A PRACTITIONER'S GUIDE TO CANNABIS

WIN TURNER • JOSEPH HYDE

WILEY

A Practitioner's Guide to Cannabis

A Practitioner's Guide to Cannabis

Win Turner
Center for Behavioral Health Integration
School of Social Welfare, Stony Brook University
Montpelier, Vermont
US

Joseph Hyde
JBS International, Inc.
School of Social Welfare, Stony Brook University
North Bethesda, Maryland
US

WILEY

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.

Library of Congress Cataloging-in-Publication Data
Names: Turner, Win, author.
Title: A practitioner's guide to cannabis / Win Turner, Joseph Hyde.
Description: Hoboken, New Jersey : John Wiley & Sons, [2023] | Includes bibliographical references and index.
Identifiers: LCCN 2022047010 (print) | LCCN 2022047011 (ebook) | ISBN 9781119634218 (paperback) | ISBN 9781119634232 (pdf) | ISBN 9781119634201 (epub)
Subjects: LCSH: Cannabis--United States. | Cannabis--Health aspects--United States.
Classification: LCC HV5822.C3 T87 2023 (print) | LCC HV5822.C3 (ebook) | DDC 362.29/50973--dc23/eng/20221123
LC record available at https://lccn.loc.gov/2022047010
LC ebook record available at https://lccn.loc.gov/2022047011

Cover Image: © fizkes/Shutterstock
Cover Design: Wiley

Set in 9.5/12.5pt STIXTwoText by Integra Software Services Pvt. Ltd, Pondicherry, India

Contents

1

Introduction

Half a century ago, the United States was in the grips of a marijuana panic. It was 1969, the year George Harrison was arrested for marijuana possession and Richard Nixon, chief architect of what would soon be called the War on Drugs, entered the White House. In October of that year, *LIFE* magazine devoted a cover story to the drug debate. The cover displayed an ominous close-up of a hand clutching a shriveled blue joint. "MARIJUANA," declared the accompanying text. "At least 12 million Americans have now tried it. Are penalties too severe? Should it be legalized?" [1].

The answer, back then at least, seemed to be a resounding no. Sure, stoned flower children and drug-addled rock stars sucked up most of the media attention, but public opinion on marijuana policy more closely reflected Nixon's "silent majority" of disapproving conservatives. In 1969, Gallup surveyed Americans for the first time on whether they believed the use of marijuana should be made legal. Only 12 percent of respondents favored legalization. Although that number rose to 28 percent during the 1970s, it remained well under half of Americans, and pro-legalization sentiment entered a lull during the Reagan and Bush Sr. era.

Fifty-one years later, everything has changed. While popular opinion often shifts at a glacial pace, US public policy surrounding cannabis use has revolutionized in just a few years. In 2012, Washington and Colorado became the first two states to pass ballot initiatives legalizing recreational use of marijuana, despite the federal government's disapproval [2]. By the spring of 2018, seven more states—as well as the District of Columbia—had legalized recreational use of marijuana, and

A Practitioner's Guide to Cannabis, First Edition. Win Turner and Joseph Hyde.

29 states altogether had either decriminalized or allowed medical marijuana use [2]. That same year, Vermont legalized marijuana through the legislative process, another national first. 2018 and 2019 were both pivotal years for the legalization movement, and the momentum is unlikely to slow in the new decade. (Things have moved even faster in Canada, which legalized marijuana nationwide, ending nearly a century of prohibition, in 2018.) Concurrently, Americans no longer disapprove of the puffy cloud in overwhelming numbers. A 2018 Gallup poll found that 66 percent of US adults approve of marijuana legalization—the highest percentage since Gallup began asking the question in 1969. Much of the shift in public opinion occurred relatively fast: Support for legalization rose by a staggering 30 percent between 2005 and 2018 [3, 4].

This legal revolution has been accompanied by a subtler and less quantifiable cultural shift. Think back again to the '60s and early '70s: Pot—or "grass" —was the preferred creative lubricant of Bob Dylan and Jerry Garcia, the healing herb of Bob Marley, the necessary concession which thousands of hippie festivalgoers brought to Woodstock, the onscreen vice of Dennis Hopper and Peter Fonda in *Easy Rider* (1969). It was the subject of admiring odes like The Beatles' "Got to Get You Into My Life" and Black Sabbath's "Sweet Leaf," which famously opens with the sound of guitarist Tony Iommi coughing after a particularly strong hit from a joint [5]. For decades to come, fictitious pot-smokers of the cinema world would still be portrayed as bumbling, jobless slackers and dimwitted goofs—Cheech & Chong, for instance, or Jeff Spicoli, the stoner character portrayed by Sean Penn in *Fast Times at Ridgemont High*.

