

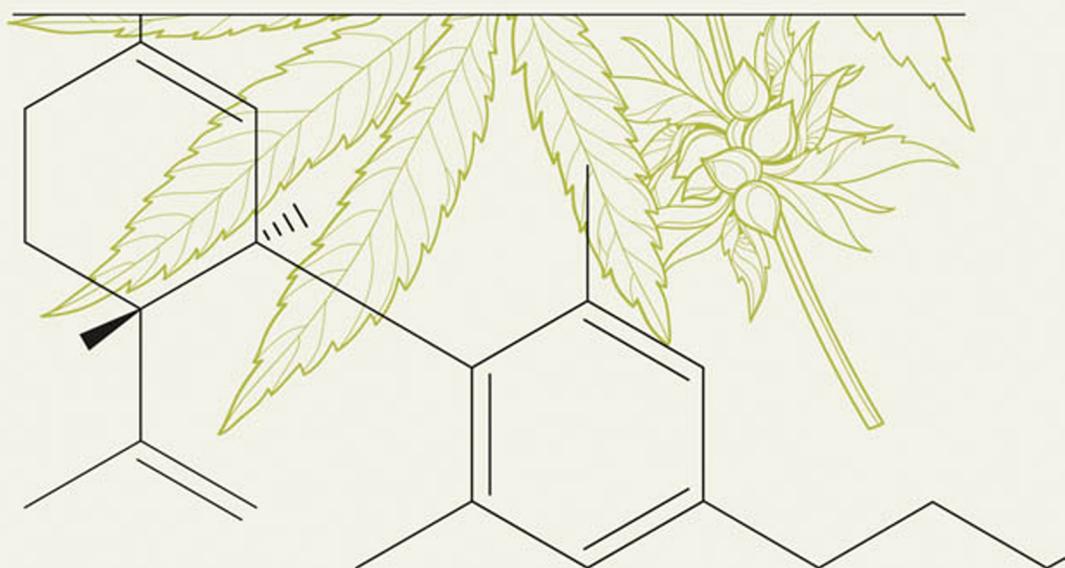


# CBD

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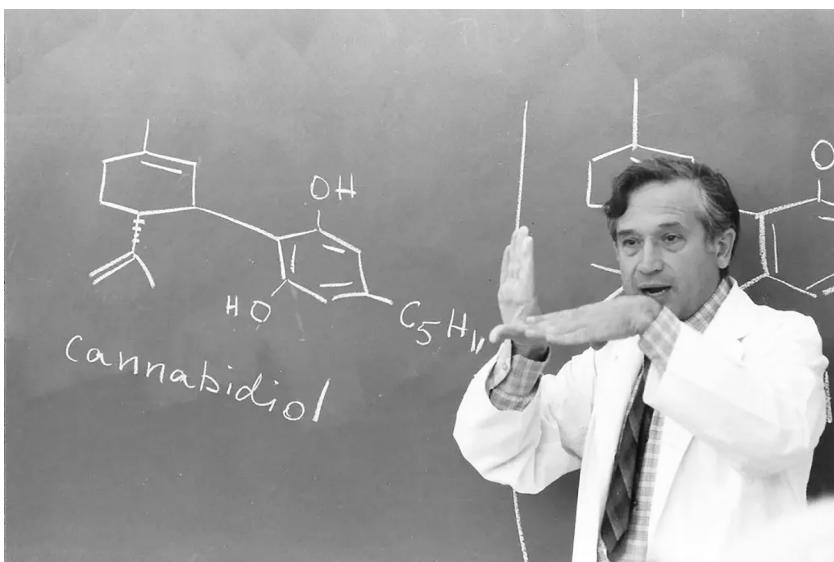
## WHAT DOES THE SCIENCE SAY?

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LINDA A. PARKER, ERIN M. ROCK,  
AND RAPHAEL MECHOULAM

CBD



Raphael Mechoulam in a lecture circa 1964 explaining the structure of cannabidiol in comparison with that of  $\Delta^9$ -Tetrahydrocannabinol (on the blackboard behind him).

