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THE MEDICINE OF CANNABIS:

AN OVERVIEW FOR MEDICAL PROFESSIONALS AND POLICYMAKERS

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INTRODUCTION & OBJECTIVES

In 2019, a Pew Research Poll found that over 90% of Americans support legalizing medical cannabis, while an even more recent Gallup poll found that 68% also support legalizing cannabis for recreational use.[1] [2] Most states have now legalized some form of cannabis use, allowing the U.S. cannabis market to grow substantially. The 2020 cannabis industry was estimated at 20 billion USD, with projections that the industry may exceed 40 billion USD by 2024.[3]

As cannabis use expands in the U.S., issues that require the guidance of scientists and clinicians are rapidly arising. Patients are looking to their medical providers for information on cannabis safety, potential for interactions with pharmaceuticals, and therapeutic applications. However, the existing legal environment significantly hinders the ability of clinicians to engage with cannabis research or offer clear guidance. The U.S. federal government continues to classify cannabis as a Schedule I Controlled Substance, by definition meaning it has no accepted medical use and is unsafe to use even under medical supervision.[4] This position cripples the ability of clinicians to advise patients or to influence the burgeoning cannabis industry.

Scientific and medical cannabis research in the U.S. lags behind other nations. While the past decades have witnessed exponential growth of compelling research on cannabis safety and therapeutics, most of it comes from international sources in Europe and Israel, as federal prohibition in this country obstructs open scientific investigation of cannabis. Without clinical guidance or a coherent regulatory framework, the U.S. cannabis industry is failing to provide consumers and medical patients with much-needed guidance on appropriate use and crucial guarantees of product safety. In order to develop a regulated cannabis industry founded on scientific research, significant shifts in U.S. cannabis policy are needed, particularly at the federal level.

The objective of this white paper is to provide medical professionals and policymakers with an up-to-date, science-based perspective on the medicine of cannabis in the United States. It includes input from medical doctors, researchers, veterinarians, and policy experts, all committed to the development of a cannabis industry founded on scientific research, patient safety, and equitable access to safe products and clinical oversight. This paper highlights the obstacles that currently hinder scientific research and concludes with succinct recommendations on policy changes that would reduce these obstacles and promote evidence-based therapeutic use of cannabis. (Page 18)

Without clinical guidance or a coherent regulatory framework, the U.S. cannabis industry is failing to provide consumers and medical patients with much-needed guidance on appropriate use and crucial guarantees of product safety.

1 Andrew Daniller, *Two-thirds of Americans support marijuana legalization*, PEW RESEARCH CENTER (Nov. 14, 2019), https://www.pewresearch.org/fact-tank/2019/11/14/americans-support-marijuana-legalization/.

2 Megan Brenan, *Support for Legal Marijuana Inches Up to New High of 68%,* GALLUP (Nov. 9, 2020), https://news.gallup.com/poll/323582/support-legal-marijuana-inches-new-high.aspx.

3 Marijuana Business Daily, ANNUAL MARIJUANA BUSINESS FACT BOOK (Kevin Huhn ed., 8th ed. 2020).

4 *Drug Scheduling*, DEA, https://www.dea.gov/drug-scheduling.

A BRIEF HISTORY OF MEDICAL CANNABIS

The federal classification of cannabis as a narcotic drug has long stigmatized it and tended to obscure the history of cannabis as a widely respected and clinically utilized medicine. The Cannabis plant has been cultivated throughout recorded history for industrial and medicinal use, but what may be even more surprising to readers today is that cannabis was once a popular and accepted medicine in the modern United States. It took decades of anti-cannabis activism by the federal government—first by the Federal Bureau of Narcotics beginning in the late 1920s, and later by the Nixon administration—to change the mainstream opinion within the medical community that cannabis was a relatively harmless substance with numerous therapeutic applications.

According to archeological evidence, cannabis extracts were utilized as anesthetics as early as 400 BC.[5] Hemp came to the United States in the 16th century as a commercial crop in the British colonies, and by the mid-1800s, medicinal preparations of cannabis were widely sold out of pharmacies and doctors' offices for pain relief and a variety of other ailments. Cannabis first appeared in the 3rd edition of the United States Pharmacopeia in 1851, where it was indicated for medical conditions including opiate addiction, pain, and leprosy.[6]

Federal restrictions on cannabis began with the 1937 Marihuana Tax Act, which aimed to curtail cannabis use with a prohibitive tax under the advice of Henry Anslinger, first director of the Federal Bureau of Narcotics.[7] The American Medical Association (AMA) opposed the passage of the Marihuana Tax Act, which imposed upon physicians and pharmacists' abilityto prescribe and sell widely-utilized medicines containing cannabis. In a 1937 statement to Congress, the AMA's Dr. William C. Woodward condemned the lack of competent evidence that cannabis was a dangerous narcotic as well as the fact that the Marihuana Tax Act foreclosed future scientific research on its medicinal use.[8]

> ***According to archeological evidence, cannabis extracts were utilized as anesthetics as early as 400 BC.[5]***

The Controlled Substances Act of 1970 made cannabis possession and use federally illegal and classified it in the same category of risk as heroin.[9] In order to justify the classification of cannabis as a narcotic, President Nixon appointed a special counsel of MDs, lawyers, and legislators called the Shafer Commission to produce a report on cannabis abuse and its social impacts. After one year of investigation, however, the Shafer Commission instead published a report called "Marihuana: A Signal of Misunderstanding," which argued that cannabis should not be classified as a narcotic at all, that it did not pose a widespread danger to society, and that its purported therapeutic qualities should be subjected to scientific inquiry. Ignoring the report, the Nixon administration kept cannabis on Schedule I.[10] Due to this classification, studies on cannabis can only be conducted with a Drug Enforcement Agency (DEA) license and approval from the Food and Drug Administration (FDA).[11] These regulatory measures make it impracticable for U.S. researchers to study cannabis with sufficient scientific scrutiny.

While research within the U.S. stagnated, scientific investigation of cannabis advanced in other countries. In 1964, Dr. Raphael

5 Joe Zlas et al., *Early medical use of cannabis*, 363 NATURE 215 (1993).

6 Martin A. Lee, *Smoke Signals: A Social History of Marijuana – Medical, Recreational, and Scientific* (2012).

7 *Taxation of Marihuana: Hearing on H.R. 6385 Before the H. Comm. on Ways and Means,* 75th Cong. (1937) (statement of Henry Anslinger, Commissioner of Narcotics, Dept. of Treasury).

8 *Taxation of Marihuana: Hearing on H.R. 6385 Before the H. Comm. on Ways and Means,* 75th Cong. (1937) (statement of Dr. William C. Woodward, Legislative Counsel, American Medical Ass'n.).

9 *The Controlled Substances Act,* DEA, https://www.dea.gov/controlled-substances-act.

10 Gabriel G. Nahas & Albert Greenwood, *The first report of the National Commission on marihuana (1972): signal of misunderstanding or exercise in ambiguity,* BULLETIN OF THE N.Y. ACAD. MED., Jan. 1974, at 55-75.

11 Alice Mead, L*egal and Regulatory Issues Governing Cannabis and Cannabis-Derived Products in the United States,* FRONTIERS IN PLANT SCI. (Jun. 14, 2019), https://www.frontiersin.org/articles/10.3389/fpls.2019.00697/full.