Yet, in 2022, marijuana is hardly a countercultural concern. For many users, cannabis has become as ordinary and routine as yoga, or a glass of wine with dinner. "It's Official: Weed's Not Cool Anymore," states a 2019 *Observer* headline. "The exclusive cool kids club of cannabis is over," the article declared. "Moms use it, Elon Musk uses it, Canada says most of its police can use it (off-duty, of course). The number of Baby Boomers who have used it has doubled since 2006. ... Every demographic you previously wouldn't have dared suspect of using cannabis is now experimenting with the plant" [6].

Indeed, cannabis is no longer the purview of societal outlaws and troublemaker teens. It has been normalized among virtually every demographic: An estimated 128 million Americans have tried it. People use it

to self-medicate for a wide variety of ailments, as evidenced by a 2019 Reddit thread asking users to share how cannabis impacted their health or mentality. One user wrote: "It reduces the pain and stress from my bowel disease and I definitely have less severe symptoms." Another said that cannabis gave them "better sleep, no more depression." And yet another respondent wrote: "Helps with insomnia, anxiety, PTSD, physical pains, adds pleasure to senses, strokes of creative thought, imagination. Makes me healthier" [7].

Yet, 50 years after that *LIFE* cover story, there remains much that we don't know about the plant. While it's possible that low doses of cannabis may help some people's depression, some studies also suggest that it *increases* depressive symptoms. And dosage matters enormously when it comes to cannabis: Marijuana use generally has a biphasic effect, which means that it can have one effect at low doses and the opposite effect at higher doses. For instance, a low dose can encourage sleep and reduce pain, while high dosages can induce anxiety. (One study even found that daily use of high-potency cannabis correlates with an increased risk of psychosis. An estimated one in five new cases of psychosis were linked to daily cannabis use. One in 10 were linked to use of high potency cannabis [8].)

Of concern, researchers have never comprehensively studied high-dose cannabis (much of the legal weed now available falls into that category). Unlike alcohol, it can be difficult to assess equivalent doses of smoked THC. The challenge for practitioners is that patients frequently don't verbalize reasons for changing their use or varying dosage. And in a market-driven setting, slick branding drives the conversation and dominates the perception: Consumer understanding of dosage is more heavily influenced by marketing and ad copy than reliable science. Meanwhile, researchers have cause for concern. Roughly one in six cannabis users meet the criteria of cannabis use disorder (CUD). Although rates in youth of cannabis use remain high, the Healthy Kids Colorado Survey (HKCS) results indicate no significant change in the past 30-day use of marijuana by middle and high school-aged youth between 2013 (19.7%) and 2019 (20.6%) [9].

In this dramatically shifting universe of cannabis use, old models no longer make sense and the conventional wisdom is as stale as last week's pot brownie. Health care providers and practitioners of all stripes—social workers, psychologists, alcohol and drug counselors, and care

providers—need to meet the post-legalization moment proactively with relevant and timely information instead of antiquated twentieth-century perceptions of marijuana use. In other words, it's crucial for practitioners interacting with users to have what we call "Cannabis Clinical Competencies." Experts need to understand patterns of use and disorder in today's shifting cannabis culture and must be equipped with tools to see through the proverbial smoke of misinformation and marketing.

This book aims to provide new tools for understanding patients' use, a heightened awareness of the complexities of cannabis science, and informed strategies for effective intervention. Throughout these nine chapters, we'll provide case illustrations, interview summaries with cannabis patients, intervention sample scripts, clinical algorithms, and evidence-based brief treatment for substance use disorders. We'll begin by summarizing the history of cannabis stretching back thousands of years, then delve into the chemistry of the drug and seek a thorough understanding of its medicinal and recreational uses. From there, we'll introduce the Cannabis Intervention Screener (CIS)—a new cannabis-specific screening tool that stratifies risk with important clinical utility—and suggest a guide for evidence-based treatment for cannabis use disorder. And we'll provide suggestions for how to talk to patients about cannabis use meaningfully and effectively.

The goal is to synthesize decades of swift transformation in cannabis culture with a thorough understanding of the challenges facing practitioners in the burgeoning legalization era. Cannabis has come a long way since 1969. Fifty years ago, Americans responded to cannabis with panic and policies that misunderstood addiction science and ultimately did more harm than good. Today's users—legal or otherwise—deserve a more mindful and informed approach from practitioners.

