MEDICAL CANNABIS HANDBOOK

For Healthcare Professionals

Authored and Envisioned by
Christine Nazarenus

SPRINGER PUBLISHING COMPANY

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ABOUT THE AUTHOR

Christine Nazarenus – Medical Marijuana 411

Before founding *Medical Marijuana 411*, Ms. Nazarenus successfully sold, implemented, and configured Digital Asset Management Systems for Fortune 500 companies and some of the largest publishers in the world. She is an expert in social media and digital strategies and is a content management specialist offering digital consulting services to top brands for their online strategies. It was after securing a contract with a major retailer out of Chicago, that Chris had an opportunity to help the *Indianapolis Motor Speedway* with an archive strategy. In 1998, she then had the vision to "flip" the traditional archival strategy and develop an online strategy unheard of at the time. She would leave the corporate world to launch her first start up, *Artemis Images* with the *Indianapolis Motor Speedway* as her first client.

Ms. Nazarenus has been quoted in D.A. Benton's book, *How to Act Like a CEO. Artemis Images'* business case is featured in *Technology Ventures – From Ideas to Enterprise, McGraw Hill* and studied by MBA students worldwide. In 2007, Chris was a nominee for the prestigious *Denver Business Journals' Woman Entrepreneur of the Year.* Chris is a graduate of the University of Puget Sound.

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DEDICATION

To the healthcare professionals who have listened to the many patients and their experiences using medical marijuana – and – those who are open to exploring cannabis as an option for patient care, this Medical Cannabis Handbook is dedicated to you.

It is with hope that you find this handbook of value regarding the potential benefits of cannabis as medicine.

SPECIAL THANKS

To Mary Gatsch, thank you for being a visionary in the healthcare field and pushing to be first, by understanding the need to have medical marijuana titles by Springer Publishing. It is with sincerest gratitude that you asked *Medical Marijuana 411* to be your partner in this endeavor. I can say without hesitation that the *Medical Cannabis Handbook For Healthcare Professionals* is one of my proudest accomplishments. I hope you are as proud as we are of this handbook.

To Frank Costanzo, without your guidance, mentorship and trust in my abilities, I would have never had the courage to take on this opportunity. Thank you for the many years of friendship as it has been an incredible tale and I am proud of your role in my professional development. Without your faith in me, the *Medical Cannabis Handbook For Healthcare Professionals* would never have happened. I am excited to see what's next and get back to the 500 with you and those who have had unwavering support of my journey. Thank you.

Sincerely,
Christine Nazarenus
Chief Vision Officer and Founder, Medical Marijuana 411

FOREWORD

Jack Cox, MD, MMM

Plants have been used for medicinal purposes since the beginning of human history. Even today, 11% of the 252 drugs that the World Health Organization considers essential are plant-based. Marijuana has been used for medical purposes for at least 5,000 years. Yet despite the study of tens of thousands of plant-based compounds for medical uses, little research has been done on this useful and common biologic.

Several years ago, I moved to Southern California to become the chief quality officer for a well-known health system. California was the first state to legalize medical marijuana in 1996. Shortly after arriving, I found myself challenged with questions from healthcare colleagues and our patients about the uses of medical marijuana and its risks. What could it be used for? Would we allow use while a patient was in the hospital? What about drug-drug interactions? What conditions would marijuana be useful for? Even though this biologic has been in use for various health issues for several millennia, I had not learned about medical marijuana and its uses while in medical school or during my residency in family medicine. This challenge was only amplified when I was diagnosed with cancer and tried researching the literature about the potential benefits for chemo-induced nausea. References abounded on the Internet, but I questioned which ones were legitimate and were backed by science. It all became a confusing blur.

Today, 33 states have legalized the use of medical marijuana, with more states considering it daily. The research on potential benefits has lagged, as marijuana is still listed as a Schedule I drug at the federal level. Not since its prohibition in 1937 has there been much work or research on this potentially helpful plant. Clinicians have been woefully under-prepared, as more and more patients seek answers to their questions on medical marijuana. The number of identified potential conditions that may benefit from the medical use of marijuana has increased; from PTSD, to chemo-induced nausea, to even helping lower the opioid use in chronic pain. Make no mistake, medical marijuana is not a panacea. We are only beginning to understand its complex chemical structure, its interaction with various areas in the body and its potential to help specific medical conditions.

Fortunately for us, since 2009, *Medical Marijuana 411* (MM411) has been educating distributors, clinicians and patients regarding the up to date research and literature surrounding medical marijuana. They were the very first medical marijuana education provider to offer online CME, CPE and CNE courses to physicians, pharmacists and nurses. MM411 was also one of the first to have authored ACCME-accredited courses for the medical professional community. They have partnered with Springer Publishing, a trusted giant in medical literature, to bring us the first comprehensive resource for clinicians on medical marijuana, *Medical Cannabis Handbook*. I believe this handbook should be a required text for every practicing clinician and every clinical training program. It covers a wealth of information from marijuana's early history, the laws effecting its use, the pharmacodynamics, potential uses, and side effects, to mention a few areas of interest.

Medical marijuana is here to stay, and we owe it to our patients and ourselves to be educated and informed. This handbook is a great start. Enjoy the read!

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Overview of Cannabis Laws and Regulations

This introductory chapter is intended to enable medical professionals to better understand the legal terrain of medical cannabis. It provides clinicians with an overview from a legal perspective of relevant medical cannabis regulations and what clinicians may and may not do when discussing cannabis in the context of a patient visit.

CHAPTER 6: CANNABINOID PHARMACEUTICALS

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CHAPTER 13: MEDICAL MARIJUANA MYTHS AND FACTS

The history of marijuana research and science is littered with many fictions masquerading as facts. Now that you are aware of the latest science and methodologies of administering medical cannabis, it is important to review some of those myths to understand where they originated, how they have been perpetuated, and where the science-based truth lies.

ACKNOWLEDGMENTS

It would not be accurate to take full credit for the authorship of the *Medical Cannabis Handbook For Healthcare Professionals*. To say that it was a team effort is an understatement. Sam Sabzehzar, without your dedication in the early days we would not be where we are today. Damon, without you trusting in my vision of what we needed to create, we would not be here as a world class educational provider. To Dr. Jake Felice whose passion for sharing his knowledge regarding medical cannabis is the foundation of the content *Medical Marijuana 411* has developed over the past 3 years.

What I will acknowledge is that it was my vision to develop a handbook with content that was based on peer reviewed research citations and be beautiful. Without a chance call from the amazing designer Steve Kennevan, the reality of what I envisioned for a gorgeous handbook would not be a reality. You took a chance and I am so thankful that you trusted me. Not only is the handbook informative, it is even beyond what I could have visually imagined.

To Elizabeth Nieginski, for your trust in the design and editing process. Joanne Jay, thank you for your expertise and guidance to ensure that every attention to detail was handled. For all the behind the scenes care, thank you Rachel Landes.

I am thankful everyday for our advisors and mentors who have given us guidance on the good and bad days. Sometimes it is not easy blazing a path that is not supported by some of the medical community. To John, who has the best Rolodex and has made key introductions.

Dr. Jack Cox, I know I am supposed to just call you Jack, but I still pinch myself to have you in our court. Having such a respected medical professional speak to how vital it is for the medical community about the importance of understanding cannabis is critical. You have helped us to remain unbiased and have taught us that it is important for the healthcare professional to make their own conclusion in regard to medical marijuana. Thank you for overseeing content development and for your recommendations.

Mark Mersman, you have been the cog of the wheel to our team of physician experts. You have taken every call, given great counsel and have such great vision regarding new opportunities. Thanks to our "Docs," Dr. Greg Smith and Dr. Kevin Smith, for your commitment to creating world class educational content and helping us navigate our CME activities.

Many thanks to Rick Beets for your extraordinary technical support and sticking with me from the beginning. I am proud to have you by my side on this journey and even more proud to have you as my brother. I couldn't have done any of this without you. Hopefully, the future will get wrongs righted and the three of us back together.

Michelle Clement, thank you for setting the visual tone of our graphic style within our courses, as the coursework is easy to navigate, beautiful and the endnotes work. Lane Trachy, who has always been there for research assistance and overall help moving projects forward I appreciate you always being willing to help with any task.

Medical Marijuana 411 has been founded on sweat equity and I am thankful every day for all of your continued support from such an exceptional team.

I would remiss if I didn't say thanks to my mom and dad. Dad, you were the smartest, most talented entrepreneur that I ever met and I was lucky enough to have you as my father. I miss you every day. Mom, thanks for giving the best advice by telling me to quit my corporate job, go pitch my idea to the Speedway, as I was smart and I could get another job if it didn't work out. You reminded me that you didn't want me to look back on my life as I got older and wonder "what if….".

Andy DeVol, you are my partner, my best friend and you have the fortunate task of dealing with me on a daily basis, which I know is not always an easy one. There is no one who inspires me more or offers me the best advice. After hearing about the requirement for certification in Washington, you said "that's what you are going to do." I seriously thought you were crazy, as I had zero idea of how to build a medical marijuana education company. You told me that I was smart and I would figure it out. We did. I am so appreciative of you understanding the time and commitment to what it would take to create the handbook, but as well the 10 years of building *Medical Marijuana 411* to become one of the premiere cannabis education companies in the world. It will be fun to finally realize an overnight success. Thank you for always believing in me. I love you.

To Nikki Wright, there are not enough words to express my appreciation for you being part of this journey. You are wickedly smart and *Medical Marijuana 411* would not be where we are today without your talent. Your ability to oversee the CME activities and to work so diligently to make my vision a reality. I cannot put into words how thankful I am for your involvement. Excited for the next chapter and to be able to enjoy the success we have created. I am ready to have the band back together.

And last, but not least, Greg Tracy. It was your grandma Connie's story of her finding relief in her dying days from cannabis that created the "ah-ha" moment which was the founding patient story of *Medical Marijuana 411*. Her experience would challenge you to find relevant, research-based information on cannabis more than 10 years ago and for you to find out that information didn't readily exist. A chance conversation at the Bonneville Salt Flats and look where we are today. I know that it hasn't been an easy road and it has been difficult to be the original entrepreneur behind our company, without anybody knowing. *Medical Marijuana 411* would not exist without your continued guidance and faith in my abilities. I know I am not always easy, but 15 years of friendship and business building later I can say without any hesitation, GT you have always believed in me even when I did not believe in myself. It is time for the world to know your intellect and business acumen. I always look forward to our conversations about what to do next. Thank you for the continued adventures.

And thanks to the Academy for not queuing the orchestra early.

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LEGAL LANDSCAPE

Overview of Cannabis Laws and Regulations

OBJECTIVE

This introductory chapter is intended to enable medical professionals to better understand the legal terrain of medical cannabis. It provides clinicians with an overview from a legal perspective of relevant medical cannabis regulations and what clinicians may and may not do when discussing cannabis in the context of a patient visit.

INTRODUCTION

This chapter provides a legal framework for the topics that will be discussed throughout this handbook as well as future interactions and conversations with patients. Further chapters will dive deeper into many of the topics touched on in this legal overview including the history of medical cannabis use, an overview of prohibition, legalization and regulation, practical information for dosing, delivery and the clinical application of cannabis, and so much more. This section will provide up to date information regarding the current regulatory landscape of medical cannabis, and the application of those regulations in a medical and legal context.

FEDERAL LEGAL OVERVIEW

Cannabis, also commonly referred to as marijuana or hemp, is a genus of flowering plants in the family *Cannabaceae* that includes at least three species, *Cannabis sativa L., Cannabis indica*, and *Cannabis ruderalis,* as determined by plant phenotypes and secondary metabolite profiles (terpene profiles).[1] In practice, cannabis nomenclature is often used interchangeably or seemingly arbitrarily. Legally, however, hemp and marijuana are distinguished by their respective concentrations of the cannabinoid delta-9 tetrahydrocannabinol (THC) found in the flowering tops and leaves. According to federal law, cannabis with 0.3% or less concentration of THC is not marijuana; it is industrial hemp.[2,3] Industrial Hemp was included in the 2018 Farm Bill, which was signed by President Trump on December 20, 2018.

This legislature removed Industrial Hemp from the Schedule I drug classification per section 10113 of the Farm Bill.[4] With the declassification of Industrial Hemp, products that contain cannabidiol (CBD) derived from legal hemp are now federally legal. The bill removes restrictions on the sale, transport, and possession of hemp-derived products, so long as those items are produced in a manner consistent with the law.

Since 1972, cannabis has been classified as a Schedule I drug under the U.S. Controlled Substances Act because the U.S. Drug Enforcement Agency considers it to have "no accepted medical use."[5] In stark contrast to this position, 33 of the 50 U.S. states and the District of Columbia have recognized the medical benefits of cannabis and have decriminalized its medical use.[6] The approved list of conditions/diseases and the other laws/rules regarding the possession and cultivation of medical marijuana generally differ by state. In addition, 11 of the 50 U.S. states and the District of Columbia legalized recreational cannabis use for adults 21 years of age and over, with varying rules and regulations.

In 2014, President Obama publicly commented on the recreational legalization of cannabis in Colorado and Washington, stating that "it's important for it to go forward because it's important for society not to have a situation in which a large portion of people have at one time or another broken the law and only a select few get punished." President Obama further remarked, "I don't think it's more dangerous than alcohol. In fact, it is less dangerous than alcohol in terms of its impact on the individual consumer."[7]

In line with the president's comments, the U.S. Attorney General Eric Holder announced that the federal government would allow states to create a regime that would regulate and implement the legalization of cannabis, including loosening banking restrictions for cannabis dispensaries and growers.[8]

The Cole Memo[9] and the Financial Crimes Enforcement Network (FinCEN) guidance[10] were published and provided states with some comfort in their respective legalization experiments. Unfortunately, enforcement priority decisions by the Attorney General are not in themselves changes in law and may change with each administration.

An October 2017 Gallup poll found an all-time high of 64 percent of Americans support full legalization. The same poll was also the first time Gallup recorded a majority of Republicans, 51 percent, favoring full legalization.[11]

Legal cannabis has become one of the fastest-growing industries in the United States, and state representatives have found that none of the problems predicted with legalization occurred. Sales jumped from $1.5 billion in 2013 (U.S.) to an estimated $10 billion (for North America) in 2017, according to Arcview Market Research. The industry now employs more than 150,000 Americans and has become more deeply entrenched in every quantifiable way.[12]

In addition to these recent developments, the U.S. government has set a precedent for patenting cannabis and cannabis-related inventions. For example, U.S. Pat. No. 6,630,507[13] issued on October 7, 2003, and assigned to the United States of America, is directed to methods of treating diseases caused by oxidative stress by administering therapeutically effective amounts of a CBD cannabinoid from cannabis that has substantially no binding to the N-methyl-D-aspartate (NMDA) receptor, wherein the CBD acts as an antioxidant and neuroprotectant. The U.S. Patent and Trademark Office (USPTO) confirmed that officials are now accepting and processing patent applications for individual varieties of cannabis, along with innovative medical uses for the plant and other associated inventions.

In contrast, the Office of Trademarks at USPTO often rejects cannabis trademarks when they determine there is no legal "use in commerce."[14] The Office of Trademarks further requires that the "use in commerce" be "the bona fide use of a mark in the ordinary course of trade, and not made merely to reserve a right in a mark."[15] In a recent decision from the Trademark Trial and Appeal Board, the Board affirmed "the fact that the provision of a product or service may be lawful within a state is irrelevant to the question of federal registration when it is unlawful under federal law."[16]

OTHER PATENT AND TRADEMARK CONSIDERATION

- Federal protection is not available for cannabis trademarks, except where it does not violate the Controlled Substances Act.[17,18] Registration is refused because applicant does not have a bona fide intent to lawfully use the applied-for mark in commerce.[19,20,21]
- Plant, design, and utility patents are available for cannabis inventions.
- Copyright registrations are enforceable for cannabis creative works.

Despite the conflicting official positions within the federal government, many states have recognized that cannabis provides substantial benefits for medical and recreational uses. Cannabis is regularly used by a wide cross-section of society to treat a variety of maladies, conditions, and symptoms including, but not limited to, the following: nausea, glaucoma, lack of appetite, Crohn's disease, epilepsy, post traumatic stress disorder, intractable pain, fever, obesity, asthma, urinary tract infections, coughing, anorexia associated with weight loss in AIDS patients, pain, and multiple sclerosis. Many of these conditions will be discussed in relation to cannabis throughout this handbook, with a special focus on clinical applications.

With the number of people depending on cannabis to treat a myriad of medical conditions, and the increase in tax revenue in the states that have decriminalized both medical and recreational cannabis, it is unlikely that a reversal in policy by the federal government will take immediate effect. There will be significant legal challenges and a call for a delisting of cannabis as a Schedule I controlled substance. At this time, the legal future of cannabis is uncertain.

FEDERAL LAW OUTLINE

This outline list provides an introductory overview of relevant federal cannabis regulations. Many sections included here may not be relevant to medical application but are important for patients to consider before deciding to use medical cannabis.

CONTROLLED SUBSTANCES Act (21 USCV 801, et seq.)

- Marijuana is a Schedule I drug.[22] Schedule I drugs are defined as:
  - The drug or other substance has a high potential for abuse.
  - The drug or other substance has no currently accepted medical use in treatment in the United States.
  - There is a lack of accepted safety for use of the drug or other substance under medical supervision.
- Federal preemption[23] of state laws is in "direct conflict" with the Controlled Substances Act.

OGDEN MEMO[24]

- First guidance from the U.S. Department of Justice (DOJ) on medical marijuana enforcement.

COLE MEMO[25]

- In an historic position change, the U.S. Justice Department's Deputy Attorney General James Cole announced in 2014 that the federal government would not interfere with a state's rights to manage and regulate marijuana based on eight conditions. This ruling is known as the Cole Memo and serves to remind individuals working in the legal marijuana industry that they remain under scrutiny.
- It is important to note that under the current Attorney General, the future of the Cole Memo is unknown.

- *THE COLE MEMO* states that the DOJ is not waiving "immunity" or offering "a free pass" to marijuana providers; instead, the Justice Department promises that federal prosecutors will aggressively investigate/prosecute any cannabis business that interferes/obstructs any one of the following eight federal priorities:
    - Distribution of marijuana to minors;
    - Revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels;
    - Diversion of marijuana from states where it is legal under state law in some form to other states;
    - State-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity;
    - Violence and the use of firearms in the cultivation and distribution of marijuana;
    - Drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use;
    - Growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands; and
    - Marijuana possession or use on federal property.

WILKINSON MEMO[26]

- Extended Department of Justice enforcement priorities to tribal lands.

THE ROHRABACHER–FARR AMENDMENT[27]
(recently known as the Rohrabacher–Blumenauer Amendment)

- Legislation first introduced by U.S. Representatives Maurice Hinchey, Dana Rohrabacher, and Sam Farr in 2003, prohibiting the Justice Department from spending funds to interfere with the implementation of state medical cannabis laws. The amendment does not change the legal status of cannabis, however, and must be renewed each fiscal year in order to remain in effect.
- There is one unpublished case in California where the federal court extended the protection to recreational cannabis.[28]
- Recreational marijuana is currently legal in 11 states plus Washington, D.C., and medical marijuana is legal in 33 states.[29]

TAXES

- The Internal Revenue Service Section 280(e)—Calculation of taxable income:
  - May discount the cost of goods sold from gross revenues.[30]
  - May not discount ordinary business expenses.

No deduction or credit shall be allowed for any amount paid or incurred during the taxable year in carrying on any trade or business if such trade or business (or the activities which comprise such trade or business) consists of trafficking in controlled substances (within the meaning of Schedule I and II of the Controlled Substances Act) which is prohibited by federal law or the law of any state in which such trade or business is conducted.[31]

NO BANKRUPTCY PROTECTION FOR CANNABIS BUSINESSES[32]

10th Circuit Bankruptcy Appellate Panel held:

- "Impossible for the Chapter 7 Trustee to administer the Arenases' estate because selling and distributing the proceeds of the marijuana assets would constitute federal offenses."
- "If the Trustee abandoned the Assets, the debtors would retain their business after exposing the Trustee to grave risk, provide the creditors with little or no recovery, and receive a discharge, protected all the while from their creditors' collection efforts by the automatic stay and then the discharge injunction. That is the epitome of prejudicial delay."
- Marijuana businesses are not eligible for Chapter 7, nor are they eligible for Chapter 13 bankruptcy protection.

Employment Law

- Drug testing is still permitted because it is still a federal crime.
- Employees can be fired for having THC in their blood/urine, even if smoking has nothing to do with their job and had no effect on their job performance.
- Cannabis smokers are not a protected class; employers are free to discriminate.
- Rightful termination may depend on whether the employment contract contains a provision with the requirement of following all federal laws, refraining from partaking illegal drugs, and so forth.[33]

ACCESS TO BANKING

The Financial Crimes Enforcement Network (FinCEN) published guidance for interstate banks to allow them to accept cannabis business accounts without violating federal money laundering statutes.[34]

ADDITIONAL LEGAL CONSIDERATIONS FOR MEDICAL PROFESSIONALS

In addition to the federal legal overview, there are several other legal details medical professionals should consider when discussing cannabis with patients and caregivers. The Cole Memo provides guidelines for the regulation of medical cannabis at the state level and includes important guidelines regarding federal prosecution of cannabis businesses. The *Conant v. Walters* decision outlines how doctors can discuss and recommend cannabis for patients and is further detailed in this section. Affirmative defense is also an important topic of conversation.

CONANT V. WALTERS—HEALTHCARE PROFESSIONALS RECOMMENDATIONS[35]

The 9th U.S. Circuit Court of Appeals ruled that doctors may discuss medical marijuana with their patients and may issue written recommendations for its use as part of a comprehensive treatment plan—*Conant v. Walters,* 309 F.3d 629 (2002). When this ruling was appealed again, the U.S. Supreme Court refused to hear the case, allowing the decision to stand.

- After California and Arizona decriminalized medical marijuana in 1996, the Federal Department of Justice and Department of Health and Human Services sent a policy to federal, state, and local practitioner associations cautioning physicians who "intentionally provide their patients with oral or written statements in order to enable them to obtain controlled substances in violation of federal law risk revocation of their DEA prescription authority."
- In 2002, the 9th Circuit affirmed an order permanently enjoining the federal government from either:
  - Revoking a physician's license to prescribe controlled substances, or
  - Conducting an investigation of a physician that might lead to such revocation, where the basis for the government action would be solely the physician's "recommendation" of the use of medical marijuana, on First Amendment grounds.
- After 2002, a provider may discuss the pros and cons of medical marijuana with his or her patient, and issue a written or oral recommendation to use marijuana within a bona fide provider–patient relationship without fear of legal reprisal.
- And this is so, regardless of whether he or she anticipates that the patient will, in turn, use this recommendation to obtain marijuana in violation of federal law.
- On the other hand, the physician may not actually prescribe or dispense marijuana to a patient or recommend it with the specific intent that the patient will use the recommendation like a prescription to obtain marijuana.

However, despite the First Amendment protections affirmed by the 9th Circuit, most healthcare providers are reluctant to recommend medical marijuana due to a claimed lack of scientific evidence or because the organization the provider works for has a policy against such recommendations.

AFFIRMATIVE DEFENSE

In states that have decriminalized medical cannabis, but not recreational cannabis, individuals possessing marijuana for a medical condition may have an "affirmative defense" for such possession. Each state's specific rules are state specific, and the medical marijuana consultant should be familiar with the laws within their respective state. Generally, an affirmative defense to a criminal charge is a fact or set of facts other than those alleged by the prosecutor, which, if proven by the defendant, defeats or mitigates the legal consequences of the defendant's otherwise unlawful conduct.

MEDICAL PROFESSIONALS

MAY:

- Discuss, fully and candidly, the risks and benefits of medical marijuana with patients.
- Recommend (or approve, endorse, suggest, or advise, etc.), in accordance with their medical judgment, marijuana for patient use.
- Record in their patients' charts discussions about and recommendations of medical marijuana.
- Sign government forms or inform state or local officials that they have recommended medical marijuana for particular patients.
- Testify in court or through written declaration about recommending medical marijuana for their patients.
- Educate themselves about the medical benefits of marijuana, its various clinical applications, and different routes of ingestion.

MAY NOT:

- Prescribe medical marijuana. This includes writing a recommendation on prescription forms.
- Assist patients in obtaining marijuana.
- Cultivate or possess marijuana for patient use.
- Physically assist patients in using marijuana.
- Recommend marijuana without a justifiable medical cause.

Early drafts of the Declaration of Independence were written on hemp paper.

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NOTES

182. *Cannabis sativa L.* **Hanf.**

AN ANCIENT PLANT FOR MODERN ILLNESSES

A Short Version of the Long History of Cannabis as Medicine

OBJECTIVE

This chapter charts the development and spread of cannabis and its various uses as a fiber, as a food, and as a medicine as far back as 5,000 years ago. Cannabis was an essential treatment for the ancient Chinese, the Indian Ayurvedics, as well as the Victorians who adopted it into the Western Pharmacopoeia in the mid-1850s. It was used in Europe and North America as a household tonic until its prohibition in 1937 in the United States.

EARLY HISTORY OF CANNABIS USE

According to biologists, botanists, and anthropologists, the cannabis plant (a relative of hops) debuted in the Caucasus Mountains, most likely in current-day Kazakhstan, some 10,000 years ago.[1] The harsh landscape and climate of Central Asia forced the plant to be hearty and, to a certain extent, inventive, in order to survive. It had to grow quickly before the short summer season ended, and it had to tempt animals and birds to gobble up the seeds and then excrete them while migrating.

Humans did their bit too, carrying seeds out of Russia along the Silk Route. The seeds that moved east into the colder regions of the Himalayas developed into the so-called Indica or Kush strains; the psychoactivity they produce tends to be more physical than cerebral, bringing on a sleepy condition, perfectly expressed by the phrase "couchlock." Indica plants are shorter and bushier, with rounder leaves. They also mature and flower quickly, in 12 to 16 weeks, to contend with their shorter growing season.

Seeds that went west to the Middle East and Africa are today commonly called the Sativa varieties. These warmer climate plants are more gangly, at times stretching 20 feet tall. They have narrow, finger-shaped leaves and rangy buds that take longer to mature (some can take up to a half year). The psychoactivity from a Sativa variety is generally more energetic. They stimulate talkativeness, nervousness, and machine gun bursts of creative flow.

Sativa

Indica

It should be noted that the terms "Sativa" and "Indica" are, by and large, meaningless, as the plant in North America has been hybridized over the last 50 to 60 years. Though the terms are unreliable at predicting effects, they are now ingrained in the common lexicon and we will use them here with that forewarning.

Ethnobotanists agree that cannabis has also made itself extremely useful to human beings as our species has adapted over thousands of years. When our hunter/gatherer ancestors were chased by a wild boar, they likely nibbled some cannabis buds to help them forget the trauma, relax, recover, and get to sleep so that they could get up the next day and hit the plains again. Archeological evidence indicates that women munched the sticky flowers to ease the nausea of pregnancy and to numb and then forget the pain of childbirth so they could repeat the experience and help our species proliferate—an undeniably strategic evolutionary benefit.[2]

Once humans settled and began to farm the land, cannabis seeds not only fed the animals but yielded an oil that contained the exact ratio of essential fatty acids to help children thrive.[3] The stalks provided fiber that was turned into tents and clothes, and eventually sails and paper (early drafts of the Declaration of Independence were written on hemp paper).[4] And the plant found its way into the healers' medicinal arsenal. Healers were plantsmen, after all. Without plants, their formulary, their stature, and not to mention their patients, all would have disappeared.

The ancient Chinese considered this wild grass one of the 50 fundamental herbs and were the first to write about its medical and spiritual benefits over 4,700 years ago. The father of Chinese medicine, Shen Nung, used "ma" to treat an array of illnesses, including gout, rheumatism, malaria, and constipation. Of the 2,000 medicinal plants known in the vast field of Indian Ayurvedic medicine, cannabis is the most important among them.[5] While all these cultures occasionally inhaled the dried plant as smoke, it was most often used as a tincture or eaten. The Egyptians used it in suppositories and to relieve eye pain; they buried kings and royalty with pounds of cannabis. The Greeks made wine steeped with cannabis, which they used to treat inflammation and ear problems.[6]

In 1993, a 2,500-year old mummy in Russia was found buried with meat, ornaments, and cannabis. A recent MRI of the so-called Siberian Ice Princess of Altai, who was perfectly preserved in ice, shows her body riddled with Stage 4 metastatic breast cancer. Scientists say she used cannabis to blunt the immeasurable pain of her illness and that she was probably a shaman who used cannabis to treat others as well.[7]

Cannabis is mentioned in the Pen-ts'ao ching, the world's oldest pharmacopoeia, which was compiled from Chinese oral traditions dating back to 2700 B.C.

CANNABIS TIMELINE

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CANNABIS IN THE WEST

With the advent of modern religion, Westerners began to view plant substances with suspicion. In its efforts to break the human bond with magic plants on earth and refocus the gaze of its followers on one God in heaven, elders in the Catholic Church branded plant users pagans, sorcerers, or witches. The Spanish Conquistadors massacred hordes of natives in Latin America for using psilocybin, peyote, datura, morning glory, salvia, and ayahuasca, in addition to cannabis.

Europeans remained largely ignorant about cannabis until Sir William Brooke O'Shaughnessy (an Irish inventor and physician) went to work in the hospitals of Calcutta, India, in 1839. While there, he developed a fascination with Indian botanical medicines, chief among them a tincture of cannabis indica, also known as hemp oil. O'Shaughnessy was curious about the ways Eastern cultures in hot, crowded regions used botanicals prophylactically to prevent diseases before they struck and then to treat them once they had.[8] He did the first animal studies on cannabis and noted that it effectively eased the pain of muscle spasms caused by rabies, tetanus, and cholera.

O'Shaughnessy brought the plant back to England, where it caused enough of a sensation that physicians and small companies began to produce their own cannabis elixir and sell it privately and in general stores.[9] In the very first issue of *The Lancet*, Queen Victoria's physician discusses tincture of cannabis in the treatment of dysmenorrhea. In this issue he also states: "When pure and administered carefully *[Cannabis Indica]* is one of the most valuable medicines we possess."[10]

In the following 60 years, over 100 medical papers were written about this "wonder drug" that treated some old-fashioned sounding illnesses (including neuralgia and melancholy) and many others that are still with us today, including sleeplessness, nausea, and neuropathy.[11] In the United States, physicians also made their own cannabis tinctures and sold them out of their offices, as did drug companies including Eli Lilly, Parke-Davis, and Squibb.[12]

The primary problem with this all-purpose plant tonic was not its efficacy, but dosing it accurately. When cannabis is swallowed, it takes 1.5 to 2 hours for the effects to come on, so patients never knew if they had taken enough. Too large of a dose could cause harrowing anxiety, but most doctors worried about prescribing too little.

In 1890, Sir John Russell Reynolds, neurologist and personal physician to Queen Victoria of the United Kingdom, prescribed a cannabis tincture for the Monarch's menstrual cramps.

"When pure and administered carefully, cannabis is one of the most valuable medicines we possess."

— Sir John Russell Reynolds as quoted in *The Lancet*

U.S. PROHIBITION

There were two powerful forces that combined to sideline cannabis as medicine and paved the way for U.S. prohibition. One was a noxious mix of anti-immigrant fever spurred on by the 27% jobless rate of the Great Depression plus corporate greed that viewed the plant as an economic threat.[13] The other force was a revolutionary medical invention: the pill.

In 1900, the conditions for which cannabis indica was most often prescribed were pain and insomnia. But in 1898, Bayer synthesized aspirin from birch bark; shortly thereafter, the first barbiturates were also produced as pills.[14] Today we take for granted the inexpensive manufacturing of precisely dosed, easy-to-swallow medications, but the invention of pills and capsules that could be measured in milligrams was groundbreaking at the time. Tincture of cannabis indica, which varied in strength depending on the crop from which it was derived and was vexing to dose, suddenly seemed very old-fashioned.[15]

Then, in the 1930s, Harry Anslinger proposed the Marihuana Tax Act to Congress. The Act did not criminalize the possession or medicinal use of hemp, marijuana, or cannabis but included penalty and enforcement provisions to which marijuana, cannabis, or hemp handlers were subject. Violation of these procedures could result in a fine of up to $2000 and five years' imprisonment. In addition, every person who sold, dealt in, dispensed, or gave away marijuana had to register with the Internal Revenue Service and pay a special occupational tax.[16]

The use of marijuana, as both a recreational and medicinal drug, began to dissipate in considerable amounts. According to U.S. Customs and Border Protection, the Marihuana Tax Act of 1937 intended to stop only the use of the plant as a recreational drug. In practice, though, Industrial Hemp was caught up in anti-marijuana legislation, making hemp importation and commercial production in this country less economical.[17] Scientific research and medical testing of marijuana also virtually disappeared. By 1941, the Marihuana Tax Act had imposed such a burden that doctors stopped prescribing cannabis. It was dropped from the American Pharmacopeia in 1941.[18] By 1970, marijuana was classified and restricted on par with narcotics and new, tighter laws were enacted.

THE MEDICAL IMPLICATIONS OF U.S. PROHIBITION

The prohibition of cannabis has had wide ranging effects on society and medicine, despite numerous attempts over 70 years to separate the myths from the facts. One of prohibition's greatest successes has been a diminution of the plant's healing qualities.

In 1944, for example, New York Mayor Fiorello La Guardia commissioned a report from the New York Academy of Medicine that questioned the prohibition. Its findings said that marijuana is not physically addictive, is not a gateway drug, and did not lead to crime.[19] Thirty years later, President Richard Nixon, who associated marijuana with the anti-Vietnam War protesters that marked his time in office, appointed the Shafer Commission to study worldwide use in hopes of proving the dangers of using the plant. Instead, the $4 million, 4,000-page study, titled "Marijuana: A Signal of Misunderstanding," concluded that the punishment for marijuana was more harmful than the drug itself and recommended decriminalizing personal possession and moving it into Schedule III alongside acetaminophen, synthesized testosterone and estrogen, drugs that "carry less potential for abuse." Nixon disavowed the commission's findings and ignored every recommendation.

Under the Controlled Substances Act, marijuana remains a Schedule I "narcotic" alongside heroin and LSD. Despite the fact that millions of patients use it medicinally with no toxic reactions, Schedule I inaccurately defines THC as having "high potential for abuse"[20] with "no accepted medical use" and a "lack of accepted safety."[21] The U.S. Drug Enforcement Agency claims the drug's chemistry is "not known and reproducible" and that there are "no adequate safety studies or studies proving efficacy." In fact, cannabis is one of the most widely studied drugs internationally. There are over 22,000 published studies in PubMed about cannabis; still the DEA, as recently as 2016, justified its decision because cannabis "does not meet the criteria for currently accepted medical use in treatment in the United States."[22]

"With cannabis, there is no risk of overdose or sudden death. Even more remarkable, cannabis treats pain in a way opioids cannot. Though both drugs target receptors that interfere with pain signals to the brain, cannabis does something more: It targets another receptor that decreases inflammation — and does it fast."

— Neurosurgeon Sanjay Gupta, MD

CLASS OF DRUG

In 1974, Congress established the National Institute on Drug Abuse (NIDA) to research only the harmful effects of cannabis and specifically prohibited studying the medical benefits of the plant. To this day NIDA is the only legal entity federally allowed to grow cannabis on U.S. soil. The legal cannabis crop is used for research purposes and is grown at the University of Mississippi. Because of a loophole in NIDA's Compassionate Investigational New Drug program,[23] it still distributes a can of pre-rolled marijuana cigarettes at no cost to four survivors of the original 20 patients in the program.[24]

A can of NIDA's pre-rolled marijuana joints, provided to an NIDA-approved glaucoma patient.

How Drugs Are

	DESCRIPTION
Schedule I	Drugs with no currently accepted medical use and a high potential for abuse. They are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence.
Schedule II	Drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.
Schedule III	Drugs with a moderate to low potential for physical and psychological dependence. Schedule III drug abuse potential is less than Schedules I and II, but more than Schedule IV.
Schedule IV	Drugs with a low potential for abuse and low risk of dependence.
Schedule V	Drugs with a lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes.

Classified in the U.S.

EXAMPLES

- Heroin
- Lysergic acid diethylamide
- Marijuana (cannabis)
- Methylenedioxymethamphetamine
- Methaqualone
- Peyote

- Combination products with less than 15 mg of hydrocodone per dosage unit
- Cocaine
- Methamphetamine
- Methadone
- Meperidine
- Oxycodone
- Fentanyl
- Morphine
- Methylphenidate
- Hydromorphone

- Combination products with less than 90 mg of codeine per dosage unit and buprenorphine
- Anabolic steroids
- Ketamine
- Testosterone

- Alprazolam
- Carisoprodol
- Propoxyphene
- Tramadol
- Benzodiazepines
- Diazepam
- Zolpidem

- Cough preparations with less than 200 mg of codeine per 100 mL
- Cannabidiol
- Ezogabine
- Attapulgite
- Difenoxin and Atropine

SOURCE: Drug Enforcement Administration

MEDICAL CANNABIS TODAY

The tide changed for medical cannabis in 1996 when the citizens of California voted in Proposition 215, the Compassionate Care Act, which created cooperatives between growers and patients and allowed anyone with a doctor's recommendation and a state-issued ID to purchase cannabis. Proposition 215 made no mention of distribution, sales, or taxation or regulation, but it brought the forgotten idea of medicinal cannabis back into the mainstream and paved the way for subsequent voter initiatives in other states.[25]

In 2013, the Justice Department in the Obama administration issued the Cole Memo which guided Federal prosecutors to not interfere with states that regulate cannabis programs and to allow states to enact their own laws.[26]

As of 2018, voters and patients in 33 states have enacted medical marijuana legalization.[27] The result is a patchwork of laws and regulations, approved medical conditions, products, and methods of delivery that vary from state to state. Because cannabis is still (confusingly) federally illegal, U.S. doctors are prohibited from prescribing medical marijuana and patients are forbidden from crossing state lines with their medications.

HEMP VERSUS CANNABIS

The differences between hemp and cannabis are thoroughly confusing, in large part because of the names. Both medical cannabis and hemp are known by the botanical name *Cannabis sativa*. Medical cannabis is also referred to as *Cannabis indica* or *Cannabis ruderalis*, but no one can seem to agree which name to use.[28]

Ruderalis

Most people today find it easier to distinguish Industrial Hemp from drug varieties. Industrial Hemp produces food, oil, fiber, and fuel, and is also planted in brown fields where it is used as a soil remediator. Most Industrial Hemp has a miniscule THC content, 0.2% to 0.4%, so it is not psychoactive. It does, however, produce CBD in the seeds and stalks, which means that much larger quantities of hemp are necessary to extract CBD than what is necessary with cannabis drug varieties.[29]

HEMP VERSUS CANNABIS

According to federal law, cannabis with 0.3% or less concentration of THC is not marijuana; it is Industrial Hemp.[30,31] In 2009, Senators Ron Paul and Barney Frank introduced the Industrial Hemp Farming Act to amend the definition of "marihuana" [sic] in the Controlled Substances Act to clarify the difference between hemp and marijuana.[32] Industrial Hemp was included in the 2018 Farm Bill which was signed by President Trump on December 20th, 2018. This legislature removed Industrial Hemp from the Schedule I drug classification per Section 10113 of the Farm Bill.[33] With the declassification of Industrial Hemp, products that contain CBD derived from legal hemp are now federally legal. The bill removes restrictions on the sale, transport, and possession of hemp-derived products, so long as those items are produced in a manner consistent with the law.

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THE DISCOVERY OF THE ENDOCANNABINOID SYSTEM

The Largest Receptor System in the Human Body

OBJECTIVE

This chapter charts how the 1964 discovery of tetrahydrocannabinol (THC) and cannabidiol (CBD) led to the 1988 discovery of the Endocannabinoid System (ECS), the largest receptor system and the master regulator of homeostasis in the human body. This chapter also discusses how and why cannabinoids (endogenous and external) interact with CB1 and CB2 receptors to treat a vast number of illnesses.

