Billing codes from the ICD-10-CM were used to define the outcomes of interest as the first calendar-year occurrence of a given medical encounter (outpatient/professional services, ED

visit, or hospitalizations) related to poisoning by or adverse effect of marijuana, cocaine, alcohol, heroin, or benzodiazepines. The main measure of interest was the rate of medical encounters involving poisonings in the relevant study population for a given calendar year.

The study included a total of 63,161,236 unique beneficiaries of Medicare FFS or MA during 2017 to 2021. A total of 26,214 (0.04%) FFS or MA beneficiaries had one or more encounters involving marijuana poisoning, 22,071 (0.03%) had one or more encounters involving cocaine poisoning, 25,657 (0.04%) had one or more encounters involving alcohol poisoning, 201,772 (0.32%) had one or more encounters involving benzodiazepine poisoning, and 36,454 (0.06%) had one or more encounters involving heroin poisoning.

Over half (53.6%) of healthcare encounters involving marijuana poisonings among Medicare FFS beneficiaries and nearly half (47.1%) of such encounters among Medicare MA beneficiaries occurred in individuals ages <65 years. As such, the mean age of Medicare beneficiaries with healthcare encounters involving marijuana poisonings was younger than the overall Medicare population (mean age (SD): 58.8 (16.6) years vs 69.7 (11.8) years in FFS; mean age (SD): 62.3 (14.0) years vs 70.2 (10.2) years in MA). The proportion of African American/Black race was higher among Medicare beneficiaries with healthcare encounters involving marijuana poisonings than among the overall Medicare population (14.7% vs 9.1% in FFS; 19.1% vs 13.0% in MA), as was the proportion of low-income beneficiaries enrolled in both Medicare and Medicaid (46.8% vs 17.6% in FFS; 42.9% vs 20.2% in MA). Also, among Medicare beneficiaries with healthcare encounters involving marijuana poisonings, certain psychiatric and chronic medical conditions were noted in the 6-month period before the encounter of interest to a greater extent than among the overall Medicare population; these conditions included opioid-, nicotine-, alcohol-, marijuana-, and cocaine-related disorders as well as opioid, marijuana, and benzodiazepine poisonings.

Beneficiaries with healthcare encounters involving marijuana poisonings had a similar age as those with alcohol poisonings, were younger than those with benzodiazepine poisonings, and older than those with cocaine and heroin poisonings. Beneficiaries with healthcare encounters involving cocaine and heroin poisonings had a higher proportion of documented cases of opioid, nicotine, alcohol, cocaine, and other substance-related disorders than those with encounters involving marijuana poisonings.

Annual rates per 100,000 beneficiaries of healthcare encounters involving marijuana poisonings in the population ages ≥ 65 years were very low, with the highest rate (7.2 per 100,000 beneficiaries) in 2019 and 2021; for disabled beneficiaries ages <65 years, the highest rate (46.7 per 100,000 beneficiaries) was recorded in 2019.

Annual rates per 100,000 beneficiaries of healthcare encounters involving cocaine poisonings were also very low and ranged from 2.3 to 3.7 per 100,000 beneficiaries ages ≥ 65 years from 2017 to 2021, respectively. For disabled beneficiaries ages <65 years, rates of encounters involving cocaine poisonings appear to follow a downward trend, ranging from 55.7 to 51.5 per 100,000 beneficiaries, with the lowest rate (47.8 per 100,000) in 2020.

Annual rates per 100,000 beneficiaries of healthcare encounters involving alcohol poisonings were also in the same range as rates of marijuana and cocaine poisoning encounters for each of the two populations, with a suggestion of downward trend. During the 2017–2021 study period, rates of alcohol poisoning encounters among beneficiaries ages ≥ 65 years went from 6.8 to 5.4 per 100,000 beneficiaries while rates for the disabled population ages < 65 years ranged from 55.4 to 30.6 per 100,000 beneficiaries.

Similarly, in the disabled population ages < 65 years, annual rates per 100,000 beneficiaries for heroin poisoning encounters showed a downward trend with 115.6 per 100,000 beneficiaries in 2017 and 90.8 per 100,000 in 2021; rates among beneficiaries ages ≥ 65 years ranged from 3.9 to 5.4 per 100,000 beneficiaries.

Finally, annual rates per 100,000 beneficiaries of healthcare encounters for benzodiazepine poisonings showed a substantial decreasing trend with rates going from 71.7 to 46.2 per 100,000 beneficiaries ages ≥ 65 years and from 349.3 to 200.8 per 100,000 beneficiaries in the disabled population ages < 65 years.

Conclusions

The risks to the public health posed by marijuana are low compared to other drugs of abuse (e.g., heroin, cocaine, benzodiazepines), based on an evaluation of various epidemiological databases for ED visits, hospitalizations, unintentional exposures, and most importantly, for overdose deaths. The rank order of the comparators in terms of greatest adverse consequences typically places heroin, benzodiazepines and/or cocaine in the first or immediately subsequent positions, with marijuana in a lower place in the ranking, especially when a utilization adjustment is calculated. For overdose deaths, marijuana is always in the lowest rankings among comparator drugs. These evaluations demonstrate that there is consistency across databases, across substances, and over time and that although abuse of marijuana produces clear evidence of a risk to public health, that risk is relatively lower than that posed by most other comparator drugs. However, as noted above in Factor 1a, there are limitations in comparing descriptive data on adverse outcomes across drugs.

FACTOR 7. ITS PSYCHIC OR PHYSIOLOGIC DEPENDENCE LIABILITY

Under the seventh factor, the Secretary must consider the psychic or physiologic dependence liability of marijuana.

Psychic Dependence

The term “psychic or psychological dependence” has been used to convey a similar state to that of addiction (O'Brien, 1996). For diagnosis purposes, the DSM-V has combined “abuse” and “drug dependence” (i.e., addiction) previously specified in the DSM’s Fourth Edition into a single “substance use disorder,” which may occur in a broad range of severity, from mild to severe (Hasin et al., 2013).

The abuse potential of a drug can be assessed, in part, by evaluating the rewarding effects produced by that drug in humans and animals (Rastegar & Fingerhood, 2020). As described in Factor 2, rodent behavioral studies show that Δ 9-THC (the primary compound in marijuana that is responsible for its abuse potential) produces both self-administration and conditioned place preference. These results demonstrate that Δ 9-THC has rewarding properties that are indicative of abuse potential. As described in Factor 5, there is ample epidemiological evidence that marijuana is self-administered by humans because of its ability to produce rewarding psychological effects, such as euphoria.

In some individuals, extensive use of marijuana can lead to a substance use disorder. In the DSM-5, Cannabis Use Disorder (CUD) shares diagnostic criteria common to substance use disorders for other drugs of abuse. In general, substance use disorders listed in the DSM-5 are defined by an inability to cease drug use despite harmful consequences (American Psychiatric Association, 2013; Connor et al., 2021). Estimates of CUD in regular individuals who use marijuana vary and range from about 10-20% (Connor et al., 2021; Leung et al., 2020). This is similar to data from the United States National Comorbidity Study, which showed that 9% of lifetime cannabis users met the DSM's Third Edition, Revised criteria for dependence at some time in their life, compared to 32% of tobacco users, 23% of opiate users, and 15% of alcohol users (Anthony et al., 1997). The National Epidemiologic Survey on Alcohol and Related Conditions also reported that there was a 9% lifetime cumulative probability of transitioning from marijuana use to dependence, with a higher risk of dependence in individuals with a history of psychiatric or substance dependence comorbidity (Lopez-Quintero et al., 2011). In the United States, data from the 2020 NSDUH show that ~14 million individuals (5.1%) aged 12 or older who use marijuana or other cannabinoid preparations met criteria for CUD.

Individuals who develop a substance use disorder, including CUD, may seek treatment for the disorder. From 2015 to 2020, TEDS documented approximately 10.8 million treatment-episode admissions reported by individuals treated at publicly funded substance use treatment programs. Out of 1.4 million treatment admissions documented by TEDS in 2020, marijuana was reported as the primary substance of abuse in approximately 10% of admissions, making it the third most frequently reported primary substance of abuse, after alcohol (31.2%) and heroin (20.6%). A similar pattern was seen from 2015-2019 for these three substances.

During 2015 to 2020, the proportion of admissions where marijuana was reported as the primary substance of abuse declined each year from 14% in 2015 to 10% in 2020. The data for heroin and alcohol show a similar reduction over time. The proportion of admissions where heroin was reported as the primary substance of abuse was ~26% from 2015-2018, decreasing to 23% in 2019 and further decreasing to 21% in 2020. For admissions where alcohol was reported as the primary substance of abuse, the proportion of admissions for this substance decreased each year from 33% in 2015 to 30% in 2018 before increasing slightly to 31% in 2019 and 2020. In contrast, the proportion of admissions where cocaine was reported as the primary substance of abuse stayed stable from 2015 to 2020 at 5-6% each year, while a similar pattern of stable admission data over time was seen for benzodiazepines (~1% from 2015-2020).

In conclusion, the animal behavioral data show that Δ 9-THC produces rewarding properties that underlie the abuse potential of marijuana. Epidemiological data demonstrate that some

individuals who use marijuana for its rewarding properties go on to develop CUD, which shows that marijuana can produce psychological dependence. Among those individuals who seek treatment for a substance use disorder (psychological dependence) on a drug of abuse, treatment for CUD (psychological dependence on marijuana as the primary substance of abuse) was the third most frequently reported reason for admission for treatment. Thus, marijuana can produce psychic dependence in some individuals who use the drug.

Physical Dependence

Physical dependence is a state of adaptation, manifested by a drug-class specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Although physical dependence is often associated with addiction, it can be produced by repeated administration of drugs both with and without abuse potential.

As described in Factor 2, $\Delta 9$ -THC (the primary compound responsible for the abuse potential of marijuana) is an agonist at CB₁ receptors. When marijuana (or isolated $\Delta 9$ -THC) is administered chronically, there is a down-regulation of CB₁ receptors, which leads to behavioral tolerance (Gonzalez et al., 2005; Lichtman & Martin, 2005). The underlying mechanism for marijuana withdrawal appears to be the uncoupling and/or desensitization of CB₁ receptors that precedes receptor down-regulation (Breivogel et al., 2003). Abrupt discontinuation of marijuana after prolonged administration produces withdrawal symptoms in rats and in humans that are typically opposite to those that occur with activation of the CB₁ receptor (Budney et al., 2004; Haney et al., 2005). Precipitated withdrawal can also be induced with administration of CB₁ antagonists following chronic administration (Lichtman et al., 2001; Wilson et al., 2006), while administration of CB₁ agonists can attenuate some withdrawal symptoms associated with marijuana discontinuation (Allsop et al., 2014; Haney et al., 2008; Haney et al., 2004; Trigo et al., 2016). These data confirm the importance of the CB₁ receptor in marijuana physical dependence.

The occurrence of withdrawal symptoms in individuals who use marijuana who only use the drug occasionally has not been established (Budney & Hughes, 2006). However, in heavy, chronic individuals who use marijuana, drug discontinuation can lead to a withdrawal syndrome (Budney & Hughes, 2006; Haney et al., 1999). Most marijuana withdrawal symptoms begin within 24-48 hours of drug discontinuation, peak within 2-6 days, and reduce over 1-2 weeks as $\Delta 9$ -THC levels decline (Connor et al., 2021).

The most commonly reported withdrawal symptoms from clinical investigations are sleep difficulties, decreased appetite and weight loss, craving, irritability, anger, anxiety or nervousness, and restlessness (Haney et al., 2008; Haney et al., 2004; Haney et al., 1999; Vandrey et al., 2008). Less commonly reported withdrawal symptoms include depressed mood, sweating, shakiness, physical discomfort, and chills (Budney & Hughes, 2006; Haney et al., 1999). The DSM-V lists symptoms of “cannabis withdrawal” that are similar in scope to those reported in the experimental studies and include: nervousness or anxiety, irritability or aggression, insomnia or unpleasant dreams, depressed mood, decreased appetite or weight loss,

restlessness, abdominal pain, shakiness or tremors, sweating, fever, chills, and headache (American Psychiatric Association, 2013).

The drug label for Marinol, which contains Δ 9-THC (as dronabinol), describes a similar withdrawal syndrome following repeated drug use and discontinuation in Section 9.3 Dependence:

"A withdrawal syndrome was reported after the abrupt discontinuation of dronabinol capsules in subjects receiving dosages of 210 mg per day for 12 to 16 consecutive days. Within 12 hours after discontinuation, subjects manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs, and anorexia. These withdrawal symptoms gradually dissipated over the next 48 hours.

Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol."

Physical dependence may occur in up to 40-50% of individuals who use marijuana on a regular basis (Kesner & Lovinger, 2021). A meta-analysis of 23,518 individuals who frequently used marijuana showed that 47% of subjects reported symptoms of marijuana withdrawal, as evaluated by standardized scales (Bahji et al., 2020). When the data were sorted by various samples, the prevalence of physical dependence was 54% in outpatient samples and 17% in community samples. However, when samples from individuals who were inpatients in drug abuse treatment centers were evaluated, the prevalence of physical dependence was 87%. This is consistent with data showing that 90% of individuals who use marijuana who were diagnosed with CUD also reported marijuana physical dependence (Bonnet & Preuss, 2017). For those individuals with CUD, the severity and duration of withdrawal symptoms associated with marijuana discontinuation are greater than in those who do not have a diagnosis of CUD. This may be a function of individuals with CUD having a more extensive exposure to marijuana (Connor et al., 2021).

The marijuana withdrawal syndrome appears to be relatively mild compared to the withdrawal syndrome associated with alcohol which can include more serious symptoms such as agitation, paranoia, seizures and even death. Multiple studies comparing the withdrawal symptoms associated with marijuana and tobacco (not scheduled in the CSA) demonstrate that the magnitude and time course of the two withdrawal syndromes are similar (Budney et al., 2008; Vandrey et al., 2008; Vandrey et al., 2005). Animal studies have shown that after short-term administration of equianalgesic doses of heroin and Δ 9-THC to monkeys, withdrawal signs were observed after heroin administration but not after Δ 9-THC administration (Ding et al., 2023), further demonstrating the decreased magnitude of withdrawal symptoms associated with marijuana relative to other drug classes.

Conclusions

In conclusion, experimental data and clinical reports demonstrate that chronic, but not acute, use of marijuana can produce both psychic and physical dependence in humans. Epidemiological data provided in greater detail in Factors 4 and 5 provide additional evidence of psychic dependence. The symptoms associated with both kinds of dependence are relatively mild for most individuals, although the severity may be greater with increased exposure to marijuana.

FACTOR 8. WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS ARTICLE

Under the eighth factor, the Secretary must consider whether marijuana is an immediate precursor of a controlled substance. Marijuana is not an immediate precursor of another controlled substance.

III. RECOMMENDATION

Upon consideration of the eight factors determinative of control of a substance (21 U.S.C. 811(c)), FDA recommends that marijuana be rescheduled from Schedule I to Schedule III of the CSA. NIDA concurs with this scheduling recommendation. Marijuana meets the three criteria for placing a substance in Schedule III of the CSA, as set forth under 21 U.S.C. 812(b)(3):

1. Marijuana has a potential for abuse less than the drugs or other substances in Schedules I and II.

Marijuana contains Δ 9-THC (also known as dronabinol when specifically referring to (-)-*trans*- Δ 9-THC stereoisomer), the substance responsible for the abuse potential of marijuana. Δ 9-THC has agonist properties at CB₁ cannabinoid receptors and produces rewarding responses in animals, as evidenced by its ability to produce self-administration and conditioned place preference. When marijuana is administered to humans under experimental conditions, it produces a wide range of positive subjective responses, in addition to certain negative subjective responses. Common responses to marijuana when it is used by individuals for nonmedical purposes include euphoria and other positive subjective responses, as well as perceptual changes, sedative responses, anxiety responses, psychiatric, social, and cognitive changes, and physiological changes.

Epidemiological data from NSDUH show that marijuana is the most frequently abused federally illicit drug in the United States on a past-year and past-month basis among the illicit comparator drugs considered. Although 50% of respondents in NSDUH reported using marijuana nonmedically less than 5 days per month, another 30% reported using it nonmedically for 20 days or more per month.

Despite the high prevalence of nonmedical use of marijuana, an overall evaluation of epidemiological indicators suggests that it does not produce serious outcomes compared to drugs in Schedules I or II. This is especially notable given the availability to marijuana consumers of marijuana and marijuana-derived products that contain extremely high levels of Δ 9-THC. Due to such availability, the epidemiological data described in this evaluation inherently include the outcomes from individuals who use marijuana and marijuana-derived products that have doses of Δ 9-THC that range from low to very high, and yet the data demonstrate that these products overall are producing fewer negative outcomes than drugs in Schedules I or II.

To illustrate this point, when a rank ordering of selected drugs that are abused was compared for various epidemiological measures, it showed that marijuana was among the drugs at the very lowest ranking for: poison control abuse cases, likelihood that any use would lead to a poison control call, accidental/unintentional poisoning, utilization-adjusted rates of unintentional exposure, utilization-adjusted and population-adjusted rates for ED visits and hospitalizations, likelihood of being diagnosed with a serious SUD, deaths reported to poison control centers, and overdose deaths when used with other drugs or as a single substance (as total numbers and when utilization-adjusted). In contrast, comparators such as heroin (Schedule I), oxycodone (Schedule II), and cocaine (Schedule II) typically were in the highest rank ordering on these measures.

For the various epidemiological measures evaluated above, it should be noted that marijuana was also compared to controlled substances in Schedule III (ketamine) and Schedule IV (benzodiazepines, zolpidem, and tramadol), as well as to other Schedule II substances (fentanyl and hydrocodone). The analyses were conducted in this manner to provide a comprehensive assessment of the relative abuse potential of marijuana. However, the rank order of these substances regarding harms does not consistently align with the relative scheduling placement of these drugs in the CSA due to the pharmacological differences between various classes of drugs. There are a number of confounding factors that likely influence the adverse outcomes measured in various epidemiological databases and account for the rank ordering of the drugs evaluated on these measures. For example, each substance has associated with it a different population that abuse that substance, a different prevalence of abuse, and a different profile of severe adverse outcomes in a setting of nonmedical use and abuse. Thus, it is challenging to reconcile the ranking of relative harms associated with the comparators used in this evaluation when the rankings differ across various epidemiological databases, and when these rankings often do not align with the scheduling placement of these comparators under the CSA. To address these challenges, we evaluated the totality of the available data and have concluded that it supports the placement of marijuana in Schedule III. Overall, these data demonstrate that, while marijuana is associated with a high prevalence of abuse, the profile of and propensity for serious outcomes related to that abuse lead to a conclusion that marijuana is most appropriately controlled in Schedule III under the CSA.

2. Marijuana has a currently accepted medical use in treatment in the United States.

HHS utilized a two-part test (referred to in this document as the “CAMU test”) that took into account the current widespread medical use of marijuana under the supervision of licensed HCPs under state-authorized programs to evaluate whether the substance has CAMU in the United States. Under Part 1 of the CAMU test, OASH concluded there is widespread current experience with medical use of marijuana in the United States by licensed HCPs operating in accordance with implemented state-authorized programs, where such medical use is recognized by entities that regulate the practice of medicine under these state jurisdictions. OASH concluded the findings from Part 1 warranted an FDA assessment under Part 2 of the CAMU test to determine if there exists credible scientific support for at least one of the medical conditions for which the Part 1 test is satisfied. Part 2 of the CAMU test was conducted based on systematic reviews of studies investigating the safety and efficacy/effectiveness of marijuana, review of relevant professional societies’ position statements, data from state medical marijuana programs and United States national surveys, and review of the labeling of FDA-approved products relevant to the analysis.

Based on the totality of the available data, there exists some credible scientific support for the medical use of marijuana in at least one of the indications for which there is widespread current experience by HCPs in the United States, as identified by OASH under Part 1 of the CAMU test. Seven indications were selected by FDA for consideration under Part 2 of the CAMU test. These indications included anorexia related to a medical condition, anxiety, epilepsy, inflammatory bowel disease, nausea and vomiting (e.g., chemotherapy-induced), pain, and post-traumatic stress disorder. The analysis of, and conclusions regarding, the available data are not meant to imply that safety and effectiveness have been established for marijuana that would

support FDA approval of marijuana for a particular indication. However, the available data do provide some credible level of scientific support for some of the therapeutic uses for which marijuana is being used in clinical practice in the United States. Thus, based on the widespread HCP experience and the extent of medical use evaluated by OASH under the Part 1 test, and the determination of some credible scientific support for at least some therapeutic uses identified in the Part 1 test, for purposes of the drug scheduling criteria in 21 U.S.C. 812(b), marijuana has a currently accepted medical use in the United States, specifically for the treatment of anorexia related to a medical condition, nausea and vomiting (e.g., chemotherapy-induced), and pain.

Additionally, and considering that marijuana is currently controlled in Schedule I of the CSA, we note that one of the criteria for control in Schedule I as set forth in 21 U.S.C. 812(b)(1) is that “(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.” Based on our evaluation of CAMU, as summarized above, we conclude that there is accepted safety for the use of marijuana under medical supervision for the treatment of anorexia related to a medical condition, nausea and vomiting (e.g., chemotherapy-induced), and pain. Thus, even apart from the findings made herein for the current recommendation for Schedule III, this criterion for control in Schedule I as set forth under 21 U.S.C. 812(b)(1)(C) is not met for marijuana.

3. Abuse of marijuana may lead to moderate or low physical dependence or high psychological dependence.

Clinical studies have demonstrated that marijuana produces physical and psychological dependence. Regarding physical dependence, as evidenced by its associated withdrawal symptomology upon abrupt discontinuation of use, the most commonly reported marijuana withdrawal symptoms in clinical investigations are sleep difficulties, decreased appetite and weight loss, craving, irritability, anger, anxiety or nervousness, and restlessness. Marijuana withdrawal symptoms typically peak within 2-6 days and decline over 1-2 weeks as $\Delta 9$ -THC is eliminated. Similarly, the drug labels for the FDA-approved drug products Marinol and Syndros (both of which contain dronabinol, the (-)-*trans*- $\Delta 9$ -THC stereoisomer) state that following chronic administration of dronabinol, drug discontinuation leads to irritability, insomnia, and restlessness at 12 hours and by 24 hours the withdrawal symptoms can include “hot flashes,” sweating, rhinorrhea, diarrhea, and anorexia.

Notably, marijuana withdrawal syndrome has been reported in individuals with heavy, chronic marijuana use, but its occurrence in occasional individuals who use marijuana has not been established. The marijuana withdrawal syndrome appears to be relatively mild compared to the withdrawal syndrome associated with alcohol, which can include more serious symptoms such as agitation, paranoia, seizures and even death. Multiple studies comparing the withdrawal symptoms associated with marijuana and tobacco demonstrate that the magnitude and time course of the two withdrawal syndromes are similar.

The ability of marijuana to produce psychic dependence is shown through its ability to produce rewarding effects that underlie its nonmedical use and epidemiological outcomes related to abuse, as detailed in the first Finding on abuse potential (above).

Thus, abuse of marijuana may lead to moderate or low physical dependence, depending on frequency and degree of marijuana exposure. It can produce psychic dependence in some individuals, but the likelihood of serious outcomes is low, suggesting that high psychological dependence does not occur in most individuals who use marijuana.

IV. REFERENCES

- AAPCC. (2016). National Poison Data System (NPDS) Data Definitions 2016. In *FDA Internal Document*.
- Abraham, A. D., Leung, E. J. Y., Wong, B. A., Rivera, Z. M. G., Kruse, L. C., Clark, J. J., & Land, B. B. (2020). Orally consumed cannabinoids provide long-lasting relief of allodynia in a mouse model of chronic neuropathic pain. *Neuropsychopharmacology*, 45(7), 1105-1114. <https://doi.org/10.1038/s41386-019-0585-3>
- Adams, I. B., & Martin, B. R. (1996). Cannabis: pharmacology and toxicology in animals and humans. *Addiction*, 91(11), 1585-1614. <https://www.ncbi.nlm.nih.gov/pubmed/8972919>
- Agrawal, A., Madden, P. A., Bucholz, K. K., Heath, A. C., & Lynskey, M. T. (2014). Initial reactions to tobacco and cannabis smoking: a twin study. *Addiction*, 109(4), 663-671. <https://doi.org/10.1111/add.12449>
- Agurell, S. (1984). *The cannabinoids: chemical, pharmacologic, and therapeutic aspects*. Academic Press.
- Agurell, S., Halldin, M., Lindgren, J. E., Ohlsson, A., Widman, M., Gillespie, H., & Hollister, L. (1986). Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev*, 38(1), 21-43. <https://www.ncbi.nlm.nih.gov/pubmed/3012605>
- AHRQ. (2021). *Checklist for Working With the NIS*. Agency for Healthcare Research and Quality. <https://hcup-us.ahrq.gov/db/nation/nis/nischecklist.jsp>
- AHRQ. (2022a). Introduction to the HCUP Nationwide Emergency Department Sample (NEDS) 2020. *Healthcare Cost and Utilization Project (HCUP)*. https://hcup-us.ahrq.gov/db/nation/neds/NEDS_Introduction_2020.jsp
- AHRQ. (2022b). Overview of the National (Nationwide) Inpatient Sample (NIS). *Healthcare Cost and Utilization Project (HCUP)*. <https://hcup-us.ahrq.gov/nisoverview.jsp>
- AHRQ. (2022c). Overview of the Nationwide Emergency Department Sample (NEDS). *Healthcare Cost and Utilization Project (HCUP)*. <https://hcup-us.ahrq.gov/nedsoverview.jsp>
- Allsop, D. J., Copeland, J., Lintzeris, N., Dunlop, A. J., Montebello, M., Sadler, C., Rivas, G. R., Holland, R. M., Muhleisen, P., Norberg, M. M., Booth, J., & McGregor, I. S. (2014). Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry*, 71(3), 281-291. <https://doi.org/10.1001/jamapsychiatry.2013.3947>
- American College of Medical Toxicology. *ToxIC: Toxicology Investigators Consortium*. Retrieved 8-23-23 from <https://www.acmt.net/toxic/>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, fifth edition* (5th ed.). American Psychiatric Association, American Psychiatric Association Arlington, VA, Washington, D.C.
- Anslinger, H. J. (1951). The Federal Narcotic Laws. *Food, Drug, Cosmetic Law Journal*, 6(10), 743-748. <http://www.jstor.org/stable/26654217>
- Anthony, J. C., Warner, L. A., & Kessler, R. C. (1997). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey.
- Appendino, G., Chianese, G., & Taglialatela-Scafati, O. (2011). Cannabinoids: occurrence and medicinal chemistry. *Curr Med Chem*, 18(7), 1085-1099. <https://doi.org/10.2174/092986711794940888>
- Augustin, S. M., & Lovinger, D. M. (2018). Functional Relevance of Endocannabinoid-Dependent Synaptic Plasticity in the Central Nervous System. *ACS Chem Neurosci*, 9(9), 2146-2161. <https://doi.org/10.1021/acchemneuro.7b00508>
- Azorlosa, J. L., Greenwald, M. K., & Stitzer, M. L. (1995). Marijuana smoking: effects of varying puff volume and breathhold duration. *J Pharmacol Exp Ther*, 272(2), 560-569. <https://www.ncbi.nlm.nih.gov/pubmed/7853169>
- 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: a systematic review and meta-analysis. *JAMA network open*, 3(4), e202370-e202370.
- Balster, R. L., & Bigelow, G. E. (2003). Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug Alcohol Depend*, 70(3 Suppl), S13-40. [https://doi.org/10.1016/s0376-8716\(03\)00097-8](https://doi.org/10.1016/s0376-8716(03)00097-8)
- Barann, M., Molderings, G., Brüss, M., Bonisch, H., Urban, B. W., & Gothert, M. (2002). Direct inhibition by cannabinoids of human 5-HT_{3A} receptors: probable involvement of an allosteric modulatory site. *Br J Pharmacol*, 137(5), 589-596. <https://doi.org/10.1038/sj.bjp.0704829>
- Barrus, D. G., Lefever, T. W., & Wiley, J. L. (2018). Evaluation of reinforcing and aversive effects of voluntary Delta(9)-tetrahydrocannabinol ingestion in rats. *Neuropharmacology*, 137, 133-140. <https://doi.org/10.1016/j.neuropharm.2018.04.018>

- Black, J. C., Rockhill, K., Forber, A., Amioka, E., May, K. P., Haynes, C. M., Dasgupta, N., & Dart, R. C. (2019). An Online Survey for Pharmacoepidemiological Investigation (Survey of Non-Medical Use of Prescription Drugs Program): Validation Study. *J Med Internet Res*, 21(10), e15830. <https://doi.org/10.2196/15830>
- Bonini, S. A., Premoli, M., Tambaro, S., Kumar, A., Maccarinelli, G., Memo, M., & Mastinu, A. (2018). Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. *J Ethnopharmacol*, 227, 300-315. <https://doi.org/10.1016/j.jep.2018.09.004>
- Bonnet, U., & Preuss, U. W. (2017). The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil*, 8, 9-37. <https://doi.org/10.2147/SAR.S109576>
- Bouaboula, M., Rinaldi, M., Carayon, P., Carillon, C., Delpech, B., Shire, D., Le Fur, G., & Casellas, P. (1993). Cannabinoid-receptor expression in human leukocytes. *Eur J Biochem*, 214(1), 173-180. <https://doi.org/10.1111/j.1432-1033.1993.tb17910.x>
- Braida, D., Iosue, S., Pegorini, S., & Sala, M. (2004). Delta9-tetrahydrocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. *Eur J Pharmacol*, 506(1), 63-69. <https://doi.org/10.1016/j.ejphar.2004.10.043>
- Braida, D., Pozzi, M., Parolaro, D., & Sala, M. (2001). Intracerebral self-administration of the cannabinoid receptor agonist CP 55,940 in the rat: interaction with the opioid system. *Eur J Pharmacol*, 413(2-3), 227-234. [https://doi.org/10.1016/s0014-2999\(01\)00766-x](https://doi.org/10.1016/s0014-2999(01)00766-x)
- Breivogel, C. S., Scates, S. M., Beletskaya, I. O., Lowery, O. B., Aceto, M. D., & Martin, B. R. (2003). The effects of delta9-tetrahydrocannabinol physical dependence on brain cannabinoid receptors. *Eur J Pharmacol*, 459(2-3), 139-150. [https://doi.org/10.1016/s0014-2999\(02\)02854-6](https://doi.org/10.1016/s0014-2999(02)02854-6)
- Breivogel, C. S., & Sim-Selley, L. J. (2009). Basic neuroanatomy and neuropharmacology of cannabinoids. *International Review of Psychiatry*, 21(2), 113-121.
- Brenneisen, R. (2007). Chemistry and analysis of phytocannabinoids and other Cannabis constituents. In *Marijuana and the Cannabinoids* (pp. 17-49). Springer.
- Brinckmann, J., Marles, R., Schiff, P., Oketch-Rabah, H., Tirumalai, G., Giancaspro, G., & Sarmab, N. (2020). Quality standards for botanicals-legacy of USP's 200 years of contributions. *HerbalGram*, 126, 50-65.
- Budney, A. J., & Hughes, J. R. (2006). The cannabis withdrawal syndrome. *Curr Opin Psychiatry*, 19(3), 233-238. <https://doi.org/10.1097/01.yco.0000218592.00689.e5>
- Budney, A. J., Hughes, J. R., Moore, B. A., & Vandrey, R. (2004). Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*, 161(11), 1967-1977. <https://doi.org/10.1176/appi.ajp.161.11.1967>
- Budney, A. J., Vandrey, R. G., Hughes, J. R., Thostenson, J. D., & Bursac, Z. (2008). Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. *J Subst Abuse Treat*, 35(4), 362-368. <https://doi.org/10.1016/j.jsat.2008.01.002>
- Busquets-Garcia, A., Bains, J., & Marsicano, G. (2018). CB(1) Receptor Signaling in the Brain: Extracting Specificity from Ubiquity. *Neuropsychopharmacology*, 43(1), 4-20. <https://doi.org/10.1038/npp.2017.206>
- Butler, S. F., Budman, S. H., Goldman, R. J., Newman, F. L., Beckley, K. E., Trotter, D., & Cacciola, J. S. (2001). Initial validation of a computer-administered Addiction Severity Index: the ASI-MV. *Psychol Addict Behav*, 15(1), 4-12. <https://doi.org/10.1037/0893-164x.15.1.4>
- Campbell, N. D. (2006). "A new deal for the drug addict": The Addiction Research Center, Lexington, Kentucky. *Journal of the History of the Behavioral Sciences*, 42(2), 135-157.
- Carroll, J. (1969). Constitutional Law-Federal Marijuana Statutes-An Empirical Appraisal of Criminal Statutory Presumptions-Leary v. United States, 395 US 6 (1969). *DePaul Law Review*, 19(1), 184.
- Castane, A., Robledo, P., Matifas, A., Kieffer, B. L., & Maldonado, R. (2003). Cannabinoid withdrawal syndrome is reduced in double mu and delta opioid receptor knockout mice. *Eur J Neurosci*, 17(1), 155-159. <https://doi.org/10.1046/j.1460-9568.2003.02409.x>
- CDC. (2018). *Drug-Involved Mortality Restricted Data*. Centers for Disease Control and Prevention (CDC): National Center for Health Statistics (NCHS), Research Data Center (RDC). <https://www.cdc.gov/rdc/b1datatype/datafiles/Drug-Involved-Mortality-Data-Documentation.pdf>
- CDC. (2020). *2019 YRBS National, State and District Combined User's Data Guide* Centers for Disease Control and Prevention. https://www.cdc.gov/healthyyouth/data/yrbs/pdf/2019/2019_YRBS_SADC_Documentation.pdf
- CDC. (2021a). *Behavioral Risk Factor Surveillance System Survey Overview BRFSS: 2021*. U.S. Department of Health and Human Services (HHS): Centers for Disease Control and Prevention (CDC). Retrieved July 22 from https://www.cdc.gov/brfss/annual_data/annual_2021.html
- CDC. (2021b). *Behavioral Risk Factor Surveillance System Survey Overview BRFSS: Calculated Variables*. U.S. Department of Health and Human Services (HHS): Centers for Disease Control and Prevention (CDC).

- Retrieved July 22 from https://www.cdc.gov/brfss/annual_data/2021/pdf/2021-calculated-variables-version4-508.pdf
- CDC. (2021c). *Mortality Multiple Cause Files 1994-2021*. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), Division of Vital Statistics. Retrieved March from https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm#Mortality_Multiple
- CDC. (2022). *2021 Summary Data Quality Report August 9, 2022*. U.S. Department of Health and Human Services (HHS): Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/brfss/annual_data/2021/pdf/2021-DQR-508.pdf
- CDC. (2023). *Youth Risk Behavior Survey. Data Summary & Trends Report, 2011-2013*. Centers for Disease Control and Prevention. Retrieved April 19 from https://www.cdc.gov/healthyyouth/data/yrbs/yrbs_data_summary_and_trends.htm
- Cerne, K. (2020). Toxicological properties of Delta9-tetrahydrocannabinol and cannabidiol. *Arh Hig Rada Toksikol*, 71(1), 1-11. <https://doi.org/10.2478/aiht-2020-71-3301>
- Chaachouay, N., Azeroual, A., Bencharki, B., Douira, A., & Zidane, L. (2023). Cannabis sativa L.: A Review on Traditional Uses, Botany, Phytochemistry, and Pharmacological Aspects. *Traditional and Integrative Medicine*, 97-116.
- Cheer, J. F., Kendall, D. A., & Marsden, C. A. (2000). Cannabinoid receptors and reward in the rat: a conditioned place preference study. *Psychopharmacology (Berl)*, 151(1), 25-30. <https://doi.org/10.1007/s002130000481>
- Clarke, R. C., & Watson, D. P. (2007). Cannabis and natural cannabis medicines. In *Marijuana and the Cannabinoids* (pp. 1-15). Springer.
- CMS. (2021). *Medicare Program - General Information*. Centers for Medicare and Medicaid Services (CMS) Retrieved April 20 from <https://www.cms.gov/medicare/medicare-general-information/medicaregeninfo>
- CMS. (2023). *Quality Measures*. Centers for Medicare and Medicaid Services (CMS) Retrieved May 8 from <https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/NursingHomeQualityInits/NHQIQualityMeasures>
- Colorado Department of Revenue, M. E. D. (2021). *Use of Regulated Marijuana Concentrate*. <https://sbg.colorado.gov/sites/sbg/files/211101%20MED%20Educational%20Resource.pdf>
- Connor, J. P., Stjepanovic, D., Le Foll, B., Hoch, E., Budney, A. J., & Hall, W. D. (2021). Cannabis use and cannabis use disorder. *Nat Rev Dis Primers*, 7(1), 16. <https://doi.org/10.1038/s41572-021-00247-4>
- Courtwright, D. T. (2004). The Controlled Substances Act: how a "big tent" reform became a punitive drug law. *Drug Alcohol Depend*, 76(1), 9-15. <https://doi.org/10.1016/j.drugalcdep.2004.04.012>
- De Petrocellis, L., & Di Marzo, V. (2009). An introduction to the endocannabinoid system: from the early to the latest concepts. *Best Pract Res Clin Endocrinol Metab*, 23(1), 1-15. <https://doi.org/10.1016/j.beem.2008.10.013>
- Devane, W. A., Dysarz, F. A., 3rd, Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol*, 34(5), 605-613. <https://www.ncbi.nlm.nih.gov/pubmed/2848184>
- Dewey, W., Martin, B., & May, E. (1984). Cannabinoid stereoisomers: pharmacological effects. *CRC Handbook of stereoisomers: drugs in psychopharmacology*, 317-326.
- Di Marzo, V. (2006). A brief history of cannabinoid and endocannabinoid pharmacology as inspired by the work of British scientists. *Trends Pharmacol Sci*, 27(3), 134-140. <https://doi.org/10.1016/j.tips.2006.01.010>
- Ding, H., Kiguchi, N., Mabry, K. M., Kishioka, S., & Ko, M. C. (2023). Functional consequences of short-term exposure to opioids versus cannabinoids in nonhuman primates. *Neuropharmacology*, 223, 109328. <https://doi.org/10.1016/j.neuropharm.2022.109328>
- Downs, D. (2016). The science behind the DEA's long war on marijuana. *Scientific American*, 19.
- Drug Enforcement Administration. *National Forensic Laboratory Information System*. <https://www.nflis.deadiversion.usdoj.gov/>
- Drug Enforcement Administration. (2021). National Forensic Laboratory Information System: NFLIS -Drug 2021 Report. <https://www.nflis.deadiversion.usdoj.gov/publicationsRedesign.xhtml> (Accessed on July, 2023).
- Drug Enforcement Administration. (2023). *DEA Drug Fact Sheet: Vaping and Marijuana Concentrates* Retrieved 07/27/2023 from <https://www.dea.gov/sites/default/files/2020-06/Vaping%20and%20Marijuana%20Concentrates-2020.pdf>
- Earleywine, M. (2002). *Understanding marijuana: A new look at the scientific evidence*. Oxford University Press.
- Eldeeb, K., Wittmann, T. G., Leone-Kabler, S., & Howlett, A. C. (2020). The CB1 cannabinoid receptor-mediated inhibition of cAMP accumulation in neuroblastoma cells: role of different Gi/o protein subtypes. *The FASEB Journal*, 34(S1), 1-1.

- ElSohly, M. A. (2007). *Marijuana and the Cannabinoids*. Springer Science & Business Media.
- ElSohly, M. A., Chandra, S., Radwan, M., Majumdar, C. G., & Church, J. C. (2021). A Comprehensive Review of Cannabis Potency in the United States in the Last Decade. *Biol Psychiatry Cogn Neurosci Neuroimaging*, 6(6), 603-606. <https://doi.org/10.1016/j.bpsc.2020.12.016>
- ElSohly, M. A., Radwan, M. M., Gul, W., Chandra, S., & Galal, A. (2017). Phytochemistry of Cannabis sativa L. *Phytocannabinoids: unraveling the complex chemistry and pharmacology of Cannabis sativa*, 1-36.
- Elsohly, M. A., & Slade, D. (2005). Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci*, 78(5), 539-548. <https://doi.org/10.1016/j.lfs.2005.09.011>
- Epidiolex drug label. (2022). HIGHLIGHTS OF PRESCRIBING INFORMATION for Epidiolex. In.
- FDA. (2023a). *About the Food and Drug Administration (FDA) Sentinel Initiative: Active Postmarket Risk Identification and Analysis (ARIA) System*. Food and Drug Administration (FDA)'s Sentinel Initiative. Retrieved April 5 from <https://www.sentinelinitiative.org/about>
- FDA. (2023b). *How Sentinel Gets Its Data*. Food and Drug Administration (FDA)'s Sentinel Initiative. Retrieved April from <https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data>
- FDA. (2023c). *Sentinel Common Data Model*. Food and Drug Administration (FDA)'s Sentinel Initiative. Retrieved April 5 from <https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model>
- FDA. (2023d). *Sentinel Routine Querying System Overview*. Food and Drug Administration (FDA)'s Sentinel Initiative. <https://dev.sentinel-system.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse>
- FDA Office of Surveillance and Epidemiology. (2023). *Office of Surveillance and Epidemiology Review Describing Prevalence and Patterns of Marijuana Nonmedical Use or Marijuana Use of Uncertain Intent and Associated Harms*.
- Fogel, J. S., Kelly, T. H., Westgate, P. M., & Lile, J. A. (2017). Sex differences in the subjective effects of oral Delta(9)-THC in cannabis users. *Pharmacol Biochem Behav*, 152, 44-51. <https://doi.org/10.1016/j.pbb.2016.01.007>
- Foltin, R. W., Fischman, M. W., Pedrosa, J. J., & Pearlson, G. D. (1987). Marijuana and cocaine interactions in humans: cardiovascular consequences. *Pharmacol Biochem Behav*, 28(4), 459-464. [https://doi.org/10.1016/0091-3057\(87\)90506-5](https://doi.org/10.1016/0091-3057(87)90506-5)
- Freels, T. G., Baxter-Potter, L. N., Lugo, J. M., Glodosky, N. C., Wright, H. R., Baglot, S. L., Petrie, G. N., Yu, Z., Clowers, B. H., Cuttler, C., Fuchs, R. A., Hill, M. N., & McLaughlin, R. J. (2020). Vaporized Cannabis Extracts Have Reinforcing Properties and Support Conditioned Drug-Seeking Behavior in Rats. *J Neurosci*, 40(9), 1897-1908. <https://doi.org/10.1523/JNEUROSCI.2416-19.2020>
- Gerard, C. M., Mollereau, C., Vassart, G., & Parmentier, M. (1991). Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem J*, 279 (Pt 1)(Pt 1), 129-134. <https://doi.org/10.1042/bj2790129>
- Ghozland, S., Matthes, H. W., Simonin, F., Filliol, D., Kieffer, B. L., & Maldonado, R. (2002). Motivational effects of cannabinoids are mediated by mu-opioid and kappa-opioid receptors. *J Neurosci*, 22(3), 1146-1154. <https://doi.org/10.1523/JNEUROSCI.22-03-01146.2002>
- Gong, J. P., Onaivi, E. S., Ishiguro, H., Liu, Q. R., Tagliaferro, P. A., Brusco, A., & Uhl, G. R. (2006). Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res*, 1071(1), 10-23. <https://doi.org/10.1016/j.brainres.2005.11.035>
- Gonsiorek, W., Lunn, C., Fan, X., Narula, S., Lundell, D., & Hipkin, R. W. (2000). Endocannabinoid 2-arachidonyl glycerol is a full agonist through human type 2 cannabinoid receptor: antagonism by anandamide. *Mol Pharmacol*, 57(5), 1045-1050. <https://www.ncbi.nlm.nih.gov/pubmed/10779390>
- Gonzalez, S., Cebeira, M., & Fernandez-Ruiz, J. (2005). Cannabinoid tolerance and dependence: a review of studies in laboratory animals. *Pharmacol Biochem Behav*, 81(2), 300-318. <https://doi.org/10.1016/j.pbb.2005.01.028>
- Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*, 42(4), 327-360. <https://doi.org/10.2165/00003088-200342040-00003>
- Gummin, D. D., Mowry, J. B., Beuhler, M. C., Spyker, D. A., Rivers, L. J., Feldman, R., Brown, K., Nathaniel, P. T. P., Bronstein, A. C., & Weber, J. A. (2022). 2021 Annual Report of the National Poison Data System((c)) (NPDS) from America's Poison Centers: 39th Annual Report. *Clin Toxicol (Phila)*, 60(12), 1381-1643. <https://doi.org/10.1080/15563650.2022.2132768>
- Hammond, D., Corsetti, D., Goodman, S., Iraniparast, M., Danh Hong, D., & Burkhalter, R. (2022). International Cannabis Policy Study- United States 2021 Summary, Sept 2022 on behalf of the ICPS Research Team.

- Haney, M., Hart, C. L., Vosburg, S. K., Comer, S. D., Reed, S. C., & Foltin, R. W. (2008). Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)*, 197(1), 157-168. <https://doi.org/10.1007/s00213-007-1020-8>
- Haney, M., Hart, C. L., Vosburg, S. K., Nasser, J., Bennett, A., Zubarán, C., & Foltin, R. W. (2004). Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*, 29(1), 158-170. <https://doi.org/10.1038/sj.npp.1300310>
- Haney, M., Rabkin, J., Gunderson, E., & Foltin, R. W. (2005). Dronabinol and marijuana in HIV(+) marijuana smokers: acute effects on caloric intake and mood. *Psychopharmacology (Berl)*, 181(1), 170-178. <https://doi.org/10.1007/s00213-005-2242-2>
- Haney, M., Ward, A. S., Comer, S. D., Foltin, R. W., & Fischman, M. W. (1999). Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology (Berl)*, 141(4), 395-404. <https://doi.org/10.1007/s002130050849>
- Harris, R. T., Waters, W., & McLendon, D. (1974). Evaluation of reinforcing capability of delta-9-tetrahydrocannabinol in rhesus monkeys. *Psychopharmacologia*, 37(1), 23-29. <https://doi.org/10.1007/BF00426679>
- Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W. M., Crowley, T., Ling, W., & Petry, N. M. (2013). DSM-5 Criteria for Substance Use Disorders: Recommendations and Rationale. *American Journal of Psychiatry*, 170(8), 834-851. <https://doi.org/10.1176/appi.ajp.2013.12060782>
- Hazekamp, A., & Fisdick, J. (2012). Cannabis—from cultivar to chemovar. *Drug testing and analysis*, 4(7-8), 660-667.
- Herkenham, M. (1992). Cannabinoid receptor localization in brain: relationship to motor and reward systems. *Ann N Y Acad Sci*, 654, 19-32. <https://doi.org/10.1111/j.1749-6632.1992.tb25953.x>
- Herkenham, M., Lynn, A. B., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1991). Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci*, 11(2), 563-583. <https://doi.org/10.1523/JNEUROSCI.11-02-00563.1991>
- Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1990). Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A*, 87(5), 1932-1936. <https://doi.org/10.1073/pnas.87.5.1932>
- Herning, R. I., Hooker, W. D., & Jones, R. T. (1986). Tetrahydrocannabinol content and differences in marijuana smoking behavior. *Psychopharmacology (Berl)*, 90(2), 160-162. <https://doi.org/10.1007/BF00181232>
- Hillig, K. W. (2005). Genetic evidence for speciation in Cannabis (Cannabaceae). *Genetic Resources and Crop Evolution*, 52, 161-180.
- Hirvonen, J., Goodwin, R. S., Li, C. T., Terry, G. E., Zoghbi, S. S., Morse, C., Pike, V. W., Volkow, N. D., Huestis, M. A., & Innis, R. B. (2012). Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol Psychiatry*, 17(6), 642-649. <https://doi.org/10.1038/mp.2011.82>
- Hively, R. L., Mosher, W. A., & Hoffmann, F. W. (1966). Isolation of trans- Δ^6 -tetrahydrocannabinol from marijuana. *Journal of the American Chemical Society*, 88(8), 1832-1833.
- Hollister, L. E. (1986). Health aspects of cannabis. *Pharmacol Rev*, 38(1), 1-20. <https://www.ncbi.nlm.nih.gov/pubmed/3520605>
- Hollister, L. E. (1988). Cannabis--1988. *Acta Psychiatr Scand Suppl*, 345, 108-118. <https://doi.org/10.1111/j.1600-0447.1988.tb08576.x>
- Howlett, A. C., & Abood, M. E. (2017). CB(1) and CB(2) Receptor Pharmacology. *Adv Pharmacol*, 80, 169-206. <https://doi.org/10.1016/bs.apha.2017.03.007>
- Howlett, A. C., Breivogel, C. S., Childers, S. R., Deadwyler, S. A., Hampson, R. E., & Porrino, L. J. (2004). Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology*, 47 Suppl 1, 345-358. <https://doi.org/10.1016/j.neuropharm.2004.07.030>
- Huestis, M. A. (2007). Human cannabinoid pharmacokinetics. *Chem Biodivers*, 4(8), 1770-1804. <https://doi.org/10.1002/cbdv.200790152>
- Huestis, M. A., Henningfield, J. E., & Cone, E. J. (1992). Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol*, 16(5), 276-282. <https://doi.org/10.1093/jat/16.5.276>
- Huestis, M. A., Sampson, A. H., Holicky, B. J., Henningfield, J. E., & Cone, E. J. (1992). Characterization of the absorption phase of marijuana smoking. *Clin Pharmacol Ther*, 52(1), 31-41. <https://doi.org/10.1038/clpt.1992.100>

- Hunault, C. C., Bocker, K. B., Stellato, R. K., Kenemans, J. L., de Vries, I., & Meulenbelt, J. (2014). Acute subjective effects after smoking joints containing up to 69 mg Delta9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. *Psychopharmacology (Berl)*, 231(24), 4723-4733. <https://doi.org/10.1007/s00213-014-3630-2>
- Hutcheson, D. M., Tzavara, E. T., Smadja, C., Valjent, E., Roques, B. P., Hanoune, J., & Maldonado, R. (1998). Behavioural and biochemical evidence for signs of abstinence in mice chronically treated with Δ -9-tetrahydrocannabinol. *British journal of pharmacology*, 125(7), 1567-1577.
- ICPS. (2023). *International Cannabis Policy Study: Surveys*. <https://cannabisproject.ca/methods/>
- Johansson, E., Halldin, M. M., Agurell, S., Hollister, L. E., & Gillespie, H. K. (1989). Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. *Eur J Clin Pharmacol*, 37(3), 273-277. <https://doi.org/10.1007/BF00679783>
- John, W. S., Martin, T. J., & Nader, M. A. (2017). Behavioral Determinants of Cannabinoid Self-Administration in Old World Monkeys. *Neuropsychopharmacology*, 42(7), 1522-1530. <https://doi.org/10.1038/npp.2017.2>
- Johnson, J. V., Christensen, A., Morgan, D., & Basso, K. B. (2020). Gas chromatography/electron ionization mass spectrometry (GC/EI-MS) for the characterization of phytocannabinoids in Cannabis sativa. In *Comprehensive Analytical Chemistry* (Vol. 90, pp. 235-274). Elsevier.
- Johnston, L. D., O'Malley, P. M., Miech, R. A., Bachman, J. G., & Schulenberg, J. E. (2016). Monitoring the Future national survey results on drug use, 1975-2015: Overview, key findings on adolescent drug use. *Institute for Social Research*.
- Justinova, Z., Goldberg, S. R., Heishman, S. J., & Tanda, G. (2005). Self-administration of cannabinoids by experimental animals and human marijuana smokers. *Pharmacol Biochem Behav*, 81(2), 285-299. <https://doi.org/10.1016/j.pbb.2005.01.026>
- Justinova, Z., Tanda, G., Munzar, P., & Goldberg, S. R. (2004). The opioid antagonist naltrexone reduces the reinforcing effects of Delta 9 tetrahydrocannabinol (THC) in squirrel monkeys. *Psychopharmacology (Berl)*, 173(1-2), 186-194. <https://doi.org/10.1007/s00213-003-1693-6>
- Justinova, Z., Tanda, G., Redhi, G. H., & Goldberg, S. R. (2003). Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology (Berl)*, 169(2), 135-140. <https://doi.org/10.1007/s00213-003-1484-0>
- Karschner, E. L., Darwin, W. D., McMahon, R. P., Liu, F., Wright, S., Goodwin, R. S., & Huestis, M. A. (2011). Subjective and physiological effects after controlled Sativex and oral THC administration. *Clin Pharmacol Ther*, 89(3), 400-407. <https://doi.org/10.1038/clpt.2010.318>
- Kaufmann, R. M., Kraft, B., Frey, R., Winkler, D., Weisenbichler, S., Backer, C., Kasper, S., & Kress, H. G. (2010). Acute psychotropic effects of oral cannabis extract with a defined content of Delta9-tetrahydrocannabinol (THC) in healthy volunteers. *Pharmacopsychiatry*, 43(1), 24-32. <https://doi.org/10.1055/s-0029-1237397>
- Kaymakalan, S. (1973). Tolerance to and dependence on cannabis. *Bulletin on Narcotics*.
- Kesner, A. J., & Lovinger, D. M. (2021). Cannabis use, abuse, and withdrawal: Cannabinergic mechanisms, clinical, and preclinical findings. *J Neurochem*, 157(5), 1674-1696. <https://doi.org/10.1111/jnc.15369>
- Klein, T. W., Newton, C., Larsen, K., Lu, L., Perkins, I., Nong, L., & Friedman, H. (2003). The cannabinoid system and immune modulation. *J Leukoc Biol*, 74(4), 486-496. <https://doi.org/10.1189/jlb.0303101>
- Krejčí, Z., & Šantavý, F. (1975). Isolation of two new cannabinoid acids from Cannabis sativa L. of Czechoslovak origin. *Acta Univ Olomuc, Fac Med*, 74, 161-166.
- Le Foll, B., Wiggins, M., & Goldberg, S. R. (2006). Nicotine pre-exposure does not potentiate the locomotor or rewarding effects of Δ -9-tetrahydrocannabinol in rats. *Behavioural pharmacology*, 17(2), 195-199.
- Lefever, T. W., Marusich, J. A., Antonazzo, K. R., & Wiley, J. L. (2014). Evaluation of WIN 55,212-2 self-administration in rats as a potential cannabinoid abuse liability model. *Pharmacol Biochem Behav*, 118, 30-35. <https://doi.org/10.1016/j.pbb.2014.01.002>
- Lemberger, L., Crabtree, R. E., & Rowe, H. M. (1972). 11-hydroxy- 9 -tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marihuana in man. *Science*, 177(4043), 62-64. <https://doi.org/10.1126/science.177.4043.62>
- Lemberger, L., & Rubin, A. (1975). The physiologic disposition of marihuana in man. *Life Sci*, 17(11), 1637-1642. [https://doi.org/10.1016/0024-3205\(75\)90108-3](https://doi.org/10.1016/0024-3205(75)90108-3)
- Lemberger, L., Silberstein, S. D., Axelrod, J., & Kopin, I. J. (1970). Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. *Science*, 170(3964), 1320-1322. <https://doi.org/10.1126/science.170.3964.1320>