2

What is Cannabis?

The herbaceous flowering plant *Cannabis sativa* is from the family Cannabaceae, which is native to Central Asia and India. It is known by many names—*marijuana, pot, grass, weed*—and can be smoked, vaporized, and consumed orally through edible products. Cannabis contains both medicinal and psychoactive properties and in its nontoxic form, hemp, can be used to make rope, textiles, clothing, paper, and biofuel. Cannabis contains more than 100 chemical compounds, called cannabinoids; the two most commonly known are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is highly potent and primarily accounts for the psychoactive response from cannabis (e.g., euphoria, heightened sensory awareness, creativity, altered sense of time and space, enhanced appetite, increased sexual desire, drowsiness), whereas CBD is generally not psychoactive and instead is often used as an anti-inflammatory agent and analgesia.

Cannabis has a long and circuitous history of sanctioned and unsanctioned use by civilizations and societies dating back to ancient times. Understanding this history can help shed light on current attitudes toward and perspectives on cannabis use in the United States, which directly impact cannabis use behaviors. This chapter will briefly discuss the geographic and historical origins of cannabis, the recent history of its use in the United States, and ideological/sociocultural factors that account for the growing increase in its acceptance and availability in the United States (For a brief summary of the chemical and botanical properties of cannabis, see Chapter 3.)

A Practitioner's Guide to Cannabis, First Edition. Win Turner and Joseph Hyde.

The Geographical and Historical Origins of Cannabis

Cannabis has been used in one form or another since the prehistoric ages and is widely believed to have originated in the steppes of Central Asia in approximately 12,000 BCE. In early human societies, it played a role in textile manufacturing (e.g., basketry, fishing nets), medicine, food (i.e., the seeds), and as a part of shamanic rites and religious rituals [10].

Its cultivation for fibers is estimated to have started around 4000 B.C. [11]. Some of the oldest evidence of its use for psychoactive purposes comes from the excavation of a shamanic tomb in China in 2700 B.C. [12]. Ancient Chinese texts also make reference to and praise the cultivation and use of cannabis and its byproduct, hemp.

Cannabis use migrated from China to Korea and Japan around 200 B.C., largely in the form of hemp (e.g., used for rope, clothing), and into the South Asian subcontinent around 2000 B.C. to 1000 B.C. [13]. Its use flourished in India, where it was often taken for psychoactive and medicinal purposes, such as during weddings and religious celebrations (e.g., Holi). Cannabis is mentioned in the Hindu scripture the *Bhagavad-Gita* and is associated with the Hindu god Ganga (giving rise to the term *ganja*). From India, the plant migrated to Tibet and Nepal in the 7th Century, where it was used as part of Tantric practices.

Cannabis appeared in the Middle East likely between 2000 B.C. and 1400 B.C. via nomadic Indo-European traders and warriors. It then moved into Russia and Ukraine, eventually spreading into Eastern Europe around 3000 B.C. to 2000 B.C. Throughout the 5th Century, cannabis was used across Germany, Britain, Scotland, and France, generally for sails, rope, paper, clothing, and nets. From the Middle East or Europe, cannabis then diffused into Greece and Rome, where it was used medicinally, as a psychotropic, and as a source of fiber. In at least the 15th Century, it likely made its way into Eastern Africa via trade routes from Egypt and Ethiopia and spread throughout Africa largely through coastal migrant settlements. There, it was often used to treat snake bites, malaria, fever, blood poisoning, anthrax, asthma, and dysentery [11]. Cannabis later arrived in South America in the 16th Century, where it became a part of religious rituals and was provided for physical ailments like toothaches and menstrual cramps [11]. Its recreational use in South and Central America did not appear

until the 19th Century and during construction of the Panama Canal in the 20th Century [13].

The popularity of cannabis fibers among the British extended to the United States via British colonization [13]. Hemp was grown on the estates of George Washington and Thomas Jefferson, and the US Constitution was written on paper made from hemp. In 1619, the Virginia Assembly passed a law requiring all farmers to grow hemp, which was considered legal tender in Pennsylvania, Virginia, and Maryland. Domestic production decreased after the Civil War, with the advent of the cotton gin offering a cheaper alternative to hemp. Strictly recreational use likely was not introduced until much later, during the early 20th Century, as a product of Mexican immigration [14].