DISCOVERING THE ENDOCANNABINOID SYSTEM

In 1804 morphine was isolated from opium. Fifty years later cocaine was extracted from coca leaves. But the chemistry of cannabis, which was used much more widely, had remained a mystery—until 1964.[1] That's when Raphael Mechoulam, PhD, then a 34-year-old biochemistry graduate student at the Weizmann Institute, and Yehiel Gaoni, PhD, employed a new separation technology to isolate the two most prevalent compounds of the plant: cannabidiol, or CBD, and the psychoactive molecule delta-9-tetrahydrocannabinol, or THC.[2]

Since then, Mechoulam and his team of scientists at the Hebrew University have become the world authorities on the chemistry of the plant and the system of receptors, the Endocannabinoid System (ECS), with which it interacts. Now in his late 80s Dr. Mechoulam has published over 400 papers, edited four books, owns 25 patents, and has received 27 honors from six countries.[3] His findings have earned him the respect of scientists, policy advisors, doctors, politicians, growers, and other researchers around the world. Yet prohibition has effectively kept him relatively unknown considering the depth of his findings.[4]

Although the discovery of THC and CBD solved one mystery, more resounding discoveries were still to come. In 1988 an American chemist, Allyn Howlett, PhD, located a large grouping of receptors in the brain that responded to THC. The densest receptor concentrations are in the cortex, cerebellum, hippocampus, and basal ganglia, the brain areas that coordinate movement and control emotions, memory, pain, pleasure, and reproduction.[5] Interestingly, there are no receptors in the cardiac and respiratory centers of the brainstem, the areas that shut down the heart and lungs in cases of overdose. This is the physiological reason no one has ever died of a cannabis overdose, and why it is one of the safest, if not *the* safest, medicine on earth.[6]

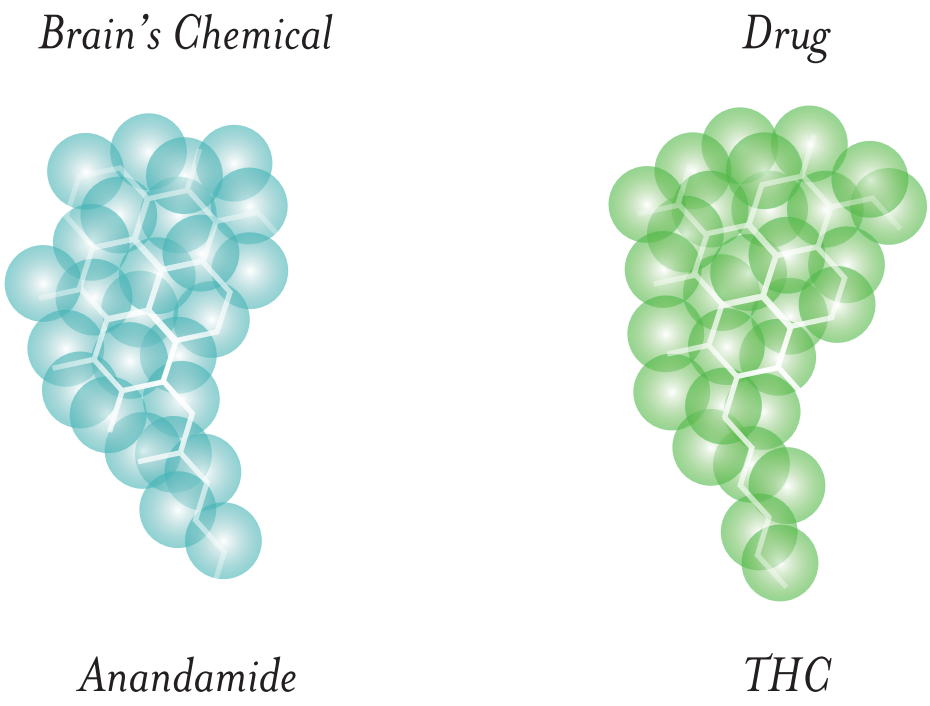
Raphael Mechoulam, PhD

In fact, the LD50 (the amount of an ingested substance that kills 50% of people) for cannabis is extremely low. It is estimated that the average human would have to smoke the equivalent of 20,000 to 40,000 joints in 15 minutes to kill him or herself.[7] This computes to more than 1,500 pounds of cannabis inhaled in 15 minutes. What's more, the rate of cannabis "dependence" is more akin to coffee than opiates or alcohol. "Withdrawal" symptoms are typically limited to insomnia, increased anxiety, and sweating.[8]

Mechoulam knew that the human body doesn't manufacture receptors to respond to plant substances—after all, it also makes endorphins that mimic the opiates found in the poppy flower from which morphine and heroin are derived.[9] So his team continued hunting for a compound similar to THC that the body itself produces to activate these receptors.

In 1992 Mechoulam's lab hit pay dirt when they found a brain chemical that mirrors the effects of THC. They named it anandamide after the Sanskrit word *ananda*, for "bliss." Just like THC, anandamide is thought to intensify sensory experience, stimulate appetite, temporarily blot out short-term memory, and create feelings of pleasure. Shortly after, the lab identified another brain chemical that mimics CBD, 2-Arachidonoylglycerol, which they named 2-AG.[10] Both are synthesized on demand from acids in cell membranes.

This led to the discovery of a galaxy of endocannabinoid receptors that extends into every organ, gland, immune cell, and connective tissue. Receptors in the brain are known as CB1 receptors; those in periphery are called CB2 receptors.[11] Many tissues contain both CB1 and CB2 receptors, each responsible for a different action.



SOURCE: NIDA

THE ENDOCANNABINOID SYSTEM: THE BODY'S SUPERCOMPUTER

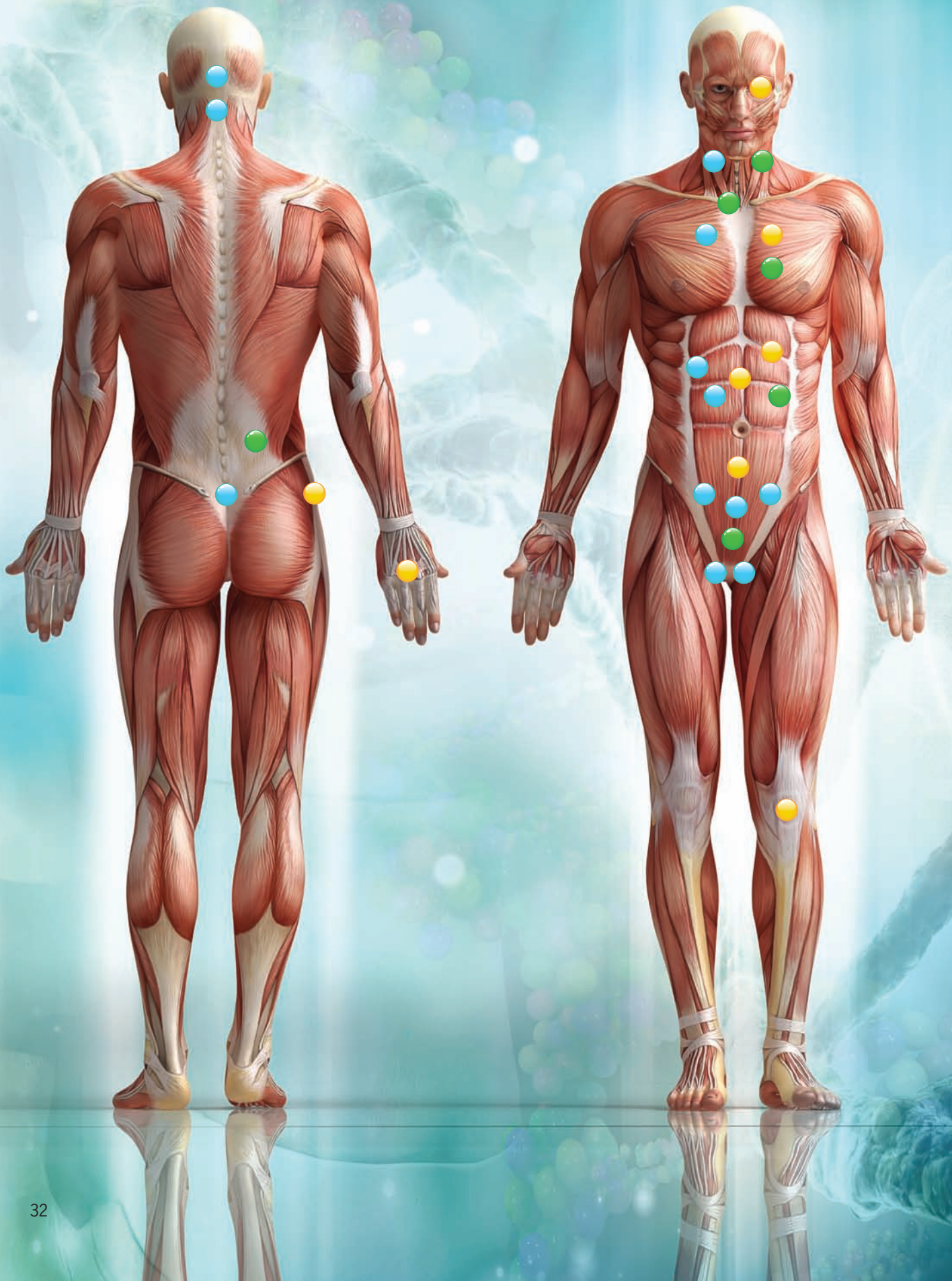
Broadly speaking, neurotransmitter systems can be compared to cell phone networks: the brain sends chemicals and electric impulses that command cells to communicate with each other.

Other neurotransmitter systems are better known because they were discovered first -- dopamine, serotonin, histamine -- but the ECS is the largest of all. One Italian researcher dubbed it "the body's supercomputer" because one of its primary functions is to keep every other bodily system in balance.[12] What's more is that it communicates with cells in two directions. Not only do commands originate from the brain, when an organ is in trouble, endocannabinoids transmit signals back to the brain in a cry for help.[13]

In the last 30 years new pharmaceuticals have been developed to activate various receptor systems, and the results have been wide ranging. Antihistamines, for example, initially targeted receptors in the nasal passages, but when additional histamine receptors were discovered in the digestive system, medications such as Zantac® or Prilosec® were developed to target and treat gastric illnesses. Underproduction of dopamine is connected to Parkinson's disease; overproduction is related to schizophrenia. Serotonin, which mimics the psychedelic compounds in psilocybin mushrooms, mitigates depression.[14]

Importantly, the ECS also maintains the body's homeostasis, acting as a chemical bridge between body and mind. It maintains a stable internal environment despite an ever-fluctuating external world. It regulates blood sugar, immune function, muscle and fat tissues, hormones, pain centers, reward centers, and metabolic functions. It maintains the heart's steady beat, the stomach's digestion, the lungs' bellows, and the speed at which bones heal. It enables us to forget pain and rewards us for eating and having sex.[15] Cannabinoids are also found at the intersection of the body's various systems, which allow different cell types to communicate. When an injury occurs, cannabinoids decrease the release of activators and sensitizers from the injured tissue, stabilize nerve cells by opening potassium channels to prevent excessive firing, and calm immune cells in the area to slow the release of inflammatory substances.[16]

Despite the fact that the U.S. government classifies cannabis as a Schedule I drug that it defined as having "no therapeutic value," it has owned patent #6,630,507[17] on cannabinoids as antioxidants and neuroprotectants since 2003. These understudied compounds are so promising that Julius Axelrod, the Nobel Prize winning biochemist who discovered dopamine pathways in the brain, is one of the patent's three signatories.



LOCATION OF CB1 AND CB2 RECEPTORS

CB1 RECEPTORS

Brain/CNS/Spinal Cord
Cortical Regions
Cerebellum
Brainstem
Basal Ganglia
Olfactory Bulb
Thalamus
Hypothalamus
Pituitary
Thyroid
Upper Airways
Adrenals
Ovaries
Uterus
Prostrate
Testes

CB2 RECEPTORS

Lymphatic and Immune System
Spleen
Thymus
Tonsils
Blood
Skin

CB1 AND CB2 RECEPTORS

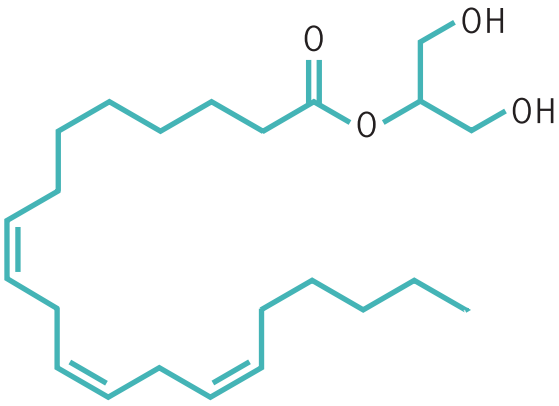
Eye
Stomach
Heart
Pancreas
Digestive Tract
Bone

WHY THE ENDOCANNABINOID SYSTEM ISN'T TAUGHT IN MEDICAL SCHOOLS

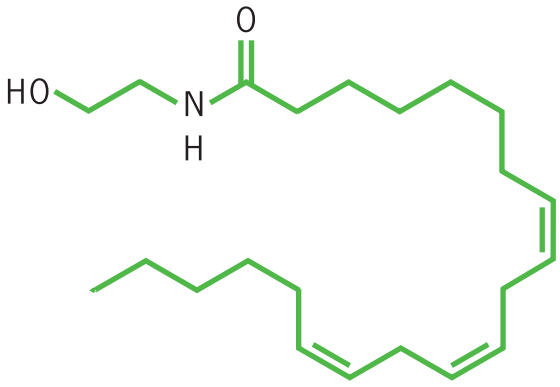
Cannabis' Schedule 1 status is the reason that no research institution has ever administered anandamide to a human being. "When insulin was discovered in the early 1920s, it was in the clinic within six months," Dr. Mechoulam has said. "When cortisone was discovered some 70 years ago, it was in the clinic within two years. No one has given anandamide or 2-AG to a human because the toxicology research – which costs millions of dollars [and is the first step in all clinical trials] hasn't been done yet. I've asked the National Institute on Drug Abuse many times -- I begged them actually, please do it—because a [pharmaceutical] company will not, and obviously an academic cannot do it. It's a technical thing. It's something that quite obviously should be done, yet it has not been done."[18]

This is also one of the reasons why the Endocannabinoid System is not taught in medical schools. It is in part due to the medical profession's bias against cannabis and botanical medicines in general, but it also makes little practical sense to spend time educating students about a bodily system that can only be treated by illegal compounds.

THE MOLECULAR STRUCTURE



2-AG
(2-Arachidonoylglycerol)

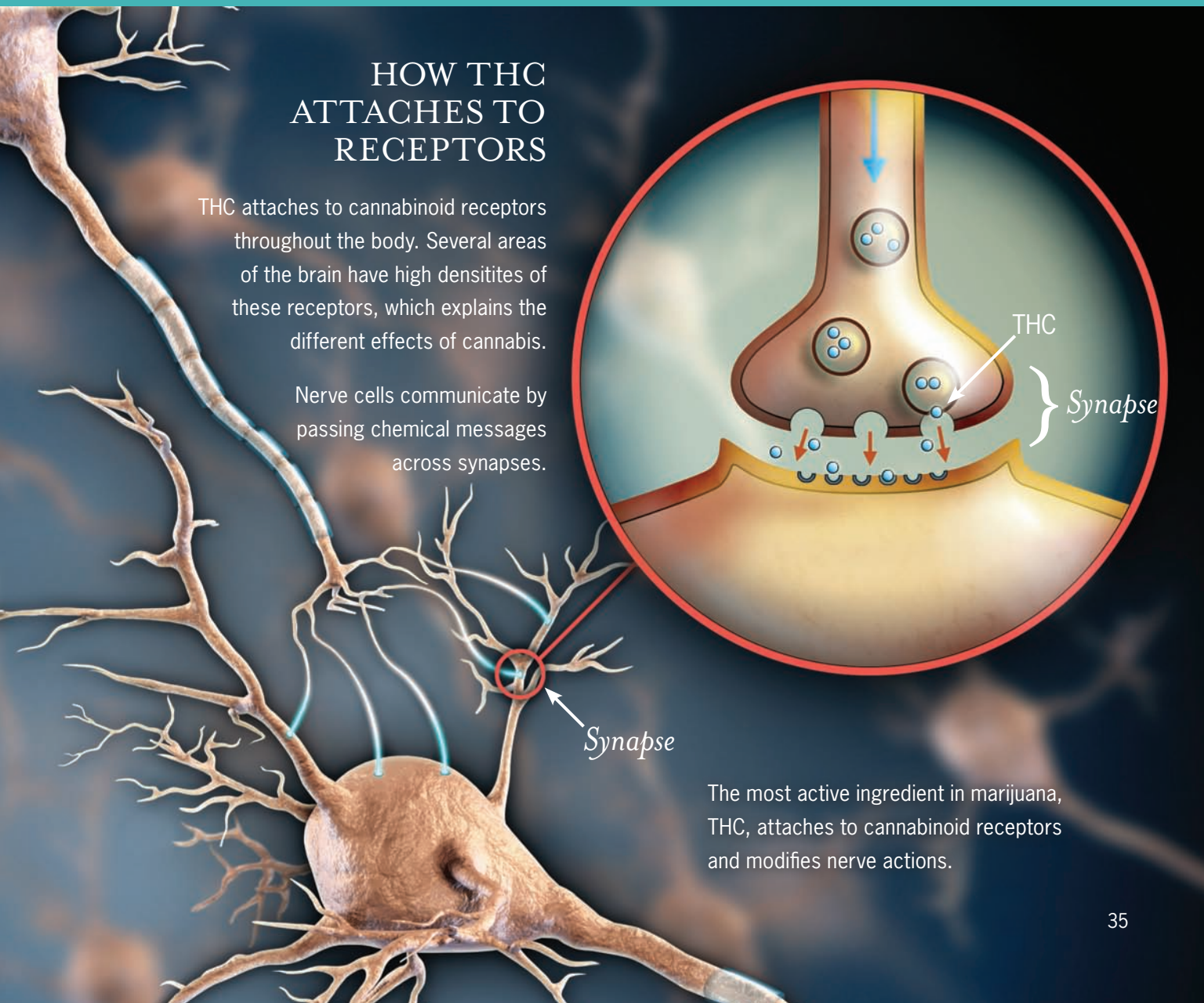


Anandamide
(N-Arachidonoylethanolamine)

"There were never so many able, active minds at work on the problems of disease as now, and all their discoveries are tending toward the simple truth that you can't improve on nature."[19]

— Thomas Edison, 1902

Cannabinoid research has proven this statement is still valid, and other countries are taking the lead by deploying cannabis to treat illnesses that have eluded modern medicine. In the last decade, Israel has built the world's largest state-supported medical cannabis program. Though it hasn't been widely advertised internationally, the program currently allows each of the 30,000 plus patients in it to receive 10 to 100 grams per month depending on the severity of the patients' conditions. The monthly cost to a patient is fixed at roughly $100 and is reimbursed by the Israeli National Health Insurance.[20]



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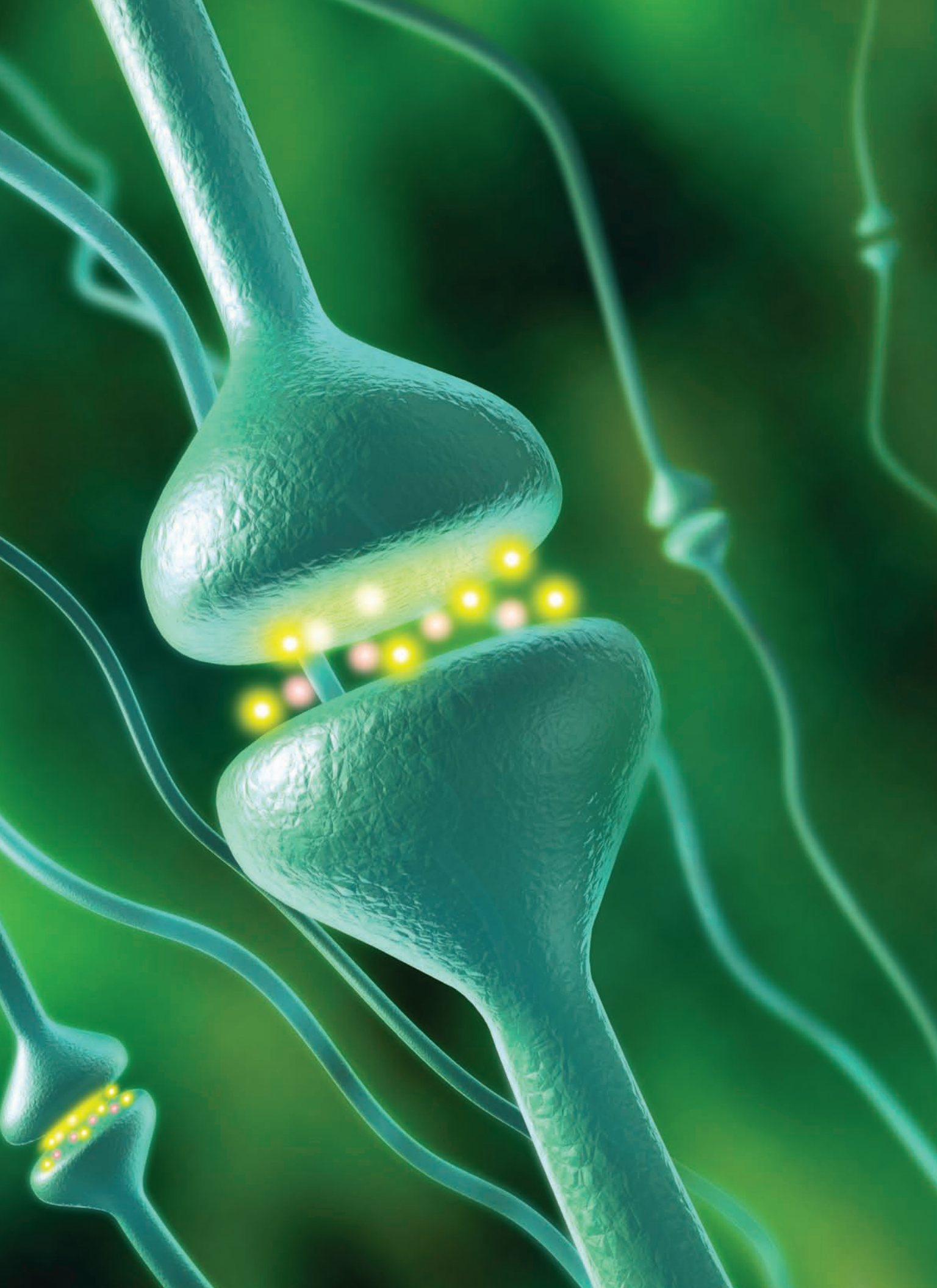


THE ENDOCANNABINOID SYSTEM

Master Regulator of the Body

OBJECTIVE

The Endocannabinoid System is deeply involved in maintaining homeostasis, neuroprotection, and other regulatory functions, many of which have yet to be discovered. It consists of endocannabinoids produced by the brain and a network of cannabinoid receptors located throughout the body. This chapter will provide an overview of how this system functions and how it is involved in so many disease states.

THE ENDOCANNABINOID SYSTEM

Cannabis is thought to treat a wide range of disparate illnesses, ranging from movement disorders such as Parkinson's and Huntington's disease, mood and anxiety disorders, PTSD, neuropathic and chronic pain, multiple sclerosis, and epilepsy to cancer, stroke, spinal cord injury, glaucoma, gastrointestinal disorders, migraine, and osteoporosis to name a few.[1] No other plant or medicine treats such a wide range of conditions,[2] and the reason is found deep within the 600-million year old endocannabinoid system (ECS), a series of regulatory mechanisms that is present in all animals except insects.[3]

The ECS is broad and complex in function. It consists of a network of endocannabinoid receptors that snakes throughout the central nervous and immune systems and within tissues including the brain, the gastrointestinal system, reproductive system, the spleen, endocrine system, and heart and circulatory system.

Endocannabinoids serve as primary messengers across nerve synapses and signal neurons to communicate with each other. They modulate the flow of neurotransmitters, keeping the nervous system running smoothly. Endocannabinoids affect circadian rhythms, rhythmical variations in blood pressure, peristalsis slow waves, and EKG and EEG rhythms.[4]

"Modulating endocannabinoid system activity may have therapeutic potential in almost all diseases affecting humans, including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy–induced nausea and vomiting, among many others."

— George Kunos, MD, PhD, and Scientific Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health (NIH) in Bethesda, Maryland, USA[5]

Research indicates that the ECS is deeply involved with homeostasis, helping to redress imbalances presented by disease or injury.[6] Many researchers believe that there are more physiological processes the ECS is involved with that have yet to be discovered.[7]

To understand how integral the ECS is to the development of complex organisms, consider the problems early life forms faced when evolving from single cells into multicellular organisms complete with bodies and organ systems. Bodies obviously face challenges that single cells do not. They need to distribute food and energy to various tissues so that cells far from the food source can receive nutrients and eliminate waste. A body must develop through stages–embryogenesis–in which embryonic cells, including stem cells, are directed to change into various types of tissues and organs as they grow. Bodies also need to cope with injury or disease, and damaged cells need to signal other parts of the body that they are in need of help; similarly, the body must be able to respond to these damaged cells with biochemical resources to heal or replace them. Not only do bodies need ways of monitoring changes within, but they also need to interpret changes in the environment and respond accordingly. The ECS directs all these processes.[8]

ENDOCANNABINOIDS

To date, five endocannabinoids have been isolated and all are derivatives of polyunsaturated fatty acids, closely related to Omega-3 fatty acids. The two most studied endocannabinoids are anandamide (arachidonoyl ethanolamide) and 2-AG (2-arachidonoylglycerol). Though they have a different molecular structure from THC and CBD, the molecules produced by the brain mirror the cannabinoids on the plant; both fit into the binding sites on cannabinoid receptors.[9]

Endocannabinoids are present in cell membranes throughout the body. Unlike traditional neurotransmitters, however, they become synthesized "on demand" from the cell membrane, rather than being stored in vesicles.[10]

ECS RECEPTORS

Cannabinoid receptors are the densest receptors in the brain, far more dense than opiate or nicotinic receptors.[11] This network is constantly relaying a massive amount of information about various states of cells, tissues, and organs. In the nervous system alone, cannabinoid receptors govern nerve transmission, memory, mood, emotion, pain perception, feeding, reproduction, metabolism, nerve protection (including nerve death caused by glutamate toxicity), as well as nervous system adaptability and brain development.[12] Of the five cannabinoid receptors identified to date, CB1 and CB2 are the most prevalent; they differ in terms of where they are located and what they do.[13]

CB1 receptors are primarily located in the central nervous system and affect many brain functions including movement, anxiety, stress, fear, pain, appetite, reward, and motor control. Activation of the CB1 receptor causes psychoactivity.[14]

In the brain, CB1 receptors are most highly concentrated in the cortex, cerebellum, hippocampus, and basal ganglia.[15] They are also present in glial cells, the support cells for neurons, and this is one likely reason why glioma tumor cells are more responsive to cannabinoid therapy than other types of cancers.[16] Much CB1 activity occurs in the nervous system at synapses, where nerve cells "talk" to each other. Because of their high densities in the brain, CB1 receptors are responsible for the effects of cannabis on short-term memory, cognition, mood and emotion, muscle motor function, pain perception, and nerve protection.[17] CB2 receptors are found in blood cells, the spleen, and in connective tissue. They control the release of cytokines – immuno-regulatory proteins – that are linked to inflammation during illness or after injury. CB2 activation causes no psychoactivity.[18]

HOW CANNABINOIDS ATTACH TO RECEPTORS

Cannabinoids and receptors interact in a lock and key paradigm, but the mechanism is more intricate than other receptor systems. CB1 receptors have at least two landing spots, one for THC and another for CBD. When there is a low amount of CBD present, THC easily occupies that binding site. However, when more CBD is present, it lands on the receptor first and makes THC binding more difficult.[19] This is how CBD modulates the effects of THC, which is important to keep in mind when dosing.

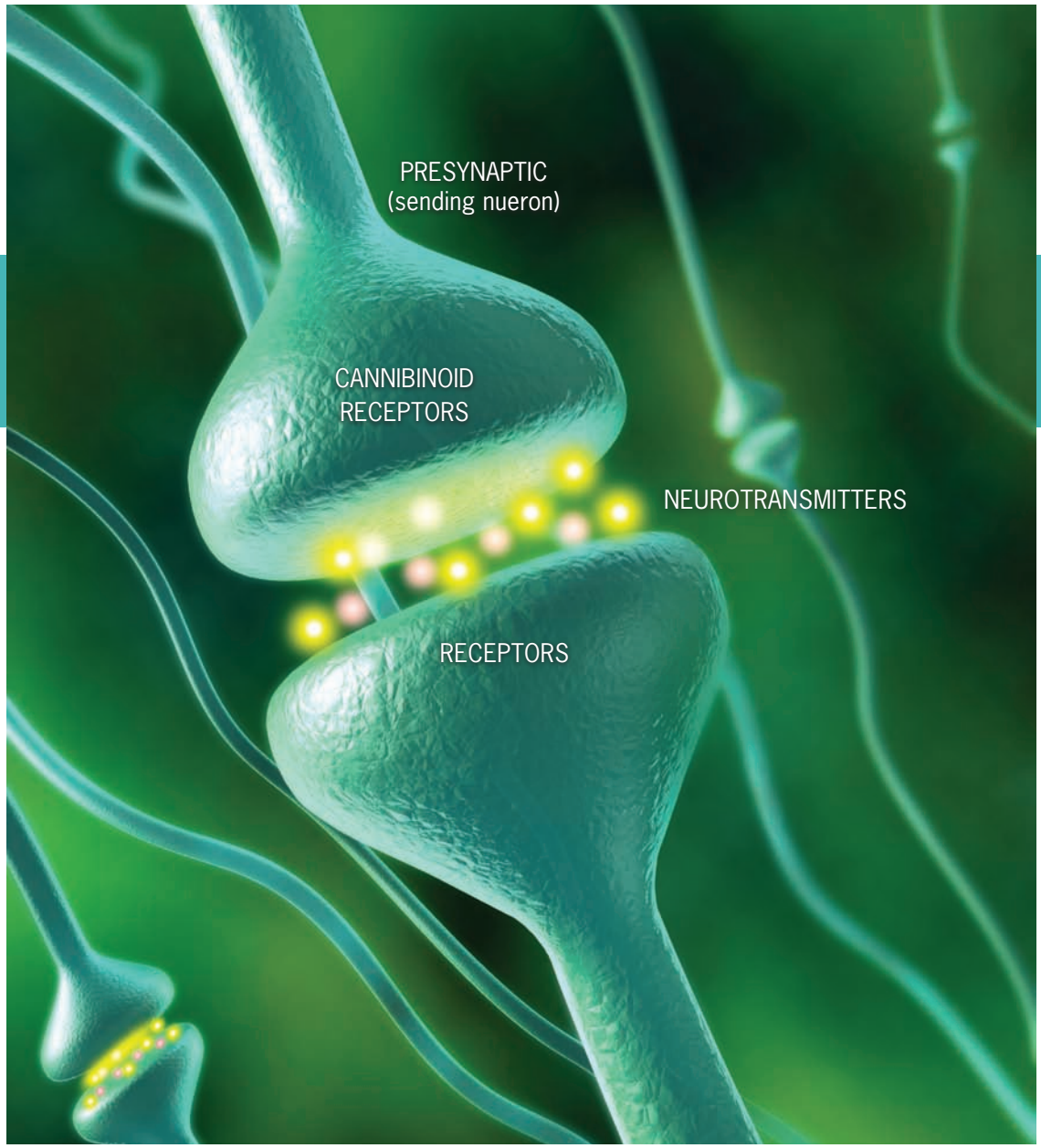
It is also why different strains with identical levels of THC can produce different medical results. When CBD is combined with THC, the entourage effect of the two molecules magnifies the positive medical aspects – such as pain relief – while reducing adverse effects, such as short-term memory loss and anxiety. In other words, THC and CBD are like some older married couples: they fight with each other, but actually get along best when they're together.[20]

Two primary endocannabinoid receptors have been identified: CB1 and CB2. CB1 receptors are found predominantly in the brain and nervous system, as well as in peripheral organs and tissues, and are the main molecular target of the endocannabinoid ligand (binding molecule), anandamide, as well as its mimetic phytocannabinoid, THC.

One other main endocannabinoid is 2-Arachidonoylglycerol (2-AG) which is active at both cannabinoid receptors, along with its own mimetic phytocannabinoid, CBD, CB2 receptors are found throughout the body in the immune cells.

Receptors Are Found on All Cell Surfaces

CB1 Receptors are responsible for marijuana's psychoactive effects. They are present in many areas of the brain and play a role in memory, mood, sleep, appetite, and pain sensation.



CB1 Receptors are responsible for marijuana's anti-inflammatory effects. They are found in immune cells and work to reduce inflammation. Inflammation is an immune response and is believed to be a factor in many diseases and conditions.

THE HUMAN ENDOCANNABINOID SYSTEM

The Endocannabinoid System (ECS) is a group of endogenous cannabinoid receptors located in the mammalian brain and throughout the central and peripheral nervous systems consisting of neuromodulatory lipids and their receptors. Known as "the body's own cannabinoid system," the ECS is involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory.

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CBD, CBN, and THC fit like a lock and key into existing human receptors. These receptors are part of the ECS which impact physiological processes, affecting pain modulation, memory and appetite, plus anti-inflammatory effects and other immune system responses.

THC/TETRAHYDROCANNABINOL

The chemical responsible for most of marijuana's psychological effects. It acts much like the cannabinoid chemicals made naturally by the body. THC bonds to the CB1 receptors.

CBD/CANNABIDIOL

Cannabidiol is one of the least 113 active cannabinoids identified in cannabis. It is a major phytocannabinoid accounting for up to 40% of the plant's extract.

CBN/CANNABINOL

CBN acts as a partial agonist at the CB1 receptors, but has a higher affinity to CB2 receptors but with lower affinities in comparison to THC.

RETROGRADE INHIBITION

Unlike other receptor systems, information from the ECS can flow backwards or "upstream" from traditional nerve pathways, a process known as retrograde inhibition. This is one of the ways the system functions to protect the nervous system from hyperactivity.[21] In certain illnesses, such as seizures seen in epilepsy, an "electrical storm" rages in the brain when too many individual neurons are overstimulated. The ECS allows nerve cells on the receiving end to call a "time-out" by sending a signal upstream to quiet the system.[22]

In traumatic brain injury, mounting data suggest that endocannabinoids have neuroprotective effects through retrograde inhibition.[23] When cannabinoids are administered within four hours of trauma, they appear to curtail glutamate toxicity and reduce neuronal damage.[24] More research is needed to demonstrate this conclusively.[25] Retrograde inhibition also works on pain pathways in a similar way. When pain signals are extreme or overwhelming, retrograde inhibition uses cannabinoids to slow or reduce the impulses coming from injury.[26]

A SPRAWLING SYSTEM UNLIKE OTHERS

The sprawling structure of the ECS makes it difficult to design drugs that target just one function. Because receptors are dispersed so widely in the body, targeting one group for activation or deactivation can unleash a host of unforeseen activity in other areas. The most striking example occurred with the drug Rimonabant, which the French pharma company Sanofi-Aventis released in 2006. Rimonabant, a CB1 antagonist, was approved in Europe to treat obesity (the FDA declined to approve it in the U.S.). Within two years Sanofi-Aventis pulled Rimonabant from the market because it was causing patients to feel darkly depressed, and at times, suicidal. Further investigation revealed that in addition to blocking appetite, Rimonabant also blocked the receptors in the brain's reward centers. It not only killed appetite, it also killed joy.[27]

Such are the challenges of trying to engineer a single molecule drug that works on selective receptors.

ENDOCANNABINOIDS AND HUMAN THRIVING BEHAVIOR

"The ECS is critical to human survival. At the most basic level it controls how we eat, sleep, relax, forget and protect ourselves". Vincenzo Di Marzo, PhD, Research Director of the Institute of Biomolecular Chemistry of the National Research Council in Pozzuoli, Naples, Italy.[28]

The effects of cannabinoids on thriving is an unusual topic because it does not fit contemporary healthcare models in which medicines are used to only treat illnesses. But the distinction is profound. While it's too early to weave together a unified theory on how cannabinoids encourage human thriving behavior, science has identified various interesting clues. Take, for example, forgetting. While most people view forgetting as a memory lapse, Professor Mechoulam has repeatedly pointed out just how important it is for our brains to edit the torrent of sensory data that assault us daily. If we were unable to block out the sights, sounds, smells, and other sensory input coming at us while driving, for example, we would be paralyzed by overstimulation, unable to focus… and miserable.

Forgetting is also crucial to treating illnesses like Post-Traumatic Stress disorder (PTSD). Cannabis is known to be useful in helping sufferers eliminate painful memories that lodge in the minds and haunt them, often for life. In Mechoulam's view, certain chemicals lock in memories and cannabinoids can help lock them out. Studies with Holocaust survivors and Vietnam War veterans indicate that cannabis effectively eradicates harrowing memories that turn sufferers into zombies. No other medicine does this.[29]

The same is true with other traumas, phobias, neuroses, and pain. Pain is one of the most difficult experiences to recall once it is over and that is evolutionarily adaptive – think about how many single child families there would be if women could not forget the agony of childbirth. Cannabinoids play a crucial role in helping human beings forget pain and move on.

The endogenous cannabinoid system—named for the plant that led to its discovery—is one of the most important physiologic systems involved in establishing and maintaining human health. Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells.

BRAIN AREAS WITH HIGH RECEPTOR GROUPINGS/CONCENTRATIONS	CORRESPONDING TEMPORARY EFFECTS OF MARIJUANA
Cerebral Cortex Memory, thinking, perceptual awareness, consciousness	Perceptual distortions, memory impairment, occasional disorientation
Hypothalamus Governs metabolic processes such as appetite	Increased appetite
Brain Stem Arousal, vomiting reflex, blood pressure, heart rate. Also involved in pain sensation, muscle tone, and movement.	Nausea relief, increased heart rate, reduced blood pressure, drowsiness
Hippocampus Memory storage and recall	Memory impairment
Cerebellum Coordination and muscle control	Reduced spasticity, impaired coordination
Amygdala Plays a role in emotions	In high doses, anxiety and panic; in low doses, reduced anxiety and blocking of traumatic memories

HOW CANNABINOIDS ATTACH TO RECEPTORS

Cannabinoids attach to receptors on nerve cells in the brain, modulating their function. In the nervous system alone, cannabinoid receptors govern nerve transmission, memory, mood, emotion, pain perception, feeding, reproduction, metabolism, nerve protection (including nerve death caused by glutamate toxicity), as well as nervous system adaptability and brain development.

INFANT AND EARLY CHILDHOOD DEVELOPMENT

Further clues that cannabinoids encourage wellness were unearthed in a 1990s study on the effects of cannabis on newborns by Dr. Melanie Dreher, the Dean of Nursing at Rush Medical Center in Chicago.

In the early 1990s, Dreher traveled to Jamaica to investigate how a group of rural and largely impoverished Rastafarian women use cannabis to maintain appetite, help them rest, and allay nausea when pregnant. These women also serve a mild cannabis tea to their families as a daily health tonic – when you are poor, forestalling illness is less expensive than treating it once it hits.

Dreher followed 30 "Roots Daughters" and their babies for five years until the children were school age. Results showed that infants of mothers who utilized cannabis socialized and made eye contact more quickly and were also easier to engage than the babies of nonsmokers. Nor were the children in the study developmentally disadvantaged. In fact, the 5-year-old children of smokers scored higher on tests for verbal ability, memory, mood, and motor, perceptual, and quantitative skills than children of non-users.[30]

Dreher's findings, while confined to a small sample group, contradicted everything that "experts" had pronounced about the plant's deleterious effects on children. Yet they were published in 1994 to resounding silence. (Dreher applied to the National Institute on Drug Abuse for additional funding to return to Jamaica to follow the same children at age 10, but her request was denied.)

A few years later, and completely independently, Dr. Ester Fride found physiological corroboration of Dreher's findings.

Fride (who died in 2010) was a neuroscientist and colleague of Mechoulam, and was investigating the ways cannabinoids affect newborn development by testing them on rats with their endocannabinoid systems "knocked out" genetically. Her science showed that without functioning ECS, newborns failed to suckle or begin maternal bonding.[31] Further investigation showed that endocannabinoids are essential to a newborn's ability to thrive as it grows and develops.[32] Even more interestingly, Dr. Fride discovered that cannabinoid receptors develop extremely slowly in babies, which is why young children do not experience psychoactivity when they take cannabis. This observation had been anecdotally reported in 19th century medical reports, which noted that children could tolerate mighty doses of cannabis that would have left their parents reeling.[33]

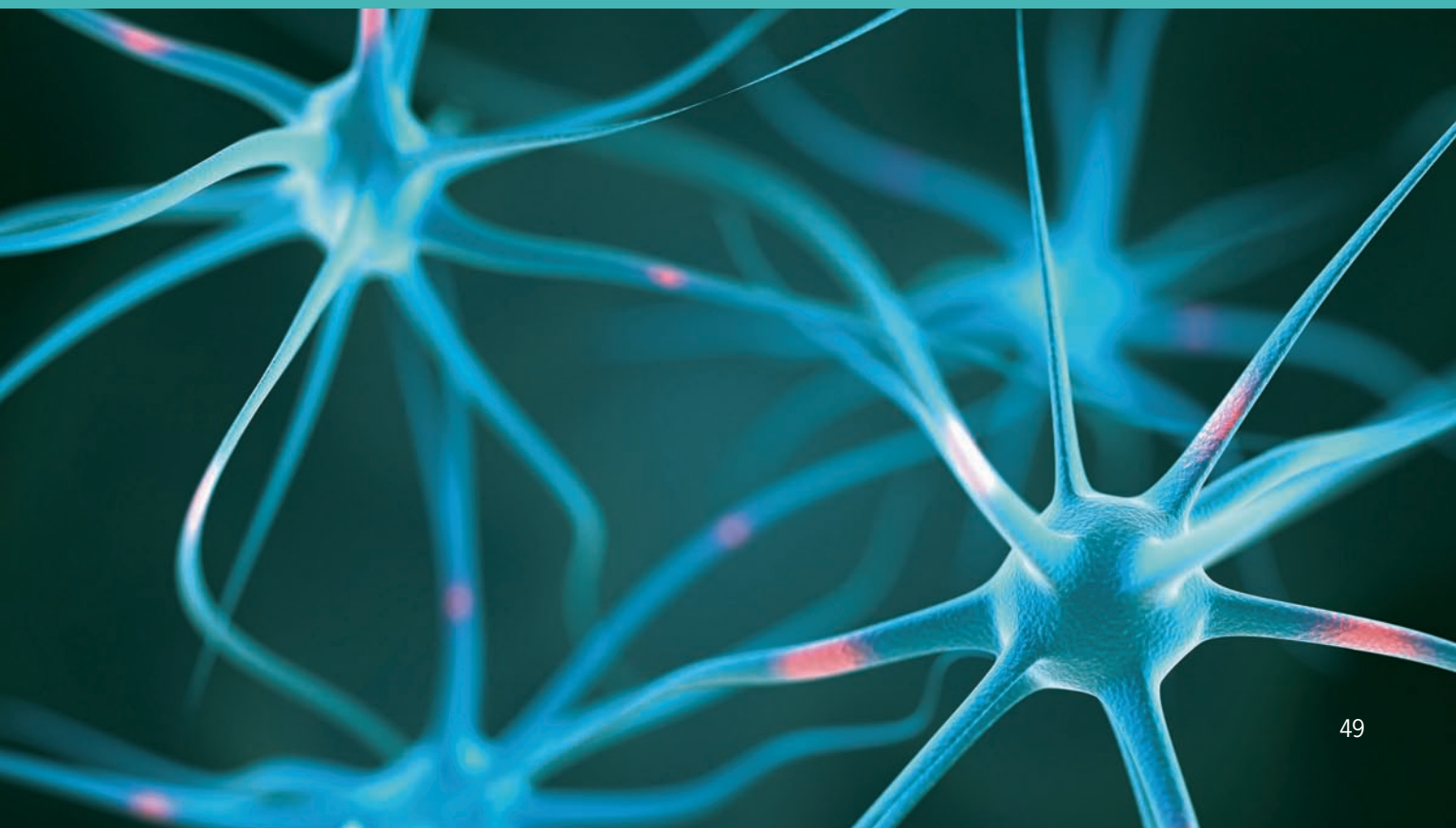
Dreher asks, "Is it an evolutionary accident that the two activities necessary to sustain life and perpetuate the species are eating and sex and that cannabis makes both things more pleasurable?"[34] Or, as Dr. Allyn Howlett put it to writer Michael Pollan: All of the things endocannabinoids do "are exactly what Adam and Eve would want after being thrown out of Eden. You couldn't design a more perfect drug for getting Eve through the pain of childbirth and helping Adam endure a life of physical toil."[35] In other words, cannabinoids help us to cope with the human condition.

