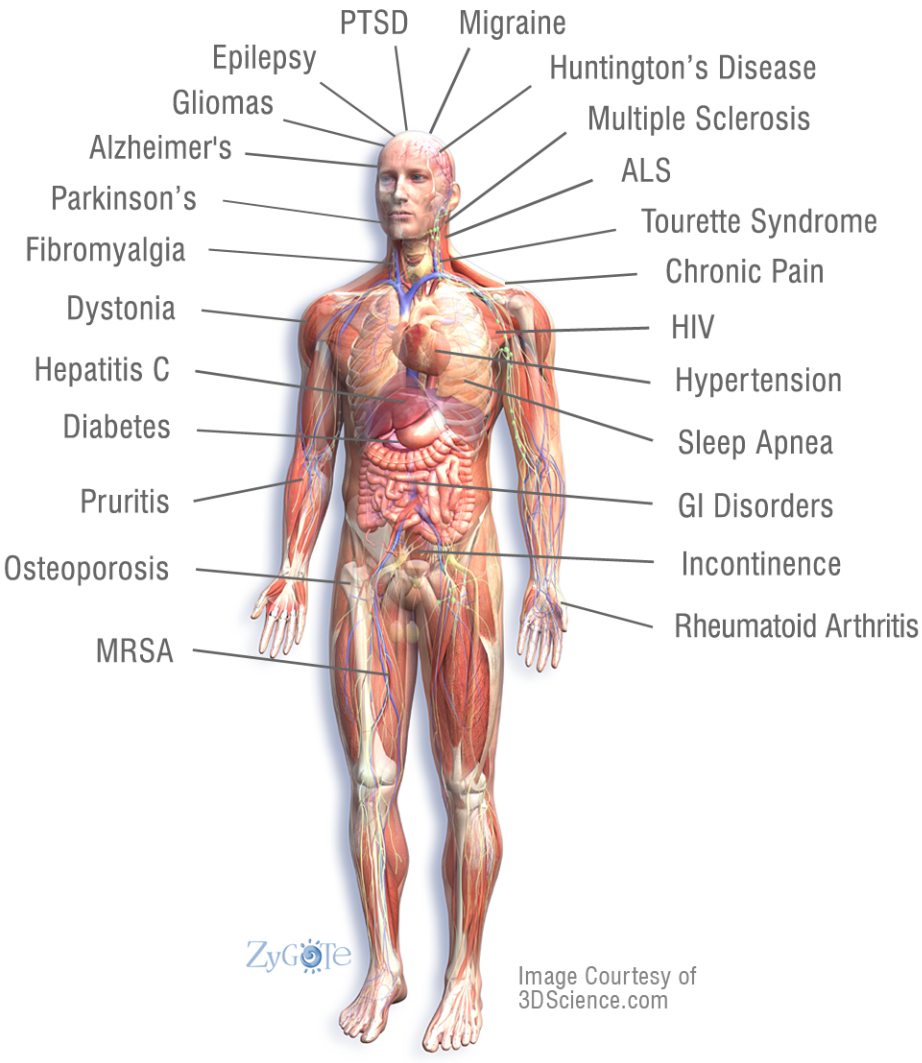
Emerging Clinical Applications For Cannabis and Cannabinoids

A Review of the Recent Scientific Literature

Expanded and Revised Eighth Edition

By Paul Armentano, NORML Deputy Director



With Greg Carter, M.D., Dustin Sulak, D.O., and Estelle Toby Goldstein, M.D.

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Introduction

Humans have cultivated and consumed the flowering tops of the female cannabis plant, colloquially known as marijuana, since virtually the beginning of recorded history. Cannabis-based textiles dating to 7,000 B.C.E have been recovered in northern China, and the plant's use as a medicinal and mood altering agent date back nearly as far. In 2008, archeologists in Central Asia discovered over two pounds of cannabis in the 2,700-year-old grave of an ancient shaman. After scientists conducted extensive testing on the material's potency, they affirmed, "[T]he most probable conclusion ... is that [ancient] culture[s] cultivated cannabis for pharmaceutical, psychoactive, and divinatory purposes."

Modern cultures continue to indulge in the consumption of cannabis for these same purposes, despite a decades-long, virtual worldwide ban on the plant's cultivation and use. In the United States, federal prohibitions outlawing cannabis' recreational, industrial, and therapeutic use were first imposed by Congress under the Marihuana Tax Act of 1937 and then later reaffirmed by federal lawmakers' decision to classify the cannabis plant -- as well as all of its organic chemical compounds (known as cannabinoids) -- as a Schedule I substance under the Controlled Substances Act of 1970. This classification, which categorizes the plant alongside heroin, defines cannabis and its dozens of distinct cannabinoids as possessing 'a high potential for abuse, ... no currently accepted medical use, ... [and] a lack of accepted safety for the use of the drug ... under medical supervision.' By contrast, cocaine and methamphetamine -- which remain illicit for recreational use but may be consumed under a doctor's supervision -- are classified as Schedule II drugs. Both alcohol and tobacco are unscheduled.