History of the Medicinal Use of Cannabis

As noted here, ancient civilizations, including those in Egypt and China, are known to have medicalized cannabis for disease such as fatigue, rheumatism, and malaria [10]. Numerous other societies, including those in India, the Middle East, Southeast Asia, South Africa, and South America, have documented histories of using cannabis as a medicine for a wide range of maladies, such as pain, malaria, constipation, fever, rheumatism, sleeplessness, dysentery, poor appetite, slow digestion, headache, female reproductive disorders, labor/childbirth pain, skin inflammation, depression, and cough [11, 15].

The medicalization of cannabis was greatly influenced by the work of Irish physician William Brooke O'Shaughnessy [11]. While working in India in the 1840s, O'Shaughnessy wrote prolifically about the medicinal benefits of cannabis (which was commonly used in India) and provided detailed records of his numerous animal and human experiments in treating cholera, rheumatism, hydrophobia, tetanus, rabies, and convulsions. His research, published in The *Bengal Dispensatory* in 1842 and The *Bengal Pharmacopoeia* in 1844, led to a surge in the medical field's interest in the potential ameliorative effects of cannabis, and the republication of his findings in British and European medical journals helped pioneer scientific inquiry into the plant. Indeed, more than 100 articles on the medical use of cannabis appeared in medical journals from 1840 and 1900. By then, the British had adopted cannabis as an

effective analgesic, anti-inflammatory, antiemetic, and anticonvulsant [10]. Nonetheless, its psychoactive properties led to public fear of misuse and addiction, and cannabis was removed from the *British Pharmacopoeia* by 1932 [10].

On the heels of O'Shaughnessy's pivotal research, cannabis began to be recognized and used by Western medicine around the mid-19th Century, including its listing in the United States Dispensatory in 1854 [15]. In the US, commercial cannabis was available in drugstores and pharmacies, and doctors often prescribed it for sedative or hypnotic purposes, as an analgesia, and for other miscellaneous uses (e.g., poor appetite, gastric upset, vertigo) [11]. Increasing research in the United States and United Kingdom throughout the late 19th Century shed light on its utility in controlling pain, anxiety, migraines, poor appetite, and restlessness [15]. However, medicinal cannabis use began to decline around 1890, replaced by the advent of synthetic (and more stable and reliable) drugs like aspirin, chloral hydrate, and barbiturates.

At the start of the 20th Century, efforts to regulate cannabis, such as through the Pure Food and Drug Act, underscored a growing concern about the plant's safety. Consequently, from 1914 to 1925, 26 states made cannabis illegal [14]. By the 1930s, public perception in the United States had solidly shifted, mirroring that of Britain and Europe [10] and fed in part by massive economic and job losses during the Great Depression. No longer embraced as a potentially powerful medicinal tool, cannabis was now deemed harmful, addictive, and a moral blight on civilized society. This was reflected in the passage of the Uniform State Narcotic Act in 1932, which gave states the ability to control the sale and use of narcotics (and cannabis). Among its most vocal supporters and lobbyists was Harry Anslinger, Commissioner of the Federal Bureau of Narcotics, who also was a central figure in the adoption of the Marijuana Tax Act of 1937. The first federal government regulation of cannabis, the Marijuana Tax Act provided an additional barrier to the research and use of cannabis for medical purposes by taxing physicians and pharmacists using cannabis medicinally. And although it technically did not criminalize cannabis, it essentially did so by making the sale and possession largely illegal. Its passage was intended to (and indeed did) dissuade the general public from recreational use, as Anslinger was an outspoken critic who claimed cannabis led to addiction, violent crime, psychosis, and mental dysfunction.

Having now effectively made the medical use and study of cannabis not only more difficult but costly and socially taboo, the federal government in 1942 had the plant removed from the *United States Pharmacopeia and National Formulary* [16], and in 1951 and 1956, enacted legal penalties for the possession of cannabis via the Boggs Act and the Narcotic Control Act, respectively. Cannabis was finally criminalized at the federal level under the Comprehensive Drug Abuse Prevention and Control Act of 1970. It should be noted that that significant political factors influenced the federal criminalization of marijuana [17].

