

## **Book Proposal**

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### **How Cannabis Heals**

*through the ancient biological system that balances health & disease*

**by**

**Cheryl Pellerin**

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**Submitted by:**

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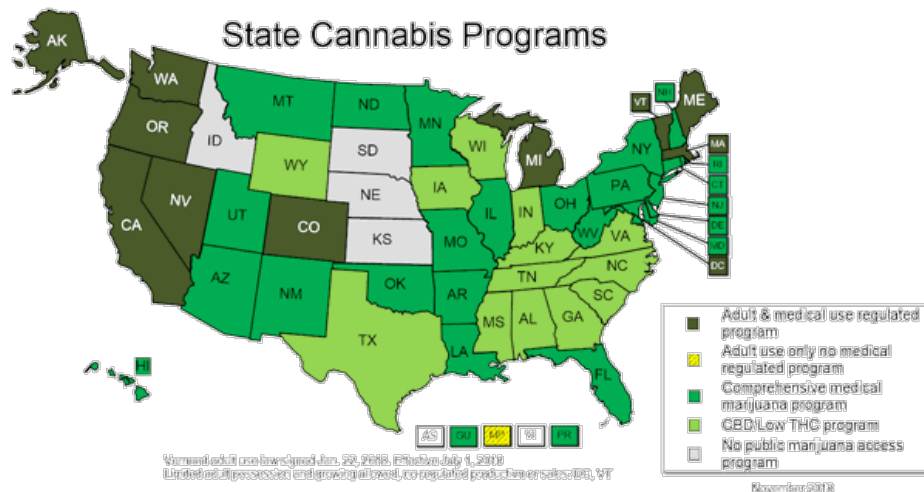
## Overview

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I'm a science writer with a B.S. degree (cum laude) in science journalism and nearly 30 years of experience writing about science in its many forms. My first book was *Trips: How Hallucinogens Work in your Brain* (Seven Stories Press, 1998). It had two printings and was translated into French (Éditions du Léopard) and German (AT Verlag) hardcover editions, featuring color medical illustrations and underground cartoons by Robert Crumb and the other underground artists featured in Zap Comix.

My new book, *How Cannabis Heals* (through an ancient biological system that balances health & disease), describes why and how medical cannabis helps treat an incredibly broad range of illnesses—maybe all of them.

A growing body of research and clinical trials shows that cannabis has positive effects on some of society's most devastating illnesses, including neurodegenerative diseases like Alzheimer's and Parkinson's, posttraumatic stress disorder and pain, depression and addiction. I've spoken with the scientists who do groundbreaking research on these disorders, and I've brought their voices to the story of how cannabis can help each disease.



In this country, 10 states and the District of Columbia have legalized cannabis, and 33 states, the District, Guam and Puerto Rico have public medical cannabis programs. Another 13 states allow medical cannabis in limited situations. All these numbers increase every time state voters have a chance to weigh in on cannabis or medical cannabis. Elsewhere in North America, Mexico legalized medical cannabis in June 2017, Canada has legalized recreational cannabis nationwide and internationally, 29 other countries have approved the use of medical cannabis.

Counted another way, the U.S. total legal cannabis demand in 2018, according to the New Frontier Data 2018-2019 Cannabis Consumer Report, was \$4.5 billion for medical cannabis (\$12.3 billion in 2025) and \$5.8 billion for adult-use cannabis (13.4 billion in 2025). Also in 2018, cannabis news highlights included the following federal, state and international actions:

- On December 20, President Trump signed into law the 2018 Farm Bill, which nationwide legalizes industrial hemp, including the plants used to produce the non-psychoactive cannabidiol (CBD) oils, gelcaps and other products. The bill removes hemp and its derivatives from the Drug Enforcement Administration's Controlled Substances Act, legally separating it from cannabis, and names the Department of

Agriculture (USDA) its regulatory agency. Hemp (also called industrial hemp) actually IS cannabis, but it's legally defined as having THC levels no higher than 0.10 percent of the plant by weight, a non-psychoactive amount. Cannabis/hemp plants with THC levels this low means hemp plants contain relatively more CBD—the plant's main non-psychoactive and equally medically important cannabinoid—than THC. For farmers, the new law means they can grow hemp legally as long as they comply with USDA regulations. For companies that make CBD-containing products, it means CBD is out from under DEA purview BUT the Food and Drug Administration will have to approve their products' safety and effectiveness before they can be sold legally. So hemp and CBD are legal, technically, but not unregulated.

The best CBD companies will have no trouble showing their products to be safe and effective, and the companies whose products are iffy will fade from the marketplace. The new law also makes it much easier for researchers to study CBD and the rest of the cannabinoids, terpenes, flavonoids and other cannabis constituents, leading to better CBD products and medicines. In the meantime for these companies, the FDA has made it clear that it's willing to work with CBD companies: "While products containing cannabis and cannabis-derived compounds remain subject to the FDA's authorities and requirements," FDA Commissioner Dr. Scott Gottlieb wrote in a December 20, 2018, press statement, "there are pathways available for those who seek to lawfully introduce these products into interstate commerce."

- According to a December 17 New York Times story, Governor Andrew Cuomo announced during a speech in Manhattan that he would push to legalize recreational cannabis in 2019. Three days later, New York City Mayor Bill de Blasio endorsed legalization for the first time.
- One of the world's biggest tobacco companies is wading into the cannabis market with a \$1.8 billion buy-in. Marlboro maker Altria Group Inc. is taking a 45 percent stake in

Cronos Group, the Canadian medical and recreational cannabis provider announced, the Associated Press reported December 7. The agreement includes a warrant to acquire more shares over the next four years that could give Altria, based in Richmond, Virginia, a 55 percent ownership stake in the Toronto company.

- On June 25, the FDA approved GW Pharmaceuticals' formulation of CBD. The drug, called Epidiolex, is the first-ever FDA-approved cannabis plant-derived purified CBD medicine. It will be used to treat two severe forms of childhood epilepsy, and it's the first in a new category of anti-epileptic drugs.
- To allow Epidiolex to be sold in the United States, the Drug Enforcement Administration had to move purified CBD, but not whole-plant CBD, out of the most restrictive Schedule 1 of the Controlled Substances Act and into Schedule 5, about the same level as cough syrup—a big step for the DEA.
- According to Forbes, pro-legalization candidates won 2018 governors' races in Illinois, Minnesota, New Mexico and Connecticut.
- Also according to Forbes, this year the new administration of Mexican President Andrés Manuel López Obrador, who took office in December, already is moving to end cannabis prohibition nationwide. And in October the Mexican Supreme Court had struck down as unconstitutional the criminalization of cannabis use, possession and growing small amounts.

But yes, cannabis is illegal so far in the United States, according to federal law. Still, tens of millions of people here and around the world already have access to legal medical cannabis and, more recently thanks to the internet, ready access despite its iffy legality, to the non-psychoactive CBD, which also has beneficial health effects. Most of

those people need help to understand why cannabis and CBD have healing effects, and how to use them to reduce ills that are intractable to current treatments or that are treatable only with drugs like opioids.

How Cannabis Heals is needed out there because permission to use cannabis and online access to CBD don't come with a user's manual. For those seeking reliable information, the internet is a blessing and a curse. The explosion of websites, blogs and books don't always address the plant's medical value. Cannabis is complicated, and those who do write about its medical effects don't always get it right. And they don't always present findings in everyday language or include useful detail. My book does. Cannabis laws also are complicated, and even knowledgeable media outlets don't always get that right. In How Cannabis Heals I help readers along with facts, plain-language writing and definitions; color photos, images and illustrations from many sources; and by engaging them with a conversational tone and humor.

Medical cannabis, widely available, will change the face of public health. But here's the thing. Even in states that allow medical cannabis, access is limited to those who have specific diseases, usually serious ones (except in California, where it's available to all). Everyone else in the state might as well live in a place with no medical cannabis program at all. I know—I live in one of them. How Cannabis Heals explains the problem, its constraints and, despite the constraints, how to benefit from a medicine that has a 5,000-year history of safe and effective use.

After working as a freelancer for the Discovery Channel and others, and then as a science writer for the State and Defense departments, I'm now writing How Cannabis Heals for a large audience that grows each day and with each state election. My book will give readers solid information about the cannabis plant's healing properties, and the biological system it works through that has been evolutionarily conserved across a billion years to realize the medicine of the future.

## About the Author

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I'm a science writer with a B.S. degree in science journalism, as I said, and I've spent nearly 30 years writing about science in its many forms for print, television and the web.

My first book *Trips: How Hallucinogens Work in Your Brain*, was a paperback with color and black-and-white illustrations, published in 1998 by Seven Stories Press. I based *Trips* on many interviews with researchers and other experts, and explained the latest advances in psychedelic science for a general audience using an informal writing style, humor, color illustrations and underground comix from the Summer of Love.

*Trips* is in its second printing and was translated into French (Éditions du Léopard) and German (AT Verlag) hardcover editions. And it has a lively second life as a used book. Booklist called it "a fine source of responsible information ... fresh, reasonable and very engaging." *How Cannabis Heals* will have the same qualities, and it will give readers a solid understanding of cannabis as medicine in all its complexity.

Since 1999 I've been writing science for general audiences as a freelancer and on staff for newspapers like the Baltimore Sun, broadcasters like the Discovery Channel and The Learning Channel, and even for NASA, for the State Department's international audiences and for the Defense Department, with its vast research and science enterprise.

In 1995, I and my producers received an honorable mention from the American Association of Science (AAAS) Science Journalism Awards for Television: Cheryl Pellerin, Jon Ward, Susan Winslow, "Understanding Sex"—Winter 1994, The Learning Channel. The show really was about evolutionary biology, and I wrote the script with



humor for a general audience. I've always suspected the show got only an honorable mention because at the time there was no laughing in science. But times have changed.

I'm writing my second book, *How Cannabis Heals*, for the same reasons I wrote *Trips*. In the late 1990s, information available on LSD and other psychedelics for a general audience came right out of the drug war—Just Say No. But I'd learned while writing an honors thesis on LSD research in college that the facts about LSD were completely different than most people knew.

Those facts, detailed even at the time in a growing number of scientific articles, might as well have been buried in a cave as far as their accessibility to general readers went. Hence *Trips*—and its everyday language, informal tone, illustrations and underground comix—all strategically used to keep readers from noticing that they were learning about the latest findings in neuroscience and pharmacology. *How Cannabis Heals* will do the same things *Trips* did, but for a broader and growing audience.

## Target Audience

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A solid majority of Americans now agree that responsible cannabis smokers should not be treated like criminals, according to the National Organization for the Reform of Marijuana Laws (NORML). Eight of 10 Americans support the medical use of cannabis, NORML says, and nearly three of four Americans support fines, not jail, for recreational smokers. More than 60 percent of Americans now favor legalizing cannabis, according a recent Gallup poll—the highest percentage of support ever reported in a nationwide scientific poll, NORML says.

Almost none of these people know that an ancient biological system in the bodies of all mammals—the endocannabinoid system—is the reason that cannabis works in the body, and that the presence of its elements in the brains and organs of every vertebrate on Earth, is the reason cannabis helps treat diseases that include neurodegenerative symptoms of diseases like Alzheimer’s and Parkinson’s, pain and depression, PTSD and addiction.

In *How Cannabis Heals*, I explain this complex technical information in language nearly anyone can understand, for readers who are new to medical cannabis and want information from reliable sources. But more experienced readers also will gain knowledge from my interviews with the researchers who are making the latest advances in cannabinoid science and in broadening the range of health disorders cannabis has been shown to affect.

Based on a thorough reading of the reviews for similar medical cannabis books on the market, I found that readers represented the following interests and motivations.

**Health care professionals.** According to the expert website <http://projectcbd.com>, many health professionals have little or no experience with cannabis therapeutics, even in states where medical cannabis is legal, and can't guide patients on the subject. And nothing is taught in medical schools (although this is changing!) about the body's endocannabinoid system, which is a billion or more years old.

**Patients and caregivers.** Among the many serious illnesses cannabis is shown to help are cancer, Alzheimer's disease, addiction, depression, epilepsy and seizures, diabetes, kidney and liver diseases, neurodegeneration, post-traumatic stress disorder, schizophrenia, spinal cord injury stroke, heart disease, traumatic brain injury and others.

**People who have less serious disorders that medical cannabis have been shown to help.** These include arthritis, digestive issues, anxiety, stress, sleep disorders, acne and other skin conditions, chronic pain, osteoporosis, nausea, motion sickness, fibromyalgia and others.

**People in states and countries where cannabis or medical cannabis recently has become legal and they want reliable information.** In the United States medical cannabis in some form is legal in 45 states and recreational cannabis is legal in nine states. Canada legalized medical cannabis in 1999, and in April 2017 Canadian Prime Minister Justin Trudeau introduced legislation to legalize recreational cannabis use countrywide. In June 2017, Mexican President Enrique Peña Nieto signed a decree legalizing medical cannabis.

**People who are hearing about cannabis in the media and want reliable information.** Here is Fortune's Tom Huddleston in 2015—a long time ago in cannabis years—on cannabis media: "Several nationally read newspapers and magazines (including Fortune) have devoted plenty of ink to the cannabis industry. Last year, The

New York Times endorsed marijuana legalization and later ran a full-page ad for a website, Leafly, a Yelp-like service for reviewing marijuana strains and dispensaries. The industry is also well-represented on television, where cable news networks CNN, CNBC and MSNBC have all produced recent series focused on the marijuana industry.”