CBD, CBN, and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system, which impacts physiological processes, affecting pain modulation, memory, appetite, plus anti-inflammatory effects, and other immune system responses.

THC, or tetrahydrocannabinol, is the chemical responsible for most of marijuana's psychological effects. It acts much like the cannabinoid chemicals made naturally by the body. THC bonds to the CB1 receptors.

CBD, or cannabidiol, is one of the least 113 active cannabinoids identified in cannabis. It is a major phytocannabinoid accounting for almost 40% of the plant's extract.

CBN acts as a partial agonist at the CB1 receptors, but has a higher affinity to CB2 receptors with lower affinities in comparison to THC.



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NOTES

CANNABINOIDS AND TERPENES

One Plant, One Very Complex Chemical Factory

OBJECTIVE

This chapter discusses endogenous and exogenous cannabinoids and the mechanisms through which they interact with the vast network of receptors in the Endocannabinoid System (ECS). It also discusses some of the other cannabinoids and terpenes naturally occurring in cannabis and the differences between treating with botanical medicines versus single molecule compounds.

MAJOR CANNABINOIDS

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the major cannabinoids produced by the cannabis plant. As discussed in the previous chapter, these cannabinoids mirror endogenous cannabinoids produced by the body. THC is a mirror image of the endocannabinoid anandamide, and CBD mirrors 2-Arachidonoylglycerol (2-AG).

- THC -

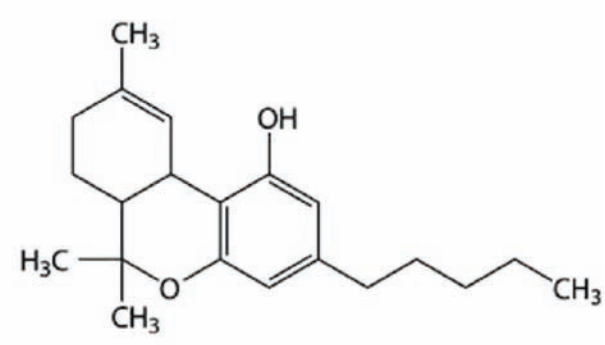
THC is the most recognized cannabinoid and is the primary psychoactive compound in cannabis. It has been found to be a neuroprotective with analgesic effects. THC produces psychoactive and euphoric effects. These effects are caused by the THC primarily binding with CB1 receptors, which are densest in the brain and central nervous system. It has been found to treat symptoms of conditions such as anxiety, glaucoma, insomnia, muscle spasticity, nausea, appetite, and pain. Although most illicit drugs are considered to be neurotoxic, THC research has found it to be a neuroprotective.

- CBD -

CBD has been attributed with many medical benefits and has resulted in new hybrid cannabis strains being created to increase the CBD content. CBD can be extracted from industrial hemp, which was legalized in 2018 with the passing of the Farm Bill. This major cannabinoid has no psychoactive effects and primarily binds with CB2 receptors. It can also mitigate the psychoactive effects of THC by interfering with THC binding. CBD is used to treat symptoms of conditions such as anxiety, seizures, inflammation, depression, migraines, inflammatory bowel disease, and pain. CBD has been found to indirectly help with sleep by easing anxiety symptoms.

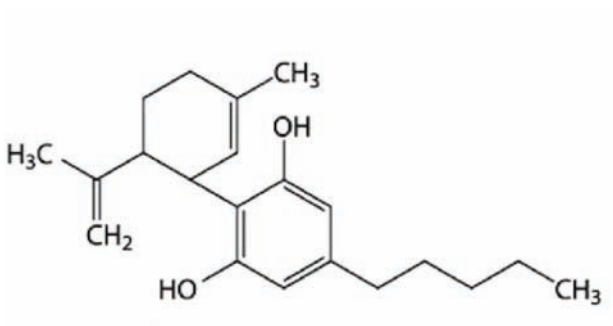
THC

(TETRAHYDROCANNABINOL)



CBD

(CANNABIDIOL)



MINOR CANNABINOIDS AND TERPENES

The cannabis plant contains over 600 chemical compounds, and more are discovered each year. The two most prevalent cannabinoids are THC and CBD. There are also so-called minor cannabinoids – CBG, CBC and CBN – and terpenes, the aromatic oils also found in spices, fruits, and vegetables. (It is mistakenly assumed that THC and CBD cause the powerful aroma of cannabis, but THC and CBD are odorless. Terpenes are the culprits.) Over the years researchers have struggled to understand why different varieties of cannabis produce such a wide range of medicinal and psychoactive effects. It is now clear that this variance is the result of all of these compounds acting in concert.

MINOR CANNABINOIDS

Of the 113 cannabinoids produced by the plant only a handful are produced in any significant quantity. In addition to THC and CBD, they include CBG, CBC, CBN, and tetrahydrocannabivarin (THCV) (though technically CBN and THCV aren't produced by the plant; they're an oxidation byproduct of THC).[1]

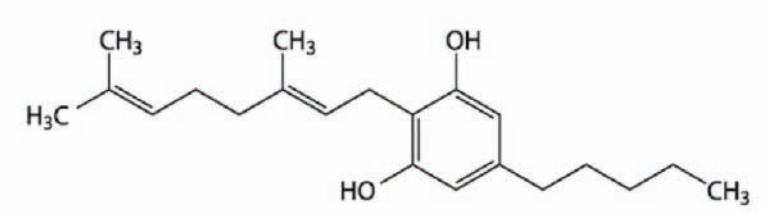
The name "minor cannabinoid" is somewhat deceiving: It is not that their power is minor, but they occur in smaller quantities.

- CBG -

Cannabigerol is the third most prevalent cannabinoid after THC and CBD, and it is more commonly found in hemp varieties than cannabis drug varieties.[2] CBG is analgesic and not psychoactive and has been shown to be effective in treating inflammatory bowel disease (IBS/IBD) in animal models.[3] It is also of interest because of its antiseptic and antibiotic properties, which are effective in fighting high-resistance staph infections including MRSA.[4] CBG has been found to be a bone stimulant, antibacterial, anti-inflammatory, antifungal, and also lowers blood pressure and inhibits tumor growth.

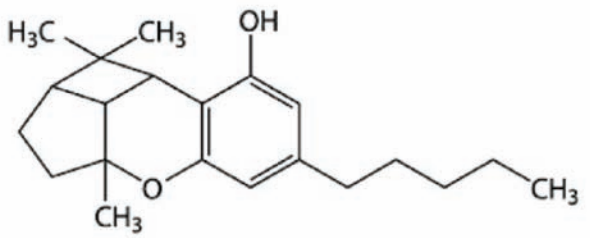
CBG

(CANNABIGEROL)



CBC

(CANNABICHROMENIC)



- CBC -

Cannabichromenic acid is rare and produced early in the plant's flowering cycle.[5] It is an antibiotic and antifungal, two properties that may protect the plant in its early life.[6] Like many cannabinoids it is also anti-inflammatory and analgesic and may have some antidepressant effects as well.[7] CBC has been found to be a bone stimulant, antibacterial, anti-inflammatory, and antifungal, and also lowers blood pressure and relaxes the veins.

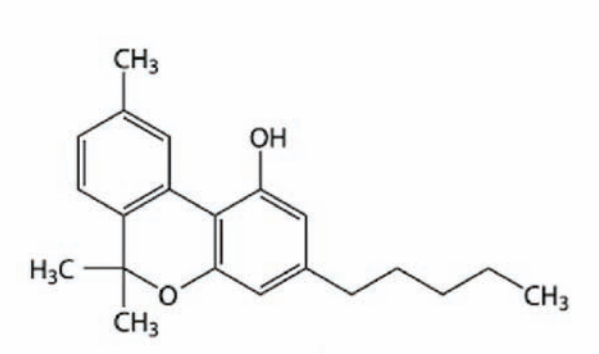
- CBN -

Cannabinol, is not produced by the plant but is a THC breakdown product that occurs after the oils have dried out. It is not psychoactive but does cause sedation when combined with THC and has some anti-seizure, anti-bacterial, and analgesic activities, demonstrating that even old cannabis might have some limited medicinal value.[8,9] CBN reportedly has three times the affinity for the CB2 receptor than the CB1 receptor, which is why it is believed to have a greater effect on the immune system than the nervous system.[10] CBN has been found to be a pain reliever, sleep aid, and anti-inflammatory, and can relieve muscle spasms.

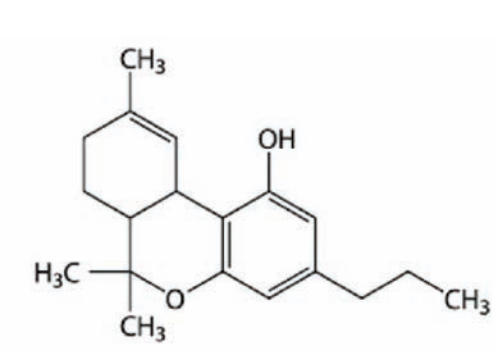
- THCV-

THCV is the bioactive neutral form of tetrahydrocannabivarinic acid or THCVA, a propyl form of THC – which means that the THC atom has a three-carbon tail instead of the more common five-carbon tail. There is no consensus about whether THCV is psychoactive or merely modulates the psychoactivity of THC. Older research considers THCV to have about 25% of the potency of THC, but more contemporary research claims that THCV produces no psychoactivity by itself. THCV has analgesic, anti-inflammatory, and anticonvulsant effects – and may encourage weight loss and increased energy expenditure.[11] THCV has been found to decrease seizures and suppress appetite. It is also a bone stimulant, analgesic, and anti-inflammatory.

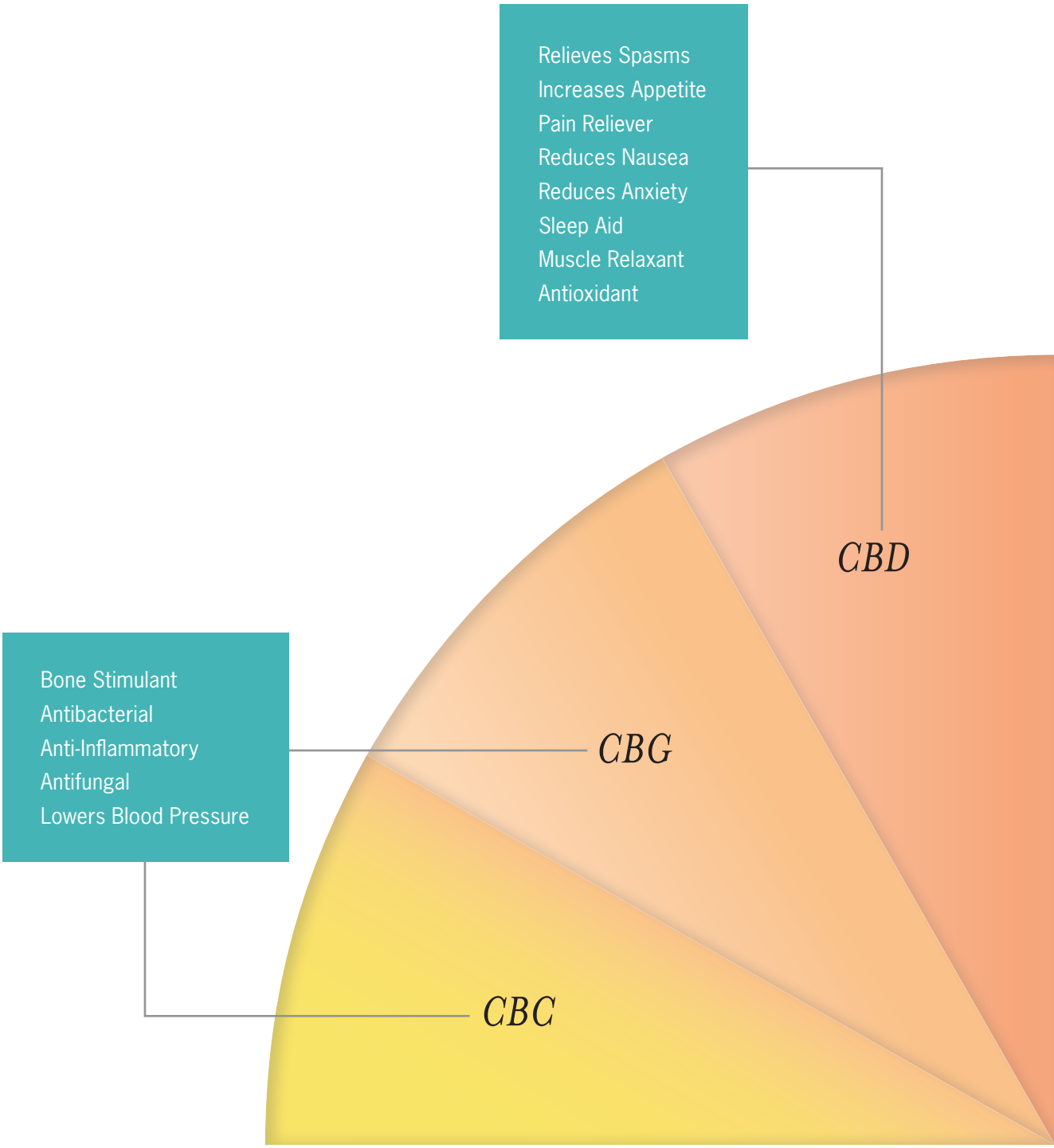
CBN
(CANNABINOL)



THCV
(TETRAHYDROCANNABIVARINIC)

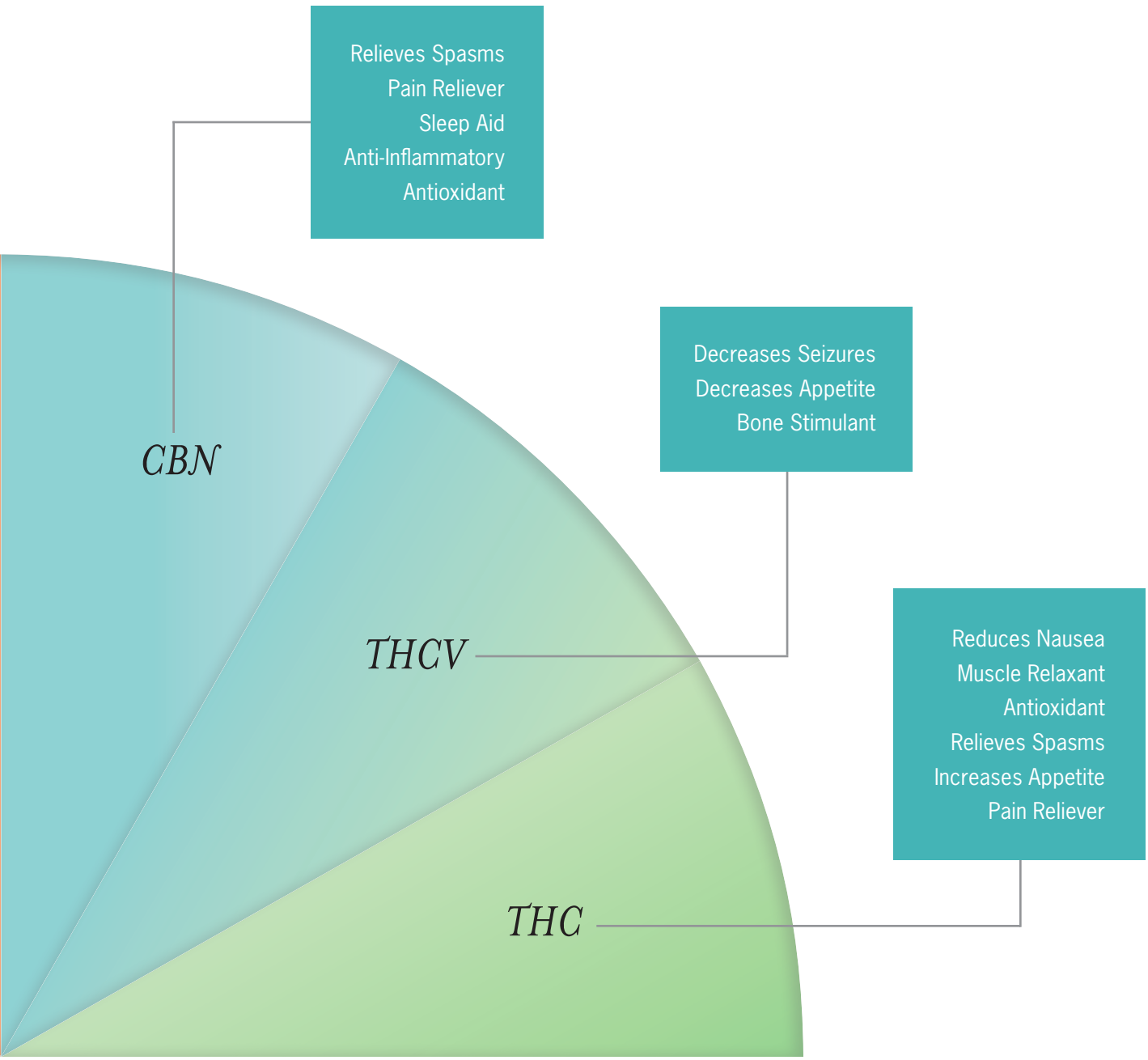


CANNABINOID



NON-PSYCHOACTIVE

GUIDE



PSYCHOACTIVE

TERPENES

Terpenes are powerful odor molecules that are found primarily in the plant's trichomes. It is thanks to terpenes that cannabis has such an enduring pungency.

Many plants make terpenes – they are part of their defense systems. Cannabis has about 200, the most common of which are also key components in lemon, pepper, lavender, hops, and pine. As previously mentioned, the terms "indica" and "sativa" are used throughout this handbook since they are part of the common lexicon, but they are not reliable indicators of the stimulating or sedative qualities of one particular strain. The strength and combination of terpenes are better guides as to how a strain will affect a patient's mood.[12]

Out of these natural compounds, several terpenes are under studies of clinical trials. The most common terpenes found in cannabis are pinene, linalool, mycrene, limonene, terpineol, ß-caryophyllene, and geraniol. These terpenes are being studied for their anti-inflammatory, analgesic, and sedative effects.

It is commonly assumed that THC and CBD cause the powerful aroma of cannabis, but THC and CBD are odorless. The strong aroma of the cannabis flower comes from the odor of the terpenes.

You can find terpenes in most plants and foods.

THE 411 ON TERPENES

- Terpenes are the most common plant chemicals found in nature - over 30,000 identified.[13]
- Cannabis produces several hundred different terpenes.[14]
- Plants use terpenes to protect themselves from disease, animals, insects, and even other more invasive plants.[15]
- Initial studies indicate terpenes must exist in a concentration of 0.05% or more of plant material for therapeutic impact.[16]
- Cannabinoids may increase the ability of terpenes to cross the blood/brain barrier.[17]

Trichomes contain terpenes, which give cannabis its distinct smell and look like "frost" on the flowering plant.

TERPENE

TERPENE	SMELLS LIKE
Limonene	Strong Citrus - The sour/sharp smell in the rinds of citrus fruits and other flowers. Prevalent in cannabis.
Myrcene	Hops, Mango - The “green” musky odor found in bay, thyme, mango, and hops. Prevalent in most types of cannabis.
Pinene	Strong Pine - Most common occurring terpenoid.
Ocimene	Fruity, floral - Some say “wet cloth” smell
Linalool	Lavender, Floral.
β-caryophyllene	Peppery, Clove - Found in the background of black pepper, oregano, and clove.
Terpinolene	Pine, Sweet Herbal, Anise, and Lime - Primarily isolated from trees, present in high amounts in turpentine.
a-humulene	Hoppy, Earthy - Responsible for an India pale ale (IPA)’s signature hoppy aroma.
Nerolidol	Floral, Citrus - And some say “fresh bark” smell.

CHART

See Terpene Reference List on page 72.

MEDICAL USES AND BENEFITS

Works as an antidepressant[1,2] and can cause breast cancer cells to commit suicide.[2] It has been used clinically to dissolve gallstones,[3] improve mood,[1,2] and relieve heartburn and gastrointestinal reflux.[2]

Works as a sedative,[1,2] muscle relaxant, hypnotic,[4] analgesic (painkiller),[1,2] and anti-inflammatory.[1,2] Also potentiates the effects of THC.

Works as an anti-inflammatory[1,2] and a bronchodilator.[1,2] It is potentially helpful for asthma[1,2] and promotes alertness and memory retention by inhibiting the breakdown of acetycholinesterase,[1,2] a neurotransmitter in the brain that stimulates these cognitive effects.

Exhibits anti-inflammatory effects in white blood cells and antifungal effects with the human specific *Candida* species and - has also been effective in fighting the SARS virus.[6] Frequently used in perfumes for its pleasant odor.[5]

Anti-anxiety[1] and stress reducing. A powerful anticonvulsant[2] that also amplifies serotonin-receptor transmission,[1,2] thus serving as an antidepressant. Found to be a calming sedative and good for sleep.

Gastro-protective,[1,2] good for certain ulcers,[1,2] and shows great promise as a therapeutic compound for inflammatory conditions[1,2] and autoimmune disorders. Can be used as a dietary supplement with strong anti-inflammatory analgesic effects and has low attributable psychoactivity.

Unlike other terpenes, does not have analgesic or anti-inflammatory effects.[6] Works as an anti-bacterial agent, increases antioxidant capacity levels in white blood cells, and has shown anti-cancer effects in rat brain cells and anti-insomnia effects in mice brain cells.[5] Further effective in fighting glial cell cancer and leukemia.[6]

Anti-inflammatory, also acts as an appetite suppressant.[5] Most prevalent in hops, where it derives its name, and often found along with β-caryophyllene. Responsible for the “hoppy” smell of strong beers such as an IPA.

Works as a sedative with potent antifungal and antimalarial activity.[5] Further effective in delivering drugs through the skin, and may be a toxin against harmful protozoa like malaria and leishmaniasis.[6] Low levels are present in orange and other citrus peels.[5]

THE ENTOURAGE EFFECT

The medicinal effect of these terpenes and cannabinoids is amplified when they are all used together. This complicated interplay of chemicals is known as the entourage effect.[18] Put simply: The sum of cannabis' chemical parts is greater than any one of its individual components.

The entourage effect is easily explained in musical terms: Individual instruments produce lovely sounds on their own, but the majesty of a symphony can only be realized when they are playing together. In this analogy, terpenes are the violins and flutes, but only when they mix with other cannabinoids is the symphonic complexity of the healing realized.

This also explains how cannabis has bedeviled pharmaceutical companies in their attempts to isolate single molecule medicines, such as Marinol® (Dronabinol), a synthetic THC developed by Unimed Pharmaceuticals and approved by the FDA in 1985. Marinol® is poorly tolerated by patients who report more unpleasant levels of sedation and dysphoria than produced from whole plant cannabis.[19] Even though the U.S. government fast-tracked Marinol® development and placed it in Schedule III to encourage use, patients didn't like it and it has never lived up to its promise.

Another benefit of the entourage effect is that secondary compounds can reduce the negative effects of THC. For example, strains containing high levels of CBD magnify the pain-relieving properties of THC, while at the same time reducing anxiety, irritability, and short-term memory loss.[20]

The entourage effect is easily explained in musical terms: Individual instruments produce lovely sounds on their own, but the majesty of a symphony can only be realized when they are playing together. In this analogy, terpenes are the violins and flutes, but only when they mix with other cannabinoids is the symphonic complexity of the healing realized.

TOLERANCE AND ENDOCANNABINOID SYSTEM DOWN REGULATION

Over time, patients may develop cannabis tolerance, which forces them to take more and more medication to achieve the same therapeutic effects. Unlike opiates, in which higher doses increase risk of death, this is not the case with cannabis due to its low toxicity and the location of ECS receptors in the brain.[21] In fact, cannabis tolerance differs from tolerance to most other medications.

Here's why:

Drugs such as heroin, cocaine, amphetamines, alcohol, and nicotine make us feel well by pumping up production of dopamine, which titillates the brain's reward receptors. Heroin and oxycodone are so addictive because the brain quickly learns to maximize the amount of dopamine it produces, which drives addicts to take more heroin, until the body requires those elevated levels to maintain homeostasis. If the body doesn't get its fix, withdrawal sets in and suffering ensues.

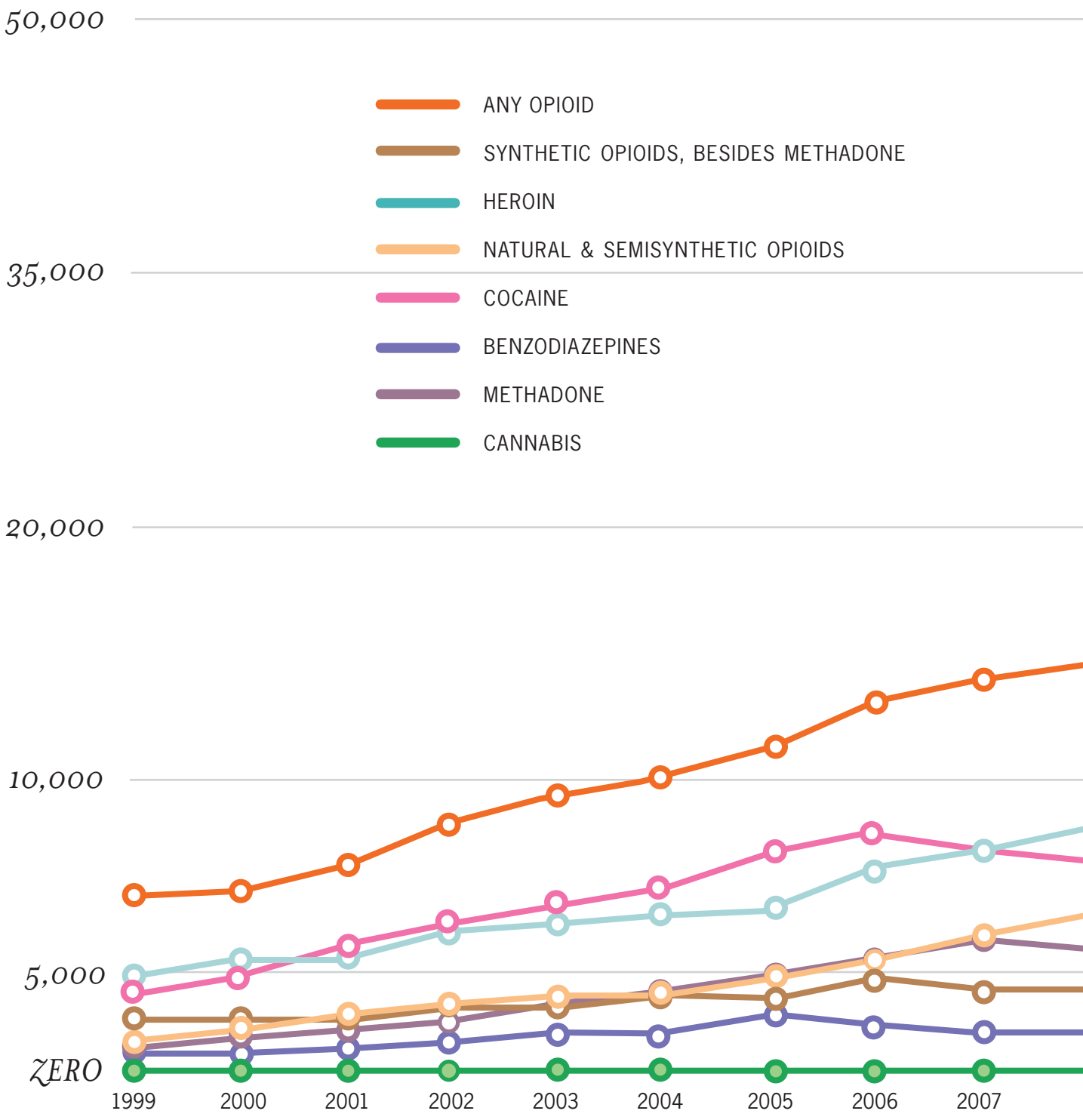
Medical professionals know a lot about opiate addiction because the dopamine neurotransmitter system was discovered in the 1970s. But cannabinoid receptors weren't understood until the 1990s, and scientists simply assumed that cannabis worked in the same way. These mistaken assumptions helped to solidify some of the unfounded myths about cannabis addiction.

One 1993 study revealed how cannabis tolerance works.[22] Researchers gave mice massive levels of radioactively-labeled synthetic THC for two weeks, the equivalent of smoking a thousand joints a day. At first, the drugged mice were so docile that the scientists could arrange their tiny limbs in different yoga positions with no resistance. But after a few days the mice hit with the highest doses began to regain motor control most quickly.

When the scientists dissected the mice's brains, they saw those exposed to extreme levels of THC had the fewest available cannabinoid receptors. Rather than demanding more and more THC, the body had downregulated the number of receptors that THC could bind to so the animals couldn't get as high. In effect, the ECS keeps the body in balance, by setting a limit on how much THC it can withstand.

Patients with tolerance require higher doses of medicine, which is not financially or medically efficient. The good news is that it is easy to rewind tolerance and "resensitize" the ECS by simply stopping use for as little as three days. When patients end their "drug holiday," they can begin medicating again with a very low dose and escalate until effects are felt.[23]

CAUSES OF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35,000
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ANY OPIOID
SYNTHETIC OPIOIDS, BESIDES METHADONE
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COCAINE
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CANNABIS
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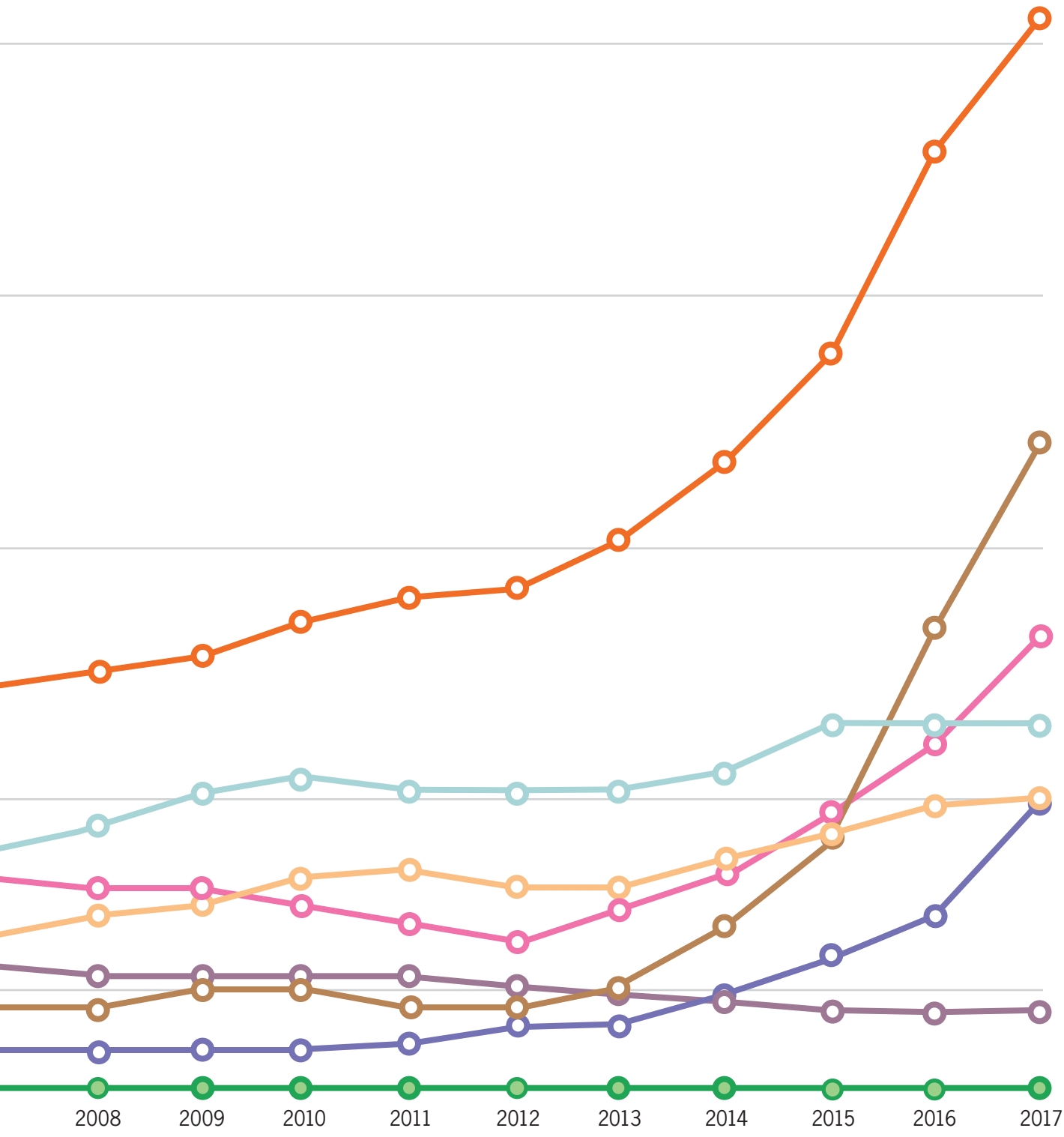
DEATH BY DRUG

SOURCE: CDC Wonder



BOTANICAL VERSUS SINGLE MOLECULE COMPOUNDS

Botanical medicines behave differently than conventional single molecule drugs. In fact, the FDA places botanical drugs in a separate regulatory class. In its 2004 white paper on this topic, the FDA discusses these differences. Non clinical data may be appropriate to help establish safe doses (for botanicals) and to determine ways to better monitor potential toxicities in humans.[24] In 2016 the FDA reiterated this position.[25]

Why cannabis – a botanical medicine – is subjected to the same clinical trials as other single pharmaceutical compounds is much debated. The U.S. government attempts to address this discrepancy by classifying cannabis as a Schedule I substance that has a high potential for abuse with no medical value.[26] If it were to be de-scheduled, cannabinoid medicines could be categorized as botanical drugs, and their regulation could fall under this guidance. In other words, botanicals are living organisms, and it is more difficult, if not impossible, to subject botanical medicines to the same sorts of clinical studies as single molecule substances.

CANNABINOIDS AND OPIOIDS

Cannabinoids enhance opioids' pain-relieving capacities while at the same time reducing opioid tolerance.[27] Cannabinoids also mitigate the flu-like side effects of opiate withdrawal – anxiety, nausea, muscle aches, cramping, and depression.[28] Recent studies of patients using opiates in conjunction with cannabis show that 67.8% used cannabis as a substitute for prescription drugs, including opiates.[29] What's more, states with medical cannabis laws now show a 25% reduction in opiate overdose deaths. New evidence suggests that this change is causal and not simply a correlation.[30]

States with medical cannabis laws now show a 25% reduction in opiate overdose deaths.

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NOTES

CANNABINOID PHARMACEUTICALS

OBJECTIVE

This chapter is an educational overview listing the research, intended use, and availability of all FDA approved cannabinoid medications in the U.S. today. It is a resource for medical professionals who may prescribe these FDA-approved cannabinoids or who are assisting patients that are currently taking these cannabinoids as part of their prescribed treatment plan.

FDA-APPROVED CANNABINOID MEDICATIONS

The FDA has approved four cannabinoid medications to date and is expected to approve a second *cannabis sativa* extract in late 2019.

Current FDA Approved Medications

- Dronabinol (Marinol®)
- Nabilone (Cesamet®)
- Dronabinol oral solution (Syndros®)
- Cannabidiol (Epidiolex®)

The FDA has reviewed several other synthetic cannabinoid drugs in the past decade; however, these were not approved. The most notorious synthetic cannabinoid was rimonabant, an anti-obesity drug that was an inverse agonist of CB1 receptors. This was later withdrawn worldwide in 2008 due to serious and life threatening psychiatric adverse effects or severe depression, including suicide.[1]

DRONABINOL (MARINOL®) CAPSULES

In 1985, the FDA approved the first cannabinoid medication, dronabinol,[2] which was before the ECS was discovered. Dronabinol was approved to work as an appetite stimulant in wasting syndromes and an anti-emetic in people receiving chemotherapy.

Dronabinol Facts

- Synthetic analog of delta-9-tetrahydrocannabinol (THC)
- Available in 2.5 mg, 5 mg, and 10 mg soft gelatin capsules
- Dose is ingested and goes through a first-pass effect of the liver
- Due to the first-pass effect, only 10% to 20% of the drug enters the circulation
- Onset of action is 30 to 60 minutes and the peak is 2 to 4 hours

There is a high degree of pharmacokinetic variability between patients. Fasting versus administration with food can also cause variability to onset.

It is not bioidentical to organic THC found in *cannabis sativa*. Unlike THC from plants or genetically-modified yeast, which is a partial agonist, dronabinol is a synthetic full agonist of CB1 receptors.

Studies in patients with HIV-associated cachexia show increased body weight, improved mood, and decreased nausea. The therapeutic effects last for 24 hours or longer. However, it is usually taken twice daily. The efficacy of an appetite stimulant lasts at least five months according to the studies.[3]

Studies of chemotherapy-induced nausea and vomiting show efficacy. However, it has a slow onset of action, and new anti-emetics, 5HT-3 and NK-1 antagonists, are felt to be superior to dronabinol. Dronabinol can be combined with other anti-emetics.[4] Dronabinol is a pure CB1 full agonist and therefore has several significant adverse effects, including sympathomimetic effects including tachycardia, hypertension, anxiety, and orthostatic hypotension.

Dronabinol has a higher potential for abuse and more euphoric and psychoactive effects. Therefore it requires closer physician supervision than the other cannabinoid medications. Patients report a dose-related euphoria with outbursts of uncontrollable laughter, elation, and heightened awareness which can last 4 to 6 hours. Patients usually develop a tolerance to these euphoric side-effects within two weeks.[5]

Adverse effects of short-term memory loss, confusion, drowsiness, and coordination are common. These adverse effects can be a particular problem in elderly patients or persons with a co-morbid condition that affects memory or coordination. Dronabinol may also lower the seizure threshold. Persons with a personal or strong family history of psychosis, schizophrenia, or panic disorder have a relative contraindication to the use of dronabinol.

Dronabinol is not recommended for use in children or adolescents under 18 years of age due to lack of safety and efficacy data. There is suggestive evidence in tissue cultures, animal models, and population studies that the use of THC in adolescents can have an impact on cognitive functions due to the increased neuroplasticity in this age group.

Dronabinol is a fat-soluble drug; therefore may be present in the fetus and breast milk. Pregnancy, planned pregnancy, or breastfeeding are strong relative contraindications to the use of dronabinol.

Persons with a history of substance abuse may chew or open the capsules to get a more rapid oromucosal absorption and miss the first-pass effect, resulting in euphoria.

It was originally placed on Schedule II of the CSA, however, it was moved to Schedule III in 1999 based on clinical experience.

An overdose of dronabinol can result in a temporary episode of several hours of severe agitation, anxiety, dysphoria, and tachycardia. A cannabidiol dose of 200 mg taken oromucosally has been reported to significantly improve these effects in case reports.[6]

NABILONE (CESAMET®) CAPSULES

In 1985, the FDA approved another synthetic cannabinoid medication, nabilone.[7]

Nabilone Facts

- Synthetic analog of delta-9-tetrahydrocannabinol (THC)
- Available in 1 mg capsules
- Dose is ingested and goes through a first-pass effect of the liver
- Due to the first-pass effect, only 10% to 20% of the drug enters the circulation
- Onset of action is 30 to 60 minutes and the peak is 2 to 4 hours

There is a high degree of pharmacokinetic variability between patients. Fasting versus administration with food can also cause variability to onset. As with dronabinol, it is not bioidentical to organic THC found in the *cannabis sativa* plant. It is a full agonist of CB1 receptors, unlike naturally occurring THC, which is a partial agonist.