Recent US History of Cannabis Use

The placement of cannabis in the most restrictive schedule under the Comprehensive Drug Abuse Prevention and Control Act (i.e., Schedule 1) meant physicians and researchers had limited access to study its therapeutic effects (interested researchers must seek licensing from the Drug Enforcement Agency (DEA) and permission from the National Institutes of Drug Abuse). But despite this, interest in medical cannabis grew throughout the 1970s, primarily through citizen activism and lobbying at the state level [18]. During this time, Oregon, Alaska, and Maine decriminalized cannabis, and the rise of activist groups, like the National Organization for the Reform of Marijuana Laws, helped further fuel grassroots efforts to sanction therapeutic cannabis [18]. National professional societies, like the American Medical Association, American Bar Association, American Public Health Association, and National Education Association, followed suit and passed declarations in support of decriminalizing the drug [14].

However, not everyone endorsed this growing movement, and a backlash against the legalization of medical cannabis eventually gave rise to highly punitive policies throughout the 1980s and early 1990s under Presidents Reagan and Bush, such as the "War on Drugs," "mandatory minimums," and the "Three Strikes" life sentencing laws for repeat drug offenders [14], laws which disproportionately impacted persons of color.

But by 1996, a milestone piece of legislation was passed in California that would reverberate across US law and culture for decades and help fuel the swing in public attitudes toward decriminalization—Proposition

215 (the Compassionate Use Act). Under this law, patients were protected from state prosecution for cultivating, possessing, and using cannabis for preapproved medical purposes. It also allowed physicians to recommend medical cannabis without reprisal. The federal government under President Clinton vehemently opposed the controversial new law, threatening to target California physicians who recommended cannabis to their patients, revoke their registration with the DEA, and block them from participating in Medicare and Medicaid. But to no avail; within 10 years, an additional 22 states, Washington D.C., and Guam followed in California's footsteps, and a national conversation about the widespread legalization of medical cannabis was already underway [19].

Support for medical cannabis helped usher in legislation on nonmedical use. On January 1, 2014, Colorado became the first state to permit recreational cannabis use and distribution. As of June 2019, 33 states and Washington D.C. had passed laws broadly legalizing cannabis in some form (all 33 states plus Washington D.C. have decriminalized cannabis for medical use, and 11 states plus Washington D.C. have decriminalized cannabis for both medical and recreational use) [20]. But what factors have given rise to this dramatic shift toward more liberal views of cannabis use and legalization? And what does this mean for public health moving forward?

Factors Influencing Cannabis Legalization in the United States

Since the early 1990s, the percentage of people in the United States favoring legalization of cannabis has increased approximately 1.5 percentage points a year, representing a dramatic fluctuation over a relatively short period of time [21]. The American publics' views of cannabis has changed as state legislation has similarly become more accepting, suggesting, at least to some extent, the latter and the former are synergistic. The legalization of cannabis and regulated dispensaries and "grow warehouses" has also given birth to a new industry, creating jobs and revenue streams that help "normalize" cannabis in the eyes of many Americans, particularly college-aged and young adults [22].

But a host of other political, ideological, and sociocultural factors are driving the wave of increased legalization in the United States and

signaling the need for greater education efforts to ensure both healthcare providers and the general public are aware of the possible risks and outcomes associated with cannabis use. For instance, a decline in punitive attitudes regarding cannabis use and increased media coverage on the medicalization of cannabis has been impactful [21]. State budgets have become increasingly strained by the costs of processing and housing persons charged with nonviolent offenses (including cannabis-related offenses). Concurrently public and medical sentiment and opposition to the incarceration of nonviolent substance users, often persons of marginalized populations have grown. In 2017, the former director of the US Center for Substance Abuse Treatment published an article building the case for decriminalization and legalization [23]. Border state policy diffusion—that is, the adoption (or rejection) of legislation in nearby states that appears to sway attitudes and legislation in remaining states—has played a modest role [19]. And political culture is also relevant, with states having a more liberal citizenry being more likely to adopt medical cannabis legislation than states with more conservative citizenry [19].

Rising interest in criminal justice reform and efforts to address policies that generate racial/ethnic and gender disparities also cannot be discounted. Now more so than ever, coalitions of politicians, legislators, and concerned citizens of all political ideologies are seeking criminal justice reform, and this dovetails directly with efforts to decriminalize cannabis. Data indicate that enforcement of cannabis laws tends to be unequal across racial/ethnic groups, with African Americans and Latinos being significantly more likely than Whites to be arrested despite comparable rates of use across ethnicities [24–26]. Vocal proponents of criminal justice reform see decriminalization or legalization of cannabis as a flagship issue and foundational opportunity to finally turn the page on the failed "War on Drugs," expunge cannabis-related convictions, reduce the number of justice-involved persons in the system (specifically, African American and Latino persons), and lower costs associated with court proceedings and incarceration.