**People who use cannabis recreationally and want to know more about its medical benefits.** According to the NORML website, cannabis is the third-most-used recreational drug in the United States after alcohol and tobacco. Nearly 100 million Americans have used cannabis. NORML says government surveys show that 25 million Americans have smoked cannabis in the past year, and that 14 million or more smoke it regularly, laws or no laws. And according to the NBC News website, an April 2017 Yahoo News and Marist poll on Weed and the American Family reported that most U.S. adults have smoked cannabis and 44 percent of people who tried it still use it.

**High school and college students and educators.** A 2016 article by Angus Chen on the National Public Radio website npr.org (College High: Students are Using More Marijuana, Fewer Opioids) reported on a University of Michigan four-decades-long study of drug, tobacco and alcohol use. In the story, Chen interviewed Dr. Lloyd Johnston, a U-M research scientist and the study’s lead investigator: “‘For the most part, among both college and high school students, their perception of how dangerous [cannabis] is has dropped like a rock,’ Johnston said. That tracks closely with [the] use of cannabis,” Chen wrote, “which has been steadily rising for the past couple of decades.”

## Competing and Complementary Books

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Last year a Publishers Weekly article, “Dope Reads: Publishers Have High Hopes for Marijuana Books,” noted that publishers are capitalizing on the new interest in cannabis. Author Daniel Lefferts said publishers large and small were feeding the trend, and that forthcoming titles included user guides, recipe books, views on the global legalization debate, historical treatments and more. He made only passing reference to books about medical cannabis. “Where there’s smoke there’s fire,” he wrote, “and if this season’s marijuana-related books are any indication, the topic of weed—once alternative, now increasingly mainstream—is burning up.” He noted that all the books aimed to “help readers enjoy, or at least contemplate,” the new legislative environment for cannabis.

Any of the various lists of cannabis books include a range of topics: cannabis history, legislation, grow guides, industrial horticulture, culture, entrepreneurship, prohibition and other controversies, legalization, cuisine, botany, genetics and, increasingly in the past several years, medical applications and treatments. Here are a few of the titles that will compete with How Cannabis Heals.

**Smoke Signals: A Social History of Marijuana - Medical, Recreational and Scientific** (Scribner, 2013) by Martin A. Lee. \$35.00 hardcover, 528 pages. ISBN 978-1439102602. Lee’s book is well written and has a broad national and even international audience. It’s the story of the history of cannabis, its use, its laws and the many reasons why cannabis should not be on Schedule 1 of the U.S. Controlled Substances Act. The book is dense with information, has a serious tone and includes some illustrations and black-and-white photos. My book focuses on medical cannabis and is written for a

general audience. It details the endocannabinoid system that allows cannabis to work throughout the brain and body, and uses everyday language, humor and color illustrations.

**Cannabis Pharmacy: The Practical Guide to Medical Marijuana** (Black Dog & Leventhal-Hachette; 2014, revised Dec. 2017) by Michael Backes with Andrew Weil. \$22.99 paperback, 320 pages. ISBN: 978-0316464185. This book mentions medical cannabis and even the endocannabinoid system and some of the disorders the plant can treat, but it also covers history, drug laws, cannabis cultivars and more. Because the treatment is broad, coverage of each topic, including medical cannabis, seems a bit superficial. The book has a few illustrations, mostly of cannabis plants, and is printed in black text with green illustrations. The author doesn't seem to have done many interviews. My book focuses on medical cannabis and the illnesses it can help. I've interviewed many researchers who have made advances in the field and translated their work for a general audience, including humor, a timeline, color illustrations and editorial-type cannabis cartoons.

**Stoned: A Doctor's Case for Medical Marijuana** (Penguin Random House, 2015) by David Casarett M.D. \$27.95 hardcover, 304 pages. ISBN: 978-1591847670. This book, by a physician, offers entertaining stories about a select number of patients and their experiences with cannabis. He discusses the evidence for medical cannabis, how California dispensaries work, cannabis safety and gives general information about the plant's use as medicine, writing for a general audience. The focus is medical cannabis but without a deep dive into why cannabis works or what the latest research indicates about treatment. My book explains for a general audience why cannabis works in the

brain and body based on my interviews with researchers who made the advances, and includes color illustrations to help inform and entertain readers.

**The Pot Book: A Complete Guide to Cannabis** (Park Street Press, 2010) by Julie Holland M.D. \$19.95 paperback, 576 pages. ISBN: 978-1594773686. This book, by a psychiatrist, is a collection of articles by scientists and celebrities who write about cannabis science, history, politics, medicine and potential. The seven-year-old book was popular with readers and offered information about a range of cannabis-related topics. The medical cannabis sections were written by some giants in the field but did not use everyday language or illustrations to help a general audience understand the content. My book has information from scientists working in the field that is translated into language a general audience can understand. It's also written in an informal way to appeal to non-technically oriented readers and includes humor and color illustrations.

**Cannabis Revealed: How the world's most misunderstood plant is treating everything from chronic pain to epilepsy** (Bonni S. Goldstein M.D. Inc., 2016) by Bonni Goldstein M.D. \$29.99 paperback, 284 pages. ISBN: 978-0998141305. Goldstein, a medical cannabis specialist, has written a book that combines a lot of good information about how cannabis and how it works in the body with personal and patient stories from her practice. She also has a chapter on disorders that cannabis can treat, and appendices that include a cannabis timeline, pharmacokinetics and dosing guidelines. My book will have similar sections—chapters on disorders treatable with cannabis and on how cannabis works in the body—but mine will focus on the latest research and what scientists are learning as they study the complex circuitry of the body's ancient endocannabinoid system, the reason cannabis works in the body at all.

My book will have a lighter tone, color illustrations and humor, along with information and discussions with the experts who are pushing scientific boundaries to understand medical cannabis.

**The Medical Marijuana Dispensary: Understanding, Medicating and Cooking with Cannabis** (Althea Press, 2016) by Laurie Wolf. \$18.99 paperback, 228 pages. ISBN: 978-1623156800. Wolf is co-owner of the medical cannabis edibles company Laurie & MaryJane, a longtime cookbook author and a classically trained chef. The book is popular and reviewers describe it as very informative. Its three sections include a primer for new patients, profiles of cannabis strains and recipes for remedies and edibles, plus appendices on marijuana laws by state and tips for cultivating cannabis at home. Of its 228 pages though, only about 20 are dedicated to cannabis as medicine. My book focuses solely on medical cannabis, how and why it works in the brain and body, the latest advances described by the scientists who are making them, and it includes much more information on the illnesses that cannabis helps treat.



## Marketing and Promotion

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I plan to market How Cannabis Heals continuously using the following resources to connect with readers online and interact with them over the long term.

### Website and Mailing List

<http://www.cherylpellerinscience.com>

My website focuses on cannabis medicine and psychedelic medicine for a general audience, with articles about the latest news and discoveries from both disciplines and a portfolio of my science writing projects over the years.

- A form at the site gives readers a chance to sign up to my mailing list to learn more about the current book and future books, learn about the progress of my latest book, and get links to my latest blog posts.
- I have dedicated content for Trips: How Hallucinogens Work in Your Brain and the same for How Cannabis Heals as I make progress on it.
- The website has a question-and-answer feature. Questions come in to me directly and I will answer the good questions and post them with good answers in a frequently asked questions column. These Q&As will work to help me generate new blog posts and other content.

- The website also offers a portfolio section that offers readers a look at my past science writing projects for the Defense Department, State Department, the Discovery Channel and the Discovery Channel Global Education Partnership, MIT Press, National Geographic and others.
- Facebook: I've had a personal Facebook page since 2008 or so and have created an official author page on the site that I haven't yet launched. There I'll post at least monthly blog posts and related content and, interact with readers.
- Twitter: I create or retweet informational posts at @pellerinscience. When it's published, I'll launch How Cannabis Heals on Twitter and Facebook and other social media platforms.

## **Collaboration with Related Organizations**

I plan to cultivate relationships with the following organizations to write blog posts, attend their meetings to sell books, invite their top officials to contribute blog posts and offer my content to them, and otherwise make myself and my book and web content available to them as a way to help them and sell my book. I have connections to the Multidisciplinary Association for Psychedelic Studies through my last book Trips, and I've already discussed sharing resources with Martin Lee, director of the excellent website Project CBD. Descriptions of Project CBD, MAPS and other organizations I interact with include the following:

- **Project CBD: Medical Marijuana & Cannabinoid Science**  
<https://www.projectcbd.org/> — I've already discussed sharing resources with

Martin Lee, director of Project CBD. Project CBD is a California-based nonprofit dedicated to promoting and publicizing research into the medical uses of cannabidiol (CBD), the main non-psychoactive element in cannabis, and other components of the plant. The organization provides educational services for physicians, patients, industry professionals and the public. It also, among other things, updates doctors and patients on developments in cannabis science, therapeutics and political economy; supports physician and researcher efforts to collect, aggregate and publish patient data to determine patterns of CBD efficacy; conducts training workshops for health workers and dispensary staff on the benefits and challenges of CBD-rich therapeutics and ways to maximize patient interactions; and publishes a free online newsletter and co-produces the education video series *Cannabis Conversations*.

- **Multidisciplinary Association for Psychedelic Studies (MAPS)**

<http://www.maps.org/> — I've also been in communication with MAPS. Founded in 1986, MAPS is a 501(c)(3) non-profit research and education organization that develops medical, legal and cultural contexts for people to benefit from the careful uses of psychedelics and cannabis. Among other important research efforts, MAPS has received regulatory approval to conduct the first ever study of smoked marijuana for symptoms of posttraumatic stress disorder (PTSD) in war veterans. It also has completed the first double-blind, placebo-controlled study of the therapeutic use of LSD in people since the early 1970s.

- **NORML: Working to Reform Marijuana Laws**

<http://www.norml.org> — The mission of the National Organization for the Reform of Marijuana Laws (NORML), established in 1970, is to move public opinion enough to legalize the responsible use of marijuana by adults. NORML also

seeks to serve as an advocate for consumers to assure they have access to high-quality marijuana that is safe, convenient and affordable.

- **Marijuana Policy Project: We Change Laws**

<https://www.mpp.org/> — MPP, founded in 1995, is the largest organization in the United States focused only on ending marijuana prohibition. Its mission is to change federal law to allow states to determine their own marijuana policies and to regulate marijuana like alcohol is regulated in all 50 states, the District of Columbia and the five U.S. territories.

- **Patients out of Time: Protecting Patients and Reducing Harm**

<http://patientsoutoftime.org/> — Patients Out of Time is a non-profit 501c3 corporation of Virginia that provides education about medical cannabis to health care professionals and their specialty and professional organizations, the legal profession and the public at large, about medical cannabis.

- **Leafly: Marijuana Dispensary & Strain Reviews**

<http://www.leafly.com> — Leafly calls itself the world's cannabis information resource. And its Wikipedia entry says it's the largest cannabis website in the world, with more than 13 million monthly visitors and 40 million page views across its website and mobile applications. According to Forbes, Leafly's founders describe it as Yelp-Consumer Reports hybrid.

- **Americans for Safe Access: Advancing Legal Medical Marijuana Therapeutics and Research**

<http://www.safeaccessnow.org/> — Americans for Safe Access (ASA) was founded in 2002 by a medical cannabis patient as a way for patients to advocate the acceptance of cannabis as medicine. It has more than 100,000 active members in all 50 states and is the largest national member-based organization

of patients, medical professionals, scientists and concerned citizens promoting safe and legal access to cannabis for therapeutic use and research. I'm attending an Americans for Safe Access medical cannabis conference in May.

### **Website/Blog Guest Posts, Podcasts, Radio**

I am working with the principals from the websites above to share content, including blog posts, articles and podcasts whose content will promote How Cannabis Heals. I can produce podcasts of my blog posts for those who prefer to listen rather than read content, and I will link to podcasts and videos from related websites. I was a guest on radio shows when Trips first was launched, and I can do similar shows on radio or other media outlets for How Cannabis Heals. Specifically, a growing number of cannabis-related podcasts have popped up on iTunes, Stitcher and other podcast platforms over the past few years. Some of those that I would pitch a medical cannabis podcast include:

- The Marijuana Agenda with Russ Belville Show, an 8-year-old podcast that used to be NORML's Daily Audio Stash show. It's a live weekly 30-minute podcast of news, science, analysis and interviews.
- The Hash, a podcast about cannabis news that uses sound effects to entertain listeners.
- M3 Medical Marijuana Movement, a podcast targeting patients of all ages who use medical cannabis to heal their illnesses.
- By the time the book is published many other podcasts will exist (and some will have failed) and I plan to offer interviews to all.

## **Book Sales at Medical Cannabis Conferences**

I regularly attend scientific and medical meetings dedicated to medical cannabis, and when the book is launched I will use these and similar venues to market it.

- Annual World Medical Cannabis Conference & Expo in Pittsburgh PA. In 2017, this conference had about 6,000 attendees and hundreds of exhibitors.
- Annual National Medical Cannabis Unity Conference in Washington DC.
- Meetings of members of Americans for Safe Access, which has about 3,000 members.
- Annual CannMed | Personalized Cannabinoid Medicine Conference. This conference usually has about 1,500 attendees.

## **Manuscript Specifications and Delivery**

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### **HOW CANNABIS HEALS**

#### **Manuscript**

300 + pages or between 70,000 and 80,000 words, plus interview list, illustration list, index, reference list.

#### **Delivery Date**

Three months or sooner after signing a publishing contract.