- Lemberger, L., Weiss, J. L., Watanabe, A. M., Galanter, I. M., Wyatt, R. J., & Cardon, P. V. (1972). Delta-9-tetrahydrocannabinol. Temporal correlation of the psychologic effects and blood levels after various routes of administration. *N Engl J Med*, 286(13), 685-688. <https://doi.org/10.1056/NEJM197203302861303>
- Lepore, M., Vorel, S. R., Lowinson, J., & Gardner, E. L. (1995). Conditioned place preference induced by delta 9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. *Life Sci*, 56(23-24), 2073-2080. [https://doi.org/10.1016/0024-3205\(95\)00191-8](https://doi.org/10.1016/0024-3205(95)00191-8)
- Leung, J., Chan, G. C. K., Hides, L., & Hall, W. D. (2020). What is the prevalence and risk of cannabis use disorders among people who use cannabis? a systematic review and meta-analysis. *Addict Behav*, 109, 106479. <https://doi.org/10.1016/j.addbeh.2020.106479>
- Lewis, M. A., Russo, E. B., & Smith, K. M. (2018). Pharmacological Foundations of Cannabis Chemovars. *Planta Med*, 84(4), 225-233. <https://doi.org/10.1055/s-0043-122240>
- Lichtman, A. H., Fisher, J., & Martin, B. R. (2001). Precipitated cannabinoid withdrawal is reversed by Delta(9)-tetrahydrocannabinol or clonidine. *Pharmacol Biochem Behav*, 69(1-2), 181-188. [https://doi.org/10.1016/s0091-3057\(01\)00514-7](https://doi.org/10.1016/s0091-3057(01)00514-7)
- Lichtman, A. H., & Martin, B. R. (2005). Cannabinoid tolerance and dependence. *Handb Exp Pharmacol*(168), 691-717. https://doi.org/10.1007/3-540-26573-2_24
- Lindgren, J. E., Ohlsson, A., Agurell, S., Hollister, L., & Gillespie, H. (1981). Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berl)*, 74(3), 208-212. <https://doi.org/10.1007/BF00427095>
- Liu, Y., Liu, H.-Y., Li, S.-H., Ma, W., Wu, D.-T., Li, H.-B., Xiao, A.-P., Liu, L.-L., Zhu, F., & Gan, R.-Y. (2022). Cannabis sativa bioactive compounds and their extraction, separation, purification, and identification technologies: An updated review. *TrAC Trends in Analytical Chemistry*, 149, 116554.
- Lopez-Quintero, C., Perez de los Cobos, J., Hasin, D. S., Okuda, M., Wang, S., Grant, B. F., & Blanco, C. (2011). Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*, 115(1-2), 120-130. <https://doi.org/10.1016/j.drugalcdep.2010.11.004>
- Lucas, C. J., Galettis, P., & Schneider, J. (2018). The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol*, 84(11), 2477-2482. <https://doi.org/10.1111/bcp.13710>
- Mackie, K. (2008). Cannabinoid receptors: where they are and what they do. *Journal of neuroendocrinology*, 20, 10-14.
- Mackie, K., & Stella, N. (2006). Cannabinoid receptors and endocannabinoids: evidence for new players. *AAPS J*, 8(2), E298-306. <https://doi.org/10.1007/BF02854900>
- Mansbach, R. S., Nicholson, K. L., Martin, B. R., & Balster, R. L. (1994). Failure of Delta(9)-tetrahydrocannabinol and CP 55,940 to maintain intravenous self-administration under a fixed-interval schedule in rhesus monkeys. *Behav Pharmacol*, 5(2), 219-225. <https://doi.org/10.1097/00008877-199404000-00014>
- Marsicano, G., & Kuner, R. (2008). Anatomical distribution of receptors, ligands and enzymes in the brain and in the spinal cord: circuitries and neurochemistry. In *Cannabinoids and the Brain* (pp. 161-201). Springer.
- McPartland, J. M., Glass, M., & Pertwee, R. G. (2007). Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *Br J Pharmacol*, 152(5), 583-593. <https://doi.org/10.1038/sj.bjp.0707399>
- Mechoulam, R., & Gaoni, Y. (1965). A total synthesis of dl- Δ^1 -tetrahydrocannabinol, the active constituent of hashish1. *Journal of the American Chemical Society*, 87(14), 3273-3275.
- Mechoulam, R., Peters, M., Murillo-Rodriguez, E., & Hanus, L. O. (2007). Cannabidiol--recent advances. *Chem Biodivers*, 4(8), 1678-1692. <https://doi.org/10.1002/cbdv.200790147>
- Mechoulam, R., & Shvo, Y. (1963). Hashish? I. *Tetrahedron*, 19(12), 2073-2078.
- Medeiros, D. d. C., Cota, V. R., Oliveira, A. C. P., Moreira, F. A., & Moraes, M. F. D. (2020). The endocannabinoid system activation as a neural network desynchronizing mediator for seizure suppression. *Frontiers in Behavioral Neuroscience*, 14, 603245.
- Medicine, I. o. (1982). *Marijuana and Health*. The National Academies Press. <https://doi.org/doi:10.17226/18942>
- Miech, R., Johnston, L., O'Malley, P. M., Bachman, J. G., & Patrick, M. E. (2019). Trends in Adolescent Vaping, 2017-2019. *N Engl J Med*, 381(15), 1490-1491. <https://doi.org/10.1056/NEJMc1910739>
- Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2022). Monitoring the Future National Survey Results on Drug Use, 1975-2021: Volume I, Secondary School Students. https://monitoringthefuture.org/wp-content/uploads/2022/08/mtf-vol1_2021.pdf

- Miech, R. A., Johnston, L. D., Patrick, M. E., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2023). Monitoring the Future National Survey Results on Drug Use, 1975–2022: Secondary School Students. <https://monitoringthefuture.org/wp-content/uploads/2022/12/mtf2022.pdf>
- Miech, R. A., Patrick, M. E., O'Malley, P. M., Johnston, L. D., & Bachman, J. G. (2020). Trends in Reported Marijuana Vaping Among US Adolescents, 2017-2019. *JAMA*, 323(5), 475-476. <https://doi.org/10.1001/jama.2019.20185>
- Morales, P., Hurst, D. P., & Reggio, P. H. (2017). Molecular Targets of the Phytocannabinoids: A Complex Picture. *Prog Chem Org Nat Prod*, 103, 103-131. https://doi.org/10.1007/978-3-319-45541-9_4
- Munro, S., Thomas, K. L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, 365(6441), 61-65.
- Musto, D. F. (1972). The Marihuana Tax Act of 1937. *Arch Gen Psychiatry*, 26(2), 101-108. <https://doi.org/10.1001/archpsyc.1972.01750200005002>
- National Academies of Sciences, E., & Medicine. (2017). The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research.
- National Center for Biotechnology Information. (2023a). *PubChem Compound Summary for CID 2978, 6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol*. Retrieved 08/11/2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/2978>.
- National Center for Biotechnology Information. (2023b). *PubChem Compound Summary for CID 16078, Dronabinol*. Retrieved 08/11/2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol>.
- National Center for Biotechnology Information. (2023c). *PubChem Compound Summary for CID 22462, 6H-Dibenzo(b,d)pyran-1-ol, 6a-beta,7,8,10a-beta-tetrahydro-3-pentyl-6,6,9-trimethyl-, (+)-Z-*. Retrieved 08/11/2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/22462>
- National Center for Biotechnology Information. (2023d). *PubChem Compound Summary for CID 134740, (6aS,10aS)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol*. Retrieved 08/11/2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/134740>.
- National Center for Biotechnology Information. (2023e). *PubChem Compound Summary for CID 638026, DELTA8-Tetrahydrocannabinol*. Retrieved 08/11/2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/638026>
- National Center for Biotechnology Information. (2023f). *PubChem Compound Summary for CID 12831993, delta9-CIS-TETRAHYDROCANNABINOL, (-)-*. Retrieved 08/11/2023 from <https://pubchem.ncbi.nlm.nih.gov/compound/delta9-CIS-TETRAHYDROCANNABINOL>.
- Nelson, N. G., Law, W. X., Weingarten, M. J., Carnevale, L. N., Das, A., & Liang, N. C. (2019). Combined $\Delta(9)$ -tetrahydrocannabinol and moderate alcohol administration: effects on ingestive behaviors in adolescent male rats. *Psychopharmacology (Berl)*, 236(2), 671-684. <https://doi.org/10.1007/s00213-018-5093-3>
- O'Brien, C. P. (1996). Drug Addiction and Drug Abuse. In J. G. Hardman, L. E. Limbird, P. B. Molinoff, R. W. Ruddon, & A. Goodman Gilman (Eds.), *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (Ninth ed., pp. 557-580).
- Parker, L. A., & Gillies, T. (1995). THC-induced place and taste aversions in Lewis and Sprague-Dawley rats. *Behav Neurosci*, 109(1), 71-78. <https://doi.org/10.1037//0735-7044.109.1.71>
- Pickens, R., Thompson, T., & Muchow, D. (1973). Cannabis and phencyclidine self-administration by animals. In *Psychic Dependence: Definition, Assessment in Animals and Man Theoretical and Clinical Implications* (pp. 78-87). Springer.
- Pisanti, S., & Bifulco, M. (2019). Medical Cannabis: A plurimillennial history of an evergreen. *Journal of cellular physiology*, 234(6), 8342-8351.
- Pitts, W. J., Heller, D., Smiley-McDonald, H., Weimer, B., Grabenauer, M., Bollinger, K., Roper-Miller, J., & Pressley, D. (2023). Understanding research methods, limitations, and applications of drug data collected by the National Forensic Laboratory Information System (NFLIS-Drug). *J Forensic Sci*, 68(4), 1335-1342. <https://doi.org/10.1111/1556-4029.15269>
- Pollastro, F., Tagliatalata-Scafati, O., Allara, M., Munoz, E., Di Marzo, V., De Petrocellis, L., & Appendino, G. (2011). Bioactive prenylogous cannabinoid from fiber hemp (*Cannabis sativa*). *J Nat Prod*, 74(9), 2019-2022. <https://doi.org/10.1021/np200500p>
- Procaccia, S., Lewitus, G. M., Lipson Feder, C., Shapira, A., Berman, P., & Meiri, D. (2022). Cannabis for medical use: versatile plant rather than a single drug. *Frontiers in Pharmacology*, 13, 894960.
- Quinn, H. R., Matsumoto, I., Callaghan, P. D., Long, L. E., Arnold, J. C., Gunasekaran, N., Thompson, M. R., Dawson, B., Mallet, P. E., Kashem, M. A., Matsuda-Matsumoto, H., Iwazaki, T., & McGregor, I. S. (2008). Adolescent rats find repeated $\Delta(9)$ -THC less aversive than adult rats but display greater residual cognitive

- deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*, 33(5), 1113-1126. <https://doi.org/10.1038/sj.npp.1301475>
- Radwan, M. M., Chandra, S., Gul, S., & ElSohly, M. A. (2021). Cannabinoids, Phenolics, Terpenes and Alkaloids of Cannabis. *Molecules*, 26(9). <https://doi.org/10.3390/molecules26092774>
- Ramesh, D., Haney, M., & Cooper, Z. D. (2013). Marijuana's dose-dependent effects in daily marijuana smokers. *Exp Clin Psychopharmacol*, 21(4), 287-293. <https://doi.org/10.1037/a0033661>
- Ranganathan, M., Carbuto, M., Braley, G., Elander, J., Perry, E., Pittman, B., Radhakrishnan, R., Sewell, R. A., & D'Souza, D. C. (2012). Naltrexone does not attenuate the effects of intravenous Delta9-tetrahydrocannabinol in healthy humans. *Int J Neuropsychopharmacol*, 15(9), 1251-1264. <https://doi.org/10.1017/S1461145711001830>
- Rastegar, D. A., & Fingerhood, M. I. (2020). *The American Society of Addiction Medicine handbook of addiction medicine*. Oxford University Press, USA.
- Rock, E. M., & Parker, L. A. (2021). Constituents of Cannabis Sativa. In E. Murillo-Rodriguez, S. R. Pandi-Perumal, & J. M. Monti (Eds.), *Cannabinoids and Neuropsychiatric Disorders* (pp. 1-13). Springer International Publishing. https://doi.org/10.1007/978-3-030-57369-0_1
- Russo, E. (2004). History of cannabis as a medicine. *Medicinal uses of cannabis and cannabinoids*, 1-16.
- Russo, E. B. (2016). Beyond Cannabis: Plants and the Endocannabinoid System. *Trends Pharmacol Sci*, 37(7), 594-605. <https://doi.org/10.1016/j.tips.2016.04.005>
- Russo, E. B., Burnett, A., Hall, B., & Parker, K. K. (2005). Agonistic properties of cannabidiol at 5-HT_{1a} receptors. *Neurochem Res*, 30(8), 1037-1043. <https://doi.org/10.1007/s11064-005-6978-1>
- Russo, E. B., Jiang, H. E., Li, X., Sutton, A., Carboni, A., del Bianco, F., Mandolino, G., Potter, D. J., Zhao, Y. X., Bera, S., Zhang, Y. B., Lu, E. G., Ferguson, D. K., Hueber, F., Zhao, L. C., Liu, C. J., Wang, Y. F., & Li, C. S. (2008). Phytochemical and genetic analyses of ancient cannabis from Central Asia. *J Exp Bot*, 59(15), 4171-4182. <https://doi.org/10.1093/jxb/ern260>
- Saad, L. (2013). *In U.S., 38% Have Tried Marijuana, Little Changed Since '80s Fewer young adults have tried it today compared with in the 1970s and 1980s*. Retrieved 8/17/23 from <https://news.gallup.com/poll/163835/tried-marijuana-little-changed-80s.aspx>
- SAMHSA. (2022a). *Findings from Drug-Related Emergency Department Visits, 2021 (HHS Publication No. PEP22-07-03-002)*. Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA). <https://www.samhsa.gov/data/>
- SAMHSA. (2022b). *Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health*. HHS: Substance Abuse and Mental Health Services Administration Retrieved from <https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report>
- SAMHSA. (2022c). *Treatment Episode Data Set (2020)*. U.S. Health and Human Services (HHS): Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality (CBHSQ) Retrieved from https://www.samhsa.gov/data/sites/default/files/reports/rpt38665/2020 TEDS%20Annual%20Report-508%20compliant_1182023_FINAL.pdf
- Sanudo-Pena, M. C., Tsou, K., Delay, E. R., Hohman, A. G., Force, M., & Walker, J. M. (1997). Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. *Neurosci Lett*, 223(2), 125-128. [https://doi.org/10.1016/s0304-3940\(97\)13424-3](https://doi.org/10.1016/s0304-3940(97)13424-3)
- Schafroth, M. A., Mazzocanti, G., Reynoso-Moreno, I., Erni, R., Pollastro, F., Caprioglio, D., Botta, B., Allegrone, G., Grassi, G., & Chicca, A. (2021). Δ^9 -cis-Tetrahydrocannabinol: natural occurrence, chirality, and pharmacology. *Journal of natural products*, 84(9), 2502-2510.
- Schindler, E. A. D., Schnakenberg Martin, A. M., Sewell, R. A., Ranganathan, M., DeForest, A., Pittman, B. P., Perrino, A., Jr., & D'Souza, D. C. (2020). In an exploratory randomized, double-blind, placebo-controlled, cross-over study, psychoactive doses of intravenous delta-9-tetrahydrocannabinol fail to produce antinociceptive effects in healthy human volunteers. *Psychopharmacology (Berl)*, 237(10), 3097-3107. <https://doi.org/10.1007/s00213-020-05595-9>
- Schlienz, N. J., Spindle, T. R., Cone, E. J., Herrmann, E. S., Bigelow, G. E., Mitchell, J. M., Flegel, R., LoDico, C., & Vandrey, R. (2020). Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. *Drug Alcohol Depend*, 211, 107969. <https://doi.org/10.1016/j.drugalcdep.2020.107969>
- Schramm-Sapota, N. L., Cha, Y. M., Chaudhry, S., Wilson, W. A., Swartzwelder, H. S., & Kuhn, C. M. (2007). Differential anxiogenic, aversive, and locomotor effects of THC in adolescent and adult rats. *Psychopharmacology (Berl)*, 191(4), 867-877. <https://doi.org/10.1007/s00213-006-0676-9>

- Schultes, R. E., Klein, W. M., Plowman, T., & Lockwood, T. E. (1974). CANNABIS: AN EXAMPLE OF TAXONOMIC NEGLECT. *Botanical Museum Leaflets, Harvard University*, 23(9), 337-367. <http://www.jstor.org/stable/41762285>
- Sevigny, E. L., Pacula, R. L., & Heaton, P. (2014). The effects of medical marijuana laws on potency. *Int J Drug Policy*, 25(2), 308-319. <https://doi.org/10.1016/j.drugpo.2014.01.003>
- Sharma, P., Murthy, P., & Bharath, M. M. (2012). Chemistry, metabolism, and toxicology of cannabis: clinical implications. *Iran J Psychiatry*, 7(4), 149-156. <https://www.ncbi.nlm.nih.gov/pubmed/23408483>
- Shi, B., Yang, R., Wang, X., Liu, H., Zou, L., Hu, X., Wu, J., Zou, A., & Liu, L. (2012). Inhibition of 5-HT(3) receptors-activated currents by cannabinoids in rat trigeminal ganglion neurons. *J Huazhong Univ Sci Technolog Med Sci*, 32(2), 265-271. <https://doi.org/10.1007/s11596-012-0047-1>
- Singla, S., & Block, R. (2022). Effect Compartment Model for the Evaluation of Tolerance to Psychological Highness Following Smoking Marijuana. *J Clin Pharmacol*, 62(12), 1539-1547. <https://doi.org/10.1002/jcph.2109>
- Small, E., & Cronquist, A. (1976). A practical and natural taxonomy for Cannabis. *Taxon*, 405-435.
- Smith, C. J., Vergara, D., Keegan, B., & Jikomes, N. (2022). The phytochemical diversity of commercial Cannabis in the United States. *PLoS One*, 17(5), e0267498. <https://doi.org/10.1371/journal.pone.0267498>
- Smoker, M. P., Hernandez, M., Zhang, Y., & Boehm, S. L., 2nd. (2019). Assessment of Acute Motor Effects and Tolerance Following Self-Administration of Alcohol and Edible $\Delta(9)$ -Tetrahydrocannabinol in Adolescent Male Mice. *Alcohol Clin Exp Res*, 43(11), 2446-2457. <https://doi.org/10.1111/acer.14197>
- Smoker, M. P., Mackie, K., Lapish, C. C., & Boehm, S. L., 2nd. (2019). Self-administration of edible Delta(9)-tetrahydrocannabinol and associated behavioral effects in mice. *Drug Alcohol Depend*, 199, 106-115. <https://doi.org/10.1016/j.drugalcdep.2019.02.020>
- Soria, G., Castane, A., Berrendero, F., Ledent, C., Parmentier, M., Maldonado, R., & Valverde, O. (2004). Adenosine A2A receptors are involved in physical dependence and place conditioning induced by THC. *Eur J Neurosci*, 20(8), 2203-2213. <https://doi.org/10.1111/j.1460-9568.2004.03682.x>
- Spencer, S., Neuhofer, D., Chioma, V. C., Garcia-Keller, C., Schwartz, D. J., Allen, N., Scofield, M. D., Ortiz-Ithier, T., & Kalivas, P. W. (2018). A model of $\Delta 9$ -tetrahydrocannabinol self-administration and reinstatement that alters synaptic plasticity in nucleus accumbens. *Biological psychiatry*, 84(8), 601-610.
- Spindle, T. R., Martin, E. L., Grabenauer, M., Woodward, T., Milburn, M. A., & Vandrey, R. (2021). Assessment of cognitive and psychomotor impairment, subjective effects, and blood THC concentrations following acute administration of oral and vaporized cannabis. *J Psychopharmacol*, 35(7), 786-803. <https://doi.org/10.1177/02698811211021583>
- Stringfield, S. J., & Torregrossa, M. M. (2021). Intravenous self-administration of delta-9-THC in adolescent rats produces long-lasting alterations in behavior and receptor protein expression. *Psychopharmacology (Berl)*, 238(1), 305-319. <https://doi.org/10.1007/s00213-020-05684-9>
- Tagen M, Klumpers LE. (2022). Review of delta-8-tetrahydrocannabinol ($\Delta 8$ -THC): Comparative pharmacology with $\Delta 9$ -THC. *Br J Pharmacol*.179(15):3915-3933. doi: 10.1111/bph.15865.
- Tallaksen, A. R. (2019). Junkies and Jim Crow: the Boggs Act of 1951 and the racial transformation of New Orleans' heroin market. *Journal of Urban History*, 45(2), 230-246.
- Tanda, G., Munzar, P., & Goldberg, S. R. (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nat Neurosci*, 3(11), 1073-1074. <https://doi.org/10.1038/80577>
- The Researched Abused, Diversion, and Addiction-related Surveillance System (RADARS). (2023). *Nonmedical Use of Prescription Drugs (NMURx) Program Report to FDA*.
- Thomas, A., Baillie, G. L., Phillips, A. M., Razdan, R. K., Ross, R. A., & Pertwee, R. G. (2007). Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol*, 150(5), 613-623. <https://doi.org/10.1038/sj.bjp.0707133>
- Thomas, B. F., & ElSohly, M. A. (2016a). Chapter 1 - The Botany of Cannabis sativa L. In B. F. Thomas & M. A. ElSohly (Eds.), *The Analytical Chemistry of Cannabis* (pp. 1-26). Elsevier. <https://doi.org/https://doi.org/10.1016/B978-0-12-804646-3.00001-1>
- Thomas, B. F., & ElSohly, M. A. (2016b). Chapter 2 - Biosynthesis and Pharmacology of Phytocannabinoids and Related Chemical Constituents. In B. F. Thomas & M. A. ElSohly (Eds.), *The Analytical Chemistry of Cannabis* (pp. 27-41). Elsevier. <https://doi.org/https://doi.org/10.1016/B978-0-12-804646-3.00002-3>
- Trigo, J. M., Lagzdins, D., Rehm, J., Selby, P., Gamaledin, I., Fischer, B., Barnes, A. J., Huestis, M. A., & Le Foll, B. (2016). Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. *Drug Alcohol Depend*, 161, 298-306. <https://doi.org/10.1016/j.drugalcdep.2016.02.020>

- Turcotte, C., Blanchet, M. R., Laviolette, M., & Flamand, N. (2016). Impact of Cannabis, Cannabinoids, and Endocannabinoids in the Lungs. *Front Pharmacol*, 7, 317. <https://doi.org/10.3389/fphar.2016.00317>
- U.S. Customs and Border Protection. (2019). Did you know... marijuana was once a legal cross-border import. *US Department of Homeland Security*.
- Underwood, J. M., Brener, N., Thornton, J., Harris, W. A., Bryan, L. N., Shanklin, S. L., Deputy, N., Roberts, A. M., Queen, B., Chyen, D., Whittle, L., Lim, C., Yamakawa, Y., Leon-Nguyen, M., Kilmer, G., Smith-Grant, J., Demissie, Z., Jones, S. E., Clayton, H., & Dittus, P. (2020). Overview and Methods for the Youth Risk Behavior Surveillance System - United States, 2019. *MMWR Suppl*, 69(1), 1-10. <https://doi.org/10.15585/mmwr.su6901a1>
- United States Department of Agriculture Agricultural Research Service, N. P. G. S. (2023). *Germplasm Resources Information Network (GRIN Taxonomy)*. Retrieved 08/22/2023 from <https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomydetail?id=8862>
- United States Department of Agriculture Natural Resources Conservation Service. (2023). *The PLANTS Database*. Retrieved 08/22/2023 from <https://plants.usda.gov/home/classification/70747>
- US Food and Drug Administration. *CFSAN Adverse Event Reporting System (CAERS)*. Retrieved 8/23/23 from: <https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers>
- US Food and Drug Administration. *Questions and answers on FDA's Adverse Event Reporting System (FAERS)*. Retrieved 8/8/23 from <https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers>
- Valjent, E., & Maldonado, R. (2000). A behavioural model to reveal place preference to delta 9-tetrahydrocannabinol in mice. *Psychopharmacology (Berl)*, 147(4), 436-438. <https://doi.org/10.1007/s002130050013>
- Valjent, E., Mitchell, J. M., Besson, M. J., Caboche, J., & Maldonado, R. (2002). Behavioural and biochemical evidence for interactions between Delta 9-tetrahydrocannabinol and nicotine. *Br J Pharmacol*, 135(2), 564-578. <https://doi.org/10.1038/sj.bjp.0704479>
- van Ree, J. M., Slangen, J. L., & de Wied, D. (1978). Intravenous self-administration of drugs in rats. *J Pharmacol Exp Ther*, 204(3), 547-557. <https://www.ncbi.nlm.nih.gov/pubmed/633066>
- Vandrey, R., Herrmann, E. S., Mitchell, J. M., Bigelow, G. E., Flegel, R., LoDico, C., & Cone, E. J. (2017). Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes. *J Anal Toxicol*, 41(2), 83-99. <https://doi.org/10.1093/jat/bkx012>
- Vandrey, R. G., Budney, A. J., Hughes, J. R., & Liguori, A. (2008). A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend*, 92(1-3), 48-54. <https://doi.org/10.1016/j.drugalcdep.2007.06.010>
- Vandrey, R. G., Budney, A. J., Moore, B. A., & Hughes, J. R. (2005). A cross-study comparison of cannabis and tobacco withdrawal. *Am J Addict*, 14(1), 54-63. <https://doi.org/10.1080/10550490590899853>
- Vinette, B., Cote, J., El-Akhras, A., Mrad, H., Chicoine, G., & Bilodeau, K. (2022). Routes of administration, reasons for use, and approved indications of medical cannabis in oncology: a scoping review. *BMC Cancer*, 22(1), 319. <https://doi.org/10.1186/s12885-022-09378-7>
- Vlachou, S., Nomikos, G. G., Stephens, D. N., & Panagis, G. (2007). Lack of evidence for appetitive effects of Delta 9-tetrahydrocannabinol in the intracranial self-stimulation and conditioned place preference procedures in rodents. *Behav Pharmacol*, 18(4), 311-319. <https://doi.org/10.1097/FBP.0b013e3282186cf2>
- Wachtel, S. R., & de Wit, H. (2000). Naltrexone does not block the subjective effects of oral Delta(9)-tetrahydrocannabinol in humans. *Drug Alcohol Depend*, 59(3), 251-260. [https://doi.org/10.1016/s0376-8716\(99\)00127-1](https://doi.org/10.1016/s0376-8716(99)00127-1)
- Wachtel, S. R., ElSohly, M. A., Ross, S. A., Ambre, J., & de Wit, H. (2002). Comparison of the subjective effects of Delta(9)-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology (Berl)*, 161(4), 331-339. <https://doi.org/10.1007/s00213-002-1033-2>
- Wakeford, A. G. P., Wetzell, B. B., Pomfrey, R. L., Clasen, M. M., Taylor, W. W., Hempel, B. J., & Riley, A. L. (2017). The effects of cannabidiol (CBD) on Delta(9)-tetrahydrocannabinol (THC) self-administration in male and female Long-Evans rats. *Exp Clin Psychopharmacol*, 25(4), 242-248. <https://doi.org/10.1037/pha0000135>
- Wilson, D. M., Varvel, S. A., Harloe, J. P., Martin, B. R., & Lichtman, A. H. (2006). SR 141716 (Rimonabant) precipitates withdrawal in marijuana-dependent mice. *Pharmacol Biochem Behav*, 85(1), 105-113. <https://doi.org/10.1016/j.pbb.2006.07.018>
- Wood, D. J. (1985). The strategic use of public policy: Business support for the 1906 Food and Drug Act. *Business History Review*, 59(3), 403-432.

- World Health Organization. (2003). *WHO guidelines on good agricultural and collection practices [GACP] for medicinal plants*. WHO Geneva.
- WorldFloraOnline. (2023). *Cannabis sativa L.* . <http://www.worldfloraonline.org/taxon/wfo-0000584001>
- Yang, K. H., Galadari, S., Isaev, D., Petroianu, G., Shippenberg, T. S., & Oz, M. (2010). The nonpsychoactive cannabinoid cannabidiol inhibits 5-hydroxytryptamine_{3A} receptor-mediated currents in *Xenopus laevis* oocytes. *J Pharmacol Exp Ther*, 333(2), 547-554. <https://doi.org/10.1124/jpet.109.162594>
- Zacny, J. P., & Chait, L. D. (1989). Breathhold duration and response to marijuana smoke. *Pharmacol Biochem Behav*, 33(2), 481-484. [https://doi.org/10.1016/0091-3057\(89\)90534-0](https://doi.org/10.1016/0091-3057(89)90534-0)
- Zacny, J. P., & Chait, L. D. (1991). Response to marijuana as a function of potency and breathhold duration. *Psychopharmacology (Berl)*, 103(2), 223-226. <https://doi.org/10.1007/BF02244207>
- Zangen, A., Solinas, M., Ikemoto, S., Goldberg, S. R., & Wise, R. A. (2006). Two brain sites for cannabinoid reward. *J Neurosci*, 26(18), 4901-4907. <https://doi.org/10.1523/JNEUROSCI.3554-05.2006>
- Zimmer, A., Zimmer, A. M., Hohmann, A. G., Herkenham, M., & Bonner, T. I. (1999). Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB₁ receptor knockout mice. *Proc Natl Acad Sci U S A*, 96(10), 5780-5785. <https://doi.org/10.1073/pnas.96.10.5780>



DATE: July 17, 2023

TO: Commissioner, Food and Drug Administration (FDA)

FROM: The Assistant Secretary for Health,
Office of the Assistant Secretary of Health (OASH)

SUBJECT: Part 1 Analysis

EXECUTIVE SUMMARY

The Department of Health and Human Services (HHS) has updated its analysis of a substance's "currently accepted medical use in treatment in the United States" ("CAMU") for purposes of the Controlled Substances Act (CSA), 21 U.S.C. § 812(b)(1). As part of this analysis, HHS includes consideration of whether there is (1) widespread current experience with medical use of the substance in the United States by licensed health care practitioners (HCPs) operating in accordance with implemented state-authorized programs, where the medical use is recognized by entities that regulate the practice of medicine ("Part 1"), and (2) whether there is scientific support for at least one of these medical uses of a substance ("Part 2"). To assist in the determination of whether marijuana has a CAMU in the United States, OASH conducted an analysis evaluating Part 1 and confirmed that more than 30,000 HCPs across 43 U.S. jurisdictions are authorized to recommend the medical use of marijuana for more than six million registered patients for at least 15 medical conditions. OASH's Part 1 analysis, therefore, supports the finding that marijuana has at least one CAMU in the United States. Additional analysis is required for evaluating Part 2 of the CAMU analysis, which considers whether there exists some credible scientific support for the use of marijuana for at least one of the medical conditions.

REQUEST

On October 6, 2022, President Biden directed the Secretary of HHS and the Attorney General to review how marijuana is currently scheduled under federal law.¹ The purpose of this memorandum is to share the findings from Part 1 and request that your Agency conduct Part 2 of the analysis to assess if there exists credible scientific support for the use of marijuana for at least one medical condition identified in this memorandum.

¹ <https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/>

BACKGROUND

Under the CSA, marijuana is currently a Schedule I substance in the United States.² Schedule I is a category for substances that are considered to have a high potential for abuse, have no CAMU in the United States, and lack accepted safety for use under medical supervision.

HHS's CAMU analysis has two parts.

- **Part 1:** There exists widespread, current experience with medical use of the substance by HCPs operating in accordance with implemented jurisdiction-authorized programs, where medical use is recognized by entities that regulate the practice of medicine. Part 1 of this approach is supported by factors such as the following (with none being dispositive):
 - a) Whether a substantial number of HCPs have gained clinical experience with at least one specific medical use of the substance under existing and implemented state authorized programs;
 - b) Whether a substantial number of entities that regulate the practice of medicine recognize at least one specific medical use of the substance; and
 - c) Whether an HCPs' clinical experience with the medical use of the substance is of sufficient extent and duration to help evaluate potential clinical uses and longer-term toxicities and potential harms of the substance when used under medical supervision.
- **Part 2:** There exists some credible scientific support for at least one of the medical uses for which Part 1 is met.

METHODOLOGY AND TERMINOLOGY

To evaluate if marijuana meets one or more of the three Part 1 factors, OASH applied the Part 1 approach described above to currently available data on the medical use(s) of marijuana in the United States. With input from other federal agencies, OASH collected pertinent programmatic and policy data, including data from states' websites, and other publicly available sources (secondary data condensed for this memo). The findings below and in TAB A are based on an interpretation of that information.

For the purposes of this memo, states and territories are henceforth referred to as 'jurisdictions.' 'Regulatory entities,' which vary widely by state, refers to the jurisdictions' respective entities which oversee implementation of the relevant marijuana for medical use statute. Additionally, 'reviewing/recommending bodies' refers to an entity that conducts a jurisdiction-level scientific medical review for the purpose of evaluating marijuana for medical use(s) and make a recommendation to the regulatory entity. Further, marijuana for medical use(s) may be directed by a ballot initiative or other legal authorization, which was not evaluated for purposes of this memo.

² 21 U.S.C. § 812(c)(10)

FINDINGS:

A summary of the Part 1 key findings and conclusions used to assess widespread, current experience with medical use of marijuana and whether it has a CAMU is listed below. Data for individual jurisdictions are provided in the tables and figures in TAB A. Part 1 uses data and information collected up to March 29, 2023.

Factor 1(a) – *Whether a substantial number of licensed health care practitioners have gained clinical experience with at least one specific medical use of the substance under existing and implemented state-authorized programs.*

Factor 1(a) Findings: There exists significant variability in HCPs’ clinical experience with recommending marijuana for medical use. Some reasons for the variability include: 1) the number of HCPs authorized by a jurisdiction to recommend marijuana for medical conditions, 2) the length of time a jurisdiction has had a marijuana for medical use program in place, 3) the educational requirements needed for HCPs to be authorized to recommend marijuana for medical conditions; 4) the number of patients who are registered in a jurisdiction to participate in marijuana for medical use programs; and 5) the availability of individual level practitioner data surrounding recommendation patterns for qualifying medical conditions.

- Currently, more than 30,000 HCPs are authorized to recommend the use of marijuana for more than six million patients with medical conditions that are enrolled in authorized marijuana for medical use programs (Table 4).
- Ten jurisdictions require specific HCP education on the use of marijuana prior to recommending marijuana for medical conditions, and two of these states require HCPs to pass an exam for certification (Table 2b).
- Because HCP-level data on the provision of marijuana prescriptions for specific medical conditions is unavailable, data on patient-reported medical conditions authorized by HCPs was used as a surrogate measure for providers’ clinical experience (Figure 1).
- The number of patients enrolled in marijuana for medical use programs who use it for chronic pain, post-traumatic stress disorder (PTSD), arthritis, and cancer increased from 2016 through 2020 (Figure 1).

Factor 1(a) Conclusion: Taken together, the data support that a substantial number of HCPs have gained clinical experience with at least one specific medical use of marijuana under state-authorized programs.

Factor 1(b) – *Whether a substantial number of entities that regulate the practice of medicine recognize at least one specific medical use of the substance.*

Factor 1(b) Findings: The identified secondary data show that, across jurisdictions that conduct medical or scientific reviews prior to authorizing marijuana for particular medical use(s), ‘reviewing/recommending bodies’ are not necessarily the same entities that regulate the practice of medicine more generally. However, marijuana for medical use programs within these jurisdictions have included provisions for a board of qualified experts to evaluate the inclusion of additional qualifying medical conditions to those specified in a jurisdiction’s law. These boards make their determinations through a process of reviewing available research as well as

considering expert and public testimony. As noted, regulatory entities with oversight of the medical use of marijuana under each jurisdiction varies widely. For example, a state Department of Health, Department of Revenue, Department of Finance, Public Safety, Board of Pharmacy, and Alcohol Control Office may have varying degrees of oversight in their jurisdiction. A review of secondary data analyzed shows that the specific type and number of qualifying medical conditions recognized by jurisdictions varies, as does the medical or scientific evidence referenced to support adding to each jurisdiction's list of qualifying medical conditions.

Thirty-eight states, the District of Columbia, and four territories³ have laws that authorize the use of marijuana for medical use(s) (Table 1). These efforts reflect actions taken to implement programs to assess and oversee the use of marijuana in their jurisdiction.

- Seventeen jurisdictions have added conditions through a medical review process (Table 2a).
- Twenty-one of the marijuana for medical use programs include provisions for a board of qualified experts to determine the inclusion of additional qualifying medical conditions to those specified in the law.⁴
- The Prescription Drug Monitoring Training and Technical Assistance Center (PDMP TTAC) tracks PDMP data, under a grant funded from the Bureau of Justice Assistance. TTAC information is reported from two sources: PDMP Administrators and a review of laws and regulations. TTAC sends out an annual survey (>90% response rate) to the respective PDMP Administrators to determine their current policies and capabilities. All 50 states, the District of Columbia, Guam, Puerto Rico, and the Northern Mariana Islands received this survey; it was not sent to the U.S. Virgin Islands as they do not have a PDMP tracking program. TTAC reports marijuana for medical use information. Such information was reported or available through the PDMP in the following jurisdictions: Arizona, Connecticut, Illinois, Massachusetts, New Jersey, New York, North Dakota, Ohio, Oklahoma, Pennsylvania, Utah, Vermont, Virginia.⁵
- Additionally, TTAC also reports specific requirements around PDMP HCP checks.⁶ Examples requiring provider checks were identified by TTAC as follows:
 1. Florida - provides that a qualified physician may issue a physician certification for the medical use of marijuana only if the physician has reviewed the patient's-controlled drug prescription history in the PDMP.
 2. Louisiana - an emergency rule, effective 8/1/2020, includes a requirement that prior to dispensing any marijuana product to a patient, the marijuana product dispensing pharmacist shall review the patient's records in the Louisiana prescription monitoring program.

³ <https://www.ncsl.org/health/state-medical-cannabis-laws>, see Table 1.

⁴ https://assets.nationbuilder.com/americansforsafeaccess/pages/27187/attachments/original/1675362731/StateoftheStates22_P5.pdf?1675362731

⁵ https://www.pdmpassist.org/Policies/Maps/PDMP_Policies

⁶ https://www.pdmpassist.org/pdf/Mandatory_Query_Conditions.pdf

3. Massachusetts - before issuing a written certification for marijuana, a certifying healthcare provider must query the PDMP and review the qualifying patient's prescription history, unless otherwise specified by the Commission.
 4. New York - requires practitioners to consult the PDMP prior to making or issuing a certification of a serious condition requiring the use of marijuana; requires dispensers to check the PDMP to ensure that a patient is not receiving greater than a 30-day supply.
 5. Rhode Island - requires practitioners query the PDMP prior to issuing a written certification for marijuana and make a judgment about the potential for drug-drug interactions, adverse events, or untoward clinical outcomes from adding marijuana.
 6. Utah - any qualified medical provider, who recommends or renews a recommendation for marijuana, to review any record related to the patient in the state's electronic verification system and the controlled substances database.
- A substantial number of jurisdictions have written procedures for addressing complaints, adverse events, and recalls in marijuana dispensaries (Table 2b).⁴
 - A substantial number of jurisdictions recognize the use of marijuana for various medical conditions such as Amyotrophic Lateral Sclerosis (ALS) (36), Autism Spectrum Disorder (34), cachexia (29), cancer (40), conditions causing chronic or intractable pain (40), Crohn's Disease (34), epilepsy or other conditions causing seizures (39), glaucoma (36), HIV/AIDS (39), Multiple Sclerosis (39), Parkinson's Disease (35), persistent/severe muscle spasm (33), persistent/severe nausea (33), PTSD (39), spasticity (31) (Table 3).

Factor 1(b) Conclusion: The above summary and attached tables demonstrate that a substantial number of regulatory entities recognize at least one specific medical use of the substance.

Factor 1(c) – Whether licensed health care practitioners' clinical experience with the medical use of the substance is of sufficient extent and duration to help evaluate potential clinical uses and longer-term toxicities and potential harms of the substance when used under medical supervision.

Factor 1(c) Findings:

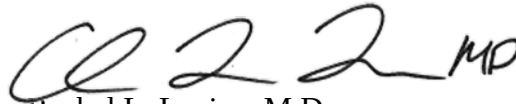
- Approximately six million individual U.S. patients are currently registered in programs that authorize the use of marijuana for various medical conditions, with 14 jurisdictions having more than 100,000 registered patients (Table 4).
- Between 1996-2000, eight jurisdictions legalized marijuana for medical use in the United States (Table 1 and Figure 1), and currently several jurisdictions have documented processes to track adverse events, complaints, and recalls (Table 2b).
- A substantial number of jurisdictions require the HCP to have an established, bona-fide, relationship with the patient. Some require a specific duration of follow up with patients after recommending marijuana for medical use.

Factor 1(c) Conclusion: The above summary and attached tables and figure demonstrate that HCPs' clinical experience with the use of marijuana for various medical conditions is of sufficient extent and duration to help evaluate potential clinical uses. However, based on the available secondary data for this analysis, it could not be conclusively determined whether HCP clinical experience with the use of marijuana is of sufficient extent and duration to help evaluate

the longer-term toxicities and potential harms of marijuana when used under medical supervision.

SUMMARY OF CONCLUSIONS

OASH's Part 1 analysis confirmed that more than 30,000 HCPs are certified to recommend the use of marijuana for more than six million registered patients, constituting widespread clinical experience associated with various medical conditions recognized by a substantial number of jurisdictions across the United States. For several jurisdictions, these programs have been in place for several years, and include features that actively monitor medical use and product quality characteristics of marijuana dispensed. Taken together, the findings from Part 1 warrant an FDA assessment under Part 2 of the Department's CAMU approach to determine if there exists credible scientific support for the use of marijuana for at least one of the medical conditions listed in Table 3.

A handwritten signature in black ink, appearing to read 'RL Levine MD', is positioned above the printed name.

Rachel L. Levine, M.D.
ADM, USPHS

Attachments

TAB A: Tables 1, 2a, 2b, 3 and 4; Figure 1

Table 1: Year of Legalization and Implementation of the Medical Use of Marijuana in the U.S.

U.S Jurisdiction	Year Legalized ^a	Year Implemented ^b
Alabama	2021	2023
Alaska	1999	2016
Arizona	2010	2012
Arkansas	2016	2019
California	1996	2018
Colorado	2000	2014
Connecticut	2012	2017
Delaware	2011	2015
District of Columbia	2011	2013
Florida	2016	2016
Guam	2014	NA
Hawaii	2000	2017
Illinois	2013	2015
Iowa	2017	2018
Louisiana	2015	2019
Maine	1999	2011
Maryland	2013	2017
Massachusetts	2012	2015
Michigan	2008	2018
Minnesota	2014	2015
Mississippi	2022	2023
Missouri	2018	2020
Montana	2004	2018
Nevada	1998	2015
New Hampshire	2013	2016
New Jersey	2010	2012
New Mexico	2007	2010
New York	2014	2016
North Dakota	2016	2019
The Northern Mariana Islands	2018	2021
Ohio	2016	2019
Oklahoma	2018	2018
Oregon	1998	2015
Pennsylvania	2016	2018
Puerto Rico	2016	2017
Rhode Island	2006	2013

TAB A - Tables and Figures

U.S Jurisdiction	Year Legalized ^a	Year Implemented ^b
Table 1, continued		
South Dakota	2020	2022
Utah	2018	2020
Vermont	2004	2013
Virginia	2020	2020
Washington	1998	2016
West Virginia	2017	2021
US Virgin Islands	2019	2023
^a Year legalized refers to the year statute was enacted. ^b Year implemented refers to the year in which the first dispensary opened.		

Table 2a: U.S. Jurisdictions That Conduct Medical or Scientific Review Prior to Recognizing a Medical Condition as Appropriate for Marijuana Use.

U.S Jurisdiction	Approved After Medical or Scientific Review (Yes/No)	Reviewing/ Recommending Bodies	Medical Conditions Recognized	Medical Conditions Denied (Listed or 'No')
Connecticut	Yes	Department of Consumer Protection/Board of Physicians	• Post Laminectomy Syndrome with Chronic Radiculopathy • Severe Psoriasis • Psoriatic Arthritis • Amyotrophic Lateral Sclerosis (ALS) • Ulcerative Colitis • Complex Regional Pain Syndrome Type 1 and Type II • Sickle Cell Disease • Spasticity • Neuropathic Pain Associated with Osteogenesis Imperfecta • Chronic Neuropathic Pain Associated with Degenerative Spinal Disorders • Interstitial Cystitis • MALS Syndrome (Median Arcuate Ligament Syndrome) • Vulvodynia • Vulvar Burning • Intractable Neuropathic Pain, unresponsive to standard medical treatments • Tourette Syndrome • Chronic Pain of at least 6 months duration, associated with a specified underlying chronic condition refractory to other treatment intervention • Ehlers-Danlos Syndrome Associated with Chronic Pain • Chronic Pancreatitis • Movement disorders associated with Huntington	No

TAB A - Tables and Figures

U.S Jurisdiction	Approved After Medical or Scientific Review (Yes/No)	Reviewing/ Recommending Bodies	Medical Conditions Recognized	Medical Conditions Denied (Listed or 'No')
Table 2a, continued				
Delaware	Yes	Delaware Department of Health and Social Services	• Autism – pediatric • Autism with Aggressive and/or Self-injurious Behaviors	• Anxiety • Opioid Use Disorder
Florida	Yes	Department of Health	• Epilepsy	No
Guam	Yes	An advisory board of nine (9) members including practitioner a variety of specialty fields	• Depression • Anxiety • Sleep disorders • Chronic pain • Autism (added to the list of approved debilitating conditions)	No
Hawaii	Yes	Department of Health	• Amyotrophic Lateral Sclerosis (ALS)	No
Illinois	Yes	Illinois Department of Public Health	• Terminal Illness • Autism • Anorexia nervosa • Chronic pain • Ehlers-Danlos syndrome • Irritable bowel syndrome • Migraines • Neuro-Bechet's autoimmune disease • Neuropathy • Osteoarthritis • Polycystic kidney disease (PKD)	No
Iowa	Yes	Medical Cannabidiol Board and Iowa Board of Medicine	• Severe Intractable Pediatric Autism with Self-Injurious Behavior • Corticobasal Degeneration • Intellectual Disability (ID) with Aggression and/or Self-Injury • Ulcerative Colitis	No

TAB A - Tables and Figures

U.S Jurisdiction	Approved After Medical or Scientific Review (Yes/No)	Reviewing/ Recommending Bodies	Medical Conditions Recognized	Medical Conditions Denied (Listed or 'No')
Table 2a, continued				
Michigan	Yes	Licensing and Regulatory Authority Medical Marijuana Review Panel	• Cerebral palsy • PTSD (post-traumatic stress disorder) • Autism • Arthritis • Chronic Pain • Colitis • IBS • Obsessive Compulsive Disorder • Parkinson's Disease • Rheumatoid Arthritis • Tourette Syndrome • Ulcerative Colitis	• Chronic Aggressive Behavior
Minnesota	Yes	Department of Health (approved by the Health Commissioner)	• Intractable Pain • PTSD (post-traumatic stress disorder) • Autism spectrum disorder • Obstructive sleep apnea • Alzheimer's disease • Chronic pain • Sickle cell disease • Motor or vocal tic disorder • Irritable bowel syndrome • Obsessive compulsive disorder	No
New Hampshire	Yes	Therapeutic Cannabis Medical Oversight Board	• Insomnia • Autism Spectrum Disorder	• Anxiety • Tick-borne illnesses • Opioid use disorder
New Jersey	Yes	State Health Commissioner after review by the Medical Marijuana Review Panel	• Tourette Syndrome • Chronic Pain of Visceral Origin • Anxiety • Migraine • Chronic pain related to musculoskeletal disorder • Chronic pancreatitis • Irritable bowel syndrome • Opioid use disorder	• Chronic fatigue syndrome • Asthma

TAB A - Tables and Figures

U.S Jurisdiction	Approved After Medical or Scientific Review (Yes/No)	Reviewing/ Recommending Bodies	Medical Conditions Recognized	Medical Conditions Denied (Listed or 'No')
Table 2a, continued				
New Mexico	Yes	Medical Cannabis Medical Advisory Board recommendation / Secretary for the Department of Health	• Anxiety Disorder • Depression • ADHD • Autism Spectrum • Dystonia • Migraines • Degenerative Neurological Disorder • Neuroprotective as Approved Conditions • Alzheimer's Disease • Tourette's (Tourette Syndrome)	• Nystagmus • Substance Use Disorder
New York	Yes	State Department of Health (approved by the Commissioner of Health)	• Severe debilitating pain • PTSD (post-traumatic stress disorder) • Any condition for which an opioid could be prescribed	No
Ohio	Yes	State Medical Board of Ohio	• Cachexia or wasting syndrome • Huntington's disease • Terminal illness • Spasticity	• Autism • Irritable Bowel Syndrome
Oregon	Yes	Public Health Division, Oregon Health Authority	• Cancer • Glaucoma • A degenerative or pervasive neurological condition • HIV/AIDS, a side effect related to the treatment of those medical conditions • Medical conditions or treatment for a medical conditions that produces cachexia • Severe pain • Severe nausea • Seizures • Persistent muscle spasms • PTSD (post-traumatic stress disorder)	No

TAB A - Tables and Figures

U.S Jurisdiction	Approved After Medical or Scientific Review (Yes/No)	Reviewing/ Recommending Bodies	Medical Conditions Recognized	Medical Conditions Denied (Listed or 'No')
Table 2a, continued				
Pennsylvania	Yes	Medical Advisory Board, PA Department of Health	• Cancer including remission therapy • Neurodegenerative diseases • Terminal illness • Dyskinetic Spastic movement disorders • Severe Chronic Intractable pain of neuropathic origin • Severe Intractable pain • Opioid use disorder • Anxiety Disorder • Chronic Hepatitis C • Tourette Syndrome	No
Rhode Island	Yes	Department of Health	• Autism Spectrum Disorder • Pain • Nausea and other symptoms associated with certain debilitating medical conditions, as found by the National Academy of Sciences' Institute of Medicine in March 1999	No

Table 2b: Other Quality Indicators of U.S. Jurisdictions' Programs for Medical Use of Marijuana.

U.S. Jurisdiction	Educational Requirements for Certification	ASA ^a Grade for Dispensary Operations	Patient Level Tracking of Marijuana Dispensed ^b
Alabama	Yes	Yes	No
Alaska	No	No	No
Arizona	No	No	No
Arkansas	No	Yes	No
California	No	Yes	No
Colorado	No	Yes	No
Connecticut	No	Yes	Yes
Delaware	No	No	Yes
District of Columbia	No	No	No
Florida	Yes	Yes	Yes
Guam	No	No	No
Hawaii	No	Yes	No
Illinois	No	Yes	No
Iowa	No	Yes	Yes
Louisiana	No	No	No
Maine	No	No	No
Maryland	No	Yes	No
Massachusetts	Yes	No	Yes
Michigan	No	Yes	No
Minnesota	No	No	No
Mississippi	Yes	No	No
Missouri	No	No	No
Montana	No	Yes	No
Nevada	No	No	No
New Hampshire	No	Yes	No
New Jersey	No	Yes	No
New Mexico	No	Yes	No
New York	Yes	Yes	Yes
North Dakota	No	Yes	No
The Northern Mariana Islands	No	No	No
Ohio	No	No	Yes
Oklahoma	No	No	No
Oregon	No	Yes	No
Pennsylvania	Yes	No	No

TAB A - Tables and Figures

U.S. Jurisdiction	Educational Requirements for Certification	ASA ^a Grade for Dispensary Operations	Patient Level Tracking of Marijuana Dispensed ^b
Table 2b, continued			
Puerto Rico	Yes	Yes	No
Rhode Island	No	Yes	Yes
South Dakota	No	No	No
Utah	Yes	No	Yes
Vermont	No	Yes	No
Virginia	No	Yes	No
Washington	Yes	Yes	No
West Virginia	Yes	No	No
US Virgin Islands	No	No	No
^a Americans for Safe Access (ASA) Annual “State of State” report include score cards for each state with a medical cannabis program in place. “Dispensary Operations” are scored on a number of variables. This analysis focuses on one variable of “Dispensary Operations”: ‘adverse event reporting and recall protocol’. This provides an impression of whether dispensaries are reporting adverse events and, if so, how they are addressing these reports. Americans for Safe Access Foundation is a non-profit 501(c)3 organization whose mission is to ensure safe and legal access to cannabis (marijuana) for therapeutic use and research.			
^b Patient Level Tracking- most jurisdictions have ‘Seed to Sale’ tracking, however, based on data provided by the Cannabis Regulators Association (CANNRA) only nine jurisdictions track amounts dispensed to patients.			

Table 3: Medical Conditions Recognized for Medical Use of Marijuana by U.S. Jurisdictions

Medical Condition	U.S Jurisdictions	Total Number of Jurisdictions That Recognize the Medical Condition
Amyotrophic Lateral Sclerosis (ALS)	AK, AL, AZ, CA, CT, DC, FL, GU, HI, IA, IL, LA, MA, ME, MI, MD, MN, MO, MS, ND, NJ, NM, NV, NY, NY, OH, OK, PA, OR, RI, SD, USVI, UT, VA, WV, WA	36
Autism Spectrum Disorder	AK, AL, AZ, CA, CO, CT, DE, DC, GU, HI, IA, IL, LA, MA, MD, ME, MI, MN, MO, MS, ND, NJ, NM, NV, NY, OK, OR, PA, RI, SD, USVI, UT, VA, WA	34
Cachexia	AK, AL, AZ, CA, CO, CT, DC, DE, GU, HI, IA, IL, LA, MA, MD, MI, MO, MT, ND, NJ, NV, NY, OK, OR, RI, SD, USVI, UT, WA	29
Cancer	AZ, AK, AL, CA, CO, CT, DC, DE, FL, GU, HI, IL, IA, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, UT, VA, VT, WA, WV	40
Condition causing chronic or intractable pain	AK, AL, AZ, CA, CO, CT, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, UT, VA, VT, WA, WV	40
Crohn's Disease	AK, AL, AZ, CA, CT, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MO, MS, MT, ND, NJ, NV, OH, OK, OR, PA, RI, SD, UT, VA, VT, WA, WV	34
Epilepsy or condition causing seizures	AK, AL, AZ, CA, CO, CT, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, UT, VA, VT, WA, WV	39
Glaucoma	AK, AZ, CA, CO, CT, DC, DE, FL, GU, HI, IL, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, VA, VT, WA	36
HIV/AIDs positive	AK, AL, AZ, CA, CO, CT, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, UT, VT, WA, WV	39

TAB A - Tables and Figures

Medical Condition	U.S Jurisdictions	Total Number of Jurisdictions That Recognize the Medical Condition
Table 3, continued		
Multiple Sclerosis	AK, AL, AZ, CA, CT, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, UT, VA, VT, WA, WV	39
Parkinson's Disease	AK, AL, AZ, CA, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MO, MS, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, USVI, VA, VT, WA, WV	35
Persistent/severe muscle spasm	AK, AL, AZ, CA, CO, CT, DC, DE, FL, GU, HI, IL, LA, MA, MD, ME, MI, MN, MO, MT, ND, NJ, NM, NV, NY, OK, OR, PR, RI, SD, USVI, UT, WA	33
Persistent/severe nausea	AK, AL, AZ, CA, CO, DC, DE, FL, GU, HI, IA, IL, MA, MD, ME, MI, MO, MS, MT, ND, NJ, NM, NV, NY, PR, OK, OR, RI, SD, USVI, UT, VT, WA	33
Post-Traumatic Stress Disorder (PTSD)	AK, AL, AZ, CA, CO, CT, DC, DE, FL, GU, HI, IA, IL, LA, MA, MD, ME, MI, MN, MO, MS, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, USVI, UT, VA, VT, WA, WV	39
Spasticity	AK, AL, AZ, CA, CT, DC, DE, FL, GU, HI, IL, LA, MA, MD, ME, MI, MO, MT, ND, NJ, NM, NV, NY, OH, OK, OR, PA, RI, SD, WA, WV	31
Note: This list includes all mechanisms for recognizing qualifying conditions to include ballot initiatives, legislation, and clinical/scientific review. Numbers include states/territories in which the specific condition is not named, but alternative situations allow for treatment for corresponding condition in that category.		

Table 4: Number of Certified Practitioners and Registered Patients Across U.S. Jurisdictions Medical Use Programs

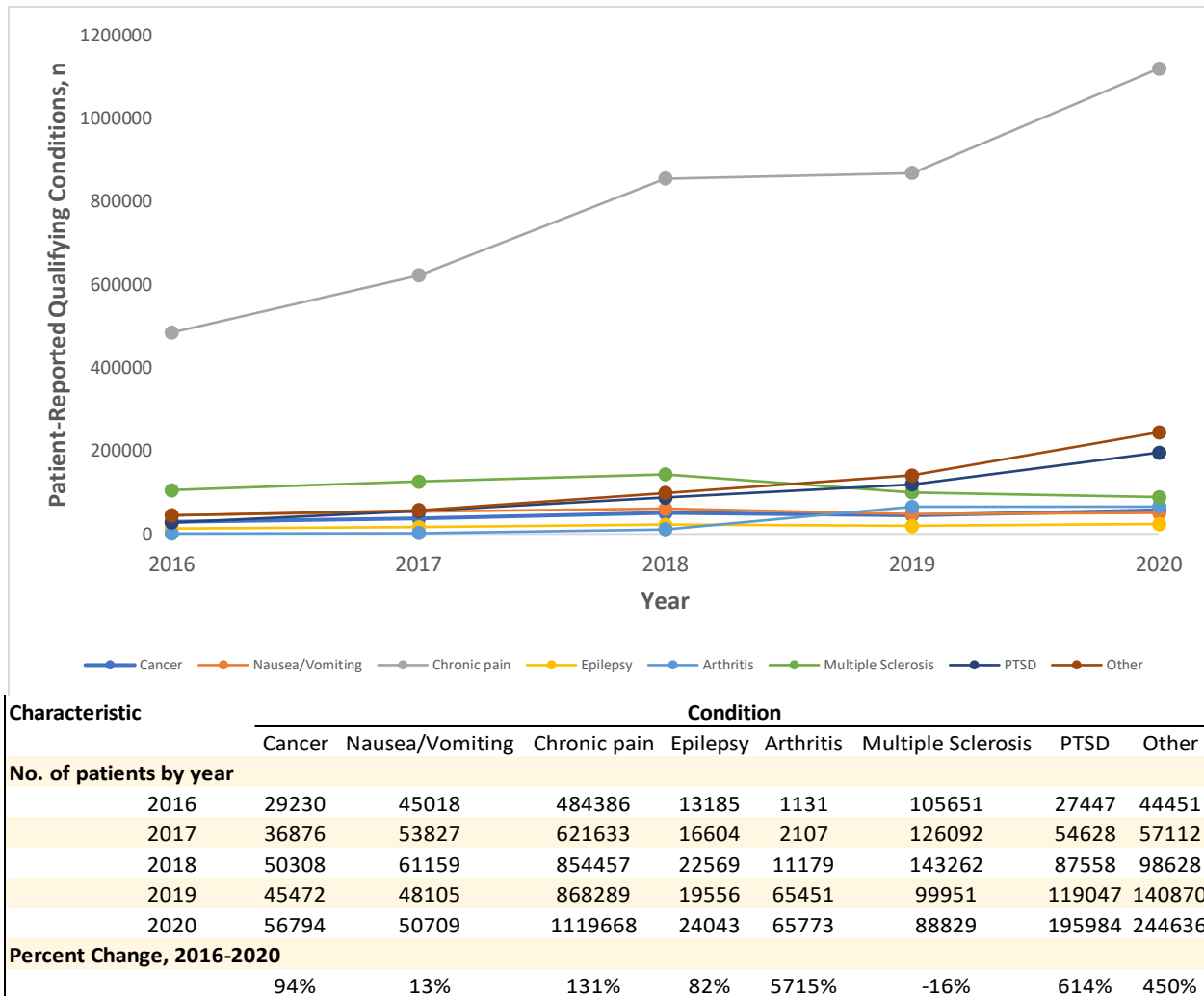
U.S. Jurisdiction	Number of Certified Practitioners	Timeframe for Practitioner Data	Number of Registered Patients ^a
Alabama	MISSING ^b	MISSING	0
Alaska	MISSING	MISSING	404
Arizona	1,667	March 23, 2023	129,836
Arkansas	989	July 1, 2022- June 30, 2022	90,266
California	MISSING	MISSING	MISSING
Colorado	306	January 1, 2022 -December 21, 2022	71,536
Connecticut	1,667	March 31, 2023	49,780
Delaware	467	2021	19,715
District of Columbia	602	December 2021	16,348
Florida	2,563	October 1, 2020 -September 30, 2021	778,781
Guam	0	2019	0
Hawaii	35	May 2021	33,424
Illinois	5,300	Between July 1, 2019 - June 30, 2020	136,574
Iowa	1,821	July 2022	11,676
Louisiana	219	Second Quarter 2021	20,321
Maine	753	2021	106,164
Maryland	1,135	April 5, 2023	161,722
Massachusetts	358	September, 2022	97,003
Michigan	243	February 28, 2023	184,564
Minnesota	2,303	February 2, 2023	39,552
Mississippi	122	December, 2022	0
Missouri	MISSING	January 1, 2022 - Dec. 21, 2022	204,165
Montana	267	January 1, 2020	40,801
Nevada	979	January, 2023	12,788
New Hampshire	1,273	July 2020-June 2021	12,237
New Jersey	1,012	April 13, 2023	112,404
New Mexico	MISSING	MISSING	112,426
New York	4,033	April 1, 2023	123,391
North Dakota	340	June 30, 2022	8,898
The Northern Mariana Islands	MISSING	MISSING	0
Ohio	660	March 8, 2023	317,018
Oklahoma	MISSING	MISSING	374,077
Oregon	1,333	January, 2023	17,957
Pennsylvania	1,812	January, 2023	423,443
Puerto Rico	MISSING	MISSING	118,007

TAB A - Tables and Figures

U.S. Jurisdiction	Number of Certified Practitioners	Timeframe for Practitioner Data	Number of Registered Patients ^a
Table 4, continued			
Rhode Island	MISSING	MISSING	16,462
South Dakota	208	April 3, 2023	6,166
Utah	473	April, 2023	61,991
Vermont	MISSING	MISSING	4,302
Virginia	938	January, 2023	52,810
Washington	MISSING	MISSING	52,479
West Virginia	131	March 31, 2023	7,000
US Virgin Islands	MISSING	MISSING	0
^a Americans for Safe Access (ASA) Foundation is a non-profit 501(c)3 organization whose mission is to ensure safe and legal access to cannabis (marijuana) for therapeutic use and research https://www.safeaccessnow.org/ . ^b Missing: data marked “missing” indicative of a) states not tracking data, b) states tracking data but the data is not available or c) it is unknown whether the state tracks the data.			