Mechoulam of the Hebrew University in Jerusalem identified and isolated the major psychoactive ingredient in cannabis, delta-9-tetrahydrocannabinol (THC). Dr. Mechoulam called the Cannabis plant a "medicinal treasure trove" based on its production of hundreds of medicinally-interesting molecules.[12] His work sparked a research movement that led to the discovery of the endocannabinoid system (ECS) in the 1980s, a medical discovery with broad implications in health and disease.[13] (The ECS is discussed in greater detail in the following section.)

In 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) published a comprehensive review of existing scientific literature on the medicinal effects of cannabinoids, one of the main types of molecules produced by the cannabis plant.[14] In a watershed moment for American cannabis research, the review found that there is "conclusive or substantial evidence" that cannabinoids are effective in the treatment of chronic pain, nausea and vomiting, and for improving multiple sclerosis symptoms in humans. The NASEM also cited "moderate evidence" for a variety of other medical conditions in which cannabis or cannabis-derived molecules may have a positive impact.

In 2018, the Agriculture Improvement Act (Farm Bill) legalized industrial hemp, which is defined as Cannabis sativa plants that contain no more than 0.3% THC by dry weight at time of harvest. This legislation finally allowed limited industrial and scientific investment in hemp, and consequently paved the way for products containing CBD (cannabidiol, a non-intoxicating compound found in cannabis) to become widely available to consumers.[15]

As anecdotal and scientific evidence accumulates, patients and medical providers are increasingly interested in therapeutic uses of cannabis. A 2019 survey of 2,130 veterinarians in the US revealed that 56% of participants had clinical experience with cannabis-derived products in dogs with reports of positive outcomes in conditions such as acute pain, chronic pain, anxiety, motion sickness, seizures, and noise phobia.[16] A 2018 survey of medical professionals conducted by Medscape also found that 67% of physicians and 82% of psychologists were in favor of legalizing medical marijuana.[17]

> *In a watershed moment for American cannabis research, the review found that there is "conclusive or substantial evidence" that cannabinoids are effective in the treatment of chronic pain, nausea and vomiting, and for improving multiple sclerosis symptoms in humans.*

12 Raphael Mechoulam, *Plant cannabinoids: a neglected pharmacological treasure trove,* 146 British Journal of Pharmacology 913-15 (2005).

13 W. A. Devane et al, *Determination and characterization of a cannabinoid reception in rat brain,* 34 Molecular Pharmacology 605-13 (1988).

14 National Academies of Sciences, Engineering, and Medicine, The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017).

15 H.R. 2, 115th Cong. (2018) (enacted).

16 Lori Kogan et al., *US Veterinarians' Knowledge, Experience, and Perception Regarding the Use of Cannabidiol for Canine Medical Conditions,* Frontiers in Veterinary Sci (Jan. 10, 2019), https://www.frontiersin.org/articles/10.3389/fvets.2018.00338/full.

17 Marcia Frellick, *Medical, Recreational Marijuana Should Be Legal, Most Clinicians Say,* Medscape (Sep 12, 2018), https://www.medscape.com/viewarticle/901761.

THE IMPORTANCE OF THE ENDOCANNABINOID SYSTEM (ECS) IN HEALTH

The Endocannabinoid System (ECS) is a biological regulatory system responsible for maintaining homeostasis—or equilibrium—throughout the body. Sleep, memory, appetite, stress response, and immunity are some of the essential functions that the ECS plays a role in modulating.[18]

The ECS functions through the interaction of molecules called endocannabinoids with special protein structures called cannabinoid receptors.[19] One simple analogy is that cannabinoid receptors function like a lock, while the endocannabinoids that bind to these receptors function like a key. This exchange acts as a mechanism of complex inter-cellular communication that regulates numerous physiological responses. Cannabinoid receptors are found throughout the body and appear to play an extremely important role in physiology. For example, mice in which the ECS has been genetically altered display many adverse effects including a disruption in pain sensitivity, increased depressive behaviors, and abnormal immune function.[20] [21]

While a thorough understanding of the ECS is still emerging, its dysfunction has been implicated in numerous medical conditions in humans such as migraine, fibromyalgia, irritable bowel syndrome, and depression.[22] [23] One example of a disease condition that may result from the disruption of ECS balance is the seizure disorder, epilepsy. Seizures occur when neurons (brain cells) become overexcited and do not receive appropriate regulatory signals. The endocannabinoid system is responsible for a regulatory process that calms the overexcitation.[24] This regulatory input from the ECS can be compared to turning down the temperature on a thermostat when it gets too hot.

Certain molecules from outside the body, including many of those produced by cannabis plants, can also interact with the ECS due to their chemical similarity to endocannabinoids. The discovery of the ECS was ground-breaking for revealing that our bodies produce molecules similar to those found in cannabis plants. This relationship begins to explain, for instance, how cannabis stimulates appetite and sleep, since these are two functions known to be influenced by the endocannabinoid system. As potential modulators of the ECS, cannabinoids hold exceptional promise as novel treatments for a variety of medical conditions. Despite the apparent importance of the ECS in health and disease, most clinicians are poorly educated on its function. It is essential that clinicians are educated on ECS function and that research continues to explore the physiological effects of all medical modalities, including cannabis, on the ECS.

> ***The endocannabinoid system is responsible for a regulatory process that calms the overexcitation.[24] This regulatory input from the ECS can be compared to turning down the temperature on a thermostat when it gets too hot.***

18 John M. McPartland et al., *Evolutionary origins of the endocannabinoid system,* Gene, Mar. 2006, at 64-74.

19 Vicenzo Di Marzo & Fabiana Piscitelli, *The Endocannabinoid System and its Modulation by Phytocannabinoids,* 12 Neurotherapeutics 692-98 (2015).

20 O. Valverde et al., *Analysis of the endocannabinoid system by using CB1 cannabinoid receptor knockout mice,* 168 Handbook of Experimental Pharmacology 117-45 (2005).

21 Anna Maria Malfitano et al., *What we know and do not know about the cannabinoid receptor 2 (CB2),* 26 Seminars in Immunology 369-79 (2014).

22 Ethan B. Russo, *Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?,* 25 Neuro Endocrinology Letters 31-39 (2004).

23 M. N. Hill & B. B. Gorzalka, *Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression?,* 16 Behavioural Pharmacology 333-52 (2005).

24 Keith A. Kwan Cheung et al., *The Interplay between the Endocannabinoid System, Epilepsy and Cannabinoids,* International Journal of Molecular Sciences, Dec. 2019.

THE COMPLEX NATURE OF THE CANNABIS PLANT

Over the past 40 years of cannabis research, much of the focus has been on two molecules produced by most cannabis plants in high concentrations, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). However, cannabis contains over 500 pharmacologically active constituents. Unlike most pharmaceutical medications that are composed of a single molecule or a single "active ingredient," the cannabis plant produces hundreds of biologically-active chemicals. Unique genetic varieties (also known as chemovars) of the *Cannabis sativa* plant contain differing concentrations and ratios of these compounds. This variability and complexity contribute to a wide range of possible therapeutic actions, while also making cannabis significantly more complex to study than single-agent pharmaceuticals.

The therapeutic compounds present in cannabis fall into three main categories: cannabinoids, terpenes, and flavonoids **(see Figure 1)**. Although a full exploration of the medicinal value of these compounds is beyond the scope of this paper, a short summary of their potential therapeutic value is provided below.