CHALLENGING CANNABIS' SCHEDULE I STATUS

Recent legal and administrative efforts to amend marijuana's scheduling under federal law have been unsuccessful. In July 2011, the Obama Administration rebuffed an eight-year old administrative inquiry seeking to reassess cannabis' Schedule I status, opining: "[T]here are no adequate and well-controlled studies proving (marijuana's) efficacy; the drug is not accepted by qualified experts. ... At this time, the known risks of marijuana use have not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy."

More recently, in April 2015, a federal judge upheld the constitutionality of cannabis' Schedule I classification in a case argued by members of the NORML Legal Committee. NORML's suit called for cannabis to be removed from the CSA so that states could regulate marijuana policy free from undue federal interference. Following one week of evidentiary hearings, the judge ruled that the federal law ought to remain in place as long as there remains any dispute among experts as to cannabis' safety and efficacy.

Most recently, in 2016, the US Drug Enforcement Administration rejected a pair of administrative petitions that sought to initiate rulemaking proceedings to reschedule marijuana under federal law. The agency opined, "[T]here is no substantial evidence that marijuana should be removed from Schedule I."

To the contrary, there exists ample scientific and empirical evidence to rebut the federal government's contention. Despite the nearly century-long prohibition of the plant, cannabis is nonetheless one of the most investigated therapeutically active substances in history. To date, there are more than 26,000 published studies or reviews in the scientific literature referencing the cannabis plant and its cannabinoids, according to a keyword search on the search engine PubMed Central, the US government repository for peer-reviewed scientific research, with over 1,000 new studies published annually. While much of the renewed interest in cannabinoid therapeutics is a result of the discovery of the endocannabinoid regulatory system (which is described in detail later in this publication), much of this increased attention is also due to the growing body of testimonials from medical cannabis patients and their physicians, as well as from state-level changes to the plant's legal status.

The scientific conclusions of the majority of modern research directly conflicts with the federal government's stance that cannabis is a highly dangerous substance worthy of absolute criminalization. For example, a summary of FDA-approved randomized clinical trials evaluating the safety and efficacy of whole-plant cannabis in various patient populations finds: "Evidence is accumulating that cannabinoids may be useful medicine for certain indications. ... The classification of marijuana as a Schedule I drug as well as the continuing controversy as to whether or not cannabis is of medical value are obstacles to medical progress in this area. Based on evidence currently available the Schedule I classification is not tenable; it is not accurate that cannabis has no medical value, or that information on safety is lacking."

More recently, a 2017 review of over 10,000 recent studies by the National Academies of Sciences, Engineering, and Medicine concluded that "conclusive or substantial evidence" exists in support of the clinical use of cannabis for the treatment of chronic pain and other conditions.

To date, over 140 gold-standard clinical trials exist examining the safety and efficacy of cannabis or individual cannabinoids in some 8,000 patients. By contrast, many FDA-approved drugs are subject to far fewer clinical trials involving far fewer subjects prior to market approval. In fact, according to a 2014 review paper published in the *Journal of the American Medical Association*, the median number of pivotal trials performed prior to FDA drug approval is two, and over one-third of newly approved pharmaceuticals are brought to market on the basis of only a single pivotal trial.

THE SHIFTING FOCUS OF CANNABIS RESEARCH

As clinical research into the therapeutic value of cannabinoids has proliferated so too has investigators' understanding of cannabis' remarkable capacity to combat disease. Whereas researchers in the 1970s, 80s, and 90s primarily assessed marijuana's ability to temporarily alleviate various disease symptoms -- such as the nausea associated with cancer chemotherapy -- scientists today are exploring the potential role of cannabinoids to modulate disease.

For example, scientists are investigating cannabinoids' capacity to moderate autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, as well as their role

in the treatment of neurological disorders such as Alzheimer's disease and amyotrophic lateral sclerosis (a.k.a. Lou Gehrig's disease).

Investigators are also studying the anti-cancer activities of cannabis, as a growing body of preclinical data concludes that cannabinoids can reduce the spread of specific cancer cells via apoptosis (programmed cell death) and by the inhibition of angiogenesis (the formation of new blood vessels).