Coupled with the documented decrease in the perceived risks of cannabis use [27], increased attitudes of permissiveness and the trend toward greater legalization efforts all raise concerns about the American public's access to and understanding of cannabis. Cannabis is a heterogenous plant with variable strengths, methods of consumption, delivery

devices, strains, and cannabinoid concentrations, any of which could affect outcomes like level of intoxication, dependency severity, and addiction potential. The recent surge in cannabis potency over the past two decades (i.e., a 300% increase from 1995 to 2014) [28] alone suggests widespread education about the harms, risks, toxicity, and addiction liability of cannabis/cannabis-derived products is critical and in fact may be a sensible prevention and harm reduction strategy. But healthcare providers need more education and guidance in how to have balanced discussions with patients addressing both the legalization of—and thus access to—cannabis as well as its adverse effects, addiction potential, rapidly changing delivery methods, concentration levels, and, as needed, options for addiction treatment and recovery.

3

The Chemistry of Cannabis

The chemical components of the biologically active cannabis plant have been the subject of extensive research for decades. Its chemistry is notably complex and marked by more than 500 constituents (and the copious potential interactions that can occur between them) as well as more than 700 varieties (e.g., indica, ruderali, sativa) [29]. Cannabis contains a plethora of chemically active compounds, including cannabinoids, terpenes (terpenoids), flavonoids, and numerous hydrocarbons, sugars, amine/amide functions, carbohydrates, phytosterols, and fatty acids [30, 31]. As cannabis is one of the most widely used substances around the world, understanding its chemical makeup and mechanisms of action is important to the development of effective prevention and treatment messaging and interventions for healthcare patients and the general public as a whole.

The purpose of this chapter is to briefly orient clinicians to the chemical complexity of cannabis and its spectrum of psychoactivity. This chapter is not intended to be a thorough primer on the botanical and chemical makeup of cannabis. Rather, the aim is to highlight key aspects of cannabis chemistry—including the ways in which cannabis functions in the human body—that may aid in improved understanding the plant's psychoactive effects, therapeutic uses, addiction potential, and other adverse outcomes.

Psychoactive Chemicals in Cannabis

The most chemically active compounds in cannabis, and the ones to which the primary psychotropic properties of cannabis are attributed, are the **cannabinoids**. Cannabinoids occur in one of three

A Practitioner's Guide to Cannabis, First Edition. Win Turner and Joseph Hyde.

forms: **Endogenous cannabinoids** (i.e., endocannabinoids) exist in the body naturally, can have neurotransmitter-like effects in the brain, and include anandamide and 2-arachidonyl glycerol.

More than 100 cannabinoids belonging to 11 different classes have been isolated from the cannabis plant, but the two main types are tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD). Δ^9-THC is highly abundant, widely studied, and is mainly responsible for the psychoactive effects of the plant, whereas CBD is a secondary, nonintoxicating component of cannabis and is responsible for much of the plant's medicinal/therapeutic effects [32, 33]. The *Cannabis sativa* species that is marked by high levels of Δ^9-THC is primarily used for recreational and medicinal purposes, and the fibrous species (known as hemp) is mainly used for textiles and food and is nearly devoid of Δ^9-THC (but high in CBD).

In terms of therapeutic effects, Δ^9-THC is known to modulate pain, spasticity, appetite, mood, respiration, inflammation, and complications from solid organ transplantation (e.g., graft-versus-host disease) [34]. Δ^9-THC is a partial CB1 and CB2 cannabinoid receptor agonist (see the section "Cannabinoids and the Human Body") and in higher doses can induce anxiety, paranoia, perceptual disturbances, and cognitive dysfunction. CBD has demonstrated anticonvulsive, anti-inflammatory, antioxidant, antipsychotic, and immunosuppressant properties and has shown efficacy in modulating neurological and neurodegenerative symptoms in several disease states, including epilepsy, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, and multiple sclerosis [34, 35].

Both Δ^9-THC and CBD are biologically active, with variable concentrations throughout the plant (though its concentration is highest in the plant's flowers). Other "minor" cannabinoids that may have therapeutic effects, though less studied than Δ9-THC and CBD, include tetrahydrocannabivarin (THCV), cannabinol (CBN), cannabichromene (CBC), and cannabigerol (CBG) [34, 35]. For instance, CBG has demonstrated anti-inflammatory, antimicrobial, antidepressant, antihypertensive, and analgesic effects in human and animal trials and may be a potent mitigator of methicillin-resistant *Staphylococcus aureus* (MRSA). CBC, also nonpsychoactive, has been implicated as a modulator of analgesic, anti-inflammatory, digestive, antibacterial/antifungal, and neurodegenerative processes. CBN appears to be useful as a sedative, anticonvulsant, anti-inflammatory agent, antibiotic, and as an MRSA

treatment. Finally, administration of THCV is associated with weight loss, anticonvulsant effects, and appetite suppression [34, 35].