Phytocannabinoids

Phytocannabinoids are cannabinoids produced by plants. They are chemically similar to the endocannabinoids produced in the bodies of humans and other mammals. Consequently, these molecules are able to act upon a patient's endocannabinoid system and potentially modulate important homeostatic functions. The best-known phytocannabinoid is delta-9-tetrahydrocannabinol (THC). This molecule's action within the nervous system is responsible for the psychotropic effects of cannabis, but it also has numerous therapeutic effects including pain relief, nausea suppression, appetite stimulation, anti-spasticity, neuroprotection, and anti-inflammatory properties.[25]

The other major cannabinoid produced by the cannabis plant is cannabidiol (CBD), which was discovered in 1940 by American chemist Roger Adams. Research has demonstrated numerous potential medical benefits of CBD, including anti-inflammatory, neuroprotective, anti-anxiety, antipsychotic, anti-nausea, and anti-convulsive effects, as well as potential anti-cancer benefits.[26][27][28][29]

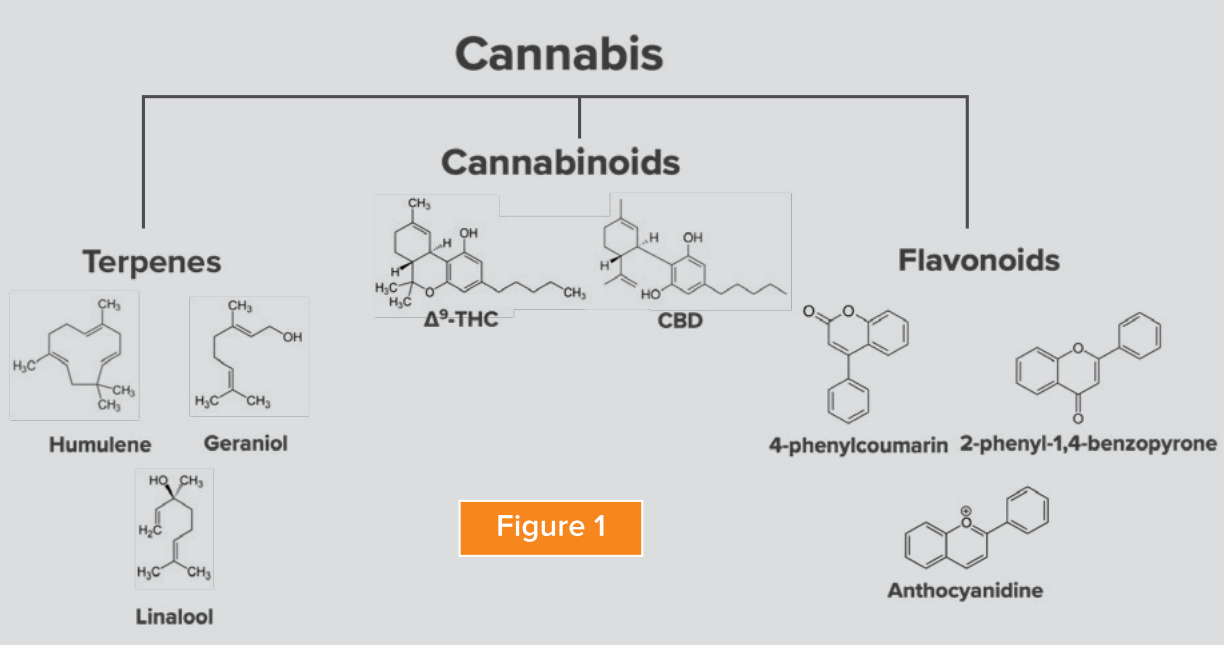


Figure 1

25 National Academies of Sciences, Engineering, and Medicine, THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH (2017).

26 Joseph Maroon & Jeff Bost, *Review of the neurological benefits of phytocannabinoids,* SURGICAL NEUROLOGY INTERNATIONAL (Apr. 26, 2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938896/pdf/SNI-9-91.pdf.

27 Linda A. Parker et al., *Regulation of nausea and vomiting by cannabinoids,* 163 BRITISH JOURNAL OF PHARMACOLOGY 1411-22 (2011).

28 Barbara Dariš et al., *Cannabinoids in cancer treatment: Therapeutic potential and legislation,* BOSNIAN JOURNAL OF BASIC MEDICAL SCIENCES, Feb. 2019, at 14-23.

29 P. Consroe & A. Wolkin, *Cannabidiol--antiepileptic drug comparisons and interactions in experimentally induced seizures in rats,* 201 JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 26-32 (1977).

CBD is of particular clinical interest as it is non-intoxicating and has an excellent safety profile.[30] [31] In 2018, the FDA approved a plant-derived formulation of purified CBD (Epidiolex) for use in treating seizures associated with two rare forms of epilepsy.[32] Epidiolex has also demonstrated potential in early clinical studies in the treatment of schizophrenia.[33]

CBD and THC modulate each other's effects in the human body. In practice, CBD can improve tolerability of THC by reducing psychoactivity and lessening potential negative side effects such as rapid heart rate, sedation, and anxiety.[34] The drug Sativex (nabiximols), which contains equal amounts of THC and CBD and lower concentrations of other molecules found in cannabis, is approved for reducing spasticity in patients suffering from multiple sclerosis in 27 countries, including Canada and much of Europe, but is not approved for prescription in the United States.[35]

Other, so-called "minor" cannabinoids have not been as thoroughly studied as THC and CBD, but early data on their pharmacological actions suggests promising areas for future research. One such cannabinoid, cannabigerol (CBG)—which, like CBD, is non-intoxicating—has garnered significant medical interest due to early lab studies demonstrating antibacterial and anti-cancer effects. CBG also shows anti-inflammatory properties that suggest potential use in the treatment of inflammatory bowel disease and neurological disorders such as multiple sclerosis and Parkinson's disease.[36] [37] [38]

Cannabichromene (CBC) has both antibiotic and antifungal properties and demonstrates the ability to reduce THC impairment in mice.[39] This compound may have therapeutic potential in cancer treatment and as an antidepressant.[40] [41] CBC appears to be linked to pain perception mechanisms, and further research may reveal important information about pain control and offer novel therapeutic options.[42]

Terpenes & Flavonoids

Terpenes and flavonoids are two other types of molecules that comprise the cannabis plant. Terpenes are found throughout the plant kingdom and are responsible for the aroma of many plants, including the characteristically pungent odors of cannabis. More than 200 terpenes have been identified from various Cannabis sativa chemovars, with each chemovar producing a unique terpene profile. There is a large body of preclinical research suggesting that many terpenes found in cannabis may have positive medicinal effects, such as limonene, a terpene found in many plants including citrus fruits, which has been shown to influence mood and immune function.[43] [44]

Flavonoids are compounds that are best-known for providing color to plants and fruits. Animal studies have documented antioxidant, anti-inflammatory, neuroprotective, and anticancer benefits of flavonoids.[45] Twenty flavonoids have been identified in cannabis, including three that are unique to the plant

30 Kerstin Iffland & Franjo Grotenhermen, *An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies,* 2 Cannabis and Cannabinoid Research 139-54 (2017).