This drug was approved as an anti-emetic in people receiving chemotherapy but only in patients who have failed to respond to conventional medications. FDA documentation of nabilone reveals that studies in patients with HIV-associated cachexia show increased body weight, improved mood, and decreased nausea. The therapeutic effects last 24 hours or longer. However, it is usually taken twice daily. The efficacy of an appetite stimulant lasts at least five months according to the studies.[8]

Studies of chemotherapy-induced nausea and vomiting show efficacy. However, it has a slow onset of action, and new anti-emetics are felt to be superior to nabilone. Nabilone can be combined with other anti-emetics.[9]

Nabilone is synthetic and is a pure CB1 full agonist and therefore has several significant adverse effect. Sympathomimetic effects including tachycardia, hypertension, anxiety, and orthostatic hypotension have been reported.

Nabilone has more euphoric and psychoactive effects than dronabinol, which may result in a higher potential for abuse. Therefore it requires close physician supervision, and greater control of dispensing than other cannabinoid medications. Patients report a dose-related euphoria with outbursts of uncontrollable laughter, elation, and heightened awareness which can last 4 to 6 hours. Patients usually develop a tolerance to these euphoric side effects within two weeks.[10]

Adverse effects of short-term memory loss, confusion, drowsiness, and coordination are common. These adverse effects can be a particular problem in elderly patients or persons with a co-morbid condition that affects memory or coordination. Nabilone may also lower the seizure threshold. Persons with a personal or strong family history of psychosis, schizophrenia, or panic disorder have a relative contraindication to the use of nabilone.

Nabilone is not recommended for use in children or adolescents under 18 years of age due to lack of safety and efficacy data. There is suggestive evidence in tissue cultures, animal models, and population studies that use of THC in adolescents can have an impact on cognitive functions due to the increased neuroplasticity in this age group.

Nabilone is a fat-soluble drug and therefore may be present in the fetus and breast milk. Pregnancy, planned pregnancy, or breastfeeding are strong relative contraindications to the use of nabilone.

Persons with a history of substance abuse may chew or open the capsules to get a more rapid oromucosal absorption and miss the first-pass effect, resulting in euphoria. Due to the heightened risk of euphoria and abuse, it is on Schedule II of the CSA.

An overdose of nabilone can result in a temporary episode of several hours of severe agitation, dysphoria, and tachycardia. A cannabidiol dose of 200 mg taken oromucosally has been reported to significantly improve these effects in many case reports.[11]

DRONABINOL ORAL SOLUTION (SYNDROS®)

A new formulation of dronabinol,[12] an oral solution, was approved by the FDA in 2016. This allows for titration and stricter control of the dose than the older capsules that have a limited choice of doses. This superior control of dosing and titration leads to an improved adverse effect profile compared to the older capsules.

Dronabinol Oral Solution Facts

- Synthetic analog of delta-9-tetrahydrocannabinol (THC)
- Available in an orally swallowed formulation of 5 mg/ml
- Dose is ingested and goes through a first-pass effect of the liver
- Due to the first-pass effect, only 10% to 20% of the drug enters the circulation
- Onset of action is 30 to 60 minutes and the peak is 2 to 4 hours

There is a high degree of pharmacokinetic variability between patients. Fasting versus administration with food can also cause variability to onset.

Dronabinol is a synthetic and is not bioidentical to organic THC found in the *cannabis sativa* plant. Unlike THC from plants, or genetically-modified yeast, which is a partial agonist, dronabinol is a full agonist of CB1 receptors.

This drug was approved to work as an appetite stimulant in wasting syndromes, and an as anti-emetic in people receiving chemotherapy. Studies in patients with HIV associated cachexia show increased body weight, improved mood, and decreased nausea. The therapeutic effects last for 24 hours or longer. However, it is usually taken twice daily. Dronabinol's efficacy as an appetite stimulant lasts at least five months according to the studies.

Studies of chemotherapy-induced nausea and vomiting show efficacy. However, it has a slow onset of action, and new anti-emetics, 5HT-3 and NK-1 antagonists, are felt to be superior to dronabinol. Dronabinol can be combined with other anti-emetics.

Unlike the other drug formulations discussed already, it can easily be used oromucosally, instead of ingested, to obtain much more rapid onset of action, with euphoric and other psychoactive effects compared to ingestion.

Patients report a dose-related euphoria with outbursts of uncontrollable laughter, elation, and heightened awareness which can last 4 to 6 hours. Patients usually develop a tolerance to these euphoric side effects within two weeks.[13]

Adverse effects of short-term memory loss, confusion, drowsiness, and coordination are common. These effects can be a particular problem in elderly patients or persons with a co-morbid condition that affects memory or coordination. Dronabinol may also lower the seizure threshold.

Dronabinol is not recommended for use in children or adolescents under 18 years of age due to lack of safety and efficacy data. There is suggestive evidence in tissue cultures, animal models, and population studies that use of THC in adolescents can have an impact on cognitive functions due to the increased neuroplasticity in this age group.

Dronabinol is a fat-soluble drug and therefore may be present in the fetus and breast milk. Pregnancy, planned pregnancy, or breastfeeding are strong relative contraindications to the use of dronabinol.

Persons with a history of substance abuse may not swallow the liquid but instead keep it under their tongue to get a more rapid oromucosal absorption and miss the first-pass effect, resulting in rapid onset of euphoria.

CANNABIDIOL (EPIDIOLEX®)

Epidiolex[14] is a 99% cannabidiol (CBD) isolate extracted from *cannabis sativa* approved by the FDA in 2018. The pure isolate of CBD does not have the combined entourage effect from minor cannabinoids and terpenes. Cannabidiol increases the amount of naturally occurring AEA available at the CB1 and CB2 receptors by blocking metabolic enzymes and transport proteins.

Cannabidiol Facts

- 99% cannabidiol (CBD) isolate extract
- Oral solution with an oral syringe for intra-oral administration
- Absorbed rapidly via the intraoral route directly into the circulation
- Any that may be ingested goes through the first-pass effect of the liver which metabolizes about 85% of the cannabidiol to inactive metabolites[15]
- Onset of action is approximately 15 minutes with peak concentrations at 45 to 120 minutes

Plant extract administered oromucosally reaches maximum plasma levels at 60 minutes. Additionally, some of the CBD may be ingested and undergo hepatic first-pass metabolism. The doses used for pediatric intractable seizures are much higher, 5 to 25 mg/kg, than the doses used to treat most other conditions.[16]

It has received the Rare Pediatric Disease and Orphan Drug Designations from the FDA for treatment of Dravet and Lennox-Gastaut syndromes (LGS). Trials are underway for tuberous sclerosis (TS) and infantile spasm (IS). The most common adverse effects reported include somnolence (57%), fatigue (57%), and increased or decreased appetite (40%). These adverse effects were reported in young children using cannabidiol in high doses for intractable seizures.

It has a low risk of abuse and dependency due to a balancing effect of CBD at the CB1 receptor, which significantly decreases euphoric and psychoactive effects.

Cannabidiol is a fat-soluble drug and therefore is present in the fetus and breast milk. Pregnancy, planned pregnancy, or breastfeeding are strong relative contraindications to the use of cannabidiol.

Even though *cannabis sativa* is a Schedule I drug, this isolated extract of cannabis is listed as a Schedule V drug.

CANNABIDIOL EXTRACT RESEARCH

During this cannabidiol study, 261 patients received at least three months of treatment. Diagnoses included Dravet syndrome, myoclonic-absence epilepsy, Lennox-Gastaut syndrome, generalized epilepsies, and other forms of treatment-resistant epilepsy. The median overall seizure frequency reduction was 45.1% in all patients and 62.7% in Dravet syndrome patients. For Lennox-Gastaut syndrome patients, the median reduction of atonic seizures from baseline was 71.1%. Among all patients, 47% had a ≥50% reduction in seizures. Seizure-freedom at three months occurred in 9% of patients and 13% of Dravet syndrome patients. Adverse events in ≥10% of patients included somnolence (23%), diarrhea (23%), fatigue (17%), decreased appetite (17%), convulsions (17%), and vomiting (10%). Fourteen patients (4%) had an adverse event leading to discontinuation of CBD.

Fourteen patients (4%) had an adverse event leading to discontinuation of CBD; 36 patients (12%) withdrew primarily due to lack of efficacy. Serious adverse events were reported in 106 patients (34%), including seven deaths, none of which were considered treatment-related. In addition, 16 patients (5%) had serious adverse effects that were considered treatment-related, including altered liver enzymes (four patients; all were also on valproate and clobazam), status epilepticus/convulsion, diarrhea, decreased weight, thrombocytopenia, and others.[17]

Review of www.ClinicalTrials.gov reveals that there are 158 high-quality research studies completed or ongoing for various therapeutic effects of CBD, either as an isolate or in whole plant extracts. The studies have shown promising therapeutic effects for chronic pain, various neurodegenerative conditions, addiction, many other forms of treatment-resistant adult and pediatric epilepsy, anxiety, tremor, graft-versus host disease, psychosis, and Crohn's disease.[18]

NABIXIMOLS (SATIVEX®)[19]

Another investigational new drug is nabiximols. This is a whole plant extract from two strains of *cannabis sativa*. It contains a ratio of CBD to THC of approximately 1:1. Since strains of cannabis with a 1:1 ratio of CBD to THC did not generally exist, two different strains were necessary to achieve this goal. One strain is high in CBD and very low in THC. The other strain is low in CBD and high in THC. The cannabis is grown under very strict conditions, and good manufacturing practices are employed to ensure consistency, potency, quality, and lack of contamination from batch to batch.

Nabiximols Facts

- Oromucosal spray
- Absorbed into the circulation from the oromucosal cavity
- Each bottle contains 100 sprays
- Each spray has 2.7 mg of THC and 2.5 mg of CBD
- Also contains small amounts of minor cannabinoids and terpenes
- Onset of action is approximately 15 minutes with peak concentrations at 45 to 120 minutes

Plant extract administered oromucosally compared with inhaled vaporized THC extract has far lower peak plasma concentrations: 5.4 ng/ml versus 118.6 ng/ml and maximum plasma levels of 60 minutes compared to 17 minutes. THC and CBD are metabolized in the liver. Additionally, some of the THC undergoes hepatic first-pass metabolism to 11-OH-THC, the primary metabolite of THC, and CBD similarly to 7-OH-CBD.[20]

Protein binding of THC is high (~97%). THC and CBD may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the bloodstream, then metabolized and excreted via the urine and feces.

Nabiximols has successfully completed phase 3 trials in the United States and is expected to be approved by the FDA by the end of 2019. Nabiximols has been approved in over 30 countries as a prescription pharmaceutical since 2010. This drug has been approved to treat MS spasticity and neuropathic and chronic cancer pain in many countries.

Nabiximols is a CB1 and CB2 partial agonist. THC extracts, such as nabiximols have several adverse effects at higher doses, usually above 10 mg of THC per dose.[21] The most common adverse effects reported include dizziness (25%), drowsiness (8%), and disorientation (4%). Twelve percent of subjects quit taking nabiximols in clinical trials due to adverse side effects including tachycardia, hypertension, anxiety, and orthostatic hypotension.

The phase 3 studies show that nabiximols has a low risk of abuse and dependency due to balancing the effect of CBD at the CB1 receptor, which significantly decreases euphoric and psychoactive effects. Nabiximols may produce undesirable effects such as dizziness and somnolence, which may impair

judgment and performance of skilled tasks. Patients should not drive, operate machinery, or engage in any hazardous activity if they are experiencing any significant central nervous system effects such as dizziness or somnolence. Patients should be aware that nabiximols has been known to cause loss of consciousness in a few cases.[22]

Nabiximols may interact with alcohol, affecting coordination, concentration, and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using nabiximols, especially at the beginning of treatment or when changing the dose. Patients should be advised that if they do drink alcohol while using nabiximols the additive effects may impair their ability to drive or use machines and increase the risk of falls.

Nabiximols has a risk of increased incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the central nervous system adverse reactions of nabiximols, particularly in elderly patients, could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.[23] Care should be taken when combining nabiximols and hypnotics, sedatives, and drugs with potentially sedating effects as there may be an additive effect on sedation and muscle relaxing effects.

As with all THC containing preparations, nabiximols is contraindicated in patients with any known or suspected history or family history of schizophrenia, or other psychotic illness, history of severe personality disorder, or other significant psychiatric disorder other than depression associated with their underlying condition.

Nabiximols is not recommended for use in children or adolescents under 18 years of age due to lack of safety and efficacy data. There is suggestive evidence in tissue culture, animal models, and population studies that use of THC in adolescents can have an impact on cognitive functions due to the increased neuroplasticity in this age group.

Nabiximols is a fat-soluble drug and therefore may be present in the fetus and breast milk. Pregnancy, planned pregnancy, or breastfeeding are strong relative contraindications to the use of nabiximols.

An overdose of nabiximols can result in a temporary episode of several hours of severe agitation, dysphoria, and tachycardia.

Persons with a history of substance abuse may take more than the recommended dose to experience increased euphoric effects.

FUTURE CANNABINOID PHARMACEUTICALS

The current and foreseeable trend for FDA-approved cannabinoid pharmaceuticals will be using whole plant extracts that contain naturally occurring versions of various cannabinoids, including THC, CBD, THCV, and CBN. Plant geneticists are developing new strains of *cannabis sativa* that have high percentages of these other cannabinoids, so that scalable quantities of THCV, CBN, and other

minor cannabinoids will be available for pharmaceutical manufacturing. Additional clinical research of these cannabinoids is needed to determine how each of these cannabinoids can be used in future FDA-approved pharmaceuticals. The same pharmaceutical company that developed nabiximols and cannabidiol has six other *cannabis sativa* extracts in phase I trials or higher for epilepsy, autism spectrum disorders, neonatal hypoxic-ischemic encephalopathy, glioblastoma, and schizophrenia.

Isolate Versus Whole Plant Extract Dosing Curve

The cannabidiol extract is a 99% isolate with essentially no terpenes or minor cannabinoids. The *cannabis sativa* extract nabiximols is a whole plant extract rich with minor cannabinoids and terpenes. A new study[24] in an animal model shows that isolate-based extracts (monomolecular) are not as effective as whole plant extract equivalent milligram doses. Isolates have an inverse-U shaped dose-response curve with a narrow therapeutic window. The addition of the entourage effect from the minor cannabinoids and terpenes moves the dose-response curve to the left with therapeutic benefits seen at lower doses and with a wider therapeutic window of increased therapeutic benefits with increasing dose, without the early drop off seen with isolates. Whole plant extracts containing major cannabinoids, minor cannabinoids, and terpenes have demonstrated greater therapeutic benefits with lower doses.

2018 FEDERAL FARM BILL AND ACCESS TO CANNABIDIOL

In December 2018, Congress passed the 2018 Farm Bill[25] that had extensive provisions which legalized growing and manufacturing hemp, transport and sale of hemp products, including certain hemp-derived products for human consumption throughout the United States. Hemp is defined as cannabis that contains less than 0.3% THC. This law removed all hemp-derived products from the DEA's Schedule I of the CSA. It allows for non-prescription access to hemp-derived cannabinoid extracts, vaporizers, edibles, drinks, hemp flower, and topicals.

The FDA has now taken over supervision of these products and formulations, and is expected to enforce the manufacturing, quality assurance, consistency, and formulation standards of these products, so that they will be in line with the millions of other products overseen by the FDA. Historically, these hemp-derived CBD formulations have not been produced using good manufacturing practices. In addition, the labeling has been inconsistent with the actual potency of CBD contained within a majority of the products.[26] This new FDA supervision is expected to address these previous quality and safety concerns. A study published in the *Journal of the American Medical Association* in 2017 found that nearly 70 percent of all CBD products sold online are incorrectly labeled and could cause serious harm to consumers.

People are able to purchase hemp-derived cannabinoid formulations that are high in CBD, and combined with whole plant non-THC cannabinoids, including the entourage components of terpenes and minor cannabinoids. These products generally cost a fraction of the price per dose of the FDA approved CMs, and providers should become familiar with these formulations so that they can advise and educate their patients, understand dose response curves, dosing, and routes of administration.[27]

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GETTING CANNABINOIDS INTO THE BLOODSTREAM

Delivery Systems for Cannabis

OBJECTIVE

This chapter familiarizes medical professionals with the many methods of delivering cannabinoids into the bloodstream — inhalation, oral mucosal absorption, edibles, and topicals — plus the advantages and disadvantages of each. Included are written and visual descriptions of all of forms of medical cannabis that a patient might encounter in a dispensary, plus the instruments that deliver them. This section also includes guides to onset times, duration of effects, and bioavailability with each method.

THE ROLE OF THE DISPENSARY

The dispensary is usually the first place patients will encounter the full range of products available to them. The experience is both overwhelming and (a little bit) thrilling to new patients. It is important that medical professionals have an understanding of how these institutions function and how widely dispensary experiences can vary.

Patients will likely interact with certified dispensary personnel, otherwise known as "budtenders." Dispensary personnel serve patients but they are not medically trained. State laws allow them to share anecdotal information about products and what other patients have used for treatment but cannot recommend products for medical conditions. In addition, many states do not require state approved training and licensing for consultants that interact with patients. Dispensary personnel cannot give medical advice or specific dosing information to treat medical conditions.

WHAT DISPENSARY CONSULTANTS ***CAN*** SAY

"In my experience..."

"Patients have said..."

"Anecdotally I hear..."

WHAT DISPENSARY CONSULTANTS ***CANNOT*** SAY

"I recommend..."

"Buy this..."

"This really works; it is the best for..."

Medical Marijuana 411 is a leader in training medical professionals and dispensary personnel to gain a deeper understanding of cannabis and the ailments it treats, in addition to state specific laws and policies governing behavior at work.

FLOWER VERSUS CONCENTRATES

Pipes, joints, water pipes, electronic vaporizers as large as blenders, or as portable as pens…there are as many ways of delivering cannabis into the system as there are forms the plant can take. Medical providers should be familiar with the best devices to deliver the precise dose for the desired duration with fewest adverse reactions. This can be a challenge for providers and cannabis-naive patients alike, but this chapter will provide a thorough overview of the various options.

- FLOWER -

Dried cannabis flower are the most widely used form of cannabis, though this is changing with the advent of concentrates, tinctures, and edibles.

In the recreational market, cannabis flower are typically identified by strains, but medical professionals can find more detailed information about the cannabinoid and terpene profiles by looking at gas or liquid chromatography lab testing. Though tests vary from lab to lab, they are more reliable guides to effects than strain classification.

ADVANTAGES VERSUS DISADVANTAGES OF FLOWER

- ADVANTAGES OF CANNABIS FLOWER
  - Lower cost to patient
  - More widely available
  - Can be grown at home if legal in the patient's state
  - Contains all cannabinoids and terpenes in the strain profile
- DISADVANTAGES OF CANNABIS FLOWER
  - Cannabinoid content may not be high enough for treatment
  - Carcinogens and plant material may be inhaled
  - Improper storage can lead to mold and plant degradation

- CONCENTRATES: DABS, SHATTER, WAX, BUDDER, BHO, ROSIN -

Dabs, shatter, wax, budder, BHO, and rosin are all different names for styles of cannabis extracts known as concentrates. Concentrates refer to the oils and terpenes once they are stripped from the plant. Though they come in different forms, all concentrates are many times more powerful than flower and are used to relieve symptoms of opiate, alcohol, or other drug withdrawals, plus other extreme pain conditions.[1]

Concentrates are consumed by vaporization or by "dabbing," a process in which a tiny sesame-size amount of concentrate is placed on a scorching hot surface and inhaled. To give you context for the potency of these concentrates, a powerful strain of cannabis contains 20% THC; a dab can reach 70% or 80%.[2]

- DIFFERENT FORMS OF CONCENTRATES -

- "BHO" (Butane Hash Oil) is the most popular concentrate—it has a gooey, thick, tar-like consistency.
- "Budder" or "wax" contains some of the waxy coverings that contain the oils on the plant, which gives them a more opaque and crumbly texture.
- "Shatter" resembles a translucent amber candy. Though it enjoys a reputation for being the purest and cleanest type of extract, translucence is not a sign of quality. Purity comes down to the way these oils are extracted.

ADVANTAGES VERSUS DISADVANTAGES OF CONCENTRATES

- ADVANTAGES OF CANNABIS CONCENTRATES
  - Increased potency for patients requiring higher cannabinoid doses
  - Large doses can be administered quickly
  - If inhaled, no risk of plant matter entering the lungs
- DISADVANTAGES OF CANNABIS CONCENTRATES
  - Increased cost to patient
  - Higher risk of overmedicating
  - May contain trace amount of solvents
  - Processing may remove minor cannabinoids and terpenes
  - May contain higher concentration of pesticides

EXTRACTION METHODS

Different extraction methods result in wide ranges of potency, consistency, and quality of concentrates. Hydrocarbon extraction is the most commonly used. It relies on butane to strip cannabinoids and terpenes from the plant.

In this method, leaves are packed into long tubes and flushed with liquid butane in a closed loop system, which safely strips the cannabinoids and terpenes from the plant material. The mix of solvent and cannabinoids is then heated to evaporate the remaining butane. The consistency of the end product is determined by several factors, the most important being the quality and terpene content of the raw material used to create the concentrate. Other factors include heat, moisture, and agitation of the cannabinoids during the extraction process.

The primary disadvantage of concentrates is the uncertainty about the amount of trace solvents, if any, that remain in the finished product, as hydrocarbons have been linked to liver and kidney disease as well as cancer. As regulation and technology improves, this uncertainty may change. Some states ban hydrocarbon extractions because they can be highly flammable if executed without a closed loop extraction system or stringent safety procedures.

Other common solvents used for extraction include CO2 or ethanol. CO2 is often used in preloaded vape pens. Though these methods are often considered “cleaner” and safer than hydrocarbon, they aren’t as effective at harvesting all of the terpenes. Even when extracting other plant material – such as pomegranate seeds – there are significant differences between these processes in the total yields of fatty acids.[3]

Rosin is an increasingly popular concentrate because producing it requires no solvents and it can be done easily with devices found in homes. Extracting rosin involves pressing dried cannabis flowers between two hot plates (home methods include a tortilla press or a hair straightener), which melt oils from plant matter. Rosin preserves the full terpene and cannabinoid content of the plant, as the heat required to melt the oils is lower than their burn point.

ADVANTAGES VERSUS DISADVANTAGES OF EXTRACTION METHODS

- ADVANTAGES OF CANNABIS EXTRACTIONS

  No plant material is inhaled and they can be made in potent doses.

- DISADVANTAGES OF CANNABIS EXTRACTIONS

  More powerful medicine increases chances of overmedicating and side effects. One side effect that has cropped up as of late is hyperemesis, cyclical bouts of vomiting followed by the need for warm showers. Is this response a reaction to a flood of cannabinoids into the ECS, or are increased reports surfacing now that concentrates are being used more widely in legal states? It's unclear, but discontinuing treatment for a period of time appears to stop hyperemesis.[4]

HOW TO DAB IN THREE EASY STEPS

Dabbing is simply the act of vaporizing a dab of cannabis concentrate. Dabbing is a slang term for cannabis concentrates. The name comes from the definition of the word “dab,” which means a tiny amount of something. The name stuck because a tiny amount of cannabis concentrate is needed to feel the potent effects.

The necessary tools for dabbing can be intimidating, but for a medical professional, it is important to understand and be familiar with the apparatus used for dabbing and to change the stigma of how to medicate cannabis concentrates.

There are many variations of the dabbing apparatus including electronic forms. Dabbing may sound like an illicit or disreputable activity, but it is also an effective and trusted method of accessing all the medical benefits of cannabis in a clean, concentrated form.

- 1 -

Using a flame or torch, heat the section of the “dab rig” that is often referred to as a skillet or nail. It is the area where the cannabis concentrate, the dab, is placed to vaporize the product. A very small amount of product is vaporized. The area where the cannabis product is vaporized has small holes in it so the person can inhale the vaporized concentrate and self titrate.

- 2 -

Once the skillet or nail is hot, the cannabis concentrate is placed on the skillet or nail by using a “dabber” to vaporize. A dabber is a utensil used to place the small amount of concentrate on the hot surface.

- 3 -

To ingest vaporized cannabis concentrate, simply place your mouth on the mouthpiece and inhale.

FORMS OF MEDICATING

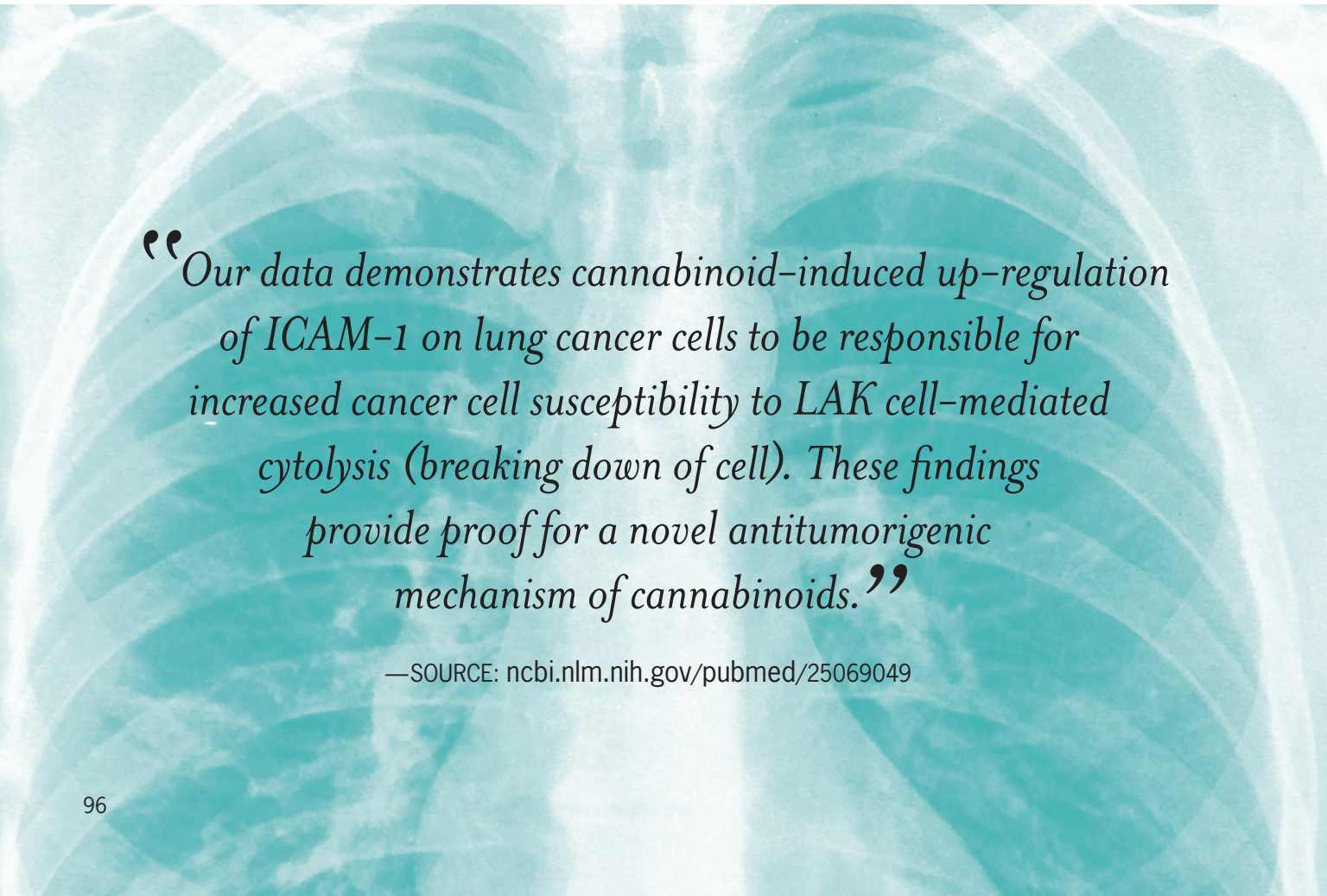
INHALATION/SMOKING

ONSET: Immediate
DURATION: 1 to 3 hours
BIOAVAILABILITY: 10 to 25%[5] or 2 to 56%[6]

Smoke absorbs into the bloodstream in seconds. Onset is immediate and decay is predictable, which makes titration easily achievable.[7] New patients are advised to wait 15 minutes between inhalations to avoid overconsumption or unwanted psychoactivity.

Cannabis smoke contains over 1,500 chemicals, including some of the same carcinogens found in tobacco, yet there is no conclusive evidence that cannabis smoke contributes to emphysema, cancer, or other adverse effects on pulmonary function.[8] This is confounding, but three decades of research led by Donald Tashkin, MD, Director of the Pulmonary Function Laboratories at UCLA, found that long term smokers of cannabis had no increased incidence of head, neck, or lung cancers.[9] They also had much lower incidence of these cancers than non smokers.[10]

Water pipes and bongs deliver a larger dose of cannabinoids per inhale. But while water cools the smoke, it also traps therapeutic cannabinoids, which make water pipes and bongs even less effective for medical use.



"Our data demonstrates cannabinoid-induced up-regulation of ICAM-1 on lung cancer cells to be responsible for increased cancer cell susceptibility to LAK cell-mediated cytolysis (breaking down of cell). These findings provide proof for a novel antitumorigenic mechanism of cannabinoids."

—SOURCE: ncbi.nlm.nih.gov/pubmed/25069049

ADVANTAGES VERSUS DISADVANTAGES OF INHALATION/SMOKING

- ADVANTAGES OF SMOKING CANNABIS
  - Rapid onset
  - Ease of titration
  - Short and predictable duration of effects
  - No investment to begin medicating
  - Little to no maintenance required
- DISADVANTAGES OF SMOKING CANNABIS
  - Nonsmokers may find smoke irritating to the lungs
  - Burned plant matter produces carbon, tar, and carcinogens
  - Inefficient if patient needs higher doses of cannabinoids
  - Up to 50% of the active ingredients are incinerated

ANATOMY OF A BONG

Commonly referred to as a bong, a glass water pipe is a standard way of smoking medical marijuana. Water provides a means of filtration through percolation.

Tube

Tubes can be straight or angled. The tube is the part of the water pipe where you place your mouth and inhale the smoke.

Ice Pinch

The small, inward points or "pinches" on the tube that help to keep any ice particles inside the tube of the water pipe. Ice pinches also allow for extra cooling of the smoke as it travels up the tube.

Many bongs also have a "splash guard" inside the tube above the percolator to prevent any water from traveling up the tube to the lips when inhaling.

Diffused Downstem

A downstem with a set of slits on the bottom that acts like a percolator in the ice water to filter and cool the smoke.

There are many types of percolators, depending on the design of the water pipe. All percolators have their pros and cons but provide the same overall function.

Bowl

The area on a pipe where you place dried marijuana (sometimes referred to as flower or bud) to be combusted by igniting the cannabis with a match or lighter.

Beaker Base

A water pipe with a beaker shaped bottom that is wider at the base and more stable than a straight tube. Beaker base bongs hold more water in comparison to a straight tube water pipe design, which allows for more cooling of the smoke.


Tube
Ice Pinch
Diffused Downstem
Bowl
Beaker Base

INHALATION/ VAPORIZATION

ONSET: Immediate
DURATION: 1 to 3 hours
BIOAVAILABILITY: 10 to 25%[12] or 2 to 56%[13]

Vaporizers heat the oils at a lower temperature than combustion but do not burn plant matter. Since cannabinoids and terpenes heat at temperatures between 340 to 428 degrees Fahrenheit (171 to 220 degrees Celsius),[14] well below the point of combustion, vaporizing is less likely to cause irritating respiratory side effects—it measurably reduces undesirable compounds in smoke.[15] Vaporization is also very efficient, as no medicine is lost in the air.

Best practices for vaporizing are simple and straightforward. Inhale, hold for three seconds, exhale. Note: Because terpenes exhaust before cannabinoids, it is important to vaporize after the flavor of a bowl disappears to get maximum therapeutic effects.

- DIFFERENT TYPES OF VAPORIZERS -

Vaporizing technology is evolving at a quick pace. There are three types of vaporizers on the market: conduction, convection, and vapor pens with replaceable oil cartridges.

Think of a conduction vaporizer like a skillet. The device heats a metal plate, which in turn melts the oils (and inevitably some amount of plant matter). Conduction vaporizers range in price from $150 to $250.

Convection vaporizers work more like an oven—they circulate hot air around the plant material to melt the oils and deliver a “cleaner” inhalation. High-end convection vaporizers are made with medical grade glass and metal parts, and allow users to adjust temperatures. Convection vaporizer prices typically top $325.

Oil cartridge vapor pens are the least expensive and easiest to use. They are also discreet. They involve a slim battery that screws into a pre filled cartridge of extracted cannabis oil. The quality and extraction methods of the oils vary from manufacturer to manufacturer, and the parts of these inexpensive pens often clog or malfunction, but they are easily replaced. The battery typically costs around $10 and cartridges can range from $20 to $60 depending on their size.

- MYTH VERSUS FACT -

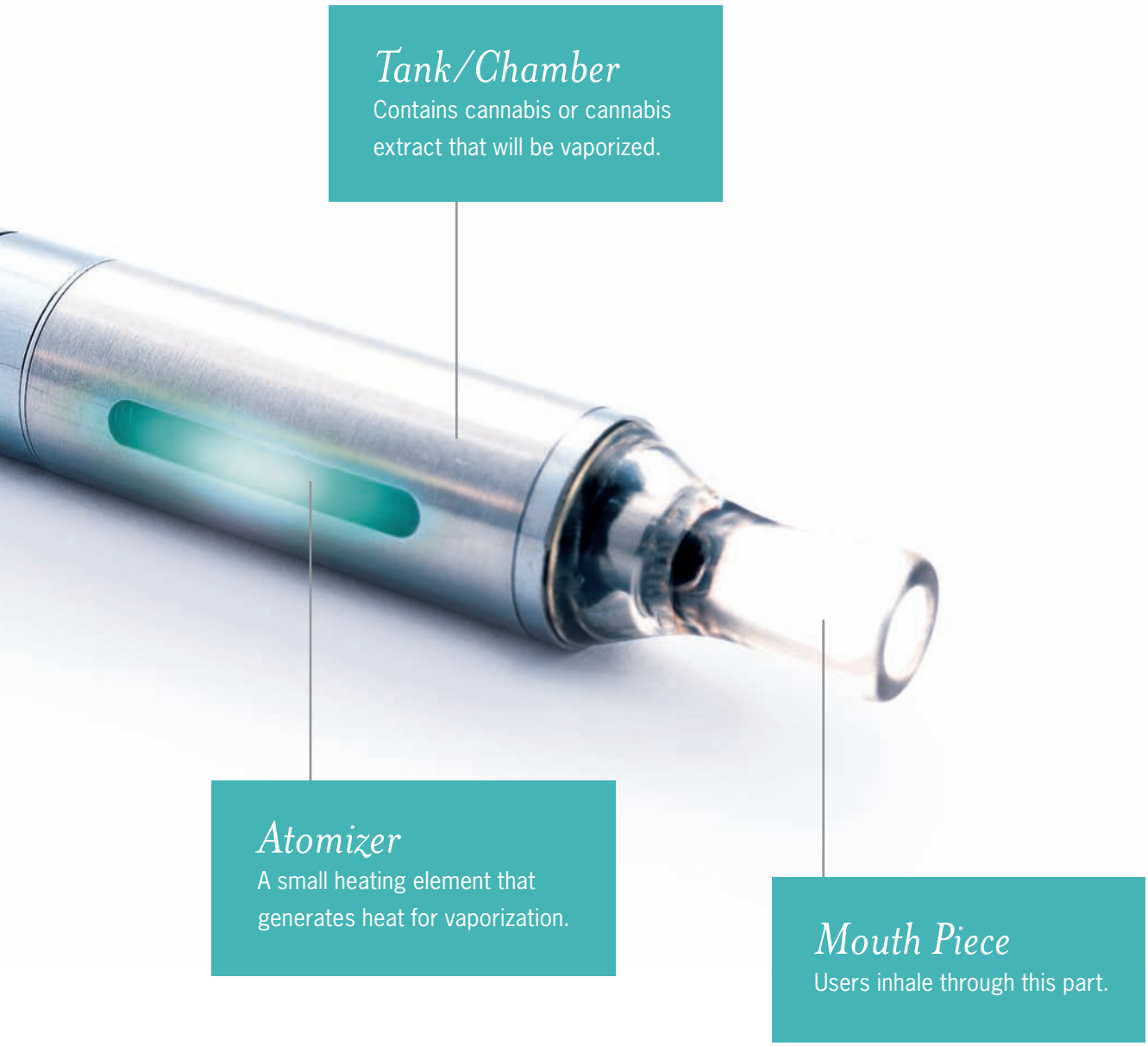
MYTH: Holding your inhale in the lungs increases absorption. Evidence shows this is NOT true for smoking; worse, holding inhaled smoke encourages absorption of more harmful compounds.[16]

FACT: However, holding a vapor inhale for 3 seconds does appear to further therapeutic cannabinoid absorption in the lungs.[17]

ADVANTAGES VERSUS DISADVANTAGES OF INHALATION/VAPORIZATION

- ADVANTAGES OF VAPORIZATION
  - Vaporized cannabinoids can be inhaled as a cooler, less irritating mist than smoke
  - Onset is immediate
  - Titration is easy to monitor and adjust
  - Allows patient to extract cannabinoids effectively
  - No harmful byproducts from smoking
  - Higher quality devices are easily cleaned with ethanol
- DISADVANTAGES OF VAPORIZATION
  - Cannabis oils, when vaporized, can clog less sophisticated machines
  - Lower quality devices must be replaced once clogged
  - Vaporizers must be cleaned and maintained
  - Patients will need to learn how to use their machine

ANATOMY OF A VAPE PEN



Tank/Chamber

Contains cannabis or cannabis extract that will be vaporized.

Atomizer

A small heating element that generates heat for vaporization.

Mouth Piece

Users inhale through this part.

EDIBLES

ONSET: 1.5 to 2 hours
DURATION: 6 to 10 hours
BIOAVAILABILITY: 5 to 20% [18] or 4 to 20% [19] or 4 to 12% [20]

Edibles do not provide immediate relief but they do provide stronger, longer- lasting relief than inhaled cannabis – 6 to 9 hours depending on the material and a patient's own endocannabinoid system. The reason? The process of passing through the gastrointestinal tract and then being metabolized in the liver before ultimately being absorbed into the bloodstream changes Delta-9 THC into Delta-11 THC, an entirely different, longer lasting, and more powerful compound. This difference is significant. Smoking results in 20% of Delta-9 THC metabolizing into Delta-11 THC, whereas ingestion results in 100%.[21]

Edibles come in a variety of forms: candies, gummy bears, chocolates, cookies, pills, and lozenges. Some of these products are delicious, which makes dose control all the more challenging.

The primary challenge with edibles is dose titration. Too small a dose produces no relief and too large a dose can produce extreme psychoactivity, which can result in paranoia and discomfort.[22] Since the onset time is so long it may take several attempts for a patient to find an optimal dose. This is why the Medical Marijuana 411 mantra, especially with inexperienced patients, is...

"Start Low, Go Slow"

ADVANTAGES VERSUS DISADVANTAGES OF EDIBLES

- ADVANTAGES OF EDIBLES
  - Long duration and stronger effects
  - Dosing may be easier for a patient to consume
  - Eliminates risk associated with smoking
  - Exact cannabinoid dosing can be achieved

- DISADVANTAGES OF EDIBLES
  - Onset of effects is delayed considerably by absorption through the gastrointestinal tract [23]
  - Edible products may be made with sugar, which can present complications with diabetic patents
  - Patients may over consume due to the long onset time
  - Serving size may need to be reduced based on patient's tolerance
  - High risk of accidental cannabis poisoning to children and pets
  - Manufacturing practices may put a patient with food allergies at risk

KNOW YOUR EDIBLES

Don't be that person who eats an edible, declares that "nothing is happening," eats four more, and proceeds to have the worst experience ever. Know yourself and know your edible servings!

Start With One

Just eat one serving of a low dose edible until you learn how you respond.

Wait, Wait, Wait

...and wait some more. Edibles can take up to two hours to work.

Start With One

Just eat one serving of a low dose edible until you learn how you respond.

Don't Mix

Do not mix edibles with alcohol or other substances.

Lock It Up

Store edibles in a child proof container and/or original packaging.

NEW TO EDIBLES?

Start here. *1 to 5 mg*

This is a single serving
for experienced users only. *5 to 10 mg*

"Professional" level users
or significant medical needs. *10 to 15 mg*

ORAL MUCOSAL: TINCTURES, SPRAYS, SUBLINGUAL DROPS

ONSET: 1 to 15 minutes if held in mouth; 1.5 hours if swallowed
DURATION: 2 to 8 HOURS
BIOAVAILABILITY: 1 to 12%[24] OR 11 to 13%[25]

Oral mucosal tinctures and extracts are easy to use and reflect the full chemical spectrum of the plant. Even better, they come in various ratios of CBD:THC, which makes dosing for experienced and inexperienced users easy to monitor and adjust. GW Pharmaceuticals has proven the efficacy of this delivery method with its sublingual prescription medication, Sativex,®[26] which has passed regulatory hurdles and been approved for use in 12 countries to date.