Researchers are also exploring the use of cannabis as a harm reduction alternative for chronic pain patients. According to the findings of a 2015 study published by the National Bureau of Economic Research, a non-partisan think-tank, "[S]tates permitting medical marijuana dispensaries experience a relative decrease in both opioid addictions and opioid overdose deaths compared to states that do not." The NBER findings are similar to those published in 2014 in the *Journal of the American Medical Association (JAMA) Internal Medicine* which reported that the enactment of statewide medicinal marijuana laws is associated with significantly lower state-level opioid overdose mortality rates. "States with medical cannabis laws had a 24.8 percent lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws," researchers concluded. Specifically, they determined that overdose deaths from opioids decreased by an average of 20 percent one year after the law's implementation, 25 percent by two years, and up to 33 percent by years five and six. (For a comprehensive summary of relevant studies finding that legal cannabis access is associated with decreases in opioid use, abuse, hospitalization, and mortality, please see NORML's fact-sheet, Relationship Between Marijuana and Opioids.)

Arguably, these recent discoveries represent far broader and more significant applications for cannabinoid therapeutics than many researchers could have imagined some thirty or even twenty years ago.

THE SAFETY PROFILE OF MEDICAL CANNABIS

Cannabinoids possess a remarkable safety record, particularly when compared to conventional prescription drugs. Most significantly, the consumption of marijuana -- regardless of quantity or potency -- cannot induce a fatal overdose. States a World Health Organization review paper, "There are no recorded cases of overdose fatalities attributed to cannabis, and the estimated lethal dose for humans extrapolated from animal studies is so high that it cannot be achieved by ... users."

The use of cannabis for therapeutic purposes is also rarely associated with significant adverse side effects. A prominent review of clinical trial data "did not find a higher incidence rate of serious adverse events associated with medical cannabinoid use" compared to non-using controls over a four decade period. A more recent review of the relevant literature concludes that among the average adult user, the health risks associated with marijuana "are no more likely to be dangerous" than many other behaviors or activities, including the consumption of acetaminophen (the pain relieving ingredient in Tylenol).

That said, cannabis should not be viewed as a 'harmless' substance. Its active constituents may produce a variety of physiological and mood-altering effects. As a result, there may be some

populations that may be vulnerable to increased risks from the use of cannabis, such as adolescents, pregnant or nursing mothers, and patients who have a family history of psychiatric illness or who possess a clinical high risk for developing a psychotic disorder. Patients with a history of cardiovascular disorders, heart disease or stroke may also be at an elevated risk of experiencing adverse side effects from marijuana, particularly smoked cannabis. As with any medication, patients should consult thoroughly with their physician before deciding whether the medical use of cannabis is safe and appropriate.

HOW TO USE THIS REPORT

As states continue to approve legislation enabling the physician-supervised use of medical marijuana, more patients with varying disease types are exploring the use of therapeutic cannabis. Many of these patients and their physicians are now discussing this issue for the first time and are seeking guidance on whether the therapeutic use of cannabis may or may not be advisable. This report seeks to provide this guidance by highlighting some of the more relevant, recently published scientific research (2000-2017) on the therapeutic potential of cannabis and cannabinoids for a variety of clinical indications.

In some of these cases, modern science is now affirming longtime anecdotal reports of medical cannabis users (e.g., the use of cannabis to alleviate GI disorders). In other cases, this research is highlighting entirely new potential clinical utilities for cannabinoids (e.g., the use of cannabinoids to modify the progression of diabetes).

For patients and their physicians, this report can serve as a primer for those who are considering using or recommending medical cannabis. For others, this report can serve as an introduction to the broad range of emerging clinical applications for cannabis and its various compounds.

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Foreword

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Marijuana is a colloquial term used to refer to the dried flowers of the female *Cannabis Sativa* and *Cannabis Indica* plants. Marijuana, or cannabis, as it is more appropriately called, has been part of humanity's medicine chest for almost as long as history has been recorded.

All forms of cannabis plants are quite complex, containing over 400 chemicals. Approximately 60 of these chemicals are classified as cannabinoids. Among the most psychoactive of the cannabinoids is delta-9-tetrahydrocannabinol (THC), the active ingredient in the prescription medications dronabinol (Marinol) and naboline (Cesamet). Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which are non-psychoactive but possess distinct pharmacological effects.

Cannabis was formally introduced to the United States Pharmacopoeia (USP) in 1854, though written references regarding the plant's therapeutic use date back as far as 2800 B.C. By 1900, cannabis was the third leading active ingredient, behind alcohol and opiates, in patent medicines for sale in America. However, following the Mexican Revolution of 1910, Mexican immigrants flooded into the United States, introducing to American culture the recreational use of marijuana. Anti-drug campaigners warned against the encroaching, so-called "Marijuana Menace," and alleged that the drug's use was responsible for a wave of serious, violent criminal activity. In 1937, after testimony from Harry Anslinger -- a strong opponent of marijuana and head of the Federal Bureau of Narcotics in the 1930s -- and against the advice of the American Medical Association, the Marijuana Tax Act was pushed through Congress, effectively outlawing all possession and use of the drug.

At the time of the law's passage, there were no fewer than 28 patented medicines containing cannabis available in American drug stores with a physician's prescription.