# CBD

What Does the Science Say?

Linda A. Parker, Erin M. Rock, and Raphael Mechoulam

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# Preface

The writing of this book has been a labor of love for all three authors, having been drawn together by our keen interest in the science of cannabidiol (CBD). The first paper that Raphael Mechoulam published in the cannabinoid field (among nearly five hundred lifetime publications) was the identification of the structure of the CBD molecule (Mechoulam and Shvo 1963), which allowed its synthesis and an evaluation of its mechanism of action in several biological assays. For the past sixty years, several groups have collaborated with Mechoulam, conducting some of the earliest studies on the potential medicinal benefits of this compound. Among those collaborations was one with Linda Parker's laboratory in Canada, investigating the effects of cannabinoids on nausea, vomiting, anxiety, pain, and addiction in pre-clinical rodent models (see Mechoulam and Parker 2013). Erin Rock joined in this collaboration, first as an undergraduate at Wilfrid Laurier University (Waterloo, Ontario) and then as a graduate master's and PhD student at the University of Guelph, identifying the mechanism of action of the antinausea and antivomiting effects of CBD for her PhD research (Rock et al. 2012). Rock continued as a postdoctoral fellow/research associate with Parker, continuing to unlock the mysteries of CBD and several other cannabinoids using these models.

People have used the cannabis plant for millennia for its medicinal and mind-altering effects. This complex plant contains over 100 plant cannabinoids, including the most well known,  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD). Of the over 100 cannabinoid compounds in the cannabis plant, THC has been identified as essentially the only psychotropic compound, based on research by Raphael Mechoulam's group in Israel and several others in the 1960s and 1970s. CBD, however, is not mind-altering.

Awareness of the potentially beneficial effects of CBD has grown at an astonishing rate in the mind of the general public, with Google Internet searches doubling in frequency every year for the past five years, and it is continuing to accelerate (Leas et al. 2019). Indeed, CBD has become a trendy ingredient in mass market products that make broad and at times unsubstantiated claims of its ability to treat a myriad of symptoms from skin disorders to chronic pain, as well as cosmetic use—and in many cases, without human clinical trial evidence. Many pet owners are also administering CBD for management of conditions such as pain and anxiety without relevant scientific evidence for these indications.

This current “CBD craze” often generalizes to human health on the basis of findings in cells or in preclinical rodent research. However, human clinical trial research has severely lagged behind the basic cellular and preclinical animal research on the beneficial effects of CBD, with the exception of the use of CBD in rare forms of childhood epilepsy. The lack of clinical trial data is surprising, given that over sixty years ago, small-scale human trials for treatment of epilepsy, addiction, and anxiety showed that CBD may be a promising potential treatment option. However, the regulatory rules governing research with cannabis, a Schedule I drug, prohibited large-scale research with humans on the therapeutic potential of CBD. In recent years with countries such as Canada and several US states legalizing cannabis, one would expect that access to CBD has become much more feasible for large-scale human clinical trials. However, at the time of writing

this book, this has not yet been the case. As consumers have increased access to a variety of cannabis products, US and Canadian scientists face the burden of strict regulatory scrutiny (Haney 2020) and have a limited variety of cannabis and CBD to evaluate in trials. Despite these barriers, a current survey of the National Institutes of Health website, [www.clinicaltrials.gov](http://www.clinicaltrials.gov), revealed 276 planned, ongoing, or completed human trials with CBD (the vast majority using oral formulations) for many of the indications that have shown promise in the preclinical research.

It must be emphasized that the standardized, chemically pure CBD available for preclinical research and human clinical trials is not necessarily the consumer CBD available for sale from vendors and the Internet. A 2017 survey (Bonn-Miller, Banks, and Sebree 2017) reported that of eighty-four online CBD and hemp oil products examined, only twenty-six were accurately labeled for CBD and THC content, with CBD often being overlabeled and THC underlabeled, consistent with warnings from the Food and Drug Administration. Buyer beware!