The best method of taking an oral mucosal tincture or extract is to drop or spray some under the tongue or between the gums and cheek where a huge number of blood vessels reside, and keep it there for a few minutes before swallowing. Avoid drinking or eating anything for ten minutes following administration. If the tincture is alcohol based, the alcohol could irritate or burn sensitive gums.[27] To lessen irritation, dilute the tincture in water and swish around the mouth for oral mucosal application. Another option is to dilute the tincture in a liquid oil or medium fat yogurt drink to increase lipophilic absorption.

ADVANTAGES VERSUS DISADVANTAGES OF ORAL MUCOSAL

- ADVANTAGESOF ORAL MUCOSAL
  - Tinctures easy to use and titrate
  - Various ratios of CBD:THC content are available
  - Minor cannabinoids and terpenes are included in some formulations
  - Tinctures can be added to food or beverages
  - Long shelf-life and flexibility
  - Discreet and portable
- DISADVANTAGES OF ORAL MUCOSAL
  - Inconsistencies in labeling on non-FDA approved formulations
  - Delayed onset if swallowed by the patient
  - Patients with allergies to carrier oils should use caution

TOPICALS

ONSET: Immediate
DURATION: 30 minutes to 3 hours
BIOAVAILABILITY: Not applicable

Topicals are available in creams, salves, roll-ons, and patches. Topicals in general will not result in a high typically associated with THC. Topicals are non psychoactive unless they contain unusually high amounts of cannabinoids. This is due to CBD crossing the skin barrier more efficiently than THC.[28] Penetration of the skin barrier can be enhanced by alcohol or lipid media, which is used in longer duration transdermal patches. Conditions topicals treat include joint/muscle pain, eczema/psoriasis, acne, and certain forms of skin cancer or precancerous lesions on the skin.[29]

ADVANTAGES VERSUS DISADVANTAGES OF TOPICALS

- ADVANTAGES OF TOPICALS
  - Avoids first-pass metabolism by the liver
  - Localized pain management
  - Reduces inflammation and arthritis
  - Non psychoactive even when containing THC
- DISADVANTAGES OF TOPICALS
  - Possibility of local irritation
  - Low skin penetration of cannabinoids
  - Patients with allergies to carrier ingredients should use caution

SUPPOSITORIES

ONSET: 15 minutes or less
DURATION: up to 12 hours
BIOAVAILABILITY: 13 to 67%[30,31] depending on suppository formulation

Suppositories are extremely efficient but not very popular, as you may have guessed. Cannabis suppositories deliver around 80 percent of the plant medicine, while taking cannabis orally delivers around 35 percent and smoking around 15 percent.[32]

When administered rectally or vaginally, the plant medicine directly enters the bloodstream through the cell walls and goes directly into the body, which is quickly distributed through the vascular system. They act quickly and efficiently by avoiding first pass metabolism through the liver, and also provide long lasting effects.[33] The liver is a key to getting high. THC travels through the liver to the brain to induce a head high. Within 10 to 15 minutes provides the greatest amount of plant medicine delivered with zero head high.

Suppositories are useful for palliative care, for all cancers of pelvic floor, certain GI diseases such as irritable bowel syndrome, and for patients who cannot swallow.[34] Suppositories used vaginally are an option for women to ease menstrual pain. CBD is known to have anti-inflammatory properties and THC to ease menstrual pain. It is important to note that the depth of insertion is very important: placement past the anal sphincter is key (roughly 1 to 1.5 inches/2.5 to 4 centimeters).[35]

ADVANTAGES VERSUS DISADVANTAGES OF SUPPOSITORIES

- ADVANTAGES OF SUPPOSITORIES
  - Avoids first pass of the liver for rapid onset
  - Effects can last up to 12 hours
  - Patients report relief without psychoactivity
  - Ideal for patients that may not be able to ingest or inhale cannabis
  - Can be administered to unresponsive patients
- DISADVANTAGES OF SUPPOSITORIES
  - Mucosal irritation
  - Patient compliance
  - Gastrointestinal state may affect absorption


Strain:
THC
Strain:
RECHARGEABLE VAPE PEN
+ REPLACEMENT CARTRIDGE
THC
Strain:
CONTAINS THC

DELIVERY METHODS AND TIMING

Compare the following delivery rates of cannabinoid absorbtion into the bloodstream.
Inhalation leads to rapid absorption and decay while ingestion leads to slower but long lasting effects.

INHALATION
2 to 10 Minutes

TINCTURE
15 to 30 Minutes

TOPICAL
15 to 45 Minutes

INGESTION
60 to 120 Minutes

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NOTES

PATIENT CENTERED DOSING

Considerations Before Medicating With Cannabis

OBJECTIVE

This chapter gives medical professionals a method of assisting patients to self-administer consistent, measurable doses of a cannabis remedy that includes as much THC as the patient is comfortable taking. It also includes the latest research on drug-drug interactions and spells out the patients for whom cannabis is a relative contraindication.

INTRODUCTION

Honing in on the ideal therapeutic dose of cannabinoids to meet a patient's needs involves several variables: the method of delivery, the ratio of cannabinoids in a product, legal access to products, and the still mysterious mechanisms of how the ECS functions. Cannabis dosing is extremely individualized; finding the correct protocol is called "patient-centered dosing."

The current standard of care with cannabis medicines is for doctors to guide patients to develop a method of self-titration, similar to how pain patients dose themselves with gabapentin (Neurontin®) or diabetics use insulin. While this method is less precise than many conventional drug dosing protocols, the safety profile of cannabis makes self-titration extremely low risk, and medical providers can take comfort knowing that no cannabis overdose deaths have ever been documented.[1] A provider's main concern is to ensure that patients are tolerating the medication and that they are educated about reducing side effects. Given what's known about the pharmacology of cannabis, this method is simple and broadly effective.

This protocol works well for cannabis naive patients who are just starting out. It begins with a CBD-rich product, which is administered in low doses two to four times daily, and increased every 1 to 4 days. The dose is increased until effects are felt. If no relief is felt, the patient is then guided to adding small amounts of THC, since THC and cannabidiol (CBD) interact to enhance each other's effects.[2]

A patient's sensitivity to THC is key to determining the ratios and dosages. While a large percentage of patients enjoy the euphoria from THC, others find it unpleasant. THC-averse patients can begin with pure CBD products.

With supervision and good record keeping, patients can find their own "sweet spot" in terms of ratios of cannabinoids and the most therapeutically beneficial dose. Since CBD can mitigate the psychoactive effects of THC, a higher ratio of CBD:THC typically means less psychoactivity and lower risk for adverse effects such as dysphoria, anxiety, or short-term memory loss.[3]

NOTE: *Titration should proceed more slowly in elderly or cannabis-naive patients, as well as those with the relative contraindications discussed.*

SET AND SETTING

To minimize risk of dysphoria, it is important to discuss the importance of "set and setting."[4] "Set" has to do with the patient's mindset prior to using cannabis, while "setting" is the physical environment in which the medication is consumed. Patients, especially the cannabis-naive or those who have anxiety or psychiatric disorders, should be cautious during early trials of cannabis to avoid heightened emotional duress. These patients can create a more pleasant environment with calming music, low light, pillows, candles, or anything that makes them feel safe and comfortable.

DRUG–DRUG INTERACTIONS

Research overwhelmingly shows that cannabinoids can be administered safely with most drugs including anti-inflammatories, NSAIDs, and opioids.[5] Although there is some evidence that cannabis may affect the processing of certain drugs via the liver's cytochrome P450 enzyme system, which may, in turn, increase levels of these drugs in the blood, no significant interactions have been reported with the pharmaceutical drugs Marinol® (synthetic THC) or Sativex®.[6]

Sativex® has been widely studied and has received regulatory approval in over 20 countries. It is currently undergoing Phase III clinical trials in the United States.[7] Studies have involved over 1,500 patients in placebo controlled trials and long-term open label studies. Even with patients using up to 48 doses daily, Sativex® was well tolerated and showed no significant drug interactions. The most common adverse reactions in the first four weeks of exposure were dizziness, which typically occurred shortly after titration, and then fatigue. These effects were dose dependent.[8]

With Marinol®, clinical trials administered the drug alongside cytotoxic agents, sedatives, opioids, or anti-infective agents. No significant drug–drug interactions were reported.[9]

Below is a list of additional drug–drug adverse reactions that have been reported to date.[10] Clinicians should be aware of these possibilities but also bear in mind that these interactions are not occurring in significantly large numbers and that with monitoring any issue can be quickly resolved.

- Cannabis may cause low blood pressure after initial titration.
- THC escalates heart rate for several minutes after inhalation so patients with arrhythmias or those at risk for syncope should be monitored.
- Cannabis can increase sedation when mixed with alcohol, benzodiazepines, antihistamines, sleep aids, and opiates.
- Cannabis can increase the cardiac effects of amphetamines, antidepressants, beta blockers, and diuretics.
- Cannabis can increase INR values in patients taking warfarin and may affect other drugs that increase risk of bleeding.

RELATIVE CONTRAINDICATIONS

There are several patient groups for whom cannabis use can be considered a relative contraindication and who require a greater degree of follow up and monitoring. They include pregnant and nursing mothers, patients with cardiac conditions, patients under age 25, patients with psychiatric diagnoses, immunocompromised patients, or patients on immunosuppressive medications.

- PREGNANT AND NURSING MOTHERS -

Pregnancy is a relatively strong contraindication to the use of cannabis. Cannabinoids are fat-soluble, therefore they may be present in the fetus and breast milk. Though current studies of cannabis use and pregnancy involved women who were polysubstance drug users, caution should be taken by pregnant and breast feeding women. At this time there is substantial evidence of a statistical association between marijuana use during pregnancy and lower birth weight.[11] However, when adjusted for other drug use such as cocaine or opiates, there was no significant association between cannabis use and lowered birth rate.[12] In addition, a recent study in Ontario, Canada, indicates there is a statistical increase in premature births between marijuana users (10%) compared with non-users (7%).[13]

There is an increased risk of both brain and behavioral problems in babies. If a pregnant woman uses marijuana, the drug may affect certain developing parts of the fetus's brain. Children exposed to marijuana in the womb have an increased risk of problems with attention[14], memory, and problem-solving compared to unexposed children.[15]

- YOUTH UNDER 25 -

The highest risk group for unintentional cannabis overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently. Several studies report that unintentional pediatric cannabis exposure is associated with potentially serious symptoms, including respiratory depression or failure, tachycardia and other cardiovascular symptoms, and temporary coma.[16]

One recent brain imaging study suggests that changes in the shape, volume, and density of certain regions correlate with cannabis use.[17] More recent studies contradict these findings, and indicate that alcohol is in fact associated with those changes in the brain, not cannabis.[18] These studies should be considered carefully when recommending high-THC cannabinoid therapy to youth. But clinicians should also weigh the conflicts of interest and biases in research, and evaluate cannabis efficacy in comparison to other substances.

The first study referenced herein–and the many others like it—was funded by the National Institute on Drug Abuse (NIDA), Counterdrug Technology Assessment Center, the Office of National Drug Control Policy, and the National Institute of Neurological Disorders and Stroke. Papers establishing the Counterdrug Technology Assessment Center state, "The Center shall operate under the authority of the Director of National Drug Control Policy and shall serve as the central counter-drug technology research and development organization of the United States Government".[19] This means that the study was funded by an organization of the federal government (NIDA), that is, by Congressional mandate, looking for harm caused from cannabis, an inherent bias.

The small sample size in this study has caused some scientists to dispute the validity of the findings. It is also unclear what exactly was being measured: the effects of cannabis or the effects of the stigma, threat, and stress related to its use. Nor did the researchers examine the behavior of cannabis users or the control group, or take baseline MRI's of the subjects before the study began. Patients in the cannabis using group also drank significantly more alcohol than in the control group.[20] This leads to the question of whether cannabis caused a change in brain structures, or if differences in neurophysiology made subjects more prone to using cannabis. (It is also notable that in other studies "social play" in rats increases anandamide levels in these same brain regions, indicating that healthy behaviors may also influence these areas through the ECS.[21])

Patients in this age group can reduce potential risks from THC by utilizing high CBD:low THC products. This is particularly relevant in cases of pediatric epilepsy, where high CBD:low THC products have dramatically reduced seizure frequency.[22]

- PATIENTS WITH CARDIAC CONDITIONS -

Marijuana raises heart rate for up to three hours after smoking. This effect may increase the chance of heart attack. Older people and those with heart problems may be at higher risk.[23] The acute cardiovascular effects of cannabis include increases in heart rate and supine blood pressure and postural hypotension.[24] Smoking cannabis also decreases exercise test duration on maximal exercise tests and increases the heart rate at submaximal levels of exercise.[25] High CBD:low THC products reduce these effects and can help minimize risk.

Overall, however, the ECS in humans appears to have a positive effect on the cardiovascular system. Studies show benefits in areas of oxidative stress,[26] inflammation,[27] fibrosis,[28] and myocardial dysfunction.[29] CB1 activation in the heart muscles of rats limits ischemia-reperfusion, indicating that THC plays a highly protective role in the heart muscle.[30]

What's more, cardiologists working with mice at Hebrew University found that CBD treatment at the time of heart attack reduces infarct size by 66%, which suggests that CBD could, in fact, protect the heart from disease. Activation of cannabinoid receptors had practically no effect on collateral blood flow in the myocardium, yet considerably decreased the area of necrosis, indicating that the mechanism of protection involves more than just an increase of blood flow to compromised areas. Interestingly, the protection from CBD is not coming from increased oxygen flow; protection is happening despite the lack of oxygen to the heart.[31]

- PATIENTS WITH PSYCHIATRIC DIAGNOSES -

Persons with a personal or strong family history of psychosis, schizophrenia, or panic disorder have a relative contraindication to using cannabis products containing THC. THC can aggravate some patients with anxiety, irritability, and memory issues, as well as those predisposed to psychosis.[32,33] Such patients should use the lowest effective ratio of THC and explore products with high CBD. This should mitigate the negative psycho-emotional effects of THC.

NOTE: *Even patients using high CBD:low THC products should monitor daily THC intake as it can build up in the system.*

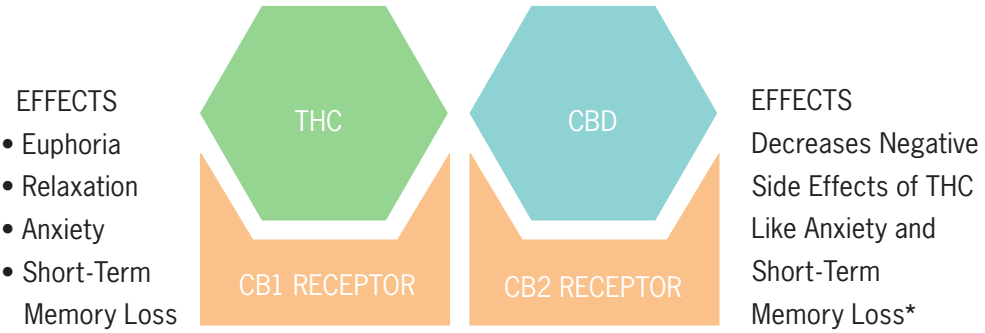
- IMMUNOCOMPROMISED PATIENTS -

Various microorganisms, primarily inhaled molds, can expose immunocompromised patients to the risk of opportunistic lung infections. There have been a small but significant number of cases linking poorly grown cannabis with invasive aspergillosis.[34] This is thought to be the result of inhaling fungal spores present on the plant's leaves. Modern microbial testing in states with medical cannabis laws reduces this risk. Patients with active bacterial infections should avoid high-dose THC medications as large doses of THC can inhibit the antibacterial activities of the immune system.[35] On the other hand, CBD possesses powerful antibacterial properties, even in very low concentrations, and both systemic and topical applications may be useful for patients at risk for bacterial infections.[36]

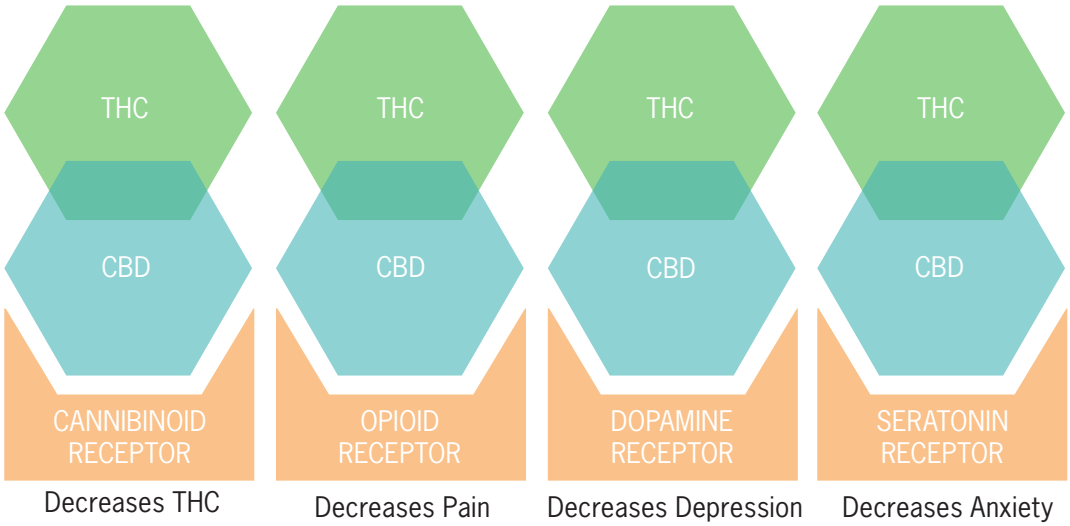
BIPHASIC EFFECT

When dosing, it is important to remember that cannabis compounds act biphasically: low doses and high doses of the same substance can have opposite effects.[37] Low doses of THC, for example, tend to stimulate, while high doses sedate. Too much THC can amplify mood disorders and anxiety and impact short-term memory.[38] CBD, on the other hand, has no known adverse effects at any dose. In some conditions such as MS or pain, high doses can actually be less effective than low doses.[39] Patients should be advised to "start low and go slow" when establishing treatment plans.

HOW CBD CUTS THE NEGATIVE EFFECTS OF THC



LEFT: Activation of CB1 receptors by THC in the brain triggers many of the classical effects of cannabis. This includes pleasant effects like euphoria and relaxation with side effects like short-term memory impairment and anxiety—especially at higher doses. RIGHT: CBD does not activate the CB1 receptor. Instead, CBD interferes with THC's ability to activate the CB2 receptor, which can decrease some of THC's side effects.



ABOVE: CBD interacts with many different receptor systems in the brain. It interacts with cannabinoid receptors indirectly by interfering with THC's ability to activate those receptors. CBD directly activates many other receptor-types in the brain, including opiod, dopamine, and seratonin receptors. This is why it treats such a wide variety of ailments.

BASIC DOSING PROTOCOL

To date, there have been few studies examining dosage or cannabinoid ratios. The most relevant is Carter, Weydt, et al's "Medicinal cannabis: rational guidelines for dosing," which reviews all current chemical and pharmacological cannabis knowledge to build rational dosing guidelines.[40] But even these guidelines are preliminary. The information included here is based on peer reviewed research as well as anecdotal information from experienced cannabis clinicians. The main priorities of medical professionals are to minimize side effects of THC, while also maximizing effectiveness of dosages and cannabinoid ratios.

The following is a step-by-step dosing protocol that patients can use to find the therapeutic dose range that works for their unique biology and medical needs.

- Decide on delivery system(s) and ensure patient understands the advantages and disadvantages of each.
- Determine if patient wants THC-rich medicine, CBD-rich medicine, or a more equal ratio of cannabinoids.
- Start Low, Go Slow: New or inexperienced patients should begin with a low dose. Take a small amount, then wait. If inhaling, wait 20 minutes before taking another small dose if you do not get to desired relief. With edibles, it is best to increase the dose the following day to avoid over-medicating.
- Titration: Begin with low doses (typically 15 mg to 20 mg) of a CBD remedy two to three times daily. The dose can then be titrated upwards relatively rapidly.
- Add THC, if indicated. THC dosing levels should be increased in 2.5 mg increments.[41]
- Once you center on the effective therapeutic dose range for symptom relief, stay the course if it's working; if not, adjust up or down in small increments or try a different product.
- Encourage the patient to journal their results. Write down the names of products, the dose amount, and the time of administration to understand what is working best. Take note of any side effects. Photograph the labels for reference. Medical professionals should review and adjust the patient's responses to cannabinoid therapy. If clinically significant improvement is not seen in 8 to 12 weeks, treatment can be stopped or the patient may be referred to a cannabinoid specialist for further adjustments to the treatment protocol.

Medical professionals should review and adjust the patient's responses to cannabinoid therapy. If clinically significant improvement is not seen in 8 to 12 weeks, treatment can be stopped or the patient may be referred to a cannabinoid specialist for further adjustments to the treatment protocol.

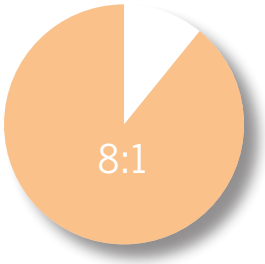
FINDING YOUR CBD:THC RATIO

CBD DOMINANT

Non-psychoactive. For novice cannabis users or people who do not want to get high. Some patients find CBD dominant medicine helpful for anxiety, depression, psychosis, and other mood disorders.

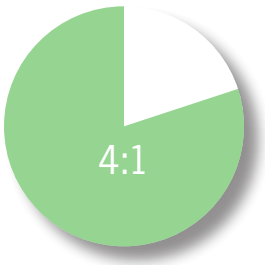
CBD BRIDGE

Non-psychoactive. Some patients find mid-range CBD:THC ratios helpful for spasms, convulsions, tremors, endocrine disorders, metabolic syndrome, and overall wellness.



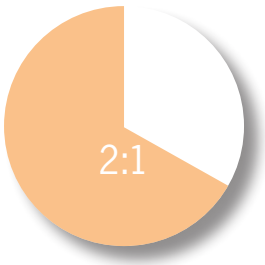
CBD HARMONY

Borderline psychoactive. For patients who have some tolerance for THC. Some patients find mid-range ratios helpful for pain relief, immune support, and other health benefits.



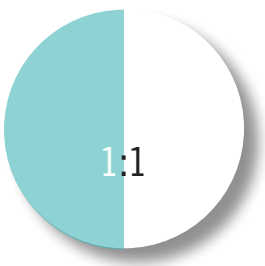
CBD SYNERGY

Psychoactive in larger doses. For patients who have some tolerance for THC. Some patients find balanced ratios helpful for chronic pain, gastrointestinal issues, and stress relief.



CBD BALANCE

Psychoactive. For patients who can tolerate THC. Some patients find a balanced ratio helpful for neuropathic pain, rheumatism, and overall mood enhancement.



RECOMMENDED RATIOS FOR SPECIFIC ILLNESSES

- Patients with seizure disorders,[42] anxiety or relative contraindications[43,44] as well as the elderly or cannabis-naive, frequently do best starting with high CBD:low THC ratios greater than 16:1. The ratio can then be decreased, moving from 16:1 » 8:1 » 4:1 » 2:1 » 1:1 until the patient finds the ratio that works best.
- Patients with no relative contraindications or who have experience with cannabis often begin with a 1:1 ratio. The ratio can be altered, moving from a 1:1 » 2:1 » 4:1 » 8:1 » 16:1 until the patient finds the ratio that works best.
- THC tends to offer the best relief for patients with nausea/vomiting, although CBD also possesses anti-nausea properties. Patients with nausea and vomiting may also want to avoid high levels of CBG.[45]
- Patients with cancer or neurologic diseases, including multiple sclerosis and pain, may benefit from a more balanced 1:1 ratio.[46]
- Extensive clinical data in humans indicates that a 1:1 CBD:THC ratio is an effective ratio for neuropathic pain.[47]

DOSING AND DELIVERY: CLINICAL PEARLS

- INHALATION -

Inhalation means rapid absorption. Blood levels peak in minutes, and reduce to 5 to 10% of peak levels after 1 hour.[48]

- EDIBLES -

Absorption of edibles is enhanced when they are delivered in lipids such as butter, coconut oil, or sesame oil.[49] Time to onset is quicker when the patient's stomach is empty. To delay onset time, direct the patient to snack before medicating.[50] Beginning patients should start with 2.5 mg of THC per dose. If no effect is noticed, patients can increase THC levels by 2.5 mg every 24 hours. If intolerable side effects appear at higher doses, the patient can revert to the previous level.[51]

- TINCTURES -

Tinctures are the most versatile of all cannabis-based medications and can be taken orally, used topically, or absorbed through the oral mucosa for rapid onset and ease of titration. Patients can vary the delivery method to improve the therapeutic effects. For example, a patient with tension-induced migraine and aura can get rapid relief by gargling with a tincture for rapid absorption into the bloodstream. The patient can then swallow the remaining tincture, where THC then undergoes first pass metabolism, thus providing long lasting relief. Finally, tinctures can be applied to the neck and shoulder to reduce muscle tension, aches, and inflammation.[52]

- TOPICALS -

Topical cannabis products possess analgesic, antispasmodic, anti-microbial, anti-itch, and anti-burning properties, and generally lack psychoactivity.[53] Effects are dose dependent, so patients should seek out products with higher concentrations of cannabinoids and be encouraged to apply them liberally. Topical cannabinoids can provide the first line of defense against pain, including neuropathic pain, chronic pain, muscle pain, and radiation burns. Onset is immediate and lasts 30 minutes to 3 hours.[54] CB1 signaling decreases release of activators and sensitizers around the site of tissue injury or irritation, thus reducing the inflammatory cascade. Additionally, CB1 hyperpolarizes nerves, making nerve endings in pain fibers less likely to fire.[55] There are also growing numbers of anecdotal reports of patients successfully treating basal cell carcinomas with topical cannabis; clinical studies are indicating that topicals can reduce tumor growth and vascularization in nonmelanoma skin cancer.[56] Animal studies show that topical cannabinoids penetrate the skin barrier and reach muscle tissue.[57]

"Journaling the products used, dosage, timing, and effects can help patients track their results and find their appropriate dose."

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NOTES

LABORATORY TESTING

How Testing Works

OBJECTIVE

This chapter familiarizes medical professionals with the most accurate methods of identifying the cannabinoid profiles of a plant and ensuring the product is free of contaminants and safe for patient use. It includes an overview of testing methods and a guide to interpreting laboratory results.

HOW TESTING WORKS

Examining the plant's structures (broad leaves vs. narrow leaves) cannot provide the insight necessary to determine whether it will cause a certain effect nor can knowing a strain's name. Medically speaking, the entire strain classification system is meaningless due to the enormous hybridization of plants over the last decades.

Although lab testing is more of a rough guide than a precise roadmap to effects, it does provide the most reliable insight into a plant's cannabinoid and terpene composition. It should also verify if the product is free of contaminants and safe for use. Ideally, all labs should be equipped to test for potency as well as microbial contaminants and pesticide residues, but this is not yet the case in all states. Potency is analyzed using gas or liquid chromatography.[1] With gas chromatography the sample being measured is vaporized into a carrier gas (helium). As the gases move up a column, they separate out into individual components, which allows chemists to identify them one by one. With liquid chromatography, a pressurized liquid solvent containing the sample is passed through a column filled with solid adsorbent material, which leads to the separation of the sample components. High pressure liquid chromatography has become the standard for cannabis testing.

CONTAMINANTS: PESTICIDES, FUNGI, AND MOLDS

Pesticides detected on cannabis are rarely toxic to mammals, but they can be dangerous to honey bees or fish. Organic pesticides, such as some pyrethrins, can be safely used on medical cannabis plants but only if the cultivator truly understands the amount of time required for the pesticide to clear the plant. Often a positive pesticide test is the result of a cultivator using the substance too close to harvest.[2]

Laboratory testing detects pesticides using chromatography, while molds and fungi are detected using culture plates.

The two most commonly reported fungal diseases are gray mold and powdery mildew, both of which are visible. Other dangerous molds that result from poor curing techniques including aspergillus, fusarium, or penicillium, and are more difficult to see with the naked eye. The biggest threat posed by these pathogenic molds is aflatoxin, a toxin that can also be carcinogenic. These occur very rarely. Consuming contaminated material can aggravate a medical condition that a patient is attempting to manage and should be avoided.[3]

Although laboratory screening can detect different types of contaminants, most states with medical cannabis laws do not yet mandate strict testing of cannabis products. What's more, laboratory certification standards vary significantly by state. Even in those with strict testing standards such as Oregon, recent investigations have revealed a number of contaminated products slipping through the cracks.[4] This situation should improve as more states introduce regulatory practices and standards are set.

HOW TO INTERPRET A TEST

Each lab testing company employs its own formats and designs when producing a label. To get a real measure of the potency of cannabis, THC Total is the best indicator. If this is not specified on the label, use the following conversion to calculate THC Total.[5]

THC Total = (%THCA x 0.877) + (%delta-9-THC)

If a cannabis product label indicates very little cannabidiol (CBD), and cannabinol (CBN) is in evidence it shows that the sample was fresh when tested.[6]

For edibles packaging and labels, the THC potency will be in milligrams instead of percentages. With edible products this information is especially important for precise dosing.

Many but not all analytical labs offer testing of terpene profile in addition to the cannabinoid content of a plant. If there is a full certificate of analysis, the full report will show major and minor cannabinoids, terpenes, pesticides, and residual solvents. Many states required dispensaries to review these certificates of analysis before intaking a cannabis product for sale, to ensure patient safety.

NOTE: *Each cannabis plant has its own terpene "bouquet," and patients should be encouraged to use their noses to identify major "tones" in the bouquet, such as six pine or citrus fragrances. These clues can help patients find terpene profiles that work best for them in the absence of terpene test results.*

Regulations and standards for acceptable limits of specific compounds are currently being developed to ensure cannabis products do not compromise a person's immune system. The two major reasons cannabis products are tested are to verify the products are safe for human consumption and to give consumers an idea of the potency of the product they are using.

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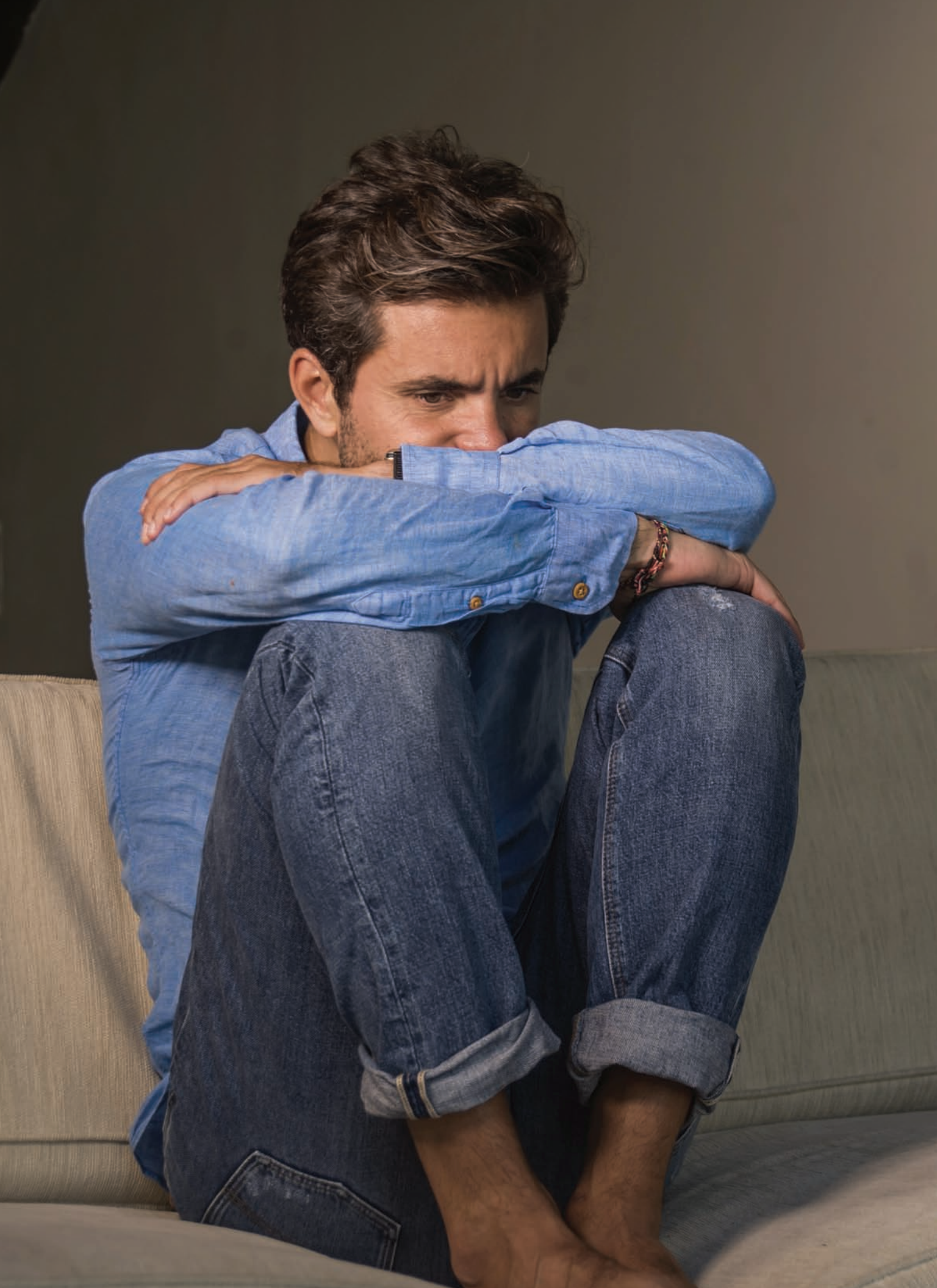


CLINICAL PRACTICE

Broad Therapeutic Uses

OBJECTIVE

Over a half dozen countries are planning to institute legal medical cannabis programs by 2020. This chapter provides an overview of some of the illnesses cannabis is being used to treat. They include certain cancers, anxiety, pain, epilepsy, insomnia, GI disorders, neurodegenerative illnesses, post traumatic stress, and migraines.

INTRODUCTION

As medical professionals, we know that there are no miracles, and cannabis is by no means a miracle medicine. It is, however, unlike any other medicine we know. It treats about 105 conditions, according to Dr. Franjo Grotenherman, MD, the founder of the International Society of Cannabis Clinicians, which makes it broader than any other therapeutic remedy.[1] Because our knowledge of the ECS is still unfolding, and because the worldwide prohibition has limited research, outcomes are far from standardized. That said, there are thousands of medical professionals (and many more patients) who have accumulated a deep clinical knowledge of cannabis medicine. This chapter is an overview of the information from the latest in clinical research regarding how medical marijuana interacts with conditions such as: anxiety, cancer, epilepsy, gastrointestinal (GI) disorders, sleep disorders, migraine headaches, neurodegenerative disorders, pain, and post traumatic stress disorder (PTSD).

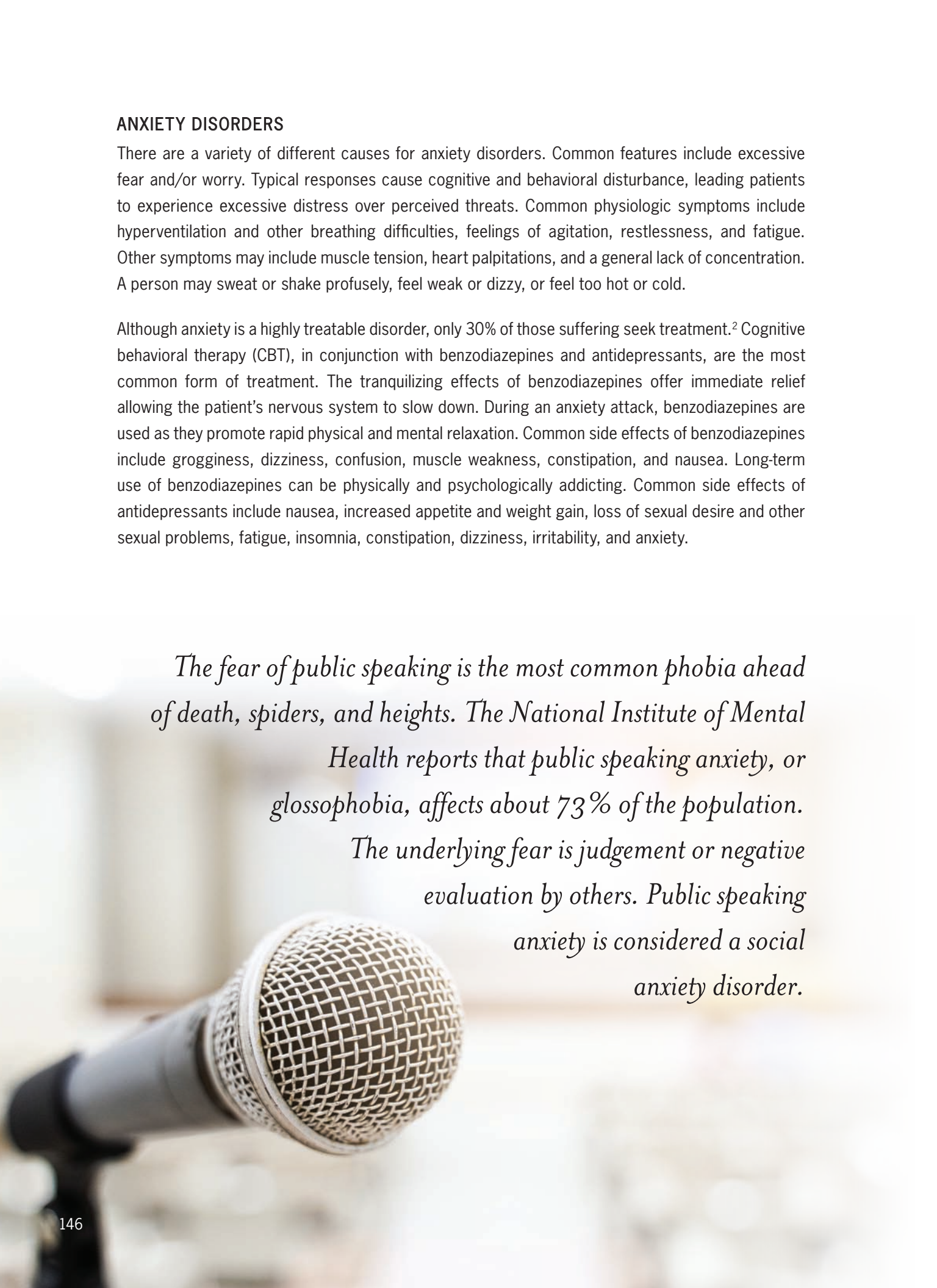
> *"Marijuana (cannabis) has been used medicinally for centuries. It has been shown to be effective in treating a wide range of symptoms and conditions."*
>
> — American Nurses Association

ANXIETY DISORDERS

There are a variety of different causes for anxiety disorders. Common features include excessive fear and/or worry. Typical responses cause cognitive and behavioral disturbance, leading patients to experience excessive distress over perceived threats. Common physiologic symptoms include hyperventilation and other breathing difficulties, feelings of agitation, restlessness, and fatigue. Other symptoms may include muscle tension, heart palpitations, and a general lack of concentration. A person may sweat or shake profusely, feel weak or dizzy, or feel too hot or cold.

Although anxiety is a highly treatable disorder, only 30% of those suffering seek treatment.[2] Cognitive behavioral therapy (CBT), in conjunction with benzodiazepines and antidepressants, are the most common form of treatment. The tranquilizing effects of benzodiazepines offer immediate relief allowing the patient's nervous system to slow down. During an anxiety attack, benzodiazepines are used as they promote rapid physical and mental relaxation. Common side effects of benzodiazepines include grogginess, dizziness, confusion, muscle weakness, constipation, and nausea. Long-term use of benzodiazepines can be physically and psychologically addicting. Common side effects of antidepressants include nausea, increased appetite and weight gain, loss of sexual desire and other sexual problems, fatigue, insomnia, constipation, dizziness, irritability, and anxiety.

The fear of public speaking is the most common phobia ahead of death, spiders, and heights. The National Institute of Mental Health reports that public speaking anxiety, or glossophobia, affects about 73% of the population. The underlying fear is judgement or negative evaluation by others. Public speaking anxiety is considered a social anxiety disorder.



Cannabis in Anxiety Treatment

Depression and related anxiety disorders cost the United States $210 billion a year, according to the newest data available, and most of those costs are from related illnesses such as anxiety and PTSD.[3] A sizeable portion of those costs come from repeat doctor visits and treatment with SSRIs, which are often ineffective. It is likely that a good deal of those costs could be reduced if patients knew how to successfully self-medicate with cannabis. Cannabis treats anxiety and depression, in many cases as effectively as antidepressants, but with fewer side effects.