#### **Images**

- Color cover art by internationally known illustrator and author Serge Seidlitz, who has agreed to work with me to produce it. I'd like the publisher to pay some or all of this fee, which Serge's representatives Bernstein & Andriulli have said will be about \$5,000.
- Biologist and graphic artist Ellen Seefelt has created some of the molecular structures for the book to help readers grasp technical concepts.
- At Shutterstock I've found illustrations and photos that work for the book, and I've bought or gotten permission from cartoonists to use their editorial work on medical cannabis in the book.

- I've found a range of photos, graphics and illustrations online and at cannabis companies, research institutions like the National Institutes of Health and in research papers that are available for public use or that I've requested permission to use.



## Chapter Descriptions

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### HOW CANNABIS HEALS

#### **Introduction: The Lay of the Land**

An overview of some topics covered in the book, with a heads up about the state of the industry for people who hope medical cannabis can help their health problems but who are unfamiliar with the constraints created by state and federal laws. I offer a path through the tangle and a glimpse of the health benefits readers will find in How Cannabis Heals, told with help from scientists who do the groundbreaking research. (Sample chapter included)

#### **Part 1. THE ENDOCANNABINOID SYSTEM**

*... In which we learn about the body's endocannabinoid system (pronounced en-doe-can-nab-in-oid). The ECS is how and why cannabis works to treat a crazy range of diseases and disorders. We'll also explore the system's ancient beginnings, its essential elements and some of the most studied of the 560 constituents of cannabis and their functions, and see why the ECS's evolutionary emergence as an internal protective system in every vertebrate on Earth may be what made possible the evolution of vertebrates' complex brains.*

#### **Chapter 1. Evolution, Revolution**

Introduces the endocannabinoid system, a biological system with ancient beginnings whose elements work throughout the bodies and brains of all vertebrates on Earth to balance health and disease. It details the system's elements, the first 590 million years of its evolution, and the relationship of cannabis (no earlier than about 34 million years ago) with the endocannabinoid system, which is the only reason cannabis even works in the body and brain.

#### **Chapter 2. The Endocannabinoid System Discovered**

Identifies one by one the elements of the endocannabinoid system, their technical names and the way they work in the body and brain to balance health and disease.

#### **Chapter 3. The Basic Machinery of Everyday Life**

Discusses ancient cultures' uses of cannabis to treat a broad range of illnesses and the spread of the plant worldwide, then jumps forward to 1964, when a now-iconic Israeli researcher discovered the psychoactive compound in cannabis. Over the next 30 years scientists identified cannabis elements inside and outside the body, and ultimately realized, a billion or more years after the system began to arise on earth, that the compounds related to cannabis are way more far-reaching and important than their relationship to a simple psychoactive plant.

#### **Chapter 4. Two Main Cannabinoids—THC & CBD**

All about THC and CBD, including how the 2018 Farm Bill affects the production and sale of CBD.

#### **Chapter 5. More Cannabinoids, Terpenes & the Entourage Effect**

Identifies the 120 main compounds in cannabis called cannabinoids, or plant (phyto) cannabinoids. And the body's own cannabinoids, called endogenous cannabinoids, or endocannabinoids, that are made by enzymes inside nerve cells and degraded once they've had their effects by other enzymes in the cell. And how they all work in the body and the many health effects they influence. Also discusses plant chemicals called terpenes, which make up some of the 440 non-cannabinoid elements in cannabis, and the entourage effect, which describes why whole-plant cannabis or CBD are better for health outcomes than purified isolates.

#### **Chapter 6. Endocannabinoid Deficiency?**

A description of illnesses whose origins may be the lack of adequate endocannabinoid tone, which is a function of several things—how many endocannabinoid receptors are present and whether they're active or inactive, the activity levels of enzymes that synthesize or degrade the endocannabinoids, and the amounts of available endocannabinoids in the body.

### **Part 2. CANNABIS AS MEDICINE**

*... In which we skim the surface of the legal blockades that make cannabis research and cannabis medicine federal if not state crimes, and watch as the dominoes stacked against the 5,000-year-old medicine begin to fall. We'll also hear from scientists whose work has made medical cannabis possible and what they're learning about how cannabis helps the many illnesses it's been used to treat. We'll discuss, despite the growing number of states that now allow the use of medical cannabis, how hard it is, still, for potential patients to learn how to best use it and to find the right products. And what potential patients can do to help themselves while the nation decides whether to*

*keep treating cannabis as a dangerous drug or to finally recognize its years of medical value and its future as a safe and novel treatment for almost any illness you can name.*

## **Chapter 7. Cannabis, Medicine & the Law**

An overview of state and federal cannabis laws, roadblocks for research and how the legal dominoes are falling and making way for the end of the 82-year prohibition of cannabis. (Sample chapter included)

## **Chapter 8. Cannabis Medicine: Who Has Access?**

Describes barriers to medical cannabis and how they negatively affect public health, and a personal guide to getting around the barriers.

## **Chapter 9. Inflammation, Stress & PTSD**

The interactions among chronic inflammation, stress and PTSD and mood, the endocannabinoid system's role in resilience and new clinical trials for smoked cannabis and PTSD. (Sample chapter included)

## **Chapter 10. Brain Trauma & Neurodegenerative Diseases**

Cannabis effects in and clinical trials for stroke and brain trauma, aging, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and a new international research collaboration for ALS-like degenerative myelopathy in dogs and ALS in people, and multiple sclerosis.

## **Chapter 11. Cannabinoids, Chronic Pain & Other Inflammatory Disorders**

Cannabinoids and how they affect chronic pain, opioid and cannabinoid interactions, cannabis and neuropathic pain, and pain in a range of other disorders. Cannabinoids and pain in the elderly, the endocannabinoid system and comorbid pain and depression, cannabinoids and osteoarthritis, rheumatoid arthritis and fibromyalgia, the endocannabinoid system and GI tract effects, and cannabinoids and inflammatory bowel diseases.

## **Chapter 12. Cannabis, Mood Disorders & Addiction**

Cannabinoids and depression, the endocannabinoid system in depression; cannabinoids and borderline personality disorder; the endocannabinoid system and

psychiatric illness; the endocannabinoid system, depression and neurogenesis; cannabinoids and CBD in schizophrenia; and cannabinoids and the endocannabinoid system in addiction, relapse and addiction treatment; and cannabinoids and nicotine use disorder, cannabis use disorder, alcohol use disorder and opioid use disorder.

### **Chapter 13. Cannabis & Cancer**

Cannabinoids for managing cancer symptoms and cancer pain. CBD and cancer, cannabinoids and brain tumors, cannabis use in cancer patients, and cannabinoids as adjunctive cancer treatment.

### **Chapter 14. The Endocannabinoid System & Lifestyle Choices**

How exercise, meditation, alcohol, acupuncture, diet, caffeine, nicotine, dietary supplements and other lifestyle choices affect the endocannabinoid system.

### **Chapter 15. The Future of Medical Cannabis**

Doctors, patients and cannabis. Steps to be taken before cannabis can become an accepted mainline medicine. Discussions with physicians who use medical cannabis in their practices.

## Sample Chapters

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### HOW CANNABIS HEALS

through the ancient biological system that balances health & disease

*Part 1 explains the ancient origins of the body's endocannabinoid system, its complex workings throughout the body and brain, and how and why it enables cannabis to treat a broad range of illnesses. Part 2 details how cannabis works to treat specific illnesses that range from brain trauma to neurodegenerative diseases and cancer. It also discusses the federal law that makes cannabis illegal even in legal states, the patchwork of state cannabis laws that determine patient access to medical cannabis, and the future of medical cannabinoids.*

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### Introduction: Lay of the Land

*How Cannabis Heals* is about medical cannabis and the ancient biological system that allows cannabis to affect the body and brain, health and disease. It's also about why cannabis can treat so many different illnesses, and about the laws in place nationwide to govern, and in many cases constrain, its use.

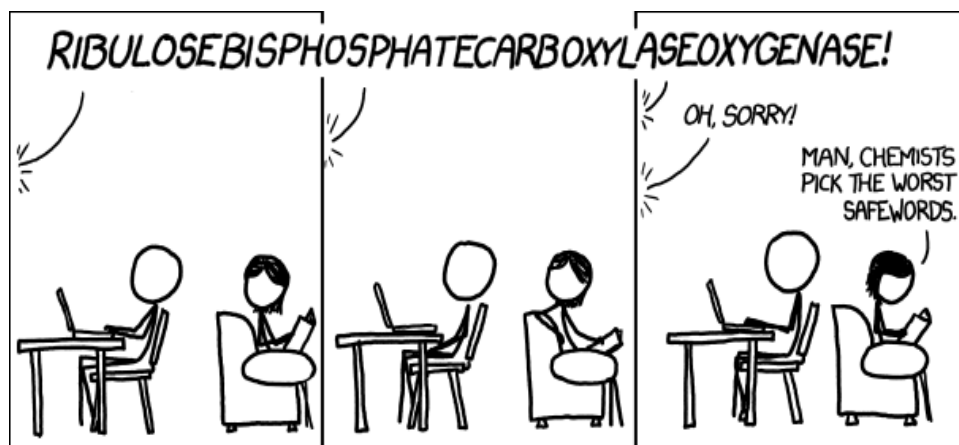


Through interviews with some of the most respected scientists in the field, the book describes the research that's beginning to explain how cannabis works in different diseases to relieve pain, anxiety, stress, inflammation, and the specific effects of brain damage, diabetes, heart disease, neurodegenerative diseases like

Alzheimer's and many others. And it describes, in these early days of medical cannabis programs in a growing number of states and U.S. territories, why it's so hard for everyone who could benefit from cannabis medicines—not just those who suffer from certain serious diseases—to gain access to them.

Now, I'm not a doctor or a cannabis grower, so I don't make cannabis dosage or treatment recommendations or give breeding or harvesting advice. But I am a science writer and in *How Cannabis Heals* I translate or explain the language of a complex cannabinoid science so that most people can understand what medical cannabis does and doesn't do, and where the science stands. Still, some of the words in these sections are **long and hard to pronounce** (ow).

Getting familiar with the language of medical cannabis will help you understand how best to buy and use the products available, especially if you read about them on the internet, where scientifically sound information about medical cannabis isn't always correct, and where some not-so-great “legal in all 50 states” products are hawked by a wretched hive of scum and villainy.<sup>1</sup>



But good products—full-spectrum products, meaning those with all the cannabinoids and terpenes and flavonoids the plant makes and that all contribute to the cannabis health effect—are increasingly available online, and available to anyone who can afford them. You'll read more about this later. At the end of the book and on my website, <http://www.cherylpuellerinscience.com>, I detail a range of excellent and reliable resources.

In *How Cannabis Heals*, when you read about the cannabis research, you'll find that a lot of what scientists know, especially about some of the more serious diseases like cancer or Huntington's disease, comes from their research in the lab and with animal models of disease. That's because the federal law that makes cannabis illegal also for

the past nearly 50 years has severely limited research and funding for research into the plant's biochemistry, pharmacology and effectiveness as a wide-ranging medicine.

In the United States, this has all but blocked clinical trials—the ones involving people—that allow results about cannabis from the lab and from animals to be confirmed and expanded in humans. But you'll hear about some clinical trials later, in the United States and other countries, and a growing body of case reports from doctors who have embraced the use of medical cannabis for their patients.

Drug laws and the stigma around marijuana (cannabis is its botanical name) have turned medical cannabis into a freight train, loaded down with the promise that its cannabinoids and other constituents hold for illnesses like posttraumatic stress disorder and all the other stress- and inflammation-related diseases; for degenerative diseases like Parkinson's, Huntington's and Alzheimer's, and for cancer, mood disorders, addiction, anxiety, irritable bowel diseases and many others.

The train won't stop as long as medical cannabis is legal only in some states and illegal according to federal law in every state. And until the 33 states (Dec 2018), the District of Columbia, and the U.S. territories of Guam and Puerto Rico allow everyone who wants or needs medical cannabis access to it, rather than making it available only by doctor's recommendation and only for certain illnesses.

## **Why Cannabis Heals**

Long-standing local and federal laws have done more than keep people away from cannabis or send them to jail. Such laws have kept scientists from studying the effects of the plant in people, and people from learning why and how cannabis even works in the body, or why its effects are so positive in so many different illnesses. I mean, what single drug can help treat cancer and acne?

Cannabis does and here's why: All vertebrates (animals with backbones) on Earth, people included, come complete with an ancient internal biological system that protects the body and brain and balances health and disease, according to **Dr. Maurice Elphick**, a biologist and professor of physiology and neuroscience in the School of Biological and Chemical Sciences at Queen Mary University in London.

It's called the endocannabinoid (en-do-can-NAB-in-oid) system (ECS) and it reaches all parts of the body, from the immune system to the brain, and its elements can be found in bones, skin, lungs, gastrointestinal tract, liver, bone marrow, muscles, spleen, pancreas, reproductive organs and vascular system. You know, everywhere.

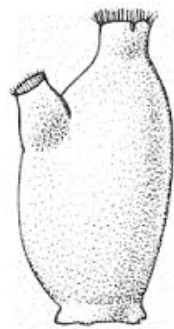
The ECS is called ancient because its primordial elements arose in some of the earliest forms of life on Earth, 1 billion or more years ago, Elphick says. Then it evolved through time until about 590 million years ago, when all its elements had come together to form



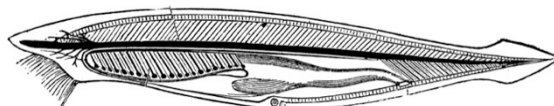
a complete endocannabinoid system in two non-vertebrate marine animals (**sea squirt** and **amphioxus**, some of our closest relatives in the sense that we're vertebrates) before it moved on to animals, people and the rest of the vertebrates.