31 Cannabidiol (CBD) Pre-Review Report Agenda Item 5.2, WORLD HEALTH ORGANIZATION [WHO], 39th ECDD Meeting (Nov. 2017), https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf.

32 Christopher S. Pauli et al., *Cannabidiol Drugs Clinical Trial Outcomes and Adverse Effects,* Frontiers in Pharmacology (Feb. 25, 2020), https://www.frontiersin.org/articles/10.3389/fphar.2020.00063/full.

33 F. M. Leweke et al., *Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia,* Translational Psychiatry, Mar. 2012, at e94.

34 Hery Chung et al., *Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An* In Silico *study,* 14 PLoS One e0220025 (2019).

35 David J. Rog et al., *Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial,* 29 Clinical Therapeutics 2068-69 (2007).

36 Rahul Nachnani et al., *The Pharmacological Case for Cannabigerol,* 376 Journal of Pharmacology and Experimental Therapeutics 204-12 (2021).

37 Francesca Borrelli et al., *Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid,* 35 Carcinogenesis 2787-97 (2014).

38 Ning Qin et al., TRPV2 *Is Activated by Cannabidiol and Mediates CGRP Release in Cultured Rat Dorsal Root Ganglion Neurons,* 28 Journal of Neuroscience 6231-38 (2008).

39 Giovanni Appendino et al., *Antibacterial cannabinoids from* Cannabis sativa: *a structure-activity study,* 71 Journal of Natural Products 1427-30 (2008).

40 Angelo A. Izzo et al., *Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice,* 166 British Journal of Pharmacology 1444-60 (2012).

41 Abir T. El-Alfy et al., *Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L,* 95 Pharmacology, Biochemistry, and Behavior 434-42 (2010).

42 Ethan B. Russo, *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects,* 163 British Journal of Pharmacology 1344-64 (2011).

43 Destinney Cox-Georgian et al., *Therapeutic and Medicinal Uses of Terpenes,* Medicinal Plants 333-359 (N. Joshee et al. eds. 2019).

44 T. Komori et al., *Effects of citrus fragrance on immune function and depressive states,* 2 Neuroimmunomodulation 174–80 (1995).

45 A. N. Panche et al., *Flavonoids: an overview,* 5 Journal of Nutritional Science e47 (2016).

(cannaflavins); these are of particular interest due to anti-inflammatory properties measured as 30 times greater than that of aspirin.[46]

Despite research-supported evidence for the pharmacological value of terpenes and flavonoids, cannabis product testing measures the presence of major cannabinoids but does not routinely include terpene or flavonoid levels. A crucial area for future study is how cannabinoids and other bioactive compounds work in different combinations to produce therapeutic effects. Current scientific research also suggests that a cannabis product's terpene profile contributes dramatically to its therapeutic effects.[47] In this regard, it is interesting to note how the cannabis industry places great emphasis on "strains" (popular term for chemovar). Cannabis users widely believe that different genetic variants produce different psychoactive experiences, and indeed that they can relieve or exacerbate different medical symptoms.[48]

Ideally, clinicians should be able to use knowledge of the complex chemistry of cannabis to guide patients toward medical products most likely to provide desired clinical effects. To this end, all cannabis products intended for medical use should be labelled with lab-verified molecular profiles including cannabinoids and terpenes. Certain educational websites intended for general adult users (e.g., leafly.com) are oddly ahead of the medical field in that their strain profiles include terpene data. However, these sites are far from scientific in their data collection, offering only approximate and anecdotal information coupled with select lab data, where available. As research on minor cannabinoids, terpenes, and the complex pharmacology of cannabis progresses, it may be possible to create targeted cannabis products for specific medical conditions or symptoms.

Synthetic Cannabinoids

The first cannabis-based drugs were approved by the FDA in the U.S. in the 1980s. Marinol (dronabinol) and Cesament (nabilone) are synthetic analogs of THC approved to treat nausea and vomiting caused by chemotherapy and to increase appetite in HIV patients. Research and anecdotal evidence over the years have indicated that Marinol is not as effective as whole-plant cannabis for relief of nausea and other symptoms.[49]

It is also relevant to note that Marinol was granted a Schedule III status by the DEA, while all-natural cannabis extracts containing more than 0.3% THC continue to be considered Schedule I. The inebriating THC is clearly the molecule of greatest concern in cannabis—and the reason used to justify its listing on Schedule I—so it is curious that the FDA approved a synthetic version of the same molecule. Marinol has shown no evidence of any diversion as a street drug.[50]

"Cannabis users widely believe that different genetic variants produce different psychoactive experiences, and indeed that they can relieve or exacerbate different medical symptoms."[48]

46 Kevin A. Rea et al., *Biosynthesis of cannflavins A and B from Cannabis sativa L,* 164 Phytochemistry 162-171 (2019).

47 *Id.*

48 Ethan B. Russo, *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects,* 163 British Journal of Pharmacology 1344-64 (2011).

49 Richard E. Musty & Rita Rossi, *Effects of Smoked Cannabis and Oral Δ9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials,* 1 Journal of Cannabis Therapeutics 29–56 (2000).

50 Sarah R. Calhoun et al., *Abuse Potential of Dronabinol (Marinol®),* 30 Journal of Psychoactive Drugs 187-96 (1998).

CLINICAL USES FOR MEDICAL CANNABIS

The success of modern medicine is dependent on sound implementation of evidence-based medicine, which is defined as "the integration of individual clinical expertise with the best available evidence from systematic research and the patient's values and expectations."[51] Evidence-based practice involves acknowledging the uncertainty that accompanies decision-making while utilizing research-based knowledge to help reduce uncertainty. Evidence-based medicine guides clinicians on which medications to select, how much medication to utilize, specific timelines for treatment therapies, and overall safety of a therapeutic intervention.

The clinical application of cannabis is no different. Given the large and growing body of evidence that cannabis is clinically useful and generally safe, clinicians must be allowed to utilize existing research, their clinical expertise, and their understanding of their patients' own goals. Effective clinical use of cannabis is characterized by intention (to relieve symptoms, i.e. to use with therapeutic intent), proper dose (a fixed amount, appropriately balanced with THC-CBD dependent on intended use), and appropriate formulation (edibles/capsules, tincture, topical, or vapor). Clinicians can bring much-needed guidance on dose and formula for patients seeking to work therapeutically with cannabis and can also help inform patient expectations.

Below follows a summary of selected clinical uses for medical cannabis. While a complete summary of potential clinical uses for cannabis exceeds the scope of this paper, the following selection highlights some of the most promising areas for future research. Given how scientific work has been stymied by the legal landscape in the U.S.—to the point that few clinical trials have been conducted with cannabis—it is uniquely necessary to consider non-traditional (anecdotal) data as well as pre-clinical and clinical evidence.