Many drugs used today are natural products or their derivatives. So far, CBD has been approved as a treatment by the US Food and Drug Administration only for some rare forms of childhood epilepsy and seizures associated with tuberous sclerosis complex in patients one year of age or older. In this book, we discuss various aspects of CBD's actions. In many disease states, mostly in animal models, but also some in human studies, positive results have been noted and published. In view of the encouraging animal as well as the limited human clinical data and the relatively low level of toxicity or major side effects, we expect that CBD or, more likely, CBD derivatives with an improved pharmacological profile may be developed as drugs to treat several additional medical conditions in the future.



# 1

## Introduction

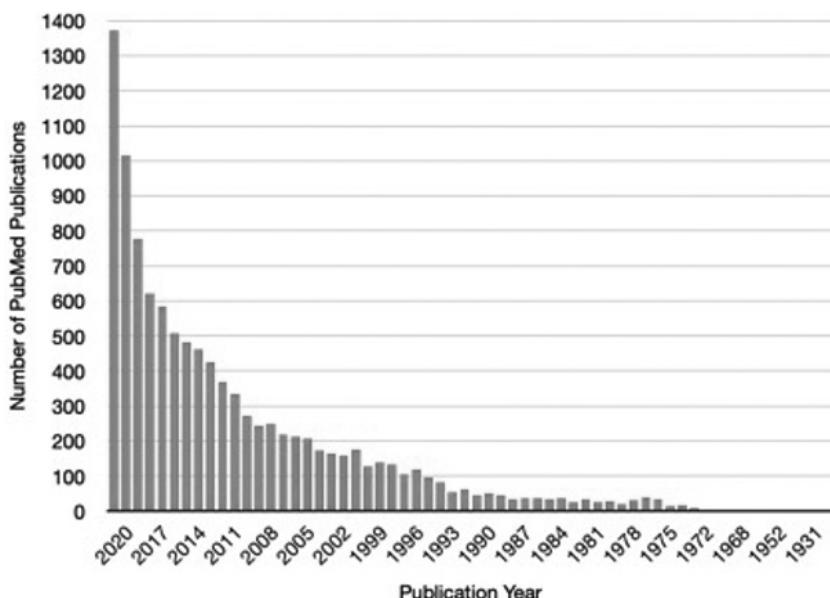
*Cannabis sativa* may be one of the oldest cultivated plants, yet its use has been associated with controversy throughout its long history (Russo, Guy, and Robson 2007). This historical use of cannabis provides clues to the potential treatment for an array of medical syndromes that remain challenging for twenty-first-century medicine. Cannabis has been used for millennia in the making of textiles, for casual recreational purposes, in religious practices, and in medicine, but its use has been associated with legal and societal controversies. In ancient China, cannabis was prescribed for several diseases but was noted to lead to “seeing devils” when taken in excess (Mechoulam et al. 2014)

We now know that the intoxicating effects produced by cannabis use are caused by the compound  $\Delta^9$ -tetrahydrocannabinol (THC), first identified in the 1960s by the young chemists Yechiel Gaoni and Raphael Mechoulam at the Weizmann Institute in Israel at that time (Gaoni and Mechoulam 1964). This discovery allowed scientists around the world to investigate the psychotropic or mind-altering effects of cannabis in the laboratory. The identification of THC led to the surprising discovery of a previously unknown neurochemical system called the endocannabinoid system, with *endo*, meaning

inside, and *cannabinoid*, meaning compound of the cannabis plant. This system, including the cannabis-like compounds that we produce in our body, is now known to be intimately involved in key regulatory functions of human health and disease states. Even if you do not use cannabis, this system is present and always active in your body, constantly working to keep your internal systems in balance. It acts as a switch to return your body to its optimal internal state.