Since then, and all the way up to now, the ECS has been in place in the bodies and brains of every vertebrate that swims or crawls or walks the earth—everything from fish to people.

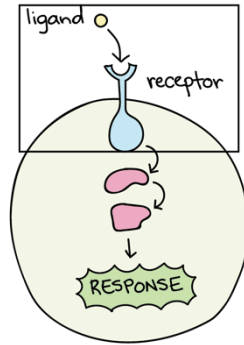
Now, the primordial element of the ECS didn't appear in bacteria a billion or more years ago just so Mother Nature could be sure that whoever smoked, ate or drank cannabis billions of years in the future would get high. No. Flowering plants like cannabis only arose within the past 100 million years or so, and cannabis itself evolved out into the world no earlier than about 34 million years ago. And starting 5,000 or more years ago, ancient civilizations began using cannabis as food and textiles and for spiritual purposes, and as medicines to treat what even back then was a really broad range of illnesses.



So why was there an endocannabinoid system







starting 590 million-ish years before people, and about 550 million years before cannabis, even appeared on Earth?

**Dr. Gregory Gerdeman**, a neuroscientist and educator based in Tampa, Florida, explained in a 2017 interview the real purpose of the endocannabinoid system—the reason

evolution had conserved it across a billion years.

To explain it, Gerdeman described how cells in the body and brain send signals to each other to run all the many integrated biological systems and processes. In medicine, beginning in the early 1900s and lasting for 100 years, everyone thought the signals went one way—from one cell (the presynaptic cell), across the synapse (the gap between cells) to the cell that receives the signal (the postsynaptic cell).

Once across the gap, this **signaling molecule** (also called a ligand) binds to a protein called a receptor on the surface of the receiving cell and delivers its message by changing the receptor's shape, producing biochemical reactions inside that cell. This is cell signaling.



An article at the [anaesthetist.com](http://anaesthetist.com) website quoted German scientist Ferdinand Hucho's definition, which I paraphrase: Receptors are proteins that interact with physiological signals outside the cell and convert them into effects inside the cell.<sup>2</sup> And this happens in every cell, all the time, all over the body and throughout the brain.

Um, easy—right?

We'll dive into this all the way in a little while, but over time, and after work by many researchers in the field of cannabinoid science, including Gerdeman, they realized in the late 1990s that, for the endocannabinoid system, cell signaling went backward—from the *postsynaptic* cell backward to a receptor on the *presynaptic* cell.

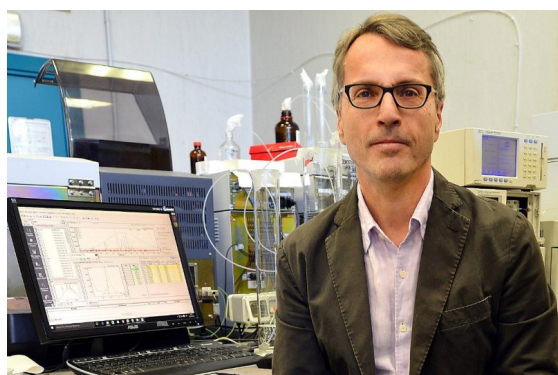
Why?

To modulate, or tone down, strong and possibly harmful signals that were coming across synapse the old-fashioned way—presynaptic, synapse, postsynaptic—and disrupting biological processes.

The researchers called this backward sort of signaling **retrograde signaling**.

The signaling molecules of the endocannabinoid system—called endogenous cannabinoids (endocannabinoids) because they're produced inside the cells themselves—was the first really clear example of retrograde signaling, Gerdeman said, and they were all over the brain.

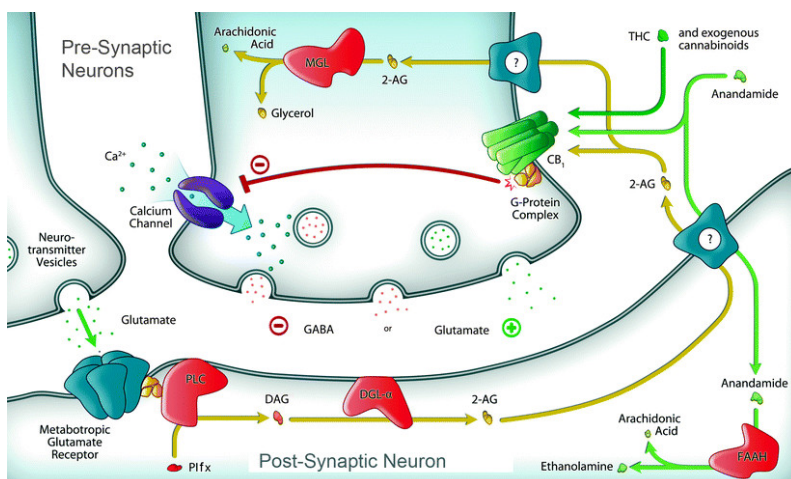
“The ability of the brain to adapt and respond and learn ... is greatly enhanced if information can go the other way as well, and cells can adjust their own synaptic inputs simply by releasing some sort of feedback molecules. The endocannabinoids act as feedback,” he added, “but not just feedback.”



Gerdeman said the two main endocannabinoids and their retrograde signaling are part of a mechanism of resilience in the brain, in response to trauma like stroke or traumatic brain injury, or electrical activity gone crazy as in epileptic seizures.

And this surprising finding was the first indication that the endocannabinoid system could be a protective mechanism—protecting the body and brain—but against insults like epilepsy, brain damage and stroke, just like the immune system is protective for the body against viruses, bacteria and other pathogens.

As **Dr. Vincenzo Di Marzo**, research director of the Endocannabinoid Research Group at the Institute of Biomolecular Chemistry, Italian National Research Council, in Naples, and colleagues wrote in a 1998 *Trends in Neuroscience*



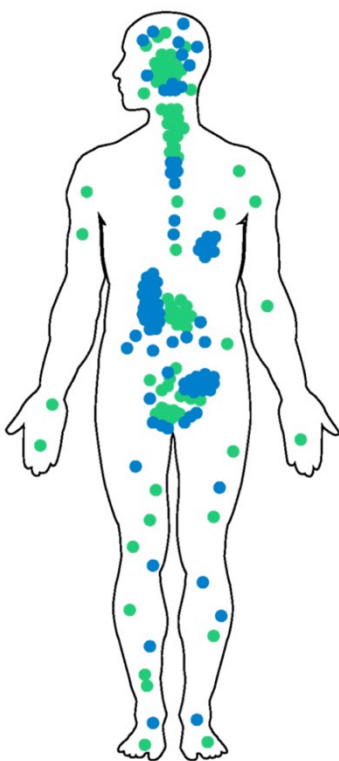
paper, “ ... Relax, eat, sleep, forget and protect might be some of the messages ... produced by the actions of endocannabinoids, alone or in combination with other mediators.”

In fact, according to neurologist and cannabinoid researcher **Dr. Ethan Russo**, in a 2015 white paper about the endocannabinoid system, the ECS is “an essential mechanism in the body’s biochemistry and physiology, the basic machinery of everyday life.” Russo is director of research and development for the International Cannabis and Cannabinoids Institute in Prague, Czech Republic.

The ECS, Russo adds, “is a key mediator of physiological homeostasis [balance], thus ensuring that various bodily systems function within tight parameters with neither a deficiency nor excess of activity.”

### **A Critical Biological System No One’s Ever Heard Of**

So the endocannabinoid system is why medical cannabis can affect so many illnesses, maybe all of them. Cannabis works in the body only because its many biological elements connect with ECS and other elements, and ECS elements are everywhere in the body and brain, critical to the basic machinery of everyday life.



For hundreds of millions of years, for vertebrates all over the planet, the endocannabinoid system has been balancing health and disease by maintaining homeostasis among all the body’s biochemical and physiological workings.

Here, an **illustration** shows the locations of the two main cannabinoid receptors—CB1 (green) and CB2 (blue).

But don’t feel bad if you’ve never heard of it. As you’ll see, you’re not alone.

Despite the endocannabinoid system's appearance in vertebrates 590 million years ago, scientists only realized in 2000-2001 that the discoveries they'd been making since about 1964—of THC as the psychoactive cannabinoid in cannabis, and later endocannabinoids, cannabinoid receptors and certain enzymes—all except THC were elements of the ancient biological system that eventually they called the ECS.

Over the years since then, cannabinoid researchers around the world have been seeking to understand the system itself, how to make it work in health and disease, and how cannabis can be used as a medicine to help people with health problems that 21st Century medicine can't fix. Still, the system that's critical to health and disease is all but unknown among most of the nation's population, sadly including physicians, most of whom were never taught, and still aren't taught, about the system in **medical school**.

So the endocannabinoid system is a neuroprotective and homeostatic gift to vertebrates, and most people on the planet have no idea that cannabis harbors what some scientists call a treasure trove of health benefits for everyone.

As Di Marzo and colleagues commented in a 2015 paper, “... a flurry of landmark studies



have demonstrated the pleiotropic [producing many effects] nature of the endocannabinoid system, which is activated locally and on demand to regulate specific physiological functions, often following perturbations of homeostasis, to help restore a physiological steady state in mammalian cells, organs and organisms.”<sup>3</sup>





## Inside How Cannabis Heals

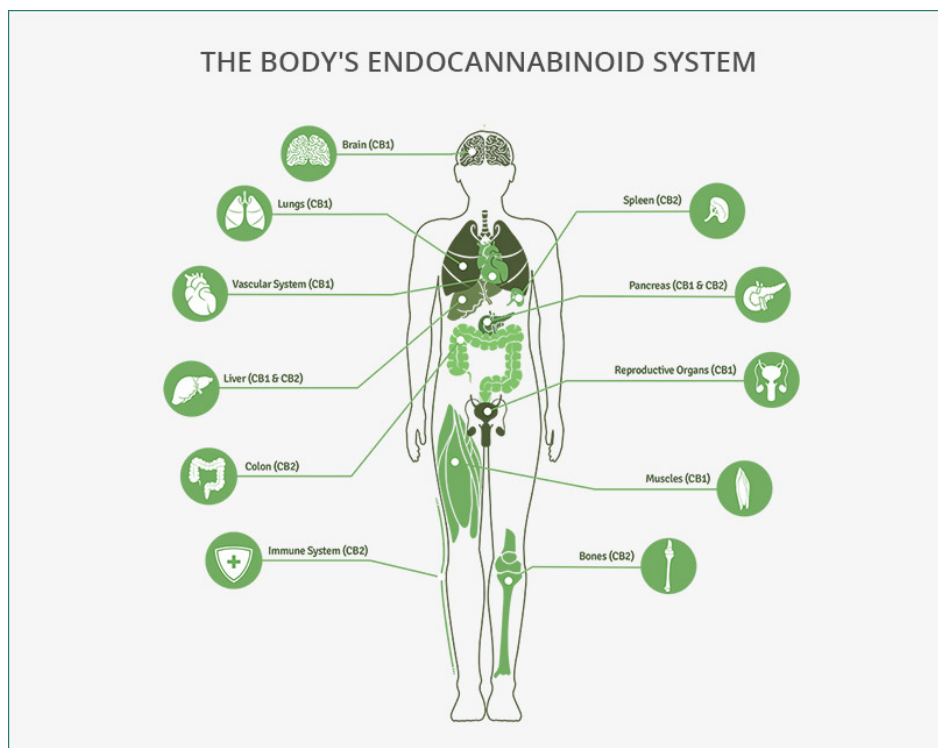
Part 1, The Endocannabinoid System, explains the ECS itself—its origins in the earliest forms of life on Earth, the evolution of its elements, the discoveries, millions of years later, of its elements over many years. And, also over many years, the realization by scientists that the elements formed a system that

reached all over the body and acted as a protective system much like the immune system but for different kinds of threats against the body and brain.

Chapters in Part 1 also discuss endocannabinoids—the body’s own cannabinoids—and how they work in the body and brain, and cannabis and its elements and the **range of health benefits** they confer on the body and brain to balance health and disease.

Part 2, Cannabis as Medicine, describes state and federal laws that govern medical cannabis, and details a range of illnesses and what researchers say—told by the researchers themselves—about why and how medical cannabis works for each one.

The chapters in Part 2 also talk about how things like diet, exercise, acupuncture and other lifestyle choices affect the ECS, and what the future of medical cannabis—when cannabis in all its forms becomes accepted as actual medicine—might look like, and what has to happen

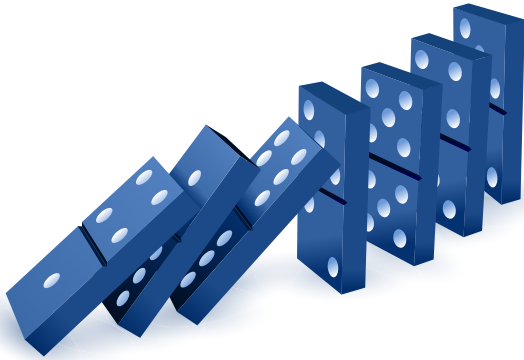


before that becomes reality. At the end of the book you'll find a resources section with the some of the most recommended medical cannabis and hemp companies and products, blogs and podcasts, books and other resources.