Cannabidiol (CBD) acts on the body's GABA receptors to activate the parasympathetic nervous system.[4] This reduces the "fight or flight" response the body experiences during an anxiety attack, and ultimately induces a state of calm.[5] CBD can aid social anxiety and everyday stress. One study, led by the National Institute for Translational Medicine in Brazil, looked at the effect of CBD on anxiety symptoms.[6] This preliminary study aimed to compare the effects of a simulation public speaking test (SPST) on healthy control (HC) patients and treatment-naïve seasonal affective disorder (SAD) patients who received a single dose of CBD or placebo. A total of 24 never-treated patients with SAD were allocated to receive either CBD or placebo in a double-blind randomized design one hour and a half before the test. The same number of HC patients performed the SPST without receiving any medication. Each volunteer participated in only one experimental session in a double-blind procedure. Subjective ratings on the Visual Analogue Mood Scale (VAMS), Negative Self-Statement scale (SSPS-N), and physiological measures of blood pressure, heart rate, and skin conductance were measured at six different time points during the SPST. The study showed CBD "significantly reduced anxiety, cognitive impairment, and discomfort in public speakers." No adverse effects were reported in the study.

"Using compounds derived from cannabis to restore normal endocannabinoid function could potentially help stabilize moods and ease depression."

— Dr. Samir Haj, *Lead Researcher*
Dahmane University of Buffalo Research Institute on Addiction

It is important to note that *cannabis sativa* plants vary in cannabinoid content; some strains may have higher THC or CBD content than others. THC can produce psychotropic effects, which further induce paranoia and anxiety symptoms, depending on how much is consumed. While CBD appears to decrease anxiety symptoms at all doses tested, THC tends to increase anxiety at higher doses.[7]

Plants with high THC/low CBD content increase the risk of anxiety and panic reactions through marijuana intoxication. Abstinence from THC after long periods of consumption can also increase anxiety, and lead to greater feelings of depression and irritability.[8]

- PROPOSED MECHANISM -

Density of CB1 receptors in the brain's amygdala, hippocampus, and anterior cingulate cortex indicates that the ECS helps regulate stress and anxiety.[9,10] As a side noteworthy of more study, depressed people show lower levels of endocannabinoids, which could indicate an ECS deficiency; supplemental low doses of cannabinoids appear to return the ECS to balance.[11]

The Department of Neurology at Xuzhou Central Hospital in China reviewed the mode of action targeted by endocannabinoids throughout the body, regarding depression and pain comorbidity. A review of clinical studies by this team suggests the involvement of the ECS in eliciting potent effects on neurotransmission, neuroendocrine, and inflammatory processes, which are known to be deranged in depression and chronic pain. They conclude depression/anxiety and pain respond positively to administered cannabinoids, although the underlying mechanism remains to be elucidated.[12]

Limonene is a terpene found in some strains of cannabis. Common side effects can be shown to reduce inflammatory parameters in several pre clinical and clinical models, could also produce an anti-stress action by altering ortho/parasympathetic parameters, as well as central neurotransmitter functions.

— SOURCE: Patrizia A. d'Alessio, Jean-François Bisson, and Marie C Béné.Rejuvenation Research. April 2014

Cannabis targets receptors in the amydgala linked to anxiety. The natural endocannabinoid system regulates anxiety and the response to stress by dampening excitatory signals that involve the neurotransmitter glutamate.

CANCER

Cannabis has been used for the symptomatic relief of cancer treatments, like nausea, for some time. There are now studies that demonstrate that cannabis is also useful in alleviating the symptoms of cancer itself and in the treatment of certain cancers. Symptoms of cancer can include fevers, extreme fatigue, unexplained weight loss, changes to skin pigment, anxiety, depression, and a compromised immune function.

The most common treatments for cancer (chemotherapy, radiation therapy, and surgery) are associated with a host of side effects and symptoms. Common symptoms associated with cancer treatment include nausea, vomiting, fatigue, hair loss, appetite loss, depressed bone marrow function, anxiety, and depression.

Cannabis in Cancer Treatment

The use of cannabinoids in cancer – treating the disease itself and the symptoms associated with chemotherapies – are at the frontier of cannabinoid therapeutics.[13] In 2000, for example, Manuel Guzmán, PhD, injected cannabinoids into cancer cells in the brains of rats. Cannabinoids triggered apoptosis in cancer cells and prevented blood vessels from feeding tumors.[14] Today, a volume of evidence indicates cannabinoids affect key cell signaling pathways that affect cancer survival and proliferation. In laboratory animals, cannabinoids slow angiogenesis and decrease metastasis in multiple tumor types.[15] In vitro and animal studies demonstrate the anti-inflammatory, anti-proliferative, anti-invasive, anti-metastatic, and pro-apoptotic effects of cannabinoids.

In 2007, Sean McAllister, PhD, reported that CBD is a potent inhibitor of breast cancer cells, metastasis, and tumor growth. Apparently, cannabidiol kills breast cancer cells and destroys malignant tumors by switching off the ID-1 gene, a protein that appears to be a cancer cell conductor. This could be a breakthrough anticancer medication.[16]

Cannabis also helps cancer patients manage symptoms of chemotherapy-induced nausea, vomiting, and pain. Additionally, cannabis medicines can stimulate appetite, encourage sleep, reduce anxiety and depression, and lift the spirits of patients undergoing treatment, thus significantly contributing to their quality of life.[17]

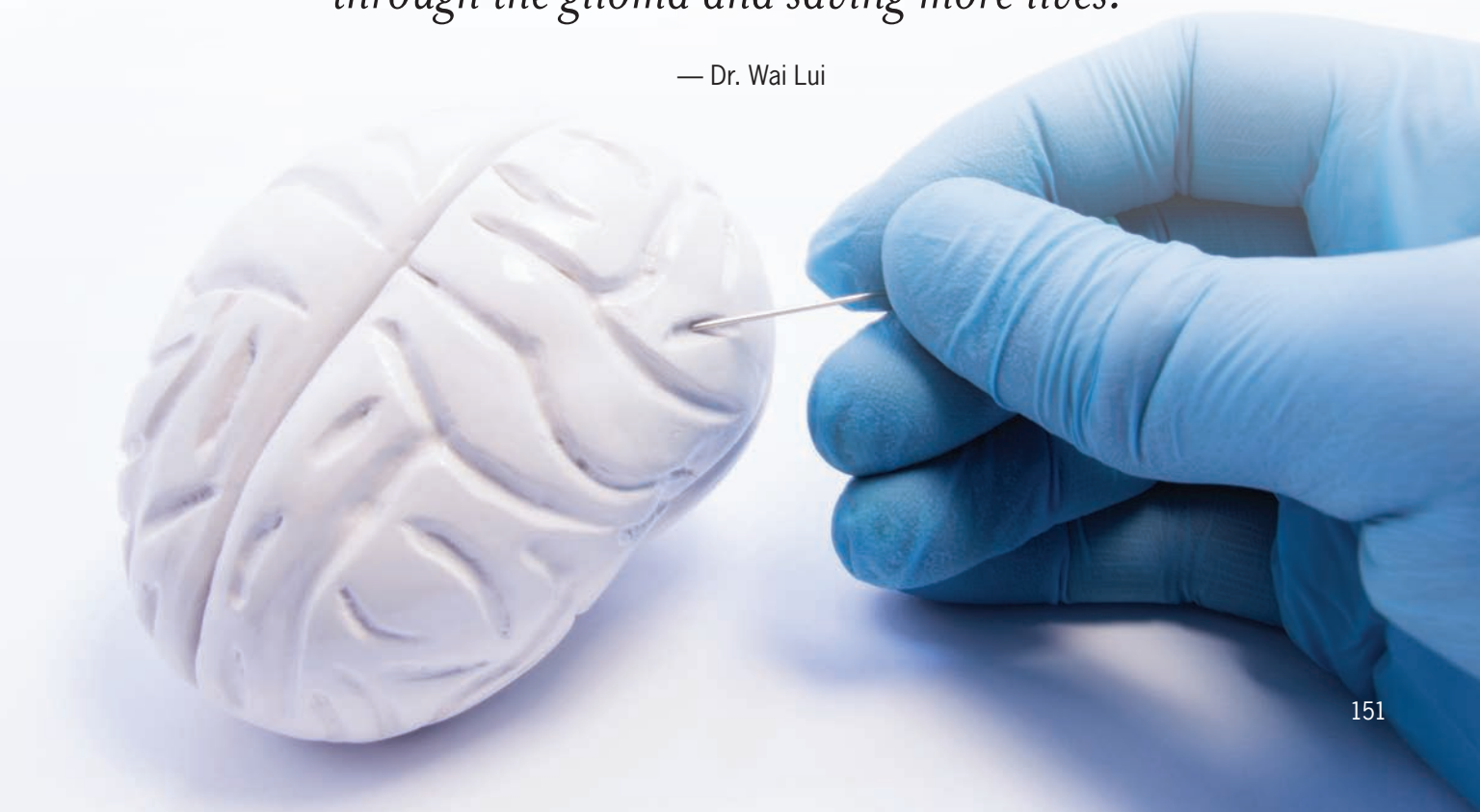
In 1974, a study at the University of Virginia produced evidence that cannabinoids could potentially treat cancer.[18] Since then, a meager few preclinical and clinical trials have assessed cannabinoids for their role in cancer cell proliferation and death, particularly in tumor growth. These shreds of evidence could lead to the development of novel cannabinoid therapeutics for cancer treatment if the research was funded and allowed to proceed.[19] Unfortunately, it has not progressed enough to develop dosing protocols or treatment plans for any type of cancer.

A growing number of states have enacted laws that legalize marijuana use, but products derived from *cannabis sativa* containing more than 0.3% THC are still considered Schedule I drugs according to the DEA.[20] However, commercially available cannabinoids, such as the FDA approved generics dronabinol and nabilone, have been approved nationwide for the treatment of cancer-related side effects. Dronabinol is an orally-administered synthetic form of THC, used to treat severe nausea and vomiting caused by cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Most common adverse reactions (≥3%) are: abdominal pain, dizziness, euphoria, nausea, paranoid reaction, somnolence, thinking abnormal thoughts, and vomiting.[21]

In the last decade, an increasing number of cancer patients have been using ultra large doses – as much as a gram or more of cannabinoids daily – of a concentrated product known by many names, such as Concentrated Cannabis Oil (CCO), Rick Simpson Oil (RSO), or Phoenix's Tears, claiming that it shrinks tumors or stops their growth. We have little data on the effectiveness of these dosing protocols but there are thousands of anecdotal reports of spontaneous remission, many of them viewable on YouTube.[22] Of course, we never hear from those for whom concentrated cannabis oils did not work, but medical professionals and patients alike could benefit from more rigorous inquiry.

"We've shown that cannabinoids could play a role in treating one of the most aggressive cancers in adults. The results are promising. It could provide a way of breaking through the glioma and saving more lives."

— Dr. Wai Lui



- PROPOSED MECHANISM -

Cannabinoids have multiple mechanisms of actions with different receptors throughout the body, and more research is needed to fully understand them. We know that at rational doses cannabinoids have low toxicity and very little drug interaction with chemotherapy agents.[23] Cancers exhibiting cannabinoid sensitivity include glioblastoma multiforme, astrocytoma,[24] neuroblastoma,[25] as well as skin, lung, liver, pancreas, breast, and prostate.[26]

In 2007, Christian, Garcia et al. reported that CBD is a potent inhibitor of breast cancer cells, metastasis, and tumor growth. Cannabidiol appears to kill breast cancer cells and destroys malignant tumors by switching off the ID-1 gene, a protein that appears to be a cancer cell conductor. Researchers infected human breast cancer cells with the Id-1 gene in order to be treated with THC, CBD, CBN, and cannabigerol (CBG). They detailed the approach to be "highly effective and safe in advanced breast cancer patients, given (a) the relationship between high Id-1 expression levels and aggressive breast cancer cell behaviors; (b) partial reduction in Id-1 activity can achieve significant outcomes; and (c) Id-1 expression is low in normal adult tissues, thereby eliminating unwanted toxicities generally associated with currently available therapeutic modalities."[27]

Cannabinoids play an anti-inflammatory, anxiolytic, and orexigenic (appetite stimulating) role through their binding with cannabinoid receptors. THC and CBD can treat recurring solid tumors and acute graft-versus-host disease, while killing cancer cells via apoptosis,[28] programmed cell suicide.

The active ingredient in marijuana or cannabinoids can relieve nausea and vomiting and increase appetite in people diagnosed with cancer and AIDS. Marijuana also has antibacterial properties and inhibits tumor growth.

"People are realizing that even when patients do well in terms of survival, there's a lot of suffering along the way that needs to be addressed. For many patients [marijuana] is an opportunity to take control over their disease and symptom management when they can't get the relief they need from the health care system."

— Dr. David Casarett
Professor of Medicine, University of Pennsylvania

EPILEPSY

Epilepsy is a neurological disorder marked by unprovoked, recurring electrical activities that can cause seizures and convulsions. The cause of epilepsy is still under investigation; however, some patients find certain situations are more likely to trigger an episode. Sleep deprivation, illness or injury, stress, low blood sugar, and alcohol and/or drug use can precipitate convulsions.

Currently, there is no cure for epilepsy, so patients attempt to manage the disease by seeking treatment for the seizures. Not all forms of epilepsy are the same, so a patient needs an accurate diagnosis of their condition before choosing the best antiepileptic drug (AED). A review of the most commonly use AEDs for seizures and epilepsy[29] reveals that there are various AEDs recommended, depending if the patient has generalized, partial, congenital epilepsy syndromes, or unclassified seizures. The first-line AEDS include valproic acid, Lamotrigine, and Topiramate. There are a dozen second-line agents. Some common side effects may include feeling tired, stomach upset or discomfort, dizziness, or blurred vision.

Anticonvulsants, such as phenytoin, primidone, and sodium valproate, can be used for both partial and tonic seizures. These are taken daily and are fairly well-tolerated. Some of the more common side effects of these drugs include sedation and other cognitive impairments, tremor, and gastrointestinal issues. Other less common side effects are effects on body weight and metabolism, and dose-related hepatic and hematologic effects. Skin, bone marrow, and hepatic toxicity can also occur due to hypersensitivity.[30]

Almost one third of epileptics have a form of the disease that is resistant to conventional drug therapies.[31] This resistance is largely associated with severe morbidity and increased mortality rates.[32]

Cannabis in Epilepsy Treatment

Treating epilepsy with cannabis is among its historically oldest uses. Animal studies provide evidence of the antiepileptic effects of cannabinoids, and THC has enhanced the anticonvulsant activity of phenytoin and diazepam. One small human study demonstrated reduced seizure frequency in adult epileptics.[33] In other studies, children using CBD reported reductions in seizure frequency as well as improved sleep, behavior, communication, motor skills, and alertness.[34] According to hundreds of reports, epileptic patients say that cannabis effectively controls otherwise unmanageable seizure disorders.

The completion of three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD product in patients with Dravet syndrome and Lennox-Gastaut syndrome was followed by FDA approval of a 99.5% CBD isolate for these two conditions. In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome.

For the first time, there is now class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes.[35] CBD has low affinity for CB1 and CB2 receptors, and other targets have been investigated to explain its anticonvulsant properties including TRPV1, voltage gated potassium and sodium channels, and GPR55, among others.[36]

In another study, children using CBD reported reductions in seizure frequency as well as improved sleep, behavior, communication, motor skills, and alertness.[37] Researchers from five Israeli Pediatric Neurology Units found CBD yielded this significant positive response in 89% of the 74 tested patients ranging in age from 1 to 18 years. The selected formula contained CBD and THC at a ratio of 20:1 dissolved in olive oil. The CBD dose ranged from 1 to 20 mg/kg/d. Seizure frequency was assessed by parental report during clinical visits. Sixty-six of the children reported reduction in seizure frequency: 13 reported 75% to 100% reduction, 25 reported 50% to 75% reduction, nine reported 25% to 50% reduction, and 19 reported <25% reduction. However, five patients reported aggravation of seizures which led to CBD withdrawal. Other adverse reactions, including somnolence, fatigue, gastrointestinal disturbances, and irritability, led to withdrawal of cannabis use in five patients.

In 2018, the FDA approved cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age or older. This is a 99% isolate extract of CBD and is the first of its kind to be approved by the FDA. Cannabidiol is to be administered orally with a recommended starting dosage of 2.5 mg/kg taken twice daily. The most common adverse reactions are: somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, rash, insomnia, sleep disorder, and poor quality sleep.[38]

- PROPOSED MECHANISM -

In a 2017 article published by the NIH's Neuropsychopharmacology Journal, authors J. Baines, A. Busquets-Garcia, and G. Marsciano show the effects of CB1 receptor signaling on seizure activity depends on how that receptor is being activated.[39] This article summarizes the current reports available on the ECS, with a focus on novel aspects that reveal how a nearly ubiquitous system can determine highly specific functions in the brain. The authors reveal CB1 receptor signaling is pleiotropic and depends on several additional factors, such as its cellular and subcellular localization.

In 2015, 1.2% of the U.S. population had active epilepsy (95% CI = 1.1–1.4). This is about 3.4 million people nationwide with epilepsy: 3 million adults and 470,000 children.*

—*CI = Confidence Interval describes the level of uncertainty of an estimate and specifies the range in which the true value is likely to fall. These reports use a 95% level of significance, which means 95% of the time, the true value falls within these boundaries.

GASTROINTESTINAL DISORDERS

Gastrointestinal disorders (GI) vary greatly but many lead to severe discomfort and distress. Irritable bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, affect a person's ability to take in food and can cause nausea, vomiting, diarrhea, constipation, and abdominal pain.

Treatment can include dietary intervention, for example, diets with a low lactose and low glucose content.[40] Pharmacologic treatment is also utilized such as antidepressants and prokinetics. Antidepressants act upon the central and peripheral nervous system to modulate mood, visceral and neuropathic pain, as well as autonomic function, in part, through anticholinergic effects. Prokinetics improve gastric and small bowel transit time, support inadequate postprandial gastric volume accommodation, augment visceral sensitivity, and increase eosinophilic infiltration indicating mucosal inflammation. Both forms of medication may introduce a variety of significant adverse effects, including extrapyramidal reactions, drowsiness, agitation, irritability, fatigue, and dystonic reactions.

Cannabis in Gastrointestinal Disorders

Using cannabis to treat GI distress goes back more than a century in western medicine, and far longer in traditional cultures.[41]

As of 2018, there are limited randomized controlled trials evaluating cannabis and gastrointestinal function, symptoms, or disease. One small study at Tel Aviv University by T. Naftali, L. Bar-Lev Schleider, et al[42] included 21 adult patients with Crohn's Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti-tumor necrosis factor agents. Patients were split into groups and given cigarettes that contained either 115 mg of THC or placebo cannabis flower that had the THC extracted. Complete remission was achieved by 5 of 11 subjects in the THC administered group and 1 of 10 in the placebo group. Also, a decrease in CDAI scores was observed in 10 of 11 subjects in the THC group. Three of the patients in the THC group were weaned from steroid dependency. Subjects receiving THC reported improved appetite and sleep, with no significant side effects.

For patients who suffer from nausea, appetite loss, and severe pain, cannabinoids can offer broad-spectrum relief not found in conventional drugs.[43] They interact with cannabinoid receptors in the digestive tract, relieving pain, reducing spasms, and improving intestinal motility. Allopathic medications for chronic GI disorders can produce serious side-effects such as acute diarrhea, relapse of IBD, microscopic colitis, and acute pancreatitis.[44] Cannabinoids modulate the actions of the GI tract,[45] while CBD has demonstrated reduction in inflammation and tissue damage,[46] as well as reduced hypermobility[47] in experimental models.

Cannabinoids modulate pain in IBD at the spinal and peripheral levels.[48] Studies show cannabinoids help control GERD in animal models.[49,50] In patients with IBD, cannabinoid receptors are upregulated in intestinal tissue,[51] and activating these receptors has therapeutic effects in the gut.[52] Allopathic medications for chronic GI disorders produce serious side-effects that can threaten a patient's health and require yet more meds to combat the side effects. Many clinicians believe that modulating the ECS provides options not offered by conventional therapies.

There have been several studies on patients and animals that indicate that cannabinoids can help control gastroesophageal reflux disease (GERD). One of the studies at Louisiana State University's Department of Pharmacology and Experimental Therapeutics examined male ferrets and found that CB1 receptor activation modulates a vago–vagal pathway that has been linked with acid reflux and the development of GERD.[53] Another review by Department of Pharmacy and Pharmacology, University of Bath, compiled current studies of CB2 receptors in the gastrointestinal tract highlighting their role in regulating abnormal motility modulating intestinal inflammation and limiting visceral sensitivity and pain. CB2 receptors represent a braking system and a pathophysiological mechanism for the resolution of inflammation and many of its symptoms. CB2 receptor activation therefore represents a very promising therapeutic target in gastrointestinal inflammatory states where there is immune activation and motility dysfunction. In patients with IBD, cannabinoid receptors are upregulated in intestinal tissue.[54]

Since cannabis masks symptoms of inflammation, it can lead patients to mistakenly perceive their disease to be in remission.[55] Thus, they may forgo routine care from their physicians, which results in long-term adverse consequences. Also, the use of cannabis is rarely communicated to healthcare specialists, which emphasizes the need for discussion among providers and patients.

- PROPOSED MECHANISM -

Cannabinoid receptors are apportioned throughout the GI system and appear to upregulate in response to a wide range of GI conditions. Some of these include appetite regulation, nausea, vomiting, gastric acid and enzyme secretion, gut motility, and intestinal inflammation. These receptors appear to reduce inflammation and pain through a mechanism similar to probiotics, namely through inhibition of NF-kB.[56]

The cannabinoids interact with cannabinoid receptors in the digestive tract to relieve pain, reduce spasms, and improve intestinal motility.

Irritable bowel syndrome (IBS) affects the large intestine. It can cause abdominal cramping, bloating, and a change in bowel habits. Some people with the disorder have constipation. IBS is common. It affects about twice as many women than men and is most often found in people younger than 45.

SLEEP DISORDERS

Sleep dysfunction can result from a variety of mental and physical factors, ranging from PTSD and anxiety to pain and inflammation. Other sleep conditions are linked to respiratory disturbances. Prescription medications, such as zolpidem and eszopiclone, are used to treat sleep disorders. These medications target GABA receptors to reduce neuronal activity and promote sleep. However, there are often side effects from sleeping pill use, which range from mild to severe. Some patients report these medications cause them to feel drowsy and excessively tired the next morning. it is quite common for patients to develop a dependency on these medications, which are not suited for long-term use.[57] In addition, most sleep medications alter cognitive and behavioral ability that lasts well into the next day.

Other adverse effects accompanying sleep aids include sleepwalking, urinary retention, memory loss, aches and pains, constipation, suicidal ideation, and unsteadiness.[58]

Cannabis in Sleep Disorders

Anecdotally, cannabis has been known for millennia as an excellent and mildly sedative sleep aid, but how it affects the various stages of sleep is still a mystery. Some patients report reduced ability to recall dreams, but for people who cannot get a full night's rest remembering dreams is of minor concern.

Early investigations of cannabis and sleep gained momentum in the 1970s. A 2017 review of existing literature found that cannabinoids have therapeutic potential for the treatment of insomnia, sleep apnea, REM sleep behavior disorder, and excessive daytime sleepiness. Led by the National Center for PTSD—Dissemination & Training Division, the review examined the state of research on cannabis and sleep up to 2014 and reviewed in detail the literature on cannabis and specific sleep disorders from 2014 to the time of publication.[59] The research suggests that short-term use of cannabinoids may have a therapeutic impact on sleep, specifically related to sleep onset latency and slow wave sleep. Long-term chronic use is associated with habituation to the sleep-enhancing benefits and is associated with increased risk for cannabis dependence. Sleep disruption is a primary withdrawal symptom from cannabis. Initial work examining specific cannabinoids suggests a potential therapeutic effect on high-dose CBD and low-dose THC for sleep. Although the majority of studies reviewed suffered from methodological issues, precluding definitive conclusions, anecdotal reports show that patients get to sleep more quickly, stay asleep longer, and feel well-rested without the morning grogginess associated with sleeping pills.[60]

While marijuana appears to offer some relief from sleep dysfunction, many studies also report certain adverse effects. Some heavy marijuana users report sleep disturbance after discontinuing long-term use as part of withdrawal syndrome. This 2008 study found that abruptly stopping marijuana consumption can lead to scary dreams, insomnia, and overall poor sleep quality.[61] Neurology units from schools and medical institutions throughout Baltimore evaluated a control group of 17 heavy marijuana users and 14 drug-free participants as a placebo. Recently-abstinent marijuana users reported longer to sleep onset and greater difficulty with sleep maintenance.

- THC -

Cannabinoids are biphasic. While high doses of THC can cause the mind to race, low doses have been found to induce sleep.[62]

- CBD -

It has been said that by itself CBD is a wake inducing agent but this is not the full story.[63] In animal studies, CBD appears to increase alertness in high light environments, but not in the dark.[64] So while CBD might be a useful antidote for daytime sleepiness, its anti-anxiety properties can augment nighttime formulations.

- CBN -

Desiccated or poorly stored cannabis is higher in CBN, a metabolite that produces little psychoactivity but fosters sedation, especially when combined with low doses of THC. It is thought that CBN is as much as 5 times more sedating than THC.

- TERPENES -

Certain terpenes, such as myrcene and linalool, have also been shown to powerfully enhance cannabis' sedative properties.[65]

Mainstream medications for sleep disorders can lead to the patient feeling tired and groggy the next day.

- PROPOSED MECHANISM -

Sleep stability is regulated by the ECS[66] while sleep deprivation and the time of day affect ECS signaling.[67] The ECS also helps regulate serotonin production.[68] High levels promote wakefulness while lower levels promote rest. Serotonin is also utilized by the pineal gland to make melatonin, a hormone directly related to healthy sleep. Cannabinoids can increase the expression of inhibitory neurotransmitters such as GABA which also have a hand in regulating sleep.[69]

A 2011 literature review on current pharmacological evidence show the administration of endocannabinoids induce cannabimimetic effects, including sleep promotion.[70] This evaluation, which included over 100 human and animal studies, indicates that CB1 activation causes the release of acetylcholine, and this could be another sleep promoting mechanism as acetylcholine levels rise in the brainstem and basal forebrain when not awake. The authors conclude by suggesting the integration of ECS mechanisms in sleep modulation.

Anecdotal reports show that patients suffering from sleep disorders can use cannabinoids to get to sleep faster, stay asleep longer, and feel well rested.

50–70 million U.S. adults have a sleep disorder; 37.9% reported unintentionally falling asleep during the day at least once in the preceding month and 4.7% reported nodding off or falling asleep while driving at least once in the preceding month.

MIGRAINE HEADACHES

Migraine headaches are a type of headache disorder associated with recurrent moderate to severe headaches that tend to be one sided and pulsing in nature. Aside from the headache, associated symptoms can include nausea, vomiting, and sensitivity to outside stimulation such as light, smells, or sounds. Episodes of headache can be triggered by hormone changes, alcohol, fatigue, and certain foods to name a few. Treatment usually begins with pain management, but can include other medications to prevent attacks.

While preventive medications avert symptoms prior to an attack, abortive medications target the migraine once it has started. Abortive medications, such as ergotamines and triptans, work to address the underlying causes of pain and other symptoms brought on by migraines. Nearly 2% of the general population (and up to 70% of those with chronic headaches) worldwide misuse these medications, further adding to the onset of their pain development.[71] In addition, opioids prescribed for chronic pain are misused by roughly 21% to 29% of patients.[72] These medications pose the risk of various comorbidities, such as depression, anxiety, and dependency.

Cannabis in Migraine Treatment

Cannabis has successfully treated headaches for thousands of years and is a good option for chronic sufferers looking for low toxic relief. Western clinicians have extensively discussed its use for migraines since the 19th century.[73] Cannabinoids are well known muscle relaxers, which help relieve the vascular spasms of smooth muscle that occur in migraines.[74] Cannabinoids are also anti-inflammatory, and show dopamine blocking effects. Anandamide levels fluctuate in the periaqueductal gray matter of the brain, a migraine generator; and THC modulates glutamate neurotransmission via NMDA receptors. Additionally, anandamide enhances 5-HT1A and inhibits 5-HT2A receptors supporting ECS modulation in acute and preventive migraine treatment.[75]

Currently, there is not enough evidence from well-designed clinical trials to support the use of cannabinoids for headache, but there are sufficient anecdotal and preliminary results, as well as plausible neurobiological mechanisms, to warrant properly designed clinical trials. Such trials are needed to determine short- and long-term efficacy for specific headache types, compatibility with existing treatments, optimal administration practices, as well as potential risks.[76]

Manipulation of the CB2 receptor is a potential new target for migraine treatments.[77] A recent study evaluated the role of CB2 receptors in two animal modes of pain relevant to migraine: the tail flick test and the formalin test performed during NTG-induced hyperalgesia. CB2 agonist, AM1241, demonstrated significant analgesic capability, while also reducing the number of shakes/flinches during the test.

Withdrawal from cannabis use, even among non-frequent users, does pose the risk of migraine or headache.[78] In a clinical study of 469 adult cannabis smokers, the National Institute on Drug Abuse found that 42.4% of subjects experienced a lifetime withdrawal syndrome, and 95.5% of subjects reported at least one short-term withdrawal symptom, including cannabis craving (75.7%), mood changes (33.7%–50.1%), sleep disturbances (21.8%–46.9%), and decreased appetite. Furthermore, a comprehensive review of marijuana and migraine history deduced that in order for marijuana to be a viable solution for headache relief, there needs to be a better understanding of different doses, formulations, and strains.[79]

- PROPOSED MECHANISM -

A migraine trigger initiates a chemical reaction in the brain that affects smooth muscle in blood vessels. Dilation and inflammation of cephalic arteries and intracranial extra cerebral arteries cause the migraine headache. The migraine-associated symptoms result from the activation of the sympathetic nervous system caused by the pain. In a healthy subject, this would normally stimulate the release of endocannabinoids to restore equilibrium but migraine sufferers do not always release these endocannabinoids. Forward thinking researchers speculate that this may be indicative of an endocannabinoid deficiency.[80]

In the U.S., more than 38 million people suffer from migraines. Some migraine studies estimate that 13% of the population have migraines, and 2 to 3 million suffer from chronic migraines. Migraines occur most often in women (18% of women versus 6% of men).

NEURODEGENERATIVE DISORDERS

When the building blocks of the nervous system are damaged, the body is unable to restore their functions. Neurodegenerative disorders (NDs) persistently destroy nerve cells, resulting in a debilitation of movement and impaired cognitive function. NDs include Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Parkinson's disease. An ever-increasing number of Americans are afflicted with neurodegenerative diseases; approximately 50 million Americans are affected each year.[81] NDs pose burdening economic costs, with the total cost of treatment approaching $1.5 trillion annually, including direct costs (i.e. treatment, disability payments, and incarceration), as well as indirect costs (i.e. lost productivity, homelessness, and crime).[82] However, NDs are debilitating and often fatal, stimulating a growing urgency for finding effective treatment and cures for the millions who are suffering.

While there is no cure for NDs, there are many symptomatic treatments. The symptoms of these diseases vary according to their origin of cell death, so different therapeutic mechanisms are frequently utilized. For example, Parkinson's disease and other movement disorders are often treated with dopaminergic treatments. Cholinesterase inhibitors inhibit the breakdown of acetylcholine, a neurotransmitter that impacts both the peripheral nervous system and central nervous system. Pain can be associated with NDs, so analgesics and anti-inflammatory medication are used to combat these progressive symptoms.

Cannabis in Neurodegenerative Disorders

Mechoulam, Shohami, et al, Hebrew University of Jerusalem Institute for Drug Research, reviewed recent journals discussing the effectiveness of cannabinoids as neuroprotectants and show leads for neurodegeneration resulting from Traumatic Brain Injury (TBI).[83] The review focused on the role the ECS plays as a self-neuroprotective mechanism and its potential as a basis for the development of novel therapeutic modality for the treatment of TBI.[84] For example, 2-Arachidonoylglycerol (2-AG) localizes at the site of a TBI and is thought to exert neuroprotection and attenuate the brain damage as a molecular regulator of pathophysiological events. They concluded that the ECS could have the ability to affect the functional outcome after TBI by a variety of mechanisms. These involve inhibition of excitatory neural transmission, inhibition of the inflammatory response, and reducing vascular tone. The research showed that synthetic cannabinoids mimic the activities of anandamide and 2-AG, as well as synthetic specific CB2 agonists, should be considered candidates for further studies.[85]

Evidence continues to show how CBD and THC act on key elements of neurodegeneration. Cannabinoids are currently being used to effectively treat conditions including multiple sclerosis, TBI, Alzheimer's disease, parkinsonism, amyotrophic lateral sclerosis (ALS), stroke, and Huntington's disease. Although current clinical use of cannabinoids focus on symptom management, there are promising signs that they might also slow the progression in neurodegenerative disorders.[86] Recent animal studies indicate CBD is found to protect differentiated neuronal cells from the detrimental action induced by peptide exposure through a combination of its antioxidant, anti-inflammatory, and antiapoptotic properties.[87] CBD also demonstrated an ability to weaken activation of the key enzyme of the wingless gene, preventing tau protein hyperphosphorylation and the consequent neurofibrillary tangle formation. ALS illustrates how the broad effectiveness of cannabinoids might support patients. Current ALS treatment involves a multidrug regimen that includes one or more of the following: microglial cell modulators (including tumor necrosis factor alpha inhibitors), antioxidants, glutamate antagonists, anti-inflammatory agents, neurotrophic growth factors, and a mitochondrial function-enhancing agent. Cannabis appears to promote actions in all of these areas,[88] in addition to aiding sleep, appetite, bronchodilation, muscle relaxation, pain relief, and saliva reduction.[89] Similar multifunctionality applies to other neurodegenerative diseases.

"Cannabinoids might alleviate some parkinsonian symptoms by their remarkable receptor-mediated modulatory action in the basal ganglia output nuclei. Moreover, it was recently observed that some cannabinoids are potent antioxidants that can protect neurons from death even without cannabinoid receptor activation. It seems that cannabinoids could delay or even stop progressive degeneration of brain dopaminergic systems, a process for which there is presently no prevention. In combination with currently used drugs, cannabinoids might represent, qualitatively, a new approach to the treatment of Parkinson's disease, making it more effective."

— SOURCE: Sevcik J, Masek K, of The Institute of Pharmacology, Academy of Sciences of the Czech Republic, Prague

Although trials with positive findings on cannabis use for NDs have been identified, definitive conclusion on its efficacy has yet to be drawn. As one systematic review of 24 randomized controlled trials points out, methodological issues such as inadequate description of allocation concealment, blinding, and underpowered sample size, challenge the Cochrane risk of bias tools.[90] There is still a need for more conclusive evidence. NDs are among the most common treatable conditions for which states permit marijuana use.

- PROPOSED MECHANISM -

How cannabinoids affect these different disorders is not yet understood, but studies have identified several neuroprotective mechanisms including oxidative stress, neuroinflammation, and glutamate excitotoxicity.[91]

"Cannabinoids are now known to have the capacity for neuromodulation, via direct, receptor-based mechanisms, at numerous levels within the nervous system. These provide therapeutic properties that may be applicable to the treatment of neurological disorders, including anti-oxidative neuroprotective effects, analgesia, anti-inflammatory actions, immunomodulation, modulation of glial cells, and tumor growth regulation. Beyond that, the cannabinoids have also been shown to be remarkably safe with no potential for overdose."

— Gregory T. Carter, MD, Clinical Professor at the School of Medicine at the University of Washington and Co-director of the Muscular Dystrophy Association (MDA)/Amyotrophic Lateral Sclerosis (ALS) Center

Neurodegenerative diseases occur when nervous system cells in the brain and spinal cord begin to deteriorate. Because neurodegenerative diseases strike primarily in mid to late life, the incidence is expected to soar as the population ages. By 2030, as many as one in five Americans will be over the age of 65.

"Cannabis has properties applicable to symptom management of ALS (amyotrophic lateral sclerosis) including analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction."

— SOURCE: *American Journal of Hospice and Palliative Care*

PAIN

In the United States, over 100 million adults a year experience chronic pain for a cost of $560 to $635 billion in treatment and lost productivity.[92] Current pharmaceutical treatments for symptomatic relief include opioids, NSAIDS, antidepressants, and muscle relaxants. These medications, especially the opioids, are frequently misused and abused, due to increased availability within the last decade.[93] The use of these medications, as well as over-the-counter treatments, have grown to be controversial, given their ability to produce such strong dependency, addiction-related problems, and unintended fatal overdoses.

Cannabis in Pain Treatment

Cannabis, which was cited as a relief for rheumatic pain over 4,000 years ago.[94] It can control pain and inflammation and relieves other negative responses (i.e. aches and pains, inflammation, tingling and numbness, locked joints, and morning stiffness) that often accompany this condition.

Pain is the most common ailment for which people use medical cannabis,[95] and over 300 studies – including 36 double blind randomized controlled clinical trials – have shown that cannabinoids can help patients with chronic pain.[96,97] Over three dozen pre clinical and clinical trials have shown that low dose cannabis also relieves neuropathic pain.[98] Several clinical trials of nabiximols, a dose-controlled sublingual spray, demonstrate its effectiveness in treating intractable cancer pain, especially when opioid painkillers fail to provide relief.[99] Interestingly, cannabis also treats inflammation: THC has 20 times the anti-inflammatory potency of aspirin and twice that of hydrocortisone.[100] Unlike pharmaceutical pain killers, cannabis has very minor adverse side effects.

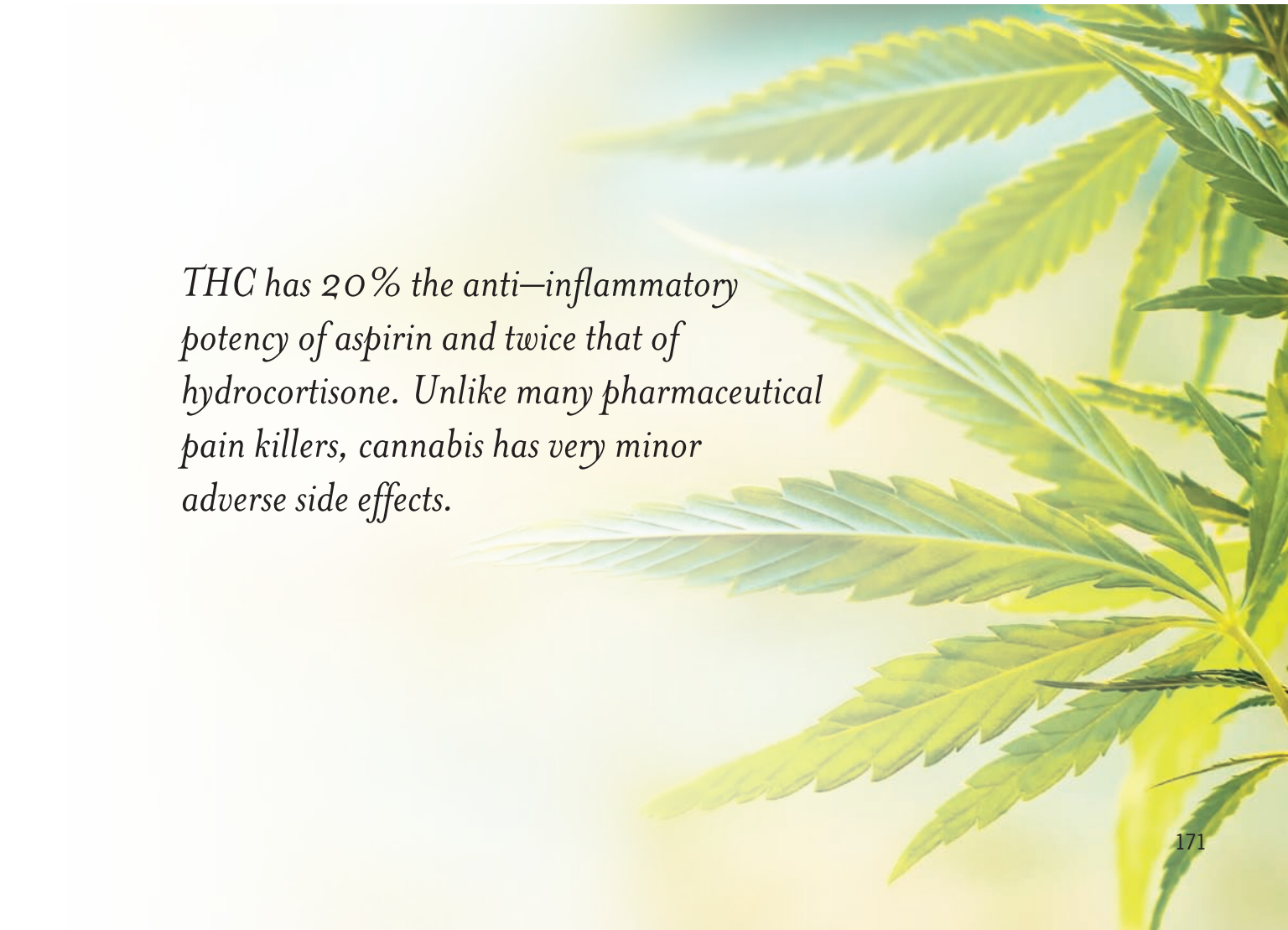
Arthritis and myofascial pain are two additional conditions patients seek relief with cannabis.[101] By altering chondrocyte signaling, cannabinoids can prevent destruction of cartilage and collagen breakdown in joints.[102] Cannabinoids have provided relief in rats with osteoarthritis by triggering release of endocannabinoids.[103] A study by Schuelert and McDougall, University of Calgary, analyzed whether local administration of the CB1 receptor agonist arachidonyl-2-chloroethylamide (ACEA) can modulate joint nociception in control rat knee joints and in experimental osteoarthritis. Local application of the CB1 agonist significantly reduced the firing rate of afferent nerve fibers by up to 50% in control knee joints and up to 62% in osteoarthritis knee joints. These findings indicate that activation of peripheral CB1 receptors reduces the sensitivity to mechanical stimuli of afferent nerve fibers in control and osteoarthritis knee joints and may be important targets in controlling pain. They also relieve muscle spasms, including those associated with multiple sclerosis (MS), and can relieve pain in fibromyalgia.[104]

Patients who incorporate marijuana into their collective pain treatment plan should pay attention to dosage. Using cannabis while taking other medications increases the risk of drug–drug interactions. A Department of Health presentation on cannabis drug interactions concludes that THC and CBD are metabolized by CYP3A4 enzymes. This can intensify effects on behavioral and cognitive function, particularly in regard to the central nervous system.[105]

Lifestyle changes including weight loss and an anti-inflammatory diet are also recommended. Additionally, Omega 3 oils increase the bioavailability of cannabinoids into the bloodstream and can increase overall ECS tone.[106]

- PROPOSED MECHANISM -

Cannabinoid receptors are located throughout the nervous system and regulate pain perception.[107] Cannabinoids relieve pain through a variety of mechanisms including analgesic and anti-inflammatory effects, modulation of neurotransmitter release, and by stimulating release of the body's own opioids.[108] Cannabis helps chronic pain by preventing nociception from reaching the brain; it helps injury by decreasing inflammatory cytokines locally, on spinal sites, and in the brain. It decreases transmission of pain signals through retrograde transmission. Other studies have shown that CBD can decrease the emotional response to the chronic pain via activity in the amygdala.[109]



THC has 20% the anti–inflammatory potency of aspirin and twice that of hydrocortisone. Unlike many pharmaceutical pain killers, cannabis has very minor adverse side effects.