> *Medical cannabis may replace or reduce the need for opioid drugs in some patients by providing a flexible, self-administered treatment for breakthrough pain.*

Pain

Overall, the most common reason patients seek to utilize medical cannabis is to alleviate pain, including pain from arthritis, headaches/migraines, neuropathy, cancer pain, and post-surgical or post-traumatic pain.[52] [53] Many patients seeking medical cannabis have already tried, unsuccessfully, to manage chronic pain with pharmaceuticals, surgery, and other therapies. Pain may disrupt sleep and normal daytime activities, often to the detriment of the patient's quality of life. For many of these individuals, medical cannabis use provides significant relief from pain as well as improved sleep.[54] Cannabis shows particular promise in the treatment of migraine and chronic headache. Many migraine patients report that medical marijuana works better than prescription drugs for decreasing the severity and frequency of headaches. [55] [56]

Anxiety & Depression

Self-medication with cannabis for anxiety and depression is common in the general population, and cannabis extracts were once commonly prescribed for anxiety and "melancholia" in the mid-19th century.[57] Early scientific research in this area has correlated depressive disorders in humans with

51 Dean R. Hess, *What is evidence-based medicine and why should I care?,* 49 Respiratory Care 730-41 (2004).

52 Kevin F. Boehnke et al., *Qualifying Conditions Of Medical Cannabis License Holders In The United States,* 38 Health Affairs 295-302 (2019).

53 Ethan B. Russo, *Cannabinoids in the management of difficult to treat pain,* 4 Therapeutics and Clinical Risk Management 245-59 (2008).

54 G. Ferguson & M. A. Ware, *Review Article: Sleep, Pain and Cannabis,* 4 Journal of Sleep Disorders and Therapy (2015).

55 M. E. Lynch & Mark A. Ware, *Cannabinoids for the treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials,* Journal of Neuroimmune Pharmacology (Mar. 22, 2015), https://www.cannabismedicinal.com.ar/images/documentos/Investigacion/dolorcronicoreviewlynch2015.pdf.

56 J. Manzares et al., *Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes,* 4 Current Neuropharmacology 239-57 (2006).

57 Statement of Lester Grinspoon, M.D. for DEA Administrative Law Judge hearing, *History of Cannabis as a Medicine* (Aug. 16, 2005), https://maps.org/research-archive/mmj/grinspoon_history_cannabis_medicine.pdf.

endocannabinoid system dysregulation.[58] Protocols for the clinical applications of medical cannabis in mental health are only beginning to emerge. However, clinician-guided medical cannabis use has the potential to provide a safe and effective alternative to psychiatric drugs for many patients with common anxiety disorders and depression.

Standard treatments for anxiety and depression include pharmaceuticals such as antidepressants, anxiolytics, and sedatives. Patients who seek out medical cannabis for anxiety and depression often have experience with pharmaceuticals and are dissatisfied with a range of side effects they cause. With a properly supervised program, many patients may achieve better results with medical cannabis than traditional psychiatric medications.[59] A growing number of psychology professionals are proponents of medical cannabis as an adjunct or replacement for prescription pharmaceuticals.[60]

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a developmental disorder with uncertain causes, highly individualized patient needs, and no specific standardized treatment. More research is needed to explore possible connections between endocannabinoid system dysfunction and autism. There is a growing body of anecdotal evidence from families of patients with autism that cannabis may provide therapeutic effects for characteristic symptoms including hyperactivity, irritability, and compulsive behavior. The use of THC-containing cannabis products with autism patients remains controversial, particularly with patients under the age of 21. However, an Israeli study released in 2019 analyzed data from 188 ASD patients using medical cannabis and reported that over 80% of patients experienced some improvement in their condition, including 30% that experienced "significant improvement."[61] [62] [63] Several clinical trials are being conducted worldwide to study the use of CBD and cannabinoids with ASD patients, including a phase III clinical trial currently being conducted in the U.S. to determine whether CBD reduces severe behavioral problems in children with autism.[64] [65]

Dementia

While research shows that multiple factors contribute to dementia, it is known that the condition develops over periods of sustained inflammation within the brain.[66] In various types of dementia, this inflammation contributes to blocked blood flow in the brain and/or the development of disruptive plaques. Preclinical data suggests that THC and CBD can potentially protect the brain from damage by blocking the formation of plaques and tangles (protein abnormalities in the brain linked to dementia).[67] This research is bolstered by anecdotal evidence in clinical practice of dementia patients who benefit (often to an unexpected degree) from medical cannabis use, suggesting it may show promise as a treatment for both the symptoms and progression of dementia.

There is limited evidence from systematic literature reviews suggesting that medical cannabis may be effective for treating agitation, disinhibition, irritability, aberrant motor behavior, and nocturnal behavior disorders.[68] Cannabis and its components hold much promise for the potential treatment of neurodegenerative diseases and should be explored further in rigorous clinical studies.

Neoplasia

Today there is widespread support across the medical fields for cannabis as an adjunct therapy for managing side effects of cancer and chemotherapy, as well as a palliative treatment for cancer pain. The use of cannabis as a primary treatment for cancer and non-malignant neoplasia has hardly been explored in clinical research to date, but cannabinoids have demonstrated cytotoxic effects in cancer cells in a

58 B. L. Hungund et al., *Upregulation of CB1 receptors and agonist-stimulated [^{35}S]GTPS binding in the prefrontal cortex of depressed suicide victims,* 9 Molecular Psychiatry 184-90 (2004).

59 Satish Kauthuria et al., *Modulation of anxiety through blockade of anandamide hydrolysis,* 9 Nature Medicine 76-8 (2003).

60 Marcia Frellick, *Medical, Recreational Marijuana Should Be Legal, Most Clinicians Say,* Medscape (Sep 12, 2018), https://www.medscape.com/viewarticle/901761.

61 Lihi Bar-Lev Schleider et al., *Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy,* 9 Scientific Reports (2019), https://www.nature.com/articles/s41598-018-37570-y.

62 Charlotte M. Pretzsch et al., *The effect of cannabidiol (CBD) on low-frequency activity and functional connectivity in the brain of adults with and without autism spectrum disorder (ASD),* 33 Journal of Psychopharmacology 1141-48 (2019).

63 Charlotte M. Pretzsch et al., *Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder,* 44 Neuropsychopharmacology 1398-405 (2019).

64 NIH, U.S. National Library of Medicine, *Trial of Cannabidiol to Treat Severe Behavior Problems in Children With Autism,* Clinical Trials.gov (last updated August 18, 2020), https://clinicaltrials.gov/ct2/show/NCT04517799.

65 NIH, U.S. National Library of Medicine, *Cannabidiol for ASD Open Trial,* Clinical Trials.gov (last updated Jan. 14, 2021), https://www.clinicaltrials.gov/ct2/show/NCT03900923.

66 Michael T. Heneka et al., *Neuroinflammation in Alzheimer's disease,* 14 The Lancet: Neurology 388-405 (2015).

67 Georgia Watt & Tim Karl, In vivo *Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease,* Frontiers in Pharmacology (Feb. 3, 2017), https://www.frontiersin.org/articles/10.3389/fphar.2017.00020/full.

68 Kwakye Peprah & Suzanne McCormack, Medical Cannabis for the Treatment of Dementia: A Review of Clinical Effectiveness and Guidelines (Canadian Agency for Drugs and Technologies in Health ed. 2019), https://www.ncbi.nlm.nih.gov/books/NBK546328/pdf/Bookshelf_NBK546328.pdf.

wealth of in-vivo and in-vitro studies.[69] [70] [71] [72] Furthermore, many cancer patients have experimented with cannabis as a cancer treatment; there are thousands of anecdotal reports from cancer patients, including several cases observed by clinicians, in which the use of concentrated cannabis oils led to improvement or resolution of the cancer.[73] On the other hand, preliminary evidence also suggests certain subsets of cancer patients where cannabis could worsen clinical outcomes, particularly with immunotherapy treatments.[74] Early evidence for the potential value of cannabinoids in cancer therapy demands a great deal more rigorous scientific study, including clinical trials. Such research remains difficult in the U.S. under current cannabis laws.