Even before the discovery of THC, another compound found in cannabis, cannabidiol (CBD), had been identified in the 1940s by Roger Adams in the United States and Alexander Todd in the United Kingdom (Adams, Hunt, and Clark 1940; Jacobs and Todd 1940). But no further work on CBD was published until 1963 when Raphael Mechoulam identified its structure (Mechoulam and Shvo 1963). No one reported on the activity or effects of CBD until the early 1970s, except to determine that it had no intoxicating properties. Since then, a great deal of research has been focused on determining the effects of CBD in the body and how it might be having these effects. A review of the journal database program PubMed reveals a dramatically accelerating base of CBD research over the past forty years, with over thirteen hundred research articles on CBD published in 2020 alone. (See figure 1.1 for a visual display of the research articles about CBD published in this database.)

Very early research in the 1970s and 1980s revealed that CBD may alleviate seizures in epileptic patients. Indeed, as reviewed in chapter 4 on epilepsy, cannabis has been historically used for the treatment of epilepsy. Over forty years ago, clinical trials demonstrated that CBD could be administered orally (at high doses) to alleviate seizures in epilepsy patients. This treatment received approval by the Food and Drug Administration (FDA) in 2018 for the treatment of a rare form of epilepsy in children, Dravet syndrome, which has a very high mortality rate and is unaffected by traditional treatments. Beginning in the first year of life, children affected by Dravet syndrome develop a severe brain disorder that results in cognitive,



**Figure 1.1**

Articles published on CBD in the PubMed database over the years.

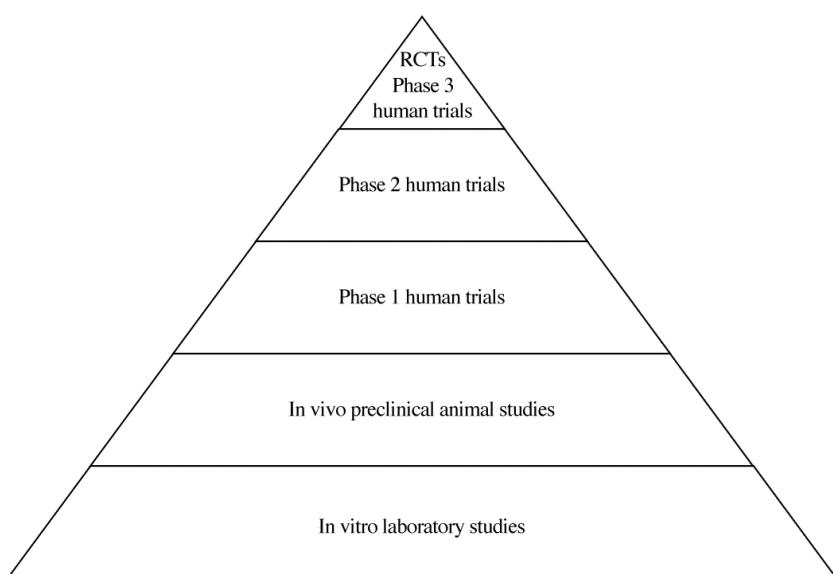
behavioral, and motor impairment. In 2016, research on the treatment of this devastating condition was accelerated by widespread press coverage of anecdotal successes of CBD-rich cannabis in treating Dravet syndrome by Sanjay Gupta, chief medical correspondent for the television channel CNN. These personal success stories inspired physicians to carry out the high-quality randomized clinical trials (RCTs) described in chapter 4 to properly demonstrate the efficacy of CBD treatment for this disorder. However, studies that investigate CBD for other medical conditions are limited in number and often lack scientific rigor, controls, and adequate sample size to be able to draw meaningful scientific conclusions (Britch, Babalonis, and Walsh 2021).