TAB A - Tables and Figures

Figure 1. Substantial Increase in Marijuana Use for Chronic Pain, PTSD, Arthritis & Cancer, 2016-2020^a



Note. Adapted from “U.S. Trends in Registration for Medical Cannabis and Reasons for Use From 2016 to 2020” by Boehnke, KF, Dean, O, Haffajee, RL, and Hosanagar, A., 2022, *Annals of Internal Medicine*, 175(7), p. 948. Includes patient-reported qualifying conditions in medical-only marijuana use states: Arkansas, Arizona, Delaware, Hawai’i, Maryland, Minnesota, Missouri, Montana, New Hampshire, New Mexico, North Dakota, Ohio, Rhode Island, Utah

Considerations for Whether Marijuana Has a Currently Accepted Medical Use in the United States for Purposes of Section 202(b) of the Controlled Substances Act

**Report prepared by the Food and Drug Administration's Center for Drug
Evaluation and Research (CDER), by personnel located in CDER's:**

Office of the Center Director's Controlled Substance Staff

and

**Office of Surveillance and Epidemiology's Office of Pharmacovigilance and
Epidemiology, Division of Epidemiology I**

August 28, 2023

Table of Contents

Table of Tables	iv
Table of Figures	ix
Glossary	1
I. Executive Summary.....	3
1. Background	3
2. Summary of Findings Under Part 2 of the CAMU Test.....	4
3. Conclusions on Marijuana and CAMU	7
II. Evaluation of Marijuana With Respect to CAMU	8
1. Introduction	8
2. Definitions Relevant to the Analysis of Whether Marijuana Has a CAMU	9
3. Overview of the Analysis of Marijuana and CAMU: Parts 1 and 2.....	10
3.1. Summary of the OASH Findings Under Part 1 of the CAMU Test	10
3.2. Approach to Part 2 of the CAMU Test	10
4. Assessment of Data Under Part 2 of the CAMU Test for Marijuana	11
4.1. Patterns of Use in the Context of Medical Use.....	11
4.1.1. International Cannabis Policy Study (ICPS).....	12
4.1.1.1. Methods	12
4.1.1.2. Results	13
4.1.1.3. Discussion.....	16
4.1.2. National Survey on Drug Use and Health (NSDUH)	17
4.1.2.1. Methods	17
4.1.2.2. Results	17
4.1.2.3. Discussion.....	24
4.1.3. Behavioral Risk Factor Surveillance System (BRFSS)	24
4.1.3.1. Methods	24
4.1.3.2. Results	25
4.1.3.3. Discussion.....	28
4.1.4. Monitoring the Future (MTF)	28
4.1.4.1. Methods	28
4.1.4.2. Results	29
4.1.4.3. Discussion.....	29

4.1.5. Conclusions on Patterns of Medical Use	29
4.2. University of Florida Systematic Literature Review	30
4.2.1. Methods.....	30
4.2.2. Results	33
4.2.2.1. Anorexia	33
4.2.2.2. Anxiety	36
4.2.2.3. Epilepsy	39
4.2.2.4. Inflammatory Bowel Disease	41
4.2.2.5. Nausea	48
4.2.2.6. Pain	51
4.2.2.7. Post-Traumatic Stress Disorder	68
4.3. Conclusions Based on the Report by the University of Florida	70
4.4. FDA Review of Published Systematic Reviews and Meta-Analyses.....	71
4.4.1. Sources of Review.....	71
4.4.1.1. Pain	72
4.4.1.2. Anxiety Disorders.....	76
4.4.1.3. Nausea and Vomiting	77
4.4.1.4. Post-Traumatic Stress Disorder	77
4.4.1.5. Inflammatory Bowel Disease	78
4.4.1.6. Epilepsy	80
4.4.1.7. Anorexia Related to Medical Conditions	80
4.5. Safety Data From Case Studies of Selected State Programs: Maryland and Minnesota.....	81
4.5.1. Maryland	81
4.5.1.1. Maryland Methods.....	81
4.5.1.2. Maryland Results	81
4.5.1.3. Maryland Discussion	83
4.5.2. Minnesota.....	84
4.5.2.1. Minnesota Methods	84
4.5.2.2. Minnesota Results	84
4.5.2.3. Minnesota Discussion.....	87
4.5.3. Conclusion	87
4.6. Summary of FDA-Approved Drug Products Related to Marijuana	88

4.7. Summary of Expert Opinions and Position Statements.....	89
5. Overall Conclusions for Part 2 of the Currently Accepted Medical Use Test for Marijuana	90
III. Appendices.....	93
1. International Cannabis Policy Study (ICPS).....	93
2. Behavioral Risk Factor Surveillance System (BRFSS)	102
3. Monitoring the Future (MTF)	105
4. State Data From State Medical Marijuana Programs.....	105
4.1. Maryland Medical Cannabis Patient Survey 2022 (MMCPS-22)	105
4.2. Maryland Medical Cannabis Commission (MMCC) Tables.....	106
4.3. Minnesota Tables.....	111
5. Tables and Figures Excerpted from University of Florida’s Systematic Review of the Medical Literature on Cannabis Use.....	115
5.1. Anorexia	115
5.2. Anxiety	117
5.3. Inflammatory Bowel Disease	119
5.4. Nausea.....	121
5.5. Pain	122
5.6. Post-Traumatic Stress Disorder	126
IV. References.....	128
1. Literature	128
2. Position Statements	134
3. Other	134
4. Government Documents.....	135
5. Prescribing Information.....	135
6. University of Florida Systematic Literature Review.....	135

Table of Tables

Table 1. Reason for Past-Year Use of Cannabis, ICPS, 2018-2021	13
Table 2. Ever Asked a Licensed Health Professional for a Recommendation to Use Medical Cannabis, Among Exclusive Past- Year Medical Cannabis Consumers, 2021	14
Table 3. Ever-Use of Cannabis to Improve or Manage Symptoms for Any of the Selected Psychiatric Conditions, Among Exclusive Past-Year Medical Cannabis Consumers, 2021.....	14
Table 4. Ever-Use of Cannabis to Improve or Manage Symptoms for Any of the Following, Among Exclusive Past-Year Medical Cannabis Consumers, 2021	15
Table 5. Used Cannabis for Pain Relief, Instead of Using Opioids or Prescription Pain Medication in the Past 12 Months, Among Exclusive Past-Year Medical Cannabis Consumers, 2021	16
Table 6. Past-Year Co-Use of Alcohol With Cannabis Among Exclusive Past-Year Medical Cannabis Consumers, 2021	16
Table 7. Marijuana Use Recommended by a Healthcare Provider, Individuals Ages 12 Years or Older With Past-Year Use of Marijuana: National Survey on Drug Use and Health, 2015-2021 (Numbers in Thousands).....	18
Table 8. Marijuana Use Recommended by a Healthcare Provider, Individuals Ages 12 Years or Older With Past-Year Use of Marijuana by Age Group: National Survey on Drug Use and Health, 2015-2021 (Numbers in Thousands)	19
Table 9. Frequency of Marijuana Use in the Past Year, by Age Group: Among Past-Year Marijuana Users With Different Use Types Aged 12 or Older, NSDUH, 2021 (Numbers in Thousands)	19
Table 10. Method of Acquiring Last Marijuana Used Among Those Who Used Marijuana in Past 12 Months by Healthcare Provider (HCP) Recommendation, Individuals Ages 12 Years or Older, NSDUH, 2021 (Numbers in Thousands).....	21
Table 11. From Whom Latest Purchased Marijuana Was Bought Among Individuals Who Purchased Marijuana in the Past 12 Months, Individuals Ages 12 Years or Older, NSDUH, 2021 (Numbers in Thousands).....	23
Table 12. Distribution by Age Group of Respondents, BRFSS 2021.....	25
Table 13. Distribution by Age Group of Respondents Who Reported Past 30-Day Marijuana Use, BRFSS, Marijuana Module, 2021	25

Table 14. Past 30-Day Marijuana Use by Reason for Use, BRFSS, Marijuana Module, 2021	26
Table 15. Past 30-Day Use of Marijuana by Age Category and Stratified by Reason of Use, BRFSS, Marijuana Module, 2021	27
Table 16. Categories and Definitions for the Overall Evidence Quality Ratings*	32
Table 17. Quality of Evidence Rating for Appetite, Certainty Rating by Study and Overall.....	35
Table 18. Quality of Evidence Rating for Quality of Life, Certainty Rating by Study and Overall.....	35
Table 19. Quality of Evidence Rating for Food/Caloric Intake, Certainty Rating by Study and Overall	35
Table 20. Quality of Evidence Rating for Body Weight, Certainty Rating by Study and Overall.....	35
Table 21. Quality of Evidence Rating for Anxiety Scales (Self-Rating Anxiety Scale; Symptom Checklist-90; Spielberger State-Trait Anxiety), Certainty Rating by Study and Overall	38
Table 22. Quality of Evidence Rating for Profile of Mood States, Certainty Rating by Study and Overall	38
Table 23. Quality of Evidence Rating for Fibromyalgia Impact Questionnaire: Anxiety Component, Certainty Rating by Study and Overall	38
Table 24. Quality of Evidence Rating for HADs: Quality of Life Component, Certainty Rating by Study and Overall	39
Table 25. Quality of Evidence Rating for Clinical Disease Activity Indexes (CDAI/Lichtiger/Mayo Score), Certainty Rating by Study and Overall	43
Table 26. Quality of Evidence Rating for Daily Function, General Well-Being, General Effect on Health, Certainty Rating by Study and Overall	43
Table 27. Quality of Evidence Rating for Quality of Life, Certainty Rating by Study and Overall.....	43
Table 28. Quality of Evidence Rating for Pain, Certainty Rating by Study and Overall	44
Table 29. Quality of Evidence Rating for Remission, Certainty Rating by Study and Overall.....	44
Table 30. Quality of Evidence Rating for Number of Bowel Movements/Stool Frequency, Certainty Rating by Study and Overall	44
Table 31. Quality of Evidence Rating for Rectal Bleeding, Certainty Rating by Study and Overall.....	45

Table 32. Quality of Evidence Rating for Weight, Certainty Rating by Study and Overall	45
Table 33. Quality of Evidence Rating for Disease-Specific Quality of Life, Certainty Rating by Study and Overall	45
Table 34. Quality of Evidence Rating for Bloating, Certainty Rating by Study and Overall.....	46
Table 35. Quality of Evidence Rating for Nausea, Certainty Rating by Study and Overall.....	46
Table 36. Quality of Evidence Rating for Appetite, Certainty Rating by Study and Overall.....	46
Table 37. Quality of Evidence Rating for Endoscopy Assessment (Simple Endoscope Score; Mayo Endoscopic Score), Certainty Rating by Study and Overall	47
Table 38. Quality of Evidence Rating for Chemotherapy-Induced Nausea and Vomiting, Certainty Rating by Study and Overall.....	50
Table 39. Quality of Evidence Rating for Nausea-Specific Quality of Life (Functional Living Index-Emesis (FLIE), Certainty Rating by Study and Overall	50
Table 40. Quality of Evidence Rating for Overall Health-Related Quality of Life, Certainty Rating by Study and Overall.....	50
Table 41. Quality of Evidence Rating for Post-Operative Nausea and Vomiting, Certainty Rating by Study and Overall.....	51
Table 42. Quality of Evidence Rating for Pain Scores Assessed Via Visual Analog Scales, Certainty Rating by Study and Overall.....	57
Table 43. Quality of Evidence Rating for Pain Scores Assessed Via Numeric Rating Scales, Certainty Rating by Study and Overall	60
Table 44. Quality of Evidence Rating for Pain Scores Via Other Types of Patient-Reported Scores or Questionnaires, Certainty Rating by Study and Overall	62
Table 45. Quality of Evidence Rating for Pain Scores Assessed Via Neuropathic-Specific Pain Scales, Certainty Rating by Study and Overall	64
Table 46. Quality of Evidence Rating for Sleep Quality in People With Pain, Certainty Rating by Study and Overall	66
Table 47. Quality of Evidence Rating for Pain Disability, Certainty Rating by Study and Overall.....	67
Table 48. Quality of Evidence Rating for Opioid Composite Score, Certainty Rating by Study and Overall	67

Table 49. Quality of Evidence Rating for the PTSD Severity Assessment Outcome (CAPS-5), Certainty Rating by Study and Overall	70
Table 50. Most Common Condition or Symptom Treated With Cannabis Among Maryland Medical Cannabis Commission (MMCC) Survey Participants.....	82
Table 51. Primary Method of Marijuana Consumption in the Past Month, Maryland Medical Cannabis Commission (MMCC) Survey Participants.....	82
Table 52. Percentage of Medical Use vs. Recreational Use in the Past Month Among Maryland Medical Cannabis Commission (MMCC) Survey Participants.....	82
Table 53. Baseline Characteristics of Minnesota Medical Cannabis Patients 2017-2022*	85
Table 54. Professional Organizations' Position Statements.....	89
Table 55. Marijuana Legalization by State, 2021.....	93
Table 56. Sample Characteristics, ICPS, 2018-2021.....	94
Table 57. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Sex, ICPS, 2021.....	96
Table 58. Time Since Last Cannabis Use Among Exclusive Past Year Medical Cannabis Consumers, Recency of Use by Age (NSDUH Age Categories), ICPS, 2021	96
Table 59. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Race, ICPS, 2021	97
Table 60. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Ethnicity, ICPS, 2021	98
Table 61. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Cannabis Source, ICPS, 2021.....	99
Table 62. Cannabis Purchasing by Type of Store Among Exclusive Past-Year Medical Cannabis Consumers Who Bought Cannabis From a Store, 2021	100
Table 63. Marijuana Use for Any Reason, Medical Reason, and Both Medical and Nonmedical Reason in the Past 30 Days in the Participating States/Territories, BRFSS, Marijuana Module, 2021.....	102
Table 64. Past 30-Day Marijuana Use by Method of Use and Stratified by Reason of Use, BRFSS, Marijuana Module, 2021	104
Table 65. Sample Size and Response Rate, MTF, 2017–2022.....	105
Table 66. Descriptive Characteristics of Maryland Medical Cannabis Commission (MMCC) Survey Participants	106

Table 67. Frequencies of Substance Use in the Past Month Maryland Medical Cannabis Commission (MMCC) Survey Participants	108
Table 68. Methods of Cannabis Administration (One Time or More) in the Past Month Maryland Medical Cannabis Commission (MMCC) Survey Participants	109
Table 69. Perceived Effectiveness of Cannabis Treatment, Maryland Medical Cannabis Commission (MMCC) Survey Participants	109
Table 70. Perceived Health and Social Effects of Cannabis Among Maryland Medical Cannabis Commission (MMCC) Survey Participants	109
Table 71. Frequency of Conditions While Consuming Cannabis Among Maryland Medical Cannabis Users	110
Table 72. Symptoms Experienced by Maryland Medical Cannabis Users in the Past Six Months, Maryland Medical Cannabis Commission (MMCC) Survey Participants	110
Table 73. Frequency of Treatment in an Emergency Room or Urgent Care Facility for Any Reason Related to Cannabis Consumption Among Maryland Medical Cannabis Users	111
Table 74. Frequency of Driving Within Three Hours of Consuming Cannabis and/or Under the Influence of Cannabis in the Past Month Among Maryland Medical Cannabis Patients	111
Table 75. Qualifying Medical Conditions for Medical Cannabis Use in Minnesota	111
Table 76. Minnesota Survey Responses and Most Common Adverse Events (AEs) for 2015-2017	112
Table 77. Frequencies of Side Effects Reported Among Minnesota Medical Cannabis Patients by Year and Severity, 2017-2022	112
Table 78. Top Ten Side Effects Reported on the MN Patient Self-Evaluation by Year (2017-2022)	112
Table 79. Patient Numbers by State: 2016-2020 (Only States With Available Data)	114
Table 80. Summary of Included Studies for Anorexia	115
Table 81. References (Studies Included in Risk of Bias Assessments, Anorexia)	115
Table 82. Summary of Included Studies for Anxiety	117
Table 83. References (Studies Included in Risk of Bias Assessments, Anxiety)	117
Table 84. Summary of Included Studies for Inflammatory Bowel Disease	119

Table 85. References (Studies Included in Risk of Bias Assessments, Inflammatory Bowel Disease)	119
Table 86. Summary of Included Studies for Nausea.....	121
Table 87. References (Studies Included in Risk of Bias Assessments, Nausea)	121
Table 88. Summary of Included Studies for Pain.....	122
Table 89. References (Studies Included in Risk of Bias Assessments, Pain)	122
Table 90. Summary of Included Studies for Post-Traumatic Stress Disorder.....	126
Table 91. References (Studies Included in Risk of Bias Assessments, Post-Traumatic Stress Disorder)	126

Table of Figures

Figure 1. Prevalence of Use of Marijuana Under a Doctor’s Order in Grades 8th, 10th, and 12th, MTF, 2017–2022	29
Figure 2. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Anorexia	34
Figure 3. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Anxiety.....	37
Figure 4. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Epilepsy	40
Figure 5. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Inflammatory Bowel Disease	41
Figure 6. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Nausea.....	49
Figure 7. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Pain.....	53
Figure 8. Meta-Analysis of Marijuana on Changes of VAS From Baseline Using A Random-Effects Model.....	55
Figure 9. Funnel Plot on Changes of VAS From Baseline.....	56
Figure 10. Meta-Analysis of Marijuana on Change in NRS From Baseline.....	58
Figure 11. Funnel Plot of Marijuana on Change of NRS From Baseline	59
Figure 12. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Post-Traumatic Stress Disorder	69
Figure 13. Top Ten Side Effects Reported on the MN Patient Self-Evaluation, 2021	87

Figure 14. Risk of Bias Assessment, Randomized Clinical Trials, Anorexia.....	116
Figure 15. Risk of Bias Assessment, Observational Studies, Anorexia.....	116
Figure 16. Risk of Bias Assessment, Randomized Clinical Trials, Anxiety.....	117
Figure 17. Risk of Bias Assessment, Observational Studies, Anxiety.....	118
Figure 18. Risk of Bias Assessment, Randomized Clinical Trials, Inflammatory Bowel Disease	120
Figure 19. Risk of Bias Assessment, Observational Studies, Inflammatory Bowel Disease	120
Figure 20. Risk of Bias Assessment, Randomized Clinical Trials, Nausea	121
Figure 21. Risk of Bias Assessment, Randomized Clinical Trials, Pain	124
Figure 22. Risk of Bias Assessment, Observational Studies, Pain	125
Figure 23. Risk of Bias Assessment, Randomized Clinical Trials, Post- Traumatic Stress Disorder	127
Figure 24. Risk of Bias Assessment, Observational Studies, Post- Traumatic Stress Disorder	127

Glossary

AAFP	American Academy of Family Physicians
AAN	American Academy of Neurology
AAPOR	American Association for Public Opinion Research
AASM	American Academy of Sleep Medicine
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
APA	American Psychiatric Association
ASAM	American Society of Addiction Medicine
BRFSS	Behavioral Risk Factor Surveillance System
CAERS	CFSAN Adverse Event Reporting System
CAMU	currently accepted medical use in treatment in the United States
CAPS-5	Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders
CBD	cannabidiol
CDAI	Crohn's disease activity index
CFSAN	Center for Food Safety and Applied Nutrition
CI	confidence interval
CPPC	Cannabis Public Policy Consulting
CSA	Controlled Substances Act
Δ 9-THC	delta-9-tetrahydrocannabinol
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DEPI	Division of Epidemiology I
DSM	Diagnostic and Statistical Manual of Mental Disorders
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FR	<i>Federal Register</i>
GRADE	grading of recommendations, assessment, development, and evaluation
HCP	healthcare provider
HHS	Department of Health and Human Services
IASP	International Association for the Study of Pain
IBD	Inflammatory Bowel Disease
ICPS	International Cannabis Policy Study
IND	investigational new drug
MD	Maryland
MMCC	Maryland Medical Cannabis Commission
MMCPs	Maryland Medical Cannabis Patient Survey
MN	Minnesota
MTF	Monitoring the Future

NAADAC	Association for Addiction Professionals
NASEM	National Academies of Sciences, Engineering, and Medicine
NDA	new drug application
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NPDS	National Poison Data System
NRS	Numeric Rating Scale
NSDUH	National Survey on Drug Use and Health
OASH	Office of the Assistant Secretary for Health
OR	odds ratio
OSE	Office of Surveillance and Epidemiology
PDAS	public online data analysis system
PRISMA	preferred reporting items for systematic reviews and meta-analysis
PTSD	post-traumatic stress disorder
PUF	public use file
RCT	randomized controlled trials
RR	relative risk
RUF	restricted use file
SAE	serious adverse event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAS	Statistical Analysis System
THC	tetrahydrocannabinol
UF	University of Florida
VAS	Visual Analog Scale

I. Executive Summary

1. Background

The Department of Health and Human Services (HHS) has conducted an evaluation of whether marijuana¹ has a “currently accepted medical use in treatment in the United States” (CAMU) for purposes of scheduling under the Controlled Substances Act (CSA), 21 U.S.C. 812(b). Such an evaluation is one of the findings relevant to the placement of a substance in one of five drug control “schedules” set forth in 21 U.S.C. 812(b).

In evaluating CAMU when considering whether to recommend rescheduling of marijuana, HHS applied a two-part test (hereinafter, “CAMU test”) that takes into account the current widespread medical use of marijuana under the supervision of licensed health care practitioners (HCPs) under state-authorized programs. Under Part 1 of the CAMU test, the Office of the Assistant Secretary for Health (OASH) considered whether there is widespread current experience with medical use of marijuana in the United States by licensed HCPs operating in accordance with implemented state-authorized programs, where such medical use is recognized by entities that regulate the practice of medicine under these state jurisdictions. Part 2 of the CAMU test, performed herein by the FDA, evaluates whether there exists some credible scientific support for at least one of the medical conditions for which the Part 1 test is satisfied. FDA’s evaluation in Part 2 is not meant to be, nor is it, a determination of safety and efficacy that meets the Federal Food, Drug, and Cosmetic Act’s (FD&C Act’s) drug approval standard for new human or animal drugs. Rather, the two-part test is to determine whether a substance, in this case marijuana, has a CAMU for purposes of drug scheduling recommendations and placement in a drug schedule consistent with criteria set forth in 21 U.S.C. 812(b).

In the evaluation and assessment under Part 1 of the CAMU test, OASH found that more than 30,000 HCPs are authorized to recommend the use of marijuana for more than six million registered patients, constituting widespread clinical experience associated with various medical conditions recognized by a substantial number of jurisdictions across the United States. For several jurisdictions, these programs have been in place for several years, and include features that actively monitor medical use and product quality characteristics of marijuana dispensed. OASH, through the Assistant Secretary for Health, concluded that, taken together, the findings from Part 1 warrant an FDA assessment under Part 2 of the CAMU test to determine if there exists credible scientific support for the use of marijuana for at least one of the medical conditions identified by OASH under Part 1.

¹ See Section II.2.

FDA conducted Part 2 of the CAMU test for seven indications, based in part on OASH's findings under Part 1 of the CAMU test² and in part on FDA's own analysis of the landscape in which marijuana is currently used medically, including information from state-authorized programs on how and to what extent marijuana is being utilized for medical purposes. The seven indications are: anorexia³, anxiety⁴, epilepsy, inflammatory bowel disease (IBD), nausea and vomiting, pain, and post-traumatic stress disorder (PTSD). FDA's evaluation under Part 2 of the CAMU test was based on systematic reviews of studies investigating the safety and effectiveness of marijuana, relevant professional societies' position statements, data from state medical marijuana programs and U.S. national surveys, and the labeling of FDA-approved products relevant to the analysis.

2. Summary of Findings Under Part 2 of the CAMU Test

In evaluating whether there exists some credible scientific support under Part 2 of the CAMU test for a particular use, factors considered in favor of a positive finding included whether: 1) favorable clinical studies of the medical use of marijuana, although not necessarily adequate and well-controlled clinical studies that would support approval of a new drug application (NDA), have been published in peer-reviewed journals and/or 2) qualified expert organizations (e.g., academic or professional societies, government agencies) have opined in favor of the medical use or provided guidance to HCPs on the medical use. Factors considered that weigh against a finding that Part 2 of the CAMU test is met included whether: 1) data or information indicate that the medical use of the substance is associated with unacceptably high safety risks for the likely patient population, e.g., due to toxicity concerns; 2) clinical studies with negative efficacy findings for the medical use of marijuana have been published in peer reviewed journals; and/or 3) qualified expert organizations (e.g., academic or professional societies,

² In Part 1 of the CAMU test, OASH identified at least 15 medical conditions where there is widespread current experience with medical use of the substance in the United States by licensed health care practitioners operating in accordance with implemented state-authorized programs, where the medical use is recognized by entities that regulate the practice of medicine. These conditions include amyotrophic lateral sclerosis (ALS), autism, cachexia, cancer, chronic pain, Crohn's disease, epilepsy or condition causing seizures, glaucoma, HIV/AIDs, multiple sclerosis, Parkinson's disease, persistent/severe muscle spasm, persistent/severe nausea, PTSD, and spasticity. FDA conducted Part 2 of the analysis for the medical conditions identified by OASH that were likely to have the most robust evidence available for review; because our analysis concluded that the Part 2 test has been met for at least one of the conditions identified in Part 1, there was no need to analyze all of them.

³ The anorexia indication reflects anorexia due to a medical condition (e.g., HIV/AIDS) and does not represent anorexia nervosa.

⁴ While anxiety was not one of the specific medical conditions identified by OASH, it is included herein because anxiety was identified by the FDA during the Part 2 review of state-level usage data. See, e.g., Table 3. FDA considered the medical use of marijuana for the treatment of anxiety of importance to evaluate given the reported prevalence of marijuana use for the treatment of anxiety regardless of the legal status of such use in a given jurisdiction.

government agencies) recommend against the medical use of marijuana (based on the available data at the time of their position statement).

Our review of the available information identified mixed findings of effectiveness across indications, ranging from data showing inconclusive findings to considerable evidence in favor of effectiveness, depending on the source. The largest evidence base for effectiveness exists for marijuana use within the pain indication (in particular, neuropathic pain). For the pain indication, a systematic review of scientific and medical literature was conducted this year by the University of Florida (UF) (see Sections [II.3.2](#) and [II.4.2](#) for additional details) under contract with FDA. UF epidemiologists identified some data supporting effectiveness of marijuana, including some within their own meta-analysis; however, they ultimately concluded the results are inconclusive or mixed. FDA also conducted a separate review of published systematic reviews. Several of those reviews drew conclusions similar to UF. In contrast, numerous other systematic reviews concluded that there exists some level of evidence supporting the use of marijuana for painful conditions. Other reviews, such as the National Academies of Sciences, Engineering, and Medicine (NASEM) report (2017), concluded there was “substantial evidence”⁵ supporting the use of cannabis products relevant to this review for pain. The Agency for Healthcare Research and Quality’s (AHRQ) living systematic review has concluded that there is some support for the use of marijuana-related products in the treatment of pain, but overall concluded these effects were small and the increased risk of dizziness, nausea and sedation may limit the benefit.

UF evaluated other therapeutic conditions mentioned above, i.e., anorexia, anxiety, epilepsy, inflammatory bowel disease (IBD), nausea, and PTSD, employing a similar systematic review of scientific and medical literature. UF found that there is low- to moderate-quality evidence⁶ supporting the use of marijuana as medical treatment for outcomes in anorexia, nausea and vomiting, and PTSD. However, FDA review of systematic reviews showed mixed results for these indications. In particular, FDA found that the potential for psychiatric adverse events associated with treating PTSD with marijuana may be more substantial than any limited benefit in observational studies. Although UF did not conclude that there was evidence in support of the effectiveness of marijuana in IBD, both their review and other systematic reviews found some benefit with respect to subjective symptoms in this condition. With regard to epilepsy and anxiety, both UF’s review and FDA’s review of other systematic reviews did not find support for marijuana providing benefit in the treatment of these conditions. Where positive results on effectiveness outcome measures were found, the effects and the quality of evidence were generally in the low-to-moderate range. UF did not find high quality evidence supporting worsening of outcomes in any indication.

None of the evidence from the systematic reviews included in our CAMU Part 2 analysis identified any safety concerns that would preclude the use of marijuana in the indications

⁵ The term “substantial evidence” refers to language used within the NASEM report (2017) and is not meant to represent “substantial evidence” as defined in 21 USC 355(d).

⁶ UF determined the quality of evidence rating in accordance to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach described in the Cochrane handbook. For further details, please refer to the Section II.4.2.1 in this document.

for which there exists some credible scientific support for its therapeutic benefit. The clinical safety data identified in the literature from controlled trials were generally consistent between sources but limited in the rigor of safety reporting. The vast majority of the observational studies evaluated in the context of medical use were excluded from the final synthesis of evidence due to concerns regarding their quality (only one observational study for the anxiety indication and one for the PTSD indication were included). Generally, data on safety from both clinical trials and observational studies were scarce. Literature shows marijuana has more adverse events when compared to a placebo or active control group, however, typically in the mild to moderate severity range. Severe adverse events were uncommon.

FDA also reviewed results from state reporting data from 37 states with medical marijuana programs and surveys of patients using marijuana in Maryland and Minnesota, which had data available for review. Surveys of patients using marijuana in these two states found most patients did not report any side effects and those that did report side effects mostly described them as mild. Neither state's databases included patients who chose to stop using marijuana, which may result in an overestimation of positive experiences.

To date, real-world data sources available to FDA, in general, lack the necessary elements to identify the exposure (i.e., marijuana), to distinguish the reason for use (medical vs. recreational) and, if applicable, the condition that prompted its medical use, and/or to permit sound inferential analyses. Therefore, they were not included in this review.

Data from U.S. national surveys, in general, lacked details on patient characteristics and factors that prompted the use of marijuana for medical purposes, and data collection for these surveys was impacted by the coronavirus disease of 2019 (COVID-19) pandemic. Despite these limitations, these data suggested that medical use of marijuana increases as age increases. Only data from one survey provided information on intended indication for use, suggesting that users often use marijuana to improve or manage conditions such as depression, anxiety, PTSD, pain, headaches or migraines, sleep disorders, nausea and vomiting, lack of appetite, and muscle spasms, but only approximately half of them reportedly had ever asked a healthcare professional for a recommendation to use medical marijuana.

Additionally, although the safety data obtained from use in a medical context are considered to be the most relevant for the CAMU analysis, FDA evaluated the safety of marijuana in the nonmedical setting to inform the potential for more severe outcomes. Specifically, FDA evaluated safety outcomes related to marijuana use in the setting of nonmedical use, use of uncertain intent, and unintentional exposure through a variety of epidemiological data sources and in relation to several comparator substances controlled under the CSA, including drugs in Schedule I: heroin (an illicit opioid drug); Schedule II: hydrocodone and oxycodone (approved opioid prescription drugs), cocaine and fentanyl (largely illicitly produced drugs in the nonmedical use setting, although there are approved prescription drugs); Schedule III: ketamine (an approved prescription drug); and Schedule IV: zolpidem, benzodiazepines, and tramadol (approved prescription drugs) ([FDA Office of Surveillance and Epidemiology, 2023](#)). The comparative data demonstrate that, even in the context of nonmedical use, marijuana has a less concerning

overall safety profile relative to the comparators for a number of important outcomes (e.g., single substance use overdose death, hospitalizations). However, in young children, population-adjusted rates of emergency department visits and hospitalizations involving marijuana poisoning were higher than heroin, cocaine, and benzodiazepines for the periods studied. Of note, some of the comparator substances are approved for use in conditions similar to the indications for which marijuana is being evaluated in this CAMU analysis (e.g., opioids for pain, benzodiazepines for anxiety related conditions).

FDA also considered position statements from professional organizations relevant to the indications discussed. The vast majority of professional organizations did not recommend the medical use of marijuana in their respective specialty; however, none specifically recommended against it, with the exception of the American Psychiatric Association (APA), which stated that marijuana is known to worsen certain psychiatric conditions.

On balance, the available data indicate that there is some credible scientific support for the use of marijuana in the treatment of pain, anorexia, and nausea and vomiting (e.g., chemotherapy-induced), with varying degrees of support and consistency of findings. Additionally, no safety concerns were identified in our review that would indicate that medical use of marijuana poses unacceptably high safety risks for the indications where there is some credible scientific evidence supporting its therapeutic use.

3. Conclusions on Marijuana and CAMU

Based on the totality of the available data, we conclude that there exists some credible scientific support for the medical use of marijuana in at least one of the indications for which there is widespread current experience in the United States, as identified by OASH under Part 1 of the CAMU test. Seven indications were selected for evaluation under Part 2 of the CAMU test based on conclusions from Part 1 of the CAMU test as well as the FDA's analysis of the landscape of medical use of marijuana. The indications evaluated included anorexia related to a medical condition, anxiety, epilepsy, inflammatory bowel disease, nausea and vomiting (e.g., chemotherapy-induced), pain, and post-traumatic stress disorder. The analysis and conclusions on the available data are not meant to imply that safety and effectiveness have been established for marijuana that would support FDA approval of a marijuana drug product for a particular indication. However, the available data do provide some level of support for the way marijuana is being used in clinical practice. Thus, based on the widespread HCP experience and the extent of medical use evaluated by OASH under the Part 1 test, and an evaluation of available credible scientific support described herein for at least some therapeutic uses identified in the Part 1 test, we find that, for purposes of the drug scheduling criteria in 21 U.S.C. 812(b), marijuana has a currently accepted medical use in the United States for: anorexia related to a medical condition; nausea and vomiting (e.g., chemotherapy-induced); and pain.

II. Evaluation of Marijuana with Respect to CAMU

1. Introduction

Drugs or other substances with abuse potential are placed into one of five schedules (i.e., Schedule I, II, III, IV, or V) under the federal Controlled Substances Act (CSA) based on whether the drug has a currently accepted medical use in treatment in the United States and its degree of abuse and dependency potential. Collectively, drugs and other substances listed among the five drug schedules are controlled substances under federal law and are subject to the federal regulatory requirements of the Drug Enforcement Administration (DEA), where regulatory requirements may vary relative to each of the five drug control schedules. Stricter regulatory controls are associated with schedules that are for those substances posing the greatest harms to public health, i.e., substances controlled under Schedule I and II which have a high potential for abuse and greatest safety concerns and potential to cause severe psychological and/or physical dependence. Specifically, drugs controlled under Schedule I have a high potential for abuse but do not have a currently accepted medical use, whereas drugs controlled under Schedule II have the same high potential for abuse but have a currently accepted medical use in treatment in the United States (CAMU) or a currently accepted medical use with severe restrictions. Drugs in Schedule III, IV, and V, have a currently accepted medical use, but substances in these schedules have incrementally decreasing degrees of abuse potential and dependence liability, i.e., Schedule V having substances with the lowest abuse potential and dependence liability while still warranting some degree of regulatory controls.

On October 6, 2022, the Biden Administration issued a statement on reforms associated with marijuana,⁷ a substance currently controlled in Schedule I of the CSA ([Biden 2022](#)). As part of the statement, the President directed the Secretary of the Department of Health and Human Services (HHS) and the Attorney General to initiate the administrative process to review expeditiously how marijuana is scheduled under federal law. The Secretary requested that the FDA, in consultation with the National Institute on Drug Abuse (NIDA), conduct a scientific and medical evaluation of marijuana that would enable the Office of the Assistant Secretary for Health (OASH), on behalf of the Secretary, to convey recommendations to the DEA regarding the appropriate scheduling of marijuana. A necessary component of the overall scientific and medical evaluation of marijuana for drug scheduling purposes is a finding as to whether marijuana is considered to have a CAMU in the United States under the CSA, where such finding will have implications for the schedule of control that is ultimately recommended by HHS as most appropriate in accordance with 21 U.S.C. 812(b). This document is intended to analyze and present the relevant data and make a determination as to whether marijuana is considered to have a CAMU in the United States under the CSA.

The approach for evaluating CAMU in this memo is a two-part test (hereafter referred to as “CAMU test”). To satisfy Part 1 of the CAMU test, there must be widespread current experience with medical use of the substance in the United States by licensed health care

⁷ “Marijuana” as defined in 21 U.S.C. 802(16)

practitioners operating in accordance with implemented state-authorized programs, where medical use is recognized by entities that regulate the practice of medicine. To satisfy Part 2 of the CAMU test, there must exist some credible scientific support for a least one of the medical uses for which Part 1 of the CAMU test has been met. The purpose of this test is not to determine that the substance is safe and effective under the FD&C Act's drug approval standard, but rather to determine whether there is some credible scientific support for at least one medical use of the substance for which Part 1 of the CAMU test is satisfied, in order to determine whether there is a CAMU for purposes of drug scheduling recommendations under the administrative drug scheduling process [21 U.S.C. 811(a-c) and 812(b)].

2. Definitions Relevant to the Analysis of Whether Marijuana Has a CAMU

Marijuana is a psychoactive drug produced from the *Cannabis sativa L.* plant. Cannabis is one of the oldest cultivated crops, providing a source of fiber, food, oil, and drug, and it contains a variety of chemical compounds, including delta-9-tetrahydrocannabinol (Δ 9-THC). Δ 9-THC is considered to be the main psychoactive component of the *Cannabis sativa L.* plant; however, the plant is also known to contain other psychoactive cannabinoids.

Marijuana is a subset of cannabis, and the CSA defines marijuana or “marihuana”⁸ as:

(16)(A) Subject to subparagraph (B), the terms "marihuana" and "marijuana" mean all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.

(B) The terms "marihuana" and "marijuana" do not include-

(i) hemp, as defined in section 1639o of title 7; or

(ii) the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

The exclusion of “hemp”-type cannabis from marijuana’s Schedule I control status reflects the provisions of the 2018 Agriculture Improvement Act (i.e., the “Farm Bill”), which defined hemp as *Cannabis sativa L.* and its derivatives with no more than 0.3 percent Δ 9-THC on a dry weight basis, and explicitly revised the definition of marijuana in the CSA to exclude, and effectively decontrol, hemp.

⁸ 21 U.S.C. 802(16)

As this document is evaluating the CAMU for marijuana, as it is defined and controlled under Schedule I of the CSA, we will use the term marijuana for our analysis. However, when describing information referenced from other sources, our language will reflect the terminology used in those sources. Additionally, for the purposes of this review, we will use Δ9-THC and THC interchangeably.

3. Overview of the Analysis of Marijuana and CAMU: Parts 1 and 2

3.1. Summary of the OASH Findings Under Part 1 of the CAMU Test

To determine whether marijuana has a CAMU in the United States, OASH conducted an analysis consisting of the first component of the aforementioned two-part test. The goal of Part 1 was to identify whether widespread, current experience with marijuana exists for at least one medical use within jurisdiction-authorized programs, where such medical use is recognized by entities that regulate the practice of medicine. Support for satisfying Part 1 was based on any of the following factors: the number of licensed HCPs who have gained clinical experience with marijuana in at least one specific medical use; the number of entities that regulate the practice of medicine recognize at least one medical use of marijuana and its extent; and the duration of HCP experience with prescribing marijuana for medical use.

OASH conducted the evaluation and assessment of marijuana under Part 1 of the CAMU test and has confirmed that more than 30,000 HCPs across 43 U.S. jurisdictions are authorized to recommend the medical use of marijuana for more than six million legally registered patients for at least 15 medical conditions. Taken together, the data support that a substantial number of HCPs have gained clinical experience with marijuana, and a substantial number of regulatory entities recognize at least one specific medical use of marijuana under authorized programs. Additionally, OASH concluded that HCPs' clinical experience with the use of marijuana for various medical conditions is of sufficient extent and duration to help evaluate potential clinical uses. OASH further noted, however, that based on the available secondary data for this analysis, it could not be conclusively determined whether HCP clinical experience with the use of marijuana is of sufficient extent and duration to help evaluate the longer-term toxicities and potential harms of marijuana when used under medical supervision.

OASH, through the Assistant Secretary for Health, concluded that “the findings from Part 1 warrant an FDA assessment under Part 2 of the Department’s CAMU approach to determine if there exists credible scientific support for the use of marijuana for at least one of the medical conditions [identified by OASH under Part 1].”

3.2. Approach to Part 2 of the CAMU Test

To satisfy Part 2 of the CAMU test, there must exist some credible scientific support for at least one of the medical uses for which Part 1 of the CAMU test has been met. In

evaluating whether there exists some credible scientific support under Part 2 of the CAMU test for a particular use, factors considered in favor of a positive finding included whether 1) favorable clinical studies of the medical use of marijuana, although not necessarily adequate and well-controlled clinical studies that would support FDA approval of a new drug application (NDA), have been published in peer-reviewed journals, and/or 2) qualified expert organizations (e.g., academic or professional societies, government agencies) have opined in favor of the medical use or provided guidance to HCPs on the medical use. Factors considered that weigh against a finding that Part 2 of the CAMU test is met included whether: 1) data or information indicate that the medical use of marijuana is associated with unacceptably high safety risks for the likely patient population, e.g., due to toxicity concerns; 2) clinical studies with negative efficacy findings for the medical use of marijuana have been published in peer reviewed journals; and/or 3) qualified expert organizations (e.g., academic or professional societies, government agencies) have recommended against the medical use of marijuana.

To evaluate marijuana under Part 2 of the CAMU test, this memo will consider data from peer-reviewed publications included in a systematic review of the medical literature on marijuana that was conducted by the Consortium for Medical Marijuana Clinical Outcomes Research at the University of Florida (hereafter referred to as the “University of Florida” or “UF”), a review of published systematic reviews, analysis of safety data that have been collected through state medical marijuana programs, data on patterns of use in the context of medical use as reported in U.S. national surveys, FDA’s findings for approved drug products related to marijuana (e.g., Marinol), and expert opinions and position statements from professional organizations. Examples of meeting the requirement for demonstrating some credible scientific support would be peer-reviewed clinical studies reporting evidence of benefit, or a reputable medical/scientific organization recommending treatment with marijuana for an indication within their area of expertise. The overall conclusions on the criteria for Part 2 of the CAMU test will be based on the totality of the available evidence described above.

4. Assessment of Data Under Part 2 of the CAMU Test for Marijuana

4.1. Patterns of Use in the Context of Medical Use

The purpose of this section is to describe the patterns of medical use of marijuana as reported in U.S. national surveys. Thus, FDA examined patterns of use among medical users of marijuana as reported in four U.S. national surveys: The International Cannabis Policy Study (ICPS), Substance Abuse and Mental Health Services Administration (SAMHSA)’s National Survey on Drug Use and Health (NSDUH), the Centers for Disease Control and Prevention (CDC)’s Behavioral Risk Factor Surveillance System (BRFSS), and the National Institute for Drug Abuse (NIDA)’s Monitoring the Future (MTF).

4.1.1. International Cannabis Policy Study (ICPS)

4.1.1.1. Methods

The ICPS is an international research collaboration led by the University of Waterloo, Canada, designed to examine the public health impact of cannabis legalization in the United States. The ICPS Project includes national population-based surveys conducted annually in the United States since 2018 via self-completed web-based surveys using a repeat cross-sectional design. ICPS recruited individuals through the Nielsen Consumer Insights Global Panel and their partners' panels using non-probability sampling methods. After targeting for age and country criteria, ICPS sent email invitations (with a unique link) to a random sample of panelists (panelists known to be ineligible were not invited).⁹ ICPS oversampled individuals from states that had legalized 'non-medical adult' cannabis in order to provide more robust estimates for individual states. Individuals were eligible to participate in the survey if they resided in the United States, were 16-65 years of age at the time of recruitment and had access to the internet. Respondents were provided with information about the study and provided consent prior to completing the survey for which they received remuneration.

ICPS assessed medical versus 'non-medical' or recreational use among past 12-month cannabis consumers beginning in the 2019 ICPS surveys, and modified the measure in 2020 and 2021 to capture exclusive vs. non-exclusive medical use.¹⁰ ICPS conducted all analyses using post-stratification weights constructed based on the U.S. census estimates. ICPS reported frequencies and descriptive statistics with 95% confidence intervals.¹¹ Analyses are presented based on the legal status of marijuana at the state-level based on three categories: 'recreational states' (states that have legalized adult 'non-medical' marijuana), 'medical states' (states that have legalized medical marijuana, but not 'non-medical' marijuana use), and 'illegal states' (states in which neither 'medical' nor 'non-medical' marijuana use has been legalized at the state level) [Appendix [Table 55](#) for calendar year 2021]. The University of Waterloo conducted all analyses using survey procedures in Statistical Analysis System [SAS] (SAS version 9.4, SAS Institute Inc., Cary, NC, USA). Technical reports for the ICPS surveys provide additional methodological description and are publicly accessible ([Corsetti et al. 2022](#)).

⁹ Individuals outside of the age range (<16 and >65 years), any panelists that resided outside the United States, or those that do not speak English.

¹⁰ The question wording was modified using a 'split half' approach, in which half of respondents in the 2020 and 2021 survey were asked the question using the original 2019 wording (i.e., "Do you self-identify as a medical marijuana user only?"), and half were asked the modified question wording (i.e., "Do you self-identify as a medical marijuana user?").

¹¹ Any estimates based on less than 30 respondents should be interpreted with caution.

4.1.1.2. Results

ICPS collected data from a total of 107,572 respondents aged 16-65 years between 2018 and 2021. The response rate was 64.2% in 2018, 62.9% in 2019, 62.0% in 2020, and 60.8% in 2021. Overall, across the four cohorts, the sample had a similar sex distribution, with approximately 60% of individuals ages 45-64 years, a majority of non-Hispanic and White people, most with some college education or a bachelor's degree, and similarly distributed in regard to income adequacy.¹² Approximately 50% of the sample reported having ever consumed cannabis for any reason (Appendix [Table 56](#)).

A total of 60,193 individuals (56% of 107,572 respondents) were asked whether they identified themselves as a user of cannabis exclusively for medical reasons in the year prior. Approximately 8-10% of this subset of the sample reported being a user of cannabis in the past year for medical reasons only (exclusive) while approximately 20% reported other (recreational) use ([Table 1](#)).

Table 1. Reason for Past-Year Use of Cannabis, ICPS, 2018-2021

	2018 ²	2019 ³	2020 ⁴	2021 ⁵
Reason for Past-Year Use	N/A	(n=30,366)	(n=14,762)	(n=14,858)
Medical use (exclusive) ¹	N/A	8.9% (2,712) (8.4% - 9.4%)	7.9% (1,170) (7.5% - 8.4%)	9.7% (1,447) (9.3% - 10.2%)
Other ('recreational')	N/A	21.7% (6,598) (21.0% - 22.4%)	19.1% (2,819) (18.5% - 19.7%)	22.0% (3,265) (21.3% - 22.7%)

Source: ([Hammond et al. 2023](#)), Table 2a

¹ Respondents were asked "Do you self-identify as a medical marijuana user only?" ('exclusive' medical use)

² In 2018, respondents were not asked if they self-identify as a medical cannabis consumer.

³ In 2019, 94 responses were excluded for refusal to answer

⁴ In 2020 the denominator only includes those who would have seen the 'split half version of the question specific to exclusive medical use; 71 responses excluded for refusal to answer.

⁵ In 2021 the denominator only includes those who would have seen the 'split half version of the question specific to exclusive medical use; 42 responses excluded for refusal to answer.

In the 2021 survey, among the 1,447 individuals reporting cannabis use exclusively for medical reasons in the past year, 56.8% (95% CI [confidence interval]: 53.0% - 60.7%) reported ever having asked a licensed health professional for a recommendation to use medical cannabis ([Table 2](#)). This prevalence rate appears to be only slightly impacted by the legal status of marijuana in the state of residence as 47% (95% CI: 38.6% - 55.4%) of users residing in states with illegal status asked their providers for a prescription/authorization to use medical cannabis.

¹² The wording of the question was "Thinking about your family's income, how difficult or easy is it to make ends meet? 'Making ends meet' means having enough money to pay for the thing your family needs."

Table 2. Ever Asked a Licensed Health Professional for a Recommendation to Use Medical Cannabis, Among Exclusive Past-Year Medical Cannabis Consumers, 2021

Response	Medical (Exclusive)			
	‘Illegal’ States (n=351)	‘Medical’ States (n=450)	‘Recreational’ States (n=646)	All States (n=1,447)
Yes	47.0% (165) (38.6% - 55.4%)	60.2% (271) (53.3% - 67.0%)	59.9% (387) (54.3% - 65.5%)	56.8% (822) (53.0% - 60.7%)
No	50.1% (176) (41.6% - 58.5%)	37.9% (170) (31.0% - 44.7%)	37.7% (244) (32.2% - 43.3%)	40.8% (590) (36.9% - 44.6%)
Missing ¹	3.0% (10) (0.1% - 5.8%)	2.0% (9) (0.0% - 3.9%)	2.4% (15) (1.2% - 3.6%)	2.4% (35) (1.3% - 3.4%)

Source: (Hammond et al. 2023), Table 95.

¹ “Missing” includes respondents who responded “Don’t know” or refused to answer.

Most (67.4%; 95% CI: 63.6-71.1) participants reporting exclusive medical use of cannabis used cannabis in the past month, without significant differences driven by state legal status. Time since last use of cannabis by sex, age group, race, and ethnicity, overall and by state legal status, is shown in the Appendix ([Table 57](#), [Table 58](#), [Table 59](#), and [Table 60](#)).

Approximately 86.7% (n=1,255) of exclusive medical users reported ever using cannabis to improve or manage symptoms related to at least one psychiatric condition. The most frequent selected conditions included anxiety (67.3%), depression (47.8%), post-traumatic stress disorder [PTSD] (31.2%), bipolar disorder (17.2%), and alcohol or other drug use (9.8%) ([Table 3](#)).

Table 3. Ever-Use of Cannabis to Improve or Manage Symptoms for Any of the Selected Psychiatric Conditions, Among Exclusive Past-Year Medical Cannabis Consumers, 2021

Symptom	Medical (Exclusive) ¹			
	‘Illegal’ States (n=351)	‘Medical’ States (n=450)	‘Recreational’ States (n=646)	All States (n=1,447)
Anxiety	69.6% (244) (61.9% - 77.2%)	68.6% (309) (62.1% - 75.1%)	65.3% (422) (60.0% - 70.5%)	67.3% (974) (63.7% - 70.9%)
Depression	55.4% (194) (47.0% - 63.8%)	53.4% (240) (46.5% - 60.3%)	39.7% (257) (34.0% - 45.4%)	47.8% (691) (43.9% - 51.7%)
PTSD	39.8% (140) (31.7% - 48.0%)	29.0% (131) (23.2% - 34.9%)	28.1% (181) (23.0% - 33.2%)	31.2% (452) (27.7% - 34.8%)
Bipolar disorder	25.6% (90) (18.2% - 33.0%)	13.4% (60) (9.3% - 17.5%)	15.4% (99) (11.5% - 19.3%)	17.2% (249) (14.4% - 20.1%)
Psychosis	8.0% (28) (3.0% - 13.1%)	9.3% (42) (5.0% - 13.6%)	8.2% (53) (5.1% - 11.4%)	8.5% (123) (6.2% - 10.8%)
Schizophrenia	5.5% (19) (1.1% - 9.8%)	5.9% (27) (2.6% - 9.3%)	2.1% (14) (1.2% - 3.1%)	4.1% (60) (2.6% - 5.7%)
Alcohol or other drug use	9.4% (33) (4.3% - 14.5%)	10.7% (48) (6.3% - 15.1%)	8.5% (55) (5.2% - 11.7%)	9.4% (136) (7.0% - 11.7%)
Eating disorder	9.5% (33) (4.6% - 14.4%)	7.4% (33) (4.0% - 10.8%)	8.8% (57) (5.8% - 11.8%)	8.5% (124) (6.5% - 10.6%)
ADD/ADHD	8.9% (31) (3.9% - 13.8%)	10.3% (46) (6.4% - 14.2%)	9.9% (64) (6.8% - 13.0%)	9.8% (141) (7.6% - 12.0%)
Other	0.0% (0) (0.0% - 0.0%)	0.5% (2) (0.0% - 1.1%)	0.4% (2) (0.1% - 0.7%)	0.3% (5) (0.1% - 0.6%)

Symptom	Medical (Exclusive) ¹			
	'Illegal' States (n=351)	'Medical' States (n=450)	'Recreational' States (n=646)	All States (n=1,447)
None	5.9% (21) (2.9% - 8.9%)	12.5% (56) (8.0% - 17.0%)	17.8% (115) (13.2% - 22.3%)	13.3% (192) (10.6% - 15.9%)
Missing ²	1.8% (6) (0.0% - 4.7%)	3.4% (15) (0.5% - 6.4%)	1.7% (11) (0.9% - 2.5%)	2.3% (33) (1.1% - 3.5%)

Source: (Hammond et al. 2023), Table 104.

¹ Response options are not mutually exclusive options, column total may sum to greater than 100%.

² "Missing" includes respondents who responded "Don't know" or refused to answer.

Exclusive medical cannabis consumers also often reported use of cannabis to improve or manage symptoms of pain (59.7%), headaches and migraines (48.0%), problems sleeping (39.3%), lack of appetite (27.1%), nausea or vomiting or chemotherapy symptoms (24.6%), and muscle spasms (22.1%) (Table 4).

Table 4. Ever-Use of Cannabis to Improve or Manage Symptoms for Any of the Following, Among Exclusive Past-Year Medical Cannabis Consumers, 2021

Symptom	Medical (Exclusive) ¹			
	'Illegal' States (n=351)	'Medical' States (n=450)	'Recreational' States (n=646)	All States (n=1,447)
Headaches/migraines	51.4% (180) (43.0% - 59.9%)	47.8% (215) (40.9% - 54.7%)	46.4% (300) (40.5% - 52.2%)	48.0% (695) (44.1% - 52.0%)
Pain	64.2% (225) (56.0% - 72.5%)	56.5% (254) (49.5% - 63.4%)	59.6% (385) (53.8% - 65.3%)	59.7% (864) (55.8% - 63.6%)
Nausea/vomiting or chemotherapy symptoms	30.6% (107) (23.2% - 37.9%)	23.2% (104) (17.4% - 28.9%)	22.5% (145) (17.9% - 27.1%)	24.6% (357) (21.4% - 27.9%)
Lack of appetite	30.5% (107) (22.6% - 38.4%)	24.5% (110) (18.6% - 30.5%)	27.0% (174) (21.5% - 32.4%)	27.1% (392) (23.5% - 30.7%)
Seizures	13.5% (47) (6.4% - 20.6%)	7.3% (33) (3.4% - 11.2%)	4.6% (30) (3.1% - 6.1%)	7.6% (110) (5.4% - 9.9%)
Muscle spasms	20.7% (73) (13.9% - 27.5%)	21.1% (95) (15.6% - 26.6%)	23.6% (152) (18.7% - 28.4%)	22.1% (320) (18.9% - 25.3%)
To shrink tumors or treat cancer	5.5% (19) (1.1% - 10.0%)	4.5% (20) (1.5% - 7.5%)	3.6% (23) (2.0% - 5.3%)	4.4% (63) (2.8% - 6.0%)
Problems sleeping	44.0% (154) (35.8% - 52.3%)	38.2% (172) (31.7% - 44.7%)	37.6% (243) (32.0% - 43.1%)	39.3% (569) (35.6% - 43.1%)
Digestion/gastrointestinal issues	17.6% (62) (10.5% - 24.7%)	12.2% (55) (8.0% - 16.4%)	14.6% (94) (10.2% - 19.0%)	14.6% (211) (11.6% - 17.5%)
Fibromyalgia	8.5% (30) (4.9% - 12.0%)	10.0% (45) (6.4% - 13.6%)	6.5% (42) (4.8% - 8.2%)	8.1% (117) (6.4% - 9.7%)
None	3.7% (13) (0.7% - 6.8%)	4.0% (18) (1.0% - 7.1%)	3.2% (20) (1.3% - 5.0%)	3.6% (52) (2.1% - 5.0%)
Missing ²	2.3% (8) (0.0% - 5.3%)	2.7% (12) (0.0% - 5.5%)	1.3% (9) (0.5% - 2.1%)	2.0% (29) (0.8% - 3.2%)

Source: (Hammond et al. 2023), Table 106.