Impact on the Opioid Crisis

Roughly 66 million Americans have clinically diagnosed chronic pain. Opioids including Fentanyl, Oxycontin, and Vicodin are commonly prescribed to treat these chronic pain conditions. The physiological dangers of opioids are well established, and more than 100 Americans die each day due to an opioid overdose.[75] There is evidence that four out of five heroin users were using prescription opioids prior to trying heroin.[76]

The opioid epidemic is a massive public health crisis that has not been adequately addressed. Medicare Part D spends 4 billion USD per year on opioid prescriptions, while the economic cost of the opioid crisis is estimated at 78 billion USD per year.[77]

Medical cannabis remains underutilized as a tool for combating addiction in patients whose struggle with drug abuse stems from chronic pain management.[78] Medical cannabis may replace or reduce the need for opioid drugs in some patients by providing a flexible, self-administered treatment for breakthrough pain. Rigorous, placebo-controlled studies (the gold standard for clinical studies) have indicated that cannabis and its components hold promise as an effective alternative treatment for pain with far fewer dangerous side effects.[79]

In support of the hypothesis that cannabis can have a positive impact on patients with opiate addictions, the use of prescription pain medications and other drugs have decreased in states that enacted medical cannabis laws.[80] In one study, patients with chronic pain voluntarily decreased opiate intake if given access to cannabis, sometimes by as much as 50%.[81] In a separate study, inhaled cannabis decreased pain further than morphine or oxycodone alone, indicating that cannabis might be used to help wean pain sufferers off of opioids.[82]

PTSD & Impact on the U.S. Veteran Population

Individuals experiencing disabilities from chronic pain and post-traumatic stress disorder (PTSD) are five-to-ten-fold higher among veterans than in the general population.[83] Upwards of 20 percent of the 2.7 million Iraq and Afghanistan War veterans

69 Thomas Powles et al., *Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway,* 105 Blood 1214-21 (2005).

70 Jane L. Armstrong et al., *Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death,* 135 Journal of Investigative Dermatology 1629-37 (2015).

71 Massimo Nabissi et al, *Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents,* 34 Carcinogenesis 48-57 (2013).

72 Anju Preet et al., *Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis,* 4 Cancer Prevention Research 65-75 (2011).

73 Y. Singh & C. Bali, *Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation,* 6 Case Reports in Oncology 585-92 (2013).

74 Gil Bar-Sela et al, *Cannabis Consumption Used by Cancer Patients during Immunotherapy Correlates with Poor Clinical Outcome, CANCERS* 12, no. 9 (August 28, 2020): 2447.

75 CDC/NCHS, *National Vital Statistics System, Mortality*. CDC WONDER, Atlanta, GA (2018).

76 Theodore J. Cicero et al., *The changing face of heroin use in the United States: a retrospective analysis of the past 50 years,* 71 JAMA Psychiatry 821-26 (2014).

77 Douglas L. Leslie et al., *The Economic Burden of the Opioid Epidemic on States,* American Journal of Managed Care (Jul. 20, 2019), https://www.ajmc.com/view/the-economic-burden-opioid-epidemic-on-states-case-of-medicaid.

78 William Notcott et al., *Initial Experiences with Medicinal Extracts of Cannabis for Chronic Pain: Results from 43 'N of 1' Studies,* 59 Anesthesia 440-52 (2004).

79 Barth Wilsey et al, *A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain,* 9 The Journal of Pain 506-21 (2008).

80 Stephen W. Patrick et al., *Implementation Of Prescription Drug Monitoring Programs Associated With Reductions In Opioid-Related Death Rates,* 35 Health Affairs 1324-32 (2016).

81 Jacob M. Vigil et al., *Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study,* 12 PLoS One e0187795 (2017).

82 D. I. Abrams et al., *Cannabinoid-opioid interaction in chronic pain,* 90 Clinical Pharmacology and Therapeutics 844-51 (2011).

83 James M. Thompson et al., *Disability correlates in Canadian Armed Forces Regular Force Veterans,* Disability and Rehabilitation (Sep. 9, 2014), https://www.tandfonline.com/doi/abs/10.3109/09638288.2014.947441.

will experience post-traumatic stress or depression,[84] and data suggests that these instances of PTSD may be higher among younger veterans.[85]

The challenges of adequately addressing the healthcare needs of our veteran population is no surprise to any health care provider. America's extensive military conflicts over the past two decades and beyond have challenged the ability of the existing health care system to appropriately address the type, extent, and severity of the continued war-related injuries. Despite demonstrations of numerous neurobiological targets for the treatment of PTSD,[86] only two medications (paroxetine and sertraline) have been approved, and both demonstrate only limited efficacy.[87] Little progress has been made in the search for effective drugs with new mechanisms of action.[88] These shortcomings have heightened interest in the use of cannabis for the treatment of PTSD.[89] Several studies have reported improvements in PTSD symptoms with the use of cannabis, [90] [91] [92] oral THC,[93] and the synthetic cannabinoid nabilone.[94] Medical cannabis has potential to be both a safe and common-sense health management option, but also a catalyst for worsening physical and mental illness in the veteran community without clinical oversight.

Cannabis use disorder (CUD) is characterized by "problematic patterns of use leading to clinically significant impairment or distress."[95] Negative outcomes often associated with CUD and excessive cannabis use include higher unemployment, increased risk of psychiatric disorders, cognitive impairment, and lower educational attainment.[96] Veterans as a population appear to be at higher risk of CUD and co-occurring mental health disorders, although negative outcomes from heavy, chronic cannabis use are a concern for all patient populations.[97] There is a serious need for greater clinical supervision of cannabis use in general, with particular emphasis on vulnerable populations including U.S. veterans. Health care providers must be able to engage with patients who are currently self-medicating with cannabis in order to guide them toward better outcomes. Changes in the legal landscape as well as cannabis education for medical providers are required to make such clinical oversight of cannabis use possible.

Safety Considerations & Clinical Cautions

Reported deaths associated directly with cannabis toxicity are extremely rare, while the annual number of deaths attributed to overdoses of prescription opiates may be as high as 63,000.[98]

84 Marshall Steele et al., *Mediation and Moderation of the Relationship Between Combat Experiences and Post-Traumatic Stress Symptoms in Active Duty Military Personnel,* 182 Military Medicine e1632-e1639 (2017).

85 Christine Ramsey et al., *Incidence of Mental Health Diagnoses in Veterans of Operations Iraqi Freedom, Enduring Freedom, and New Dawn,* 2001–2014, 107 American Journal of Public Health 329-55 (2017).

86 Behavioral Neurobiology of PTSD (Eric Vemetten et al. eds., 1st ed. 2018).

87 Andrea Cipriani et al., *Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis,* 48 Psychological Medicine 1975-84 (2018).

88 John H. Krystal et al., *It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group,* 82 Biological Psychiatry e51-e59 (2017).

89 Luke J. Ney et al., *Cannabinoid interventions for PTSD: Where to next?,* 93 Progress in Neuro-Psychopharmacology and Biological Psychiatry 124-40 (2019).

90 Torsten Passie et al., *Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence,* 4 Drug Testing and Analysis 649-59 (2012).