Beyond cannabinoids, the other primary constituent in cannabis are the **terpenes**—the most common of which are limonene, myrcene, and alpha-pinene [36]. Terpenes are responsible for cannabis' characteristic aromas and tastes and are produced by many different plants (e.g., lemon, orange, pine, hops, lavender, green tea) as a way of attracting pollinators and warding off predators. Myrcene is an anti-inflammatory that has sedative effects; limonene is a potent anxiolytic that also appears to have antibiotic and chemotherapeutic properties; and alpha-pinene—the most widely distributed terpenoid in nature—is an anti-inflammatory, antibiotic, antibacterial, and anxiolytic compound [34]. It is unclear, the role that terpenes play in the pharmacologic outcomes of cannabis [34]. But in animal studies, even low concentrations of terpenes may significantly increase or decrease activity levels, and their effects may extend to those occurring in ion channels, neurotransmitters, and smell and taste receptors.

Cannabinoids and terpenoids are extracted from the bracts and flowers of the cannabis plant chemically (e.g., petroleum ether, ethanol), through high-pressure liquid CO2, or through natural solvents (e.g., olive oil, coconut oil). The extract—called "oil"—can be administered medicinally as an oral spray, pill, or tincture (e.g., Sativex®, a Δ^9-THC/CBD oral spray; Cannador®, a Δ^9-THC/CBD capsule). Terpenoids are hypothesized to work synergistically with phytocannabinoids to modify or enhance each other's effects such that the resulting outcome is stronger than that which would be produced by either alone—a complex interaction known as the "**entourage effect**." This effect may explain why some people report experiencing more of an effect from cannabinoid extracts than from Δ^9-THC alone [33, 35]. For instance, the addition of limonene to Δ^9-THC can greatly enhance euphoria, and adding myrcene to Δ^9-THC increases sedation [34]. However, randomized controlled trials are still needed to compare the efficacy of cannabinoid-terpene combinations with either or alone.

Synthetic Cannabinoids

Although outside of the scope of this guide, the authors recognize the need to briefly summarize some information concerning the category called **synthetic cannabinoids**. These substances were developed first to investigate cannabinoid receptors for research and then introduced

into the European consumption market in 2005 and then the United States in 2008. The primary initial organic chemist researcher and developer of synthetic cannabinoids John William Huffman was funded by NIDA to investigate potential for new medicines. Huffman's Clemson university lab produced more than 400 new cannabinoid compounds from 1990 to 2011. Huffman never intended them for public consumption and in an interview Dr. Huffman stated, "synthetic cannabinoids do not belong to the same structural group as THC; they are really dangerous compounds."

By 2010, fake marijuana was cheaply and widely available legally in stores and did not show up on drug tests. The synthetics are chemical compounds dissolved in solvents (e.g., acetone) and then spayed onto dried leaves to resemble cannabis. Plant-Based THC is a partial agonist of cannabinoid receptors vs. synthetics which are full agonists heightening and making the physiological response unpredictable. Cannabis often causes a quick response whereas synthetics can take a while and thus users over-consume trying to get high at the same rate as plant-based cannabis. Additionally, unaware users can overdose when the synthetics are mixed intentionally or unintentionally in the lab with potent opioid additives like fentanyl. Usually sold in small plastic packets often as "potpourri" with "not for human consumption" warning labels the synthetics are often labeled names such as: Spice, K2, King Kong, Scooby Snacks, Laugh Out Loud, and Power Diesel.

The method of use is similar to plant-based cannabis for example, smoking out of a pipe but the effects are dramatically different. Rather than being described by users as a mellow, relaxing high, synthetics are listed by the CDC as potentially causing the following:

Clinical features of synthetic cannabinoid poisoning vary and may include:

- Neurologic signs and symptoms including agitation, sleepiness, irritability, confusion, delirium, dizziness, incoordination, inability to concentrate, stroke, and seizures;
- Psychiatric signs and symptoms including hallucinations, delusions, psychosis, violent behavior, and suicidal thoughts;
- Other physical signs and symptoms including tachypnea, tachycardia, hypertension, severe nausea and vomiting, chest pain and heart attack, rhabdomyolysis, kidney failure, and death.
- The long-term effects of using synthetic cannabinoids are unknown.