¹ Response options are not mutually exclusive options, column total may sum to greater than 100%.

² "Missing" includes respondents who responded "Don't know" or refused to answer.

Although 34.1% of respondents did not provide an answer, 60.5% of those who reported use of cannabis exclusively for medical reasons in the past year reported having used cannabis for pain relief, instead of using opioids or prescription pain medication in the past 12 months (Table 5).

Table 5. Used Cannabis for Pain Relief, Instead of Using Opioids or Prescription Pain Medication in the Past 12 Months, Among Exclusive Past-Year Medical Cannabis Consumers, 2021

Medical (Exclusive)				
Response	‘Illegal’ States (n=351)	‘Medical’ States (n=450)	‘Recreational’ States (n=646)	All States (n=1,447)
Yes	62.1% (218) (53.9% - 70.6%)	58.7% (264) (51.7% - 65.6%)	61.0% (393) (55.3% - 66.6%)	60.5% (876) (56.7% - 64.4%)
No	8.3% (29) (3.2% - 13.0%)	4.7% (21) (1.6% - 7.6%)	4.3% (28) (2.5% - 6.1%)	5.3% (77) (3.6% - 7.0%)
Missing ¹	29.6% (104) (21.7% - 37.5%)	36.7% (165) (29.9% - 43.6%)	34.8% (225) (29.2% - 40.4%)	34.1% (494) (30.3% - 37.9%)

Source: (Hammond et al. 2023), Table 110.

¹ “Missing” includes respondents who responded “Don’t know” or refused to answer.

At least 40% of exclusive medical users reported using cannabis and alcohol simultaneously, with approximately 11.7% of individuals reporting often or always consuming both substances together (Table 6).

Table 6. Past-Year Co-Use of Alcohol With Cannabis Among Exclusive Past-Year Medical Cannabis Consumers, 2021

Medical (Exclusive)^{1,2}				
Frequency	‘Illegal’ States (n=351)	‘Medical’ States (n=450)	‘Recreational’ States (n=646)	All States (n=1,447)
Never ³	59.3% (208) (50.9% - 67.6%)	55.7% (251) (48.8% - 62.6%)	56.2% (363) (50.3% - 62.0%)	56.8% (821) (52.8% - 60.7%)
Sometimes	24.1% (84) (17.2% - 30.9%)	29.9% (134) (23.5% - 36.2%)	32.8% (212) (27.1% - 38.6%)	29.8% (431) (26.1% - 33.4%)
Often	10.8% (38) (4.9% - 16.7%)	6.6% (30) (3.1% - 10.2%)	7.6% (49) (5.2% - 9.9%)	8.1% (117) (6.0% - 10.2%)
Every time I use cannabis	5.9% (21) (1.0% - 10.7%)	4.4% (20) (1.4% - 7.5%)	1.9% (12) (0.5% - 3.3%)	3.6% (53) (2.0% - 5.3%)

Source: (Hammond et al. 2023), Table 91.

¹ This question was asked only to respondents who had used cannabis in the past 12 months and ever used alcohol.

² ‘Don’t know’ responses are not shown in the table: ‘medical states’ n=15; ‘recreational states’ n=10; ‘all states’ n=25.

³ Those who never used alcohol were included in the “Never” category for this table.

Past-year users of cannabis exclusively for medical purposes more often reported obtaining cannabis from stores/dispensaries (49.7%), followed by family/friends (44.7%), and dealers, while 18.6% reported growing cannabis or making their own cannabis products (Appendix Table 61). Among those reporting purchasing cannabis from a store, approximately 6.3% reported sourcing their cannabis from an illegal/unauthorized store (Appendix Table 62).

4.1.1.3. Discussion

FDA primarily summarized findings among the 1,447 users of cannabis ages 16–65 years surveyed in 2021 who self-reported exclusive use for medical reasons in the past 12 months. Most (67.1%) of these individuals reported use in the past month. Slightly more than half reported ever asking a licensed health professional for a recommendation to use medical cannabis, with slightly higher levels in states that had legalized medical or recreational marijuana. Approximately 86.7% of medical users reported using cannabis to improve or manage psychiatric symptoms, most commonly for depression, anxiety and

PTSD. Medical cannabis users also often reported using cannabis to manage pain, followed by headaches or migraines, sleep disorders, to manage nausea and vomiting, lack of appetite, and muscle spasms. At least 40% of individuals reported using cannabis and alcohol simultaneously. Medical users reported obtaining cannabis through different sources with stores and dispensaries being the most commonly reported cannabis source, followed by family and friends, and dealers. Approximately 19% reported growing cannabis or making their own cannabis products.

These analyses are subject to the limited sample of self-identified exclusive medical users as well as to limitations inherent to survey research, which include the cross-sectional nature of the data and potential for response bias. Self-reported measures of cannabis use are subject to social desirability bias, including for prevalence of use and measures such as purchasing cannabis from illegal retail sources. ICPS recruited respondents using non-probability-based sampling; therefore, the findings do not necessarily provide nationally representative estimates. Lastly, ICPS did not restrict to marijuana in their questions, therefore, to some extent, respondents might have been referring to cannabis-derived products instead that are legal at the federal level (i.e., hemp as defined by the 2018 Farm Bill) as both terms are often used interchangeably.

4.1.2. National Survey on Drug Use and Health (NSDUH)

4.1.2.1. Methods

The NSDUH is an annual, nationally representative, cross-sectional household survey of individuals ages 12 and older that provides information on the use of prescription and illicit drugs in the United States. Since 2015, NSDUH has elicited information on any use, as well as nonmedical use (abuse or misuse), of select prescription and illicit drugs in the past year.

FDA used data from SAMHSA's public online data analysis system (PDAS) to analyze public use data from 2015 to 2020 ([SAMHSA 2023](#)). FDA requested that SAMHSA conduct custom analyses of 2021 using the restricted use file (RUF) rather than the public use file. Due to disclosure avoidance methods used in creating the public use file (PUF), national estimates in terms of numbers and percent may differ between sources; however, disclosure methods have been implemented in such a way that the PUF continues to be representative of civilian members of the noninstitutionalized population in the United States ([CBHSQ 2022b](#)). FDA reported national estimates in terms of numbers of individuals, percent of the total population, and percent of people with any past-year or past-month as well as use as per health care provider recommendation. Additional details are described elsewhere ([FDA Office of Surveillance and Epidemiology, 2023](#)).

4.1.2.2. Results

The weighted sample included a total of 267,694,489 individuals ages 12 years and older in 2015; 269,430,135 in 2016; 272,103,335 in 2017; 273,753,043 in 2018; 275,221,248 in 2019; 276,911,975 in 2020; and 279,843,944 in 2021. The prevalence in use of

marijuana (any use) in the past year ranged from 13.6% in 2015 to 18.7% in 2021([FDA Office of Surveillance and Epidemiology, 2023](#)).

The use of marijuana was not recommended by a healthcare provider for the large majority (>84.2%) of participants who reported its use in the year prior ([Table 7](#)). The percent of individuals who used marijuana only for the reason for which it was recommended to them by an HCP ranged from 6.8% to 10.0%. An additional 3.6% to 5.8% of respondents had an HCP recommendation but also used it for nonmedical purposes ([Table 7](#)).

Table 7. Marijuana Use Recommended by a Healthcare Provider, Individuals Ages 12 Years or Older With Past-Year Use of Marijuana: National Survey on Drug Use and Health, 2015-2021 (Numbers in Thousands)

Year	Nonmedical Use Only: No Recommendation by Healthcare Provider	Medical Use Only: Use as Per Recommendation by Healthcare Provider	Both Medical and Nonmedical Use: Some Use as Per Recommendation by Healthcare Provider
	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)
2015	32,027 (89.0%)	2,631 (7.3%)	1,344 (3.7%)
2016	32,951 (88.6%)	2,907 (7.8%)	1,341 (3.6%)
2017	35,934 (89.0%)	2,745 (6.8%)	1,716 (4.3%)
2018	38,024 (87.9%)	3,312 (7.7%)	1,913 (4.5%)
2019	41,897 (87.5%)	3,723 (7.8%)	2,292 (4.8%)
2020	40,064 (84.2%)	4,746 (10.0%)	2,751 (5.8%)
2021	43,784 (85.8%)	4,502 (8.8%)	2,750 (5.4%)

Source: 2015-2020 provided using NSDUH Public Data Analysis System (PDAS) system analysis of Public Use File ([SAMHSA 2023](#)). 2021 estimates provided using custom SAMHSA analysis of Restricted Use File ([CBHSQ 2022a](#)).

Note: Analysis excluded under 1% of observations with values coded as "bad data" (i.e., usually inconsistent with other data). People who used marijuana in the past year but did not specify whether their use was recommended by a doctor or other healthcare professional were excluded.

Data cited at ([FDA Office of Surveillance and Epidemiology, 2023](#)), Table 3.1.1.

Nearly all adolescents who used marijuana did not have an HCP recommendation ([Table 8](#)). Individuals ages 35-64 and 65+ years appeared to be more likely to have used marijuana only under an HCP recommendation in the year prior than the younger age groups. As such, in 2021, 97.0% of individuals ages 12-17 years with past-year use of marijuana reported use without a recommendation by their HCP, with only 1.0% of individuals reporting use exclusively as per HCP recommendation and an additional 1.9% reporting some use of marijuana as per HCP recommendation and some use for other reasons. For the same year, 83.7% of individuals ages 65+ years with past-year use of marijuana reported use without a recommendation by their HCP, with 11.6% of individuals reporting use exclusively as per HCP recommendation and an additional 4.7% reporting some use of marijuana as per HCP recommendation and some use for other reasons.

Table 8. Marijuana Use Recommended by a Healthcare Provider, Individuals Ages 12 Years or Older With Past-Year Use of Marijuana by Age Group: National Survey on Drug Use and Health, 2015-2021 (Numbers in Thousands)

Year	12-17 Years	18-25 Years	26-34 Years	35-64 Years	65+ Years
	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)
Nonmedical Use Only: No Recommendation by Healthcare Provider					
2015	2,950 (97.3%)	10,370 (91.8%)	7,091 (88.4%)	10,773 (86.0%)	843 (74.8%)
2016	2,773 (96.4%)	10,350 (91.9%)	7,683 (88.2%)	10,945 (85.3%)	1,199 (78.8%)
2017	2,949 (97.1%)	10,852 (92.0%)	7,956 (87.5%)	12,703 (86.6%)	1,476 (81.7%)
2018	2,918 (96.7%)	10,826 (92.1%)	8,934 (86.7%)	13,588 (84.6%)	1,758 (82.7%)
2019	3,105 (96.7%)	10,811 (91.6%)	10,147 (88.4%)	15,694 (83.6%)	2,140 (81.0%)
2020	2,286 (96.2%)	10,480 (90.9%)	9,339 (86.4%)	15,460 (78.6%)	2,498 (78.9%)
2021	2,414 (97.0%)	10,345 (90.6%)	10,376 (85.6%)	17,455 (82.3%)	3,194 (83.7%)
Medical Use Only: Use as Per Recommendation by Healthcare Provider					
2015	21 (0.7%)	522 (4.6%)	653 (8.1%)	1,196 (9.5%)	240 (21.3%)
2016	31 (1.1%)	530 (4.7%)	625 (7.2%)	1,461 (11.4%)	260 (17.1%)
2017	34 (1.1%)	484 (4.1%)	692 (7.6%)	1,270 (8.7%)	264 (14.6%)
2018	34 (1.1%)	464 (4.0%)	881 (8.6%)	1,681 (10.5%)	252 (11.9%)
2019	37 (1.2%)	510 (4.3%)	707 (6.2%)	2,171 (11.6%)	298 (11.3%)
2020	62 (2.6%)	487 (4.2%)	852 (7.9%)	2,849 (14.5%)	496 (15.7%)
2021	25 (1.0%)	553 (4.8%)	1,019 (8.4%)	2,463 (11.6%)	441 (11.6%)
Both Medical and Nonmedical Use: Some Use as Per Recommendation by Healthcare Provider					
2015	62 (2.0%)	401 (3.5%)	282 (3.5%)	556 (4.4%)	44 (3.9%)
2016	74 (2.6%)	379 (3.4%)	401 (4.6%)	423 (3.3%)	64 (4.2%)
2017	54 (1.8%)	460 (3.9%)	448 (4.9%)	688 (4.7%)	66 (3.7%)
2018	66 (2.2%)	459 (3.9%)	491 (4.8%)	798 (5.0%)	116 (5.4%)
2019	67 (2.1%)	488 (4.1%)	625 (5.4%)	907 (4.8%)	205 (7.7%)
2020	27 (1.2%)	559 (4.9%)	620 (5.7%)	1,371 (7.0%)	174 (5.5%)
2021	47 (1.9%)	513 (4.5%)	726 (6.0%)	1,284 (6.1%)	179 (4.7%)

Source: 2015-2020 provided using NSDUH Public Data Analysis System (PDAS) system analysis of Public Use File ([SAMHSA 2023](#)). 2021 estimates provided using custom SAMHSA analysis of Restricted Use File ([CBHSQ 2022a](#)).

Note: Analysis excluded under 1% of observations with values coded as "bad data" (i.e., usually inconsistent with other data). People who used marijuana in the past year but did not specify whether their use was recommended by a doctor or other healthcare professional were excluded (<1%).

Data cited at ([FDA Office of Surveillance and Epidemiology, 2023](#)), Appendix Tables 7.7.7 to 7.7.11.

Individuals without an HCP recommendation for marijuana use were more likely to report use of marijuana in the 30 days prior compared to those with HCP recommended use while the opposite pattern was observed in the 241-365 days prior ([Table 9](#)).

Table 9. Frequency of Marijuana Use in the Past Year, by Age Group: Among Past-Year Marijuana Users With Different Use Types Aged 12 or Older, NSDUH, 2021 (Numbers in Thousands)

Frequency	Weighted Frequency in Thousands	Weighted Prevalence (%)
All Past-Year Marijuana Users		
1-30 days	19,610	37.4
31-60 days	5,446	10.4
61-180 days	7,704	14.7
181-240 days	2,868	5.5
241-365 days	16,826	32.1

Frequency	Weighted Frequency in Thousands	Weighted Prevalence (%)
Past-Year Marijuana Users for Whom No Use Recommended by a Doctor or Other Health Care Professional		
1-30 days	17,636	40.2
31-60 days	4,517	10.3
61-180 days	6,528	14.9
181-240 days	2,380	5.4
241-365 days	12,777	29.1
Past-Year Marijuana Users for Whom All Use Recommended by a Doctor or Other Health Care Professional		
1-30 days	816	18.5
31-60 days	417	9.4
61-180 days	589	13.3
181-240 days	245	5.5
241-365 days	2,356	53.3
Past-Year Marijuana Users for Whom Some, but Not All Use Recommended by a Doctor or Other Health Care Professional		
1-30 days	451	16.4
31-60 days	298	10.8
61-180 days	440	16.0
181-240 days	168	6.1
241-365 days	1,396	50.7

Source: Estimates provided using custom SAMHSA analysis of Restricted Use File, 2021 ([CBHSQ 2022a](#)).

Note: Analysis excluded under 1% of observations with values coded as "bad data" (i.e., usually inconsistent with other data). People who used marijuana in the past year but did not specify whether their use was recommended by a doctor or other healthcare professional were excluded.

Data cited at ([FDA Office of Surveillance and Epidemiology, 2023](#)), Figure 3.1.2.

In 2021, most individuals who used marijuana in the past year bought or paid for it ([Table 10](#)). Individuals with no HCP recommended marijuana use were more likely to receive marijuana for free and less likely to purchase marijuana, compared to those with all or some HCP recommended use.

Table 10. Method of Acquiring Last Marijuana Used Among Those Who Used Marijuana in Past 12 Months by Healthcare Provider (HCP) Recommendation, Individuals Ages 12 Years or Older, NSDUH, 2021 (Numbers in Thousands)

Method of Obtaining Latest Marijuana Used	Any Marijuana Use	Nonmedical Use Only: No Recommendation by Healthcare Provider	Medical Use Only: Use as Per Recommendation by Healthcare Provider	Both Medical and Nonmedical Use: Some Use as Per Recommendation by Healthcare Provider
	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)
Bought/Paid for it	30,794 (59.1%)	25,101 (57.4%)	3,653 (81.3%)	1,935 (70.4%)
Traded something else for it	1,059 (2.0%)	858 (2.0%)	105 (2.3%)	83 (3.0%)
Got it from someone for free or shared someone else's	17,065 (32.7%)	16,071 (36.7%)	428 (9.5%)	552 (20.1%)
Grew it myself	1,172 (2.2%)	866 (2.0%)	166 (3.7%)	141 (5.1%)
Don't know/Refused	2,039 (3.9%)	858 (2.0%)	139 (3.1%)	39 (1.4%)

Source: Estimates provided using custom SAMHSA analysis of Restricted Use File, 2021 ([CBHSQ 2022a](#)).

Note: Analysis excluded under 1% of observations with values coded as "bad data" (i.e., usually inconsistent with other data). People who used marijuana in the past year but did not specify whether their use was recommended by a doctor or other healthcare professional were excluded.

Data cited at ([FDA Office of Surveillance and Epidemiology, 2023](#)), Table 3.1.3.

Among those who reported paying for the last marijuana they used, most purchased marijuana from a dispensary, particularly those reporting use as per recommendation by a healthcare provider ([Table 11](#)). Individuals without HCP recommendation and those with some use as per HCP recommendation for marijuana use were more likely to purchase it from a friend, relative, or other family member compared to those with some or all HCP recommended marijuana use.

Table 11. From Whom Latest Purchased Marijuana Was Bought Among Individuals Who Purchased Marijuana in the Past 12 Months, Individuals Ages 12 Years or Older, NSDUH, 2021 (Numbers in Thousands)

Source of Last Marijuana Used	Any Marijuana Use	Nonmedical Use Only: No Recommendation by Healthcare Provider	Medical Use Only: Use as Per Recommendation by Healthcare Provider	Both Medical and Nonmedical Use: Some Use as Per Recommendation by Healthcare Provider
	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)	Weighted Frequency in Thousands (%)
Dispensary	18,977 (55.0%)	14,060 (49.6%)	3,423 (89.7%)	1,470 (66.5%)
Friend, relative, or family	12,230 (35.5%)	11,336 (40.0%)	295 (7.7%)	547 (24.8%)
Someone I just met or didn't know well	2,661 (7.7%)	2,446 (8.6%)	63 (1.6%)	139 (6.3%)
Don't know/Refused	626 (1.8%)	517 (1.8%)	34 (0.9%)	53 (2.4%)

Source: Estimates provided using custom SAMHSA analysis of Restricted Use File, 2021 ([CBHSQ 2022a](#)).

Note: Analysis excluded under 1% of observations with values coded as "bad data" (i.e., usually inconsistent with other data). People who used marijuana in the past year but did not specify whether their use was recommended by a doctor or other healthcare professional were excluded.

Data cited at ([FDA Office of Surveillance and Epidemiology, 2023](#)), Figure 3.1.4.

4.1.2.3. Discussion

Nearly all adolescents who used marijuana in the year prior did not have an HCP recommendation. Overall, older individuals appeared to be more likely to have used marijuana only under an HCP recommendation than the younger age groups. The large majority of individuals who used marijuana in the past year as per HCP recommendation bought or paid for it, often from a dispensary.

Because SAMHSA restricted the question to use of marijuana as per HCP recommendation, the results reflect the proportion of respondents for which use of marijuana is supported by medical judgment. However, HCP's ability to provide such recommendation is likely influenced by the legal status of the state of residence.

The coronavirus disease of 2019 (COVID-19) pandemic disrupted NSDUH data collection in 2020 and 2021 ([FDA Office of Surveillance and Epidemiology, 2023](#)). Thus, the 2020 results reflect a combination of results collected in the first 3 months of 2020, prior to the beginning of COVID-19 restrictions, and the last 3 months of 2020, which consisted of a mix of in-person collection in areas where COVID-19 rates were low and web-based data collection in other areas. In 2021, SAMHSA collected data both in-person and online web-based surveys, and the frequency of collection mode varied by quarter, with more in-person surveys in later quarters than in earlier quarters. SAMHSA also found mode effects as in-person respondents were more likely to have used certain substances and more likely to have experienced mental health issues than online respondents ([FDA Office of Surveillance and Epidemiology, 2023](#)).

4.1.3. Behavioral Risk Factor Surveillance System (BRFSS)

4.1.3.1. Methods

BRFSS is a national state-based cross-sectional telephone survey that collects data on health-related risk behaviors, chronic health conditions, and use of preventive services from more than 400,000 noninstitutionalized adults ages 18+ years each year ([CDC 2018](#)). Initially established in 1984 in 15 states by the CDC, the survey is currently administered by state health departments—with technical and methodological assistance from CDC—in all 50 states, the District of Columbia, and three U.S. territories. The states use a standardized core questionnaire, optional modules (including a module on marijuana use),¹³ and state-added questions.

FDA analyzed BRFSS data for the calendar year 2021, which included a combination of core and marijuana module-specific questions from states and territories that participated in the optional marijuana questionnaire. Marijuana module data included questions on 1) past 30-day marijuana use, 2) reasons for using marijuana (i.e., medical, non-medical, or

¹³ The states and territories participating in the optional marijuana module are Alaska, Connecticut, Delaware, Guam, Hawaii, Idaho, Illinois, Indiana, Kentucky, Maine, Maryland, Minnesota, Montana, Nebraska, Nevada, New Hampshire, New York, North Dakota, Ohio, Oklahoma, Rhode Island, Utah, Vermont, and Wyoming.

both), and 3) method of use (i.e., smoking, eating, drinking, vaporizing, dabbing, or other). Response rates for BRFSS were calculated using standards set by the American Association for Public Opinion Research (AAPOR) Response Rate Formula. In 2021, the overall median survey response rate was 44.0% and ranged from 23.5 to 60.5% across all states/territories that participated. FDA reported population-level estimates based on complex survey weights and survey designs that adjusted for nonresponse bias and non-coverage areas. Additional details are described in the CDC's BRFSS website ([CDC 2023](#)).

4.1.3.2. Results

A total of 182,212 adults ages ≥ 18 years residing in the participating states and territories responded to the marijuana module in 2021, representing an estimated weighted frequency of 68,152,868 individuals. These individuals were mostly White, Non-Hispanic (67.0%, 95% CI: 66.5, 67.5), Black, Non-Hispanic (11.8%, 95% CI: 11.4, 12.2), or Hispanic (10.5, 95% CI: 10.1, 10.9). Their age distribution is shown in [Table 12](#).

Table 12. Distribution by Age Group of Respondents, BRFSS 2021

Age (Years)	Frequency	Weighted Frequency	Percent	95% Confidence Limits	
18-24	9,390	7,830,004	11.5	11.1	11.9
25-34	17,605	11,077,448	16.3	15.8	16.7
35-44	23,483	10,905,138	16.0	15.6	16.5
45-54	27,902	10,528,936	15.4	15.1	15.9
55-64	35,616	11,614,979	17.0	16.7	17.4
65+	68,216	16,196,364	23.8	23.4	24.2
Total	182,212	68,152,868	100.0	-	-

Of them, a total of 17,889 individuals reported past 30-day use of marijuana, representing a weighted prevalence rate of 11.9% (95% CI: 11.5, 12.3). Among them, 56.9% (95% CI: 55.3, 58.6) were male, 66.6% (95% CI: 65.1, 68.1) White, Non-Hispanic, and 15.0% (95% CI: 13.6, 16.3) Black, Non-Hispanic. Their age distribution is shown in [Table 13](#).

Table 13. Distribution by Age Group of Respondents Who Reported Past 30-Day Marijuana Use, BRFSS, Marijuana Module, 2021

Age (Years)	Frequency	Weighted Frequency	Percent	95% Confidence Limits	
18-24	2,001	1,654,965	20.6	19.1	22.2
25-34	3,512	2,292,084	28.6	27.0	30.2
35-44	3,349	1,485,146	18.5	17.3	19.7
45-54	2,620	954,256	11.9	10.9	12.9
55-64	3,287	1,033,502	12.9	11.9	13.9
65+	2,897	597,458	7.5	6.8	8.1
Total	17,666	8,017,412	100.0	-	-

* Excludes individuals who responded, "Don't know/not sure" and those who refused to answer.

A total of 24.9% (95% CI: 23.6, 26.2) reported use for medical reasons and 38.8% (95% CI: 37.2, 40.5) for both medical and nonmedical reasons ([Table 14](#)). Reason for use in the participating states or territories is shown in the Appendix (Appendix, [Table 63](#)).

Table 14. Past 30-Day Marijuana Use by Reason for Use, BRFSS, Marijuana Module, 2021

Reason for Past 30-Day Marijuana Use*	Frequency	Weighted Frequency	Weighted % (95% CI)
Medical reason	5,357	1,997,581	24.9 (23.6, 26.2)
Nonmedical reason	5,700	2,905,432	36.2 (34.6, 37.8)
Both reasons	6,609	3,114,399	38.8 (37.2, 40.5)
Total (any use)	17,666	8,017,412	100.0

* Excludes individuals who responded, "Don't know/not sure" and those who refused to answer.

Overall, past 30-day use of marijuana for medical reasons increased with age with 12.6% (95% CI: 10.1, 15.1) of individuals ages 18-24 years and 37.1% (95% CI: 33.1, 41.1) of individuals ages 65+ years reporting its use exclusively for this purpose ([Table 15](#)).

Conversely, past 30-day use of marijuana for nonmedical reasons decreased with increasing age with 48.8% (95% CI: 44.5, 53.1) of individuals ages 18-24 years and 32.3% (95% CI: 28.4, 36.1) of individuals ages 65+ years. Among individuals who reported past 30-day use of marijuana for both medical and nonmedical reasons, although CIs overlap, use appears to decrease starting from age 55 years with 30.6% (95% CI: 26.8, 34.5) of individuals ages 65+ years reporting its dual use.

Table 15. Past 30-Day Use of Marijuana by Age Category and Stratified by Reason of Use, BRFSS, Marijuana Module, 2021

Age Group (Years)	Any Reason		Nonmedical Reason		Medical Reason		Both Medical and Nonmedical Reason	
	Frequency	Weighted Frequency	Weighted Frequency (%)	Weighted % (95% CI)	Weighted Frequency (%)	Weighted % (95% CI)	Weighted Frequency (%)	Weighted % (95% CI)
18-24	2,001	1,654,965	807,187	48.8 (44.5, 53.1)	208,576	12.6 (10.1, 15.1)	639,203	38.6 (34.4, 42.8)
25-34	3,512	2,292,084	859,936	37.5 (34.2, 40.9)	444,111	19.4 (17.0, 21.7)	988,037	43.1 (39.8, 46.4)
35-44	3,349	1,485,146	491,771	33.1 (29.9, 36.3)	401,714	27.0 (24.1, 30.0)	591,662	39.8 (36.4, 43.3)
45-54	2,620	954,256	251,969	26.4 (22.8, 30.0)	336,105	35.2 (31.3, 39.2)	366,182	38.4 (33.9, 42.9)
55-64	3,287	1,033,502	301,838	29.2 (25.5, 32.9)	385,463	37.3 (33.2, 41.4)	346,201	33.5 (29.6, 37.4)
65+	2,897	597,458	192,731	32.3 (28.4, 36.1)	221,613	37.1 (33.1, 41.1)	183,114	30.6 (26.8, 34.5)
Total	17,666	8,017,412	2,905,432	36.2 (34.6, 37.8)	1,997,581	34.9 (23.6, 26.2)	3,114,399	38.8 (37.2, 40.5)

* Excludes individuals who responded, "Don't know/not sure" and those who refused to answer.

Regardless of the reason for use, data showed that smoking was the most frequent method of use with 60.3% (95% CI: 57.5, 63.1) among medical users and 73.9% (95% CI: 71.6, 76.3) among those who reported both medical and recreational use (Appendix, [Table 64](#)). Edibles represented 21.3% (95% CI, 19.1, 23.5) of method of use among medical users and 12.6% (95% CI: 10.7, 14.5) among those who reported both medical and recreational use.

4.1.3.3. Discussion

CDC's BRFSS survey data suggest that, among those who report past 30-day use of marijuana, medical use increases with increasing age. Regardless of the reason for use, smoking and edibles were the most frequent methods of use.

Besides limitations inherent to survey research, which include the cross-sectional nature of the data and potential for response bias, the BRFSS data were limited to the 24 states and territories that participated in the 2021 module on marijuana use. Also, response rates differed widely across states and territories with some states having survey response rates as low as 23.5%.

4.1.4. Monitoring the Future (MTF)

4.1.4.1. Methods

Since 1975, MTF collects information on medical and nonmedical use of selected prescription and illicit drugs and alcohol by conducting an annual, nationally representative, cross-sectional survey of 8th, 10th, and 12th graders ([NIDA 2022](#)). The survey is funded by the NIDA, a component of the National Institutes of Health (NIH), and conducted by the University of Michigan. Schools are invited to participate in the MTF study for a 2-year period ([Miech et al. 2023](#)). Informed consent (active or passive, per school policy) is obtained from parents of students younger than 18 years and from students aged 18 years or older. Starting in 2017, the survey included information on marijuana use under a doctor's recommendation.

To secure a nationally representative sample of high school seniors, the survey uses a three-stage sampling procedure, sampling geographic regions, schools, and individual students. MTF used paper-and-pencil surveys prior to 2019, and in 2019, a randomly selected half of students were administered paper-and-pencil surveys while the other half recorded their answers on electronic tablets. From 2020, all students recorded their responses using electronic tablets. In-school data collection stopped on March 15, 2020, as a result of the COVID-19 pandemic resulting in a sample size for the calendar year 2020 that was 25% of the size of a typical data collection.

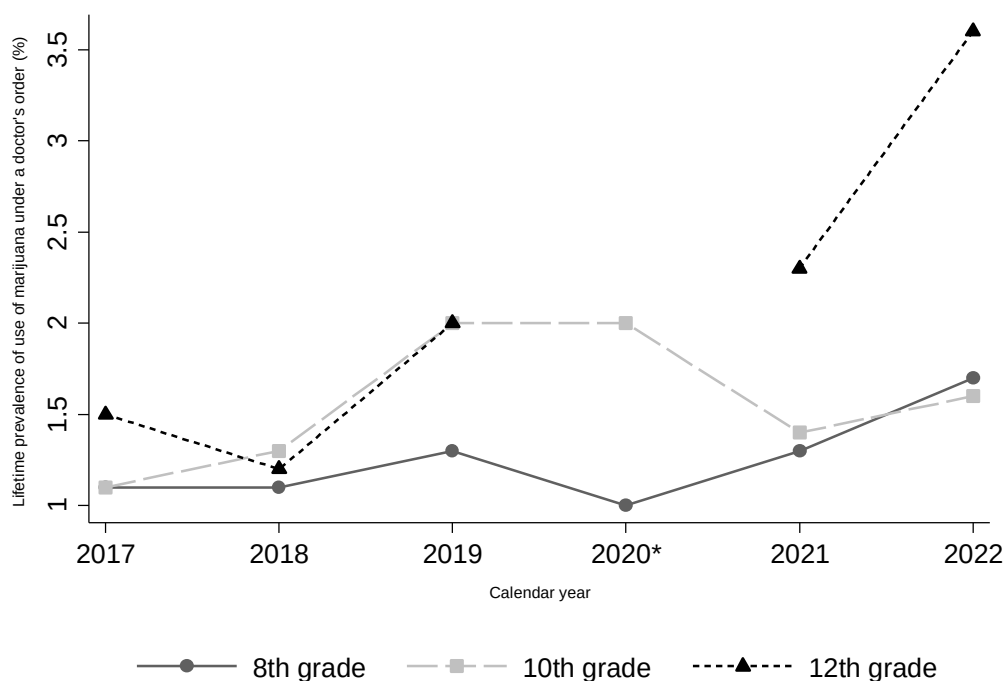
FDA abstracted data on response rate and lifetime prevalent use of marijuana under a doctor's recommendation from the National Survey Results on Drug Use, 1975-2022: Secondary School Students ([Miech et al. 2023](#)). Additional details are described elsewhere ([FDA Office of Surveillance and Epidemiology, 2023](#)).

4.1.4.2. Results

The survey included the lowest number of students in 2020 (n=11,821) and the highest in 2018 (n=44,482) with a response rate across the entire study period of $\geq 82\%$ among 8th graders, $\geq 78\%$ among 10th graders, and $\geq 69\%$ among 12th graders (Appendix [Table 65](#)).

The lifetime prevalent use of marijuana under a doctor's recommendation among 8th graders ranged from 1.1% in 2017 to 1.7% in 2022 ([Figure 1](#)). The lifetime prevalence among 10th graders ranged from 1.1% in 2017 to 1.6% in 2022, although peaking up to 2.0% in 2019 and 2020. The lifetime prevalence of use among 12th graders ranged from 1.5% in 2017 to 3.6% in 2022.

Figure 1. Prevalence of Use of Marijuana Under a Doctor's Order in Grades 8th, 10th, and 12th, MTF, 2017–2022



* Insufficient data for the 2020 estimate in 12th graders, due to curtailed data collection during the COVID-19 pandemic.

4.1.4.3. Discussion

NIDA's MTF data suggest that lifetime prevalent use of marijuana under HCP recommendation among 8-12th graders is rare ($<3.6\%$). Because this survey is school-based (and not household-based) it does not provide estimates of prevalence of use for dropouts and home-schooled teenagers.

4.1.5. Conclusions on Patterns of Medical Use

FDA examined patterns of use among medical users of marijuana as reported in four U.S. national surveys: ICPS, SAMHSA's NSDUH, CDC's BRFSS, and NIDA's MTF. In

general, most data sources other than ICPS lacked details on patient characteristics and factors that promoted the use of marijuana for medical purposes. Some data sources were impacted by the COVID-19 pandemic, and, for ICPS and BFRSS data were largely restricted to the calendar year 2021. Despite these limitations, these data suggest that medical use increases as age increases. NSDUH data suggested that individuals who reported use as per an HCP recommendation were more likely to use marijuana more frequently over the year compared to those without any recommended use. Only data from ICPS provided information on intended indication for use, which suggested that medical users often use marijuana to improve or manage conditions such as depression, anxiety, PTSD, pain, headaches or migraines, sleep disorders, nausea and vomiting, lack of appetite, and muscle spasms. In ICPS, approximately 50-60% of exclusive medical users reported having ever asked an HCP for a recommendation to use medical cannabis. In 2021, as per BRFSS data, smoking appears to be the most frequent method of use and, as per ICPS, at least 40% of individuals reported using cannabis and alcohol simultaneously. Generally, medical users reported obtaining cannabis through different sources with stores and dispensaries being the most commonly reported cannabis source, followed by family and friends.

4.2. University of Florida Systematic Literature Review

The purpose of Section [II.4.2](#) is to summarize the findings from a systematic literature review of the credible evidence of effectiveness and safety of marijuana as a medical treatment for the indications of anorexia, anxiety, epilepsy, inflammatory bowel disease (IBD), nausea, pain, and post-traumatic stress disorder (PTSD).

4.2.1. Methods

The University of Florida (UF), under contract with FDA, conducted a series of systematic reviews to critically evaluate and interpret literature on patient-level controlled observational and controlled interventional studies (original research or systematic reviews/meta-analyses of original research) evaluating the effectiveness of marijuana for the treatment of anorexia³, anxiety, epilepsy, inflammatory bowel disease, nausea,¹⁴ pain, and PTSD. They also evaluated the potential harms from marijuana use as they relate to these seven indications.

The seven indications that were identified for further analysis were determined by FDA, in part informed by OASH's findings under Part 1 of the CAMU test and in part informed by FDA's own analysis of the landscape in which marijuana is currently used medically, including information from state-level programs on how and to what extent marijuana is being utilized for medical purposes. The FDA analysis of the landscape was to determine the most appropriate indications to be further evaluated, including by the UF team in a systematic literature review. The landscape analysis was based on the following: a representative sample of available state-level data on authorized medical uses, expedited review of key professional organizations' recommendations, indications for active

¹⁴ Broadly defined as inclusive of vomiting/emesis.

investigational new drug (IND) applications for all cannabinoids, preliminary PubMed search for topics related to marijuana, and currently FDA-approved cannabinoid product indications. Based on these factors considered, the chosen indications were based on state-level utilization, scientific interest (e.g., publications, INDs, professional organizations), and indications previously approved for other cannabinoids.

UF conducted searches, one per indication, in PubMed, the Cochrane Library, American Psychiatric Association (APA) PsycInfo, and Embase in February 2023. The search criteria, agreed upon with FDA, were defined according to marijuana exposure¹⁵ and indication-specific keywords and controlled vocabulary.¹⁶ The searches were restricted to publications in English and to the period between January 2000 through February 2023 to identify literature published since the 1999 Institute of Medicine's *Marijuana and Medicine* review ([IOM 1999](#)).

After removal of duplicates, screening, and assessment for eligibility by two independent reviewers (a third one in case of disagreement), all included studies were critically evaluated for risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2) or the "Risk of Bias In Non-randomised Studies - of Interventions" (ROBINS-I) ([Sterne et al. 2016](#); [Sterne et al. 2019](#)). The RoB 2 contains assessment of risk of bias for five domains: 1) bias arising from the randomization process, 2) bias due to deviations from intended intervention, 3) bias due to missing outcome data, 4) bias in measurement of the outcome, and 5) bias in selection of the reported result. Within each of the five domains, raters respond to a series of questions that generate a numerical score per response. Based on the score total from each domain, the risk of bias within each of the domains is then ranked as "low risk", "some concern", or "high risk" as per pre-specified score thresholds. The ROBINS-I scores each study on seven domains: 1) bias due to confounding, 2) selection bias, 3) bias in classification of interventions, 4) bias due to deviations from intended interventions or measured exposure, 5) bias due to missing data, 6) bias in the measurement of outcomes, and 7) bias in the selection of reported results. Within each of the seven domains, raters respond to a series of questions that generate a numerical score per response. Based on the score total from each domain, the risk of bias within each of the domain is then ranked as "low", "moderate", "serious", or "critical". Each study was independently rated by two investigators; when there was disagreement amongst raters, a third investigator conducted an independent rating.¹⁷

Observational studies with serious or critical risk of bias and, for the pain indication, randomized controlled trials (RCTs) and observational studies that investigated the pain

¹⁵ The exposure definition excluded FDA-approved cannabis-derived products, hemp as defined in the 2018 Farm Bill, topical formulations, synthetic forms of Δ^9 -THC, and combinations of marijuana and synthetics except in cases where the effects of an exposure for the marijuana agent were investigated separately from the combination.

¹⁶ Controlled vocabulary represents the standardized words and phrases employed by databases to organize literature on related subjects.

¹⁷ As specified in the protocol, studies where two out of three raters did not achieve consensus, quality rating was determined by a faculty team lead.

as a secondary outcome, were not further considered. For the remaining RCTs and observational studies, evidence quality was rated for primary outcome(s) assessed within each indication (rather than for individual studies) in accordance to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach within the Cochrane handbook ([Schünemann et al. 2019](#)).¹⁸ The rating for each outcome was informed by the rating assessment of five quality domains (Certainty, Imprecision, Inconsistency, Generalizability, and Publication Bias). The GRADE approach allows raters to promote or demote ‘Certainty’ in the evidence rating based on several criteria. To demote ‘Certainty’ in evidence, key considerations included risk of bias, imprecision, inconsistency, indirectness, and publication bias.¹⁹ To promote ‘Certainty’ in evidence, key considerations included large magnitude of effect, dose-response gradient, and residual confounding that would decrease the magnitude of effect (where an effect was observed or reported). In cases where an outcome was only assessed in a single study, the raters were unable to rate the domain of ‘Inconsistency’ as this describes consistency in direction of findings as compared across studies (or across analysis groupings if multiple analyses of the outcome are reported within a single study). The overall quality of evidence rating was stated as a categorical judgement ([Table 16](#)).

Table 16. Categories and Definitions for the Overall Evidence Quality Ratings*

Evidence Quality Rating	Definition of Rating
Very low quality	The true effect of marijuana is probably significantly different from the estimated (reported or observed) effect.
Low quality	The true effect of marijuana may be similar to the estimated (reported or observed) effect.
Moderate quality	The true effect of marijuana is probably similar to the estimated (reported or observed) effect.
High quality	The true effect of marijuana is similar to the estimated (reported or observed) effect.

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

* Based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach

Quantitative meta-analysis, including pooled estimates and/or meta-regressions as applicable, were calculated in instances where a minimum of five studies reported the outcome with sufficient homogeneity in reporting to support a pooled estimate. Additionally, FDA required that the studies reporting that outcome be rated as ‘moderate’ or ‘high’ quality evidence to avoid amplifying bias in reported effects that may be present in lower quality studies.

For a full list of references that were considered for the systematic literature review, refer to the Appendix under each listed indication (Sections [III.5.1](#), [III.5.2](#), [III.5.3](#), [III.5.4](#), [III.5.5](#), and [III.5.6](#)). All the information included in this section is based on the UF review; the Appendix provides the references for the RCTs, observational studies, and supporting literature relevant to the text included in this review ([Table 81](#), [Table 83](#), [Table 85](#), [Table 87](#), [Table 89](#), [Table 91](#)).

¹⁸ The RCTs with ‘high’ risk of bias were considered in quality of evidence ratings, but resulted in evidence quality rating demotion as per Cochrane guidance.

¹⁹ The risk of bias assessments conducted prior to the evidence rating activity informed these decisions.

Further methodological details, including those on data extraction, screening, assessment for eligibility, risk of bias assessments, quality of evidence ratings, and strategy for data synthesis are described in the Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use Project 2/1B Report.

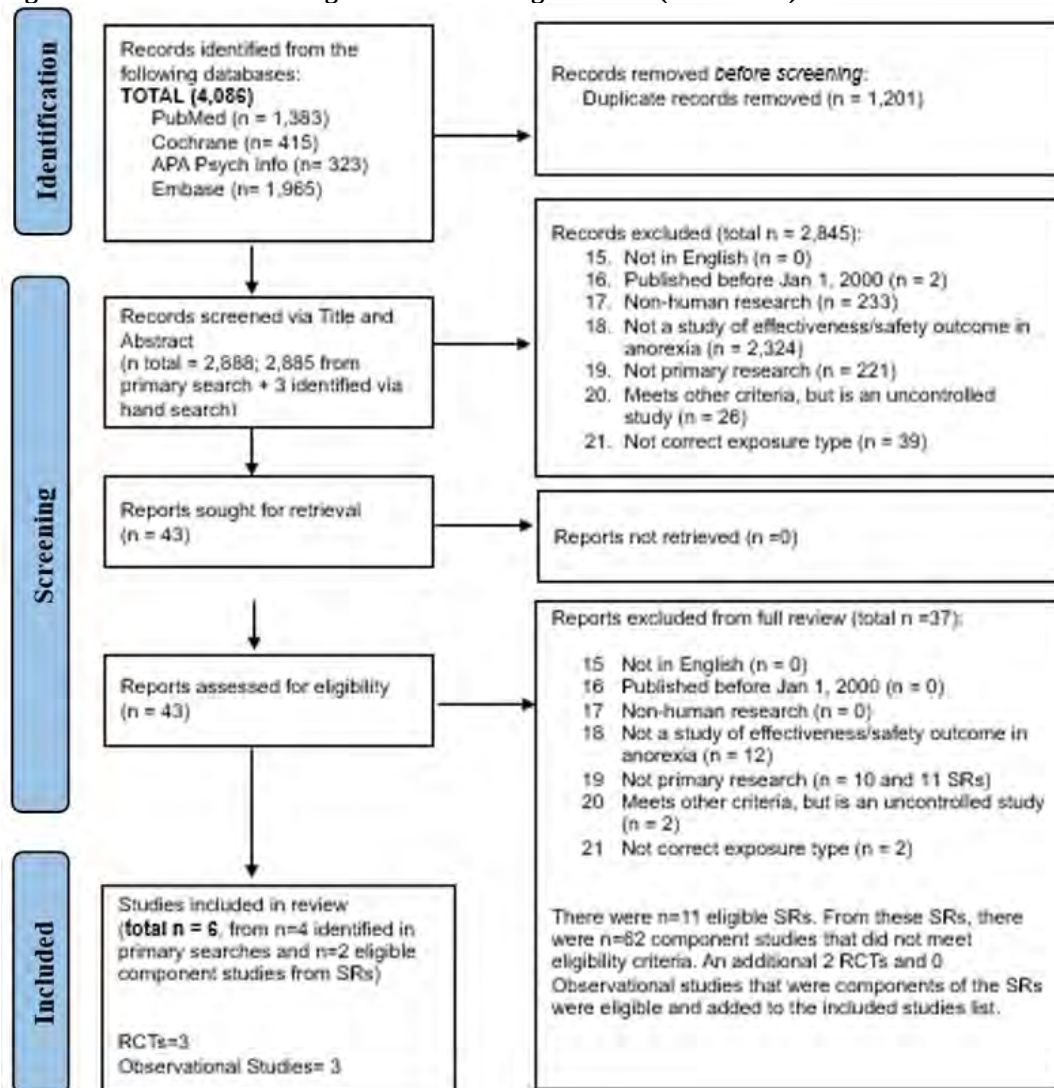
4.2.2. Results

4.2.2.1. Anorexia

Anorexia and weight loss are common in many health conditions, such as cancer and human immunodeficiency virus (HIV) infection, that impact patients' quality of life. Evidence suggests cannabinoids, particularly tetrahydrocannabinol (THC), may produce appetite stimulation by activating cannabinoid receptors (CB), especially CB1, in the brain via a complex process incorporating digestive signaling hormones, thereby serving as a potential treatment for anorexia.

The protocol-specified searches of the scientific literature yielded a total of 4,086 publications. After removal of duplicates, screening, and assessment for eligibility, there were six studies that met all the eligibility criteria—four of these directly identified through the searches and two identified through the systematic reviews that underwent extraction of component studies ([Figure 2](#)). Three of the six studies were RCTs categorized as having high or some risk of bias and three were observational studies, all of them with critical risk of bias. The summary of studies included in the risk of bias assessments as well as their references and risk of bias assessment are displayed in Appendix [III.5.1](#).

Figure 2. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Anorexia



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023

The three observational studies eligible for inclusion were not considered further because each was rated as having a critical risk of bias. Thus, only three RCTs were further considered; each one of them examined different sets of outcomes among the following: (1) appetite, (2) quality of life, (3) food intake, and (4) body weight. The quality of evidence rating for the studies by outcome are shown in [Table 17](#), [Table 18](#), [Table 19](#), [Table 20](#). There were insufficient studies of moderate or high quality to support the calculation of meta-analytic estimates for any of the outcomes within the anorexia indication.

Table 17. Quality of Evidence Rating for Appetite, Certainty Rating by Study and Overall

Domain Assessed	(Strasser et al. 2006)	Overall Certainty Rating Across Studies
Certainty	High concern	High concern
Imprecision	High concern	High concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Unable to rate
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 18. Quality of Evidence Rating for Quality of Life, Certainty Rating by Study and Overall

Domain Assessed	(Strasser et al. 2006)	Overall Certainty Rating Across Studies
Certainty	High concern	High concern
Imprecision	High concern	High concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Unable to rate
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 19. Quality of Evidence Rating for Food/Caloric Intake, Certainty Rating by Study and Overall

Domain Assessed	(Haney et al. 2005)	(Haney et al. 2007)	Overall Certainty Rating Across Studies
Certainty	Moderate concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Moderate concern	Moderate concern
Inconsistency			Low concern
Generalizability	Moderate concern	Moderate concern	Moderate concern
Publication bias			Unable to rate
Overall quality of evidence rating			Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 20. Quality of Evidence Rating for Body Weight, Certainty Rating by Study and Overall

Domain Assessed	(Haney et al. 2007)	Overall Certainty Rating Across Studies
Certainty	Moderate concern	Moderate concern
Imprecision	Unable to rate	Unable to rate
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Unable to rate
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Summary of Effectiveness for Anorexia

Two studies assessed the benefit of marijuana cigarettes on several outcome measures related to HIV anorexia-cachexia. In participants with HIV, there was moderate quality of evidence that cannabis increased caloric intake and low quality of evidence that cannabis increased body weight. One of these studies showed a significant increase in weight in participants but only in those participants who had significant loss of muscle mass prior to treatment. The other study showed an increase in caloric intake in participants with HIV.

One RCT assessed whether marijuana had any benefit in cancer-related anorexia and showed no benefit compared with placebo.

There was no significant effect of marijuana on the outcomes of improved appetite or quality of life, in any of the RCTs based on a low quality of evidence.

Summary of Safety for Anorexia

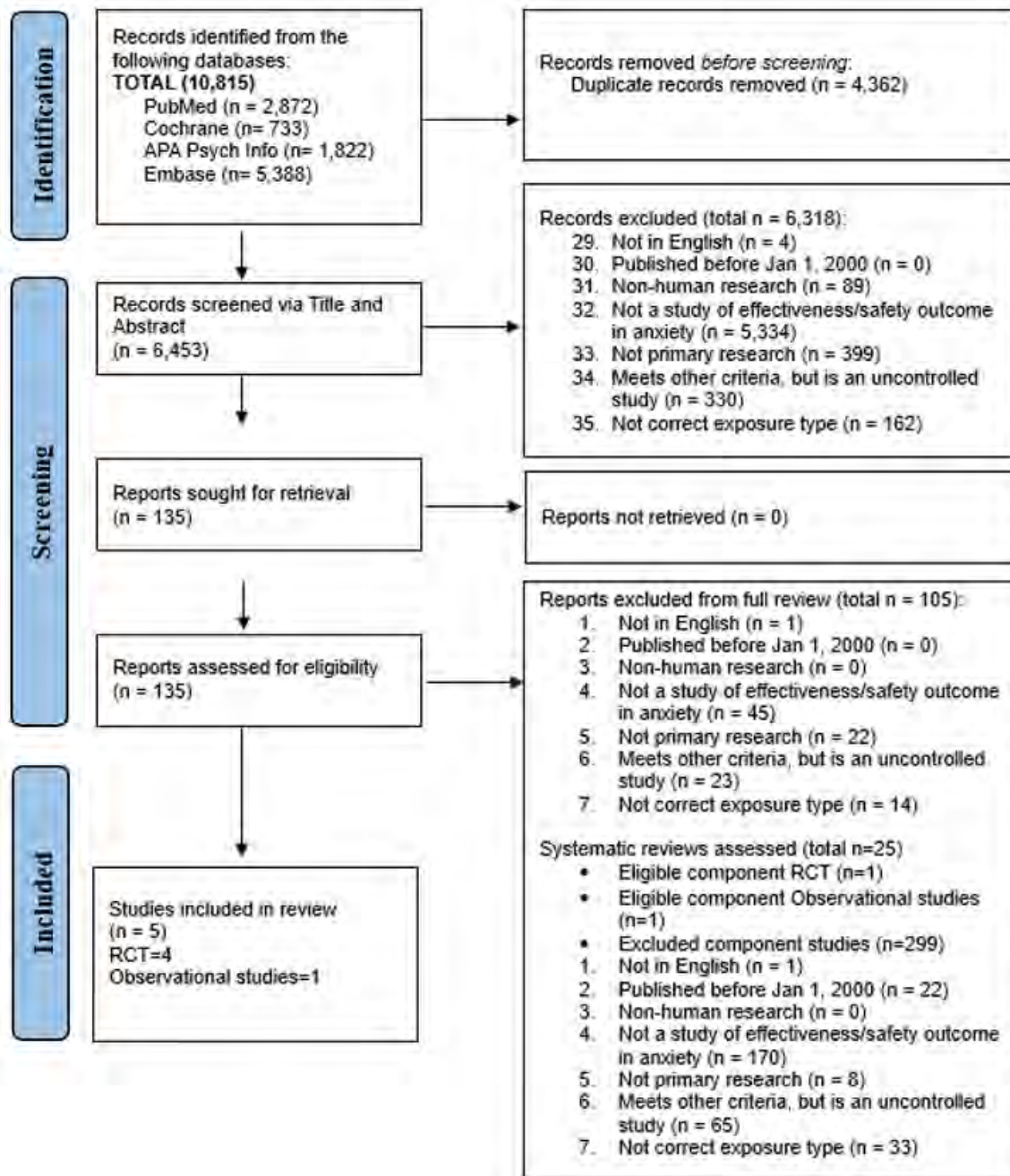
A higher proportion of patients experienced adverse events (AEs) with treatment compared to placebo in one study but not in two others examined by UF. No serious adverse events (SAEs) were reported in these studies.

4.2.2.2. Anxiety

The endocannabinoid system is distributed broadly throughout the brain and modulates other neurotransmitter systems such as gamma-aminobutyric acid (GABA), dopamine, and serotonin. Therefore, some have hypothesized that marijuana may impact anxiety and anxiety-related symptoms through its effects on the endocannabinoid system.

The searches in the scientific literature retrieved a total of 10,815 publications. After removal of duplicates, screening, and assessment for eligibility, UF identified five studies relevant to the indication of anxiety where marijuana was utilized for several conditions with an anxiety outcome measure. These included fibromyalgia, obsessive compulsive disorder (OCD), multiple sclerosis, Parkinson disease, and non-cancer pain. None of the identified studies included a primary anxiety disorder. Four were RCTs and one was an observational study ([Figure 3](#)). The summary of studies included in the risk of bias assessments as well as their references and risk of bias assessment are displayed in Appendix [III.5.2](#).

Figure 3. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Anxiety



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

The observational study was rated with sufficiently low risk of bias to be included in quality of evidence ratings along with the four RCTs, all of them categorized as having low risk of bias. Each one of the studies assessed examined different sets of outcomes among the following: (1) Self-Rating Anxiety Scale; Symptom Checklist-90 (SCL-90); Spielberger State-Trait Anxiety (STAI-S); (2) Profile of Mood States; (3) Fibromyalgia Impact Questionnaire- Anxiety Component; and (4) HADs- Quality of Life Component. The quality of evidence rating for the studies by outcome are shown in [Table 21](#),

[Table 22](#), [Table 23](#), [Table 24](#). The studies did not report sufficiently homogeneous outcomes to be eligible for meta-analysis calculations per outcome.

Table 21. Quality of Evidence Rating for Anxiety Scales (Self-Rating Anxiety Scale; Symptom Checklist-90; Spielberger State-Trait Anxiety), Certainty Rating by Study and Overall

Domain Assessed	(Aragona et al. 2009)	(Kayser et al. 2020)	Overall Certainty Rating Across Studies
Certainty	Low concern	Low concern	Low concern
Imprecision	Moderate concern	Low concern	Moderate concern
Inconsistency			Moderate concern
Generalizability	High concern	High concern	High concern
Publication bias			Low concern
Overall quality of evidence rating			Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 22. Quality of Evidence Rating for Profile of Mood States, Certainty Rating by Study and Overall

Domain Assessed	(Ware et al. 2015)	Overall Certainty Rating Across Studies
Certainty	Moderate concern	Moderate concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to Rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Low concern
Overall quality of evidence rating		Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 23. Quality of Evidence Rating for Fibromyalgia Impact Questionnaire: Anxiety Component, Certainty Rating by Study and Overall

Domain Assessed	(Chaves et al. 2020)	Overall Certainty Rating Across Studies
Certainty	Low concern	Low concern
Imprecision	Low concern	Low concern
Inconsistency		Unable to Rate
Generalizability	High concern	High concern
Publication bias		Low concern
Overall quality of evidence rating		Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 24. Quality of Evidence Rating for HADs: Quality of Life Component, Certainty Rating by Study and Overall

Domain Assessed	(Kanjanaangsichai et al. 2022)	Overall Certainty Rating Across Studies
Certainty	Low concern	Low concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to Rate
Generalizability	High concern	High concern
Publication bias		Low concern
Overall quality of evidence rating		Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023

Summary of Effectiveness for Anxiety

None of the RCTs showed any improvement in anxiety outcome measures and potentially worsened symptoms of paranoia or performed worse than placebo (in obsessive compulsive disorder) based on a moderate quality of evidence. THC-rich cannabis oil showed a significant decrease in symptoms of fibromyalgia and improvement in quality of life based on the Fibromyalgia Impact Questionnaire (FIQ) score compared to the placebo group and baseline scores. However, this questionnaire and findings are not specific to anxiety.