91 Ilya Reznik, *Post-traumatic stress disorder and medical cannabis use: a naturalistic observational study,* 22 European Neuropsychopharmacology S363-S364 (2012).

92 George R. Greer et al., *PTSD symptom reports of patients evaluated for the New Mexico medical cannabis program,* 46 Journal of Psychoactive Drugs 73-77 (2014).

93 Pablo Roitman et al., *Preliminary, Open-Label, Pilot Study of Add-On Oral Δ9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder,* 34 Clinical Drug Investigation 587-91 (2014).

94 Rakesh Jetly et al., *The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study,* 51 Psychoneuroendocrinology 585-88 (2015).

95 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) 305.20, 304.20 (American Psychiatric Association ed., 2013).

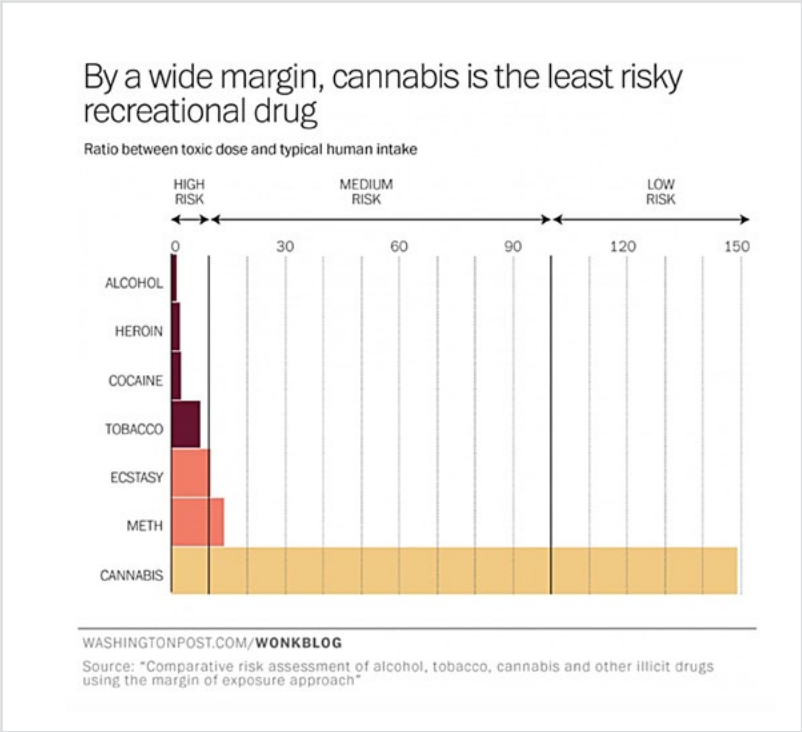
96 Brian J. Sherman & Aimee L. McRae-Clark, *Treatment of Cannabis Use Disorder: Current Science and Future Outlook,* 35 Pharmacotherapy 511-35 (2016).

97 Anthony H. Ecker et al., *Cannabis use disorder among veterans: Comorbidity and mental health treatment utilization,* 109 Journal of Substance Abuse Treatment 46-49 (2020).

98 Benno Hartung, Silke Kauferstein et. al., *Sudden unexpected death under acute influence of cannabis,* 237 Forensic Sci. Int. e11-e13 (2014).

Alcohol-related deaths total approximately 88,000 annually and the figure for tobacco is 480,000.[99] [100] A study comparing the relative risk assessment of alcohol, tobacco, cannabis, and other illicit drugs showed that cannabis, by a wide margin, is the least risky of what are considered recreational drugs **(see Figure 2).**

FIGURE 2[101]



However, despite this safety and clinical information, cannabis remains listed as a DEA Schedule I substance along with dangerous narcotics, such as heroin. In contrast, cocaine and methamphetamines are classified as Schedule II substances, while alcohol and tobacco—the dangers of which have been widely recognized by science—are not included in the drug schedule at all.

Unlike opioid receptors, which are located on brain structures responsible for essential body mechanisms such as respiration, there are no cannabinoid receptors in the respiratory centers of the brain. Thus, even with extreme overconsumption of cannabis, there is no chance of respiratory depression in any species (human or veterinary). Extreme overconsumption may result in the need for hospitalization for supportive care and monitoring, but they do not compromise important life-sustaining mechanisms, unlike many other commonly-utilized drug therapies.

In medicine there is a cost vs. benefit analysis when it comes to the use of different drugs to treat particular ailments. If the benefits of the medication outweigh the side effect profile, the medication is more widely prescribed and accepted by physicians. For example, the popular blood sugar-controlling medication Metformin has stomach and intestinal side effects that are eclipsed by the benefits of the medication for Type II diabetics. This same cost-to-benefit paradigm exists for cannabis as a medicine, and clinicians should be aware of medical conditions that deserve higher levels of clinical caution.

There are several known areas where caution should be exercised when considering medical cannabis as a therapy. Patients with a personal or familial history of schizophrenia,[102] who are pregnant or lactating,[103] who have had a recent cardiovascular event or a history of cardio-pulmonary disease, who are currently taking seizure medication or anti-coagulants,[104] or who have exhibited cannabis hyperemesis syndrome and/or a true cannabis allergy[105] should consult a clinician and carefully examine the available research to weigh both risks and benefits before adding cannabis to their treatment plan. While direct clinical evidence of the interaction of cannabis with those conditions, histories, and relevant medications is limited, there is preliminary evidence that suggests associations with negative health impacts in specific cases.

In addition, research suggests that heavy cannabis use by people whose brains are still developing may be associated with long term negative neurological and behavioral changes.[106]

99 Marissa B. Esser et al., *Deaths and Years of Potential Life Lost From Excessive Alcohol Use — United States, 2011–2015,* 69 Morbidity and Mortality Weekly Report 1429-1433 (2020), http://dx.doi.org/10.15585/mmwr.mm6939a6

100 National Institutes of Health, *National Institute on Drug Abuse,* https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-institute-drug-abuse-nida (last visited Feb. 16, 2021).

101 Dirk W. Lachenmeier & Jürgen Rehm, *Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach,* 5 Scientific Reports (Jan. 30, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4311234/.

102 Darby JE Lowe, Julia D Sasiadek et. al. *Cannabis and mental illness: a review.* 269 Eur Arch Psychiatry Clin Neurosci 107-120 (Feb 2019).

103 Hannan El Marroun, Henning Tiemeier et. al., *Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study,* 48 J Am Acad Child Adolesc Psychiatry 1173–81 (2009)

104 Stephen Sidney, *Cardiovascular consequences of marijuana use,* 42 Journal of Clinical Pharmacology 64S-70S (2002).

105 Cecilia J Sorensen, Kristen DeSanto et. al. *Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review.* 13 J MED TOXICOL 71-87 (Mar 2017).

106 Joanna Jacobus & Susan F. Tapert, *Effects of cannabis on the adolescent brain,* 20 Current Pharmaceutical Design 2186-93 (2014).

Research into the nature or outcomes of those changes is inconclusive and overall impact depends on multiple factors specific to each person. These include the amount of THC being consumed, how often it is used, the age of first use, and whether other substances (e.g., tobacco and alcohol) are used concomitantly.