Synthetic cannabinoid use can lead to physical and psychological dependence on these drugs. Patients who have used synthetic cannabinoids for long periods and abruptly stop have reported withdrawal-like symptoms, suggesting that the substances are addictive. Overdose can occur when the compound is tainted with fentanyl and other highly potent chemicals [37].

The chemistry of synthetic cannabinoids is a cause of real concern and poses a significant public health risk due to their adverse and potentially dangerous, if not fatal, side effects. Further, overdose of synthetic cannabinoids appears to be more cardiotoxic and neurotoxic than overdose of true cannabis [38]. Authors of this book remind readers, "synthetic cannabis" like K2 should not be confused with real cannabis that is grown.

Synthetic cannabinoids are unregulated and often made outside the US; thus, their exact compositions of chemicals, components, and variations can differ across products, and are continuously changing. Consequently, their precise toxicology, physiology, and consequences are difficult to fully understand or for healthcare providers to predict and respond to during acute crisis [39]. And because these easily accessible products are typically street sourced, it is usually not possible for consumers to know which—or how many—additives a synthetic product contains, increasing the odds of adverse effects such as overdose. In July 2012 a national ban was enacted against the sale of synthetic cannabinoids in the US. Local and state laws also regulate synthetic cannabinoids. While synthetic cannabinoids are illegal in the US, the product may still be sold illegally on the streets and produced in countries outside the US.

Cannabinoids and the Human Body

The human body is replete with cannabinoid receptors designed specifically to respond to cannabis; in combination with the endocannabinoids themselves as well as their metabolic enzymes, the trio is known collectively as **the endocannabinoid system**. Functioning much like a lock-and-key structure, cannabinoid receptors (i.e., "locks") located on various cell membranes throughout several organ systems become activated by cannabinoids (i.e., "keys"), allowing the plant to induce a variety of physiological processes such as those pertaining to appetite, pain, mood, digestion, sensory integration (e.g., balance, sense of space),

stress response, and memory [31]. The human endocannabinoid system also regulates processes like inflammation, immune system functioning, nerve functioning, and metabolism.

Two cannabinoid receptors have been identified and are particularly well-studied: The CB1 and CB2 receptors. CB1 receptors are found in high concentration in various tissues within the brain and throughout the central nervous system but also are located in the lungs, liver, and kidneys. This distribution explains why cannabis can affect functions like heart rate, mood, appetite, motor activity, pain tolerance, learning, memory, and decision making. Further, the paucity of CB1 receptors in the brainstem, which controls breathing and consciousness, explains why cannabis is not linked to life-threatening overdose. CB2 receptors are mainly located on T-cells throughout the immune system (e.g., bone marrow, thymus, spleen, tonsils) but also exist in the gastrointestinal tract, uterus, lung, and bone [31, 34].

Δ^9-THC is a partial agonist that binds to CB1 and reduces excitability by inhibiting the release of neurotransmitters affected by endogenous cannabinoids [34]. It may inhibit the release of GABA, thereby increasing the release of dopamine, glutamate, and acetylcholine. This latter mechanism of action is thought to be the primary factor underlying cannabis' psychoactive effects. Δ9-THC also activates CB2 receptors to reduce immune cell functions, including those that lead to inflammation. CBD, on the other hand, has a low affinity for both receptors and works as an inverse agonist, reducing pro-inflammatory markers like tumor necrosis factor-alpha, inducible nitric oxide synthase, and cyclooxygenase-2.

Δ^9-THC and CBD are activated by heat and light, which results in removal of a carboxyl group (i.e., decarboxylation). The resulting vapor can then be inhaled, resulting in rapid onset and quick peak blood concentration (e.g., immediate onset; 5–10 minutes' peak plasma time). Effects begin to taper off after a few hours. Onset and peak concentration are delayed when cannabinoids are ingested orally (e.g., 30–90 minutes' onset; 1–6 hours peak plasma time), but they last longer compared with inhalation, tapering off in 4–8 hours. Similarly, the bioavailability (that is, the amount of the drug entering the blood stream once administered) of Δ^9-THC and CBD is much higher when inhaled (2–56%) versus oral administration (<20%). Both cannabinoids are mainly metabolized by the group of liver enzymes known as cytochrome P450, which help the body to excrete the drug.