The observational study was a prospective cohort study with the primary objective of assessing the safety of cannabis use as a self-management strategy for chronic non-cancer pain. Secondary efficacy parameters included mood, which was measured using the Profile of Mood States. This study reported that individuals who used cannabis experienced significant improvement in total mood disturbance scale compared to controls, with improvements observed in the tension-anxiety, depression-dejection, anger-hostility, and fatigue-inertia subscales. Despite low concerns in other domains, this outcome was assessed by the UF investigators as having a moderate quality of evidence rating as it was driven by a moderate risk of bias in the reporting of the study outcome (investigators who assessed the outcomes were not blinded to cannabis treatment status) together with a moderate concern regarding imprecision in the reported effect.

Summary of Safety for Anxiety

The studies reported varying levels of adverse events with no increased risk of SAEs reported relative to the control group in the controlled studies. Marijuana was associated with an increased risk of AEs related to nervous system disorders, psychiatric disorders, and respiratory events when compared to placebo. A study conducted in multiple sclerosis patients treated with marijuana plant extract did not induce psychopathology or impair cognition in marijuana-naïve patients, but a positive correlation was found between blood levels of THC and psychopathological scores.

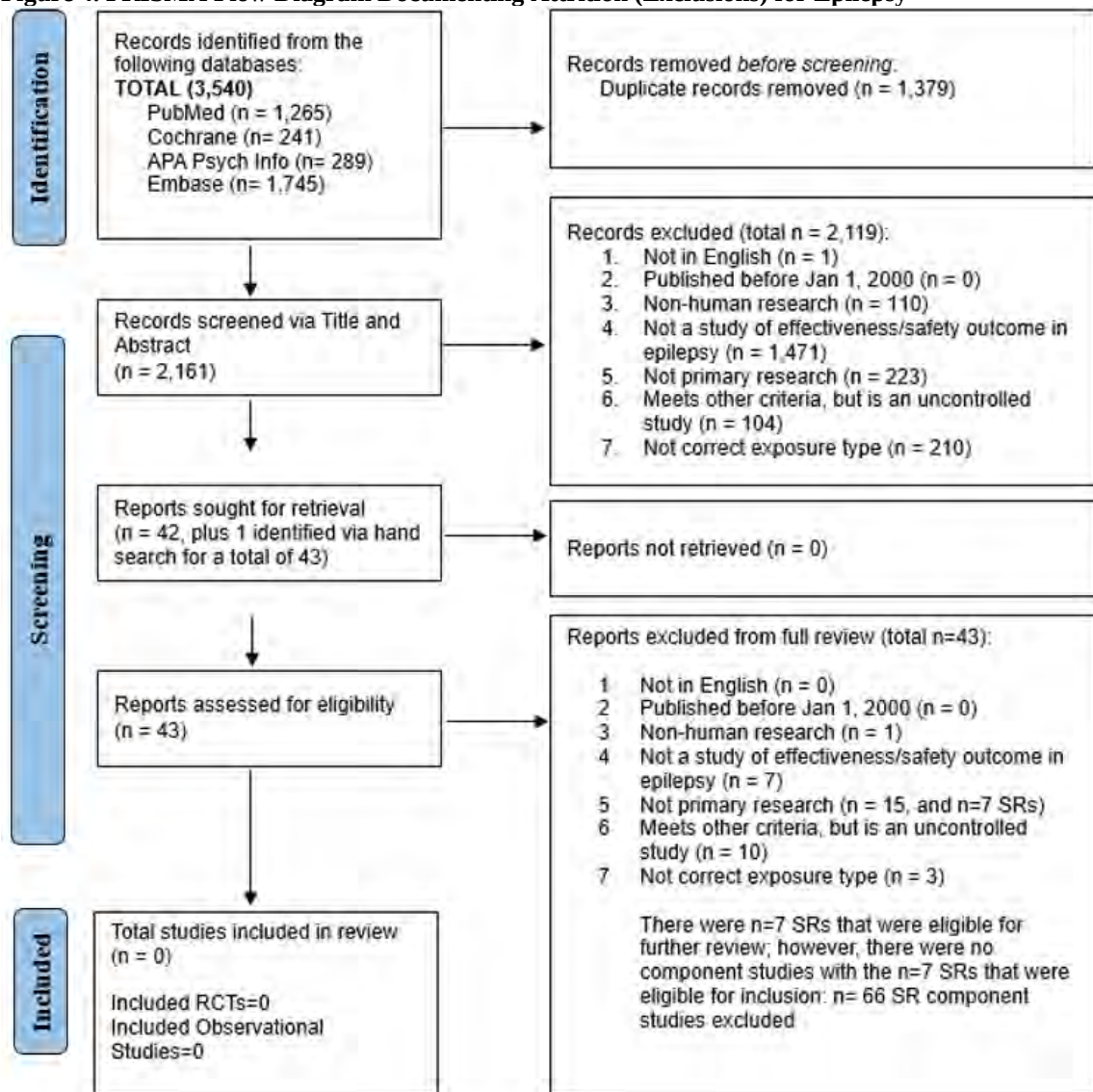
4.2.2.3. Epilepsy

The first FDA-approved cannabis-derived cannabidiol (CBD) human drug product (Epidiolex, GW Research, Ltd., Research Triangle Park, NC, approved in June 2018) is currently indicated for the treatment of seizures associated with Lennox-Gastaut

syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age or older ([Greenwich Biosciences 2018](#)). The precise mechanisms by which Epidiolex exerts its anticonvulsant effect in humans are unknown. CBD does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors ([Greenwich Biosciences 2018](#)). While CBD has clearly shown anti-seizure properties, contradictory pro-convulsant and anti-seizure effects have been reported for delta-9-tetrahydrocannabinol (Δ 9-THC) ([Li et al. 2023](#)).

The searches identified a total of 3,540 studies. After removal of duplicates, screening, and assessment for eligibility, there were no studies (nor component studies included in the systematic reviews) that met all the protocol-specified criteria for inclusion in the review for the indication of epilepsy ([Figure 4](#)).

Figure 4. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Epilepsy



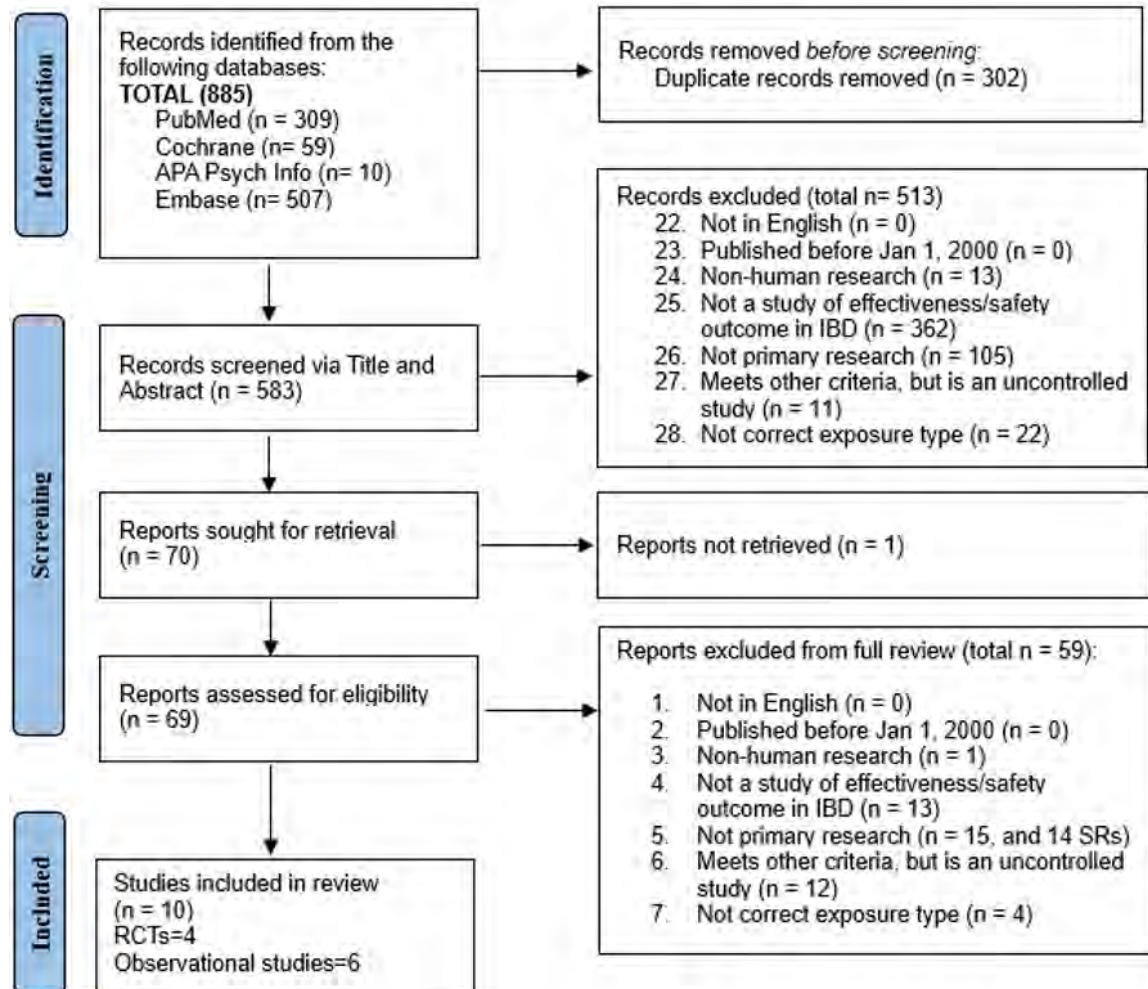
Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

4.2.2.4. Inflammatory Bowel Disease

The endocannabinoid system (ECS) plays a key role in regulating several gastrointestinal functions and is also involved in immune function, suggesting that it may be a viable target for treating inflammatory bowel disease (IBD).

UF's searches identified 885 records. After removal of the duplicated records and article screening, 10 records were included in the review (four RCTs and six observational studies) ([Figure 5](#)). Numerous outcomes were utilized in these studies, and not all studies identified a primary endpoint and/or adjusted for multiplicity. Most of the studies included patients with mild to moderate disease severity. Summary of studies included in the risk of bias assessments as well as their references and risk of bias assessment are displayed in Appendix [III.5.3](#).

Figure 5. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Inflammatory Bowel Disease



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

The six observational studies eligible for inclusion were not considered further because each was rated as having a serious or critical risk of bias. The four RCTs assessed a total of 13 effectiveness outcomes: (1) Disease activity; (2) Quality of life; (3) Daily function,

general well-being, general effect on health; (4) Pain; (5) Remission; (6) Number of bowel movements/stool frequency; (7) Rectal bleeding; (8) Weight; (9) Disease-specific quality of life; (10) Bloating; (11) Nausea; (12) Appetite; and (13) Endoscopy assessment. The quality of evidence rating for the studies by outcome are shown in [Table 25](#), [Table 26](#), [Table 27](#), [Table 28](#), [Table 29](#), [Table 30](#), [Table 31](#), [Table 32](#), [Table 33](#), [Table 34](#), [Table 35](#), [Table 36](#), [Table 37](#). There were insufficient studies of moderate or high quality to support the calculation of meta-analytic estimates for any of the outcomes within the IBD indication.

Table 25. Quality of Evidence Rating for Clinical Disease Activity Indexes (CDAI/Lichtiger/Mayo Score), Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2013)	(Naftali et al. 2021a)	(Naftali et al. 2021b)	(Irving et al. 2018)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern	Moderate Concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Low concern	Low Concern	High concern	Moderate concern
Inconsistency					Moderate concern
Generalizability	Moderate concern	Moderate concern	Moderate concern	High concern	Moderate concern
Publication bias					Moderate concern
Overall quality of evidence rating					Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 26. Quality of Evidence Rating for Daily Function, General Well-Being, General Effect on Health, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	High concern	High concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 27. Quality of Evidence Rating for Quality of Life, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2013)	(Naftali et al. 2021a)	(Naftali et al. 2021b)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern	Moderate concern	Moderate concern
Imprecision	Low concern	Low concern	Low concern	Low concern
Inconsistency				Moderate concern
Generalizability	Moderate concern	Moderate concern	Moderate concern	Moderate concern
Publication bias				Moderate concern
Overall quality of evidence rating				Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023

Table 28. Quality of Evidence Rating for Pain, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	(Naftali et al. 2021b)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Low concern	Moderate concern
Inconsistency			Moderate concern
Generalizability	Moderate concern	Moderate concern	Moderate concern
Publication bias			Moderate concern
Overall quality of evidence rating			Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 29. Quality of Evidence Rating for Remission, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2013)	(Naftali et al. 2021a)	(Irving et al. 2018)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	High concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Moderate concern	Moderate concern	Moderate concern
Inconsistency				Low concern
Generalizability	Moderate concern	Moderate concern	Moderate concern	Moderate concern
Publication bias				Low concern
Overall quality of evidence rating				Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 30. Quality of Evidence Rating for Number of Bowel Movements/Stool Frequency, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	(Naftali et al. 2021b)	(Irving et al. 2018)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Serious concern	Serious concern	Serious concern	Serious concern
Imprecision	Moderate concern	Low concern	Unable to report	Moderate concern
Inconsistency				Moderate concern
Generalizability	Moderate concern	Moderate concern	Moderate concern	Moderate concern
Publication bias				Moderate concern
Overall quality of evidence rating				Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 31. Quality of Evidence Rating for Rectal Bleeding, Certainty Rating by Study and Overall

Domain Assessed	(Irving et al. 2018)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Serious concern	Serious concern
Imprecision	Serious concern	Serious concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Low concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 32. Quality of Evidence Rating for Weight, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Low concern
Imprecision	Low concern	Low concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Low concern
Overall quality of evidence rating		High quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 33. Quality of Evidence Rating for Disease-Specific Quality of Life, Certainty Rating by Study and Overall

Domain Assessed	(Irving et al. 2018)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Low concern
Overall quality of evidence rating		Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 34. Quality of Evidence Rating for Bloating, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	High concern	High concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 35. Quality of Evidence Rating for Nausea, Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Serious concern	High concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 36. Quality of Evidence Rating for Appetite, Certainty Rating by Study and Overall

Domain assessed	(Naftali et al. 2021a)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	High concern	High concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 37. Quality of Evidence Rating for Endoscopy Assessment (Simple Endoscope Score; Mayo Endoscopic Score), Certainty Rating by Study and Overall

Domain Assessed	(Naftali et al. 2021a)	(Naftali et al. 2021b)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Moderate concern	Moderate concern
Inconsistency			Low concern
Generalizability	Moderate concern	Moderate concern	Moderate concern
Publication bias			Moderate concern
Overall quality of evidence rating			Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Summary of Effectiveness for IBD

Four RCTs, each assessing one or more of 13 effectiveness outcomes, were included in the synthesis of evidence. Overall, within the four RCTs, marijuana demonstrated positive effects on the Lichtiger score (eight components of colitis disease activity), response rate, Subject Global Impression of Change (SGIC), self-reported mood, sleep, pain, bloating, appetite, general well-being, and satisfaction.

All four RCTs considered clinical disease activity [e.g., Lichtiger score, Crohn's disease activity index (CDAI), Mayo score], with heterogeneous results based on a moderate quality of evidence. Similarly, mixed results were shown for the Inflammatory Bowel Disease Questionnaire (IBDQ) score, which showed significant improvement in one study, but not in another. Additionally, two studies suggested an enhancement in the quality of life via the 36-Item Short Form Survey (SF-36), while one study contradicted this finding, with the overall evidence quality being rated as moderate. A similar level of evidence quality was observed for the impact on pain, although one study indicated no significant alteration in abdominal pain, all based on a moderate quality of evidence. The outcomes concerning remission (definitions and measures differed amongst studies), disease-specific quality of life, and endoscopic evaluations were also classified as having moderate evidence quality, with all studies indicating no significant alteration.

Several effectiveness outcomes were classified as having low evidence quality. Among these, nausea and rectal bleeding did not demonstrate a significant alteration in the included studies following treatment with cannabis. Daily function, general well-being, overall health impact, and bowel movement/stool frequency exhibited heterogeneous results, with the overall evidence quality being low. Lastly, bloating and appetite were also classified as having low evidence quality, with both outcomes showing improvement in the included studies.

Summary of Safety for IBD

The RCTs assessed adverse events, however, limited safety information was reported overall.

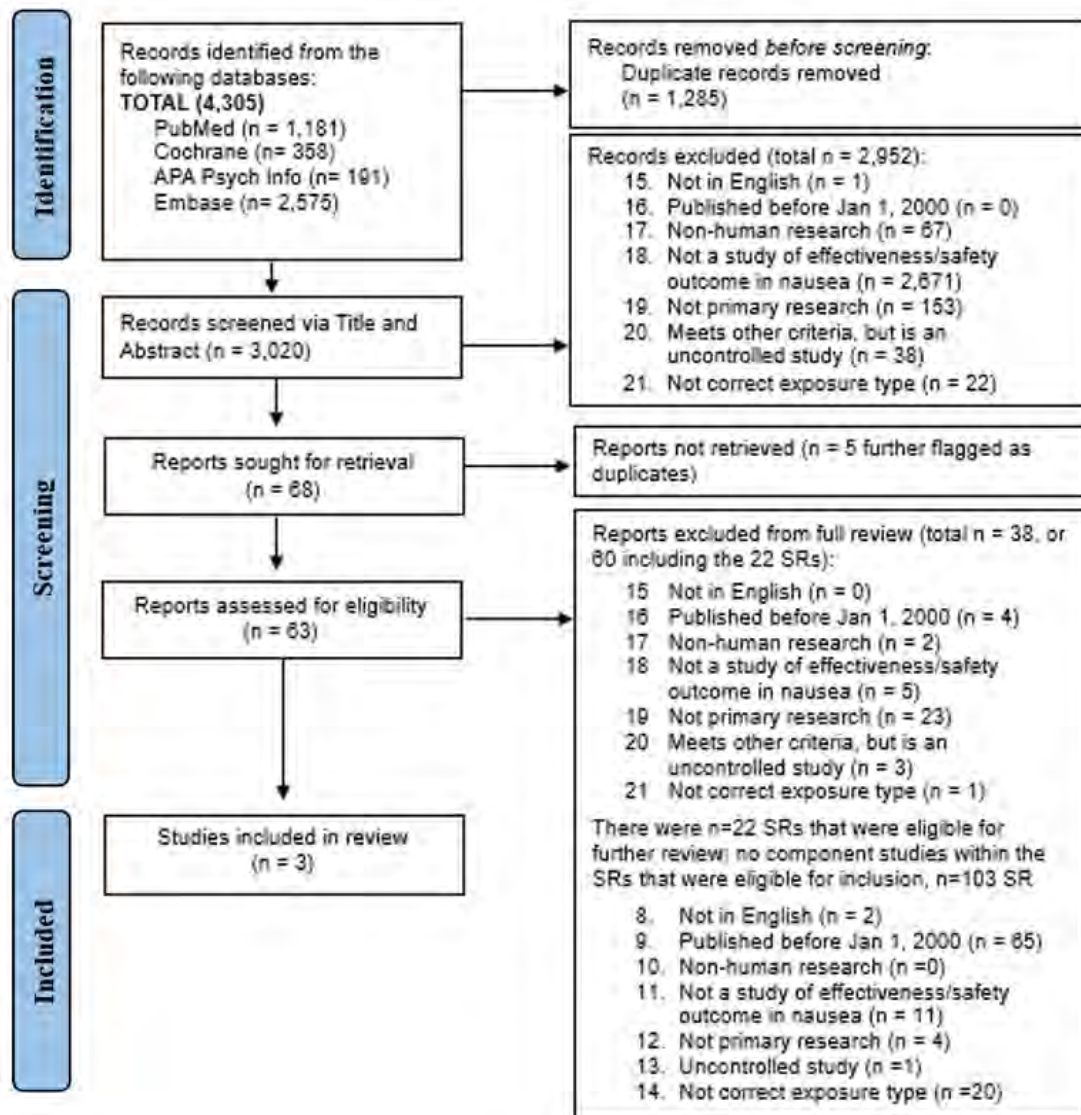
4.2.2.5. Nausea

Nausea and vomiting are common side effects of chemotherapy and in the postoperative setting, and currently there are two synthetic cannabinoids, dronabinol and nabilone, approved for treatment of chemotherapy-induced nausea and vomiting. Given established efficacy in clinical trials for the approved products and an established pharmacological pathway within the endocannabinoid system, marijuana has been studied to see if it exerts similar effects.

The literature searches identified a total of 4,305 studies. After removal of duplicates, screening, and assessment for eligibility, there were three studies, all RCTs, that met all the eligibility criteria. The risk of bias assessment suggested some concerns in one study and low risk of bias in two studies. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) Flow Diagram Documenting Attrition (Exclusions) is

presented in [Figure 6](#). Summary of studies included in the risk of bias assessments as well as their references and risk of bias assessment are displayed in Appendix [III.5.4](#).

Figure 6. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Nausea



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Each of the three RCTs reported one or more of three major outcome constructs, which were reported using one or more of 36 different metrics across the studies. They were grouped as follows (1) chemotherapy-induced nausea and vomiting; (2) nausea-specific quality of life (Functional Living Index-Emesis); general health-related quality of life; and (4) post-operative nausea and vomiting. The quality of evidence rating for the studies by outcome are shown in [Table 38](#), [Table 39](#), [Table 40](#), [Table 41](#).

Table 38. Quality of Evidence Rating for Chemotherapy-Induced Nausea and Vomiting, Certainty Rating by Study and Overall

Domain Assessed	(Grimison et al. 2020)	(Duran et al. 2010)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Low concern	Low concern
Imprecision	Moderate concern	High concern	Moderate concern
Inconsistency			Low concern
Generalizability	Moderate concern	Moderate concern	Moderate concern
Publication bias			Low concern
Overall quality of evidence rating			Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 39. Quality of Evidence Rating for Nausea-Specific Quality of Life (Functional Living Index-Emesis (FLIE), Certainty Rating by Study and Overall

Domain Assessed	(Grimison et al. 2020)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Moderate concern*
Imprecision	Low concern	Low concern
Inconsistency		Unable to rate
Generalizability	High concern	High concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

*Certainty and generalizability ratings for nausea-specific quality of life relies on a single study with n=16 and another study indicating no improvement without sharing quantitative estimates (hence, not shown in this table)

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 40. Quality of Evidence Rating for Overall Health-Related Quality of Life, Certainty Rating by Study and Overall

Domain Assessed	(Grimison et al. 2020)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	High concern	High concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 41. Quality of Evidence Rating for Post-Operative Nausea and Vomiting, Certainty Rating by Study and Overall

Domain Assessed	(Kleine-Brueggene et al. 2015)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	High concern	High concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	Moderate concern	Moderate concern
Publication bias		Moderate concern
Overall quality of evidence rating		Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Per protocol, the RCTs did not meet thresholds for the minimum number of studies to qualify for any meta-analysis calculation.

Summary of Effectiveness for Nausea

Three RCTs were included in the analysis, and numerous outcome measures were assessed. Two of the three studies, which administered either THC-CBD extract or whole plant cannabis, showed benefit of marijuana compared with placebo. The quality of evidence rating of these studies was rated as moderate. The two positive studies assessed chemotherapy-induced nausea and vomiting in patients with refractory nausea after standard treatment, whereas the failed study assessed the effect of intravenous THC in the prevention of post-operative nausea and vomiting. Although the primary endpoint showed significant difference in two studies, it was noted that the effect was small and imprecise. Additionally, there was inconclusive or marginal benefit in the domains of quality of life, nausea-specific quality of life and post-operative nausea and vomiting, all based on a low quality of evidence. Overall, there is evidence supporting a positive effect of cannabis on chemotherapy-induced nausea and vomiting based on a moderate quality of evidence.

Summary of Safety for Nausea

A total of 98 patients were exposed to marijuana products in the three RCTs evaluated. A higher proportion were noted to experience AEs than placebo, but no excess risk of SAEs was reported. Adverse events reported were consistent with safety findings in other indications (e.g., sedation, dizziness, disorientation, dry mouth, anxiety). Although AEs were reported for marijuana, one study did show 83% of participants preferred marijuana to placebo.

4.2.2.6. Pain

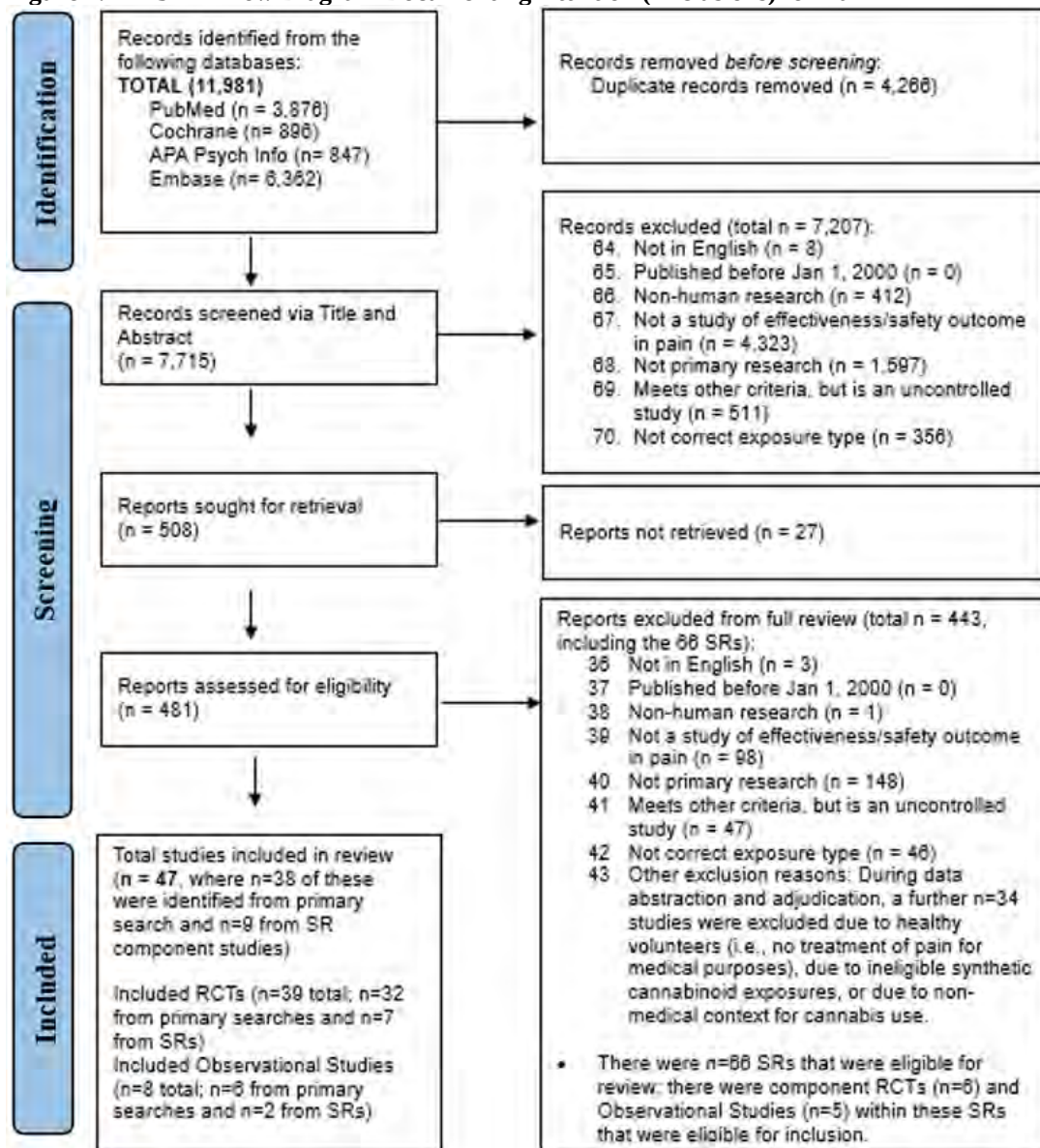
The UF reported noted that phytocannabinoids, including Δ^9 -THC, have been demonstrated by preclinical research to have analgesic effects in numerous types of pain (e.g., inflammatory or nociceptive pain, as well as neuropathic pain) according to a recent systematic review and meta-analysis of studies employing animal models. UF further noted that, in clinical research, a systematic review and meta-analysis concluded that marijuana products containing high THC-to-CBD ratios may be associated with short-

term improvements in chronic pain from neuropathic or non-cancer nociceptive pain sources. The UF review systematically examined evidence quality from studies that investigated effectiveness and safety of marijuana for the pain indication regardless of pain type (e.g., neuropathic, nociceptive, or cancer).

Pain has the most investigations amongst any of the indications in the review. The searches identified a total of 11,981 studies. After removal of duplicates, screening, and assessment for eligibility, there were 38 studies—32 RCTs and 6 observational studies—identified from the primary searches. Additionally, seven RCTs and two observational studies were identified from the eligible systematic reviews. Therefore, there were a total of 47 studies, 39 RCTs and 8 observational studies²⁰ that met all the protocol-specified criteria for inclusion in the review for the indication of pain ([Figure 7](#)). The summary of studies included in the risk of bias assessments, their references, and their risk of bias assessment are displayed in Appendix [III.5.5](#).

²⁰ Two of the eight observational studies were included in other indications (i.e., anorexia and anxiety) as pain was a secondary outcome.

Figure 7. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Pain



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Seven of the eight eligible observational studies were not considered further as they were classified as having a serious or critical risk of bias assessment. The eighth observational study included pain as a secondary outcome; as described in the methods (Section [II.4.2.1](#)), only studies that assessed pain as a primary outcome were further assessed. Similarly, four RCTs were not further considered as the pain outcomes were not assessed in primary analyses. Thus, a total of 35 studies, all RCTs, were considered in the quality of evidence ratings. Overall, these RCTs assessed a total of seven outcomes: (1) Visual Analog Scale (VAS) Pain score; Spontaneous Pain VAS score; (2) Numerical Rating Scale (NRS) Pain score; Body Pain Category Rating Scale (CRS); (3) Other pain scores [Sum of Pain Intensity Differences (SPID); Brief Pain Inventory (BPI); Pain at Present; McGill Pain Questionnaire; Edmonton Symptom Assessment System (ESAS) Pain]; (4) Neuropathic-Specific Pain

scores [Neuropathic Pain Scale; Intensity of Global Neuropathic Pain NRS; Fibromyalgia impact score (pain)]; (5) Sleep Quality [Sleep quality NRS; Sleep disturbance NRS; Sleep disruption NRS]; (6) Pain Disability Index; and (7) Opioid composite score.²¹ Of these, there were two outcomes that met all protocol-specified criteria to undergo meta-analysis calculations: VAS Pain scores and NRS Pain scores. The types of pain spanned across clinical contexts such as multiple sclerosis, post-operative pain, neuropathic pain, chronic pain, and fibromyalgia. Formulations of marijuana administered included smoked, oromucosal sprays, and oral forms.

Summary of Effectiveness for Pain

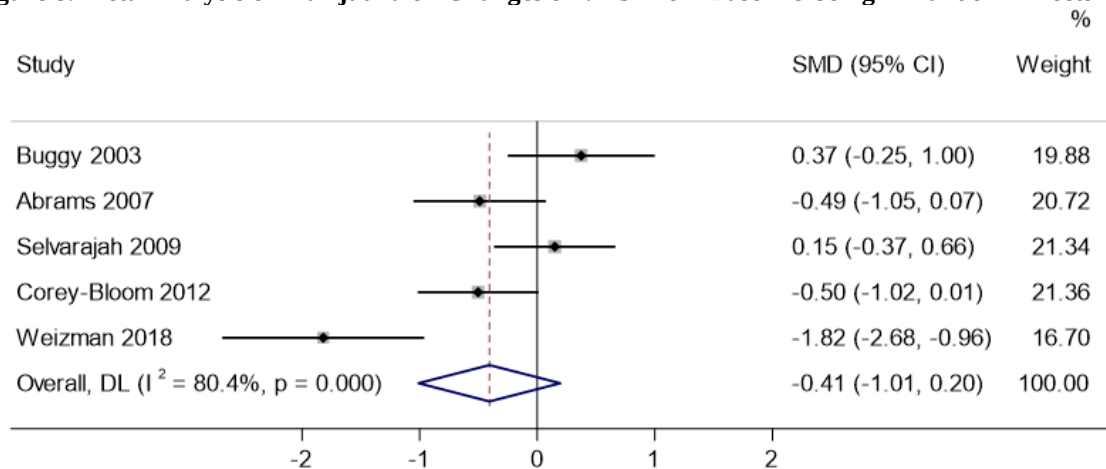
VAS as Primary Outcome

Twelve RCTs were reviewed with a primary outcome of pain measured on the VAS. Six of these studies reported improvement with administration of marijuana and six showed no significant difference when compared to a control. Among the 12 RCTs, five were identified to have homogeneity in assessment strategy and calculation method, and thus were sufficient to calculate meta-analytic estimates. Each of the studies discussed in this section measure change in the pain score from baseline by calculating standard mean difference in VAS. A random effects model was selected and a meta-analysis for standard mean difference (SMD) in VAS was performed. Overall, findings from the pooled analysis trended towards favoring a treatment effect for marijuana over control; however, pooled estimates were not statistically significant ([Figure 8](#)). The reported heterogeneity metric, I^2 , suggests that a high (80.4%) proportion of variance in the findings may be due to heterogeneity in the examined studies, and that the accompanying p-value ($p < 0.001$) *suggests* confidence in this assessment of heterogeneity, but this p-value has limited utility. Thus, there was significant heterogeneity present between the studies included in this meta-analysis and the pooled estimate from these studies may not be representing a true effect of marijuana.

Overall, findings were favoring treatment with marijuana over control; however, pooled estimates were not statistically significant.

²¹ This score captures the quantity of opioid medications used for pain control.

Figure 8. Meta-Analysis of Marijuana on Changes of VAS From Baseline Using A Random-Effects Model²²



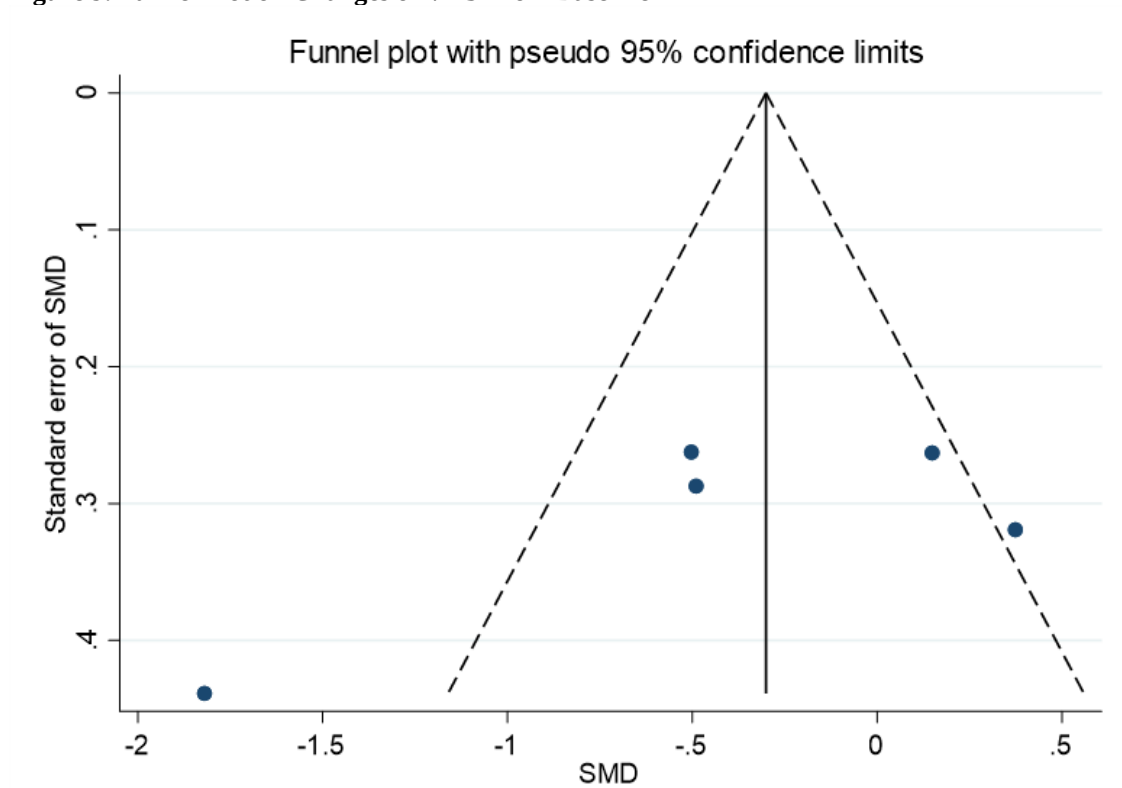
Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Note: Weights are from random-effects model.

A funnel plot for these studies was also constructed ([Figure 9](#)). Most studies fell within the pseudo 95% confidence limits with a notable outlier. The asymmetry in the funnel plot may be indicative of publication bias and/or heterogeneity in the studies assessing this outcome.

²² The p-value reported in the figure is in reference to the accompanying heterogeneity metric I^2

Figure 9. Funnel Plot on Changes of VAS From Baseline



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

The overall quality of evidence for pain scores assessed via VAS was rated as moderate quality, and this was driven by moderate concerns with certainty, imprecision, and inconsistency ([Table 42](#)). Publication bias was primarily rated as informed by the funnel plot, where, as indicated above, some asymmetry was observed as well as an outlier study.

Table 42. Quality of Evidence Rating for Pain Scores Assessed Via Visual Analog Scales, Certainty Rating by Study and Overall

Domain Assessed	(Corey-Bloom et al. 2012)	(Weizman et al. 2018)	(Abrams et al. 2007)	(Buggy et al. 2003)	(Selvarajah et al. 2010)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Moderate concern	Low concern	Low concern	Moderate concern	Moderate concern
Imprecision	Low concern	High concern	Low concern	Moderate concern	Low concern	Moderate concern
Inconsistency						Moderate concern
Generalizability	High concern	High concern	High concern	High concern	High concern	High concern
Publication bias						Moderate concern
Overall quality of evidence rating						Moderate quality

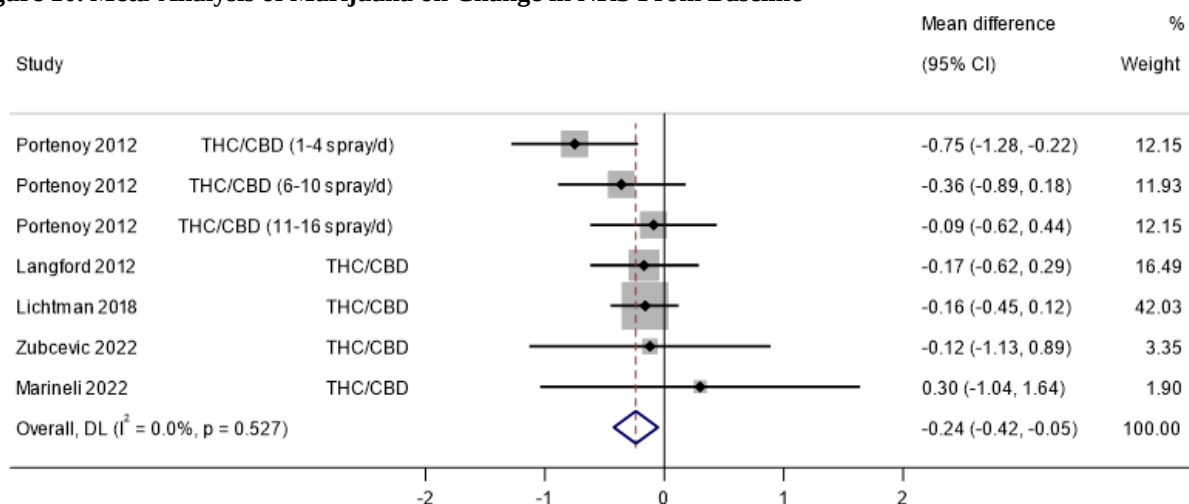
Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

NRS as Primary Outcome

Eleven RCTs that assessed NRS pain outcomes were included in the review. Two reported improvement, one reported worsening of pain, and eight reported no change when compared to a control group. Five of the studies reported change in NRS from baseline with sufficient homogeneity to allow a calculation of a pooled estimate. Of these five studies, one assessed marijuana's effect for three different dosing regimens, and all dosing regimens were included in the pooled estimates.

A random effects model was selected and meta-analysis for change in NRS from baseline was performed, with results in the figure below (Figure 10). Overall, findings were favoring treatment with marijuana over control. The reported heterogeneity metric, I^2 , suggests that essentially no (0.0%) variance in the findings may be due to heterogeneity in the examined studies, but the accompanying p-value ($p=0.527$) suggests this assessment of heterogeneity may not be informative as it was not statistically significant.

Figure 10. Meta-Analysis of Marijuana on Change in NRS From Baseline²³



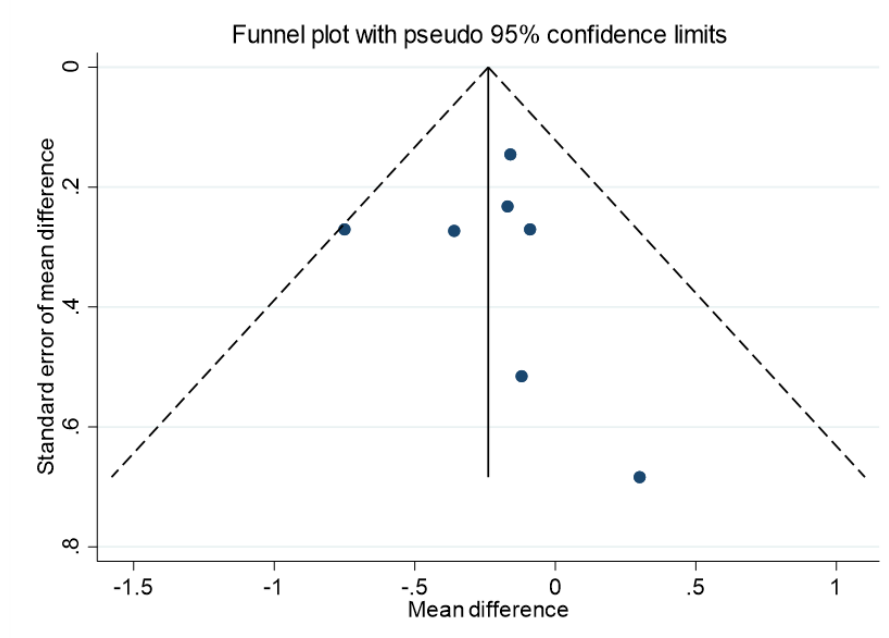
Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Note: Weights are from random-effects model.

A funnel plot for these studies was also constructed (Figure 11). All studies assessing pain via NRS fell within the pseudo 95% confidence limits. The asymmetry in the funnel plot may be indicative of publication bias and/or heterogeneity in the studies assessing this outcome.

²³ The p-value reported in the figure is in reference to the accompanying heterogeneity metric I^2

Figure 11. Funnel Plot of Marijuana on Change of NRS From Baseline



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

The overall quality of evidence for pain scores assessed via NRS was rated as low, and this was driven by moderate and high concerns in four out of five quality domains ([Table 43](#)). This was especially notable due to a high degree of inconsistency of study results.

Table 43. Quality of Evidence Rating for Pain Scores Assessed Via Numeric Rating Scales, Certainty Rating by Study and Overall

Domain Assessed	(Portenoy et al. 2012)	(Langford et al. 2013)	(Lichtman et al. 2018)	(Zubcevic et al. 2023)	(Marinelli et al. 2022)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Moderate concern	Moderate concern	Low concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Low concern	Low concern	Moderate concern	Moderate concern	Moderate concern
Inconsistency						High concern
Generalizability	High concern	High concern	High concern	High concern	High concern	High concern
Publication bias						Low concern
Overall quality of evidence rating						Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Additional Measures of Pain

There were four RCTs that assessed pain via other types of patient-reported scores or questionnaires [e.g., Sum of Pain Intensity Differences (SPID); Brief Pain Inventory (BPI)]. All four studies reported no significant change in pain resulting from treatment with cannabis as compared with placebo or other comparator. The quality of evidence ratings for these four RCTs are shown in [Table 44](#).

Table 44. Quality of Evidence Rating for Pain Scores Via Other Types of Patient-Reported Scores or Questionnaires, Certainty Rating by Study and Overall

Domain Assessed	(Buggy et al. 2003)	(Langford et al. 2013)	(Jefferson et al. 2013)	(Blake et al. 2006)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Moderate concern	High concern	High concern	High concern
Imprecision	Moderate concern	Low concern	Moderate concern	Moderate concern	Moderate concern
Inconsistency					Low concern
Generalizability	High concern	High concern	High concern	High concern	High concern
Publication bias					Low concern
Overall quality of evidence rating					Low quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Additionally, three RCTs assessed neuropathic pain and fibromyalgia pain using neuropathic pain-specific outcome assessment tools. One of the three RCTs reported an improvement in pain, and the others reported mixed results, or no change based on a moderate quality of evidence rating ([Table 45](#)).

Table 45. Quality of Evidence Rating for Pain Scores Assessed Via Neuropathic-Specific Pain Scales, Certainty Rating by Study and Overall

Domain Assessed	(Nurmikko et al. 2007)	(Wilsey et al. 2016a)	(Selvarajah et al. 2010)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Low concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Low concern	Moderate concern	Moderate concern
Inconsistency				Moderate concern
Generalizability	High concern	High concern	High concern	High concern
Publication bias				Low concern
Overall quality of evidence rating				Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Sleep quality was assessed in three RCTs, and two of the studies showed improvement with marijuana administration compared with a control group based on a moderate quality of evidence ([Table 46](#)).

Table 46. Quality of Evidence Rating for Sleep Quality in People With Pain, Certainty Rating by Study and Overall

Domain Assessed	(Nurmikko et al. 2007)	(Lichtman et al. 2018)	(Langford et al. 2013)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern	Moderate concern	Moderate concern
Imprecision	Moderate concern	Low concern	Low concern	Moderate concern
Inconsistency				Moderate concern
Generalizability	High concern	High concern	High concern	High concern
Publication bias				Low concern
Overall quality of evidence rating				Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

There was one RCT assessing pain disability index as an outcome. The quality of evidence rating is shown in [Table 47](#).

Table 47. Quality of Evidence Rating for Pain Disability, Certainty Rating by Study and Overall

Domain Assessed	(Nurmikko et al. 2007)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	High concern	High concern
Publication bias		Low concern
Overall quality of evidence rating		Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Opioid composite score was an identified outcome in one RCT. The study assessing the opioid composite score outcome investigated three different dosing regimens of marijuana as compared with placebo. The results were mixed across the three comparator groups. The overall quality of evidence was rated as moderate ([Table 48](#)).

Table 48. Quality of Evidence Rating for Opioid Composite Score, Certainty Rating by Study and Overall

Domain Assessed	(Portenoy et al. 2012)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Low concern	Low concern
Imprecision	Moderate concern	Moderate concern
Inconsistency		Unable to rate
Generalizability	High concern	High concern
Publication bias		Low concern
Overall quality of evidence rating		Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Overall UF Effectiveness Conclusions for Pain

The evidence for improvement of pain disability was rated as moderate quality based on one RCT. The evidence for pain scores and opioid composite scores were also rated as moderate quality, but findings were mixed or inconclusive across studies. The evidence for other pain scores, sleep quality, and other quality of life outcomes was rated as low quality, but findings were mixed across studies, with some reporting improvements and many reporting inconclusive findings, but none reporting worsening. The meta-analyses performed were based on studies that were able to be combined for analysis, which does exclude some of the studies reviewed due to design differences. Although there was a trend towards benefit for VAS scores for marijuana, it did not reach significance in five of the combined studies that assessed this outcome. Additionally, the meta-analysis for the NRS outcome did show a small but statistically significant benefit (SMD -0.24) based on a low quality of evidence.

Summary of Safety for Pain

There was a limited amount of information reported with respect to safety. Overall, more participants reported AEs when treated with marijuana than those treated with an active

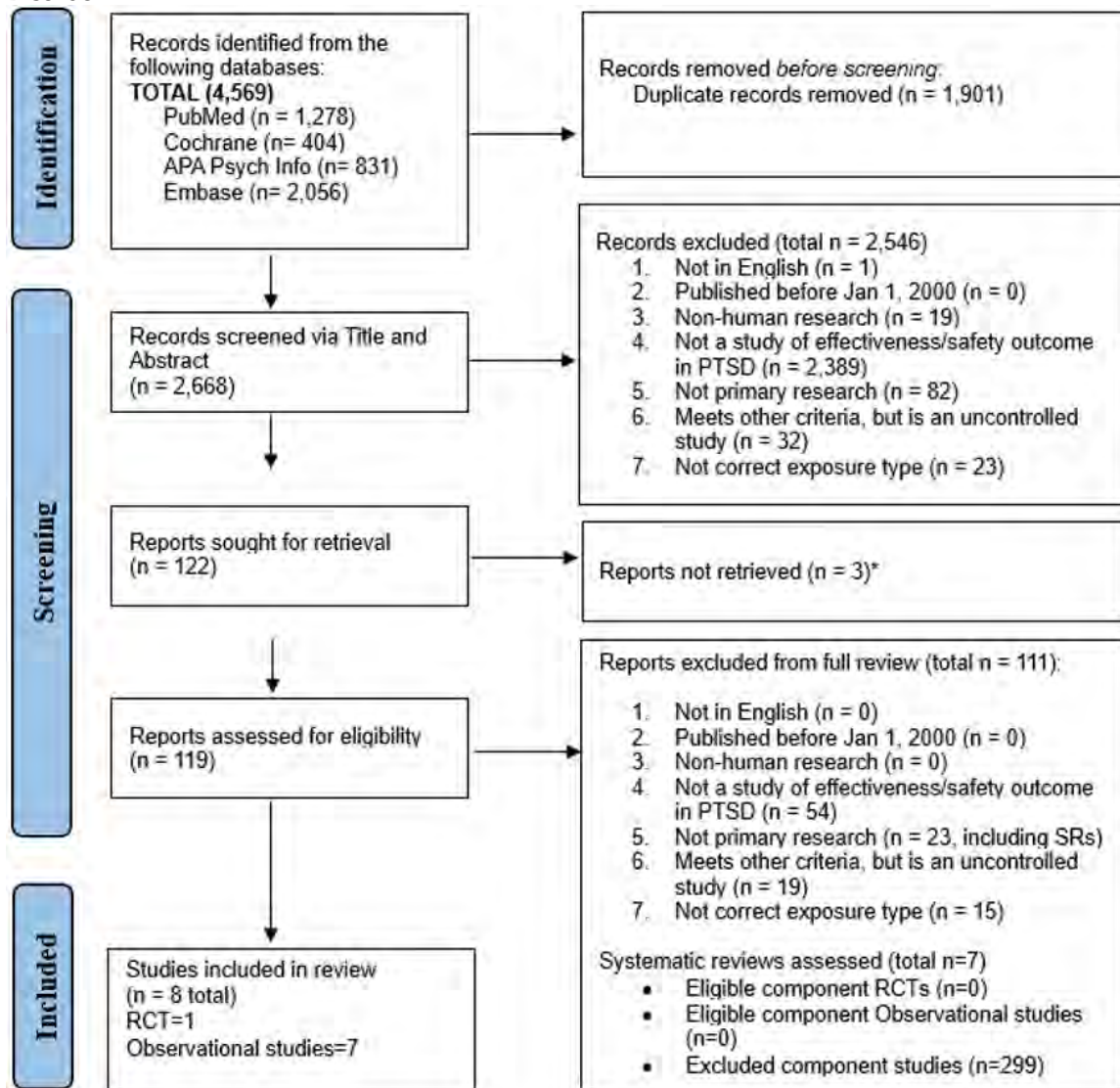
control or placebo. When reported, AEs consisted of dizziness, fatigue, headache, and feeling high. Few of the RCTs reported any SAEs.

4.2.2.7. Post-Traumatic Stress Disorder

The endocannabinoid system may have an impact on the symptoms of PTSD. CB1 receptors modulate mood states, stress, learning, and memory. Therefore, through its effects on the endocannabinoid system, marijuana could potentially inhibit fear and anxiety with potential antidepressant activity, and stimulation of limbic and paralimbic areas may decrease hypervigilance and hyperarousal. Additionally, CB1 receptors have been linked to PTSD and severity of intrusive symptoms. Therefore, marijuana may have clinical applications for PTSD.

The searches identified a total of 4,569 studies. After removal of duplicates, screening, and assessment for eligibility, there were eight studies—one RCT and seven observational studies—that met all the protocol-specified criteria for inclusion in the review for the indication of PTSD. No additional studies were identified from the included systematic reviews ([Figure 12](#)). The summary of studies included, as well as the references and the risk of bias assessment for the eligible RCT and the seven observational studies, are shown in Appendix [III.5.6](#).

Figure 12. PRISMA Flow Diagram Documenting Attrition (Exclusions) for Post-Traumatic Stress Disorder



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

Six of the seven observational studies eligible for inclusion were rated as having a critical risk of bias and were not considered further. Thus, the final systematic review included an RCT and an observational study, both with the Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders (CAPS-5) assessment as the outcome. The quality of evidence rating for the two studies for the CAPS-5 outcome is shown in [Table 49](#).

Table 49. Quality of Evidence Rating for the PTSD Severity Assessment Outcome (CAPS-5), Certainty Rating by Study and Overall

Domain Assessed	(Bonn-Miller et al. 2021)	(Bonn-Miller et al. 2022)	Overall Certainty Rating Across Studies Assessing That Outcome
Certainty	Moderate concern	Moderate concern	Moderate concern
Imprecision	High concern	Moderate concern	High concern
Inconsistency			Moderate concern
Generalizability	Low concern	Low concern	Low concern
Publication bias			Low concern
Overall quality of evidence rating			Moderate quality

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Cannabis Use. Project 2/1B Report dated July 7, 2023.

As specified in the protocol, these two studies did not meet thresholds for the minimum number of studies to qualify for meta-analysis calculation.

Summary of Effectiveness for PTSD

The single identified RCT evaluated short-term impact of three formulations of smoked marijuana and found all treatment groups (placebo, High CBD, High THC, THC+CBD) achieved statistically significant reductions in PTSD severity on the CAPS-5; however, the study did not find a significant difference in change in PTSD symptom severity between the active cannabis concentrations and placebo.

The prospective observational study conducted in Colorado residents with PTSD ages 18 years or older showed that, over the course of a year, the group using cannabis reported a more significant reduction in PTSD symptom severity over time compared to the control group not using cannabis.

The evidence for this outcome ‘PTSD severity’ was rated by the UF investigators as moderate quality.

Summary of Safety for PTSD

Within the single RCT, the most common AEs reported (i.e., those with >10% frequency) were cough (12.3%), followed by throat irritation (11.7%), and anxiety (10.4%). Three SAEs were reported and determined to be unrelated (heart palpitations, pulmonary embolism, and abscess). The number of participants who reported an AE did not differ significantly from placebo.

The observational study did not examine safety outcomes.

4.3. Conclusions Based on the Report by the University of Florida

UF concluded there is low to moderate quality evidence supporting efficacy²⁴ of marijuana as medical treatment for outcomes in several indications, including anorexia, nausea and vomiting, and PTSD. UF performed meta-analyses for VAS and NRS outcome measures in the pain indication, based on studies with sufficient homogeneity

²⁴ The systematic reviews largely relied on RCTs as there were only two observational studies included in the quality of evidence assessments: one for the anxiety indication and one for the PTSD indication.

and where the quality of evidence was considered at least moderate. UF concluded that pooled VAS reported outcomes trended towards showing a benefit for marijuana but did not reach statistical significance when compared to a control group. The results for the pooled NRS reported outcomes showed a small but significant difference when compared to a control group. Although a large literature base was identified for the pain indication, with a number of RCTs showing benefit and their meta-analysis showing a small but significant effect for marijuana on the NRS outcome measure, UF concluded the data were too inconsistent to provide a conclusive statement on the benefit of marijuana for the treatment of pain.

The UF report summarized the limited available safety data contained in the published reports. FDA did not identify any safety concerns described in the UF report that would indicate the medical use of marijuana poses unacceptably high safety risks for the indications evaluated for its therapeutic effect.

4.4. FDA Review of Published Systematic Reviews and Meta-Analyses

As a part of the assessment of CAMU, FDA also conducted a separate review of published systematic reviews and meta-analyses of botanical forms of marijuana and those results are discussed below. This was a high-level review of the literature assessing the effectiveness and safety of these forms of marijuana on the identified indications based on Part 1 of the CAMU test and in the informal landscape analysis performed by FDA. This portion of our review is intended to compare the findings from UF's review with other experts in the field. The most commonly identified forms in the literature included nabiximols oromucosal spray,²⁵ inhaled marijuana (whole plant or plant-derived), and botanically derived marijuana extracts. Within this section, we examined reviews including The National Academies of Sciences, Engineering, and Medicine (NASEM) Comprehensive Review of the Health Effects of Using Cannabis and Cannabis-Derived Products (2017), the Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain by the Agency for Healthcare Research and Quality (AHRQ), as well as identified published systematic reviews and meta-analyses relevant to this document.