While there are no absolute contraindications for the use of cannabis in non-human patients, areas of clinical caution exist similarly for veterinary practitioners, including existing cardiac conditions, existing renal disease, pregnancy or lactation, anxiety or aggressive behavioral disorders, concurrent pharmaceutical use, and physical immaturity.

The risk of toxicity from product contaminants is a pressing concern. Contaminants may result in direct toxicity for patients (human and veterinary) as well as negatively affecting clinical outcomes due to interactions with active molecules.[107] Chemical contaminants in untested cannabis vaping products were identified by the CDC as the primary cause of a highly-publicized outbreak of lung illnesses in 2019 that included 27 deaths[108]

In light of these serious safety concerns, the federal government must establish a regulatory regime that ensures universal laboratory testing of cannabis products, both to confirm the presence of desired molecules (cannabinoid, terpene, and flavonoid profiles) and the absence of contaminants including heavy metals, pesticides, and residual solvents. As clinicians and regulators work together to establish a cannabis industry with appropriate emphasis on medical applications and consumer safety, clear and consistent product labeling should be of highest priority.

Practitioners must be well versed in those clearly documented cases with negative outcomes, as much as they are in the positive ones. They should also be on the lookout for additional adverse or beneficial events and contribute to the clear documentation and publication regarding those patients that would or would not benefit from medical cannabis therapy.

> *"In medicine there is a cost vs. benefit analysis when it comes to the use of different drugs to treat particular ailments. If the benefits of the medication outweigh the side effect profile, the medication is more widely prescribed and accepted by physicians."*

107 Laura M. Dryburgh et al., *Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects,* 84 British Journal of Clinical Pharmacology 2468-76 (2018).

108 Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, *Products,* Center for Disease Control and Prevention (updated Feb. 25, 2020), https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html (last visited Feb. 12, 2021).

KEY TAKEAWAYS

> *Rescheduling to Schedule II or III, however, would not resolve conflict between federal and state cannabis laws, perpetuate confusion for clinicians, and do little to ease DEA control over scientific research. Rescheduling would also throw existing state cannabis systems into disarray at substantial cost to state governments and regulated businesses.*

There is no longer any serious debate whether numerous cannabinoids have accepted medical uses. In 2003, the United States Department of Health and Human Services was awarded a patent entitled "Cannabinoids as Antioxidants and Neuroprotectants."[109] Despite cannabis having been classified as having no medicinal use, the United States government itself has a patent on its medicinal use. Significantly, the federal government has also approved multiple drugs that contain cannabis derivatives or their synthetic equivalents (e.g., Marinol, Epidiolex), while regulatory restrictions on wide-scale cannabis research prevents many other potentially beneficial drugs from being developed.

Numerous states (thirty-six at the time of this writing), in direct conflict with federal law, have licensed medical cannabis sales and consumption. These efforts have left cannabis in a unique and unsustainable legal status. Products containing THC are sold both for general adult and medical purposes by state-licensed facilities, but they remain criminalized at the federal level. These discrepancies could, and should, be corrected immediately.

President Biden has made clear that he wants to see more research on cannabis safety and medicinal value.[110] So, as the Administration contemplates next steps, we can likely expect a shift in current policy and a recognition that research is absolutely essential and must play a central role. There are three requisite paths forward: (1) deschedule- remove cannabis from the Controlled Substances Act schedule -; (2) reschedule to Schedule II; or (3) reschedule to Schedule III. President Biden has discussed rescheduling cannabis to Schedule II or III to more easily facilitate research.[111] Rescheduling to Schedule II or III, however, would not resolve conflict between federal and state cannabis laws, perpetuate confusion for clinicians, and do little to ease DEA control over scientific research. Rescheduling would also throw existing state cannabis systems into disarray at substantial cost to state governments and regulated businesses.

From the standpoint of public health and scientific research, descheduling (legalizing) cannabis is the clear path forward. Over 22 million Americans currently use cannabis (defined as past-month use), despite the Schedule I designation and potential legal consequences, many of whom obtain it from unregulated and concerning sources.[112] As doctors, researchers, and advocates for those in our care, it is our responsibility to explore all potential therapeutic avenues with scientific scrutiny and to advocate for the advancement of medicine for the sake of our patients, both human and animal. With government resources and leadership invested in cannabis research, the U.S. could make enormous strides in cannabis science, setting new international standards where we have previously fallen far behind. Despite the stagnation of American research in the 20th century, evidence of the therapeutic value of cannabis has continued to grow. It is possible that cannabis could become one of the most important medicines available to physicians, but not without opening the door to rigorous research. The scientific and medical communities are eager to push forward, but fundamental policy changes must come first.

109 U.S. Patent No. 6,630,507 (filed Apr. 21, 1999).

110 Natalie Fertig, *Joe Biden kinda, sorta, almost endorses legalizing marijuana,* POLITICO (Feb. 6, 2020), https://www.politico.com/news/2020/02/06/joe-biden-legalize-marijuana-111642.

111 Mona Zhang, *Biden's wariness on marijuana puts another target on his back,* POLITICO (Nov. 21, 2019), https://www.politico.com/news/2019/11/21/joe-biden-marijuana-072441.

112 Center for Behavioral Health Statistics and Quality, *Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health,* SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION, 2015. p. 5. http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.

RESEARCH INITIATIVES: SCIENTIFIC & CLINICAL PRIORITIES

1. Explore the impact of the endocannabinoid system on health and disease. Investigate the effect of cannabis on the endocannabinoid system, as well as the factors that influence individualized responses to cannabis such as genetics, environment, and concurrent disease conditions.
2. Explore the extensive family of cannabis-derived molecules (including minor cannabinoids, terpenes, and flavonoids). Identify the clinical effects of these molecules when utilized individually, in combination, or in conjunction with pharmaceuticals.
3. Explore the interactions of cannabis in patients with psychiatric conditio ns and behavioral disorders.
4. Prioritize rigorous investigation (double blind, randomized, placebo-controlled studies) of existing pre-clinical and anecdotal data, including data suggesting positive clinical outcomes from cannabinoid use in cancer, palliative, and end-of-life care; chronic pain and the reduction of opioid abuse; mental and emotional health; seizures; and neurodegenerative brain diseases such as Alzheimer's and Parkinson's.

POLICY RECOMMENDATIONS

In order for these research objectives to be achieved, there must be a fundamental shift in cannabis policy in the U.S. The following actions are essential first steps for Congress and the Executive Branch in the 117th Congress:

1. Deschedule cannabis and remove DEA jurisdiction from cannabis-related research, allowing an actionable path for new clinical research.[113]
2. Establish and fund a National Institute of Cannabis Research within the National Institutes of Health (NIH) to facilitate cannabis research.
3. Support state regulators by establishing national industry guidelines and minimum safety measures that ensure safe products and equity in access to medical cannabis and clinical guidance for all patients.
4. Support graduate-level education and continuing-education resources on cannabis and the endocannabinoid system for medical professionals.
5. Allow cannabis to be recommended at the discretion of a licensed clinician.

113 Despite the DEA finally issuing a few research licenses, after many years of ignoring the applications, the DEA is law enforcement and not the appropriate agency for issuing scientific research licenses. Gurman, Sadie, *Marijuana Medical Research Growers Receive U.S. Approval,* Wall Street Journal (May 14, 2021). https://www.wsj.com/articles/marijuana-research-growers-receive-u-s-approval-11621024843

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