## Onward

Like everything else in the realm of medical cannabis, the products and websites and research I've written about here change, mostly for the better, so fast you can't believe it. So if something in the book or in the marketplace doesn't match your needs today, keep searching, you'll find it. Lots of organizations out there are working every day to make medical cannabis available to anyone who needs or wants it. Researchers have been working for decades to understand why evolution has conserved elements of the endocannabinoid system across billions of years, and, despite legal barriers, they

continue to learn how the ECS works as a protective system in the bodies and brains of Earth's vertebrates, including all of us. And the federal and legal dominoes are starting to fall.



## Chapter 7. Cannabis Medicine & the Law

The history of medical cannabis stretches across at least 5,000 years, and its mechanism for interacting with every biological and physiological process—the endocannabinoid system (ECS)—is a 590-million-year-old internal biological network responsible for homeostasis and neuroprotection in every vertebrate, including people, on Earth.

Before 1937, at least 27 **cannabis-containing medicines** were legally available in the United States, according to a briefing paper on the website of the Marijuana Policy Project (MPP) in Washington, D.C. Respected pharmaceutical firms, like Parke, Davis & Co. (now Pfizer subsidiary Parke-Davis), Squibb (now Bristol-Myers Squibb) and Eli Lilly produced many of those medicines.<sup>4</sup>

And yet.

In 1937, MPP says, U.S. legislators used the Marijuana Tax Act to federally prohibit cannabis. At the time, Dr. William C. Woodward of the American Medical Association opposed the act and testified before Congress that prohibition ultimately would prevent the medical uses of cannabis. He was so right.



Then, beginning in 1969, the Federal Bureau of Narcotics, which evolved into the Drug Enforcement Administration (DEA), created the Comprehensive Drug Abuse Prevention and Control Act of 1970. This, also called the Controlled Substances Act, categorized cannabis along with LSD, mescaline, ecstasy, heroin, methamphetamine and other drugs under Schedule I—meant for drugs with no currently accepted medical use, a high potential for abuse, and a lack of accepted safety for use under medical supervision. And they're all still there, under Schedule I, the most restrictive category of illegal substances in the United States, way too dangerous to study.



Snort. No currently accepted medical use? With a 5,000-year history of safe treatments for every disease you can think of, on nearly every continent on Earth? Well, except for that **demon thing** noted 5,000 years ago in the Chinese pharmacopeia. But for cannabis and its long history of safety and broad applications, Schedule I is ridiculously harsh. And, you know, ridiculous.

## Dominoes Fall

Despite that constraint, in 1973 Oregon became the first state to decriminalize small amounts of cannabis, and in 1996 California voters passed a statewide initiative called Proposition 215, the Compassionate Use Act, making it the first state to approve the use of medical cannabis.<sup>5</sup> Under the initiative, some California patients could use medical cannabis, even though it was untested by the U.S. Food and Drug Administration (FDA), unregulated by the DEA, and illegal under the federal Controlled Substances Act.

Since 1996, according to the National Conference of State Legislators (NCSL),<sup>6</sup> 33 states, the District of Columbia, and U.S. territories Guam and Puerto Rico have enacted comprehensive public medical cannabis and cannabis programs (as of November 2018). Approved efforts in 13 states allow the use of low THC-high CBD products for medical reasons in limited situations or as a legal defense (oh great). NCSL says these programs don't count as comprehensive medical cannabis programs.

So the dominoes are falling for medical cannabis and increasingly for cannabis use legalization for adults.



Among the 33 states mentioned above, NCSL says voters in Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, Washington and the District of Columbia have legalized small amounts of marijuana for adult use. Colorado and Washington's measures passed in 2012. Initiatives in Alaska, Oregon and the District passed in 2014, and initiatives in California, Maine, Massachusetts and Nevada passed in 2016. Most recently, in January 2018, the Vermont legislature passed adult-use cannabis legalization legislation and the governor signed the bill, but the measure doesn't set up a regulatory system for sales or production. And during the 2018 mid-term elections, Michigan voters said yes to a ballot question (Proposal 18-1) about legalizing and regulating cannabis.

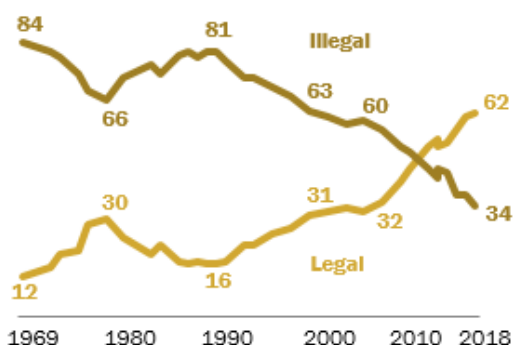
Also in 2018, Ralph Torres, governor of the Commonwealth of the Northern Mariana Islands signed into law (excepting several items), House Bill No. 20-178: HD4, to regulate cannabis in the Northern Mariana Island by establishing the Taulamwaar Sensible CNMI Cannabis Act of 2018, and for other purposes. And two more states approved medical cannabis programs during the midterms: Utah (the Utah Medical Cannabis Act, Proposition 2) and Missouri (Amendment 2), both passed by large majorities of voters.

In the United States, according to an October Pew Research Center survey, 62 percent—that's 6 in 10 people—say cannabis use should be legalized, reflecting a steady increase over the past decade and double what it was in 2000 (31 percent).

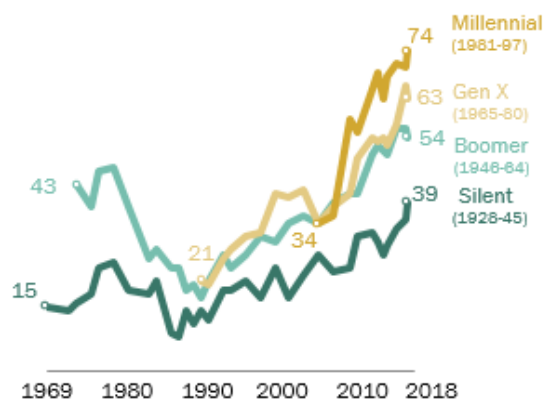
National polls consistently show that most Americans support letting seriously ill patients use cannabis as medicine with their doctors' approval, the Marijuana Policy

### U.S. public opinion on legalizing marijuana, 1969-2018

*Do you think the use of marijuana should be made legal, or not? (%)*



*% who say marijuana should be made legal*



Note: Don't know responses not shown.

Source: Survey of U.S. adults conducted Sept. 18-24, 2018.

PEW RESEARCH CENTER

Still, even now, doctors can't write prescriptions for medical cannabis because cannabis is federally illegal (except the FDA-approved Epidiolex) but they are allowed to recommend its use to qualified patients in medical cannabis states.

The legal status of medical cannabis has long been contentious and now, says Gerald Caplan, a law professor and dean emeritus of Pacific McGeorge School of Law, it's also a legislative oddity, "because state governments authorize cannabis possession and use in clear violation of federal criminal law."<sup>8</sup>

The federal law against cannabis is the main reason doctors can't prescribe but can only recommend medical cannabis to patients, and the reason it's so hard for scientists to get funding for cannabis research. The too-dangerous-to-study plant and its constituents actually are simply too-against-federal-law to study, especially for universities and other research institutions whose scientists depend on federal funds to do their important work.

or with animals, and receive government approval to do so, have to get the cannabis from the National Institute on Drug Abuse (NIDA) Drug Supply Program, which gets its cannabis from one source, the University of Mississippi School of



Pharmacy's National Center for Natural Products Research.

There are two problems with that. One is that much of the approved research focuses mainly on drug-abuse questions rather than on therapeutics (cannabis medicine), and the other is that for federally funded research there is only one source of cannabis, so researchers, no matter what their research needs, have to work with whatever they get.

"There was this big fanfare in 2015 about how [the federal government] was going to open up the ability to grow cannabis for scientific purposes to other academic institutions," neurologist and cannabinoid scientist Ethan Russo explained in a recent interview.

"A lot of people were fooled by that into thinking, 'This is it, now things are going to turn around for research.' What they didn't realize was it was a stacked deck. They knew full well that almost nobody would want to do this and here's why," he added. Only one institution was really interested, the University of Massachusetts-Amherst, he said.

"But it's been 14 or 15 years that they've been trying to get a license," Russo said, "and now perhaps even they have lost interest. Every time this comes up—that somebody wants to do research at a U.S. university—their legal counsel gets ahold of it and says 'Whoa, this puts our federal funding at risk,' and that puts the kibosh on it."

What's really needed, he added, is for private enterprise to be able to grow cannabis and standardize the products for medical use.

## **Roadblocks for Cannabis Research**

"Roadblocks for doing research are still substantial ... [including] the idea that everything's funneled through NIDA," Russo said. "It has to be their cannabis, and, with apologies to my friends at [the University of] Mississippi, the cannabis is neither representative nor suitable for what I would require to do *bona fide* clinical studies aimed toward developing cannabis as medicine."

He added, “To be quite frank, it's a system that's designed to fail. What we have so far in terms of clinical research on cannabis in this country is purely studies done with unstandardized material from NIDA. The studies have been very small, of limited duration, and they would serve no purpose in advancing regulatory approval of cannabis by the FDA or any international regulatory body.”

Russo once worked for the British company GW Pharmaceuticals, the company whose Epidiolex product now is approved by FDA, and whose Sativex compound is approved for use in 30 countries, except the United States.

In contrast to the protracted and undesirable U.S. process for studying cannabis, he explained, “GW Pharmaceuticals could cultivate, process and manufacture cannabis medicines with the full backing of the British Home Office and export it around the world, including to the USA, to do full-scale phase 2 and phase 3 clinical trials.” In fact, almost every scientific presentation delivered at the 2017 International Cannabinoid Research Society meeting in Montreal, Canada, and at the 2017 International Association for Cannabinoid Medicines in Cologne, Germany, ended with heartfelt recommendations and sometimes pleas for more funding and fewer barriers to cannabinoid research.



“First and foremost,” Russo said,<sup>9</sup> “we need to better understand the role of the endocannabinoids in our lives and our health status. That’s been ignored, possibly because of its name—having the term [marijuana] in the name and that pejorative connotation has impeded education, even in medical school. Basically, it hardly exists.”



Consider this, he added. “There are more cannabinoid receptors in the brain than there are for all of the neurotransmitters put together. ... Recognizing that fact, why would one ignore this system? Why isn’t this being taught? Our public needs to know about this, and how lifestyle



and diet affect this system, and how it could be brought to bear to improve their life conditions.”

### Pennsylvania Revolts

The commonwealth of Pennsylvania’s medical cannabis program, approved by the legislature and signed into law by **Governor Tom Wolfe** in April 2016, is doing something that no other medical cannabis state has done. It added a cannabis research program to its legislation and, according to the governor’s office, in May 2018 the Wolf administration approved eight PA universities as certified medical cannabis academic clinical research centers (the maximum number of institutes allowed by the legislation and amendments), calling it the “first step toward clinical research to commence in the commonwealth.”

Mike Adams, the author of a May 15, 2018, Forbes article,<sup>10</sup> put it another way: “Pennsylvania is determined to lead the nation in medical marijuana research. The state has already taken a bold leap, sticking its **middle finger** in the face of Uncle Sam's bureaucratic labyrinth of red tape when it comes to examining Schedule I drugs, to become a driving force behind the discovery of how the cannabis plant can benefit the masses in the realm of safe and effective medicine.”

The certified centers are Drexel University College of Medicine, Lake Erie College of Osteopathic Medicine, Lewis Katz School of Medicine at Temple University, Penn State College of Medicine-Hershey, Perelman School of Medicine at the University of Pennsylvania, Philadelphia College of Osteopathic Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, and University of Pittsburgh School of Medicine with University of Pittsburgh Medical Center.

The PA Health Department also has issued grower/processor permits (25 allowed) and dispensary permits (50 allowed).



In a May 14, 2018, statement announcing the eight certified centers, Wolf said more than 37,000 patients so far had registered to participate in the medical cannabis program, more than 16,000 had gotten ID cards and received medical cannabis at a dispensary, and 1,000 physicians so far had registered for the program and more than 600 were certified as practitioners.

The program began by allowing people with 17 serious conditions to be able to use medical cannabis after recommendation by a doctor. These were amyotrophic lateral sclerosis (Lou Gehrig's disease), autism, cancer, Crohn's disease, damage to spinal cord nerve tissue causing intractable (hard to control) spasticity, epilepsy, glaucoma, HIV/AIDS, Huntington's disease, inflammatory bowel disease, intractable seizures, multiple sclerosis, nerve damage, Parkinson's disease, posttraumatic stress disorder, severe chronic or neuropathic pain for which opiate therapy can't be used or doesn't work, and sickle cell anemia.

Also in the May 14 statement, PA Secretary of Health Dr. Rachel Levine said the administration had "expanded the number of serious medical conditions [approved for medical cannabis treatment] to include neurodegenerative diseases [although the list already included Huntington's and Parkinson's diseases and multiple sclerosis], terminal illness, [involuntary] and spastic movement disorders, and opioid-use disorder," making PA the first state to add opioid-use disorder separately as an approved condition for medical cannabis patients.

Levine, trained in pediatric and adolescent medicine, said medical cannabis is not a substitute for proven opioid-use disorder treatments, but because only approved conditions can be studied through the new research program, adding opioid-use disorder as an approved medical condition gives doctors another tool for treating "this devastating disease [and] allow for research to be conducted on medical marijuana's effectiveness in treatment."