4.4.1. Sources of Review

The National Academies of Sciences, Engineering, and Medicine (NASEM)

The NASEM report (2017) consists of a comprehensive review of evidence regarding the health effects of using cannabis and cannabis-derived products. The NASEM report covered a broader range of products, inclusive of all cannabinoids, in contrast to our review, which focuses on marijuana. For purposes of this summary, we will only focus

²⁵ Nabiximols (brand name Sativex in countries where it is approved) is a botanically derived oromucosal spray consisting of 2.7 mg of THC and 2.5 mg of CBD per spray. Nabiximols has been approved for the treatment of spasticity due to multiple sclerosis in the United Kingdom since June 2010.

on the NASEM report's findings for forms that fall under the definition of marijuana. A section of the NASEM report summarized potential therapeutic uses of marijuana based on a literature search, evidence review, grading, and synthesis of information. The committee's conclusions are based on the findings from published systematic reviews. Where no systematic review existed, the committee reviewed all fair and good-quality relevant primary research published between January 1, 1999, and August 1, 2016. Primary research was assessed using standard approaches (e.g., Cochrane Quality Assessment, Newcastle–Ontario scale) as a guide. The committee weighed the evidence and placed conclusions into one of five categories in decreasing order of strength of evidence: Conclusive, substantial, moderate, limited and insufficient. The standard of some credible scientific support required for our review would appear to be consistent with at least the limited strength of evidence standard in the NASEM report.

Agency for Healthcare Research and Quality (AHRQ)

The AHRQ is conducting a living systematic review on cannabis and other plant-based treatments for chronic pain that includes randomized controlled trials and comparative observational studies with a minimum of 4 weeks duration for noncancer chronic pain in adults. Cannabinoid interventions were categorized according to their THC-to-CBD ratio (comparable, high, low) and according to the source of the compound (whole-plant, extracted from whole-plant, or synthetic). Strength of evidence was assessed as low, moderate, high, or insufficient, and magnitude of effect was assessed. The living review is updated on a quarterly basis.

FDA Review of Systematic Reviews and Meta-Analyses

We conducted our own high-level analysis of published systematic reviews and meta-analyses over the past 10 years to evaluate the potential evidence for a therapeutic effect for marijuana, as well as its potential harms when used in this context. Although the primary research covered by each review (i.e., AHRQ, NASEM, UF review, our review of systemic reviews and meta-analyses) overlapped with one another, the purpose of our review was to analyze several groups' conclusions on the data for each of the selected indications, if available.

For the purposes of this analysis, we focused on those studies or treatment arms relevant to marijuana. If the formulation of the marijuana product could not be determined, FDA attempted to review the individual source studies. Of note, the majority of AE data were accumulated mostly from studies that evaluated pain. Therefore, any pooled analysis of AEs across indication will be discussed in the pain section (Section [II.4.4.1.1](#)), and AE data will only be discussed in other sections if there was a dedicated evaluation of AE data in that specific indication.

4.4.1.1. Pain

The mechanism of marijuana's effect on pain relief is not fully clear; however, there is some evidence from experimental pain studies in healthy subjects that all cannabinoids may prevent pain through small increases in pain thresholds and making pain feel less

unpleasant through altering the affective processes as opposed to reducing pain intensity already experienced ([De Vita et al. 2018](#)).

NASEM Report Conclusions and Highlights

The NASEM report (2017) stated there is substantial evidence for treatment of chronic pain in adults with cannabis ([NASEM 2017](#)). This determination was based on mostly plant-derived formulations. The relevant information from this report as it pertains to our analysis of marijuana is described in this section.

One systematic review cited in this report ([Whiting et al. 2015](#)) evaluated studies across numerous types of chronic pain (e.g., cancer pain, diabetic peripheral neuropathy) and NASEM heavily factored these findings into their conclusions. The Whiting (2015) publication included a total of 22 trials of plant-derived cannabinoids (thirteen studies with nabiximols; five trials of plant flower smoked or vaporized form, three trials of THC oramucosal spray; and one trial of oral THC). Whiting (2015) performed an analysis across seven trials that evaluated the effects of nabiximols and one that evaluated the effects of inhaled cannabis, which suggested plant-derived cannabinoids increased the odds for improvement of pain by approximately 40 percent versus the control condition (odds ratio [OR], 1.41, 95% confidence interval [CI] = 0.99-2.00; eight trials). One notable study showing efficacy (N = 50) examined inhaled vaporized cannabis and was included in the effect size estimates. This single study (Abrams, 2007) showed that cannabis reduced pain versus a placebo (OR, 3.43, 95% CI = 1.03–11.48).

The NASEM report noted the effect size for inhaled cannabis observed with the Abrams (2007) study is consistent with another meta-analysis of five trials which studied the effect of inhaled cannabis on neuropathic pain ([Andreae et al. 2015](#)). The pooled OR from these trials showed a pooled effect estimate of 3.22 for pain relief versus placebo (95% CI = 1.59–7.24) tested across nine THC concentrations ([Andreae et al. 2015](#)). Of note, two of the primary studies included in this review by Andreae (2015) were also included in the Whiting (2015) review.

In the addition to the reviews above ([Andreae et al. 2015](#); [Whiting et al. 2015](#)), the NASEM report identified two additional primary studies which examined the effect of cannabis flower on acute pain ([Wallace et al. 2015](#); [Wilsey et al. 2016a](#)). NASEM concluded that these two studies have consistent findings with the meta-analyses described above, suggesting a reduction in pain after cannabis administration, and thus contributed to NASEM's conclusion of substantial evidence of efficacy.

AHRQ Conclusions and Highlights

The AHRQ reviewed and summarized randomized controlled trials (mostly placebo controlled) of patients with chronic pain (mostly neuropathic in origin) with treatment duration between four weeks and less than 6 months ([AHRQ 2023](#)). The AHRQ determined that oral sprays containing comparable amounts of THC and CBD (e.g., nabiximols) are “probably associated with small improvements in pain severity and overall function,” but there may be a large increased risk of dizziness and sedation with moderate risk of nausea. Evidence on whole-plant cannabis, low-THC-to-CBD ratio products, other cannabinoids, or comparators with other active interventions was insufficient to draw conclusions. Overall, the AHRQ has determined thus far that “select

individuals with chronic neuropathic pain may experience moderate short-term improvements in pain when using cannabis products [(synthetic or extracted from whole-plant)] that have a high-THC to CBD ratio.” Additionally, cannabis with a comparable amounts of THC and CBD may result in small improvements in pain severity with increased AEs when the THC-to-CBD ratio is higher.

FDA Review of Systematic Reviews and Meta-Analyses

These reviews covered a number of routes of administration (e.g., oromucosal, smoked) and product types. The content below is separated by each respective route of administration or product type for ease of review.

There have been a number of studies completed using nabiximols to treat pain associated with multiple sclerosis and other pain-related conditions (i.e., neuropathic pain), that demonstrated findings of efficacy ranging from inconclusive to a moderate beneficial effect. Nabiximols has been shown in meta-analyses to demonstrate a modest benefit in chronic neuropathic pain where the NRS was assessed and the evidence was determined to be of moderate quality ([Whiting et al. 2015](#); [Meng et al. 2017](#)). Specifically, one meta-analysis of six chronic neuropathic pain trials (Meng, 2017) revealed a significant but clinically small reduction on the 11-point pain NRS with nabiximols when compared to placebo in patients with neuropathic pain (mean difference -0.50 points; 95% CI, -0.89 to -0.12 points; $P = 0.010$) with some evidence of heterogeneity between studies ($I^2 = 43\%$). Another meta-analysis ([Whiting et al. 2015](#)) of six chronic neuropathic pain trials reached a similar conclusion showing a greater average reduction in the NRS assessment of pain for marijuana (weighted mean difference [WMD], -0.46 [95% CI, -0.80 to -0.11]) with no evidence of heterogeneity ($I^2=0\%$). A number of authors of systematic reviews and meta-analyses have concluded that nabiximols may be considered as an adjunct analgesic in neuropathic pain, with a benefit ranging from weak to moderate effect in a number of neuropathic pain conditions ([Meng et al. 2017](#); [Nielsen et al. 2018](#); [Stockings et al. 2018a](#); [Bilbao and Spanagel 2022](#)).

Another common route of marijuana administration is via the inhalation route (i.e., smoked or vaped). One meta-analysis of inhaled cannabis, supplied by the NIDA, that consisted of five randomized, placebo-controlled, double-blind trials in numerous types of neuropathic pain (e.g., HIV neuropathy, diabetic neuropathy, complex regional pain) with treatment up to two weeks of dosing provided evidence of benefit ([Andreae et al. 2015](#)). The estimated OR for a more than 30% reduction in pain scores in response to inhaled cannabis versus placebo for chronic painful neuropathy was 3.2 with a Bayesian 95% credible interval [1.59, 7.24], and the number needed to treat as 5.55. Additionally, the data showed effect increased with THC content. Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definition of at least moderate benefit (OR 3.1), this meta-analysis suggested a moderate benefit for inhaled cannabis. The authors concluded the studies in their analysis were of mostly good quality and homogenous across studies. However, the nature of the intervention likely interfered with effective blinding which may have resulted in high risk of performance bias and possible detection bias. A more recent meta-analysis pooled eight clinical studies assessing inhaled cannabis (five smoked and three vaporized) versus placebo in patients with chronic pain ([Wong et al. 2020](#)). This meta-analysis showed inhaled cannabis was

associated with statistically significant analgesic effect, with a mean difference of -0.97 ($p < 0.001$, random effect) on the NRS; however, significant heterogeneity was identified ($I^2 = 58.4\%$). Additionally, a further subgroup analysis showed no difference in effect between smoked or vaporized forms. Other systematic reviews similarly concluded a moderate level of benefit for inhaled cannabis in the neuropathic pain population ([Deshpande et al. 2015](#); [Lynch and Ware 2015](#); [Nabata et al. 2021](#)).

Cannabis extracts derived from *Cannabis sativa* are another form of marijuana used to treat pain conditions. In a meta-analysis of studies using cannabis extract in patients with multiple sclerosis, pooled data showed statistical significance for cannabis extract with a small effect size of -0.33 (-0.50 to -0.16), which indicated a small-moderate clinical effect of the treatment with no evidence of heterogeneity between analyzed studies ([Torres-Moreno et al. 2018](#)). A recent meta-analysis of six chronic neuropathic pain trials assessing cannabis extracts versus placebo with THC at varying strengths (1% to 9.4%) showed significant improvement in pain intensity by -8.7 units on a 0-100 scale ($P < .001$) based on a moderate quality of evidence ([Sainsbury et al. 2021](#)). Within this meta-analysis, the authors also showed pooled data from five of the studies that included reports on response rates and showed that patients receiving cannabis extract were 1.855 times more likely to achieve a 30% reduction in pain than patients in the placebo group ($P < .001$).

Other systematic reviews and meta-analyses showed limited to no appreciable effect in some pain groups such as cancer-related pain and spinal cord injuries ([Fitzcharles et al. 2016](#); [Boland et al. 2020](#); [Tsai et al. 2022](#); [Barakji et al. 2023](#)). When attempting to identify whether cannabis may have an opioid-sparing effect, the data showed any effect was uncertain ([Noori et al. 2021](#)) or there was likelihood of an effect, but a causal inference could not be determined ([Okusanya et al. 2020](#)). A lack of evidence of efficacy was also shown in the acute post-operative period in a meta-analysis of all cannabinoids (botanical and synthetic) and notably an increased risk of hypotension with an OR of 3.24 ([Abdallah et al. 2020](#)). In contrast, recently published Canadian clinical practice guidelines ([Bell et al. 2023](#)) identified observational studies with a positive association between cannabis use and opioid sparing and made a strong recommendation based on moderate-quality evidence for the use of cannabis-based medicines among people using moderate/high doses of opioids (> 50 morphine equivalents) for the management of chronic pain and/or increase opioid sparing.

In general, the adverse event profile of marijuana has been well-characterized based on years of clinical studies, observational studies, and harms data. The systematic reviews and meta-analyses did not reveal any new safety signal. It is clear that adverse events are more common in marijuana groups when compared to placebo control and are also a considerable reason for the risk of bias in studies due to potential unmasking of the treatment group. Adverse events commonly identified consisted of anxiety, dry mouth, tiredness, drowsiness, dizziness, nausea, diarrhea, constipation, and euphoria in the mild to moderate range of severity with serious adverse events generally uncommon ([Deshpande et al. 2015](#); [Lynch and Ware 2015](#); [Whiting et al. 2015](#); [Meng et al. 2017](#); [Torres-Moreno et al. 2018](#); [Wong et al. 2020](#); [Sainsbury et al. 2021](#)). In general, no differences in adverse events were identified between types of cannabinoids or mode of administration ([Whiting et al. 2015](#); [Torres-Moreno et al. 2018](#)). For example, one meta-

analysis noted when compared with placebo groups, patients receiving cannabinoids were more likely to report individual adverse events such as dizziness (OR 5.52, 95% CI 4.47-6.83), cognitive attention or disturbance (OR 5.67, 95% CI 2.72-11.79), and confusion and disorientation (OR 5.35, 95% CI 2.31-12.3) when pooling safety data for all types of cannabinoids ([Stockings et al. 2018a](#)). One systematic review also showed adverse events were consistently identified in a number of pain indications, and individuals who are experienced with cannabis use have a reduced risk of adverse events likely due to development of tolerance ([Allan et al. 2018](#)). Dosing varied per study, and dose optimization cannot be determined from the available literature. However, it has been suggested that self-titrating cannabis through inhalation may result in more potent dosages ([Price et al. 2022](#)).

A recently published clinical practice guideline concluded with a strong recommendation based on moderate-quality of evidence for the use of cannabis-based medicines (includes synthetic forms, CBD alone, and botanical) in chronic pain as a monotherapy, replacement, or adjunct treatment ([Bell et al. 2023](#)). This conclusion was based on a number of controlled-studies, systematic reviews, meta-analyses, and observational studies. Although these findings are not specific to botanically-derived marijuana, they draw a conclusion that either the key elements of marijuana, or marijuana itself, is beneficial for chronic pain.

Our review of published systematic reviews and meta-analyses shows most authors concluded there is some benefit with marijuana in the treatment of pain conditions, generally ranging from low to moderate effect based on low to moderate quality of evidence.

4.4.1.2. Anxiety Disorders

There is a lack of high-quality studies examining marijuana in the treatment of anxiety. THC has psychoactive effects that include an anxiogenic response, whereas CBD is associated with anxiolytic properties ([de Almeida and Devi 2020](#); [Sharpe et al. 2020](#)). However, there is some very low-quality evidence that synthetic THC and nabiximols may lead to small improvement in anxiety symptoms in patients with other medical conditions such as multiple sclerosis and chronic non-cancer pain ([Black et al. 2019](#)).

There is also data from a meta-analysis ([Hindley et al. 2020](#)) to indicate that synthetic and botanical forms of THC worsen general psychiatric symptoms such as depression and anxiety when compared to placebo with a large effect size (1.01 [95% CI 0.77-1.25], $p < 0.0001$). Another systematic review suggested THC (includes both synthetic and botanically derived forms) worsened or caused anxiety symptoms and showed little benefit in several psychiatric disorders ([Stanciu et al. 2021](#)).

Based on the available literature, there is not any good evidence to suggest marijuana is an effective treatment of anxiety. Alternatively, it appears the THC component of marijuana is more likely to have anxiogenic effects rather than benefit.

4.4.1.3. Nausea and Vomiting

The most common reason patients with cancer use cannabis and cannabinoids is for the relief of nausea and vomiting ([Sawtelle and Holle 2021](#)). Most studies evaluated nausea and vomiting related to cancer, and if specified, as a complication of chemotherapy. Systematic reviews and meta-analyses were identified but the vast majority of information relates to synthetic forms of THC (i.e., dronabinol, nabilone and levoantrandol). This is not surprising given synthetic oral formulations have FDA approval for chemotherapy-induced nausea and vomiting (e.g., nabilone and dronabinol). For example, the NASEM report (2017) only provided a conclusion relating to the oral cannabinoid preparations nabilone and dronabinol (conclusive evidence of effectiveness) ([NASEM 2017](#)).

As stated above, the vast majority of studies evaluated synthetically derived Δ^9 -THC. A number of older studies from the mid-1970s to 1980s showed significant benefit, but have methodological limitations compared to more recent studies, and it should be noted these older studies were conducted prior to the availability of more modern effective antiemetics ([Sawtelle and Holle 2021](#)). A systematic review concluded there was a low-quality of evidence that cannabinoids (including nabiximols and synthetic THC) were associated with improvements in nausea and vomiting due to chemotherapy ([Whiting et al. 2015](#)). A recent meta-analysis did not show nabiximols was better than placebo for nausea and vomiting ([Bilbao and Spanagel 2022](#)). However, other systematic reviews suggested cannabinoids show a clinically meaningful improvement compared with placebo in patients with nausea and vomiting after chemotherapy; however, the findings appear to be based mostly on synthetically-derived Δ^9 -THC ([Allan et al. 2018](#); [Montero-Oleas et al. 2020](#)).

4.4.1.4. Post-Traumatic Stress Disorder

Although there is some observational data suggesting people with PTSD self-treat with cannabis ([Bonn-Miller et al. 2014a](#); [Bonn-Miller et al. 2014b](#)), there is limited high quality, controlled clinical trial data available on marijuana and PTSD. A systematic review concluded there is some association of a reduction in PTSD symptoms measured by psychometric outcomes and improved quality of life, but this finding was based on observational studies with a high risk of bias ([Rehman et al. 2021](#)). This same review concluded that the most common adverse effects reported were dry mouth, headaches, psychoactive euphoria and agitation, and palpitations but that cannabinoids (numerous formulations studied including synthetic THC, CBD, unknown formulations) were overall well-tolerated. A recent systematic review identified two cohort studies, one retrospective and one prospective, which provided some evidence of benefit of cannabinoids but not specific to marijuana ([Forsythe and Boileau 2021](#)). Specifically, the retrospective analysis evaluated Clinician Administered Post-traumatic Scale for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (CAPS) scores prior to entering a medical cannabis program in New Mexico and then a second score after being enrolled and treated ([Greer et al. 2014](#)). A significant decrease ($p < 0.0001$) in CAPS scores was observed from before and after cannabis use, from 98.8 ± 17.6 (mean $\pm$ SD) to 22.5 ± 16.9 , indicating a reduction in overall PTSD symptoms. The identified

prospective cohort study evaluated THC in patients with chronic PTSD in ten patients ([Roitman et al. 2014](#)). There was a significant decrease in specific symptoms of PTSD: Clinical Global Impression-Improvement Scale (3.5 ± 0.52 to 2.7 ± 1.25 , $p < 0.03$), hyperarousal (32.3 ± 4.73 to 24.3 ± 9.11 , $p < 0.02$), sleep quality (17.20 ± 2.65 to 13.9 ± 4.48 , $p < 0.05$), frequency of nightmares (0.81 ± 0.55 to 0.44 ± 0.41 , $p < 0.04$), and total Nightmare Effects Survey (NES) scores (32.2 ± 11.29 to 22.9 ± 8.7 , $p < 0.002$). The above studies reported marijuana was well-tolerated with mild AEs (e.g., dry mouth, dizziness).

The NASEM report (2017) did not identify any evidence for treatment of PTSD with a botanically-derived form of marijuana and concluded there is limited evidence of effectiveness for any cannabinoid ([NASEM 2017](#)). The only evidence NASEM identified for any THC product in this condition was a small study which administered synthetic THC (nabilone). Other systematic reviews also concluded there was insufficient evidence to draw a conclusion or support use of plant-based forms of marijuana ([O'Neil et al. 2017](#); [Shishko et al. 2018](#); [Hindocha et al. 2020](#); [Jugl et al. 2021](#)).

Overall, there is a lack of quality clinical data to support the use of marijuana for PTSD. Evidence of benefit was based mostly on case-reports and observational studies with high risk of bias.

4.4.1.5. Inflammatory Bowel Disease

Numerous survey data suggest marijuana has patient-reported improvement in symptoms of IBD suggesting potential benefit as a treatment option in this population ([Norton et al. 2017](#); [Desmarais et al. 2020](#); [Doeve et al. 2021](#)). A number of reviews, including meta-analyses, have been performed and are described below. Given the small number of studies performed, there is overlap in studies across these reviews. However, review of different authors' analyses are intended to provide further insights into the available data.

A systematic review of Cochrane Database systematic reviews identified three studies that assessed cannabis in patients with active Crohn's disease and two studies in patients with ulcerative colitis ([Kafil et al. 2020](#)). The studies were small with varying THC/CBD ratios. Two of the Crohn's disease trials assessed botanically derived marijuana products (smoked cannabis and sublingual cannabis oil) and showed induction of remission was greater in the cannabis groups compared to placebo. The smoked cannabis study showed that a clinical response (defined as a 100-point Crohn's Disease Activity Index (CDAI) reduction from baseline) at eight weeks was reported in 91% (10 of 11) of participants in the treatment group compared with 40% (4 of 10) of participants in the placebo group (relative risk [RR] 2.27; 95% CI, 1.04-4.97;) with a very low certainty of evidence and high risk of bias. The second study administered cannabis oil (4% THC) for eight weeks and showed the mean quality of life score was 96.3 in the cannabis oil group compared with 79.9 in the placebo group (mean difference 16.40; 95% CI, 5.72-27.08, low certainty evidence). In addition, the mean CDAI score at 8 weeks was 118.6 in the cannabis oil group compared with 212.6 in the placebo group (mean difference -94.00; 95% CI, 148.86–39.14, low certainty evidence). Two randomized trials were identified in ulcerative colitis patients and the authors concluded there was no firm evidence to support efficacy or safety of cannabis use in patients with active ulcerative colitis.

Adverse events in the above studies included dizziness, headache, sleepiness, dry mouth, fatigue, and nausea. There did not appear to be any serious adverse events related to marijuana treatment. The authors concluded that there is low to very low certainty of evidence of efficacy and no firm conclusion could be made due to limitations of the studies, such as small sample sizes.

A recent meta-analysis of the available studies utilizing botanically derived oil or dried plant marijuana products for smoking or oral administration showed some benefit in Crohn's disease [pooled risk-ratio 0.42 (-0.04, 0.890)] coming close to statistical significance with a low degree of heterogeneity in studies ([Vinci et al. 2022](#)). Also, mean CDAI reduction was greater in patients treated with marijuana products than with placebo (mean CDAI reduction of 36.63, CI 95% 12.27-61.19). This same meta-analysis did not find benefit based on the ulcerative colitis pooled data. The authors concluded marijuana as an adjuvant therapy may improve Crohn's Disease symptoms, but the studies had numerous limitations including small sample sizes. Another meta-analysis of available data did not show any benefit of marijuana with regard to remission status or a clinical response when compared to placebo in IBD, but the authors suggested there may be a role as an adjunct to standard therapy ([Desmarais et al. 2020](#)).

Another analysis of available randomized control studies and observational studies showed cannabis products do not induce remission in IBD ([Doeve et al. 2021](#)). The majority of interventional products in this review were botanically derived. A meta-analysis did not show any statistically significant benefit with remission status [RR 1.56 (0.99, 2.46)] but did show significance for perceived efficacy on various Likert-scales [RR 0.61 (0.24, 0.99)]. The authors concluded these types of cannabinoids were not effective in induction of remission but did produce a perceived benefit to patients. They postulate THC's CB1 activity and reciprocal TRPV1 downregulation correlate with improved visceral hypersensitivity and reduced colonic motility, thereby improving abdominal pain, diarrhea, and nausea. Although there was some evidence of a therapeutic benefit, the authors did not reach a firm recommendation and believed a larger randomized-controlled trial is warranted.

Evidence in a systematic review assessing abdominal pain related to IBD was limited to one open-label pilot study and two surveys. These studies showed some possible benefit in short-term pain relief, but these studies have significant limitations such as no control group, significant amount of data relied on survey data, and significant risks of biases ([Norton et al. 2017](#)).

It appears from the available data that there is some evidence of benefit in Crohn's disease when treated with marijuana. However, this appears mostly limited to subjective symptoms and not disease activity. There is no significant evidence to suggest benefit in ulcerative colitis. Some authors recommended marijuana may be useful as an adjunct in Crohn's disease if other options have failed, but a general consensus is more data from large randomized controlled trial(s) are required to provide a firm conclusion with regard to efficacy, safety, and dosing optimization.

4.4.1.6. Epilepsy

Although there is some evidence of efficacy for CBD in reducing seizure activity in pediatric drug-resistant epilepsy in the literature and FDA has approved a product containing highly purified plant-derived CBD for seizures related to specific syndromes (i.e., Lennox-Gastaut epilepsy, tuberous sclerosis, myoclonic epilepsy in infancy), there are not sufficient data to determine that other cannabis-based products (i.e., marijuana) are effective in the treatment of epilepsy, given the lack of quality studies ([Stockings et al. 2018b](#); [Elliott et al. 2019](#); [Elliott et al. 2020](#)). See Section [II.4.6](#) of this document for further information related to Epidiolex and its approval. The 2017 NASEM report also concluded there was insufficient evidence to support or refute a conclusion that cannabinoids, such as marijuana, are effective for epilepsy ([NASEM 2017](#)).

4.4.1.7. Anorexia Related to Medical Conditions

Dronabinol (a synthetic form THC) is FDA approved to treat anorexia associated with HIV. However, data based on botanically derived marijuana are more limited. NASEM reviewed systematic reviews and individual primary literature as well, which included botanically derived marijuana and synthetic THC ([NASEM 2017](#)). The report concluded there is little evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss in the population with HIV and/or acquired immunodeficiency syndrome (AIDS). It was also concluded that there is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for anorexia-cachexia due to cancer.

A systematic review and meta-analysis did not find any high-quality evidence suggesting cannabinoids are beneficial for anorexia or cachexia in cancer or HIV patients ([Whiting et al. 2015](#); [Mucke et al. 2018](#); [Simon et al. 2022](#)). These analyses were based on combined studies of herbal marijuana and plant-derived and synthetic THC; therefore, these analyses are not entirely specific to botanical forms. In addition, one of these reviews included uncontrolled studies in the analysis. Mucke (2018) identified one study comparing herbal marijuana with synthetic dronabinol and noted that both groups gained 3.0 and 3.2 kg, respectively, with no serious AEs reported ([Mucke et al. 2018](#)). Alternatively, another meta-analysis of three studies, including what appeared to be both botanical extracts and synthetic THC, showed a trend towards increased appetite (mean difference 0.27, 95% CI -0.51 to 1.04) when compared with a placebo ([Wang et al. 2019](#)). The Whiting et al. review only identified one study which evaluated weight gain with marijuana and found no benefit when compared with placebo ([Whiting et al. 2015](#)). However, this same analysis showed a trend towards a decrease in quality of life in the two studies which assessed this outcome. The authors hypothesized this trend may be due to adverse events related to marijuana.

In summary, it appears the majority of systematic reviews covered synthetic forms of THC with limited information supporting marijuana's benefit related to this review.

4.5. Safety Data From Case Studies of Selected State Programs: Maryland and Minnesota

The purpose of this section is to describe the number of individuals using marijuana based on medical advice and the safety experience of these patients in states with authorized medical marijuana programs. FDA reviewed results from state reporting data from 37 states with medical marijuana programs and surveys of patients using marijuana in Maryland and Minnesota.

The University of Michigan provided state annual reports for 37 states. The number of patients using marijuana for medical purposes increased every year from 661,990 in 2016 to 2,974,433 in 2020 (Appendix [Table 79](#)). There were no safety data relevant to this review included in these annual reports (i.e., no inferential analyses of epidemiologic data). There was no information provided regarding the quality control processes for data analysis or data management for these results.

We considered patient survey data from Maryland and Minnesota in more depth than the other 35 states because they had available survey data and were able to provide the results and/or data to FDA. Therefore, these two states were used as an approximate representative sample of safety data from jurisdictions with state-legalized use of marijuana for medical purposes.

4.5.1. Maryland

4.5.1.1. Maryland Methods

In 2022, the Maryland Medical Cannabis Commission (MMCC) conducted an online survey of certified medical cannabis patients in Maryland (MD). Participation was anonymous and voluntary. Participants were entered in a raffle to win a \$50 Visa gift card. The initial participation goal of 7,500 completed responses was met in 5 hours and 13,011 completed responses were collected ([MMCC 2023](#)).

FDA discussed the survey with MMCC investigators and requested summary data regarding the characteristics of survey participants, perceived effectiveness, and adverse events. These results were provided by MMCC investigators in tabular form. A description of the quality control process conducted by MMCC is described in the Appendix (*Cannabis Public Policy Consulting, Quality Control Processes*).

4.5.1.2. Maryland Results

All questions were optional in the survey; thus, the number of respondents varies by question. Descriptive characteristics of MMCC study participants are presented in Appendix [Table 66](#). Participants were mostly White or Caucasian (78.2%), female (53.8%), not Hispanic or Latino (93.7%), and employed full-time (56%); most had been in the medical cannabis program for less than 4 years (79.5%).

The frequencies of condition or symptom treated with cannabis are presented in [Table 50](#). The most frequently treated symptom was chronic pain (46%), other chronic condition (33.4%) and post-traumatic stress syndrome (12.5%).

Table 50. Most Common Condition or Symptom Treated With Cannabis Among Maryland Medical Cannabis Commission (MMCC) Survey Participants

Qualifying condition	n	%
Anorexia	131	1
Severe or persistent muscle spasms	387	3
Epileptic seizures	85	0.7
Severe or chronic pain	5980	46
Cachexia or wasting syndrome	20	0.2
Post-traumatic stress disorder (PTSD)	1622	12.5
Severe nausea	334	2.6
Other chronic condition	4343	33.4
Total	12902	

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Most participants reported using cannabis all or most days in the past month (65.1%). They used alcohol at least once in the past month (60%) and did not use other substances (Appendix [Table 67](#)). The primary methods of cannabis use were smoking, eating edibles, or vaping ([Table 50](#)). Additional information regarding the methods of consumption is provided in Appendix [Table 68](#).

Table 51. Primary Method of Marijuana Consumption in the Past Month, Maryland Medical Cannabis Commission (MMCC) Survey Participants

Method of Consumption	n	%
Smoking	6101	46.9
Ingesting edibles	2622	20.2
Vaping	2737	21
Dabbing, oil, wax, shatter, butter concentrate	467	3.6
Tinctures or oral sprays (elixirs)	178	1.4
Capsules or tablets	128	1
Topicals (balm, lotion, cream)	176	1.4
Transdermal (patch)	5	0
Rectal/Vaginal suppositories	10	0.1
Total	12424	

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Patients were asked if they used cannabis for recreational purposes; most patients used cannabis for medical use only (63.8%, [Table 52](#)). A small number of patients reported using cannabis for only (0.8%) or mostly recreational purposes (1.8%).

Table 52. Percentage of Medical Use vs. Recreational Use in the Past Month Among Maryland Medical Cannabis Commission (MMCC) Survey Participants

Percentage of Medical Use	n	%
100% medical	8298	63.8
75% med, 25% rec	2474	19
50% med, 50% rec	1547	11.9
25% med, 75% rec	231	1.8

Percentage of Medical Use	n	%
100% rec	100	0.8
Didn't use in past month	271	2.1
Total	12921	

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Most patients reported that they perceived cannabis treatment to be moderately (21.4%), very (46%), or extremely (28.3%) effective (Appendix [Table 69](#)). Patients were asked about the perceived health and social effects of cannabis treatment, most said it improved their physical (71.9%) and mental (88.6%) health as well as their social relationships (54.3%, Appendix [Table 70](#)). They reported cannabis either improved (37%) or had no impact (54.6%) on their memory or concentration.

Most patients reported never experiencing adverse events or symptoms while using cannabis (Appendix [Table 71](#) and [Table 72](#)). Over 80% reported never experiencing panic, psychotic or paranoid feelings, suicidal thoughts or ideation, breathing problems, and nausea/vomiting. The most common adverse condition experienced was anxiety, which was reported as experienced at least once among 31.1% of patients. There were very few patients who were treated in an emergency room or urgent care as a result of their cannabis use (< 2%, Appendix [Table 73](#)).

Patients were asked to report on a scale of 1= not interested at all to 10= very interested their degree of interest in reducing or cutting back cannabis consumption and most were not interested (Mean = 1.69, Standard Deviation =2.19).

Most medical cannabis users reported not driving within 3 hours of consuming cannabis or under the influence of cannabis (79.8%, Appendix [Table 74](#)).

4.5.1.3. Maryland Discussion

Overall patients using marijuana for medical purposes in MD reported very few side effects and a high level of perceived effectiveness. A strength of this study was the high participation rate. Additionally, since participation was anonymous and voluntary, patients were more likely to accurately report their experiences because there is no concern that they may lose access to marijuana based on their responses. However, participation was voluntary, thus generalizability may be limited.

There are several limitations of this study that should be considered. This was a cross-sectional study that only included patients currently enrolled in the program. Patients who were previously registered to use marijuana and experienced an adverse event or lack of perceived effectiveness were not included in this study, thus the number of adverse events may be underreported, and the perceived effectiveness may be overreported. Patients may also have been more motivated to report positive experiences with medical cannabis since the survey was conducted by the MMCC and patients would want to keep marijuana accessible in MD.

4.5.2. Minnesota

4.5.2.1. Minnesota Methods

Minnesota legalized the use of medical marijuana in 2014. The qualifying medical conditions for Minnesota (MN) are presented in Appendix [Table 75](#). Patients must complete a patient self-evaluation through the online MN medical cannabis patient registry before each medical cannabis purchase. For each adverse effect reported, patients were required to indicate the severity of that adverse effect as mild (symptoms do not interfere with daily activities), moderate (symptoms may interfere with daily activities), or severe (symptoms interrupt usual daily activities). MN provided summary data for 2015-2017 and raw data that were analyzed by two separate FDA analysts to ensure agreement from 2017-present.

4.5.2.2. Minnesota Results

Baseline characteristics of MN medical cannabis patients are presented in [Table 53](#). Most patients were white, and the primary qualifying conditions were chronic or intractable pain. A limitation of this study design is that patients who experienced an adverse event or did not perceive a benefit of marijuana likely would not make another marijuana purchase and these events would not be identified. To assess these potential differences in patient characteristics, FDA stratified baseline characteristics by the number of patient visits.

Table 53. Baseline Characteristics of Minnesota Medical Cannabis Patients 2017-2022*

Characteristic	Overall		Patients With at Least 1 Returning Visit		Patients Without a Returning Visit	
	n	%	n	%	n	%
Receive Medical Assistance	36606	50.04	16164	53.81	20442	47.41
Race/Ethnicity						
Hispanic	2760	3.77	1059	3.53	1701	3.94
American Indian	2881	3.94	1153	3.84	1728	4.01
Asian	1044	1.43	388	1.29	656	1.52
Black	5187	7.09	1693	5.64	3494	8.1
Unknown race	280	0.38	99	0.33	181	0.42
Hawaiian	204	0.28	67	0.22	137	0.32
No response for race	2845	3.89	1148	3.82	1697	3.94
Other race	1757	2.40	694	2.31	1063	2.47
White	61961	84.69	26057	86.74	35904	83.27
Certified Condition						
Cancer, where this illness or its treatment produces cachexia or severe wasting. Live July 1, 2015	1686	2.3	250	0.83	1436	3.33
Terminal illness, where this illness or its treatment produces severe or chronic pain. Live July 1, 2015	345	0.47	64	0.21	281	0.65
Terminal illness, where this illness or its treatment produces nausea or severe vomiting. Live July 1, 2015	220	0.3	40	0.13	180	0.42
Terminal illness, where this illness or its treatment produces cachexia or severe wasting. Live July 1, 2015	213	0.29	30	0.1	183	0.42
Glaucoma. Live July 1, 2015	403	0.55	185	0.62	218	0.51
HIV/AIDS. Live July 1, 2015	387	0.53	174	0.58	213	0.49
Tourette syndrome. Live July 1, 2015	313	0.43	149	0.5	164	0.38
Amyotrophic lateral sclerosis. Live July 1, 2015	130	0.18	36	0.12	94	0.22
Seizures, incl. those characteristic of epilepsy. Live July 1, 2015	1708	2.33	790	2.63	918	2.13
Severe and persistent muscle spasms, incl those characteristic of multiple sclerosis. Live July 1, 2015	5467	7.47	2997	9.98	2470	5.73
Inflammatory bowel disease, incl. Crohn's disease. Live July 1, 2015	1697	2.32	825	2.75	872	2.02
Intractable pain. Live August 1, 2016	31168	42.6	15668	52.16	15500	35.95
Post-traumatic stress disorder. Live August 1, 2017	20445	27.95	7991	26.6	12454	28.88
Autism. Live August 1, 2018	1421	1.94	664	2.21	757	1.76
Obstructive sleep apnea. Live August 1, 2018	2980	4.07	1526	5.08	1454	3.37

Alzheimer's disease. Live August 1, 2019	119	0.16	19	0.06	100	0.23
Chronic pain. Live August 1, 2020	24189	33.06	7310	24.34	16879	39.15
Sickle cell disease. Live August 1, 2021	14	0.02	2	0.01	12	0.03
Chronic vocal or motor tic disorder. Live August 1, 2021	70	0.1	10	0.03	60	

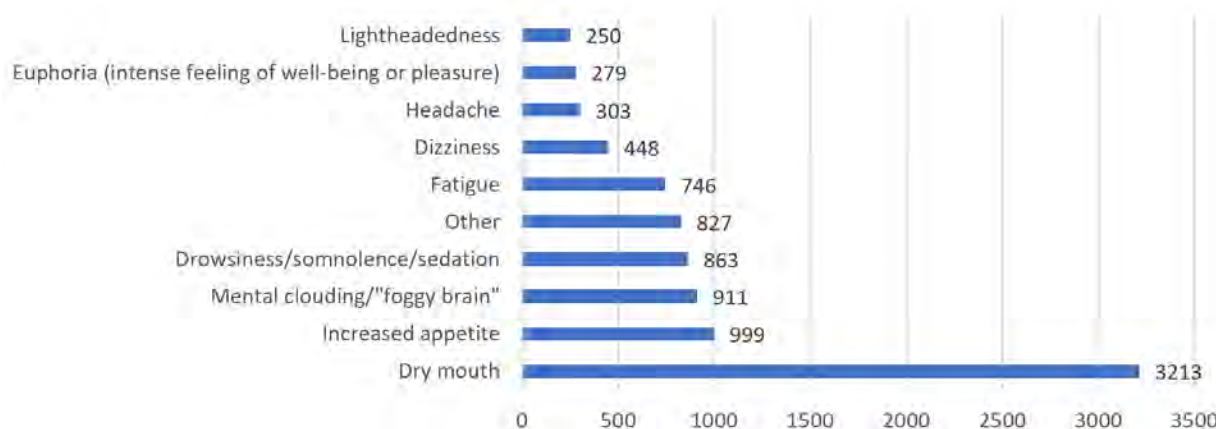
Source: Estimates generated by FDA using data provided by Minnesota Department of Health April 3, 2023 and April 12, 2023.

Note:

- "Live" refers to when the certified condition was added to the patient survey
- When selecting race, patients can select more than one race
- Patients can be certified for multiple conditions at one time
- Patients must first be certified by a registered health care practitioner for at least one qualifying condition. After that certification is submitted, patients can enroll to be in the program. Enrollment is good for 1 year.

The most common side effects reported in 2021 are presented in [Figure 13](#), additional data regarding side effects are presented in Appendix [Table 76](#), [Table 77](#), and [Table 78](#). From 2017-2022, any side effect was reported in <10% of all patient surveys and less than 1% reported severe side effects (Appendix [Table 77](#)). The majority (>90%) of side effects reported by MN medical cannabis users were mild (symptoms do not interfere with daily activities) to moderate (symptoms may interfere with daily activities) in severity. The most common side effect reported was dry mouth; other side effects were increased appetite, somnolence, and mental clouding/foggy brain.

Figure 13. Top Ten Side Effects Reported on the MN Patient Self-Evaluation, 2021



Source: Estimates generated by FDA using data provided by Minnesota Department of Health April 3, 2023 and April 12, 2023.

4.5.2.3. Minnesota Discussion

An advantage of the MN database is that all medical marijuana users are required to complete the patient survey before every purchase, thus these findings reflect the experience of medical marijuana patients in MN. However, patients may underreport side effects if they are concerned about the results of the survey being used to limit access to medical marijuana. Another limitation of the MN database is the lack of information from patients who chose to stop using medical marijuana. This could lead to an underestimation of the number of adverse events as well as an overestimation of perceived effectiveness and an underestimation of adverse events as patients who experienced adverse events or lack of effectiveness may not make a second purchase.

4.5.3. Conclusion

Chronic pain was the most common condition treated with marijuana. The side effects reported by marijuana patients in Minnesota were generally defined as mild (symptoms do not interfere with daily activities) by respondents. Most patients did not report any side effects in either Maryland or Minnesota. Patients in Maryland reported a high level of perceived effectiveness and symptom improvement because of their marijuana use. Survey participation was voluntary in Maryland, which may limit generalizability. Both the Maryland and Minnesota databases are limited because they did not include patients who stopped using marijuana, which may result in an overestimation of positive patient experiences.

4.6. Summary of FDA-Approved Drug Products Related to Marijuana

Although the focus of this document is on marijuana, CBD and Δ 9-tetrahydrocannabinol (Δ 9-THC) are the two major phytocannabinoids present in the *Cannabis sativa* plant, and there are several FDA approved products that contain botanical, synthetic, or structurally related forms of these components of marijuana. The following sections summarize FDA's findings for these products as reflected in their approved labeling, and, although these products do not fall under the definition of marijuana, the findings for these products are relevant to the discussion of the medical use of marijuana.

Marinol (Dronabinol) Capsules, for Oral Use, Approved by FDA in 1985

Marinol capsules, a Schedule III controlled substance, contains synthetically derived Δ 9-THC (the (-)-trans stereoisomer, also known as dronabinol) that is approved for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Marinol is supplied as capsules in strengths of 2.5 mg, 5 mg, and 10 mg.

Marinol has identical warnings and precautions, as well as common adverse events, to Syndros.

Syndros (Dronabinol) Oral Solution, Approved by FDA in 2016

Syndros oral solution, a Schedule II controlled substance, contains synthetically-derived Δ 9-THC (dronabinol) that is approved for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Syndros is supplied as a 5 mg/ml solution.

Syndros has warnings and precautions within the labeling describing neuropsychiatric effects, hemodynamic effects, seizures, substance use, and paradoxical nausea/vomiting, as well as drug interactions. The most common adverse reactions ($\geq 3\%$) are abdominal pain, dizziness, euphoria, nausea, paranoid reaction, somnolence, thinking abnormal, and vomiting.

Cesamet (Nabilone) Capsules, Approved by FDA in 1985

Nabilone, the active ingredient in Cesamet capsules, is a Schedule II controlled substance that is a synthetic analogue of Δ 9-THC. Cesamet is approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Cesamet is supplied as 1 mg capsules.

Cesamet has similar safety information to other synthetic forms of Δ 9-THC.

Epidiolex (Cannabidiol) Oral Solution, Approved by FDA in 2018

Epidiolex oral solution is not a controlled substance and is a highly purified form of cannabidiol approved for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older.

Epidiolex is considered to have no meaningful potential for abuse.

FDA included a review of approved products relevant to marijuana because the active pharmaceutical ingredients (APIs) in the approved products, such as synthetic forms of THC, are

expected to have the same clinical effect as botanically-derived THC. Therefore, if the above approved formulations of THC were considered to have proven benefit for various indications, it is logical to conclude that a similar dose administered through a marijuana preparation would be relevant to informing potential therapeutic uses of marijuana for drug scheduling purposes.

4.7. Summary of Expert Opinions and Position Statements

Summary of Professional Organizations’ Positions

[Table 54](#) provides a summary of a representative list of professional organizations’ position statements on marijuana as it relates to their respective medical specialty. Most of these organizations did not arrive at a firm recommendation for use of marijuana in their specialty, but some acknowledged there may be preliminary evidence showing marijuana may have some therapeutic benefits. Otherwise, the majority of organizations acknowledged patient reported benefits and some evidence from clinical studies for cannabis-based treatments in their respective specialties, though they recommended more extensive research into cannabis rather than a recommendation to prescribe it for a particular disorder. Additionally, a number of organizations recommended rescheduling of cannabis from Schedule I to Schedule II to facilitate less barriers to quality research.

Table 54. Professional Organizations’ Position Statements

Professional Organization	Highlights
American Academy of Family Physicians (2019) (AAFP 2019)	• “AAFP acknowledges preliminary evidence indicates marijuana and cannabinoids may have potential therapeutic benefits, while also recognizing subsequent negative public health and health outcomes associated with cannabis use.” • Opposes the recreational use of marijuana. However, the AAFP supports decriminalization of possession of marijuana for personal use. • “The AAFP calls for decreased regulatory barriers to facilitate clinical and public health cannabis research, including reclassifying cannabis from a Schedule I controlled substance.”
American Academy of Neurology (2020) (AAN 2020)	• Does not support the use of, nor any assertion of therapeutic benefits of, cannabis products as medicines for neurologic disorders in the absence of sufficient scientific peer-reviewed research to determine their safety and specific efficacy • Supports efforts to allow rigorous research to evaluate long term safety and efficacy
American Epilepsy Society (2022) (AES 2022)	• Scientific evidence for the use of cannabis itself in the treatment of epilepsy is highly limited • Calls for increased rigorous clinical research, AES urges that the status of cannabis as a United States Drug Enforcement Administration (DEA) Schedule I controlled substance be reviewed. • The AES call for rescheduling is not an endorsement of the legalization of cannabis but rather is a recognition that the current restrictions on the use of cannabis products for research continue to significantly limit scientifically rigorous research
American Psychiatric Association (2019) (APA 2018)	• Does not endorse cannabis as medicine • Association with onset of psychiatric disorders

Professional Organization	Highlights
American Society of Addiction Medicine (2020) (ASAM 2020)	• “Cannabis used for medical purposes should be rescheduled from Schedule 1 of the Controlled Substances Act (CSA) to promote more clinical research and FDA oversight typical of other medications.” • Position paper summarized risks and benefits but did not state whether they agreed with findings on efficacy. • Healthcare professionals should only recommend non-FDA-approved cannabis if there is evidence that the potential benefits outweigh the potential harms.
The Association for Addiction Professionals (NAADAC) (NAADAC 2022)	• Does not currently support the use of cannabis as medicine or for recreational purposes • Acknowledges some early evidence of efficacy and encourages further research
International Association for the Study of Pain (2021) (IASP 2021)	• The IASP found a lack of high-quality evidence • The evidence base regarding efficacy and safety fails to reach the threshold at which IASP can endorse their general use for pain control • Acknowledge patient experience can show benefit and call for more rigorous and robust research
American Academy of Sleep Medicine Position Statement (Ramar et al. 2018)	• Limited evidence citing small pilot or proof of concept studies suggest that the synthetic medical cannabis extract dronabinol may improve respiratory stability and provide benefit to treat obstructive sleep apnea (OSA). • “It is the position of the American Academy of Sleep Medicine (AASM) that medical cannabis and/or its synthetic extracts should not be used for the treatment of OSA due to unreliable delivery methods and insufficient evidence of effectiveness, tolerability, and safety.” • Further research recommended

5. Overall Conclusions for Part 2 of the Currently Accepted Medical Use Test for Marijuana

Based on the totality of the available data described in Section [II.4](#) of this document, we conclude that there exists some credible scientific support for the use of marijuana in at least one of the indications for which there is widespread current experience with its medical use in the United States, as identified under Part 1 of the CAMU test. The analysis and conclusions on the available data are not meant to imply that safety and efficacy have been established for marijuana that would support FDA approval of marijuana for any particular indication. However, the available data do provide some level of substantiation to support the way marijuana is evidently being used in clinical practice.

As previously noted, in evaluating whether there exists some credible scientific support under Part 2 of the CAMU test for a particular use, factors considered in favor of a positive finding included whether 1) favorable clinical studies, although not necessarily FDA approval-level studies, of the medical use of marijuana have been published in peer-reviewed journals and/or 2) qualified expert organizations (e.g., academic or professional societies, government agencies) have opined in favor of the medical use or provided guidance to practitioners on the medical use. Factors considered that weigh against a finding that Part 2 of the CAMU test is met

included whether 1) data or information indicate that medical use of the substance is associated with unacceptably high safety risks for the likely patient population, e.g., due to toxicity concerns; 2) clinical studies with negative efficacy findings for the medical use of marijuana have been published in peer reviewed journals; and/or 3) qualified expert organizations (e.g., academic or professional societies, government agencies) have recommended against the medical use of marijuana.

Our analysis of the available information showed mixed findings across indications. The largest evidence base substantiating the use of marijuana in clinical practice exists for its use in treating pain (in particular, neuropathic pain). In the pain indication, the UF analysis found inconclusive results; however, numerous other systematic reviews concluded that there exists some level of evidence supporting the use of marijuana for pain. UF found that there is low to moderate quality evidence supporting the effectiveness of marijuana as medical treatment for outcomes in anorexia related to certain medical conditions, nausea and vomiting, and PTSD; however, FDA review of systematic reviews showed mixed results, mostly in support of synthetic forms or evidence only in observational studies with high risk of bias, which are not relevant to this discussion. In particular, FDA found that the potential for psychiatric adverse events associated with treating PTSD with marijuana may be more substantial than any limited benefit in observational studies. Although UF did not conclude that there was evidence in support of the efficacy/effectiveness of marijuana in IBD, both their review and other systematic reviews found some benefit with respect to subjective symptoms in this condition. With regard to epilepsy and anxiety, both UF's review and FDA's review of systematic reviews did not find support for the benefit of marijuana in the treatment of these conditions. Where positive, the effects of marijuana use and the quality of evidence were generally in the low to moderate range. UF did not find high quality evidence supporting worsening of outcomes in any indication.

None of the evidence from the systematic reviews included in our analysis demonstrated substantial safety concerns that would argue against the use of marijuana in any of the indications where there exists some support for its benefit. However, generally, data on safety from both clinical trials and observational studies were sparse. Literature shows marijuana has more adverse events when compared to a placebo or active control group, however, typically in the mild to moderate range. Severe adverse events were uncommon. Surveys of patients using marijuana in Maryland and Minnesota found most patients did not report any side effects and those that did report side effects mostly described them as mild. Neither of the state databases included patients who chose to stop using marijuana, which may result in an overestimation of positive experiences and an underestimation of adverse events. To date, observational data sources available to FDA, in general, lack the necessary elements to identify the exposure, to distinguish the reason for use (medical vs. recreational) and the condition that prompted its medical use, and/or to permit sound inferential analyses. Data from U.S. national surveys, although, overall, lacking sufficient details on patient's characteristics and factors that prompted the use of marijuana for medical purposes, and impacted by the COVID-19 pandemic, suggested that medical use of marijuana increases as age increases. Only data from one survey provided information on intended indication for use, suggesting that users often use marijuana to improve or manage conditions such as depression, anxiety, PTSD, pain, headaches or migraines, sleep disorders, nausea and vomiting, lack of appetite, and muscle spasms, but approximately only half of them reportedly had ever asked a healthcare professional for a recommendation to use medical marijuana.

Although the safety data obtained from use in a medical context are considered to be the most relevant for the CAMU Part 2 analysis, FDA evaluated the safety of marijuana in the nonmedical setting to inform the potential for more severe outcomes. Specifically, FDA evaluated safety outcomes related to the nonmedical use of, use of uncertain intent of, and unintentional exposure to marijuana through a variety of epidemiological data sources, including the National Poison Data System (NPDS), Drug-Involved Mortality (DIM), National Vital Statistics System-Mortality (NVSS-M), National Emergency Department Sample (NEDS), National Inpatient Sample (NIS), FDA's Sentinel, FDA Adverse Event Reporting System/Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (FAERS/CAERS), Medicare, ToxIC Core Registry, and Drug Abuse Warning Network (DAWN). Safety outcomes for marijuana were evaluated relative to several comparator substances controlled under the CSA, including drugs in Schedule I: heroin (an illicit opioid drug); Schedule II: hydrocodone and oxycodone (approved opioid prescription drugs), cocaine and fentanyl (largely illicitly produced drugs in the nonmedical use setting, although there are approved prescription drugs); Schedule III: ketamine (an approved prescription drug); and Schedule IV: zolpidem, benzodiazepines, and tramadol (approved prescription drugs). The comparative data demonstrate that, although marijuana is frequently used nonmedically, marijuana has a less concerning overall safety profile relative to the comparators for a number of important outcomes (e.g., single substance use overdose death, hospitalizations). However, in young children, population-adjusted rates of emergency department visits and hospitalizations involving marijuana poisoning were higher than heroin, cocaine, and benzodiazepines for the periods studied. Of note, some of the comparator substances are approved for use in conditions similar to the indications for which marijuana is being evaluated in this CAMU analysis (e.g., opioids for pain, benzodiazepines for anxiety related conditions) ([FDA Office of Surveillance and Epidemiology, 2023](#)).

We also considered position statements from professional organizations relevant to the indications discussed. The vast majority of professional organizations did not recommend the use of marijuana in their respective specialty; however, none specifically recommended against it, with the exception of the APA, who stated that marijuana is known to worsen certain psychiatric conditions.

On balance, the available data indicate that there is some credible scientific support to substantiate the use of marijuana in the treatment of: pain; anorexia related to certain medical conditions; and nausea and vomiting (e.g. chemotherapy-induced), with varying degrees of support and consistency of findings.

III. Appendices

1. International Cannabis Policy Study (ICPS)

Table 55. Marijuana Legalization by State, 2021

No Legal Marijuana	Legal Medical Marijuana Only	Legal Medical and ‘Recreational’ Marijuana
Alabama*	Arkansas	Alaska
Georgia	Delaware	Arizona
Idaho	Florida	California
Indiana	Hawaii	Colorado
Iowa	Louisiana	Connecticut
Kansas	Maryland	Illinois
Kentucky	Minnesota	Maine
Mississippi	Missouri	Massachusetts
Nebraska	New Hampshire	Michigan
North Carolina	North Dakota	Montana
South Carolina	Ohio	Nevada
Tennessee	Oklahoma	New Jersey
Texas	Pennsylvania	New Mexico
Wisconsin	Rhode Island	New York
Wyoming	South Dakota	Oregon
	Utah	Vermont
		Virginia
		Washington, DC
		Washington State

Source: ([Hammond et al. 2023](#)).

*Alabama legalized medical marijuana in 2021, however, no licenses had been issued at the time of the ICPS data collection

Table 56. Sample Characteristics, ICPS, 2018-2021

Characteristic	Wave 1 - 2018 (n=17,112)	Wave 2 - 2019 (n=30,479)	Wave 3 - 2020 (n=29,900)	Wave 4 - 2021 (n=30,081)
Sex				
Female	50.2% (8,586)	50.2% (15,290)	50.1% (14,995)	50.1% (15,080)
Male	49.8% (8,526)	49.8% (15,189)	49.9% (14,905)	49.9% (15,001)
Age (NSDUH)				
16-17	14.1% (2,358)	8.1% (2,432)	7.1% (2,062)	6.7% (1,954)
18-25	6.2% (1,042)	12.1% (3,619)	13.8% (4,027)	13.8% (4,056)
26-44	19.6% (3,270)	19.8% (5,924)	18.6% (5,437)	19.0% (5,576)
45-64	60.1% (10,054)	59.9% (17,914)	60.5% (17,645)	60.5% (17,757)
Race				
White	76.4% (13,068)	76.0% (23,158)	75.8% (22,655)	75.6% (22,730)
Black/African American	13.6% (2,335)	13.8% (4,201)	13.9% (4,148)	13.9% (4,183)
Asian	3.8% (648)	4.0% (1,207)	4.6% (1,368)	3.8% (1,132)
American Indian or Alaskan Native	0.8% (140)	1.3% (383)	1.0% (288)	1.1% (324)
Native Hawaiian or Pacific Islander	0.2% (34)	0.3% (105)	0.4% (110)	0.4% (129)
Other	5.2% (887)	4.7% (1,424)	4.5% (1,331)	5.3% (1,583)
Ethnicity				
Hispanic	8.8% (1,493)	12.6% (3,788)	11.5% (3,391)	13.7% (4,063)
Non-Hispanic	91.2% (15,507)	87.4% (26,355)	88.5% (26,086)	86.3% (25,616)
Education				
< High school	14.5% (2,470)	10.4% (3,146)	9.8% (2,900)	10.4% (3,106)
High school	18.7% (3,192)	22.0% (6,688)	23.2% (6,889)	22.7% (6,783)
Some college	39.2% (6,691)	37.8% (11,481)	36.9% (10,946)	36.6% (10,922)
Bachelor's degree	27.6% (4,702)	29.8% (9,039)	30.1% (8,916)	30.2% (9,012)
Income Adequacy				
Very difficult/Difficult	31.3% (5,268)	34.1% (10,213)	27.7% (8,090)	29.7% (8,677)
Neither easy nor difficult	32.2% (5,421)	33.6% (10,075)	35.7% (10,416)	33.6% (9,824)
Easy/Very easy	35.8% (6,029)	31.1% (9,335)	35.1% (10,226)	35.1% (10,266)
Not reported	0.8% (137)	1.2% (350)	1.5% (425)	1.6% (458)
Jurisdiction				
'Illegal' states	22.7% (3,890)	13.9% (4,230)	18.2% (5,437)	16.6% (4,980)
'Medical' states	34.0% (5,824)	19.8% (6,045)	23.6% (7,071)	17.2% (5,160)
'Recreational' states	43.2% (7,398)	66.3% (20,204)	58.2% (17,392)	66.3% (19,941)

Characteristic	Wave 1 - 2018 (n=17,112)	Wave 2 - 2019 (n=30,479)	Wave 3 - 2020 (n=29,900)	Wave 4 - 2021 (n=30,081)
Frequency of Use				
Ever consumer	53.6% (5,150)	49.0% (9,563)	50.1% (8,809)	46.7% (9,001)
Past 12-month consumer (<monthly)	13.3% (1,280)	13.5% (2,627)	12.0% (2,113)	12.7% (2,448)
Monthly consumer	9.9% (951)	9.6% (1,876)	9.5% (1,675)	10.3% (1,992)
Weekly consumer	8.4% (809)	8.0% (1,555)	8.3% (1,451)	8.9% (1,718)
Daily consumer ¹	14.7% (1,415)	20.0% (3,897)	20.1% (3,531)	21.4% (4,122)

Source: [Hammond et al. 2023](#), Table 1.