These cannabis-based medicines were produced by reputable drug companies like Squibb, Merck, and Eli Lily, and were used safely by tens of thousands of American citizens. The enactment of the Marijuana Tax Act abruptly ended the production and use of medical cannabis in the United States, and by 1942 cannabis was officially removed from the *Physician's Desk Reference*.

Fortunately, over the past few decades there has been a significant rebirth of interest in the viable medical uses of cannabis. Much of the renewed interest in cannabis as a medicine lies not only in the drug's effectiveness, but also in its remarkably low toxicity. Lethal doses in humans have not been described. This degree of safety is very rare among modern medicines, including most over-the-counter medications. As a result, the National Institutes of Health (NIH), the National Academy of

Sciences Institute of Medicine, and even the US Food and Drug Administration have all issued statements calling for further investigation into the therapeutic use of cannabis and cannabinoids.

The discovery of an endogenous cannabinoid system, with specific receptors and ligands, has progressed our understanding of the therapeutic actions of cannabis from folklore to valid science. It now appears that the cannabinoid system evolved with our species and is intricately involved in normal human physiology -- specifically in the control of movement, pain, reproduction, memory, and appetite, among other biological functions. In addition, the prevalence of cannabinoid receptors in the brain and peripheral tissues suggests that the cannabinoid system represents a previously unrecognized ubiquitous network in the nervous system.

Cannabinoid receptor sites are now known to exist in the nervous systems of all animals more advanced than hydra and mollusks. This is a result of at least 500 million years of evolution. The human body's neurological, circulatory, endocrine, digestive, and musculoskeletal systems have now all been shown to possess cannabinoid receptor sites. Indeed, even cartilage tissue has cannabinoid receptors, which makes cannabis a prime therapeutic agent to treat osteoarthritis. Cannabinoids have been shown to produce an anti-inflammatory effect by inhibiting the production and action of tumor necrosis factor (TNF) and other acute phase cytokines, which also makes them ideal compounds to treat the autoimmune forms of arthritis. It is now suggested by some researchers that these widely spread cannabinoid receptor systems are the mechanisms by which the body maintains homeostasis (the regulation of cell function), allowing the body's tissues to communicate with one another in this intricate cellular dance we call "life." With this knowledge of the widespread action of cannabinoids within all these bodily systems, it becomes much easier to conceptualize how the various forms of cannabinoids might have a potentially therapeutic effect on diseases ranging from osteoarthritis to amyotrophic lateral sclerosis (ALS).

Another one of the exciting therapeutic areas that cannabis may impact is chronic pain. Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a manner similar to, but pharmacologically distinct from, that of morphine. This analgesic effect is also exerted by some endogenous cannabinoids (anandamide) and synthetic cannabinoids (methanandamide). Ideally, cannabinoids could be used alone or in conjunction with opioids to treat people with chronic pain, improve their quality of life and allow them to return to being productive citizens.

When discussing the therapeutic use of cannabis and cannabinoids, opponents inevitably respond that patients should not smoke their medicine. Patients no longer have to. Medical cannabis patients who desire the rapid onset of action associated with inhalation, but who are concerned about the potential harms of noxious smoke eliminate their intake of carcinogenic compounds by engaging in vaporization rather than smoking. Cannabis vaporization limits respiratory toxins by heating cannabis to a temperature where cannabinoid vapors form (typically around 180-190 degrees Celsius), but below the point of combustion where noxious smoke and associated toxins (e.g., carcinogenic hydrocarbons) are produced (near 230 degrees Celsius). This eliminates the inhalation of any particulate matter and removes the health hazards of smoking. In clinical trials, vaporization has been shown to safely and effectively deliver pharmacologically active, aerosolized cannabinoids

deeply into the lungs, where the rich vascular bed will rapidly deliver them to tissues throughout the body.

The following report summarizes the most recently published scientific research on the therapeutic use of cannabis and cannabinoids for more than a dozen diseases, including Alzheimer's, amyotrophic lateral sclerosis, diabetes, hepatitis C, multiple sclerosis, rheumatoid arthritis, and Tourette syndrome. It is my hope that readers of this report will come away with a fair and balanced view of cannabis -- a view that is substantiated by scientific studies and not by anecdotal opinion or paranoia. Cannabis is neither a miracle compound nor the answer to everyone's ills. However, it does appear to have remarkable therapeutic benefits that are there for the taking if the governmental barriers for more intensive scientific study are removed.

The cannabis plant does not warrant the tremendous legal and societal commotion that has occurred over it. Over the past 40 years, the United States has spent billions in an effort to stem the use of illicit drugs, particularly marijuana, with limited success. Many very ill people have had to fight long court battles to defend themselves for the use of a compound that has helped them. Rational minds need to take over the war on drugs, separating myth from fact, right from wrong, and responsible medical use from other less compelling behavior.