POSTTRAUMATIC STRESS DISORDER (PTSD)

Nearly 61% of men and over 51% of women are exposed to some terrible, traumatic event in their lifetimes; PTSD occurs in an estimated 8% of these men and 20% of women.[110] Afflicted individuals suffer from higher levels of mental illness and suicide, as well as increased frequency of hypertension, ulcers, and bronchial asthma, and they can develop frequent social phobias and increased avoidance symptoms.[111]

PTSD treatment involves different types of trauma-focused psychotherapy, including cognitive behavioral therapy, in addition to medication. Selective serotonin reuptake inhibitors (SSRIs), antipsychotics, antidepressants, and benzodiazepines are among the more prominent drug classifications for PTSD treatment. The effectiveness of combining these medications has seen mixed success. Since PTSD has a high comorbidity with other psychological disorders, such as depression and anxiety, patients are prescribed these medications to treat certain symptoms, rather than the psychological disorder itself. This increases the need for more medication. Polypharmacy tends to reduce PTSD symptoms, including frequency of nightmares and mood alterations. However, polypharmacy can result in more side effects, which impact cognitive and behavioral function, contributing to noncompliance to treatment by the patient.[112]

Symptoms of PTSD occur in four major areas:

- Recurring memories of the traumatic event including nightmares
- Avoidance of people, places or things reminiscent of the trauma
- Negative mood and thought changes
- Chronic hyperarousal, including insomnia

Cannabis Benefits PTSD Treatment

Symptoms of PTSD occur in four major areas: 1) recurring memories of the traumatic event including nightmares; 2) avoidance of people, places, or things reminiscent of the trauma; 3) negative mood and thought changes; 4) chronic hyperarousal, including insomnia.[113] Cannabinoids benefit PTSD in several areas: reduction of anxiety, reduction of fear response, improved sleep, and reduction of night terrors.[114] Endocannabinoids exert their effects through interactions with the CNS related to PTSD, that is, regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, function of the hippocampus and amygdala, and control of cortical regulation of memory processes.

A study by G.A. Fraser, Canadian Forces Health Services Centre, reviewed the effects of the synthetic cannabinoid nabilone on the symptoms of PTSD, specifically nightmares. The small study charted 47 patients diagnosed with PTSD and having continuing nightmares despite being treated with conventional antidepressants and hypnotics. The use of nabilone was used in conjunction with conventional treatment plans. The results indicated that 72% of patients receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. Subjective improvement in sleep time, quality of sleep, reduction of daytime flashbacks, and night sweats were also noted by some patients.[115] The study was limited and contained no placebo group.

Follow up randomized clinical trials are needed to further evaluate the effectiveness of synthetic cannabinoids on the full spectrum of PTSD symptoms.

- PROPOSED MECHANISM -

A recent brain-scanning study indicated that abnormal endocannabinoid signaling in the brain is strongly implicated when trauma occurs.[116] PTSD actually affects the functioning and size of the amygdala, which is involved in the emotional processing of fear, anger, and pleasure in addition to the way pain is interpreted.

When THC is introduced, it changes the way people experience the quality of physical pain, but not necessarily its intensity.[117] It is a shift of focus. In the same way THC alters the processing of physical pain, its dissociative effects may be responsible for relieving the emotional distress and painful memories caused by trauma.

Studies of cannabinoids, specifically CBD, have demonstrated potential in mitigating the maladaptive responses to trauma.[118] In addition, CBD has also been studied in its effects in reducing responses to aversive memories by blocking the process of reconsolidation and enhancing the process of the extinction of aversive memories.[119] Appropriate dosage is imperative to PTSD treatment, which is why CBD is the focus of recent PTSD studies. Cannabis products containing THC can induce a psychosis, which may escalate PTSD symptoms in high-risk patients.[120] Patients with a personal or strong family history of psychosis, schizophrenia, or panic disorders have a relative contraindication to the use of products containing THC.

Women are more than twice as likely to develop PTSD than men (roughly 20% for women and 8% for men). Experts speculate that women might get PTSD more than men because women are more likely than men to experience sexual assault and sexual assault, is more likely to cause PTSD than many other traumatic events. Women are also more prone to blame themselves for trauma experiences.

— SOURCE: National Center for PTSD, U.S. Department of Veterans Affairs, 2015

THC / Tetrahydrocannabinol

THC is the best known cannabinoid and is the primary psychoactive compound in cannabis. It has also been found to be neuroprotective with analgesic (pain relieving) effects.

THCV / Tetrahydrocannabivarin

THCV is psychoactive and an appetite suppressant. Recent research suggests that this compound may be helpful in treating metabolic disorders including diabetes.

CBN / Cannabinol

CBN is mildly to non-psychoactive and is generally attributed with a sedative effect. The typical amount of CBN found in most samples of cannabis is less than 1%.

THCA / Tetrahydrocannabinolic Acid

THCA is the most prominent compound in fresh, undried cannabis. While the compound does not have psychoactive effects in its own right, it does have anti-inflammatory and neuroprotective effects.

CBD / Cannabidiol

CBD has been attributed with many medical benefits and has resulted in many strains being “enriched” to increase their CBD content. Non-psychoactive.

CBG / Cannabigerol

CBG is a non-psychoactive cannabinoid and early studies suggest it plays an important role in fighting glaucoma symptoms, inflamed bowels, and as a treatment for bacterial infections like MRSA.

CBC / Cannabichromene

CBC is the least understood cannabinoid, but potentially among the most important. It is believed to stimulate bone growth and inhibit inflammation. Non-psychoactive.

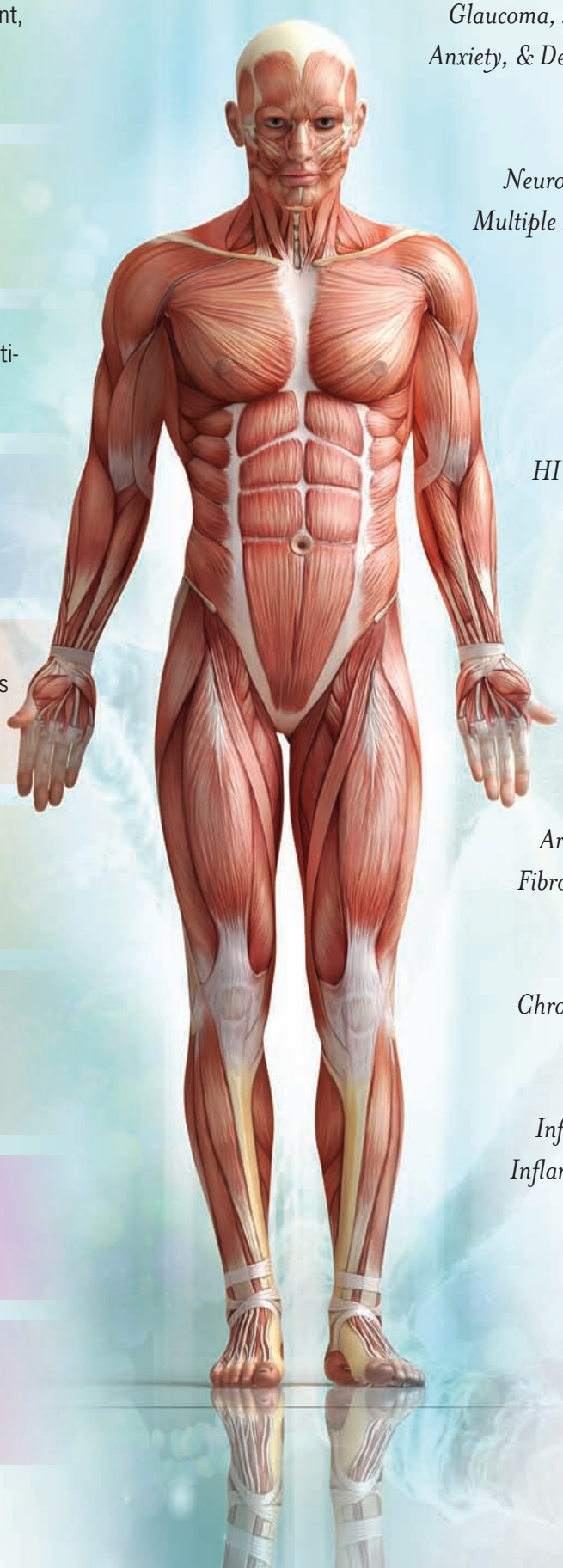
CBDA / Cannabidiolic Acid

CBDA is a non-psychoactive cannabinoid believed to have anti-inflammatory properties. The compound is also thought to offer relief from nausea and vomiting.

CBDV / Cannabidivarin

CBDV has been a relatively ignored cannabinoid until recently where researchers believe that it may offer another option for the treatment of epilepsy.

WHAT IS MEDICAL MARIJUANA USED FOR?



Reduces nausea, muscle relaxant, antioxidant, relieves spasms, increases appetite, pain reliever, glaucoma pressure relief.

Glaucoma, Nausea, Anxiety, & Depression

Decreases seizures, decreases appetite, bone stimulant.

Neuropathy & Multiple Sclerosis

Relieves spasms, pain reliever, sleep aid, anti-inflammatory, antioxidant.

Asthma

Bone stimulant, antibacterial, anti-inflammatory, antifungal, lowers blood pressure, inhibits tumor cell growth.

HIV/AIDS

Antidiabetic, antipsoriatic, bone stimulant, inhibits tumor cell growth, lupus and arthritis relief, reduces artery blockage, relaxes veins, minimizes organ rejection.

Cancer

Bone stimulant, antibacterial, anti-inflammatory, antifungal, lowers blood pressure, inhibits tumor growth.

Arthritis & Fibromyalgia

Bone stimulant, antibacterial, anti-inflammatory, antifungal, lowers blood pressure, relaxes veins.

Chronic Pain

Bone stimulant, antibacterial, anti-inflammatory, antifungal, lowers blood pressure.

Infection & Inflammation

Bone stimulant, epilepsy relief.

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NOTES

CANNABIS AND OPIOIDS

Pain Management Today

OBJECTIVE

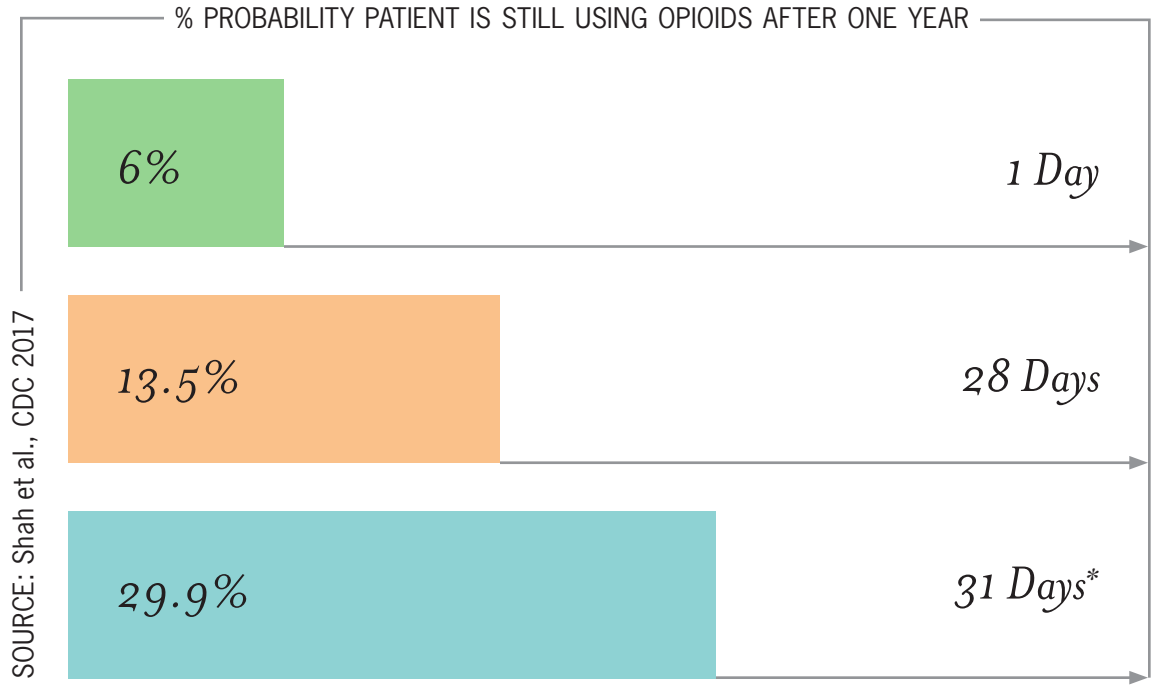
The opioid crisis in America is worsening daily with addiction rates and the associated costs of addiction soaring. Counter to its ill-founded reputation as a "gateway drug," cannabis is proving to be more of a "terminus drug" that can increase the analgesic effects of opioid medications and also help patients cut their dosages.

PAIN MANAGEMENT TODAY

Pain is a widespread phenomenon that affects over 100,000,000 Americans, more than diabetes, heart disease, and cancer combined.[1] An estimated 20% of American adults (42 million people) report that pain or physical discomfort disrupts their sleep a few nights a week or more.[2]

The total annual cost of health care due to pain ranges from $560 billion to $635 billion, which equals about $2,000 per year for everyone living in the U.S.[3] Pain steals time from patients, from society, and from the workforce. Over half (52.7%) of the workforce surveyed reported having headache, back pain, arthritis, or other musculoskeletal pain in the past two weeks, and 12.7% of them lost productive time due to pain. This is estimated to cost $61.2 billion per year.[4] People are hurting and at the moment opioids and NSAIDs are the most commonly prescribed medications for what ails them.

THE ADDICTIVE POTENTIAL OF OPIOID PRESCRIPTIONS



*Approximately 7% of first time opiate prescriptions exceed a one month supply.

One of the problems is that even a short term prescription for opioid-naïve patients significantly increases the chances that patients will be using the opioids for the long term. Physicians may think they're writing a prescription for one week, but according to a March 2017 report from the CDC, opiate-naive patients with a six-day prescription have a 12% chance of being on opioids one year later. If the prescription is for two weeks, the patient's chances of being on opioids for a year doubles to 24%. And those with a month-long prescription face a 30% likelihood that they will still be using opiates a year later. Notably, approximately 7% of initial opiate prescriptions exceed a one-month supply.[5]

Physicians do not typically receive a lot of training on pain management. In the U.S., veterinarians receive four to five times the number of education hours on pain than conventional doctors. Even though the opioid problem has reached crisis proportions, a good number of physicians remain unaware of the scope and breadth of problems caused by the long-term use of opiates and NSAIDs.

The other glaring problem is that prescription opioids and heroin killed more than 47,000 people in 2017, more than any year on record.[6] Actual numbers may be much higher as deaths from infection caused by opioid immune suppression may be masking this count.[7] According to 2018 CDC statistics, 130 Americans die every day from an opioid overdose.[8] The CDC reports, "The amount of prescription opioids sold to pharmacies, hospitals, and doctors' offices nearly quadrupled from 1999 to 2010[9,10] yet no apparent change in the amount of pain that Americans reported.[11,12] Deaths from drugs like oxycodone, hydrocodone, and methadone have more than quadrupled since 1999."[13,14]

THE MAJORITY OF DRUG OVERDOSE DEATHS

(More than six out of 10 involve an opioid)

130 AMERICANS DIE EVERY DAY

From an opioid overdose (including prescription opioids and heroin).
— 2018 CDC STATISTICS

THE CDC reports, *"The amount of prescription opioids sold to pharmacies, hospitals and doctors' offices nearly quadrupled from 1999 to 2010, yet there had not been an overall change in the amount of pain that Americans reported. Deaths from...drugs like oxycodone, hydrocodone and methadone have more than quadrupled since 1999."*

Neuropathic pain is also referred to as nerve pain and is usually chronic.

CANNABIS AND OPIOIDS: THE GOOD NEWS

Medicare data from 2010 to 2013 show that once a state institutes medical cannabis laws and cannabis is used as a substitute, the use of prescription drugs falls significantly.[15] U.S. states with medical cannabis laws report 25% lower opioid overdose mortality rates.[16]

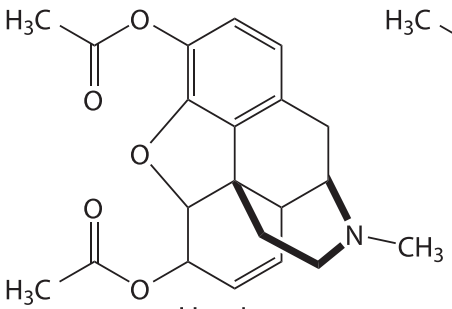
In 1889, writing in *The Lancet* about his experience helping patients addicted to pain medications including opiates, Dr. Edward A. Birch stated:

"I prescribed the cannabis simply with a view to utilizing a well-known remedy for insomnia, but it did much more than procure sleep. I think it will be found that there need be no fear of peremptorily withdrawing the deleterious drug, if hemp be employed." [17]

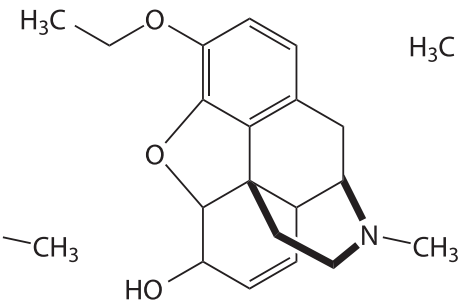
Surveys of medical cannabis patients indicate that about half of all patients have been able to reduce their use of opiate medication.[18,19] What's more synergistic and additive interactions also exist between cannabis and opiates.[20,21,22] When combined with opiates, medical cannabis helps patients find better relief[23] and can aid those from whom opiates were ineffective.[24] Additionally, cannabinoids can prevent the development of tolerance to opiates.[25]

Whereas opiates can increase risk for depression, dependence, and overdose in neuropathic pain patients without increasing their functional status,[26] cannabis is effective and low risk. In terms of withdrawal, cannabis is associated with less severe symptoms on the clinical opiate withdrawal scale, a guide designed to assist clinicians to judge the stage or severity of opiate withdrawal.[27] Research suggests that cannabis can be also be used as an exit drug to reduce the use of substances that are more harmful, including opioids,[28,29] alcohol,[30] and cocaine.[31] This is why modern science is now viewing cannabis more as a terminus drug than the gateway drug it was long rumored to be.

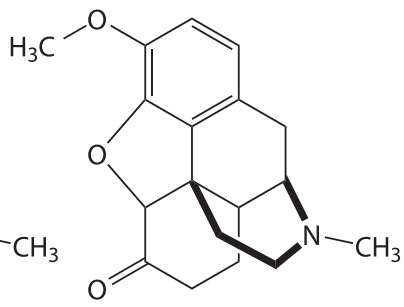
SEMI-SYNTHETIC OPIATES (OPIOIDS)



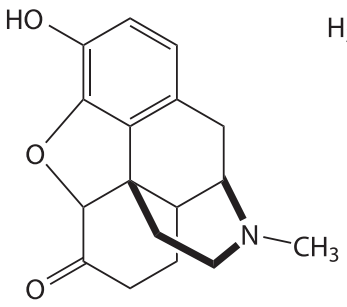
Heroin
(diacetylmorphine)



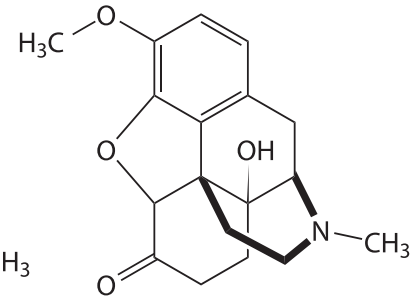
Ethylmorphine



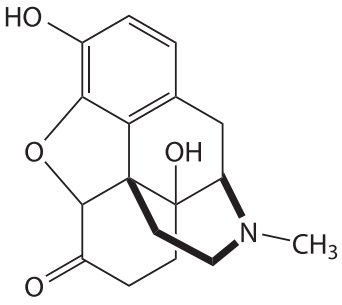
Hydrocodone



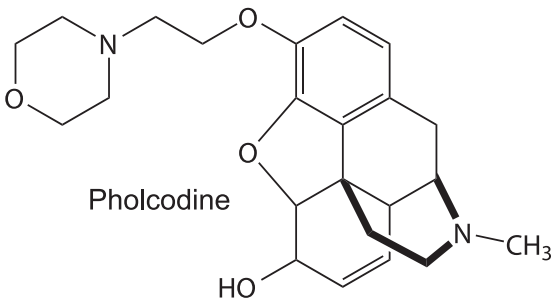
Hydromorphone



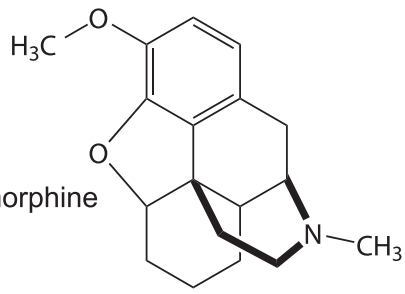
Oxycodone



Oxymorphone



Pholcodine



Desomorphine

Acetaminophen has been used to treat pain for 100 years; however, the mechanism of action was only discovered in the past decade. It exerts its effects on pain and body temperature via the endocannabinoid system (ECS) by the acetaminophen metabolite, N–archidonoylphenolamine.

CANNABIS AND NSAIDS: MORE GOOD NEWS

The July 1998 issue of *The American Journal of Medicine* stated the following: "Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures of all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated."[32]

In June 1999, the prestigious *New England Journal of Medicine* concurred: "It has been estimated conservatively that 16,500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States. This figure is similar to the number of deaths from the acquired immunodeficiency syndrome and considerably greater than the number of deaths from multiple myeloma, asthma, cervical cancer, or Hodgkin's disease."[33]

If deaths from toxic effects from NSAIDs were tabulated separately in the *National Vital Statistics Reports*, they would constitute the 15th most common cause of death in the United States.[34] Given these data medical cannabis makes an excellent substitute treatment.

These numbers remain largely unchanged in the last 15 years. A more recent study in *Therapeutics and Clinical Risk Management* notes that the number of deaths and hospitalizations from GI bleeding due to NSAIDs has remained unchanged since the 1999 study. Human and animal studies show that cannabis protects the stomach from alcohol, NSAIDs, and stress,[35] as well as gastric inflammation. Interestingly, COX-2 inhibitors such as NSAIDs preserve the anti-inflammatory effects of cannabis; they also reduce cognitive effects and lethargy associated with high THC.[37]

NSAIDs can also be damaging to the liver. Cannabis acts as a liver protectant, and several models of liver injury show that CB2 activation by exogenous and endogenous cannabinoids protects this organ.[38]

Substituting safer drugs for harmful ones is intelligent medicine, especially if they deliver the same relief. Perhaps cannabinoid therapy will someday be considered first line therapy with pain and other illnesses mentioned here.

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NOTES

SIDE EFFECTS OF CANNABIS USE

OBJECTIVE

This chapter discusses the adverse side effects of marijuana and marijuana products. It also discusses the risks of developing chronic conditions such as Cannabinoid Hyperemesis Syndrome and marijuana use disorder.

EFFECTS OF MARIJUANA AND MARIJUANA PRODUCTS

The short-term and long-term effects of marijuana consumption can fluctuate from person to person. Certain variables impact a person's reaction to cannabis, such as how much was consumed and how long that person has been using. Also, age can impact the body's reaction to marijuana, as well as the time interval between uses.

After marijuana is inhaled through the lungs, cannabinoids enter the bloodstream and target the brain and most organs, as well as the nervous system and immune system. However, if consumed orally (by food or beverage), it may take longer for the body to absorb the THC. It can take 30 to 90 minutes for effects to come on.[1] Users may experience heightened sensory perception, or the enhancement of primary senses. Marijuana over activates parts of the brain that contain the highest number of Endocannabinoid receptors. This causes the "high" that people feel.[2]

Short-Term Side Effects

As listed on the National Institute of Drug Abuse (NIDA) site, marijuana over activates parts of the brain that contain the highest number of cannabinoid receptors. Short-term side effects include:[3]

- Altered senses (for example, seeing brighter colors)
- Altered sense of time
- Changes in mood
- Impaired body movement
- Difficulty with thinking and problem-solving
- Impaired memory
- Hallucinations (when taken in high doses)
- Delusions (when taken in high doses)
- Paranoia and psychosis (when taken in high doses)

Long-Term Side Effects

Similar to the lack of clinical studies regarding the therapeutic qualities of cannabinoids, there are also limited studies regarding the long-term effects of marijuana. In addition, many of the current studies regarding long-term side effects do not account for the use of cigarettes or other illicit drug use. This can pose a significant public health concern, especially for vulnerable populations such as pregnant women and adolescents. NIDA lists the following wide range of side effects depending on the frequency and duration of use. These effects can be both physical and mental.[4]

Physical Effects

- Synthetic analog of delta-9-tetrahydrocannabinol (THC)
- Breathing problems
- Increased heart rate
- Problems with child development during and after pregnancy
- Intense nausea and vomiting
- Risk of stroke

Breathing Problems

Marijuana smoke irritates the lungs, and people who smoke marijuana frequently can have the same breathing problems as those who smoke tobacco. These problems include daily cough and phlegm, more frequent lung illnesses, and a higher risk of lung infections.[5] A study of volunteers suggested that smoking cannabis in a joint form can result in four times the exposure to carbon monoxide and three to five times more tar deposition than smoking a single cigarette.[6] This may be due to the fact that cannabis smokers generally inhale the smoke more deeply than cigarettes and hold the smoke in their lungs longer.[7] However, unlike heavy tobacco smokers, heavy cannabis smokers exhibit no obstruction of the lung's small airways.

Researchers so far have not found a higher risk for lung cancer in people who smoke marijuana. Zhang et al. (2015) pooled data on 2,159 lung cancer cases and 2,985 controls from six case-control studies, four of which were unpublished. Among all study participants there was no statistically significant difference in the risk of lung cancer for habitual cannabis smokers as compared to non-habitual smokers (odds ratio [OR], 0.96, 95% confidence interval [CI] = 0.66–1.38); similarly, among participants who did not smoke tobacco, the risk of lung cancer was not significantly higher or lower for habitual cannabis smokers than for non-habitual cannabis smokers (OR, 1.03, 95% CI = 0.51–2.08).[8] While researchers have shown some cannabis smoke-induced cellular damage, they have been unable to demonstrate a link between cannabis smoke and lung cancer.

Increased Heart Rate

Marijuana raises the heart rate for up to 3 hours after smoking. This effect may increase the chance of heart attack. Older people and those with heart problems may be at higher risk.[9] The acute cardiovascular effects of cannabis include increases in heart rate, supine blood pressure, and postural hypotension.[10] Smoking cannabis also decreases exercise test duration on maximal exercise tests and increases the heart rate at submaximal levels of exercise.[11]

Problems With Child Development During and After Pregnancy

There is substantial evidence of a statistical association that marijuana use during pregnancy is linked to lower birth weight.[12] A study of 9,521 mothers showed an 84.20 gram difference in birth weight for the children of mothers who had used cannabis at least once per week before and throughout pregnancy versus nonusers.[13] However, when adjusted for other drug use such as cocaine or opiates, there was no significant association between cannabis use and lowered birth rate.[14] At this time, all studies of cannabis use and pregnancy involved women who were polysubstance drug users.

There is an increased risk of both brain and behavioral problems in babies. If a pregnant woman uses marijuana, the drug may affect certain developing parts of the fetus's brain. Children exposed to marijuana in the womb have an increased risk of problems with attention,[15] memory, and problem-solving compared to unexposed children.[16]

Cannabinoids are fat-soluble, therefore they may be present in the fetus and breast milk. Pregnancy, planned pregnancy, or breastfeeding are strong relative contraindications to the use of marijuana.

Intense Nausea and Vomiting

Regular, long-term marijuana use increases the risk of developing Cannabinoid Hyperemesis Syndrome. This causes users to experience regular cycles of severe nausea, vomiting, and dehydration, sometimes requiring emergency medical attention.[17]

Stroke

Reports have suggested that risk of stroke increases with cannabis use. The cardiovascular effects of smoking cannabis have been proposed as a possible mechanism.[18] In a 2015[19] study of 64 patients, 34 cases reported an 81% temporal relationship between cannabis and the indexed event. However, half of the patients also had concomitant stroke risk factors such as tobacco use (34%) and alcohol consumption (11%). Additional reports support the causal link between cannabis and cerebrovascular events.[20] However, concomitant risk factors in each study may account for the cerebrovascular event. At this time there is limited evidence of statistical association between cannabis use and risk of stroke.

Additional Physical Effects

Due to the increased use of cannabis, other physical effects should be considered and are undergoing research as to the risk factors they pose to patients. Cannabis users who orally inhale smoke have higher occurrences of oral health effects such as xerostomia (dry mouth),[21] leukoedema,[22] gingival enlargement, and chronic inflammation of the oral mucosa. Cannabis use may contribute to erectile dysfunction and sexual health concerns in men.[23] Discontinuing heavy cannabis use showed measures of sleep disturbance in cannabis users.[24] At this time there is limited evidence of statistical association between cannabis use and these physical effects due to the fact that many of the current studies contain concomitant risk factors such as tobacco, alcohol, and illicit drug use.

Mental Effects

Long-term marijuana use has been linked to mental illness in some people, such as:

- Temporary hallucinations
- Temporary paranoia
- Worsening symptoms in patients with schizophrenia—a severe mental disorder with symptoms such as hallucinations, paranoia, and disorganized thinking

Marijuana use has also been linked to other mental health problems, such as depression, anxiety, and suicidal thoughts among teens. However, study findings have been mixed. It is important to note that national survey studies suggest that it is not uncommon for individuals with mental health disorders to use substances of abuse and, likewise, it is not uncommon for individuals who abuse or are dependent on drug substances to also meet diagnostic criteria for a mental health disorder. In a 2014 national survey, almost 8 million adults in the United States reported co-occurring substance abuse and mental health disorders.[25]

It is important to note that THC has been shown to produce anxiety and psychotic effects, especially in higher doses, whereas CBD has been shown to produce anxiolytic and antipsychotic effects. Persons with a personal or strong family history of psychosis, schizophrenia, or panic disorder have a relative contraindication to using cannabis products containing THC.

Important Information/What to Avoid [26]

- Marijuana may cause dizziness, drowsiness, and/or impaired judgment, so users should avoid engaging in potentially hazardous activity. This includes, but is not limited to, driving and operating heavy machinery.
- Consuming alcohol after marijuana may further enhance any dizziness, drowsiness, or impaired judgement. Users should reduce or avoid alcohol intake after the use of cannabis, especially ingestible products.
- Conversely, cannabis and other cannabis-infused products can enhance dizziness, drowsiness, and/or impaired judgement from other drug substances, including antidepressants, alcohol, antihistamines, sedatives, pain relievers, anxiety medicines, seizure medicines, and muscle relaxants.

Cannabis and Driving

Marijuana, like alcohol, negatively affects a number of skills required for safe driving. Marijuana use can slow reaction time and the ability to make decisions. High dose cannabis is associated with decreased mean speed, increased mean and variability in headways, and long reaction times.[27] Several studies[28] have shown increased crash and culpability risks, even after adjusting for such confounders as age, sex, risky behaviors, and polypharmacy. Increased blood THC concentrations and driving within an hour after smoking were strongly associated with higher crash and culpability risks. Human laboratory-controlled drug-administration studies showed THC-induced driving-performance decrements within the first hour that lasted □2 hours after smoking, results that are largely consistent with epidemiologic data.[29] Combining alcohol with THC products exacerbates observed impaired driving effects, especially with respect to reaction time and stopping distance of lateral position.

According to the National Highway Traffic Safety Administration, 12.6% of weekend nighttime drivers in 2013 to 2014 tested positive for tetrahydrocannabinol (THC), the component that gives marijuana its psychological effects, compared to 8.6% in 2007.

HEALTH EFFECTS OF MARIJUANA ABUSE

Like other substances, marijuana has the potential to be abused. Though there have been no reported cases of overdose resulting in death due to cannabis use, there are still substantial risks that need to be considered. These include the risk of poisoning, developing Cannabinoid Hyperemesis Syndrome, and/or marijuana use disorder.

Unintentional Cannabis Overdose

With the increased number of states that have legalized medical or recreational marijuana, the availability to cannabis has increased the risk of unintentional cannabis overdose injuries. The highest risk group for unintentional cannabis overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently. Colorado Department of Public Health and Environment found moderate evidence that more unintentional pediatric cannabis exposures have occurred in states with increased legal access to cannabis and that the exposures can lead to significant clinical effects requiring medical attention.[30] Several studies report that unintentional pediatric cannabis exposure is associated with potentially serious symptoms, including respiratory depression or failure, tachycardia and other cardiovascular symptoms, and temporary coma.[31] National Poison Data System found that between 2000 and 2013, U.S. poison centers received 1,969 calls related to cannabis exposure among children younger than 6 years old. Most exposures were unintentional (92.2%) and occurred as a result of ingesting cannabis or a cannabis product (75.0%).[32] Drowsiness and/or lethargy accounted for nearly half of reported clinical symptoms (45.5%), while more serious effects, including coma (0.9%), cardiovascular symptoms (4.1%), and respiratory depression (0.7%), occurred less frequently.[33]

Cannabinoid Hyperemesis Syndrome

Coinciding with the increasing rates of cannabis use, has been the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome (CHS). This recently discovered condition is classified by symptoms which include severe nausea, abdominal pain, and vomiting. CHS is most common in individuals with a long history of chronic marijuana use. Many patients find that their symptoms subside after only a few minutes of exposure to hot water,[34] such as bathing or showering, or after discontinuing marijuana use. Knowledge of the epidemiology, pathophysiology, and natural course of CHS is limited.

As the availability of marijuana increases in legalized states, this condition will require further investigation. Cannabis concentrates and access to products containing higher levels of cannabinoids may lead to an increase in occurrences of CHS in patients.

Marijuana Use Disorder

In 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defined marijuana use disorder as occurring when the recurrent use of marijuana causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home. Symptoms of marijuana use disorder include:

- Disruptions in functioning due to cannabis use
- The development of marijuana tolerance
- Cravings for cannabis
- Development of withdrawal symptoms, such as the inability to sleep, restlessness, nervousness, anger, or depression within a week of ceasing heavy use

In 2015, there was an estimated 4 million people in the United States that met the diagnostic criteria for marijuana use disorder and 138,000 voluntarily sought treatment for their use. Recent data suggest that 30% of heavy marijuana users may have some degree of marijuana use disorder.[35] Greater frequency of cannabis use increases the likelihood of developing problem cannabis use. Studies suggest that 9% of users will become addicted to marijuana and that number increases to 17% addiction rate if the user begins in their teens.[36] This is in comparison to 32% of tobacco users, 17% of cocaine users, and 15% of alcohol users.[37]

Illicit Drug Addiction Rates

- Cannabis 9%
- Alcohol 15%
- Cocaine 17%
- Tobacco 32%

Symptoms of Overuse, Abuse, and Addiction[38]

- Regular use of marijuana (daily or several times a day)
- Developing an urgency to use marijuana; not being able to focus until after consumption
- Using more and more marijuana to feel the same effects as before
- Consuming larger amounts of marijuana than expected
- Experiencing withdrawal symptoms when not using
- Missing or refraining from usual social and recreational activities
- Interference with work, school, and other responsibilities
- Maintaining a steady supply of marijuana is a priority; especially when exhibiting patterns of hasty behavior to obtain, that is, lying, stealing, using money you don't have, and so forth

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NOTES

MEDICAL MARIJUANA MYTHS AND FACTS

OBJECTIVE

The history of marijuana research and science is littered with many fictions masquerading as facts. Now that you are aware of the latest science and methodologies of administering medical cannabis, it is important to review some of those myths to understand where they originated, how they have been perpetuated, and where the science-based truth lies.

CANNABIS IS A GATEWAY DRUG

MYTH: Even if it is relatively harmless, it leads to heroin, cocaine, or harder drug use.

FACT: The gateway theory presents a causal explanation for a statistical association between commonly and less commonly used drugs. Cannabis is the most popular federally illegal drug in the United States.[1]

People who use other drugs – heroin, cocaine, or ecstasy – are also likely to have used cannabis. But this correlation is not causal, and it has varied over time and between groups.[2] Cannabis use rose in the 1960s to 1970s, but heroin use declined. Cocaine was popular in the early 1980s, but cannabis use was down. Through the 1990s, cannabis usage surged at faster rates than overall illegal drug use before it dipped again after 2000.[3,4] Recent data on the current opioid crisis shows that cannabis is more accurately considered a terminus drug than a gateway to more powerful substances.[5]

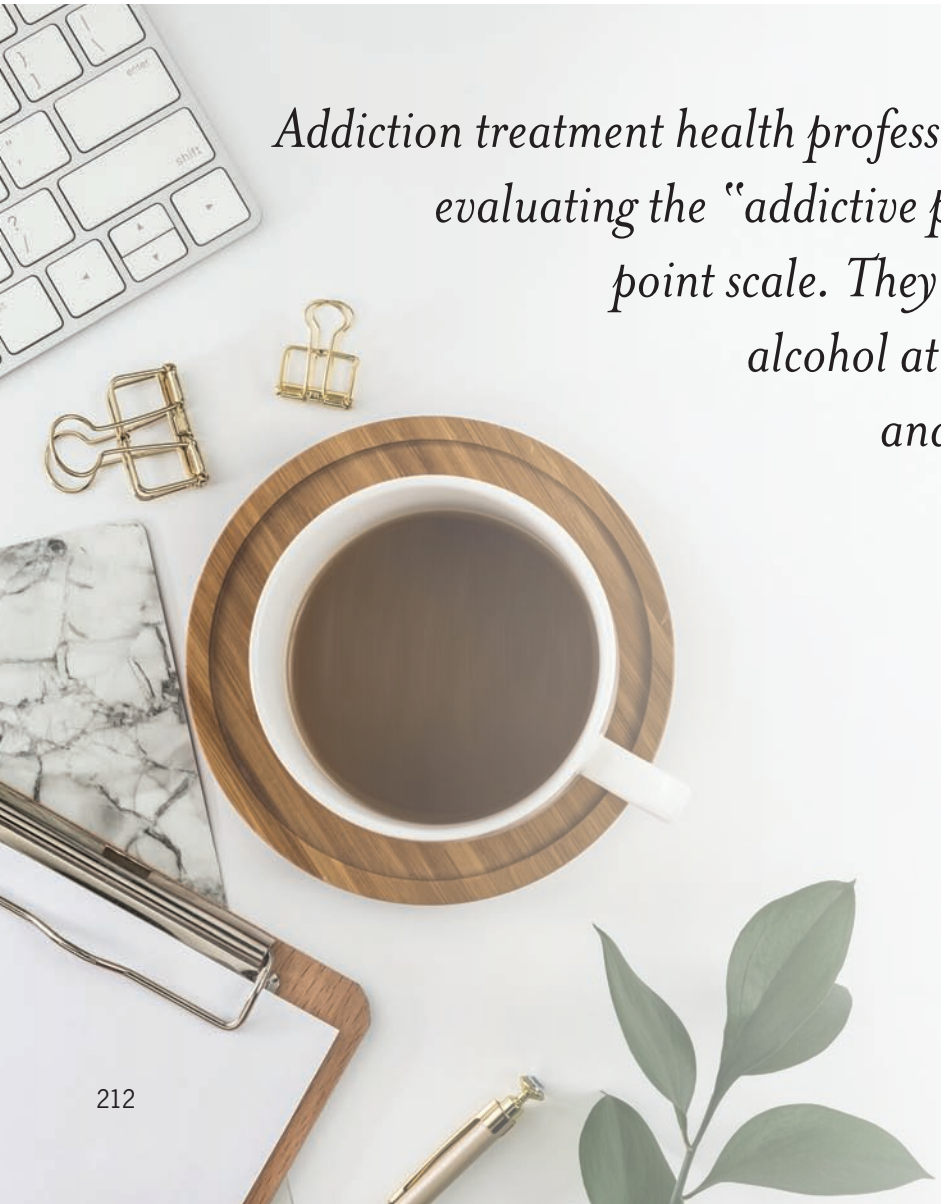
In states where medical marijuana is an option for patients, doctors prescribe 1,826 fewer doses of painkillers in a given year.[6]

CANNABIS IS HIGHLY ADDICTIVE

MYTH: Long-term users establish physical dependence[7] and experience withdrawal.