At the same time, we are currently in an era in which CBD is claimed to effectively treat almost any disorder, including anxiety, psychosis, sleep, pain and inflammation, stroke, neurological

diseases, acne, and even cancer. Most of these claims are not based on the results of high-quality human clinical trial data necessary for FDA approval described at the end of this chapter. Our book reviews the scientific evidence for these claims. CBD can be found in everything from “health food drinks,” lotions, and chewable gummy candies to pet products, with the marketing of these products being way ahead of the scientific evidence. Most troubling is the lack of standardization and validation of these CBD products. Many do not contain what is claimed on the label. This is especially problematic for those subject to random drug tests for employment when they incorrectly believe that they are taking only CBD. CBD is also poorly absorbed into the circulatory system when taken orally or rubbed as a lotion on the skin (as reviewed in chapter 2). Understanding the effect of CBD in humans has been greatly affected by government regulations and policies that can make it difficult to conduct the clinical trials that are needed to collect high-quality evidence for CBD’s effects.

The gold standard seal of approval of a drug for the treatment of a medical condition is in its rigorous approval by the FDA. Pure oral CBD (Epidiolex) for rare forms of childhood epilepsy discussed in chapter 4 received FDA approval in 2018. Many drugs begin the FDA approval process, but considerably fewer actually gain approval. Figure 1.2 presents a schematic of the process of FDA approval. Each ascending level represents a more rigorous form of evidence supporting the efficacy of the treatment for a particular indication in humans.

At the base of the pyramid are basic laboratory studies—in vitro studies. In vitro (meaning in the glass) studies are performed with microorganisms, cells, or biological organisms outside the human or animal body. The compound is applied to these organisms or cells, and measures such as molecular changes, toxicity, or binding affinity are taken. With in vitro evidence that a treatment like CBD effectively modifies cellular signals coincident with a specific disease, testing then moves up the pyramid to preclinical in vivo studies with



**Figure 1.2**

Schematic of FDA approval process

animal models of the disease. In vivo (within the living organism) work is done with a whole, living organism; common laboratory species are mice and rats. With appropriate controls in place, these studies can be conducted to infer cause and effect in a specific animal model, such as an animal model of epilepsy. Such studies are scrupulously vetted by institutional animal care committees, in compliance with national and international standards of animal care for laboratory animals to ensure minimal distress for the animal in light of the benefits of the experimental question for human health. These preclinical tests are required before a new treatment can be considered for testing in humans.

Human clinical trials then occur in three phases. Phase 1 trials, the first in humans, involve testing multiple doses of the drug on healthy volunteers for safety and often pharmacokinetic properties (discussed in chapter 2). The doses that are evaluated are usually only a fraction of the dose tested in preclinical trials to ensure safety. The

results of phase 1 studies determine the doses to be tested in later phase trials. Phase 2 involves testing the drug on patients with the indication of interest, such as epilepsy, to assess whether the drug has efficacy against the disease. Phase 1 and often phase 2 trials are open label, meaning the participant and the experimenter (or physician) know which drug is being administered in the trial. That is, there is no control for the expectancy effects of placebos. If the drug is found to work and maintains safety with minimal side effects, it can be tested in phase 3 clinical trials. In phase 3, the drug of interest for an indication is usually compared with the standard-of-care drug. The most rigorous standard for human clinical trials is a double-blind, randomized, controlled trial (RCT), with a randomized group of patients in an experimental group (receiving the drug of interest) and a control group (usually receiving a known standard treatment or placebo). This is called a double-blind study—no one knows who is assigned to which group—and ensures against expectancy effects. Participants, caregivers, outcome assessors, and analysts are all candidates for being blinded. To assess whether a drug is beneficial, a comparison between the experimental group and the control group is examined for the outcome(s) of interest. In the approval process, the FDA evaluates a drug's clinical benefit and its risk information, with continued monitoring after approval.

This is the process that the pure oral form of CBD, Epidiolex, went through in order to be prescribed by physicians to treat patients with Dravet syndrome and Lennox-Gastaut syndrome, two rare forms of childhood epilepsy. The FDA has since also approved Epidiolex for the treatment of seizures associated with tuberous sclerosis complex in patients one year of age or older. This means that the FDA has concluded that it is safe and effective for this intended use. Following its approval in 2018, Epidiolex was designated as schedule 5 (the least restrictive category for medications with low abuse potential) and has subsequently been descheduled (meaning that it is no longer a controlled substance under the federal Controlled Substances Act).