In Pennsylvania, Levine said, medical cannabis will be available to patients if all other treatment fails, or if a doctor recommends that it be used along with traditional treatments.

(Chapter 7 Highlights)

## Chapter 9. Cannabinoids for Inflammation, Stress & PTSD

Really generally, inflammation is the immune system's response to a stimulus like bacteria, a virus or some kind of insult to the body, according to PubMed Health, a service provided by the National Center for Biotechnology Information at the U.S. Library of Medicine.<sup>11</sup>

### Inflammation: The Immune System's Response

When a wound swells, turns red and hurts, the website says, this can signal the presence of inflammation. Inflammation doesn't start with the wound itself, but as the body starts fighting the stimulus. Some inflammation happens silently and causes no immediate symptoms, like the sort of chronic inflammation that lots of doctors are starting to think is at the root of most major diseases, including neurodegenerative diseases, heart disease and some aspects of aging.

So inflammation starts out as a natural response to threats that seeks to protect the body, and as a chronic condition can end up doing the worst kind of damage.

Inflammation does one more thing, according to Assistant Prof. **Dr. Matthew Hill** at Canada's University of Calgary's Hotchkiss Brain Institute, it "profoundly stresses the body."

People generally think of stress as arising from things in their environment that psychologically stress them out, like relationship troubles, financial troubles and work troubles, Hill said in a September 2017 interview.

"These and other variables we see as being adverse and stressful to us, and that makes us feel like crap and we get stressed out and anxious and depressed from it," he added, noting that stress at a biological level is really anything that challenges the body or makes the body

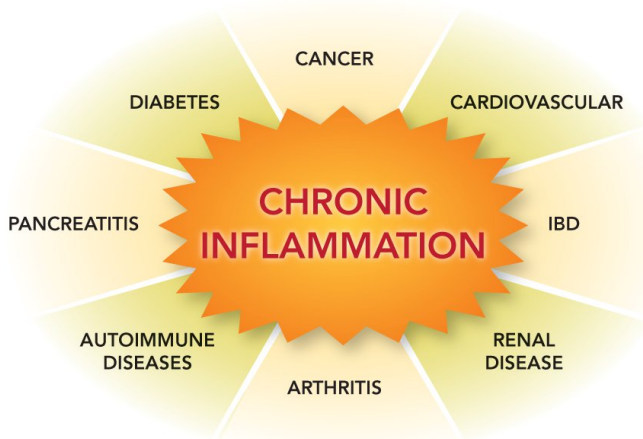


move out of its standard state.

People get stressed because of relationships, for example, Hill said, but evolutionarily that stress response was built into the body to deal with predators and to mobilize energy to get away from dangerous or threatening situations.

“Inflammation in the body is also a stressor, it's just a different kind,” he said. “We refer to psychological stressors as top-down because we have to process them cortically [in the brain] and understand that they're a threat to us. Once we recognize that we mount a stress response.”

Inflammation is more of a bottom-up stressor, Hill added, “because it's a challenge, it's a disturbance in the body that requires the physiology of the body to change, and one of the ways it does this is by mounting a stress response.”



Hill says inflammation drives the same hormonal stress response—elevating cortisol, sometimes called the stress hormone—as psychological stress.

“In the context of chronic psychological stress,” Hill said, “cortisol is a big mediator of a lot of the adverse effects on the brain and

body that are related to chronic stress. So our reasoning is essentially that, if inflammation is just a different flavor of stressor, it's probably mediating its effects on anxiety and depression in a similar manner as psychological stress because both of them [recruit] the same hormonal systems.”

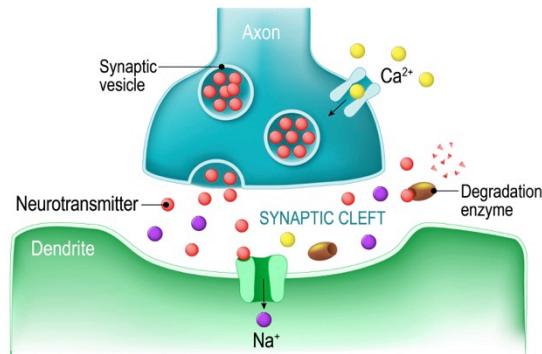
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### **Clinical Trials: Cannabinoids for Stress**

- Anxiety, Inflammation and Stress



A Colorado observational study (now recruiting) is investigating whether the anxiety-relieving and anti-inflammatory effects of cannabis vary as a function of the ratio of CBD to THC to try to shed light on the mixed data linking cannabis use and anxiety. The study start date was April 2018 and the estimated completion date will be June 2022. Estimated enrollment will be 210 participants, 21 years old to 70. The official title is Novel Approaches to Understanding the Role of Cannabinoids and Inflammation in Anxiety, and it's being held at the Center for Innovation and Creativity in Boulder. Study details are available at <https://clinicaltrials.gov/ct2/show/NCT03491384>



*Keep checking [clinicaltrials.gov](https://clinicaltrials.gov) for the clinical studies that surely will be added over time. Search for the disease name and cannabis and cannabinoids.*

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## ECS Signaling Collapse: Chronic Stress

Several years earlier, Hill and colleagues had established that chronic psychological stress could modulate (affect) anxiety related to changes in endocannabinoid function.

“Chronic stress seems to cause a collapse of the endocannabinoid system ... so you have fewer receptors and fewer endocannabinoid molecules in the brain,” he said. “The things that [the ECS] normally does to buffer against the effects of stress on anxiety and other aspects of the brain, that doesn't work so good anymore under conditions of chronic stress.”

Hill added, “In the brain, what endocannabinoids do is kind of temper neurotransmitter release.”

“Neurons **talk to each other** by releasing chemicals that often excite other neurons, so while it's an electrical current that goes down one neuron, it's a chemical signal that

drives communications between neurons. This is how neurons talk to each other,” he said, “and basically endocannabinoids limit the amount of transmitter chemical that gets released. Therefore, they can act to quiet down parts of the brain that become hyperactive.”

According to Hill’s website at the Hotchkiss Brain Institute, research from his and other labs shows that endocannabinoid signaling tends to relax stress responses.

“Deficits in endocannabinoid signaling in rodents can increase neuroendocrine and behavioral responses to stress, and in people disruption of endocannabinoid signaling can produce symptoms of depression and anxiety,” he wrote.

The term neuroendocrine refers to cells that receive signals from nerve cells (neuro) that cause them to release hormones (endocrine) into the bloodstream.

Hill and colleagues have shown that stress can mobilize endocannabinoid signaling, and that this increase is needed for normal recovery from acute stress and the larger adaptive processes created by repeated exposure to stress.

Such chronic stress—experiencing stressors over an extended period of time—can be a long-term drain on the body, according to the American Psychological Association website,<sup>12</sup> affecting the musculoskeletal system, respiration, the heart and blood vessels, the adrenal glands and liver and the gastrointestinal system.

Hill and colleagues also have found that, under conditions of chronic stress, endocannabinoid signaling breaks down and that the loss of this buffer system may be one of the ways that chronic stress increases the risk of mood disorders like depression and anxiety.

“This hypothesis has been supported by translational clinical studies we have performed demonstrating that circulating levels of endocannabinoids are reduced in individuals afflicted with major depression,” Hill wrote.

## **Cannabinoids, Inflammation & Mood**

In earlier work with colleagues in Calgary’s Department of Physiology and Pharmacology, Hill examined early-life inflammation and how that influences the endocannabinoid system.

More recently they've explored the idea that psychiatric behavioral comorbidities (two or more disorders occurring at once) are present in people who have chronic inflammatory diseases like inflammatory bowel disease, arthritis, multiple sclerosis and even things like asthma, Hill said.

"You often see high incidences of anxiety and depression in these populations," he added, "and it's always been hard to understand if this is just a consequence of having a chronic disease and [the accompanying] emotional burden."

But, he said, it's becoming more apparent that a biological underpinning related to chronic inflammation seems to modify how the brain works in a way that makes some people more prone to anxiety and depression.

Anxiety disorders affect about 40 million people in the United States alone, according to the National Institute of Mental Health, and antianxiety drugs are among the top prescription drugs.<sup>13</sup>



"What's interesting," Hill said, "is that a lot of the chronic inflammatory diseases like arthritis, multiple sclerosis and inflammatory bowel [disease] have the largest patient populations

who self-medicate with cannabis."

He said there's some evidence from animal testing that cannabinoids are anti-inflammatory, but the data from clinical (with people) studies involving inflammatory diseases hasn't been very impressive, Hill said. "That's not surprising," he added, "just because there's a lot of heterogeneity [diversity] in the clinical inflammatory conditions and they probably have a lot of different causes. But there is certainly a subset of people who seem to respond to [cannabinoids] positively, it's just a matter of whether it's a genuine effect or not."

A recent review paper by a colleague of Hill's—Dr. David Finn, professor of pharmacology and therapeutics at the National University of Ireland-Galway—said that in all the studies he reviewed,<sup>14</sup> comorbid changes in anxiety and depression often improved in people who used cannabis or cannabinoid therapy in some way, even if it

didn't cure the disease. Hill said this finding suggests that the disease somewhat induces the emotional comorbidities, but the comorbidities might be unrelated to the disease biology.

"There may be some changes going on in the brain," Hill said, "so we've started investigating this."

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### **Clinical Trials: Cannabinoids, Inflammation & Mood**

- Cannabis Observational Study on Mood, Inflammation, and Cognition (COSMIC)

An observational study (recruiting) by researchers from the University of Colorado-Boulder, collaborating with the University of Colorado-Denver, examines the effects of cannabis on cognition and other domains of function (inflammation, inflammatory response, mood) and whether those effects depend on the ratio of THC to CBD in the product. The study began in July 2016 and the estimated completion date is April 2021. The study will have 280 participants, 21 years old to 70. The official title is Marijuana Harm Reduction: Innovative Strategies for Developing New Knowledge. Study details are available at <https://clinicaltrials.gov/ct2/show/NCT03522103>.

*Keep checking [clinicaltrials.gov](https://clinicaltrials.gov) for the clinical studies that surely will be added over time. Search for the disease name and cannabis and cannabinoids.*

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### **ECS Signaling Collapse: Chronic Inflammation**

In their research, Hill and colleagues found that, just as chronic stress seemed to cause a collapse of the endocannabinoid system, chronic inflammation pretty much did the same thing. Chronic inflammation, Hill said, "seemed to compromise the way the endocannabinoid system functioned, and that seems to contribute to the elevations in anxiety. So one of the thoughts is that, in some of these disease states where the endocannabinoid system isn't functioning properly, people may have a propensity to self-medicate with cannabis."

Mentioning a severe form of stress, Hill said that with posttraumatic stress disorder (PTSD) the endocannabinoid system may not be functioning properly and, by

supplementing with something like THC, people are normalizing a deficit in the system, and that may help improve some of their symptoms.

“This, of course, is still a theory [and] we're trying to conceptualize why there's so much consistency in the reports of people who self-medicate with cannabis,” he said.

The problem is that reports of self-medication are anecdotal so it's hard to capture the information scientifically. But he and his colleagues use the reports to generate hypotheses about how things might work.

“That’s kind of where we are,” Hill said of his inflammation studies.

“We think that maybe these comorbid behavioral psychiatric changes associated with inflammatory diseases like anxiety and depression may relate to a dysfunctional endocannabinoid system that's driven by the chronic inflammation itself.”



Hill says he thinks this is true for most stress-related psychiatric illnesses. If the system isn’t working properly, some things may become apparent.

“You might be more sensitive to developing anxiety after stress or you might not recover as quickly from stressful experiences in your life. We know the endocannabinoid system is

very important for processing rewarding stimuli,” he added, “so if it's not working properly you might become more anhedonic,” meaning unable to find joy in life.

All these systems engage the same biological processes in the body, Hill said, and the hypothesis is that if the ECS isn’t working properly, someone with this problem may be more vulnerable to developing a psychiatric illness like depression or PTSD.

## **Posttraumatic Stress Disorder**

PTSD is a mental health problem that some people develop after experiencing or witnessing life-threatening events like combat, natural disasters, car accidents or sexual assaults, according to the Department of Veterans Affairs National PTSD Center website.<sup>15</sup>



After these events it's normal to have **upsetting memories**, feel on edge, or have trouble sleeping, the website says. At first, it may be hard to do normal daily activities like going to work or school, or spending time with family and friends. But most people start feeling better after a few weeks or months. If symptoms continue for more than a few months, it could be

PTSD. For some people, PTSD symptoms may start later, or come and go over time.

In the case of service members, some may carry psychological and physical wounds of their military service back into civilian life. In one study, according to the PTSD Center website, one in four veterans returning from Iraq and Afghanistan reported symptoms of a mental or cognitive disorder; one in six reported PTSD.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, lists PTSD in the trauma- and stressor-related disorders category, according to Nachson Korem and colleagues in the Psychology Department at the University of Haifa in Israel.<sup>16</sup>

In their 2015 paper, “Targeting the endocannabinoid system to treat anxiety-related disorders,” they list four diagnostic clusters of behavioral symptoms:

- Re-experiencing symptoms involves spontaneous, uncontrollable intrusions of the traumatic memory that manifest themselves as **nightmares** or memory flashbacks.
- Avoidance symptoms, or an individual’s efforts to distance himself or herself from trauma-related stimuli. These can include emotional and social withdrawal.
- Negative changes in cognition and mood.
- Hyperarousal symptoms that include physiological reactions like irritability, hypervigilance and an exaggerated startle response.