FACT : Cannabis does not cause physical dependence and most people use it occasionally; on average 5% of people surveyed use it daily,[8] and of those that do, most stop without adverse physical or psychological consequences. Studies even ranked cannabis as less addictive than caffeine.[9] Research suggests that about 9% of marijuana users became clinically dependent at some point, compared to 15% of cocaine users and 24% of heroin users.[10]

However, when "withdrawal" symptoms do occur they tend to be "mild and transitory" and include restlessness, insomnia, nausea, decreased appetite, and sweating.[11] A 1991 U.S. Dept of Health and Human Services report to Congress stated, "Given the large population of marijuana users and the infrequent reports of medical problems from stopping use, tolerance and dependence are not major issues at present."[12] Most of the articles claiming that cannabis use is an exploding problem have been written by drug treatment providers who have benefited enormously from the expansion of treatment services to patients.[13]



Addiction treatment health professionals took a survey evaluating the "addictive potential" on a 100 point scale. They put nicotine at 99, alcohol at 81, caffeine at 70, and marijuana at 22.[14]

CANNABIS KILLS BRAIN CELLS

MYTH: Over time it permanently alters brain structure and function, causing permanent memory loss and cognitive impairment.

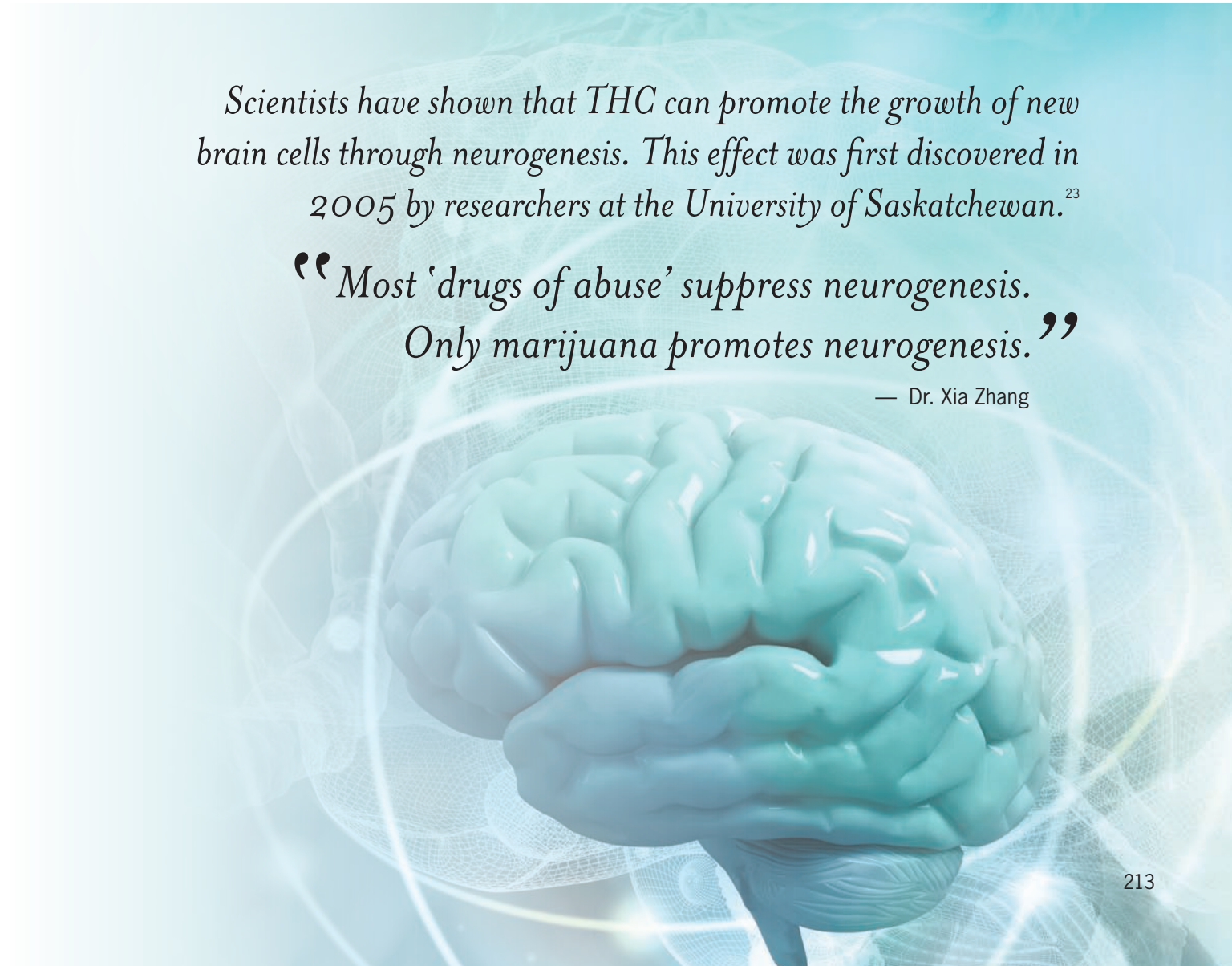
FACT: The claim that cannabis kills brain cells is based on a speculative report dating back to 1971[15] that was later disproven through more modern brain imaging technologies.[16] Moreover, the claim that cannabis induced brain damage is not supported by current scientific evidence. Most medical studies actually point to cannabis as a neuroprotective agent with potential therapeutic benefit for a range of illnesses.[17,18,19]

During the later part of the 20th century, the U.S. government issued reports and drug education pamphlets that still included the warning that "Marijuana kills brain cells."[20] Most modern studies on memory loss, apathy, and cognition report that effects are temporary and not long lasting.[21] U.S. government reports now focus their warnings on short-term physical effects, the risks of smoking, and withdrawal symptoms.[22]

Scientists have shown that THC can promote the growth of new brain cells through neurogenesis. This effect was first discovered in 2005 by researchers at the University of Saskatchewan.[23]

"Most 'drugs of abuse' suppress neurogenesis. Only marijuana promotes neurogenesis."

— Dr. Xia Zhang



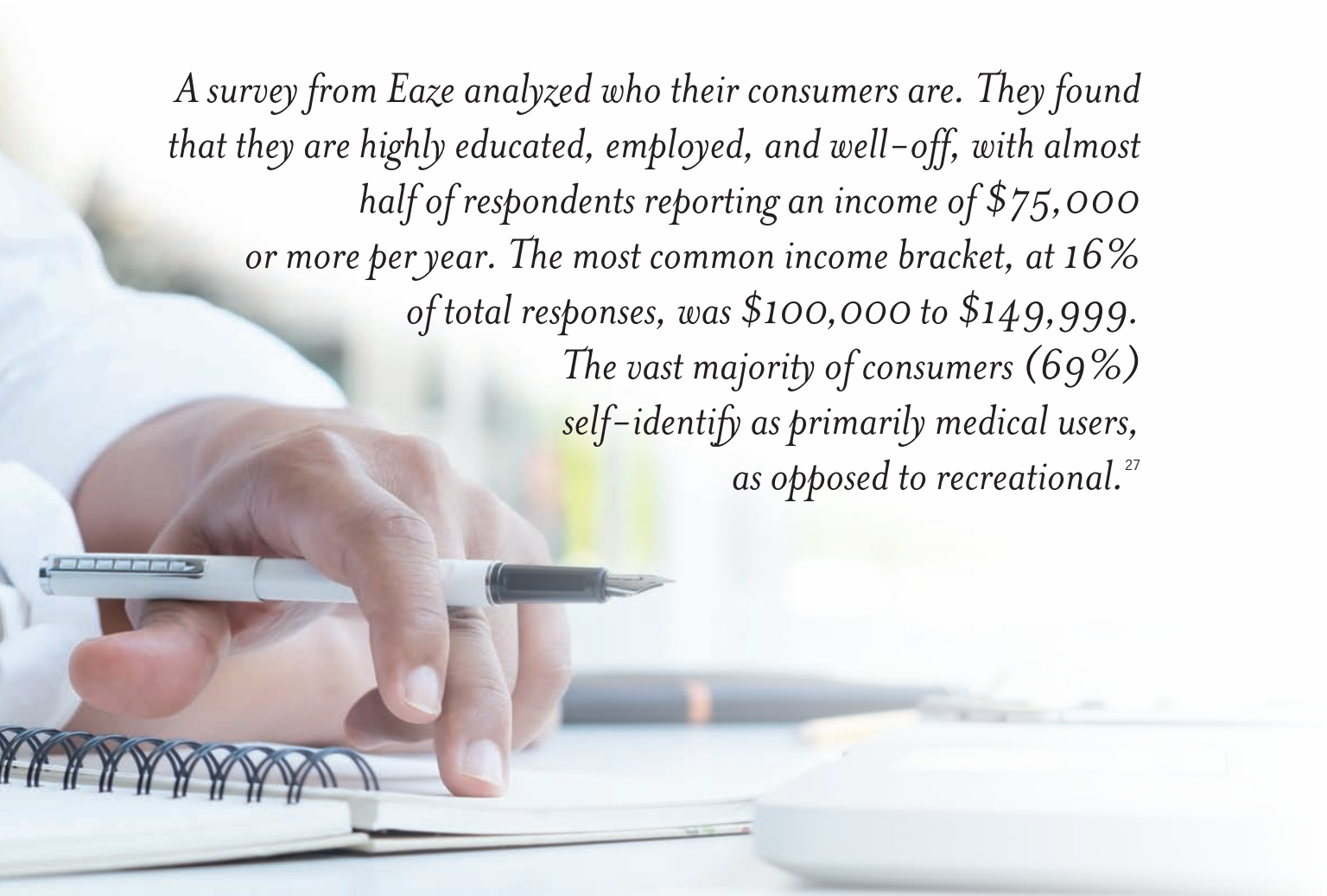
CANNABIS KILLS MOTIVATION

MYTH: It makes users passive and apathetic. Workers become unproductive, and students are unlikely to achieve academic potential.

FACT: In the 1960s and 1970s, as claims about cannabis-induced crime and insanity were debunked, a new set of claims focusing on the danger to youth emerged. Among them was "amotivational syndrome."[24] For almost a half century researchers have sought to find evidence for this syndrome but have come up empty handed. A 2006 study in *Substance Abuse Treatment, Prevention, and Policy* plainly states, "daily use of cannabis does not impair motivation."[25]

While it is true that people who are constantly intoxicated, regardless of the drug, are likely to be less productive, there is nothing about cannabis that causes a loss of drive. Among working adults, cannabis users tend to earn more than non users, and college students who use have the same grades as non users.[26]

A survey from Eaze analyzed who their consumers are. They found that they are highly educated, employed, and well-off, with almost half of respondents reporting an income of $75,000 or more per year. The most common income bracket, at 16% of total responses, was $100,000 to $149,999. The vast majority of consumers (69%) self-identify as primarily medical users, as opposed to recreational.[27]



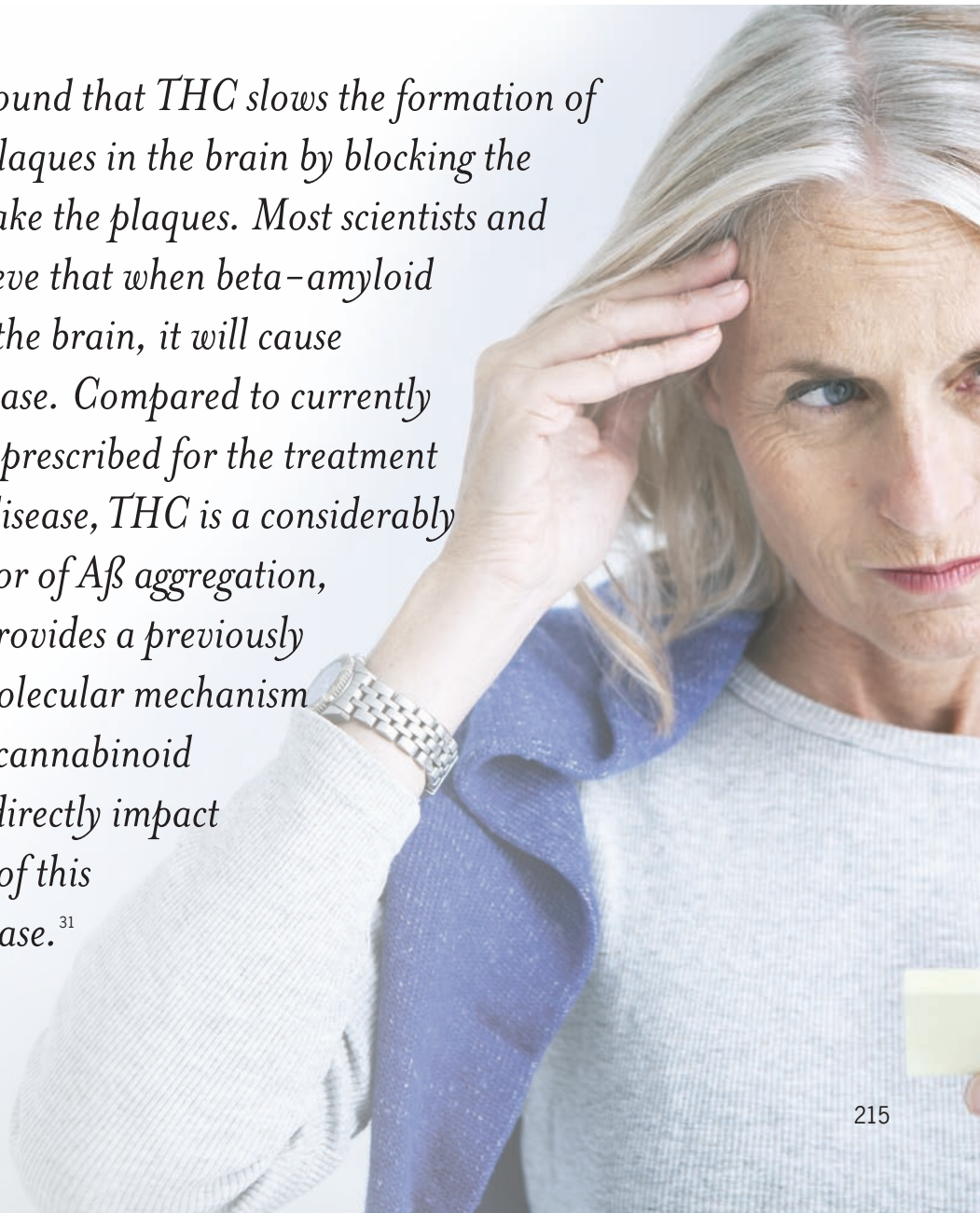
CANNABIS IMPAIRS MEMORY

MYTH: Cannabis savages memory cells and the ability to concentrate.

FACT: Without a doubt THC produces immediate and temporary change in thoughts, perception, and information processing; the most obvious cognitive process affected is short-term memory. This diminishment lasts only for the duration of psychoactivity.[28] Other studies have reported impairments in learning and memory, but note that other factors including nutrition, overall health, and socio-economics are just as likely to be contributing.[29,30]

Bottom line? Over the last 50 years researchers have found minor cognitive differences between chronic cannabis users and non users but long-term use does not appear to cause any permanent harm to intellectual ability. There is no conclusive evidence that cannabis permanently impairs memory or other cognitive functions.

A recent study found that THC slows the formation of beta-amyloid plaques in the brain by blocking the enzymes that make the plaques. Most scientists and researchers believe that when beta-amyloid accumulates in the brain, it will cause Alzheimer's disease. Compared to currently approved drugs prescribed for the treatment of Alzheimer's disease, THC is a considerably superior inhibitor of Aß aggregation, and this study provides a previously unrecognized molecular mechanism through which cannabinoid molecules may directly impact the progression of this debilitating disease.[31]

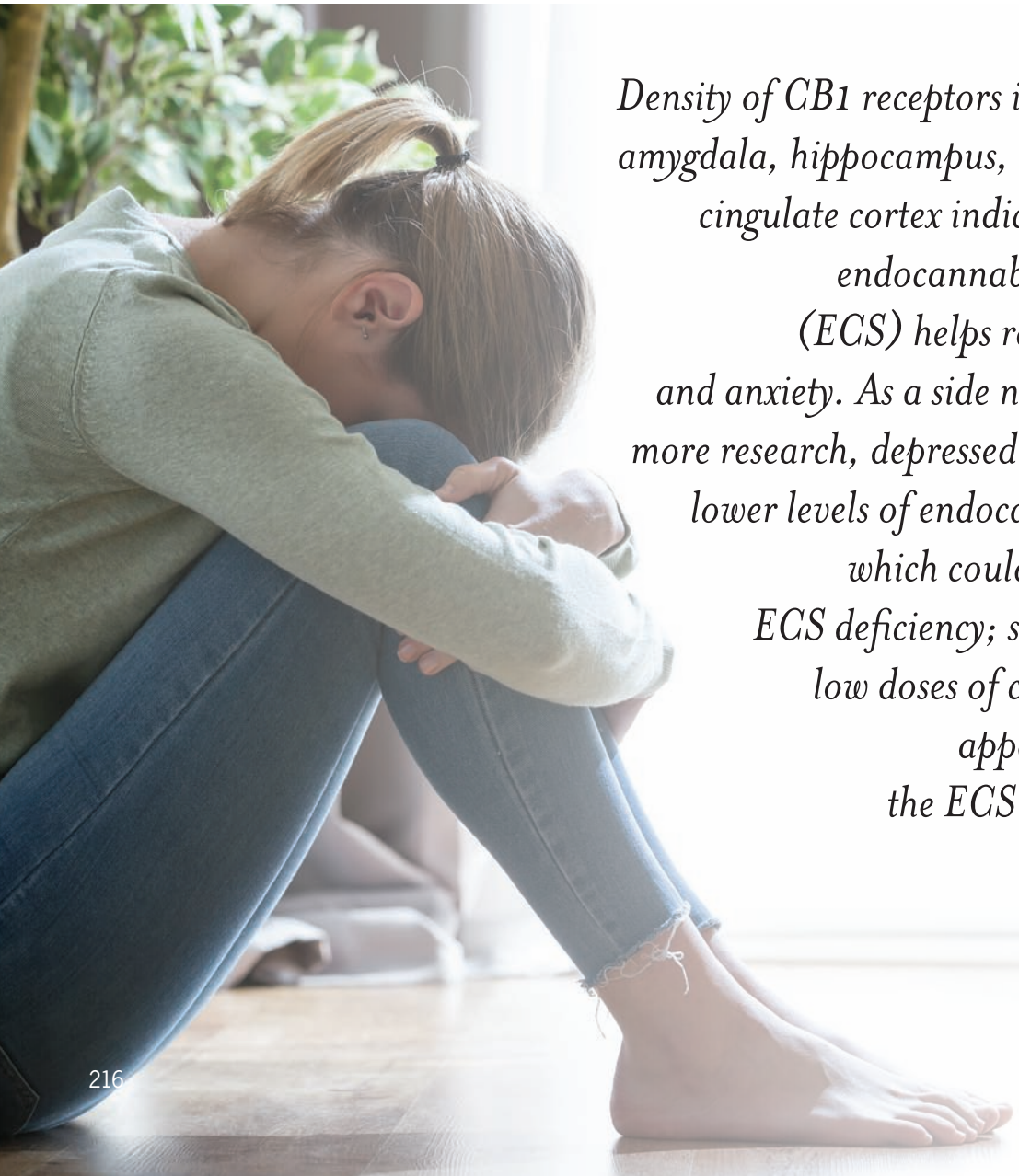


CANNABIS LEADS TO INSANITY

MYTH: Cannabis triggers insanity or mental illness.

FACT: There is no conclusive evidence that cannabis causes mental illness in adults or teens.[32] Some users report paranoia, panic, anxiety, and extreme discomfort after ingesting high doses of THC, but while such experiences may be frightening, effects are temporary. Interestingly, in studies with schizophrenic patients marijuana use is much more likely to follow rather than precede the onset of psychiatric symptoms, indicating that it may well be a form of self- medication rather than a spur to mental illness.[33] Recent studies are recognizing the potential of cannabis to be a novel approach for treating schizophrenia and other psychiatric disorders.[34,35]

One extremely rare but adverse response called "toxic psychosis" entails disorientation, confusion, and visual and auditory distortions, though it appears to be self-limiting and occurs more commonly in individuals with pre-existing psychiatric disturbances.[36]



Density of CB1 receptors in the brain's amygdala, hippocampus, and anterior cingulate cortex indicates that the endocannabinoid system (ECS) helps regulate stress and anxiety. As a side noteworthy of more research, depressed people show lower levels of endocannabinoids, which could indicate an ECS deficiency; supplemental low doses of cannabinoids appear to return the ECS to balance.[37]

CANNABIS CAUSES LUNG CANCER

MYTH: It is more damaging to lungs than tobacco, and users are more likely to develop lung cancer, bronchitis, and emphysema.

FACT: Thirty-five years of research by Donald Tashkin, MD, professor emeritus of medicine at UCLA and an award-winning pulmonologist, shows that inhalation of cannabis smoke poses far less danger to the lungs than tobacco smoke, even in heavy regular cannabis use.[38] This is confounding. Like tobacco smoke, cannabis smoke contains a number of carcinogens and irritants, but over time cannabis users typically inhale much less often and much less material than tobacco smokers.[39]

While researchers have shown some cannabis smoke-induced cellular damage, they have been unable to demonstrate a link between cannabis smoke and lung cancer.[40] Unlike heavy tobacco smokers, heavy cannabis smokers exhibit no obstruction of the lung's small airways.[41] Heavy users do, however, report greater occurrences of chronic cough, phlegm, wheezing and episodes of bronchitis than non-users, but these users report fewer of these symptoms than cigarette smokers.[42]

Data demonstrates cannabinoid-induced upregulation of ICAM-1 on lung cancer cells to be responsible for increased cancer cell susceptibility to LAK cell-mediated cytolysis. These findings provide proof for a novel antitumorigenic mechanism of cannabinoids.[43]

MOST RECREATIONAL USERS ARE HEAVY USERS

MYTH: Of those who use cannabis recreationally, most are chronic, heavy users.

FACT: Most cannabis users use it only occasionally, and surveys indicate that the large majority of those who try it do not become long-term frequent users.[44] About half of those who have tried it report a lifetime total of fewer than 12 days of use.[45] About one-third report having used it for 10 days or less in the past year. In a 2015 survey of national drug use, only 13% of those surveyed reported using cannabis in the past two years.[46] About 6 million of America's 30 million users over the age of 12 use cannabis on a daily or almost-daily basis according to household survey data, and they account for approximately 80% of all marijuana consumed.[47]

IS CANNABIS DANGEROUS?

For years, the discourse surrounding marijuana has been overshadowed by extreme claims of marijuana's dangers. Since prohibition began, governments have appointed commissions and research organizations to investigate every conceivable way marijuana might be harmful to individuals and society. But these commissions and studies have found little scientific support for the claimed dangers.[48] In 1944, a panel of medical experts commissioned by New York mayor Fiorello LaGuardia found that "the sociological, psychological, and medical ills commonly attributed to marihuana have been . . . exaggerated."[49] Since then, numerous studies have found that cannabis is less harmful than alcohol and tobacco, and much less harmful than "hard" drugs like cocaine and heroin.[50,51,52] As of 2017, there have been no overdose deaths related to cannabis, according to the DEA.[53] While the number of deaths from all drugs continues to soar,[54] cannabis remains one of the safest "drugs of abuse" used today.

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GLOSSARY OF TERMS

2-AG (2-arachidonoylglycerol) - an endocannabinoid, an endogenous agonist of the CB1 receptor and the primary endogenous ligand for the CB2 receptor.

11-HYDROXY-THC - the metabolite produced by the liver metabolism of THC.

***a*HUMULENE** - Humulene, also known as *a*humulene or œcaryophyllene, is a naturally occurring monocyclic sesquiterpene, containing an 11-membered ring and consisting of 3 isoprene units containing three nonconjugated C=C double bonds, two of them being triply substituted and one being doubly substituted.

ANANDAMIDE (N-arachidonoylethanolamine or AEA) - a derivative of arachidonic acid that occurs naturally in the brain and in some foods, and binds to the same receptors as cannabinoids (THC).

AUTHORIZE - any act of recommendation; certification from an approved medical professional to affirm that a patient may benefit from medical cannabis. This is explicitly not a prescription, as a Schedule 1 substance by definition has no medicinal benefit and cannot be prescribed.

BETA-CARYOPHYLLENE - a spicy terpene produced by plants and found in clove oil, cannabis, rosemary, and hops.

BIOAVAILABILITY - the portion of a drug or other substance which enters the circulation when introduced into the body and is so able to have an active effect.

BIPHASIC EFFECT - low and high doses can produce opposite effects. A bell curve forms when comparing the strength of dose versus benefits.

BLOOD-BRAIN BARRIER (BBB) - a highly selective semipermeable border that separates the circulating blood from the brain and extracellular fluid in the central nervous system (CNS).

BLUNT - a cigar that has been hollowed out and filled with ground cannabis. Typically, blunts are rolled with the same tobacco leaf wrappers used for cigars.

BONG - a water pipe typically used to smoke cannabis. The bowl is the part of the bong where cannabis buds are contained and heated. The smoke filters through water by traveling through the downstem, a cylinder glass piece with holes that connects the bowl to the bong. The smoke travels through the neck and up to the mouthpiece where users inhale.

GLOSSARY OF TERMS

BUDDER (also known Badder or Batter) - cannabis concentrate of cannabinoids and terpenes that contains some of the waxy coverings that contain the oils on the plant, which gives an opaque and crumbly texture.

BUDTENDER OR CONSULTANT - an employee who works at the storefront and represents the cannabis dispensary. Budtenders or consultants are responsible for educating consumers about the cannabis products. Budtenders cannot give medical advice or take the place of the medical professional in regard to authorizing medical marijuana or advising patients.

BUTANE HASH OIL (BHO) - a resinous oil extracted from marijuana using butane as a solvent, and is ingested, smoked, or vaporized as an intoxicant.

CANNABACEAE - a small family of flowering plants consisting of about 170 species including Cannabis (hemp, marijuana), Humulus (hops), and Celtis (hackberries).

CANNABICHROMENE (CBC) - non-psychoactive minor cannabinoid produced early in the cannabis plant's flowering cycle. Found to be a bone stimulant, antibacterial, anti-inflammatory, antifungal, and also lowers blood pressure and relaxes the veins.

CANNABIDIOL (CBD) - non-psychoactive phytocannabinoid used to treat symptoms of conditions such as anxiety, seizures, inflammation, depression, migraines, inflammatory bowel disease, and pain. CBD has also been found to indirectly help with sleep by easing anxiety symptoms.

CANNABIDIOLIC ACID (CBDA) - the acidic form of CBD produced naturally by the cannabis plant.

CANNABIGEROL (CBG) - non-psychoactive cannabinoid used by the plant's enzymes to produce THC and CBD. Found to be a bone stimulant, antibacterial, anti-inflammatory, antifungal, and also lowers blood pressure and inhibits tumor growth.

CANNABINOID HYPEREMESIS SYNDROME - a condition in which a cannabis consumer becomes nauseated after prolonged cannabis use. The user also may experience other symptoms including vomiting and abdominal pain.

CANNABINOIDS - compounds that activate cannabinoid receptors, including endocannabinoids produced by humans and animals, phytocannabinoids produced by cannabis and a few other plants, and synthetic cannabinoids.

GLOSSARY OF TERMS

CANNABINOL (CBN) - a phytocannabinoid produced by the degradation of THC. Found to be a pain reliever, sleep aid, anti-inflammatory, and can relieve muscle spasms.

CANNABIS - any raw preparation of the leaves or flowers from the plant genus Cannabis. This report uses "cannabis" as a shorthand that also includes cannabinoids.

CANNABIS INDICA - a subspecies of the cannabis plant, having a long stem and broad leaves. Indica plant varieties typically have a sedating and relaxing psychoactive side effect.

CANNABIS RUDERALIS - a subspecies of the cannabis plant, having short and stalky features. Ruderalis is a low-THC species of cannabis and typically used to grow Industrial Hemp.

CANNABIS SATIVA - a subspecies of the cannabis plant, having a long stem and narrow leaves. Sativa plant varieties typically have a boost of energy psychoactive side effect.

CB1 RECEPTOR - a cannabinoid receptor located primarily in the central nervous system.

CB2 RECEPTOR - a cannabinoid receptor located primarily in the peripheral tissues of the immune system, the gastrointestinal system, the peripheral nervous system, and elsewhere.

CERTIFICATE OF ANALYSIS - a document issued by an internal quality assurance team or third-party analytical testing lab that confirms a cannabis product has passed inspection and meets regulatory standards. A certificate of analysis can include information on the following; cannabinoids, terpenes, heavy metals, pesticides, microbes, mycotoxins, moisture content, water activity, residual solvents, and the presence of foreign materials.

CERTIFIED CONSULTANT - consultant or budtender working in a dispensary that has been certified by an approved education company like Medical Marijuana 411.

CHEMOTYPE - a term for a plant type, including cannabis, that produces a distinct combination of chemical compounds.

CHROMATOGRAPHY - the separation of a mixture by passing it in solution or suspension, or as a vapor (as in gas chromatography) through a medium in which the components move at different rates.

GLOSSARY OF TERMS

COLE MEMO - The Cole Memorandum is a U.S. Department of Justice memorandum issued August 29, 2013, by U.S. Deputy Attorney General James M. Cole during the presidency of Barack Obama. The memorandum, sent to all U.S. Attorneys, governed federal prosecution of offenses related to marijuana. The memo stated that given its limited resources, the Justice Department would not enforce federal marijuana prohibition in states that "legalized marijuana in some form and . . . implemented strong and effective regulatory and enforcement systems to control the cultivation, distribution, sale, and possession of marijuana," except where a lack of federal enforcement would undermine federal priorities (such as preventing violence in marijuana cultivation and distribution, preventing cannabis impaired driving, and preventing marijuana revenues from going to gangs and cartels).

CONANT V. WATERS - *Conant v. Walters,* 309 F.3d 629, is a legal case decided by the U.S. Court of Appeals for the Ninth Circuit, which affirmed the right of physicians to recommend medical marijuana.

CONCENTRATES - the oils and terpenes once they are stripped from the plant.

CONTROLLED SUBSTANCE ACT (CSA) - Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 is the federal U.S. drug policy under which the manufacture, importation, possession, use, and distribution of certain narcotics, stimulants, depressants, hallucinogens, anabolic steroids, and other chemicals is regulated.

CULTIVAR - a plant variety produced in cultivation through selective breeding.

DABBING - vaporizing concentrated marijuana, usually in the form of wax or hash, by placing it on an extremely hot metal object called a nail and inhaling the vapors produced.

DECARBOXYLATION - a chemical reaction that removes a carboxyl group and releases carbon dioxide (CO2). In cannabis, it is the process of converting acidic cannabinoids into a more bioavailable form by applying heat to the raw plant material.

DESIGNATED CAREGIVER - an individual who is selected by the qualifying patient and authorized by the Medical Marijuana Program to purchase and/or administer cannabis on the patient's behalf. Also sometimes referred to as an "alternate caregiver."

GLOSSARY OF TERMS

DISPENSARY - a cannabis storefront that dispenses medical or adult-use cannabis products.

DRONABINOL (MARINOL®) - Marinol® is an FDA-approved medication with the active ingredient, dronabinol, a synthetic form of THC (delta-9-tetrahydrocannabinol) used to treat chemotherapy-induced nausea and vomiting, as well as anorexia related to weight loss in patients with AIDS. Marinol was approved by the FDA in August 2017.

DRONABINOL ORAL SOLUTION (SYNDROS®) - Syndros® is an orally administered liquid formulation of the pharmaceutical cannabinoid dronabinol, a pharmaceutical version of tetrahydrocannabinol (THC). Dronabinol has complex effects on the CNS, including central sympathomimetic activity.

EDIBLES - food products that have been infused with cannabinoids.

ENDOCANNABINOID SYSTEM (ECS) - a biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors, and cannabinoid receptor proteins that are expressed throughout the vertebrate central nervous system (including the brain) and peripheral nervous system.

ENDOCANNABINOIDS - any of several chemical compounds (as anandamide) that are naturally produced by the body and bind to the same brain receptors as compounds (as THC) derived from cannabis.

FARM BILL 2018 - this legislation moved Cannabidiol (CBD) from Schedule I drug classification to Schedule V drug classification. The bill removed restrictions on the sale, transport, and possession of hemp derived products, so long as those items are produced in a manner consistent with the law.

FIRST-PASS EFFECT - a phenomenon where the concentration of a drug is greatly reduced through metabolism before reaching systemic circulation.

FLOWER - a general term that refers to the smokable, trichome-covered part of a female cannabis plant.

FOOD AND DRUG ADMINISTRATION (FDA) - a federal agency of the U.S. Department of Health and Human Services, one of the United States' federal executive departments.

GLOSSARY OF TERMS

GENOTYPE - specific characteristics of a plant, which are controlled by gene expression.

HEMP - Cannabis sativa varieties that contain low concentrations of THC. The U.S. government regulates hemp to not exceed 0.3 percent THC on a dry-weight basis. Also referred to as *"Industrial Hemp."*

HEMP OIL - obtained by pressing hemp seeds and does not contain THC. Typically used in the production of body care products.

HYBRID - a combination of any plant types where the flower will either be sativa-dominant, indica-dominant, or equally balanced. There is a significant amount of hybridization occurring with the cannabis plant, where indica dominant species are crossbred with sativa dominant species in order to impact effects.

HYDROCARBON EXTRACTION - hydrocarbon extraction is the most popular extraction method used to strip the cannabinoids, such as tetrahydrocannabinol (THC), and terpenes from cannabis plant material. The process involves the use of hydrocarbons such as propane or butane as the solvent to extract the concentrate.

INDICA - cannabis plants that are typically short in stature and feature broad leaves and shorter growing cycles. Indica cultivars are well-suited for growth in cooler climates due to their shorter flowering periods. Indica dominate strains are often known for their sedating, relaxing, and heavy physical effects.

INDUSTRIAL HEMP - cannabis that contains 0.3% or less concentration of THC. Hemp contains a higher concentration of CBD.

JOINT - cannabis rolled into a thin sheet of smokable paper. Joints that include a mixture of tobacco and cannabis are called "spliffs," and a "preroll" refers to a ready-to-smoke joint created by a manufacturer or a dispensary.

LIMONENE - a citrus-smelling terpene produced by some cannabis varieties.

LINALOOL - a spicy, floral terpene produced by some cannabis varieties.

MARIJUANA - a cannabis plant, whether for recreational or medicinal use. The words "marijuana" "marihuana" and "cannabis" are often used interchangeably. Most state programs reference "marijuana".

GLOSSARY OF TERMS

MARIHUANA TAX ACT - a U.S. federal law that imposed tax on the sale of cannabis, hemp, or marijuana. This Act was enacted in 1937. The Act was drafted by Harry Anslinger and introduced by Rep. Robert L. Doughton of North Carolina on April 14, 1937.

MEDICAL MARIJUANA PROGRAM (MMP) - The official jurisdictional resource for the use of cannabis for medical purposes. (National Conference of State Legislatures, 2017).

MICRO-DOSING - Taking smaller doses of cannabis products that deliver the desired outcome of level of medication.

MYRCENE - a sedating terpene produced by some cannabis varieties.

NABILONE (CESAMET®) - a synthetic form of delta-9-tetrahydrocannabinol, the primary psychoactive component of cannabis (marijuana). Nabilone was approved by the U.S. Food & Drug Administration in 2006.

NABIXIMOLS (SATIVEX®) - a whole plant extract from the cannabis species *Cannabis sativa L.* that has been purified into the active components CBD (cannabidiol) and THC (delta-9-tetrahydrocannabinol).

NAIL - a titanium or quartz used to vaporize concentrate dabs. The nail is heated and, when the dab is applied to the hot nail, the cannabis product is vaporized for inhalation.

NEROLIDOL - a terpene that gives certain cannabis strains a distinctive woody aroma.

OCIMENE - a fruity, floral terpene produced by some cannabis varieties.

OGDEN MEMO - a 2009 memo stating that with the exception of large, for-profit commercial operators, the Department of Justice should not prioritize prosecution of medical marijuana operators in “clear and unambiguous compliance” with state laws.

PHENOTYPE - the distinct characteristics of an individual plant resulting from the interaction between a plant’s genotype and its surrounding environment.

PINENE - one of the most commonly occurring terpenes in cannabis. There are two forms of pinene: alpha-pinene and beta-pinene, with alpha-pinene being the more prevalent in cannabis. Alpha-pinene is also the most abundant terpenoid found in nature.

GLOSSARY OF TERMS

PROPOSITION 215 - a California law allowing the use of medical cannabis despite marijuana's lack of the normal Food and Drug Administration testing for safety and efficacy. Also known as *The Compassionate Use Act of 1996*.

PSYCHOACTIVITY - the measure of how cannabis and other drugs affect the mind, mood, or other mental states.

RECEPTOR DOWN REGULATION - decrease in the number of receptors available for a cannabinoid molecule to bind which therefore reduces the sensitivity to cannabinoid effects and creates the build up of tolerance.

RESIN - the sticky exudation of the cannabis plant that is produced by its trichomes.

RETROGRADE INHIBITION - a process whereby the function of one part of a cell is controlled by feedback from another part of the cell, or where one cell sends reciprocal messages back to another cell that regulates it.

ROHRABACHER-FARR AMENDMENT - legislation first introduced by U.S. Rep. Maurice Hinchey in 2001 prohibiting the Justice Department from spending funds to interfere with the implementation of state medical cannabis laws.

ROSIN - an extraction process that utilizes a combination of heat and pressure to squeeze resinous sap from cannabis containing cannabinoids and terpenes.

SATIVA - cultivars that feature long, thin, fan leaves and tend to have long flowering times. Sativas flourish in warmer climates and can naturally grow up to 12 feet tall in a season. Sativas are often described to provide an uplifting, cerebral, and energetic effect.

SCHEDULE I CONTROLLED SUBSTANCES - defined in the federal Controlled Substances Act as those substances that have a high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use of the substance under medical supervision.

SHAFER COMMISSION - formally known as the National Commission on Marihuana and Drug Abuse, was appointed by President Richard Nixon in the early 1970s. Its chairman was former Pennsylvania Governor Raymond P. Shafer. The commission issued a report on its findings in 1972 that called for the decriminalization of marijuana possession in the United States. The report was ignored by the White House and President Nixon.

GLOSSARY OF TERMS

SHATTER - translucent cannabis concentrate, created by extracting the cannabinoids and terpenes, with a specific texture that breaks and shatters like glass.

STRAIN - a term used interchangeably with "variety" and "selection" in the cannabis industry. It has no official botanical meaning. In the world of cannabis, the term refers to the flower's particular variety, be it Sour Diesel, or Jack Herer.

TERPENES - volatile hydrocarbons found in the essential oils produced by many plants, including cannabis.

TERPINOLENE - is a cannabis terpene that displays a piney or woody aroma with hints of citrus and herbal spice.

TETRAHYDROCANNABINOL (THC) or **DELTA-9 THC** - the principle phytocannabinoid of the cannabis plant, responsible for much of the plant's psychoactivity.

TETRAHYDROCANNBINOLIC ACID (THCA) - the most common cannabinoid found in the raw cannabis plant. THCA is non-intoxicating but converts into the intoxicating THC when exposed to heat through a process called decarboxylation.

TETRAHYDROCANNABIVARINIC (THCV) - a homologue of tetrahydrocannabinol (THC) having a propyl (3-carbon) side chain instead of the pentyl (5-carbon) group on the molecule, which makes it produce very different effects from THC.

TINCTURE - a solution of a medicinal substance in an alcoholic solvent.

TOLERANCE - an individual's reaction to the dose of cannabis in which the effects are progressively reduced, requiring an increase in the dosage in order to achieve the desired therapeutic effect.

TOPICAL - a lotion, ointment, oil, or transdermal patch that is applied directly to the body's skin surface. Topics allow patients to enjoy the plant's therapeutic effects without THC's attendant psychoactivity.

GLOSSARY OF TERMS

TRICHOME - "ball-like" clear "globes" on the surface of the cannabis flower that produce and hold the plant's cannabinoids and terpenes. Trichomes have a sugary, crystal-like appearance.

VAPE - the process of inhaling and exhaling vapor with the use of a vaporizer, dab rig, or similar device. These devices utilize a heating element to quickly vaporize the active ingredients in cannabis for smooth, non-combusting consumption.

VAPE PEN OR VAPORIZOR - a handheld device consisting of a battery attached to a cartridge filled with cannabis concentrate. With a Vape Pen, concentrates are heated not burned. Instead of smoke, the output is vapor.

WAX - cannabis concentrate of cannabinoids and terpenes that contains some of the waxy coverings that contain the oils on the plant, which gives a opaque and crumbly texture.

WILKINSON MEMO - issued in October 2014; provides that eight enumerated federal priorities *"will guide United States Attorneys' marijuana enforcement efforts in Indian Country,"* including where *"sovereign Indian Nations seek to legalize the cultivation or use of marijuana in Indian Country".*

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