## Legal Status of Cannabis and Cannabis-Derived Products in the United States

Over the past two decades, the legal status of cannabis in the United States has substantially changed. Prior to 1996, cannabis was not legalized for use for any purpose in the United States. California became the first state to legalize cannabis use for medical purposes. As of publication of this book, thirty-three US states have legalized adult use of cannabis for medical purposes. Eleven states have legalized its adult recreational use. In the November 2020 US election, four additional states voted to enact legalization of recreational use.

Federally, cannabis currently remains classified as a Schedule I substance in the United States, which means that it has no current acceptable medical use and has a high abuse potential. Access to a Schedule I substance is highly controlled for researchers, and the cannabis that is authorized is often not representative of the cannabis products that are commercially available. However, the legal status is likely to change from the time of publication of this book, with the US Congress currently discussing federal legalization of cannabis.

The legal status of CBD has been intricately linked with that of cannabis. The Agriculture Improvement Act of 2018 (also known as the Farm Bill) removed hemp (defined as plant material having less than 0.3 percent THC) from the list of controlled substances in the Controlled Substance Act, meaning that if CBD is derived from hemp, it does not fall within the jurisdiction of the US Drug Enforcement Administration (DEA). This means that any CBD derived from cannabis plants that contain more than 0.3 percent THC remains Schedule I. The 2018 Farm Bill preserves the FDA's regulation of products derived from cannabis, including CBD. Under these regulations, because CBD is listed as an active ingredient in an approved pharmaceutical drug, it cannot be added to food products and dietary supplements. In the eyes of the FDA, this would be akin to your favorite barista adding acetaminophen to your morning espresso, which is not

permitted according to federal law. Consumers are rightly confused because CBD is commercially available to them in many products.

Clinical studies using CBD must still be approved by the FDA. To protect human participants, the FDA regulates how the cannabis product is cultivated, manufactured, and tested. These requirements have made it difficult to conduct the properly controlled RCTs that are needed. Therefore, it is ironic that as consumers have greater access to CBD, US scientists face greater regulatory scrutiny, including federal and state Schedule I licenses, and extensive regulations on storing and dispensing Schedule I drugs (Haney 2020). FDA regulations are appropriately cautious about what scientists can test in patients, and none of the CBD products that are available online or in dispensaries have gone through the safety and manufacturing procedures necessary for FDA approval. How can researchers proceed under such strict regulations? It has been suggested (Haney 2020) that one step to addressing some of the barriers to cannabinoid researchers is to give scientists a Schedule I exemption in order to increase the number of RCTs to provide empirical evidence of efficacy of cannabinoid compounds. As well, policy-oriented and regulatory research to guide rules about advertising, labeling, and evaluating the effect of different formulations of cannabis products is needed.

## The Cannabis Act in Canada

With the Cannabis Act, Canada legalized cannabis for recreational use in 2018, leaving researchers hopeful that Canada could become a key player in cannabis RCTs. With the act, patients authorized by their health care provider to use cannabis for medical purposes were authorized to buy product from a federally licensed seller or register to produce their own medical cannabis (or designate someone to produce it for them).

Unfortunately, despite the urgent need for researchers to conduct RCTs on cannabis products for medical purposes, the boom in Canadian cannabis research that was expected did not happen. This is mostly because of how clinical trials have been regulated by Health Canada. The barriers facing cannabis research include research funding prioritizing intervention research and the onerous processes involved in obtaining research licenses from Health Canada. At this time, most medical cannabis products that are available to purchase cannot be used in research trials because clinical trial products have more stringent manufacturing practice standards. This means it is not possible to conduct RCTs on the medical cannabis products that are currently being used by Canadians. Canada's opportunity to be a leader in medical cannabis research has so far been lost.

The barriers hindering researchers from conducting RCTs have affected cannabis research in general, and certainly research on its constituent, CBD. In each chapter of this book, for each indication discussed, we review the levels of evidence available for CBD from *in vitro* to RCTs.



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