The medical marijuana user should not be considered a criminal in any state. Most major medical groups, including the Institute of Medicine, agree that cannabis is a compound with significant therapeutic potential whose "adverse effects ... are within the range of effects tolerated for other medications." Over three decades ago, the Drug Enforcement Administration (DEA) studied the medical properties of cannabis. After considerable study, DEA Administrative Law Judge Francis L. Young concluded: "The evidence clearly shows that marijuana is capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision. ... It would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance."

Despite this conclusion, over a decade later the DEA and the rest of the federal government persist in their policy of total prohibition. Nevertheless, the scientific process continues to evaluate the therapeutic effects of cannabis through ongoing research and assessment of available data. With regard to the medical use of cannabis, our legal system should take a similar approach, using science and logic as the basis of policy making rather than relying on political rhetoric and false perceptions regarding the alleged harmful effects of recreational marijuana use.

Introduction to the Endocannabinoid System

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As you read this review of the scientific literature regarding the therapeutic effects of cannabis and cannabinoids, one thing will become quickly evident: cannabis has a profound influence on the human body. This one herb and its variety of therapeutic compounds seem to affect every aspect of our bodies and minds. How is this possible?

At our integrative medical clinics in Maine and Massachusetts, my colleagues and I treat over 18,000 patients with a huge diversity of diseases and symptoms. In one day I might see cancer, Crohn's disease, epilepsy, chronic pain, multiple sclerosis, insomnia, Tourette syndrome and eczema, just to name a few. All of these conditions have different causes, different physiologic states, and vastly different symptoms. The patients are old and young. Some are undergoing conventional therapy. Others are on a decidedly alternative path. Yet despite their differences, almost all of my patients would agree on one point: cannabis helps their condition.

As a physician, I am naturally wary of any medicine that purports to cure-all. Panaceas, snake-oil remedies, and expensive fads often come and go, with big claims but little scientific or clinical evidence to support their efficacy. As I explore the therapeutic potential of cannabis, however, I find no lack of evidence. In fact, I find an explosion of scientific research on the therapeutic potential of cannabis, more evidence than one can find on some of the most widely used therapies of conventional medicine.

At the time of this writing (February 2015), a PubMed search for scientific journal articles published in the last 20 years containing the word "cannabis" revealed 8,637 results. Add the word "cannabinoid," and the results increase to 20,991 articles. That's an average of more than two scientific publications per day over the last 20 years! These numbers not only illustrate the present scientific interest and financial investment in understanding more about cannabis and its components, but they also emphasize the need for high quality reviews and summaries such as the document you are about to read.

How can one herb help so many different conditions? How can it provide both palliative and curative actions? How can it be so safe while offering such powerful effects? The search to answer these questions has led scientists to the discovery of a previously unknown physiologic system, a central component of the health and healing of every human and almost every animal: the endocannabinoid system.

WHAT IS THE ENDOCANNABINOID SYSTEM?

The endogenous cannabinoid system, named after the plant that led to its discovery, is perhaps the most important physiologic system involved in establishing and maintaining human health. Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells. In each tissue, the cannabinoid system performs different tasks, but the goal is always the same: homeostasis, the maintenance of a stable internal environment despite fluctuations in the external environment.

Cannabinoids promote homeostasis at every level of biological life, from the sub-cellular, to the organism, and perhaps to the community and beyond. Here's one example: autophagy, a process in which a cell sequesters part of its contents to be self-digested and recycled, is mediated by the cannabinoid system. While this process keeps normal cells alive, allowing them to maintain a balance between the synthesis, degradation, and subsequent recycling of cellular products, it has a deadly effect on malignant tumor cells, causing them to consume themselves in a programmed cellular suicide. The death of cancer cells, of course, promotes homeostasis and survival at the level of the entire organism.

Endocannabinoids and cannabinoids are also found at the intersection of the body's various systems, allowing communication and coordination between different cell types. At the site of an injury, for example, cannabinoids can be found decreasing the release of activators and sensitizers from the injured tissue, stabilizing the nerve cell to prevent excessive firing, and calming nearby immune cells to prevent release of pro-inflammatory substances. Three different mechanisms of action on three different cell types for a single purpose: minimize the pain and damage caused by the injury.

The endocannabinoid system, with its complex actions in our immune system, nervous system, and all of the body's organs, is literally a bridge between body and mind. By understanding this system we begin to see a mechanism that explains how states of consciousness can promote health or disease.

In addition to regulating our internal and cellular homeostasis, cannabinoids influence a person's relationship with the external environment. Socially, the administration of cannabinoids clearly alters human behavior, often promoting sharing, humor, and creativity. By mediating neurogenesis, neuronal plasticity, and learning, cannabinoids may directly influence a person's open-mindedness and ability to move beyond limiting patterns of thought and behavior from past situations. Reformatting these old patterns is an essential part of health in our quickly changing environment.