Korem and colleagues described the ECS as a potential target for preventing and treating anxiety-related disorders, especially PTSD.

“Preclinical and clinical data strongly suggest that anxiety is associated with decreased endocannabinoid tone,” they wrote, “and that CB1 receptors in the fear circuit in the brain are crucially involved in the [anxiety-reducing] effects of cannabinoids.”

Endocannabinoid tone, according to Ethan Russo, is a function of how many endocannabinoid receptors are present, whether they are active or inactive, the activity levels of enzymes that synthesize or break down the endocannabinoids, and the levels of available endocannabinoids in the body.

The authors also called for extensive clinical research on the effects of cannabinoids in PTSD patients. (See the end of the chapter for information about the very first clinical trial of smoked cannabis for PTSD, still recruiting at September 7, 2018.)

### A Natural Response to Extreme Circumstances

Networks of stress in the brain are interconnected with networks broadly attributed to emotional processing in the brain, so there are well-studied, discrete brain networks that are responsible for emotional wellbeing, emotional affect and how people integrate fear and stress, **Dr. Gregory Gerdeman**, the Florida-based neuroscientist and educator we heard from earlier, said during a recent interview.

“The neurobiology of emotion is highly dependent on the network called the limbic system or the corticolimbic-midbrain system, but these corticolimbic (cor-tih-co-LIM-bick) networks of emotion, affect [expression of emotion] and stress are highly regulated by the endocannabinoids,” he said.



These areas have dense expressions of CB1 receptors, Gerdeman added, “and it’s possible that every single neuron in these networks that are so important for emotion and personality and our responses to the world either releases endocannabinoids in certain circumstances or responds to them or both.” So the ECS can be fully expected to regulate the neuroscience of emotion, and

therefore disorders of emotional processing like PTSD, he said.

“This is what matters to us in life, right? Our sense of joy, our sense of resilience, our sense of fear and vulnerability,” Gerdeman said, “and these involve the senses in so many different disorders, whether it's posttraumatic stress or general anxiety or major depression or part of the suite of symptoms in schizophrenia.”

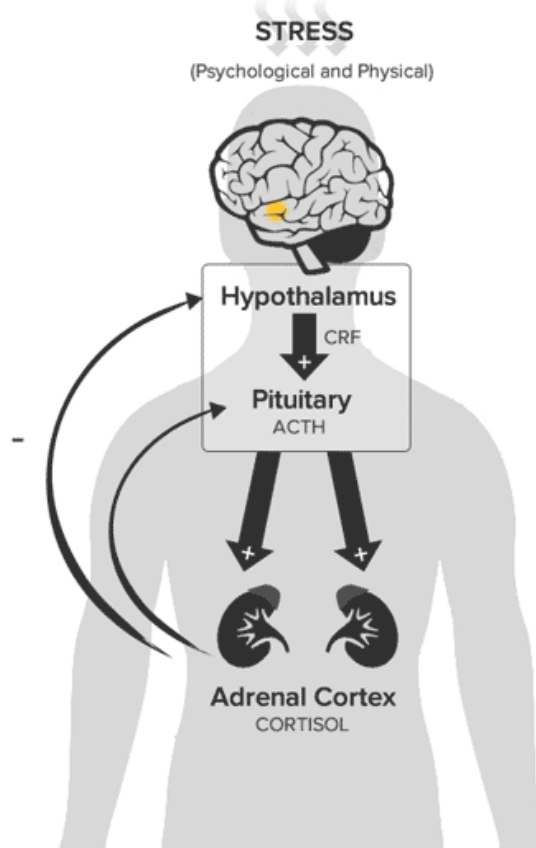
Gerdeman thinks posttraumatic stress shouldn't be called a disorder because it's “a natural defensive extreme response to extreme circumstances that human beings are exposed to.” It's an adaptive response to shut down and become hypervigilant when someone is exposed to things that are inescapable, he says, and such narrow adaptations result in the dysfunction called posttraumatic stress.

#### Anandamide as a Stress Buffer

In animal models of stress, Gerdeman explained, some research focuses on homotypic stress—the same stress over and over again, like an animal being restrained in a little tube repeatedly against its will. And the repeat homotypic stress that the animal has no control over causes changes in the endocannabinoid system.

“It upregulates the FAAH enzyme [which breaks down the endocannabinoid called anandamide] in numerous brain areas, including limbic system areas like the amygdala that control fear and stress. FAAH levels go up and that means anandamide levels go down,” he said.

“In the cortical limbic system and particularly the amygdala, anandamide acts like a buffer to stress. And when anandamide levels drop, it's more likely that stress-evoking stimuli are going to activate your physiological stress response—the whole **hypothalamic-pituitary-adrenal axis**,” Gerdeman explained. “But when your







anandamide levels are high in the amygdala, you're more resilient to potential stressors actually stressing you out.”

Part of what goes on with posttraumatic stress, he added, “is that the buffer system has gotten shocked, we believe. There's a really good body of evidence that supports this from many different lines of work ...

and it's coming into a pretty coherent picture.”

So, “in the neurobiology of stress, anandamide is a buffer, and 2-AG, the other endocannabinoid, is used in other important ways that are relevant to how you turn off the stress response. Both of the endocannabinoids are,” Gerdeman said.

He recalled a 2002 paper published in the journal *Nature* in which Dr. Giovanni Marsicano from the Max Planck Institute of Psychiatry in Germany and colleagues, writing about the endocannabinoid system, showed that the ECS is critical when extinguishing learned fear in animals.<sup>17</sup>

“Part of the study of this limbic system of fear and emotion includes the biology of learned fear, and classical associative conditioning is how you study this in **rodents**, and humans, really. You get them to associate a neutral stimulus with a so-called unconditioned aversive stimulus,” Gerdeman said.

“The animal gets in a room, a light comes on and it hears a tone and it gets a shock in the foot. In short order, after a few of those sessions, when the animal hears the tone in the context with which the shock could occur, it freezes up. It's scared. It's learned to anticipate and be afraid. That's learned fear,” he added, noting that the neural circuitry of the amygdala is highly involved in the process.

So the animal learns fear, Gerdeman says, “but then there's a process called extinction where, if the animal is exposed to that conditioned cue over time and does not receive the shock, then the memory is, as we say, extinguished. The animal stops being afraid of the cue. The tone is now neutral again. And it's not just a matter of forgetting, it's active relearning ... or maybe call it unlearning.” Gerdeman said the Marsicano paper showed that when an animal is undergoing the extinction training ... anandamide—the stress buffer—is being actively released in the amygdala.

## Supplementing the ECS for Resilience

Since that time, more sophisticated studies have shown in animal models that during fear extinction, if anandamide levels are high, the



animal—or the human, Gerdeman says—moves past the fearful memory more rapidly. And if CB1 receptors are blocked either with a drug or with genetic techniques, fear extinction is harder—animals hold on longer to that fearful stimulus and reactivity.

The same sort of thing is shown in studies with animals that are made to have the same kind of genetic variant as a substantial number of Western Europeans.

“This variant in the human population, the FAAH enzyme, has a single nucleotide difference that leads to lower levels of activity, and lower levels of the FAAH enzyme mean that anandamide is not broken down as effectively,” Gerdeman said. “So we believe that in these variants in human beings, you will have a greater level of anandamide signaling” and a faster fear-extinction process.

With people this is tested using **virtual reality**, he said, “where you've got a VR headset and you're walking through a building and you subconsciously detect cues before something jumps out and scares you. Then, later in the behavioral testing, those cues are popped up and you can measure autonomic responses like sweat production and that kind of thing.”

Gerdeman says the paradigm of learned helplessness—which psychologist Martin Seligman discovered in 1965 in **experiments with dogs**—also stems from studies where a pair of rats got foot shocks on an electric grid delivered at exactly the same time.

One rat has a lever in the cage and if he presses it, the shocking will stop. He has to learn this, but they do, Gerdeman said. The other rat is called a yoked control, and his shocks depend on what the other rat does but he's completely unaware of it. The magnitude of shocks delivered between the two animals is precisely the same, but only one animal can learn that it has the power to turn the shocks off.

The animal that learns it has no control over the stressor goes through a whole constellation of gene changes, physiological changes associated with the chronic stress. These don't happen in the animal that learns it can control the stress.

Later on in the animals' lives, Gerdeman says, “the animal that had control over its early-life stress in that experiment is much more likely to be resilient to future stressors and not go into a locked-down, fearful animal model of PTSD.”

Part of what may go on in the war theater, or in abuse by a spouse or in a troubled childhood, he said, “is if someone grows up in a situation where as a child they learned helplessness, they may be more vulnerable to being triggered into what we call PTSD.”

Gerdeman said this information is “hugely relevant” to the idea that using cannabinoid supplements to balance the endocannabinoid system is therapeutic.

Doing so “makes all the sense in the world,” he said, adding, “I fully anticipate that—especially in people who are fully grown and looking toward the second half of their lives—I think we are very close to the time when people are going to say, ‘You're not on some sort of cannabis supplement? Why not?’”

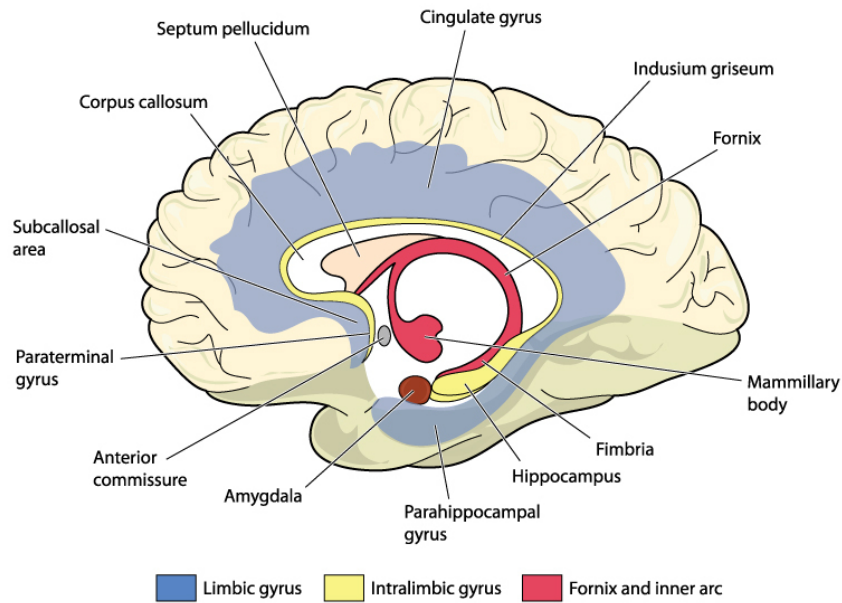
## A Consistent Kind of Neural Signature

Dr. Matthew Hill, through his research in determining the endocannabinoid system's role



*Dogs who had previously been shocked did not try to escape the shocks in a subsequent experiment.*

in the effects of stress on neuroendocrine function, emotional behavior and other conditions, said in a recent interview that researchers don't totally understand what's different in the brain of someone who's been exposed to trauma and develops PTSD, versus someone who's been exposed to trauma and doesn't.



“But one of the things that reliably pops up from study to study in humans,” Hill said, “... is that people with PTSD have what appears to be hyperactivity of neurons in an area of the brain called the **amygdala**,” he said, the part of the brain “involved in understanding the emotional salience [weight], of, let's say,

stimuli in your environment.”

He explained, “If you put your hand on a hot oven and burn your hand and it's a very aversive experience, your amygdala is important for recognizing that it was bad and learning the association between the stovetop and the burning pain. And you don't want to do that again.” (Hot ovens have salience.) The amygdala is important in understanding cues in the environment related to emotional responses and threatening outcomes, Hill said, and it's important for scanning the environment almost unconsciously to determine if there's a threat that could cause harm.

“In PTSD it's thought that individuals start generalizing. A trauma can be a very specific thing, like a car accident, for example,” he explained. “But someone who got PTSD after the accident starts to generalize to all cars and to **traffic** in general, and may start to exhibit anxiety and panic responses when they see any stimulus that's similar to what was associated with their initial trauma.”

Depending on how common or familiar the stimuli are,





generalizing can cause a huge amount of distress, Hill said.

But cannabinoids seem to be very efficient at calming down neural activity in the amygdala, at least in animal studies, he said.

“This is probably not the only way [cannabinoids] influence aspects of PTSD,”

Hill added, “because there's a huge sleep component as well in PTSD, but hyperactivity of the amygdala seems to be a relatively consistent kind of neural signature of an abnormality that's present in PTSD.”

This has been a lot of the focus, for example in looking at drugs that may have benefit in PTSD, he said, “by looking at whether the drugs have the ability to blunt amygdala reactivity to the threat cues in your environment.”

### PTSD: Acquired Endocannabinoid Deficiency

The concept of endocannabinoid deficiency, which neurologist and psychopharmacology researcher Dr. Ethan Russo proposed in 2001, is based on endocannabinoid tone.

Russo says endocannabinoid tone reflects a person's levels of the endocannabinoids anandamide and 2-AG and their production and metabolism, and the relative abundance and states of the cannabinoid receptors, among them CB1 and CB2.

If endocannabinoid levels drop, this tone declines and illness results, he said, adding that PTSD could be one of those illnesses.

When he proposed the concept, Russo named migraine, fibromyalgia and irritable bowel syndrome, all of which are common subjective pain syndromes, as indicative of clinical endocannabinoid deficiency. But PTSD is an example of an acquired endocannabinoid deficiency, Russo said in a recent interview.