¹. Daily consumption = consumption ≥ 5 days per week.

Abbreviations: ICPS, International Cannabis Policy Study; NSDUH, National Survey on Drug Use and Health

Table 57. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Sex, ICPS, 2021

Time Since Last Use¹	Male (n=780)	Female (n=667)	Overall (n=1,447)
All States			
Past 12-months	36.2% (282) (30.4% - 42.0%)	29.0% (194) (24.7% - 33.4%)	32.9% (476) (29.2% - 36.6%)
Past month	63.8% (498) (58.0% - 69.6%)	71.0% (473) (66.6% - 75.3%)	67.1% (971) (63.4% - 70.8%)
'Illegal' States			
Past 12-months	44.0% (81) (30.1% - 57.9%)	37.7% (63) (28.7% - 46.7%)	41.0% (144) (32.5% - 49.5%)
Past month	56.0% (103) (42.1% - 69.9%)	62.3% (104) (53.3% - 71.3%)	59.0% (207) (50.5% - 67.5%)
'Medical' States			
Past 12-months	37.7% (93) (27.2% - 48.3%)	21.7% (44) (15.4% - 28.0%)	30.6% (138) (24.0% - 37.2%)
Past month	62.3% (155) (51.7% - 72.8%)	78.3% (157) (72.0% - 84.6%)	69.4% (312) (62.8% - 76.0%)
'Recreational' States			
Past 12-months	31.0% (108) (23.7% - 38.2%)	29.1% (87) (22.0% - 36.1%)	30.1% (194) (25.0% - 35.2%)
Past month	69.0% (240) (61.8% - 76.3%)	70.9% (212) (63.9% - 78.0%)	69.9% (452) (64.8% - 75.0%)

Source: [Hammond et al. 2023](#), Table 57.¹. The categories 'Past 12-months' and 'Past month' are mutually exclusive.**Table 58. Time Since Last Cannabis Use Among Exclusive Past Year Medical Cannabis Consumers, Recency of Use by Age (NSDUH Age Categories), ICPS, 2021**

Time Since Last Use^{1,2,3}	16-17 (n=37)	18-25 (n=180)	26-34 (n=327)	35-64 (n=891)	Overall (n=1,435)
All States					
Past 12-months	33.0% (12) (10.5% - 55.5%)	30.7% (55) (20.8% - 40.6%)	32.2% (105) (23.4% - 41.1%)	33.7% (300) (29.1% - 38.2%)	33.0% (473) (29.2% - 36.7%)
Past month	67.0% (25) (44.5% - 89.5%)	69.3% (125) (59.4% - 79.2%)	67.8% (222) (58.9% - 76.6%)	66.3% (591) (61.8% - 70.9%)	67.0% (962) (63.3% - 70.8%)

Time Since Last Use^{1,2,3}	16-17 (n=37)	18-25 (n=180)	26-34 (n=327)	35-64 (n=891)	Overall (n=1,435)
'Illegal' States					
Past 12-months	19.7% (3) (0.0% - 46.4%)	30.3% (17) (11.5% - 49.2%)	64.3% (44) (42.8% - 85.9%)	38.2% (80) (28.4% - 48.0%)	41.3% (144) (32.7% - 49.8%)
Past month	80.3% (12) (53.6% - 100.0%)	69.7% (39) (50.8% - 88.5%)	35.7% (24) (14.1% - 57.2%)	61.8% (130) (52.0% - 71.6%)	58.7% (205) (50.2% - 67.3%)
'Medical' States					
Past 12-months	58.4% (4) (9.2% - 100.0%)	38.8% (18) (15.9% - 61.7%)	26.1% (31) (12.3% - 39.9%)	30.1% (82) (22.1% - 38.0%)	30.4% (135) (23.8% - 37.1%)
Past month	41.6% (3) (0.0% - 90.8%)	61.2% (29) (38.3% - 84.1%)	73.9% (86) (60.1% - 87.7%)	69.9% (191) (62.0% - 77.9%)	69.6% (309) (62.9% - 76.2%)
'Recreational' States					
Past 12-months	32.8% (5) (0.0% - 68.2%)	26.0% (20) (14.3% - 37.7%)	21.8% (31) (13.3% - 30.4%)	33.8% (138) (27.0% - 40.5%)	30.2% (194) (25.1% - 35.3%)
Past month	67.2% (10) (31.8% - 100.0%)	74.0% (57) (62.3% - 85.7%)	78.2% (111) (69.6% - 86.7%)	66.2% (270) (59.5% - 73.0%)	69.8% (448) (64.7% - 74.9%)

Source: (Hammond et al. 2023), Table 51.

¹. The categories 'Past 12-months' and 'Past month' are mutually exclusive.

². 12 responses were excluded.

³. In some cases, the sum of the weighted frequencies for state categories does not equal the total frequency as a result of rounding.

Abbreviations: ICPS, International Cannabis Policy Study; NSDUH, National Survey on Drug Use and Health

Table 59. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Race, ICPS, 2021

Time Since Last Use^{1,2}	American Indian or Alaskan Native (n=25)	Asian (n=18)	Black or African American (n=227)	Native Hawaiian or Pacific Islander (n=8)	White (n=1,086)	Other (n=83)	Overall (n=1,447)
All States							
Past 12-months	18.6% (5) (3.0% - 34.2%)	45.6% (8) (8.9% - 82.3%)	41.2% (94) (29.8% - 52.7%)	56.0% (4) (0.2% - 100.0%)	32.1% (348) (28.0% - 36.2%)	20.0% (17) (8.6% - 31.4%)	32.9% (476) (29.2% - 36.6%)
Past month	81.4% (20) (65.8% - 97.0%)	54.4% (10) (17.7% - 91.1%)	58.8% (133) (47.3% - 70.2%)	44.0% (3) (0.0% - 99.8%)	67.9% (737) (63.8% - 72.0%)	80.0% (67) (68.6% - 91.4%)	67.1% (971) (63.4% - 70.8%)
'Illegal' States							
Past 12-months	0.0% (0) (0.0% - 0.0%)	76.4% (2) (25.9% - 100.0%)	52.2% (52) (33.0% - 71.4%)	0.0% (0) (0.0% - 0.0%)	36.4% (84) (27.2% - 45.6%)	41.4% (6) (7.2% - 75.6%)	41.0% (144) (32.5% - 49.5%)
Past month	100.0% (4) (100.0% - 100.0%)	23.6% (0)* (0.0% - 74.1%)	47.8% (48) (28.6% - 67.0%)	0.0% (0) (0.0% - 0.0%)	63.6% (146) (54.4% - 72.8%)	58.6% (9) (24.4% - 92.8%)	59.0% (207) (50.5% - 67.5%)

Time Since Last Use^{1,2}	American Indian or Alaskan Native (n=25)	Asian (n=18)	Black or African American (n=227)	Native Hawaiian or Pacific Islander (n=8)	White (n=1,086)	Other (n=83)	Overall (n=1,447)
‘Medical’ States							
Past 12-months	25.8% (1) (0.0% - 69.5%)	0.0% (0) (0.0% - 0.0%)	39.3% (21) (15.7% - 62.8%)	0.0% (0) (0.0% - 0.0%)	29.9% (109) (22.8% - 37.1%)	25.9% (6) (1.9% - 49.9%)	30.6% (138) (24.0% - 37.2%)
Past month	74.2% (4) (30.5% - 100.0%)	100.0% (3) (100.0% - 100.0%)	60.7% (33) (37.2% - 84.3%)	100.0% (1) (100.0% - 100.0%)	70.1% (255) (62.9% - 77.2%)	74.1% (17) (50.1% - 98.1%)	69.4% (312) (62.8% - 76.0%)
‘Recreational’ States							
Past 12-months	20.7% (3) (0.5% - 40.8%)	49.3% (7) (3.2% - 95.5%)	27.5% (20) (14.7% - 40.3%)	66.4% (4) (11.3% - 100.0%)	31.6% (156) (25.7% - 37.5%)	10.2% (5) (0.7% - 19.7%)	30.1% (194) (25.0% - 35.2%)
Past month	79.3% (12) (59.2% - 99.5%)	50.7% (7) (4.5% - 96.8%)	72.5% (52) (59.7% - 85.3%)	33.6% (2) (0.0% - 88.7%)	68.4% (336) (62.5% - 74.3%)	89.8% (41) (80.3% - 99.3%)	69.9% (452) (64.8% - 75.0%)

Source: (Hammond et al. 2023), Table 53.

* Weighted frequency rounded down to 0.

¹ The categories ‘Past 12-months’ and ‘Past month’ are mutually exclusive

² In some cases, the sum of the weighted frequencies for state categories does not equal the total frequency as a result of rounding.

Table 60. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Ethnicity, ICPS, 2021

Time Since Last Use^{1,2}	Hispanic (n=274)	Non-Hispanic (n=1,158)	Overall (n=1,432)
All States			
Past 12-months	31.7% (87) (23.0% - 40.4%)	32.9% (380) (28.7% - 37.0%)	32.6% (467) (28.9% - 36.4%)
Past month	68.3% (187) (59.6% - 77.0%)	67.1% (778) (63.0% - 71.3%)	67.4% (965) (63.6% - 71.1%)
‘Illegal’ States			
Past 12-months	29.6% (13) (10.1% - 49.2%)	42.3% (128) (33.0% - 51.6%)	40.7% (141) (32.1% - 49.2%)
Past month	70.4% (31) (50.8% - 89.9%)	57.7% (175) (48.4% - 67.0%)	59.3% (206) (50.8% - 67.9%)
‘Medical’ States			
Past 12-months	18.2% (12) (5.3% - 31.2%)	32.2% (122) (25.0% - 39.5%)	30.2% (134) (23.6% - 36.8%)
Past month	81.8% (52) (68.8% - 94.7%)	67.8% (257) (60.5% - 75.0%)	69.8% (309) (63.2% - 76.4%)

Time Since Last Use^{1,2}	Hispanic (n=274)	Non-Hispanic (n=1,158)	Overall (n=1,432)
‘Recreational’ States			
Past 12-months	37.4% (62) (25.1% - 49.8%)	27.4% (130) (22.0% - 32.7%)	30.0% (192) (24.9% - 35.1%)
Past month	62.6% (104) (50.2% - 74.9%)	72.6% (346) (67.3% - 78.0%)	70.0% (450) (64.9% - 75.1%)

Source: (Hammond et al. 2023), Table 55.

¹ The categories ‘Past 12-months’ and ‘Past month’ are mutually exclusive.

² 15 responses were excluded.

Table 61. Time Since Last Cannabis Use Among Exclusive Past-Year Medical Cannabis Consumers, Recency of Use by Cannabis Source, ICPS, 2021

Source^{1,2}	Made/ Grown by Self	Family/ Friend	Dealer	Internet/ Mail Order	Store/ Dispensary	Other	Unknown
All States							
Past 12-months (n=476)	19.9% (95) (14.3% - 25.6%)	48.4% (230) (41.5% - 55.4%)	34.7% (165) (27.8% - 41.6%)	20.8% (99) (14.6% - 26.9%)	34.8% (166) (28.3% - 41.4%)	0.1% (0*) (0.0% - 0.3%)	1.2% (6) (0.0% - 2.5%)
Past month (n=971)	17.9% (174) (13.9% - 21.8%)	42.8% (416) (38.2% - 47.5%)	30.1% (293) (25.8% - 34.4%)	16.8% (164) (12.6% - 21.1%)	57.0% (553) (52.2% - 61.7%)	0.6% (6) (0.0% - 1.3%)	1.1% (10) (0.3% - 1.8%)
Overall (n=1,447)	18.6% (268) (15.3% - 21.8%)	44.7% (646) (40.8% - 48.6%)	31.6% (458) (28.0% - 35.3%)	18.1% (262) (14.7% - 21.6%)	49.7% (719) (45.8% - 53.6%)	0.5% (7) (0.0% - 0.9%)	1.1% (16) (0.5% - 1.8%)
‘Illegal’ States							
Past 12-months	24.1% (35) (10.9% - 37.3%)	45.3% (65) (31.1% - 59.6%)	46.4% (67) (31.8% - 61.1%)	21.9% (32) (8.6% - 35.3%)	33.3% (48) (19.3% - 47.2%)	0.0% (0) (0.0% - 0.0%)	0.0% (0) (0.0% - 0.0%)
Past month	15.6% (32) (7.3% - 23.8%)	56.2% (116) (46.0% - 66.5%)	41.1% (85) (30.9% - 51.4%)	14.4% (30) (7.4% - 21.4%)	37.3% (77) (27.4% - 47.1%)	0.0% (0) (0.0% - 0.0%)	0.2% (0*) (0.0% - 0.7%)
Overall	19.1% (67) (11.8% - 26.4%)	51.8% (182) (43.3% - 60.2%)	43.3% (152) (34.8% - 51.8%)	17.5% (61) (10.6% - 24.4%)	35.6% (125) (27.6% - 43.7%)	0.0% (0) (0.0% - 0.0%)	0.1% (0*) (0.0% - 0.4%)
‘Medical’ States							
Past 12-months	20.9% (29) (9.4% - 32.5%)	51.6% (71) (38.1% - 65.2%)	29.4% (40) (16.8% - 42.0%)	19.6% (27) (8.3% - 30.9%)	24.0% (33) (13.2% - 34.8%)	0.0% (0) (0.0% - 0.0%)	2.9% (4) (0.0% - 7.1%)
Past month	19.2% (60) (12.2% - 26.3%)	38.7% (121) (31.0% - 46.4%)	29.7% (93) (22.5% - 36.8%)	7.1% (22) (3.4% - 10.8%)	58.0% (181) (50.0% - 66.1%)	0.4% (1) (0.0% - 1.3%)	1.9% (6) (0.0% - 3.8%)
Overall	19.7% (89) (13.8% - 25.7%)	42.6% (192) (35.9% - 49.4%)	29.6% (133) (23.3% - 35.8%)	10.9% (49) (6.5% - 15.3%)	47.6% (214) (40.7% - 54.5%)	0.3% (1) (0.0% - 0.9%)	2.2% (10) (0.4% - 4.0%)

Source ^{1,2}	Made/ Grown by Self	Family/ Friend	Dealer	Internet/ Mail Order	Store/ Dispensary	Other	Unknown
‘Recreational’ States							
Past 12- months	16.1% (31) (10.7% - 21.6%)	48.4% (94) (38.7% - 58.2%)	29.9% (58) (21.3% - 38.5%)	20.7% (40) (12.5% - 29.0%)	43.7% (85) (34.0% - 53.3%)	0.2% (0*) (0.0% - 0.7%)	0.9% (2) (0.0% - 2.0%)
Past month	18.0% (81) (12.0% - 23.9%)	39.6% (179) (32.7% - 46.5%)	25.4% (115) (19.3% - 31.5%)	24.7% (112) (17.2% - 32.3%)	65.3% (295) (58.4% - 72.1%)	1.1% (5) (0.0% - 2.3%)	0.9% (4) (0.0% - 1.8%)
Overall	17.4% (113) (13.0% - 21.9%)	42.2% (273) (36.6% - 47.9%)	26.8% (173) (21.8% - 31.8%)	23.5% (152) (17.6% - 29.4%)	58.8% (380) (53.1% - 64.5%)	0.8% (5) (0.0% - 1.7%)	0.9% (6) (0.2% - 1.6%)

Source: (Hammond et al. 2023), Table 59.

* Weighted frequency rounded down to 0.

¹. Response options are not mutually exclusive, row totals may sum to greater than 100%.

². The categories ‘Past 12-months’ and ‘Past month’ are mutually exclusive.

Table 62. Cannabis Purchasing by Type of Store Among Exclusive Past-Year Medical Cannabis Consumers Who Bought Cannabis From a Store, 2021

Store ^{1,2,3,4}	Legal Medical Dispensary	Legal Recreational Store	An Illegal/ Unauthorized Store	Other Type of Store/ Dispensary
All States				
Past 12-months (n=164)	69.9% (115) (59.8% - 80.1%)	41.2% (67) (29.7% - 52.6%)	10.1% (16) (3.6% - 16.6%)	1.3% (2) (0.0% - 2.8%)
Past month (n=553)	80.6% (446) (75.9% - 85.3%)	44.5% (246) (38.2% - 50.7%)	5.2% (29) (2.5% - 7.9%)	1.4% (8) (0.0% - 3.0%)
Overall (n=717)	78.2% (561) (73.9% - 82.5%)	43.7% (313) (38.2% - 49.2%)	6.3% (45) (3.7% - 8.8%)	1.4% (10) (0.1% - 2.6%)
‘Illegal’ States				
Past 12-months	60.6% (29) (34.1% - 87.1%)	46.1% (22) (17.6% - 74.6%)	9.1% (4) (0.0% - 22.9%)	1.8% (1) (0.0% - 5.6%)
Past month	67.2% (52) (51.4% - 82.9%)	74.0% (57) (60.2% - 87.9%)	7.6% (6) (0.0% - 16.7%)	1.2% (1) (0.0% - 3.6%)
Overall	64.7% (81) (51.2% - 78.2%)	63.3% (79) (50.0% - 76.6%)	8.2% (10) (0.8% - 15.6%)	1.4% (2) (0.0% - 3.4%)
‘Medical’ States				
Past 12-months	79.7% (25) (60.8% - 98.6%)	19.2% (6) (0.0% - 38.9%)	13.2% (4) (0.0% - 30.1%)	3.0% (1) (0.0% - 9.3%)
Past month	91.6% (166) (86.9% - 96.4%)	21.3% (39) (13.5% - 29.2%)	2.6% (5) (0.0% - 6.4%)	0.0% (0) (0.0% - 0.0%)
Overall	89.9% (191) (85.0% - 94.7%)	21.0% (45) (13.8% - 28.3%)	4.2% (9) (0.2% - 8.2%)	0.4% (1) (0.0% - 1.3%)

Store^{1,2,3,4}	Legal Medical Dispensary	Legal Recreational Store	An Illegal/ Unauthorized Store	Other Type of Store/ Dispensary
'Recreational' States				
Past 12-months	71.6% (60) (59.5% - 83.6%)	46.7% (39) (32.3% - 61.1%)	9.5% (8) (1.0% - 18.0%)	0.3% (0*) (0.0% - 0.9%)
Past month	77.3% (228) (70.3% - 84.3%)	51.0% (150) (42.0% - 59.9%)	6.1% (18) (2.2% - 9.9%)	2.3% (7) (0.0% - 5.2%)
Overall	76.0% (288) (70.0% - 82.1%)	50.0% (189) (42.3% - 57.7%)	6.8% (26) (3.3% - 10.4%)	1.9% (7) (0.0% - 4.1%)

Source: ([Hammond et al. 2023](#)), Table 61.

* Weighted frequency rounded down to 0.

^{1.} The denominator is medical only users who have bought cannabis from a store in the past 12 months.

^{2.} The categories 'Past 12-months' and 'Past month' are mutually exclusive.

^{3.} 2 responses were excluded.

^{4.} Response options are not mutually exclusive, row totals may sum to greater than 100%.

2. Behavioral Risk Factor Surveillance System (BRFSS)

Table 63. Marijuana Use for Any Reason, Medical Reason, and Both Medical and Nonmedical Reason in the Past 30 Days in the Participating States/Territories, BRFSS, Marijuana Module, 2021

State/Territory*	Any Reason		Nonmedical Reason			Medical Reason			Both Medical and Nonmedical Reason		
	Frequency	Weighted Frequency (%)	Frequency	Weighted Frequency	Weighted % (95% CI)	Frequency	Weighted Frequency	Weighted % (95% CI)	Frequency	Weighted Frequency	Weighted % (95% CI)
Overall	17,666	8,017,412 (100)	5,700	2,905,432	36.2 (23.6, 26.2)	5,357	1,997,581	24.9 (23.6, 26.2)	6,609	3,114,399	38.8 (37.2, 40.5)
Alaska	863	93,885 (100)	368	44,102	47.0 (42.2, 51.7)	176	16,022	17.1 (14.0, 20.1)	319	33,761	36.0 (31.5, 40.4)
Connecticut	788	282,425 (100)	310	106,466	37.7 (33.1, 42.3)	175	57,045	20.2 (16.6, 23.8)	303	118,913	42.1 (37.1, 47.1)
Delaware	257	68,544 (100)	91	27,793	40.5 (32.6, 48.5)	88	21,125	30.8 (23.6, 38.0)	78	19,627	28.6 (21.7, 35.6)
Hawaii	748	106,338 (100)	215	32,495	30.6 (25.6, 35.5)	275	35,019	32.9 (28.1, 37.7)	258	38,824	36.5 (31.4, 41.6)
Idaho	401	106,816 (100)	128	36,134	33.8 (27.9, 39.8)	106	25,467	23.8 (18.7, 29.0)	167	45,215	42.3 (36.3, 48.4)
Illinois	290	1,026,164 (100)	126	425,699	41.5 (34.6, 48.3)	66	198,027	19.3 (14.1, 24.5)	98	402,438	39.2 (32.1, 46.4)
Indiana	566	369,827 (100)	187	128,361	34.7 (30.0, 39.4)	131	74,793	20.2 (16.5, 24.0)	248	166,674	45.1 (40.2, 50.0)
Kentucky	331	277,702 (100)	104	93,783	33.8 (27.8, 39.8)	90	64,935	23.4 (18.0, 28.8)	137	118,983	42.8 (36.2, 49.5)
Maine	2,577	413,256 (100)	669	110,925	26.8 (23.6, 30.1)	1,005	148,545	35.9 (32.5, 39.4)	903	153,786	37.2 (33.5, 40.9)
Maryland	2,034	883,969 (100)	510	240,704	27.2 (22.9, 31.5)	758	287,527	32.5 (28.0, 37.0)	766	355,739	40.2 (35.5, 45.0)
Minnesota	1,120	345,770 (100)	458	144,091	41.7 (38.2, 45.2)	272	80,123	23.2 (20.2, 26.2)	390	121,555	35.2 (31.8, 38.5)
Montana	645	112,874 (100)	179	31,185	27.6 (23.5, 31.7)	232	34,082	30.2 (25.9, 34.5)	234	47,607	42.2 (37.3, 47.0)
Nebraska	286	94,743 (100)	114	40,236	42.5 (35.0, 50.0)	61	17,716	18.7 (13.6, 23.8)	111	36,791	38.8 (31.5, 46.2)

State/Territory*	Any Reason		Nonmedical Reason			Medical Reason			Both Medical and Nonmedical Reason		
	Frequency	Weighted Frequency (%)	Frequency	Weighted Frequency	Weighted % (95% CI)	Frequency	Weighted Frequency	Weighted % (95% CI)	Frequency	Weighted Frequency	Weighted % (95% CI)
Nevada	358	359,031 (100)	138	144,810	40.3 (33.3, 47.4)	87	87,766	24.4 (17.7, 31.2)	133	126,455	35.2 (28.4, 42.0)
New Hampshire	486	120,462 (100)	183	47,227	39.2 (33.5, 44.9)	126	23,774	19.7 (15.6, 23.9)	177	49,460	41.1 (35.3, 46.8)
New York	1,208	1,611,364 (100)	477	788,848	49.0 (44.3, 53.6)	255	210,651	13.1 (10.5, 15.7)	476	611,864	38.0 (33.4, 42.6)
North Dakota	303	44,161 (100)	105	16,206	36.7 (29.9, 43.5)	97	12,870	29.1 (22.9, 35.4)	101	15,085	34.2 (27.4, 40.9)
Ohio	1,592	866,871 (100)	431	251,600	29.0 (24.9, 33.2)	512	243,665	28.1 (24.0, 32.2)	649	371,606	42.9 (38.3, 47.4)
Oklahoma	273	401,216 (100)	26	50,448	12.6 (6.9, 18.2)	175	244,845	61.0 (53.6, 68.4)	72	105,924	26.4 (19.9, 32.9)
Rhode Island	620	118,445 (100)	194	36,350	30.7 (25.7, 35.7)	159	26,989	22.8 (18.3, 27.3)	267	55,106	46.5 (41.1, 51.9)
Utah	659	184,017 (100)	168	51,998	28.7 (24.2, 33.1)	244	61,415	33.8 (29.4, 38.3)	241	68,068	37.5 (32.9, 42.1)
Vermont	1,006	97,963 (100)	422	43,946	44.9 (40.3, 49.4)	197	15,572	15.9 (12.9, 18.9)	387	38,445	39.2 (34.8, 43.7)
Wyoming	146	22,624 (100)	49	8,427	37.2 (26.4, 48.1)	41	5,192	23.0 (14.1, 31.8)	53	9,005	39.8 (29.1, 50.6)
Guam	118	11,481 (100)	48	3,597	31.3 (18.3, 44.4)	29	4,416	38.5 (22.1, 54.8)	41	3,467	30.2 (17.9, 42.5)

* Excludes individuals who responded, "Don't know/not sure" and those who refused to answer.

Table 64. Past 30-Day Marijuana Use by Method of Use and Stratified by Reason of Use, BRFSS, Marijuana Module, 2021

Method of Use*	Any Reason		Recreational Reason			Medical Reason			Both Medical and Nonmedical		
	Frequency	Weighted Frequency (%)	Frequency	Weighted Frequency	Weighted % (95% CI)	Frequency	Weighted Frequency	Weighted % (95% CI)	Frequency	Weighted Frequency	Weighted % (95% CI)
Any	17,605	7,971,458	5,679	2,884,067	100	5,334	1,989,539	100	6,592	3,097,852	100
Smoke	11,684	5,453,712	3,881	1,963,413	68.1 (65.4, 70.8)	2,961	1,200,016	60.3 (57.5, 63.1)	4,842	2,290,283	73.9 (71.6, 76.3)
Eat	3,408	1,370,291	1,171	555,280	19.3 (16.9, 21.6)	1,354	424,142	21.3 (19.1, 23.5)	883	390,868	12.6 (10.7, 14.5)
Drink	170	58,107	39	13,981	0.5 (0.2, 0.8)	84	30,421	1.5 (0.8, 2.3)	47	13,705	0.4 (0.2, 0.7)
Vaporize	1,561	760,394	469	287,442	10.0 (8.3, 11.7)	542	202,612	10.2 (8.5, 11.8)	550	270,340	8.7 (7.2, 10.2)
Dab	404	183,290	74	34,688	1.2 (0.8, 1.6)	113	44,979	2.3 (1.5, 3.1)	217	103,623	3.3 (2.5, 4.2)
Other	378	145,664	45	29,263	1.0 (0.3, 1.7)	280	87,368	4.4 (3.2, 5.6)	53	29,033	0.9 (0.5, 1.4)

* Excludes individuals who responded, "Don't know/not sure" and those who refused to answer.

3. Monitoring the Future (MTF)

Table 65. Sample Size and Response Rate, MTF, 2017–2022

Year	Number of Students				Response Rate (%)		
	8th Grade	10th Grade	12th Grade	Total	8th Grade	10th Grade	12th Grade
2017	16,010	14,171	13,522	43,703	87	85	79
2018	14,836	15,144	14,502	44,482	89	86	81
2019	14,223	14,595	13,713	42,531	89	86	80
2020	3,161	4,890	3,770	11,821	88	89	79
2021	11,446	11,792	9,022	32,260	82	78	69
2022	9,889	11,950	9,599	31,438	86	84	75

4. State Data From State Medical Marijuana Programs

4.1. Maryland Medical Cannabis Patient Survey 2022 (MMCPS-22)

Cannabis Public Policy Consulting, Quality Control Processes (Excerpt From the CPPC Project Proposal)

Quality control is built into our projects in a variety of ways, beginning with the assignment of record keeping to one researcher (“record keeper”), who is the single owner of documentation for the project. Key personnel on the project will [be] able to access files necessary to complete work through permission settings, but all changes to files and documents must be approved [by] the record keeper to ensure quality control. This prohibits the duplication of files, the corruption of files, or compromising of critical data when multiple personnel are working in one document from separate computers. The record keeper follows Cannabis Public Policy Consulting (CPPC)’s standard operating procedures for documentation, such as keeping consistent naming conventions for files and encrypting documentation with passwords when necessary.

Additionally, the record keeper is responsible for routine quality control checks throughout the survey administration period. These checks will ensure representativeness of the sample, identify system errors or failures, confirm patient privacy, and protect data integrity.

These checks will include, but not be limited to, the following actions:

- (1) Review geographic and demographic participation data during the survey collection period to ensure sampling is representative in an ongoing fashion (i.e., ensure there are no hotspots that compromise representation early on).
- (2) Ensure that the questionnaire is at a reading level approved by the client and 508 compliant if deemed necessary.
- (3) Perform multiple quality assurance checks on data analysis and all data cleaning performed and verified by key personnel individually.
- (4) Guarantee that the questionnaire language is equitable when capturing demographic data (i.e., providing adequate options for pronouns, gender identities, and race/ethnicity).

- (5) Perform test runs on survey links, databases, and other systems used for data collection, storage, and analysis.
- (6) For all analysis, run statistical methods three individual times to make sure outcome and finding is consistent prior to final documentation.
- (7) Back up all files and data documentation every 24 hours.
- (8) Perform other checks requested in collaboration by the State of Maryland and CPPC.

Should an error be discovered through any of the quality control checks or quality control procedures built into the project, the record keeper will document the error and provide this notification in writing to the Contract Monitor. CPPC commits itself to remedying all issues within 5 days of notification at no cost to the Commission. All correction actions will be thoroughly documented and provided to the Commission upon remediation. Further, CPPC commits itself to seeking the appropriate approval process prior to taking corrective actions as to ensure the Commission has agreed to and approved the next steps and remediation procedures as outlined in the Problem Escalation Procedure in Section 3.8 [of the CPPC project proposal].

4.2. Maryland Medical Cannabis Commission (MMCC) Tables

Table 66. Descriptive Characteristics of Maryland Medical Cannabis Commission (MMCC) Survey Participants

Characteristic	N	%
Age in Years		
18-20	206	1.6
21-25	676	5.2
26-35	2674	20.6
36-45	3140	24.1
46-55	2245	17.3
56-65	2207	17
66-75	1665	12.8
76-85	181	1.4
86+	16	0.1
Gender Identity		
Male	5684	43.7
Female	6994	53.8
Transgender female	25	0.2
Transgender male	35	0.3
Non-binary	161	1.2
Not included in above	12	0.1
Prefer not to answer	100	0.8
Race		
White or Caucasian	10181	78.2
Black or African American	1778	13.7
Asian	153	1.2
Native Hawaiian or Other Pacific Islander	19	0.1
American Indian or Alaskan Native	69	0.5
Not included above	376	2.9
More than one race	330	2.5

Characteristic	N	%
Ethnicity		
Hispanic or Latino	813	6.2
Not Hispanic or Latino	12185	93.7
Missing	13	
Highest Level of Education		
Less than high school	165	1.3
High school or equivalent	2159	16.6
Trade school certificate/diploma	743	5.7
Some college, or associates degree	4177	32.1
Bachelor's degree	3241	24.9
Master's degree, doctoral degree (e.g, PhD, MD, etc.)	2524	19.4
Missing	2	
Medicaid Enrollment Status		
Not currently enrolled	10311	79.2
Currently enrolled	2187	16.8
Employment Status		
Working full-time	7285	56
Working part-time	1078	8.3
Student	234	1.8
Stay-at-home parent or homemaker	594	4.6
Not working	689	5.3
Not working, seeking employment	370	2.8
Retired	2350	18.1
Missing	411	
Annual Household Income		
No income	222	1.7
Less than \$14,000	567	4.4
\$14,000 to \$29,999	1086	8.3
\$30,000 - \$49,999	1786	13.7
\$50,000 - \$74,999	2000	15.4
\$75,000 - \$99,000	1612	12.4
\$100,000 to \$150,000	2176	16.7
\$150,000 - \$200,000	1099	8.4
More than \$200,000	987	7.6
Prefer not to answer	1227	9.4
Sensory or Physical Disability		
Serious difficulty hearing	761	5.8
Serious difficulty seeing, even when wearing glasses	645	5
Serious difficulty concentrating or making decisions due to a physical, mental, or emotional condition	2312	17.8
Serious difficulty walking or climbing stairs	1730	13.3
Serious difficulty bathing or dressing	384	3
Serious difficulty doing errands alone	1257	9.7
Years of Certification in the Maryland Medical Cannabis Program		
1	3721	28.6
2	3397	26.1
3	3233	24.8
4	1630	12.5
5	893	6.9

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 67. Frequencies of Substance Use in the Past Month Maryland Medical Cannabis Commission (MMCC) Survey Participants

Frequency of Substance Use	N	%
Cannabis		
0 days	521	4
1-4 days	1134	8.7
5-10 days	1216	9.3
11-19 days	1652	12.7
20-29 days	2602	20
All 30 days	5868	45.1
Tobacco		
0 days	10095	77.6
1-4 days	430	3.3
5-10 days	231	1.8
11-19 days	233	1.8
20-29 days	252	1.9
All 30 days	1693	13
Alcohol		
0 days	5207	40
1-4 days	3784	29.1
5-10 days	1975	15.2
11-19 days	1168	9
20-29 days	569	4.4
All 30 days	259	2
Psychedelics		
0 days	12453	95.7
1-4 days	409	3.1
5-10 days	30	0.2
11-19 days	10	0.1
20-29 days	3	0
All 30 days	27	0.2
Benzodiazepines		
0 days	11774	90.5
1-4 days	526	4
5-10 days	176	1.4
11-19 days	77	0.6
20-29 days	66	0.5
All 30 days	313	2.4
Stimulants		
0 days	12178	93.6
1-4 days	168	1.3
5-10 days	85	0.7
11-19 days	74	0.6
20-29 days	130	1
All 30 days	295	2.3
Opioids		
0 days	12306	94.6
1-4 days	175	1.3
5-10 days	67	0.5
11-19 days	48	0.4
20-29 days	42	0.3
All 30 days	284	2.2

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 68. Methods of Cannabis Administration (One Time or More) in the Past Month Maryland Medical Cannabis Commission (MMCC) Survey Participants

Method of Cannabis Administration	n	%
Flower or smoked dried herb	9375	72.1
Cartridge/Vaporizer	7978	61.3
Concentrate	2294	17.6
Edibles	8630	66.3
Capsules or tablets	1575	12.1
Tinctures or oral sprays	1597	12.3
Topicals	2879	22.1
Transdermal patch	177	1.4
Rectal/Vaginal suppositories	64	0.5

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 69. Perceived Effectiveness of Cannabis Treatment, Maryland Medical Cannabis Commission (MMCC) Survey Participants

Perceived Effectiveness	n	%
Not effective at all	70	0.5
Slightly effective	447	3.4
Moderately effective	2782	21.4
Very effective	5981	46
Extremely effective	3648	28.2

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 70. Perceived Health and Social Effects of Cannabis Among Maryland Medical Cannabis Commission (MMCC) Survey Participants

Perceived Effect	Worsened		Improved		Neither	
	n	%	n	%	n	%
Physical health	127	1	9359	71.9	3444	26.5
Mood or mental health	64	0.5	11527	88.6	1338	10.3
Memory or concentration	998	7.7	4817	37	7109	54.6
Social relationships	107	0.8	7064	54.3	5758	44.3

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 71. Frequency of Conditions While Consuming Cannabis Among Maryland Medical Cannabis Users

Condition	Never		Once		About Monthly		About Weekly		About Daily	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Anxiety	8965	68.9	1995	15.3	1122	8.6	473	3.6	352	2.7
Panic	10784	82.9	1270	9.8	527	4.1	184	1.4	143	1.1
Psychotic or paranoid feelings	11238	86.4	1044	8	433	3.3	119	0.9	74	0.6
Suicidal thoughts or ideation	12538	96.4	168	1.3	116	0.9	45	0.3	40	0.3
Breathing problems	11593	89.1	691	397	397	3.1	146	1.1	73	0.6
Nausea/vomiting	11726	90.1	740	5.7	255	2	102	0.8	71	0.5

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 72. Symptoms Experienced by Maryland Medical Cannabis Users in the Past Six Months, Maryland Medical Cannabis Commission (MMCC) Survey Participants

Survey Question on Symptoms	Never		Sometimes		About Half the Time		Most of the Time		Always	
	n	%	n	%	n	%	n	%	n	%
Had a problem with memory or concentration after using cannabis?	8473	65.1	3818	29.3	348	2.7	205	1.6	65	0.5
Devoted a great deal of time to getting, using, or recovering from cannabis?	11362	87.3	1241	9.5	172	1.3	86	0.7	39	0.3
Felt like you are not in control of your cannabis consumption or could not reduce your consumption even when you wanted to?	11880	91.3	712	5.5	110	0.8	85	0.7	91	0.7

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 73. Frequency of Treatment in an Emergency Room or Urgent Care Facility for Any Reason Related to Cannabis Consumption Among Maryland Medical Cannabis Users

Frequency	n	%
Never	12784	98.3
Once	96	0.7
Twice	27	0.2
Three times	10	0.1
More than three times	9	0.1
Total	12926	

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

Table 74. Frequency of Driving Within Three Hours of Consuming Cannabis and/or Under the Influence of Cannabis in the Past Month Among Maryland Medical Cannabis Patients

Frequency	n	%
0 times	10382	79.8
1 time	482	3.7
2-3 times	835	6.4
4-5 times	226	1.7
6 or more times	831	6.4
Total	12756	

Source: Maryland Medical Cannabis Commission in a report dated March 7, 2023.

4.3. Minnesota Tables

Table 75. Qualifying Medical Conditions for Medical Cannabis Use in Minnesota

Condition
Alzheimer's disease
Amyotrophic lateral sclerosis (ALS)
Autism spectrum disorder (must meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5])
Cancer (If illness or its treatment produces one or more of the following: severe or chronic pain; nausea or severe vomiting; or cachexia or severe wasting.)
Chronic motor or vocal tic disorder
Chronic pain
Glaucoma
HIV/AIDS
Inflammatory bowel disease, including Crohn's disease
Intractable pain
Irritable bowel syndrome (effective Aug. 1, 2023)
Obsessive-compulsive disorder (effective Aug. 1, 2023)
Obstructive sleep apnea
Post-traumatic stress disorder (PTSD)
Seizures, including those characteristic of epilepsy
Severe and persistent muscle spasms, including those characteristic of multiple sclerosis (MS)
Sickle cell disease
Terminal illness, with a probable life expectancy of less than one year (If illness or its treatment produces one or more of the following: severe or chronic pain; nausea or severe vomiting; or cachexia or severe wasting.)
Tourette syndrome

Source: Estimates generated by FDA using data provided by Minnesota Department of Health April 3, 2023 and April 12, 2023.

Table 76. Minnesota Survey Responses and Most Common Adverse Events (AEs) for 2015-2017

Year	Response Rate	# Patients	# Experiencing AEs	Degree of AEs	Most Common AES
2015-2016	91%	1,502	272 (18%)	The majority (91%) of side effect responses were reported to be mild or moderate in severity	Dry mouth (3.9%), drowsiness/somnolence/sedation (3.9%), and fatigue (3.5%).
2016-2017	96%	5,412	759 (14%)	90% (N = 1,421) of the 1,584 side effect responses were mild (n = 758; 48%) or moderate (n = 663; 42%) in severity	Dry mouth (4.1%), fatigue (3%), drowsiness/somnolence/sedation (3%), and mental clouding/"foggy brain" (3%)

Source: Estimates generated by FDA using data provided by Minnesota Department of Health April 3, 2023 and April 12, 2023.

Table 77. Frequencies of Side Effects Reported Among Minnesota Medical Cannabis Patients by Year and Severity, 2017-2022

Year	Number of Patient Completed Surveys	Number Reporting Any Side Effect (% of Patient Surveys)	Number Reporting Severe Side Effect (% of Patient Surveys)	Number Reporting Moderate Side Effect (% of Patient Surveys)	Number Reporting Mild Side Effect (% of Patient Surveys)
2017	34140	2805 (8.22)	252 (0.74)	988 (2.89)	1565 (4.58)
2018	86196	6627 (7.69)	681 (0.79)	2305 (2.67)	3641 (4.22)
2019	125995	9001 (7.14)	808 (0.64)	2967 (2.35)	5226 (4.15)
2020	152861	7654 (5.01)	575 (0.38)	2231 (1.46)	4848 (3.17)
2021	192719	10681 (5.54)	595 (0.31)	3204 (1.66)	6882 (3.57)
2022	357078	15656 (4.38)	793 (0.22)	4254 (1.19)	10609 (2.97)

Source: Estimates generated by FDA using data provided by Minnesota Department of Health April 3, 2023 and April 12, 2023.

Table 78. Top Ten Side Effects Reported on the MN Patient Self-Evaluation by Year (2017-2022)

Side Effect	Number of Patient Reports	% of Patient Reports
2017		
Dry mouth	636	1.86
Mental clouding/"foggy brain"	287	0.84
Other	273	0.80
Drowsiness/somnolence/sedation	218	0.64
Fatigue	218	0.64
Increased appetite	206	0.60
Euphoria (intense feeling of well-being or pleasure)	85	0.25
Dizziness	82	0.24
Nausea	75	0.22
Difficulty concentrating	71	0.21
2018		
Dry mouth	1421	1.65
Mental clouding/"foggy brain"	600	0.7
Drowsiness/somnolence/sedation	570	0.66
Other	548	0.64
Fatigue	526	0.61
Increased appetite	467	0.54
Dizziness	312	0.36
Headache	252	0.29
Lightheadedness	212	0.25
Anxiety	175	0.2

Side Effect	Number of Patient Reports	% of Patient Reports
2019		
Dry mouth	2151	1.71
Mental clouding/"foggy brain"	898	0.71
Drowsiness/somnolence/sedation	777	0.62
Other	727	0.58
Fatigue	698	0.55
Increased appetite	669	0.53
Dizziness	384	0.3
Lightheadedness	314	0.25
Headache	272	0.22
Anxiety	225	0.18
2020		
Dry mouth	2134	1.4
Increased appetite	687	0.45
Mental clouding/"foggy brain"	687	0.45
Fatigue	640	0.42
Drowsiness/somnolence/sedation	616	0.4
Other	551	0.36
Dizziness	302	0.2
Lightheadedness	196	0.13
Headache	188	0.12
Euphoria (intense feeling of well-being or pleasure)	176	0.12
2021		
Dry mouth	3213	1.67
Increased appetite	999	0.52
Mental clouding/"foggy brain"	911	0.47
Drowsiness/somnolence/sedation	863	0.45
Other	827	0.43
Fatigue	746	0.39
Dizziness	448	0.23
Headache	303	0.16
Euphoria (intense feeling of well-being or pleasure)	279	0.14
Lightheadedness	250	0.13
2022		
Dry mouth	5823	1.63
Other	1347	0.38
Increased appetite	1295	0.36
Mental clouding/"foggy brain"	1234	0.35
Drowsiness/somnolence/sedation	969	0.27
Fatigue	943	0.26
Dizziness	488	0.14
Headache	429	0.12
Anxiety	376	0.11
Lightheadedness	315	0.09

Source: Estimates generated by FDA using data provided by Minnesota Department of Health April 3, 2023 and April 12, 2023.

Table 79. Patient Numbers by State: 2016-2020 (Only States With Available Data)

State	2016	2017	2018	2019	2020
Alaska	1084	1053	621	404	NR
Arizona	114439	152979	186002	219817	295295
Arkansas	NR	NR	5459	15351	66638
Colorado	94577	93372	86641	81610	85814
Connecticut	15136	22573	26641	36700	49562
Delaware	1414	3274	6060	11213	15495
Florida	NR	42724	167211	299914	456594
Hawaii	15334	19858	23746	27152	30868
Illinois	7707	21800	39808	76939	121775
Louisiana	NR	NR	NR	4350	NR
Maryland	NR	11489	51589	90120	121994
Massachusetts	33543	45319	58920	60110	92240
Michigan	218556	269553	297515	268566	243372
Minnesota	2806	8075	14481	18249	28522
Missouri	NR	NR	NR	22706	69397
Montana	7785	22849	31186	36422	41638
Nevada	25358	23489	17211	15839	13303
New Hampshire	2089	3493	6480	8302	10688
New Jersey	12154	16937	44000	63062	81111
New Mexico	29046	46645	67574	80257	104655
New York	4998	57960	98101	111358	133362
North Dakota	NR	NR	0	707	3233
Ohio	NR	NR	3575	78376	176387
Oklahoma	NR	NR	30786	238869	367053
Oregon	68032	50400	31251	24801	22603
Pennsylvania	NR	10532	100027	243433	297317
Rhode Island	16418	18533	16963	16218	19803
Utah	NR	NR	NR	NR	16096
Vermont	3332	5313	NR	NR	NR
Washington DC	4600	5386	5836	6160	9618
Total	661990	953606	1417684	2157005	2974433

Source: University of Michigan tabulation of state annual reports, provided to the FDA on February 28, 2023.

Abbreviations: NR, not reported

5. Tables and Figures Excerpted from University of Florida’s Systematic Review of the Medical Literature on Cannabis Use

5.1. Anorexia

Table 80. Summary of Included Studies for Anorexia

Study Type	Count of Included Studies	Notes
Randomized controlled trials (RCTs)	1	2 RCTs were excluded during abstraction due to reporting of non-clinically relevant outcomes
Observational studies	3	---
Systematic reviews (SRs)	11	1 SR was added during quality control resulting from hand searches
Eligible RCTs identified from SRs	2	Duplicate included studies not reported
Eligible observational studies identified from SRs	0	Duplicate included studies not reported
Total non-eligible studies identified from SRs	62	Unique component studies
Total studies included in risk of bias assessments	6	SRs not included in quantitative synthesis

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 81. References (Studies Included in Risk of Bias Assessments, Anorexia)

Randomized Clinical Trials	
1	(Haney et al. 2005)
2	(Strasser et al. 2006)
3	(Haney et al. 2007)
Observational Studies	
1	(Zhang et al. 2018)
2	(Worrest et al. 2022)
3	(Huang et al. 2023)

Figure 14. Risk of Bias Assessment, Randomized Clinical Trials, Anorexia

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Strasser 2006						
	Haney 2005						
	Haney 2007						

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Figure 15. Risk of Bias Assessment, Observational Studies, Anorexia

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Worrest 2022								
	Zhang 2018								
	Huang 2022								

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
 Critical
 Moderate
 Low
 No information

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

5.2. Anxiety

Table 82. Summary of Included Studies for Anxiety

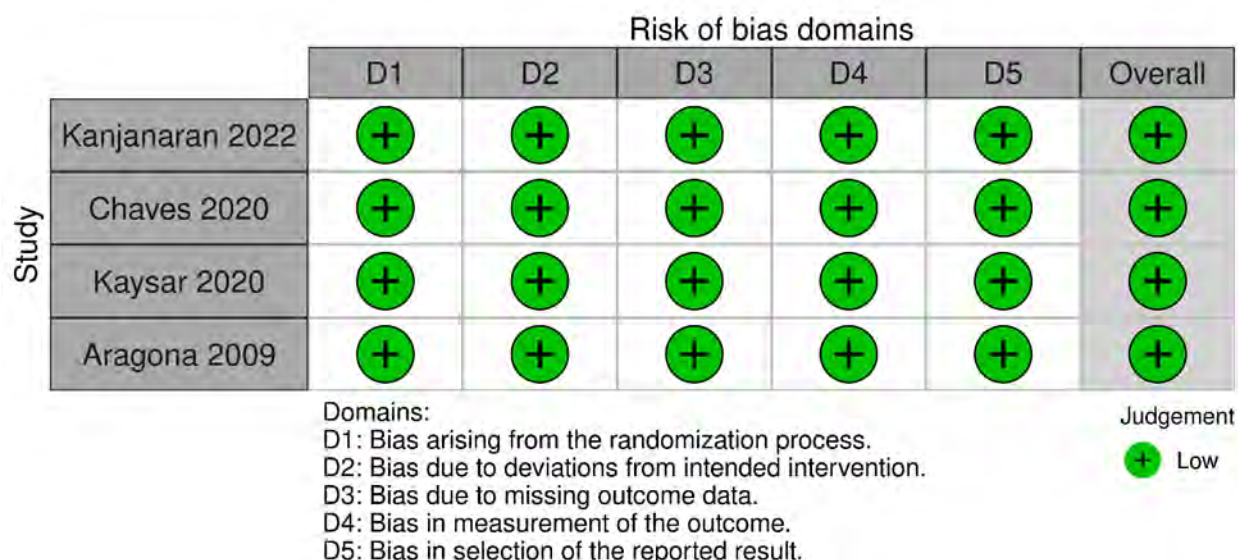
Study Type	Count of Included Studies	Notes
Randomized controlled trials (RCTs)	3	---
Observational studies	0	---
Systematic reviews (SRs)	25	---
Eligible RCTs identified from SRs	1	Duplicate included studies not reported
Eligible observational studies identified from SRs	1	Duplicate included studies not reported
Total non-eligible studies identified from SRs	299	Unique component studies
Total studies included in risk of bias assessments	5	SRs not included in quantitative synthesis

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 83. References (Studies Included in Risk of Bias Assessments, Anxiety)

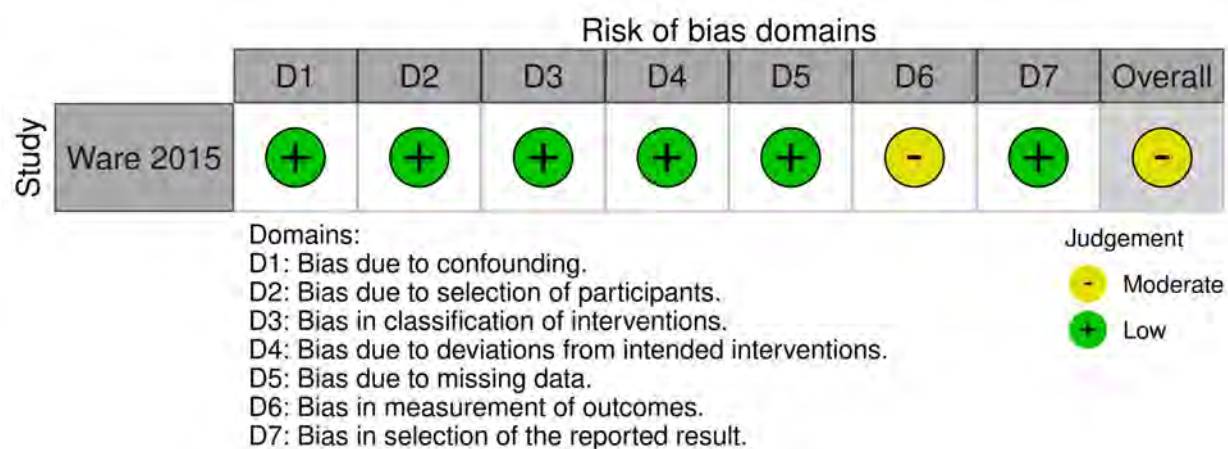
Randomized Clinical Trials	
1	(Chaves et al. 2020)
2	(Kayser et al. 2020)
3	(Aragona et al. 2009)
4	(Kanjanaarangsichai et al. 2022)
Observational Studies	
1	(Ware et al. 2015)

Figure 16. Risk of Bias Assessment, Randomized Clinical Trials, Anxiety



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Figure 17. Risk of Bias Assessment, Observational Studies, Anxiety



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

5.3. Inflammatory Bowel Disease

Table 84. Summary of Included Studies for Inflammatory Bowel Disease

Study Type	Count of Included Studies	Notes
Randomized controlled trials (RCTs)	4	2 RCT were excluded during abstraction due to reporting of clinical not relevant outcomes, and use of synthetic cannabinoids.
Observational studies	6	5 OS excluded during abstraction due to unclear exposure definition, did not assess safety or effectiveness of cannabis products in patients with IBD or did not assess clinically relevant outcomes
Systematic reviews (SRs)	14	---
Eligible RCTs identified from SRs	0	Duplicate studies not reported
Eligible observational studies identified from SRs	0	Duplicate studies not reported
Total non-eligible studies identified from SRs	67	Unique component studies
Total studies included in risk of bias assessments	10	SRs not included in quantitative synthesis

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 85. References (Studies Included in Risk of Bias Assessments, Inflammatory Bowel Disease)

Randomized Clinical Trials	
1	(Naftali et al. 2013)
2	(Naftali et al. 2021a)
3	(Irving et al. 2018)
4	(Naftali et al. 2021b)
Observational Studies	
1	(Desai et al. 2020)
2	(Desai et al. 2019)
3	(Mbachii et al. 2019b)
4	(Mbachii et al. 2019a)
5	(Choi et al. 2022)
6	(Coates et al. 2022)

Figure 18. Risk of Bias Assessment, Randomized Clinical Trials, Inflammatory Bowel Disease

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Naftali 2013	-	X	+	+	-	X
	Naftali 2021a	+	-	+	+	X	X
	Irving 2018	+	+	X	+	X	X
	Naftali 2021b	+	-	+	X	X	X

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Figure 19. Risk of Bias Assessment, Observational Studies, Inflammatory Bowel Disease

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Desai 2020	!	X	!	?	+	-	?	!
	Desai 2019	!	X	!	?	+	-	?	!
	Mbachii 2019a	!	!	!	?	X	X	?	!
	Mbachii 2019b	!	!	!	?	X	X	?	!
	Coates 2022	X	X	X	?	+	-	?	X
	Choi 2022	-	X	X	?	X	-	+	X

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
! Critical
X Serious
- Moderate
+ Low
? No information

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

5.4. Nausea

Table 86. Summary of Included Studies for Nausea

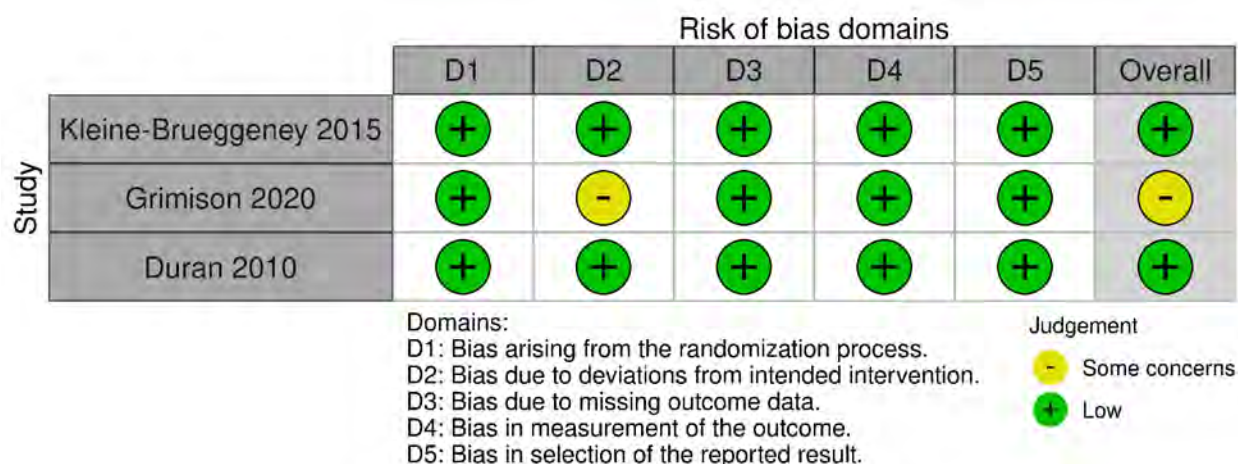
Study Type	Count of Included Studies	Notes
Randomized controlled trials (RCTs) obtained from literature search	3	---
Observational studies obtained from literature search	0	---
Total studies included in risk of bias assessments	3	---

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 87. References (Studies Included in Risk of Bias Assessments, Nausea)

Randomized Clinical Trials	
1	(Grimison et al. 2020)
2	(Kleine-Brueggeneay et al. 2015)
3	(Duran et al. 2010)

Figure 20. Risk of Bias Assessment, Randomized Clinical Trials, Nausea



Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

5.5. Pain

Table 88. Summary of Included Studies for Pain

Study Type	Count of Included Studies	Notes
Randomized controlled trials (RCTs)	32	Total RCTs remaining following review of exposure criteria
Observational studies	6	Total Observational studies remaining following review of exposure criteria
Systematic reviews (SRs)	66	---
Eligible RCTs identified from SRs	7	Duplicate included studies not reported
Eligible observational studies identified from SRs	2	Duplicate included studies not reported
Total non-eligible studies identified from SRs	313	Unique component studies
Total studies included in risk of bias assessments	47	SRs not included in quantitative synthesis

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Table 89. References (Studies Included in Risk of Bias Assessments, Pain)

Randomized Clinical Trials	
1	(Corey-Bloom et al. 2012)
2	(Weizman et al. 2018)
3	(Abrams et al. 2007)
4	(Wilsey et al. 2008)
5	(Wallace et al. 2015)
6	(Wilsey et al. 2013)
7	(van de Donk et al. 2019)
8	(Wallace et al. 2020)
9	(Conte et al. 2009)
10	(Notcutt et al. 2004)
11	(Buggy et al. 2003)
12	(Selvarajah et al. 2010)
13	(Zajicek et al. 2012)
14	(van Amerongen et al. 2018)
15	(Zubcevic et al. 2023)
16	(Gilman et al. 2022)
17	(Lichtman et al. 2018)
18	(Portenoy et al. 2012)
19	(Langford et al. 2013)
20	(Johnson et al. 2010)
21	(Marinelli et al. 2022)
22	(Meuth et al. 2020)
23	(Lynch et al. 2014)
24	(Nurmikko et al. 2007)
25	(Wilsey et al. 2016b)
26	(Wilsey et al. 2016a)
27	(Zylla et al. 2021)
28	(Blake et al. 2006)
29	(Chaves et al. 2020)
30	(de Vries et al. 2016)
31	(de Vries et al. 2017)
32	(Ellis et al. 2009)
33	(Ware et al. 2010)
34	(Zajicek et al. 2003)

35	(Naftali et al. 2013)'
36	(Abrams et al. 2020)
37	(Berman et al. 2004)
38	(Jefferson et al. 2013)
39	(Almog et al. 2020)

Observational Studies

1	(Fiz et al. 2011)
2	(Hjorthoj et al. 2022)
3	(Pawasarat et al. 2020)
4	(Wilson et al. 2020)
5	(Sharma et al. 2022)
6	(Zhang et al. 2018)
7	(Ware et al. 2015)
8	(Habib and Artul 2018)

Background

1	(Soliman et al. 2021)
2	(McDonagh et al. 2022)

Figure 21. Risk of Bias Assessment, Randomized Clinical Trials, Pain

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Abrams 2007	+	+	+	+	+	+
Buggy 2003	+	+	+	+	-	+
Chaves 2020	-	+	+	+	+	-
Corey-Bloom 2012	+	+	+	+	+	+
De Vries 2016a	+	+	+	+	+	+
De Vries 2016b	+	+	-	+	+	+
Ellis 2009	+	-	+	+	+	-
Gilman 2022	-	✗	+	-	+	✗
Jefferson 2013	✗	-	+	+	✗	✗
Johnson 2010	+	+	+	+	+	+
Marinelli 2022	+	-	-	+	+	-
Meuth 2022	-	+	+	+	+	+
van Amerongen 2018	+	+	+	+	+	+
van de Donk 2019	-	-	✗	✗	✗	✗
Wallace 2020	+	+	+	+	+	+
Wallace 2015	-	+	+	✗	+	✗
Ware 2010	-	+	+	+	+	-
Wilsey 2013	+	-	+	+	+	-
Wilsey 2008	✗	-	+	+	+	✗
Zajicek 2012	+	+	+	+	+	+
Zubcevik 2022	+	+	+	+	-	+
Zylla 2021	-	+	-	+	+	-
Wilsey 2016a	+	+	+	+	+	+
Conte 2009	+	+	+	+	+	+
Blake 2005	-	✗	-	+	+	✗
Langford 2012	+	+	+	-	+	-
Lichtman 2018	-	-	+	+	+	-
Nurmikko 2007	+	+	-	+	-	-
Selvarajah 2009	-	-	+	+	+	-
Lynch 2014	+	✗	✗	✗	-	✗
Portenoy 2012	+	+	-	+	+	+
Wilsey 2016b	+	+	+	+	+	+
Zajicek 2003	+	-	+	+	-	-
Weizman 2018	+	-	+	+	+	-
Abrams 2020	+	+	+	+	+	+
Berman 2004	+	+	-	-	+	-
Almog 2020	+	+	+	+	-	-
Notcutt 2004	+	✗	+	+	+	✗
Naftali 2013	-	✗	+	+	-	✗

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
✗ High
- Some concerns
+ Low

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Figure 22. Risk of Bias Assessment, Observational Studies, Pain

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Pawasarat 2020	!	X	+	?	+	-	+	!
	Wilson 2020	X	!	+	?	!	+	X	!
	Sharma 2022	!	+	+	-	-	-	-	!
	Habib 2018	!	X	X	?	-	-	+	!
	Fiz 2011	X	!	X	-	?	+	X	X
	Horthoj 2022	X	-	+	?	!	+	+	!
	Zhang 2018	!	!	-	?	!	-	+	!
	Ware 2015	+	+	+	+	+	-	+	-

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
! Critical
X Serious
- Moderate
+ Low
? No information

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

5.6. Post-Traumatic Stress Disorder

Table 90. Summary of Included Studies for Post-Traumatic Stress Disorder

Study Type	Count of Included Studies	Notes
Randomized controlled trials (RCTs)	1	2 RCTs were excluded during abstraction due to incomplete study report (1) and synthetic cannabinoid as exposure (1)
Observational studies	7	9 observational studies were excluded for incorrect exposure or had ineligible control group
Systematic reviews (SRs)	7	As reported in attrition deliverables
Eligible RCTs identified from SRs	0	Duplicate included studies not reported
Eligible observational studies identified from SRs	0	Duplicate included studies not reported
Total non-eligible studies identified from SRs	52	Unique component studies
Total studies included in risk of bias assessments	8	SRs are not included in quantitative synthesis

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Note: Component studies from systematic reviews that were eligible but already represented within the included studies list are not counted.