WHAT ARE CANNABINOID RECEPTORS?

Sea squirts, tiny nematodes, and all vertebrate species share the endocannabinoid system as an essential part of life and adaptation to environmental changes. By comparing the genetics of cannabinoid receptors in different species, scientists estimate that the endocannabinoid system evolved in primitive animals over 600 million years ago.

While it may seem we know a lot about cannabinoids, the estimated twenty thousand scientific articles have just begun to shed light on the subject. Large gaps likely exist in our current understanding, and the complexity of interactions between various cannabinoids, cell types, systems and individual organisms challenges scientists to think about physiology and health in new ways. The following brief overview summarizes what we do know.

Cannabinoid receptors are present throughout the body, embedded in cell membranes, and are believed to be more numerous than any other receptor system. When cannabinoid receptors are stimulated, a variety of physiologic processes ensue. Researchers have identified two cannabinoid receptors: CB1, predominantly present in the nervous system, connective tissues, gonads, glands, and organs; and CB2, predominantly found in the immune system and its associated structures. Many tissues contain both CB1 and CB2 receptors, each linked to a different action. Researchers speculate there may be a third cannabinoid receptor waiting to be discovered.

Endocannabinoids are the substances our bodies naturally make to stimulate these receptors. The two most well understood of these molecules are called anandamide and 2-arachidonoylglycerol (2-AG). They are synthesized on-demand from cell membrane arachidonic acid derivatives, have a local effect and short half-life before being degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).

Phytocannabinoids are plant substances that stimulate cannabinoid receptors. Delta-9-tetrahydrocannabinol, or THC, is the most psychoactive and certainly the most famous of these substances, but other cannabinoids such as cannabidiol (CBD) and cannabinol (CBN) are gaining the interest of researchers due to a variety of healing properties. Most phytocannabinoids have been isolated from *cannabis sativa*, but other medical herbs, such as *echinacea purpura*, have been found to contain non-psychoactive cannabinoids as well.

Interestingly, the cannabis plant also uses THC and other cannabinoids to promote its own health and prevent disease. Cannabinoids have antioxidant properties that protect the leaves and flowering structures from ultraviolet radiation - cannabinoids neutralize the harmful free radicals generated by UV rays, protecting the cells. In humans, free radicals cause aging, cancer, and impaired healing. Antioxidants found in plants have long been promoted as natural supplements to prevent free radical harm.

Laboratories can also produce cannabinoids. Synthetic THC, marketed as dronabinol (Marinol), and nabilone (Cesamet), a THC analog, are both FDA approved drugs for the treatment of severe nausea and wasting syndrome. Some clinicians have found them helpful in the off-label treatment of chronic pain, migraine, and other serious conditions. Many other synthetic cannabinoids are used in animal research, and some have potency up to 600 times that of THC.

CANNABIS, THE ENDOCANNABINOID SYSTEM, AND GOOD HEALTH

As we continue to sort through the emerging science of cannabis and cannabinoids, one thing remains clear: a functional cannabinoid system is essential for health. From embryonic implantation

on the wall of our mother's uterus, to nursing and growth, to responding to injuries, endocannabinoids help us survive in a quickly changing and increasingly hostile environment. As I realized this, I began to wonder: can an individual enhance his/her cannabinoid system by taking supplemental cannabis? Beyond treating symptoms, beyond even curing disease, can cannabis help us prevent disease and promote health by stimulating an ancient system that is hard-wired into all of us?

I now believe the answer is yes. Research has shown that small doses of cannabinoids from cannabis can signal the body to make more endocannabinoids and build more cannabinoid receptors. This is why many first-time cannabis users don't feel an effect, but by their second or third time using the herb they have built more cannabinoid receptors and are ready to respond. More receptors increase a person's sensitivity to cannabinoids; smaller doses have larger effects, and the individual has an enhanced baseline of endocannabinoid activity. I believe that small, regular doses of cannabis might act as a tonic to our most central physiologic healing system.

Many physicians cringe at the thought of recommending a botanical substance, and are outright mortified by the idea of smoking a medicine. Our medical system is more comfortable with single, isolated substances that can be swallowed or injected. Unfortunately, this model significantly limits the therapeutic potential of cannabinoids.

Unlike synthetic derivatives, herbal cannabis may contain over one hundred different cannabinoids, including THC, which all work synergistically to produce better medical effects and less side effects than THC alone. While cannabis is safe and works well when smoked, many patients prefer to avoid respiratory irritation and instead use a vaporizer, cannabis tincture, or topical salve. Scientific inquiry and patient testimonials both indicate that herbal cannabis has superior medical qualities to synthetic cannabinoids.

In 1902 Thomas Edison said, "There were never so many able, active minds at work on the problems of disease as now, and all their discoveries are tending toward the simple truth that you can't improve on nature." Cannabinoid research has proven this statement is still valid.