“Some of these things are genetic,” he said, “but here you've got a situation of, say, a **young soldier**, well-adjusted before, has this terrible experience and comes back with



this florid syndrome that subsequently is ruining their life. The Department of Defense needs to be interested in this explanation because the areas of application are legion.”

For victims of PTSD, Russo added, “and those who get blown up and have traumatic brain injuries, and people who have lost limbs and have phantom limb pain, absolutely the best thing is cannabis.”

For example, he says, when people have an **amputation** they're at risk for developing phantom-limb pain. “This is not just a phenomenon in which the patient says, ‘I still feel my leg even though it's not there any longer.’ Rather, it is a severe and chronic form of neuropathic pain—a burning, relentless, difficult-to-treat pain originating from the severed nerves. The conventional drugs to treat this are pretty ineffective, so often the cases are intractable to treatment.”

Russo says such patients may not be taken care of properly and doctors find themselves using narcotics in efforts to control the pain. Opioids don't work in this context and eventually create problems of their own, he said, including exacerbating neuropathic pain and risking addiction and overdose.

This process of neuropathic pain seems to be driven by an excess of the excitatory neurotransmitter glutamate, he said.

“When present in excess, [glutamate] spills over and drives the neuropathic pain. Similarly, in the brain after head injury, there's so much glutamate that it actually produces what's called excitotoxicity—an overreaction that kills the cells,” Russo said.

The initial injury may kill certain brain cells, but in the next few days the cells that are only damaged become so driven by this release of glutamate that they also succumb, even though they may have been salvageable with the right treatment, he said.

“Cannabinoids, and especially CBD, turn off this process and can save the damaged-but-not-yet-dead cells from the head injury,” Russo said. “THC specifically and CBD probably, when used chronically, also turn down this glutamate excitability and



can reduce, and eventually in some cases extinguish, neuropathic pain.”

## Preventing PTSD?

Russo says that when a patient has an established PTSD syndrome they need to be treated on an ongoing basis, but he also advocates prevention.

“If we had the option to jump in at the beginning of a traumatic event with opiates and cannabinoids in combination, maybe PTSD doesn't eventuate, or at least not with the terrible frequency that it now occurs in warfare,” he said.

If battlefield medics had opiates and cannabinoids to administer **in the field**, he added, “you could probably substantially eliminate PTSD if you treated them [with cannabinoids] at the time you controlled their pain [with opioids]. You may allow them to sleep. The multifaceted therapeutic effects of cannabis on these biochemical mechanisms may prevent the development of the PTSD cycle in the brain that doesn't allow you to forget and that is producing intrusive dreams and making it impossible to function in society.”

One of the things THC does is suppress REM sleep, dreaming sleep, Russo said.

“If REM sleep is suppressed, you can't have nightmares. [And] what's one of the cardinal side effects of THC? Forgetfulness. In PTSD you can't forget. So with THC you're reinforcing the ability to forget, and that's what patients with PTSD need, so they can once again look forward in their lives,” he said.

If society really wants an approach that's cost effective, Russo added, “it is, treat in the field and follow up with those people while they're recovering physically with counseling so they can process what they've been through, and I think you can prevent almost all of this. But this is a crazy idea in the estimation of most people.”

The alternative is the status quo, he said. “A huge population of victims who suffer endlessly along with their



families, and who end up as suicide victims with horrible frequency.”

Russo added, “If you've actually got the chance to intervene on behalf of injured soldiers at risk for PTSD, you can treat them acutely, prevent it, and they can return to a normal life. That's good for him or her, for the family and for society.”

For treating PTSD if it can't be prevented, Russo said researchers and physicians don't yet know what treatment is optimal.

“My suspicion is that, like with a lot of things, you'd need a little THC to work on the memory and intrusive dream aspect [of PTSD], and a larger amount of CBD to increase endocannabinoid tone, and help with any pain and other damage,” he added. “It's a formula that has a lot of applicability broadly because there are so many things that it would help.”

### Mired in PTSD Symptoms

The federal classification of cannabis as too dangerous to study, as discussed earlier, is a barrier to research and keeps patients whose illnesses don't respond well to traditional medicines—opioids, for example—mired in pain, anxiety, insomnia and other symptoms. Severe posttraumatic stress disorder is one of those illnesses.

But because of the federal restriction on cannabis, even the U.S. Department of Veterans Affairs can't prescribe, or until recently couldn't even discuss, medical cannabis for veterans with PTSD, pain, anxiety or any other illness that cannabis can help treat.

The same restriction has created a research environment in which most studies of cannabinoids and PTSD are done with animal models of PTSD, and only a few small studies have examined PTSD and cannabinoids in people.

One small 2014 study in Israel,<sup>18</sup> for example, explored the use of THC as an add-on to traditional treatments.

The researchers knew that many PTSD patients got only partial relief with current treatments and that patients with uninterrupted PTSD showed high rates of substance abuse.



The open-label study (they didn't disguise the THC or use a placebo) evaluated the tolerance and safety of orally absorbable THC for chronic PTSD. The 10 patients, who already were on stable medication for PTSD, received 5 milligrams of THC (a low dose, also called a microdose, that wouldn't be psychoactive) twice a day as an add-on treatment.

The researchers reported that three patients had mild adverse effects but didn't drop out of the study, and that the intervention with THC improved the severity of all symptoms—sleep quality, nightmare frequency and PTSD hyperarousal (increase in anxiety and irritability, among others) symptoms. They concluded that THC was safe and well tolerated by patients with chronic PTSD.

### PTSD: A Handful of Small Studies

Hill said that there isn't a lot of well-executed clinical work (with people) in the realm of looking at cannabinoids for PTSD, but there are a handful of small studies.

"These ... usually don't have enough subjects in them to make strong conclusions or to generalize at all, but what I find interesting ... is that three or four of them have been done now and only one of them has been done properly, with a placebo-controlled double-blind trial," he said. That study was done by the Canadian military with 10 patients.

This kind of study uses a placebo—a harmless substance with no drug effect—and makes sure that no one among the participants or investigators knows which substance is the drug being studied and which is the placebo (blinded), eliminating the possibility of some kind of bias. Double blind means that no information about test results is released until after the test.

The 2015 study<sup>19</sup> that Hill discussed used a synthetic cannabinoid (made in the lab) called nabilone. Nabilone (trade name Cesamet®) mimics THC but has more predictable side effects and few or no psychoactive effects,



both important for studying other kinds of effects.

The researchers wanted to see if nabilone capsules would reduce the frequency and intensity of nightmares in **Canadian male military members** with PTSD who were already on standard treatment (psychotherapy, antidepressants). During the study, which was registered with Health Canada, the Canadian public health department, subjects received 3 milligrams of nabilone before bed each night for seven weeks.

Afterward, the researchers said nabilone had “provided significant relief for military personnel with PTSD, indicating that it shows promise as a clinically relevant treatment for patients with nightmares and a history of non-response to traditional therapies.”

They added that the findings should be replicated in a larger group of subjects and that more research should explore the effect of nabilone on other PTSD symptoms, like re-experiencing hypervigilance and insomnia.

“What the people who had PTSD found from taking [nabilone],” Hill said, “was that it dramatically reduced their frequency of nightmares and it improved their quality of sleep,” Hill said, “and in PTSD, sleep disturbances are a massive problem.”

PTSD sufferers “have a lot of vivid, lucid nightmares,” he added. “They wake up a lot, so their sleep is fragmented through the night. The thought is, these memories that come back in the form of nightmares are almost hyper-consolidating (hyper-stabilizing) the memory ... and the lucid nightmares during REM [rapid-eye movement] sleep are thought to be one of the things that sensitizes the disease.”

Because this was a double-blind placebo-controlled trial, Hill said, the research staff could switch subjects over to the placebo without anyone involved in the study knowing who was on drug and who was on placebo at what time. And almost immediately when the subjects who had been on the drug went on the placebo, all the nightmares came back within a day or two.

“It seemed to be a pretty robust effect,” Hill said, “but again, it's a very small sample size.”

Still, he hopes the Canadian government, especially in light of the legalization of cannabis across that country, will put more money into cannabinoid research, which would help produce more well-rounded and broader clinical trials.

## Finally: A Placebo-Controlled, Triple-Blind, Randomized PTSD Trial

After seven years of submitting applications and working with multiple federal agencies, the Multidisciplinary Association for Psychedelic Studies (MAPS) was approved to conduct the very first clinical trial of smoked cannabis for PTSD.

The study, sponsored by MAPS, is called “Placebo-controlled, triple-blind, randomized crossover pilot study of the safety and efficacy of four different potencies of smoked marijuana in 76 veterans with chronic, treatment-resistant posttraumatic stress disorder (PTSD).” It’s also known as the WeCan Study.

As mentioned earlier in the chapter, a double-blind study uses a placebo—a harmless substance with no drug effect—and makes sure that no one among the participants or investigators knows which substance is the drug being studied and which is the placebo (blinded), eliminating the possibility of some kind of bias. Double blind means that no information about test results is released until after the test. A triple-blind study is a double-blind study in which participant identities and test drug details aren’t given to the statisticians who analyze the test data, another bias-reducing step. Randomized means that participants are given the study drug or placebo randomly, so no one knows who has placebo or test drug. A crossover study refers to a trial in which, over time, participants get a series of different treatments or doses of the study drug. So this trial really covered all the research-standard bases.



**Dr. Sue Sisley** is the study’s principal Investigator at Scottsdale Research Institute in Phoenix, Arizona, and is working with MAPS, whose mission since 1986 has included collecting objective information about the efficacy of cannabis-based treatments for PTSD and other disorders.

The latest study explores whether smoked cannabis can help reduce PTSD symptoms in 76 U.S. military veterans with chronic, treatment-resistant PTSD. Participants have to be veterans, men or women 18 or older, with a diagnosis of PTSD that hasn’t improved

with medication or psychotherapy. The Colorado Department of Public Health and Environment awarded a \$2.1 million grant for the study.

The FDA accepted the research protocol (2011) and sent it to the Department of Health and Human Services (HHS) to be submitted for review to the Drug Enforcement Administration (DEA).

HHS eventually approved a revised protocol (2014) and the National Institute on Drug Abuse produced four cannabis varieties needed for the study (2015). The DEA approved the study site in Phoenix (2016), and in 2017 the study enrolled its first participant. As of October 2018 it was still recruiting (<http://www.wecanstudy.org/>).

According to the study website, “Results from the WeCan Study will help to advance the standard of care for PTSD in veterans, potentially providing avenues for new research and treatment, as well as providing clear, scientifically sound data on the efficacy of cannabis for PTSD.”

Learning more about cannabis for PTSD also will tell researchers and physicians more about using cannabis to treat the related conditions discussed above: stress, anxiety, pain, depression, insomnia and others.

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### **Clinical Trials: Cannabinoids for PTSD**

- Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With PTSD

Here’s the listing for the study mentioned above. The sponsor is MAPS and the official study title is Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Posttraumatic Stress Disorder (PTSD). The study start date was January 2017 and the estimated completion date is January 2019. During the study, each participant will smoke two of the four types of cannabis, up to 1.8 grams per day, for 3 weeks. Participants can smoke their daily 1.8 g cannabis at any time, using as much as they need. After each 3-week cannabis-use period, they will stop smoking cannabis for two weeks, during which no cannabis use will be allowed. Study findings will help researchers better understand the risks and benefits associated with cannabis use among veterans with PTSD, information that can be used to help shared decision-making among people with PTSD and their doctors or therapists. Study details are available at <https://clinicaltrials.gov/ct2/show/NCT02759185>.

- Nabilone in Cannabis Users With PTSD

Researchers at the New York State Psychiatric Institute are studying nabilone (also Cesamet®; synthetic THC) in cannabis users with PTSD (recruiting). The study start date was October 2015 and the estimated completion date is August 2019. The study is seeking 14 participants 21 years old to 45, and the official title is Effects of Nabilone on Trauma-Related Cue Reactivity in Cannabis Users with PTSD. Despite the prevalence of cannabis use among the PTSD population and self-reports that it is used to help cope with PTSD symptoms, the brief summary says, the direct effects of cannabis on PTSD symptomology are unknown. The purpose of this placebo-controlled, within-subject study is to assess the effects of smoked cannabis and orally administered nabilone, a synthetic analog of THC, the primary psychoactive component of cannabis on multiple dimensions of PTSD symptomatology in cannabis smokers with PTSD. Study details are available at <https://clinicaltrials.gov/ct2/show/NCT03251326>.

- Add-on Study on  $\Delta$ 9-THC Treatment for Posttraumatic Stress Disorders

This is an older study, 2009-2013, by the Hadassah Medical Organization in Jerusalem, Israel, to study THC as add-on treatment for PTSD. The 70 study participants were 19 years old to 60 and each had a PTDS diagnosis and was on stable medication for PTSD. In 2014 Roitman and colleagues, among them Dr. Arie Y. Shalev, head of the Department of Psychiatry at Hadassah University Hospital, who was responsible for the study, published preliminary results of 10 outpatients who received 5 mg of THC twice a day as add-on treatment for PTSD. The intervention, the researchers wrote, “caused a statistically significant improvement in global symptom severity, sleep quality, frequency of nightmares and PTSD hyperarousal symptoms.”<sup>20</sup> Study details are available at <https://clinicaltrials.gov/ct2/show/NCT00965809>.

*Keep checking [clinicaltrials.gov](https://clinicaltrials.gov) for the clinical studies that surely will be added over time. Search for the disease name and cannabis and cannabinoids.*

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