Table 91. References (Studies Included in Risk of Bias Assessments, Post-Traumatic Stress Disorder)

Randomized Clinical Trials	
1	(Bonn-Miller et al. 2021)
Observational Studies	
1	(Wilkinson et al. 2015)
2	(Hale et al. 2021)
3	(Bonn-Miller et al. 2022)
4	(Ruglass et al. 2017)
5	(Petersen et al. 2021)
6	(Murkar et al. 2022)
7	(Johnson et al. 2016)
Additional Background	
1	(Bailey et al. 2013)
2	(Berardi et al. 2012)
3	(Bitencourt and Takahashi 2018)
4	(Ney et al. 2019)
5	(Patel et al. 2017)
6	(Shishko et al. 2018)

Figure 23. Risk of Bias Assessment, Randomized Clinical Trials, Post-Traumatic Stress Disorder

		Risk of bias						
		D1	D2	D3	D4	D5	D6	Overall
Study	Bonn-Miller 2021							
	D1: Bias arising from the randomization process D2: Bias arising from period and carryover effects D3: Bias due to deviations from intended interventions D4: Bias due to missing outcome data D5: Bias in measurement of the outcome D6: Bias in selection of the reported outcome							Judgement  Some concerns  Low

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

Figure 24. Risk of Bias Assessment, Observational Studies, Post-Traumatic Stress Disorder

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Wilkinson 2015								
	Hale 2021								
	Bonn-Miller 2022								
	Ruglass 2017								
	Petersen 2021								
	Murkar 2022								
	Johnson 2016								
		Domains: D1: Bias due to confounding. D2: Bias due to selection of participants. D3: Bias in classification of interventions. D4: Bias due to deviations from intended interventions. D5: Bias due to missing data. D6: Bias in measurement of outcomes. D7: Bias in selection of the reported result.							Judgement Critical Serious Moderate Low No information

Source: Consortium for Medical Marijuana Clinical Outcomes Research in Partnership with the Sentinel Initiative. Medical Literature and Data on Marijuana Use. Project 2/1B Report dated July 19, 2023.

IV. References

1. Literature

Abdallah, FW, N Hussain, T Weaver, and R Brull, 2020, Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis, *Reg Anesth Pain Med*, 45(7):509-519, <https://www.ncbi.nlm.nih.gov/pubmed/32471924>.

AHRQ, 2023 Products: Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain, U.S. Department of Health and Human Services (HHS): Agency for Healthcare Research and Quality (AHRQ), accessed, <https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/protocol>.

Allan, GM, CR Finley, J Ton, D Perry, J Ramji, K Crawford, AJ Lindblad, C Korownyk, and MR Kolber, 2018, Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms, *Can Fam Physician*, 64(2):e78-e94, <https://www.ncbi.nlm.nih.gov/pubmed/29449262>.

Andreae, MH, GM Carter, N Shaparin, K Suslov, RJ Ellis, MA Ware, DI Abrams, H Prasad, B Wilsey, D Indyk, M Johnson, and HS Sacks, 2015, Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data, *J Pain*, 16(12):1221-1232, <https://www.ncbi.nlm.nih.gov/pubmed/26362106>.

Barakji, J, SK Korang, J Feinberg, M Maagaard, O Mathiesen, C Gluud, and JC Jakobsen, 2023, Cannabinoids versus placebo for pain: A systematic review with meta-analysis and Trial Sequential Analysis, *PLoS One*, 18(1):e0267420, <https://www.ncbi.nlm.nih.gov/pubmed/36716312>.

Bell, AD, C MacCallum, S Margolese, Z Walsh, P Wright, PJ Daeninck, E Mandarino, G Lacasse, J Kaur Deol, L de Freitas, M St Pierre, L Belle-Isle, M Gagnon, S Bevan, T Sanchez, S Arlt, M Monahan-Ellison, J O'Hara, M Boivin, C Costiniuk, and P External Review, 2023, Clinical Practice Guidelines for Cannabis and Cannabinoid-Based Medicines in the Management of Chronic Pain and Co-Occurring Conditions, *Cannabis Cannabinoid Res*, <https://www.ncbi.nlm.nih.gov/pubmed/36971587>.

Bilbao, A and R Spanagel, 2022, Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications, *BMC Med*, 20(1):259, <https://www.ncbi.nlm.nih.gov/pubmed/35982439>.

Black, N, E Stockings, G Campbell, LT Tran, D Zagic, WD Hall, M Farrell, and L Degenhardt, 2019, Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis, *Lancet Psychiatry*, 6(12):995-1010, <https://www.ncbi.nlm.nih.gov/pubmed/31672337>.

Boland, EG, MI Bennett, V Allgar, and JW Boland, 2020, Cannabinoids for adult cancer-related pain: systematic review and meta-analysis, *BMJ Support Palliat Care*, 10(1):14-24, <https://www.ncbi.nlm.nih.gov/pubmed/31959586>.

Bonn-Miller, MO, KA Babson, and R Vandrey, 2014a, Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD, *Drug Alcohol Depend*, 136:162-165, <https://www.ncbi.nlm.nih.gov/pubmed/24412475>.

Bonn-Miller, MO, MT Boden, MM Bucossi, and KA Babson, 2014b, Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users, *Am J Drug Alcohol Abuse*, 40(1):23-30, <https://www.ncbi.nlm.nih.gov/pubmed/24205805>.

CBHSQ, 2022a 2021 National Survey on Drug Use and Health (NSDUH): Custom Analysis of National Survey on Drug Use and Health Restricted Use File, U.S. Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA): Center for Behavior Health Statistics and Quality (CBHSQ), accessed.

CBHSQ, 2022b 2021 National Survey on Drug Use and Health (NSDUH): Public Use File Codebook, Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA): Center for Behavior Health Statistics and Quality (CBHSQ), accessed, <https://www.datafiles.samhsa.gov/sites/default/files/field-uploads-protected/studies/NSDUH-2021/NSDUH-2021-datasets/NSDUH-2021-DS0001/NSDUH-2021-DS0001-info/NSDUH-2021-DS0001-info-codebook.pdf>.

Corsetti, D, S Goodman, R Burkhalter, and D Hammond, 2022, International Cannabis Study Code Book Wave 4 (2021), <http://cannabisproject.ca/methods/>.

de Almeida, DL and LA Devi, 2020, Diversity of molecular targets and signaling pathways for CBD, *Pharmacol Res Perspect*, 8(6):e00682, <https://www.ncbi.nlm.nih.gov/pubmed/33169541>.

De Vita, MJ, D Moskal, SA Maisto, and EB Ansell, 2018, Association of Cannabinoid Administration With Experimental Pain in Healthy Adults: A Systematic Review and Meta-analysis, *JAMA Psychiatry*, 75(11):1118-1127, <https://www.ncbi.nlm.nih.gov/pubmed/30422266>.

Deshpande, A, A Mailis-Gagnon, N Zoheiry, and SF Lakha, 2015, Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials, *Can Fam Physician*, 61(8):e372-381, <https://www.ncbi.nlm.nih.gov/pubmed/26505059>.

Desmarais, A, S Smiddy, S Reddy, M El-Dallal, J Erlich, and JD Feuerstein, 2020, Evidence supporting the benefits of marijuana for Crohn's disease and ulcerative colitis is extremely limited: a meta-analysis of the literature, *Ann Gastroenterol*, 33(5):495-499, <https://www.ncbi.nlm.nih.gov/pubmed/32879596>.

Doeve, BH, MM van de Meeberg, FDM van Schaik, and HH Fidder, 2021, A Systematic Review With Meta-Analysis of the Efficacy of Cannabis and Cannabinoids for Inflammatory Bowel Disease: What Can We Learn From Randomized and Nonrandomized Studies?, *J Clin Gastroenterol*, 55(9):798-809, <https://www.ncbi.nlm.nih.gov/pubmed/32675631>.

Elliott, J, D DeJean, T Clifford, D Coyle, BK Potter, B Skidmore, C Alexander, AE Repetski, V Shukla, B McCoy, and GA Wells, 2019, Cannabis-based products for pediatric epilepsy: A systematic review, *Epilepsia*, 60(1):6-19, <https://www.ncbi.nlm.nih.gov/pubmed/30515765>.

Elliott, J, D DeJean, T Clifford, D Coyle, BK Potter, B Skidmore, C Alexander, AE Repetski, V Shukla, B McCoy, and GA Wells, 2020, Cannabis-based products for pediatric epilepsy: An updated systematic review, *Seizure*, 75:18-22, <https://www.ncbi.nlm.nih.gov/pubmed/31865133>.

Fitzcharles, MA, PA Ste-Marie, W Hauser, DJ Clauw, S Jamal, J Karsh, T Landry, S Leclercq, JJ McDougall, Y Shir, K Shojania, and Z Walsh, 2016, Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials, *Arthritis Care Res (Hoboken)*, 68(5):681-688, <https://www.ncbi.nlm.nih.gov/pubmed/26548380>.

Forsythe, ML and AJ Boileau, 2021, Use of cannabinoids for the treatment of patients with post-traumatic stress disorder, *J Basic Clin Physiol Pharmacol*, 33(2):121-132, <https://www.ncbi.nlm.nih.gov/pubmed/33662194>.

Greer, GR, CS Grob, and AL Halberstadt, 2014, PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program, *J Psychoactive Drugs*, 46(1):73-77, <https://www.ncbi.nlm.nih.gov/pubmed/24830188>.

Hammond, D, D Danh Hong, F Fataar, M Iraniparast, and D Corsetti, 2023, Findings from the International Cannabis Policy Study: Prepared on Behalf of the US Food and Drug Administration, May 2023.

Hindley, G, K Beck, F Borgan, CE Ginestet, R McCutcheon, D Kleinloog, S Ganesh, R Radhakrishnan, DC D'Souza, and OD Howes, 2020, Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis, *Lancet Psychiatry*, 7(4):344-353, <https://www.ncbi.nlm.nih.gov/pubmed/32197092>.

Hindocha, C, J Cousijn, M Rall, and MAP Bloomfield, 2020, The Effectiveness of Cannabinoids in the Treatment of Posttraumatic Stress Disorder (PTSD): A Systematic Review, *J Dual Diagn*, 16(1):120-139, <https://www.ncbi.nlm.nih.gov/pubmed/31479625>.

IOM, 1999, Marijuana and Medicine: Assessing the Science Base, Institute of Medicine (IOM), United States, <https://www.ncbi.nlm.nih.gov/pubmed/25101425>.

Jugl, S, A Okpeku, B Costales, EJ Morris, G Alipour-Haris, JM Hincapie-Castillo, NE Stetten, R Sajdeya, S Keshwani, V Joseph, Y Zhang, Y Shen, L Adkins, AG Winterstein, and A Goodin, 2021, A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019, *Med Cannabis Cannabinoids*, 4(1):21-42, <https://www.ncbi.nlm.nih.gov/pubmed/34676348>.

Kafil, TS, TM Nguyen, JK MacDonald, and N Chande, 2020, Cannabis for the Treatment of Crohn's Disease and Ulcerative Colitis: Evidence From Cochrane Reviews, *Inflamm Bowel Dis*, 26(4):502-509, <https://www.ncbi.nlm.nih.gov/pubmed/31613959>.

Li, J, CC Areal, DH Toffa, D Citherlet, C Deacon, D Jutras-Aswad, MR Keezer, and DK Nguyen, 2023, Use of non-medical cannabis in epilepsy: A scoping review, *Front Neurol*, 14:1132106, <https://www.ncbi.nlm.nih.gov/pubmed/36949852>.

Lynch, ME and MA Ware, 2015, Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials, *J Neuroimmune Pharmacol*, 10(2):293-301, <https://www.ncbi.nlm.nih.gov/pubmed/25796592>.

Meng, H, B Johnston, M Englesakis, DE Moulin, and A Bhatia, 2017, Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis, *Anesth Analg*, 125(5):1638-1652, <https://www.ncbi.nlm.nih.gov/pubmed/28537982>.

Miech, RA, LD Johnston, ME Patrick, PM O'Malley, JG Bachman, and JE Schulenberg, 2023, Monitoring the Future National Survey Results on Drug Use, 1975–2022: Secondary School Students, <https://monitoringthefuture.org/wp-content/uploads/2022/12/mtf2022.pdf>.

Montero-Oleas, N, I Arevalo-Rodriguez, S Nunez-Gonzalez, A Viteri-Garcia, and D Simancas-Racines, 2020, Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews, *BMC Complement Med Ther*, 20(1):12, <https://www.ncbi.nlm.nih.gov/pubmed/32020875>.

Mucke, M, M Weier, C Carter, J Copeland, L Degenhardt, H Cuhls, L Radbruch, W Hauser, and R Conrad, 2018, Systematic review and meta-analysis of cannabinoids in palliative medicine, *J Cachexia Sarcopenia Muscle*, 9(2):220-234, <https://www.ncbi.nlm.nih.gov/pubmed/29400010>.

Nabata, KJ, EK Tse, TE Nightingale, AHX Lee, JJ Eng, M Queree, M Walter, and AV Krassioukov, 2021, The Therapeutic Potential and Usage Patterns of Cannabinoids in People with Spinal Cord Injuries: A Systematic Review, *Curr Neuropharmacol*, 19(3):402-432, <https://www.ncbi.nlm.nih.gov/pubmed/32310048>.

NASEM, 2017 The National Academies Collection: Reports funded by National Institutes of Health: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, National Academies of Sciences, Engineering, and Medicine (NASEM), accessed, <https://www.ncbi.nlm.nih.gov/pubmed/28182367>.

NIDA, 2022 Trends & Statistics: Monitoring the Future, National Institute of Health (NIH): National Institute on Drug Abuse (NIDA), accessed April 3, 2023, <https://nida.nih.gov/research-topics/trends-statistics/monitoring-future>.

Nielsen, S, R Germanos, M Weier, J Pollard, L Degenhardt, W Hall, N Buckley, and M Farrell, 2018, The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews, *Curr Neurol Neurosci Rep*, 18(2):8, <https://www.ncbi.nlm.nih.gov/pubmed/29442178>.

Noori, A, A Miroshnychenko, Y Shergill, V Ashoorion, Y Rehman, RJ Couban, DN Buckley, L Thabane, M Bhandari, GH Guyatt, T Agoritsas, and JW Busse, 2021, Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies, *BMJ Open*, 11(7):e047717, <https://www.ncbi.nlm.nih.gov/pubmed/34321302>.

Norton, C, W Czubier-Dochan, M Artom, L Sweeney, and A Hart, 2017, Systematic review: interventions for abdominal pain management in inflammatory bowel disease, *Aliment Pharmacol Ther*, 46(2):115-125, <https://www.ncbi.nlm.nih.gov/pubmed/28470846>.

O'Neil, ME, SM Nugent, BJ Morasco, M Freeman, A Low, K Kondo, B Zakher, C Elven, M Motu'apuaka, R Paynter, and D Kansagara, 2017, Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder: A Systematic Review, *Ann Intern Med*, 167(5):332-340, <https://www.ncbi.nlm.nih.gov/pubmed/28806794>.

Okusanya, BO, IO Asaolu, JE Ehiri, LJ Kimaru, A Okechukwu, and C Rosales, 2020, Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review, *Syst Rev*, 9(1):167, <https://www.ncbi.nlm.nih.gov/pubmed/32723354>.

Price, RL, KV Charlot, S Frieler, JR Dettori, R Oskouian, and JR Chapman, 2022, The Efficacy of Cannabis in Reducing Back Pain: A Systematic Review, *Global Spine J*, 12(2):343-352, <https://www.ncbi.nlm.nih.gov/pubmed/35128969>.

Ramar, K, IM Rosen, DB Kirsch, RD Chervin, KA Carden, RN Aurora, DA Kristo, RK Malhotra, JL Martin, EJ Olson, CL Rosen, JA Rowley, and D American Academy of Sleep Medicine Board of, 2018, Medical Cannabis and the Treatment of Obstructive Sleep Apnea: An American Academy of Sleep Medicine Position Statement, *J Clin Sleep Med*, 14(4):679-681, <https://www.ncbi.nlm.nih.gov/pubmed/29609727>.

Rehman, Y, A Saini, S Huang, E Sood, R Gill, and S Yanikomeroglu, 2021, Cannabis in the management of PTSD: a systematic review, *AIMS Neurosci*, 8(3):414-434, <https://www.ncbi.nlm.nih.gov/pubmed/34183989>.

Roitman, P, R Mechoulam, R Cooper-Kazaz, and A Shalev, 2014, Preliminary, open-label, pilot study of add-on oral Delta9-tetrahydrocannabinol in chronic post-traumatic stress disorder, *Clin Drug Investig*, 34(8):587-591, <https://www.ncbi.nlm.nih.gov/pubmed/24935052>.

Sainsbury, B, J Bloxham, MH Pour, M Padilla, and R Enciso, 2021, Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis, *J Dent Anesth Pain Med*, 21(6):479-506, <https://www.ncbi.nlm.nih.gov/pubmed/34909469>.

Sawtelle, L and LM Holle, 2021, Use of Cannabis and Cannabinoids in Patients With Cancer, *Ann Pharmacother*, 55(7):870-890, <https://www.ncbi.nlm.nih.gov/pubmed/33070617>.

Schünemann, H, J Higgins, G Vist, P Glasziou, E Akl, N Skoetz, and G Guyatt, 2019, Completing 'Summary of Findings' Tables and Grading the Certainty of the Evidence, *Cochrane Handbook for Systematic Reviews of Interventions*, 6.3, <https://doi.org/10.1002/9781119536604.ch14>.

Sharpe, L, J Sinclair, A Kramer, M de Manincor, and J Sarris, 2020, Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties, *J Transl Med*, 18(1):374, <https://www.ncbi.nlm.nih.gov/pubmed/33008420>.

Simon, L, C Baldwin, AZ Kalea, and A Slee, 2022, Cannabinoid interventions for improving cachexia outcomes in cancer: a systematic review and meta-analysis, *J Cachexia Sarcopenia Muscle*, 13(1):23-41, <https://www.ncbi.nlm.nih.gov/pubmed/34881518>.

Stanciu, CN, MF Brunette, N Teja, and AJ Budney, 2021, Evidence for Use of Cannabinoids in Mood Disorders, Anxiety Disorders, and PTSD: A Systematic Review, *Psychiatr Serv*, 72(4):429-436, <https://www.ncbi.nlm.nih.gov/pubmed/33530732>.

Sterne, JA, MA Hernan, BC Reeves, J Savovic, ND Berkman, M Viswanathan, D Henry, DG Altman, MT Ansari, I Boutron, JR Carpenter, AW Chan, R Churchill, JJ Deeks, A Hrobjartsson, J Kirkham, P Juni, YK Loke, TD Pigott, CR Ramsay, D Regidor, HR Rothstein, L Sandhu, PL Santaguida, HJ Schunemann, B Shea, I Shrier, P Tugwell, L Turner, JC Valentine, H Waddington, E Waters, GA Wells, PF Whiting, and JP Higgins, 2016, ROBINS-I: a tool for

assessing risk of bias in non-randomised studies of interventions, *BMJ*, 355:i4919, <https://www.ncbi.nlm.nih.gov/pubmed/27733354>.

Sterne, JAC, J Savovic, MJ Page, RG Elbers, NS Blencowe, I Boutron, CJ Cates, HY Cheng, MS Corbett, SM Eldridge, JR Emberson, MA Hernan, S Hopewell, A Hrobjartsson, DR Junqueira, P Juni, JJ Kirkham, T Lasserson, T Li, A McAleenan, BC Reeves, S Shepperd, I Shrier, LA Stewart, K Tilling, IR White, PF Whiting, and JPT Higgins, 2019, RoB 2: a revised tool for assessing risk of bias in randomised trials, *BMJ*, 366:l4898, <https://www.ncbi.nlm.nih.gov/pubmed/31462531>.

Stockings, E, G Campbell, WD Hall, S Nielsen, D Zagic, R Rahman, B Murnion, M Farrell, M Weier, and L Degenhardt, 2018a, Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies, *Pain*, 159(10):1932-1954, <https://www.ncbi.nlm.nih.gov/pubmed/29847469>.

Stockings, E, D Zagic, G Campbell, M Weier, WD Hall, S Nielsen, GK Herkes, M Farrell, and L Degenhardt, 2018b, Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence, *J Neurol Neurosurg Psychiatry*, 89(7):741-753, <https://www.ncbi.nlm.nih.gov/pubmed/29511052>.

Torres-Moreno, MC, E Papaseit, M Torrens, and M Farre, 2018, Assessment of Efficacy and Tolerability of Medicinal Cannabinoids in Patients With Multiple Sclerosis: A Systematic Review and Meta-analysis, *JAMA Netw Open*, 1(6):e183485, <https://www.ncbi.nlm.nih.gov/pubmed/30646241>.

Tsai, SHL, CR Lin, SC Shao, CH Fang, TS Fu, TY Lin, and YC Hung, 2022, Cannabinoid Use for Pain Reduction in Spinal Cord Injuries: A Meta-Analysis of Randomized Controlled Trials, *Front Pharmacol*, 13:866235, <https://www.ncbi.nlm.nih.gov/pubmed/35571093>.

Vinci, A, F Ingravalle, D Bardhi, N Cesaro, S Frassino, F Licata, and M Valvano, 2022, Cannabinoid Therapeutic Effects in Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, *Biomedicines*, 10(10), <https://www.ncbi.nlm.nih.gov/pubmed/36289701>.

Wang, J, Y Wang, M Tong, H Pan, and D Li, 2019, Medical Cannabinoids for Cancer Cachexia: A Systematic Review and Meta-Analysis, *Biomed Res Int*, 2019:2864384, <https://www.ncbi.nlm.nih.gov/pubmed/31341892>.

Whiting, PF, RF Wolff, S Deshpande, M Di Nisio, S Duffy, AV Hernandez, JC Keurentjes, S Lang, K Misso, S Ryder, S Schmidtkofer, M Westwood, and J Kleijnen, 2015, Cannabinoids for Medical Use: A Systematic Review and Meta-analysis, *JAMA*, 313(24):2456-2473, <https://www.ncbi.nlm.nih.gov/pubmed/26103030>.

Wong, SSC, WS Chan, and CW Cheung, 2020, Analgesic Effects of Cannabinoids for Chronic Non-cancer Pain: a Systematic Review and Meta-Analysis with Meta-Regression, *J Neuroimmune Pharmacol*, 15(4):801-829, <https://www.ncbi.nlm.nih.gov/pubmed/32172501>.

2. Position Statements

AAFP, 2019 All Policies: Marijuana and Cannabinoids: Health, Research and Regulatory Considerations (Position Paper), American Academy of Family Physicians (AAFP), accessed, <https://www.aafp.org/about/policies/all/marijuana-position-paper.html>.

AAN, 2020 Advocacy: AAN Position: Use of Medical Cannabis for Neurologic Disorders, American Academy of Neurology (AAN), accessed, <https://www.aan.com/advocacy/medical-cannabis-position-statement/>.

AES, 2022 Position Statements: AES Position Statement on Cannabis as a Treatment for Patients with Epileptic Seizures, American Epilepsy Society (AES), accessed, <https://www.aesnet.org/about/about-aes/position-statements/aes-position-statement-on-cannabis-as-a-treatment-for-patients-with-epileptic-seizures>.

APA, 2018 Resource Documents: 2018: Opposition to Cannabis as Medicine, Approved by the Joint Reference Committee, October 2018, American Psychiatric Association (APA), accessed, <https://www.psychiatry.org/Psychiatrists/Search-Directories-Databases/Resource-Documents/2018/Opposition-to-Cannabis-as-Medicine>.

ASAM, 2020 Public Policy Statements: 2020: Public Policy Statement on Cannabis, American Society of Addiction Medicine (ASAM), accessed, <https://www.asam.org/advocacy/public-policy-statements/details/public-policy-statements/2020/10/10/cannabis>.

IASP, 2021 News: IASP Position Statement on the Use of Cannabinoids to Treat Pain, International Association for the Study of Pain (IASP), accessed, <https://www.iasp-pain.org/publications/iasp-news/iasp-position-statement-on-the-use-of-cannabinoids-to-treat-pain/>.

NAADAC, 2022 Position Statements and Issue Briefs: NAADAC Position Statement on the Medical and Recreational Use of Cannabis, accessed, 2023, <https://www.naadac.org/position-statement-on-the-medical-and-recreational-use-of-cannabis>.

3. Other

Biden, P, 2022 Briefing Room: Statements and Releases: Statement from President Biden on Marijuana Reform, accessed March 31, 2023, <https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/>.

CDC, 2018 About BRFSS: BRFSS Frequently Asked Questions (FAQs), U.S. Department of Health and Human Services (HHS): Centers for Disease Control and Prevention (CDC), accessed March 28, 2023, https://www.cdc.gov/brfss/about/brfss_faq.htm.

CDC, 2023 Behavioral Risk Factor Surveillance System, U.S. Department of Health and Human Services (HHS): Centers for Disease Control and Prevention (CDC), accessed June 14, 2023, <https://www.cdc.gov/brfss/>.

MMCC, 2023 Maryland Medical Cannabis Patient Survey (MMCPS): 2022 Maryland Medical Cannabis Patient Survey FAQs, Maryland Cannabis Administration (MCA): Maryland Medical Cannabis Commission (MMCC), accessed March 10, 2023, <https://mmcc.maryland.gov/Pages/Patient-Survey-Info-FAQs.aspx>.

SAMHSA, 2023 Substance Abuse and Mental Health Data Archive, Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA), accessed, 2023, <https://pdas.samhsa.gov/#/>.

4. Government Documents

57 FR 10499, March 26, 1992, *Marijuana Scheduling Petition; Denial of Petition; Remand [Docket No. 86-22]* U.S. Department of Justice (DOJ): Drug Enforcement Administration (DEA), https://archives.federalregister.gov/issue_slice/1992/3/26/10498-10508.pdf#page=2.

FDA Office of Surveillance and Epidemiology. (2023). *Office of Surveillance and Epidemiology Review Describing Prevalence and Patterns of Marijuana Nonmedical Use or Marijuana Use of Uncertain Intent and Associated Harms*.

5. Prescribing Information

Greenwich Biosciences, 2018 Prescribing Information: EPIDIOLEX, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210365s015lbl.pdf.

6. University of Florida Systematic Literature Review

Abrams, DI, P Couey, N Dixit, V Sagi, W Hagar, E Vichinsky, ME Kelly, JE Connett, and K Gupta, 2020, Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease: A Randomized Clinical Trial, *JAMA Netw Open*, 3(7):e2010874, <https://www.ncbi.nlm.nih.gov/pubmed/32678452>.

Abrams, DI, CA Jay, SB Shade, H Vizoso, H Reda, S Press, ME Kelly, MC Rowbotham, and KL Petersen, 2007, Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial, *Neurology*, 68(7):515-521, <https://www.ncbi.nlm.nih.gov/pubmed/17296917>.

Almog, S, J Aharon-Peretz, S Vulfsons, M Ogintz, H Abalia, T Lupo, Y Hayon, and E Eisenberg, 2020, The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial, *Eur J Pain*, 24(8):1505-1516, <https://www.ncbi.nlm.nih.gov/pubmed/32445190>.

Aragona, M, E Onesti, V Tomassini, A Conte, S Gupta, F Gilio, P Pantano, C Pozzilli, and M Inghilleri, 2009, Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study, *Clin Neuropharmacol*, 32(1):41-47, <https://www.ncbi.nlm.nih.gov/pubmed/18978501>.

Bailey, CR, E Cordell, SM Sobin, and A Neumeister, 2013, Recent progress in understanding the pathophysiology of post-traumatic stress disorder: implications for targeted pharmacological treatment, *CNS Drugs*, 27(3):221-232, <https://www.ncbi.nlm.nih.gov/pubmed/23483368>.

Berardi, A, V Trezza, and C Campolongo, 2012, Modeling specific phobias and posttraumatic stress disorder in rodents: the challenge to convey both cognitive and emotional features, *Rev Neurosci*, 23(5-6):645-657, <https://www.ncbi.nlm.nih.gov/pubmed/23006899>.

Berman, JS, C Symonds, and R Birch, 2004, Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial, *Pain*, 112(3):299-306, <https://www.ncbi.nlm.nih.gov/pubmed/15561385>.

Bitencourt, RM and RN Takahashi, 2018, Cannabidiol as a Therapeutic Alternative for Post-traumatic Stress Disorder: From Bench Research to Confirmation in Human Trials, *Front Neurosci*, 12:502, <https://www.ncbi.nlm.nih.gov/pubmed/30087591>.

Blake, DR, P Robson, M Ho, RW Jubb, and CS McCabe, 2006, Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis, *Rheumatology (Oxford)*, 45(1):50-52, <https://www.ncbi.nlm.nih.gov/pubmed/16282192>.

Bonn-Miller, MO, M Brunstetter, A Simonian, MJ Loflin, R Vandrey, KA Babson, and H Wortzel, 2022, The Long-Term, Prospective, Therapeutic Impact of Cannabis on Post-Traumatic Stress Disorder, *Cannabis Cannabinoid Res*, 7(2):214-223, <https://www.ncbi.nlm.nih.gov/pubmed/33998874>.

Bonn-Miller, MO, S Sisley, P Riggs, B Yazar-Klosinski, JB Wang, MJE Loflin, B Shechet, C Hennigan, R Matthews, A Emerson, and R Doblin, 2021, The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial, *PLoS One*, 16(3):e0246990, <https://www.ncbi.nlm.nih.gov/pubmed/33730032>.

Buggy, DJ, L Toogood, S Maric, P Sharpe, DG Lambert, and DJ Rowbotham, 2003, Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain, *Pain*, 106(1-2):169-172, <https://www.ncbi.nlm.nih.gov/pubmed/14581124>.

Chaves, C, PCT Bittencourt, and A Pelegrini, 2020, Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial, *Pain Med*, 21(10):2212-2218, <https://www.ncbi.nlm.nih.gov/pubmed/33118602>.

Choi, C, M Abougergi, H Peluso, SH Weiss, U Nasir, and N Pyrsopoulos, 2022, Cannabis Use is Associated With Reduced 30-Day All-cause Readmission Among Hospitalized Patients With Irritable Bowel Syndrome: A Nationwide Analysis, *J Clin Gastroenterol*, 56(3):257-265, <https://www.ncbi.nlm.nih.gov/pubmed/33471483>.

Coates, MD, S Dalessio, V Walter, A Stuart, N Bernasko, A Tinsley, S Razeghi, ED Williams, K Clarke, and K Vrana, 2022, Symptoms and Extraintestinal Manifestations in Active Cannabis Users with Inflammatory Bowel Disease, *Cannabis Cannabinoid Res*, 7(4):445-450, <https://www.ncbi.nlm.nih.gov/pubmed/33998892>.

Conte, A, CM Bettolo, E Onesti, V Frasca, E Iacovelli, F Gilio, E Giacomelli, M Gabriele, M Aragona, V Tomassini, P Pantano, C Pozzilli, and M Inghilleri, 2009, Cannabinoid-induced effects on the nociceptive system: a neurophysiological study in patients with secondary progressive multiple sclerosis, *Eur J Pain*, 13(5):472-477, <https://www.ncbi.nlm.nih.gov/pubmed/18603457>.

Corey-Bloom, J, T Wolfson, A Gamst, S Jin, TD Marcotte, H Bentley, and B Gouaux, 2012, Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial, *CMAJ*, 184(10):1143-1150, <https://www.ncbi.nlm.nih.gov/pubmed/22586334>.

- de Vries, M, DC Van Rijckevorsel, KC Vissers, OH Wilder-Smith, and H Van Goor, 2016, Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability, *Br J Clin Pharmacol*, 81(3):525-537, <https://www.ncbi.nlm.nih.gov/pubmed/26505163>.
- de Vries, M, DCM van Rijckevorsel, KCP Vissers, OHG Wilder-Smith, H van Goor, Pain, and G Nociception Neuroscience Research, 2017, Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study, *Clin Gastroenterol Hepatol*, 15(7):1079-1086 e1074, <https://www.ncbi.nlm.nih.gov/pubmed/27720917>.
- Desai, P, C Mbachii, I Vohra, M Salazar, M Mathew, T Randhawa, Z Haque, Y Wang, B Attar, and I Paintsil, 2020, Association Between Cannabis Use and Healthcare Utilization in Patients With Irritable Bowel Syndrome: A Retrospective Cohort Study, *Cureus*, 12(5):e8008, <https://www.ncbi.nlm.nih.gov/pubmed/32528750>.
- Desai, R, U Patel, H Goyal, AH Rimu, D Zalavadia, P Bansal, and N Shah, 2019, In-hospital outcomes of inflammatory bowel disease in cannabis users: a nationwide propensity-matched analysis in the United States, *Ann Transl Med*, 7(12):252, <https://www.ncbi.nlm.nih.gov/pubmed/31355219>.
- Duran, M, E Perez, S Abanades, X Vidal, C Saura, M Majem, E Arriola, M Rabanal, A Pastor, M Farre, N Rams, JR Laporte, and D Capella, 2010, Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting, *Br J Clin Pharmacol*, 70(5):656-663, <https://www.ncbi.nlm.nih.gov/pubmed/21039759>.
- Ellis, RJ, W Toperoff, F Vaida, G van den Brande, J Gonzales, B Gouaux, H Bentley, and JH Atkinson, 2009, Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial, *Neuropsychopharmacology*, 34(3):672-680, <https://www.ncbi.nlm.nih.gov/pubmed/18688212>.
- Fiz, J, M Duran, D Capella, J Carbonell, and M Farre, 2011, Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life, *PLoS One*, 6(4):e18440, <https://www.ncbi.nlm.nih.gov/pubmed/21533029>.
- Gilman, JM, RM Schuster, KW Potter, W Schmitt, G Wheeler, GN Pachas, S Hickey, ME Cooke, A Dechert, R Plummer, B Tervo-Clemmens, DA Schoenfeld, and AE Evins, 2022, Effect of Medical Marijuana Card Ownership on Pain, Insomnia, and Affective Disorder Symptoms in Adults: A Randomized Clinical Trial, *JAMA Netw Open*, 5(3):e222106, <https://www.ncbi.nlm.nih.gov/pubmed/35302633>.
- Grimison, P, A Mersiades, A Kirby, N Lintzeris, R Morton, P Haber, I Olver, A Walsh, I McGregor, Y Cheung, A Tognela, C Hahn, K Briscoe, M Aghmesheh, P Fox, E Abdi, S Clarke, S Della-Fiorentina, J Shannon, C Gedye, S Begbie, J Simes, and M Stockler, 2020, Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial, *Ann Oncol*, 31(11):1553-1560, <https://www.ncbi.nlm.nih.gov/pubmed/32801017>.
- Habib, G and S Artul, 2018, Medical Cannabis for the Treatment of Fibromyalgia, *J Clin Rheumatol*, 24(5):255-258, <https://www.ncbi.nlm.nih.gov/pubmed/29461346>.

Hale, AC, J Bremer-Landau, TP Wright, JE McDowell, and JL Rodriguez, 2021, Residential PTSD treatment outcomes during cognitive processing therapy for veterans with and without recent histories of cannabis use, *Psychol Serv*, 18(4):497-503, <https://www.ncbi.nlm.nih.gov/pubmed/32134304>.

Haney, M, EW Gunderson, J Rabkin, CL Hart, SK Vosburg, SD Comer, and RW Foltin, 2007, Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep, *J Acquir Immune Defic Syndr*, 45(5):545-554, <https://www.ncbi.nlm.nih.gov/pubmed/17589370>.

Haney, M, J Rabkin, E Gunderson, and RW Foltin, 2005, Dronabinol and marijuana in HIV(+) marijuana smokers: acute effects on caloric intake and mood, *Psychopharmacology (Berl)*, 181(1):170-178, <https://www.ncbi.nlm.nih.gov/pubmed/15778874>.

Hjorthoj, C, P La Cour, M Nordentoft, and CM Posselt, 2022, Cannabis-based medicines and medical cannabis for patients with neuropathic pain and other pain disorders: Nationwide register-based pharmacoepidemiologic comparison with propensity score matched controls, *Eur J Pain*, 26(2):480-491, <https://www.ncbi.nlm.nih.gov/pubmed/34624164>.

Huang, EY, RC Broderick, JZ Li, JL Serra, P Ahuja, S Wu, M Genz, E Grunvald, DC Kunkel, BJ Sandler, S Horgan, and GR Jacobsen, 2023, Weight loss outcomes are not compromised in bariatric patients using cannabis, *Surg Endosc*, 37(3):2194-2201, <https://www.ncbi.nlm.nih.gov/pubmed/35861881>.

Irving, PM, T Iqbal, C Nwokolo, S Subramanian, S Bloom, N Prasad, A Hart, C Murray, JO Lindsay, A Taylor, R Barron, and S Wright, 2018, A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis, *Inflamm Bowel Dis*, 24(4):714-724, <https://www.ncbi.nlm.nih.gov/pubmed/29538683>.

Jefferson, DA, HE Harding, SO Cawich, and A Jackson-Gibson, 2013, Postoperative analgesia in the Jamaican cannabis user, *J Psychoactive Drugs*, 45(3):227-232, <https://www.ncbi.nlm.nih.gov/pubmed/24175487>.

Johnson, JR, M Burnell-Nugent, D Lossignol, ED Ganae-Motan, R Potts, and MT Fallon, 2010, Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain, *J Pain Symptom Manage*, 39(2):167-179, <https://www.ncbi.nlm.nih.gov/pubmed/19896326>.

Johnson, MJ, JD Pierce, S Mavandadi, J Klaus, D Defelice, E Ingram, and DW Oslin, 2016, Mental health symptom severity in cannabis using and non-using Veterans with probable PTSD, *J Affect Disord*, 190:439-442, <https://www.ncbi.nlm.nih.gov/pubmed/26551402>.

Kanjanarangsichai, A, W Mitarnun, W Mitarnun, W Pangwong, N Laoharattanahirun, W Kajornrith, P Junlaor, P Nonghan, W Witthayapirote, and G Sangkarom, 2022, Cannabidiol-enriched cannabis extraction product in Parkinson's disease: A randomized, double-blind, and placebo-controlled trial in Buriram Hospital, *J Neurosci Rural Pract*, 13(4):663-668, <https://www.ncbi.nlm.nih.gov/pubmed/36743777>.

Kayser, RR, M Haney, M Raskin, C Arout, and HB Simpson, 2020, Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study, *Depress Anxiety*, 37(8):801-811, <https://www.ncbi.nlm.nih.gov/pubmed/32383271>.

Kleine-Brueggene, M, R Greif, R Brenneisen, N Urwyler, F Stueber, and LG Theiler, 2015, Intravenous Delta-9-Tetrahydrocannabinol to Prevent Postoperative Nausea and Vomiting: A Randomized Controlled Trial, *Anesth Analg*, 121(5):1157-1164, <https://www.ncbi.nlm.nih.gov/pubmed/26426861>.

Langford, RM, J Mares, A Novotna, M Vachova, I Novakova, W Notcutt, and S Ratcliffe, 2013, A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis, *J Neurol*, 260(4):984-997, <https://www.ncbi.nlm.nih.gov/pubmed/23180178>.

Lichtman, AH, EA Lux, R McQuade, S Rossetti, R Sanchez, W Sun, S Wright, E Kornyeieva, and MT Fallon, 2018, Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain, *J Pain Symptom Manage*, 55(2):179-188 e171, <https://www.ncbi.nlm.nih.gov/pubmed/28923526>.

Lynch, ME, P Cesar-Rittenberg, and AG Hohmann, 2014, A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain, *J Pain Symptom Manage*, 47(1):166-173, <https://www.ncbi.nlm.nih.gov/pubmed/23742737>.

Marinelli, L, L Puce, L Mori, M Leandri, GM Rosa, A Curra, F Fattapposta, and C Trompetto, 2022, Cannabinoid Effect and Safety in Spasticity Following Stroke: A Double-Blind Randomized Placebo-Controlled Study, *Front Neurol*, 13:892165, <https://www.ncbi.nlm.nih.gov/pubmed/35812088>.

Mbachi, C, B Attar, O Oyenu, W Yuchen, A Efesomwan, I Paintsil, M Madhu, O Ajiboye, CR Simons-Linares, WE Trick, and V Kotwal, 2019a, Association between cannabis use and complications related to ulcerative colitis in hospitalized patients: A propensity matched retrospective cohort study, *Medicine (Baltimore)*, 98(32):e16551, <https://www.ncbi.nlm.nih.gov/pubmed/31393356>.

Mbachi, C, B Attar, Y Wang, I Paintsil, B Mba, S Fugar, R Agrawal, RC Simons-Linares, P Jaiswal, W Trick, and V Kotwal, 2019b, Association Between Cannabis Use and Complications Related to Crohn's Disease: A Retrospective Cohort Study, *Dig Dis Sci*, 64(10):2939-2944, <https://www.ncbi.nlm.nih.gov/pubmed/30825109>.

McDonagh, MS, BJ Morasco, J Wagner, AY Ahmed, R Fu, D Kansagara, and R Chou, 2022, Cannabis-Based Products for Chronic Pain : A Systematic Review, *Ann Intern Med*, 175(8):1143-1153, <https://www.ncbi.nlm.nih.gov/pubmed/35667066>.

Meuth, SG, T Henze, U Essner, C Trompke, and C Vila Silvan, 2020, Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial, *Int J Neurosci*, 130(12):1199-1205, <https://www.ncbi.nlm.nih.gov/pubmed/32065006>.

Murkar, A, T Kendzerska, J Shlik, L Quilty, M Saad, and R Robillard, 2022, Increased cannabis intake during the COVID-19 pandemic is associated with worsening of depression symptoms in people with PTSD, *BMC Psychiatry*, 22(1):554, <https://www.ncbi.nlm.nih.gov/pubmed/35978287>.

Naftali, T, L Bar-Lev Schleider, S Almog, D Meiri, and FM Konikoff, 2021a, Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial, *J Crohns Colitis*, 15(11):1799-1806, <https://www.ncbi.nlm.nih.gov/pubmed/33858011>.

Naftali, T, L Bar-Lev Schleider, I Dotan, EP Lansky, F Sklerovsky Benjaminov, and FM Konikoff, 2013, Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study, *Clin Gastroenterol Hepatol*, 11(10):1276-1280 e1271, <https://www.ncbi.nlm.nih.gov/pubmed/23648372>.

Naftali, T, L Bar-Lev Schleider, F Scklerovsky Benjaminov, FM Konikoff, ST Matalon, and Y Ringel, 2021b, Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial, *PLoS One*, 16(2):e0246871, <https://www.ncbi.nlm.nih.gov/pubmed/33571293>.

Ney, LJ, A Matthews, R Bruno, and KL Felmingham, 2019, Cannabinoid interventions for PTSD: Where to next?, *Prog Neuropsychopharmacol Biol Psychiatry*, 93:124-140, <https://www.ncbi.nlm.nih.gov/pubmed/30946942>.

Notcutt, W, M Price, R Miller, S Newport, C Phillips, S Simmons, and C Sansom, 2004, Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies, *Anaesthesia*, 59(5):440-452, <https://www.ncbi.nlm.nih.gov/pubmed/15096238>.

Nurmikko, TJ, MG Serpell, B Hoggart, PJ Toomey, BJ Morlion, and D Haines, 2007, Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial, *Pain*, 133(1-3):210-220, <https://www.ncbi.nlm.nih.gov/pubmed/17997224>.

Patel, S, MN Hill, JF Cheer, CT Wotjak, and A Holmes, 2017, The endocannabinoid system as a target for novel anxiolytic drugs, *Neurosci Biobehav Rev*, 76(Pt A):56-66, <https://www.ncbi.nlm.nih.gov/pubmed/28434588>.

Pawasarat, IM, EM Schultz, JC Frisby, S Mehta, MA Angelo, SS Hardy, and TWB Kim, 2020, The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain, *J Palliat Med*, 23(6):809-816, <https://www.ncbi.nlm.nih.gov/pubmed/32101075>.

Petersen, M, K Koller, C Straley, and E Reed, 2021, Effect of cannabis use on PTSD treatment outcomes in veterans, *Ment Health Clin*, 11(4):238-242, <https://www.ncbi.nlm.nih.gov/pubmed/34316419>.

Portenoy, RK, ED Ganae-Motan, S Allende, R Yanagihara, L Shaiova, S Weinstein, R McQuade, S Wright, and MT Fallon, 2012, Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial, *J Pain*, 13(5):438-449, <https://www.ncbi.nlm.nih.gov/pubmed/22483680>.

Ruglass, LM, A Shevorykin, V Radoncic, KM Smith, PH Smith, IR Galatzer-Levy, S Papini, and DA Hien, 2017, Impact of Cannabis Use on Treatment Outcomes among Adults Receiving Cognitive-Behavioral Treatment for PTSD and Substance Use Disorders, *J Clin Med*, 6(2), <https://www.ncbi.nlm.nih.gov/pubmed/28178207>.

Selvarajah, D, R Gandhi, CJ Emery, and S Tesfaye, 2010, Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic

neuropathy: depression is a major confounding factor, *Diabetes Care*, 33(1):128-130, <https://www.ncbi.nlm.nih.gov/pubmed/19808912>.

Sharma, V, L Laubach, JW Krumme, and J Satpathy, 2022, Cannabis Use Among Lower-Extremity Arthroplasty Patients Does Not Lead to Worse Postoperative Outcomes, *Cureus*, 14(11):e31964, <https://www.ncbi.nlm.nih.gov/pubmed/36582568>.

Shishko, I, R Oliveira, TA Moore, and K Almeida, 2018, A review of medical marijuana for the treatment of posttraumatic stress disorder: Real symptom re-leaf or just high hopes?, *Ment Health Clin*, 8(2):86-94, <https://www.ncbi.nlm.nih.gov/pubmed/29955551>.

Soliman, N, S Haroutounian, AG Hohmann, E Krane, J Liao, M Macleod, D Segelcke, C Sena, J Thomas, J Vollert, K Wever, H Alaverdyan, A Barakat, T Barthlow, ALH Bozer, A Davidson, M Diaz-delCastillo, A Dolgorukova, MI Ferdousi, C Healy, S Hong, M Hopkins, A James, HB Leake, NM Malewicz, M Mansfield, AK Mardon, D Mattimoe, DP McLoone, G Noes-Holt, EM Pogatzki-Zahn, E Power, B Pradier, E Romanos-Sirakis, A Segelcke, R Vinagre, JA Yanes, J Zhang, XY Zhang, DP Finn, and ASC Rice, 2021, Systematic review and meta-analysis of cannabinoids, cannabis-based medicines, and endocannabinoid system modulators tested for antinociceptive effects in animal models of injury-related or pathological persistent pain, *Pain*, 162(Suppl 1):S26-S44, <https://www.ncbi.nlm.nih.gov/pubmed/33729209>.

Strasser, F, D Luftner, K Possinger, G Ernst, T Ruhstaller, W Meissner, YD Ko, M Schnelle, M Reif, and T Cerny, 2006, Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabis-in-cachexia-study-group, *Journal of Clinical Oncology*, 24(21):3394-3400, <https://pubmed.ncbi.nlm.nih.gov/16849753/>.

van Amerongen, G, K Kanhai, AC Baakman, J Heuberger, E Klaassen, TL Beumer, RLM Strijers, J Killestein, J van Gerven, A Cohen, and GJ Groeneveld, 2018, Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Delta9-tetrahydrocannabinol in Patients With Progressive Multiple Sclerosis, *Clin Ther*, 40(9):1467-1482, <https://www.ncbi.nlm.nih.gov/pubmed/28189366>.

van de Donk, T, M Niesters, MA Kowal, E Olofsen, A Dahan, and M van Velzen, 2019, An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia, *Pain*, 160(4):860-869, <https://www.ncbi.nlm.nih.gov/pubmed/30585986>.

Wallace, MS, TD Marcotte, JH Atkinson, HT Padovano, and M Bonn-Miller, 2020, A Secondary Analysis from a Randomized Trial on the Effect of Plasma Tetrahydrocannabinol Levels on Pain Reduction in Painful Diabetic Peripheral Neuropathy, *J Pain*, 21(11-12):1175-1186, <https://www.ncbi.nlm.nih.gov/pubmed/32565122>.

Wallace, MS, TD Marcotte, A Umlauf, B Gouaux, and JH Atkinson, 2015, Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy, *J Pain*, 16(7):616-627, <https://www.ncbi.nlm.nih.gov/pubmed/25843054>.

Ware, MA, T Wang, S Shapiro, JP Collet, and Cs team, 2015, Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS), *J Pain*, 16(12):1233-1242, <https://www.ncbi.nlm.nih.gov/pubmed/26385201>.

Ware, MA, T Wang, S Shapiro, A Robinson, T Ducruet, T Huynh, A Gamsa, GJ Bennett, and JP Collet, 2010, Smoked cannabis for chronic neuropathic pain: a randomized controlled trial, *CMAJ*, 182(14):E694-701, <https://www.ncbi.nlm.nih.gov/pubmed/20805210>.

Weizman, L, L Dayan, S Brill, H Nahman-Averbuch, T Hendler, G Jacob, and H Sharon, 2018, Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity, *Neurology*, 91(14):e1285-e1294, <https://www.ncbi.nlm.nih.gov/pubmed/30185448>.

Wilkinson, ST, E Stefanovics, and RA Rosenheck, 2015, Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder, *J Clin Psychiatry*, 76(9):1174-1180, <https://www.ncbi.nlm.nih.gov/pubmed/26455669>.

Wilsey, B, T Marcotte, R Deutsch, B Gouaux, S Sakai, and H Donaghe, 2013, Low-dose vaporized cannabis significantly improves neuropathic pain, *J Pain*, 14(2):136-148, <https://www.ncbi.nlm.nih.gov/pubmed/23237736>.

Wilsey, B, T Marcotte, A Tsodikov, J Millman, H Bentley, B Gouaux, and S Fishman, 2008, A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain, *J Pain*, 9(6):506-521, <https://www.ncbi.nlm.nih.gov/pubmed/18403272>.

Wilsey, B, TD Marcotte, R Deutsch, H Zhao, H Prasad, and A Phan, 2016a, An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease, *J Pain*, 17(9):982-1000, <https://www.ncbi.nlm.nih.gov/pubmed/27286745>.

Wilsey, BL, R Deutsch, E Samara, TD Marcotte, AJ Barnes, MA Huestis, and D Le, 2016b, A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis, *J Pain Res*, 9:587-598, <https://www.ncbi.nlm.nih.gov/pubmed/27621666>.

Wilson, JD, LH Pecker, S Lanzkron, SM Bediako, D Han, and MC Beach, 2020, Marijuana use and health behaviors in a US clinic sample of patients with sickle cell disease, *PLoS One*, 15(7):e0235192, <https://www.ncbi.nlm.nih.gov/pubmed/32663844>.

Worrest, T, CC Malibiran, J Welshans, E Dewey, and F Husain, 2022, Marijuana use does not affect weight loss or complication rate after bariatric surgery, *Surg Endosc*, 36(9):6931-6936, <https://www.ncbi.nlm.nih.gov/pubmed/35024935>.

Zajicek, J, P Fox, H Sanders, D Wright, J Vickery, A Nunn, A Thompson, and UMR Group, 2003, Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial, *Lancet*, 362(9395):1517-1526, <https://www.ncbi.nlm.nih.gov/pubmed/14615106>.

Zajicek, JP, JC Hobart, A Slade, D Barnes, PG Mattison, and MR Group, 2012, Multiple sclerosis and extract of cannabis: results of the MUSEC trial, *J Neurol Neurosurg Psychiatry*, 83(11):1125-1132, <https://www.ncbi.nlm.nih.gov/pubmed/22791906>.

Zhang, H, M Xie, SD Archibald, BS Jackson, and MK Gupta, 2018, Association of Marijuana Use With Psychosocial and Quality of Life Outcomes Among Patients With Head and Neck Cancer, *JAMA Otolaryngol Head Neck Surg*, 144(11):1017-1022, <https://www.ncbi.nlm.nih.gov/pubmed/30073295>.

Zubcevic, K, M Petersen, FW Bach, A Heinesen, TP Enggaard, TP Almdal, JV Holbech, L Vase, TS Jensen, CS Hansen, NB Finnerup, and SH Sindrup, 2023, Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment, *European Journal of Pain*, 27(4):492-506, <https://pubmed.ncbi.nlm.nih.gov/36571471/>.

Zylla, DM, J Eklund, G Gilmore, A Gavenda, J Guggisberg, G VazquezBenitez, PA Pawloski, T Arneson, S Richter, AK Birnbaum, S Dahmer, M Tracy, and A Dudek, 2021, A randomized trial of medical cannabis in patients with stage IV cancers to assess feasibility, dose requirements, impact on pain and opioid use, safety, and overall patient satisfaction, *Support Care Cancer*, 29(12):7471-7478, <https://www.ncbi.nlm.nih.gov/pubmed/34085149>.