So, is it possible that medical cannabis could be the most useful remedy to treat the widest variety of human diseases and conditions, a component of preventative healthcare, and an adaptive support in our increasingly toxic, carcinogenic environment? Yes. This was well known to the indigenous medical systems of ancient India, China, and Tibet, and as you will find in this report, is becoming increasingly well known by Western science. Of course, we need more human-based research studying the effectiveness of cannabis, but the evidence base is already large and growing constantly, despite the DEA's best efforts to discourage cannabis-related research.

Does your doctor understand the benefit of medical cannabis? Can he or she advise you in the proper indications, dosage, and route of administration? Likely not. Despite the two largest U.S. physician associations (American Medical Association and American College of Physicians) calling for more research, the U.S. Congress prohibiting federal interference in states' medical cannabis

programs, a 5,000 year history of safe therapeutic use, and a huge amount of published research, most doctors know little or nothing about medical cannabis.

This is changing, in part because the public is demanding it. People want safe, natural and inexpensive treatments that stimulate our bodies' ability to self-heal and help our population improve its quality of life. Medical cannabis is one such solution. This summary is an excellent tool for spreading the knowledge and helping to educate patients and healthcare providers on the scientific evidence behind the medical use of cannabis and cannabinoids.

Why I Recommend Medical Cannabis

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Why would a highly credentialed MD psychopharmacologist, board-certified psychiatrist and former FDA clinical trials primary investigator become a champion of medicinal cannabis?

Especially considering I have never used it.

I'll tell you why.

For the past two years, I have been working to bring honest, scientific and medical information to those who really need medical cannabis. I blog regularly at betterbrainsonline.com and have done so for several years. I consider myself not only an educator, but a watchdog and public guardian, a whistle-blower and an activist for public health and consumer protection.

Some have questioned my motivation for swimming outside the mainstream of the medical establishment. My motives are selfish – I want to be true to myself, sleep well at night, and be able to look at myself in the mirror each morning.

I originally wanted to be a brain surgeon and did my internship and residencies in that field, also picking up a fellowship in neurology. After a stint in the US Army, I changed specialties to psychiatry with a fellowship in psychopharmacology.

Immediately following my education, I became a junior professor at the University of Kansas and later the University of Oklahoma. In those institutions, I performed many clinical trials during the development phases of such familiar drugs as Prozac and Zyprexa.

I picked up the "Renegade Doctor" sobriquet when I broke with academia -- not only disillusioned by the back-stabbing politics of publish-or-perish, but also with the restrictions on research imposed by Big Pharma. I had always been aware of the pervasive influence of the drug companies from my days in medical school and in private practice. The government-pharma connections have gradually become public knowledge (although not to the full extent possible, as the public won't believe it all), but my personal break with traditional medicine came after a catastrophic illness.

In 1999, I found myself dying of a congenital condition that traditional medicine misdiagnosed and mistreated. I had to cure myself to survive. I wrote a book about this struggle, but for the sake of brevity, let's just say I had to broaden my horizons beyond the medical establishment if I wanted to live.

I basically cured myself, in the process losing around 200 lbs without drugs, diet, exercise or surgery. Then I launched an alternative medicine practice specializing in not only vitamins and mineral

supplements, but amino acids and other exotic -- but entirely non-toxic and totally safe -- treatments.

But despite my own past experience with non-traditional therapies, I was still skeptical about medicinal cannabis when it became legal in California. I was practicing in San Diego at the time. My practice had to be cash-only as insurance would only pay for prescription treatments. As my practice dwindled and people became more and more dependent upon government-paid programs for their health care, I started doing some more research (in the most literal and technical sense).

I opened my mind to cannabis. I read literature from all over the world. I examined research protocols to find flaws in their designs. I tried to deconstruct the results to see if they were warranted by the data. In the end, I was convinced that marijuana was a valuable addition to the *Pharmacopoeia* of medicinal products and pharmaceutical substances.

In 2012, I became a Cannabis doctor. Marijuana is the safest drug I have ever recommended to a patient. I prefer it to any anti-anxiety drug, mood stabilizer, sleep medicine or pain remedy currently on the market in the USA.

My field is still a challenge, due to the refusal of the federal government to recognize the medical use of cannabis. But as more states allow medical use – and as more states make marijuana legal for all adults – cannabis can be taken seriously as a useful, safe and superior remedy to a huge variety of problems plaguing medical consumers today.

I proudly hold my head high when I tell people, "I am a medical marijuana doctor."

Alzheimer's Disease

Alzheimer's disease (AD) is a neurological disorder of unknown origin that is characterized by a progressive loss of memory and learned behavior. Patients with Alzheimer's are also likely to experience depression, agitation, and appetite loss, among other symptoms. Over 4.5 million Americans are estimated to be afflicted with the disease. No approved treatments or medications are available to modulate the progression of AD, and few pharmaceuticals effectively treat symptoms of the disease.

Preclinical data shows the potential of cannabinoids to moderate the progression of AD while clinical data demonstrates that these compounds can provide symptom relief.

Writing in the *Journal of Neuroscience*, investigators at Madrid's Complutense University and the Cajal Institute in Spain reported that the intracerebroventricular administration of the synthetic cannabinoid WIN 55,212-2 prevented cognitive impairment and decreased neurotoxicity in rats injected with amyloid-beta peptide (a protein believed to induce Alzheimer's). Additional synthetic cannabinoids were also found to reduce the inflammation associated with Alzheimer's disease in human brain tissue in culture. "Our results indicate that ... cannabinoids succeed in preventing the neurodegenerative process occurring in the disease," investigators concluded.[1] Follow up studies by investigators demonstrated that the administration of the nonpsychotropic plant cannabinoid cannabidiol also mitigated memory loss in a mouse model of the disease.[2]

Investigators at The Scripps Research Institute in California have reported that THC administration inhibits the enzyme responsible for the aggregation of amyloid plaque — the primary marker for Alzheimer's disease — in a manner "considerably superior" to approved AD drugs such as donepezil and tacrine. "Our results provide a mechanism whereby the THC molecule can directly impact Alzheimer's disease pathology," researchers concluded. "THC and its analogues may provide an improved therapeutic [option] for Alzheimer's disease [by]... simultaneously treating both the symptoms and the progression of [the] disease."[3] Investigators at the Salk Institute in 2016 reported similar findings in a series of exploratory studies.[4]

The administration of both THC and synthetic cannabinoid agonists have been shown to influence memory loss in animal models. For example, investigators at Ohio State University, Department of Psychology and Neuroscience, reported that older rats administered daily doses of WIN 55,212-2 for a period of three weeks performed significantly better than non-treated controls on a water-maze memory test. Writing in the journal *Neuroscience*, they reported that rats treated with the compound experienced a 50 percent improvement in memory and a 40 to 50 percent reduction in inflammation compared to controls.[5] Israeli researchers in 2017 reported that THC administration can reverse age-related memory impairment in rats, and may offer a potential treatment option in patients with dementia and other neurodegenerative illnesses.[6]

Previous preclinical studies have demonstrated that cannabinoids can prevent neuronal cell death.[7] Some experts believe that these neuroprotective properties could play a role in moderating AD.[8]

Writing in the *British Journal of Pharmacology*, investigators at Ireland's Trinity College Institute of Neuroscience concluded, "[C]annabinoids offer a multi-faceted approach for the treatment of Alzheimer's disease by providing neuroprotection and reducing neuroinflammation, whilst simultaneously supporting the brain's intrinsic repair mechanisms by augmenting neurotrophin expression and enhancing neurogenesis. ... Manipulation of the cannabinoid pathway offers a pharmacological approach for the treatment of AD that may be efficacious than current treatment regimens."[9]

Clinical trials demonstrate that cannabinoid therapy can mitigate certain AD symptoms. For instance, investigators at Berlin Germany's Charite Universitatmedizin, Department of Psychiatry and Psychotherapy, reported that the daily administration of 2.5 mg of synthetic THC over a two-week period reduced nocturnal motor activity and agitation in AD patients in an open-label pilot study.[10]

Clinical data presented at the 2003 annual meeting of the International Psychogeriatric Association reported that the oral administration of up to 10 mg of synthetic THC reduced agitation and stimulated weight gain in late-stage Alzheimer's patients in an open-label clinical trial.[11] Improved weight gain and a decrease in negative feelings among AD patients administered cannabinoids were previously reported by investigators in the *International Journal of Geriatric Psychiatry* in 1997.[12]

Most recently, Israeli researchers assessed the safety and efficacy of THC-infused oil in Alzheimer's patients in a four-week trial. Participants experienced decreased incidences of delusions, agitation, irritability, and apathy following treatment. Their quality of sleep also improved. "Adding medical cannabis oil to AD patients' pharmacotherapy is safe and a promising treatment option," investigators concluded.[13]

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Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal neurodegenerative disorder that is characterized by the selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. An estimated 30,000 Americans are living with ALS, which often arises spontaneously and afflicts otherwise healthy adults. More than half of ALS patients die within 2.5 years following the onset of symptoms.

At present, there is an absence of clinical trials investigating the use of cannabinoids as a disease-modifying therapy for ALS. However, preclinical models indicate that cannabinoids may hold the potential to delay ALS progression, lending support to anecdotal reports by some patients that cannabinoids may be efficacious in moderating the disease's development and in alleviating certain ALS-related symptoms such as pain, appetite loss, spasticity, depression and drooling.[1]

For example, investigators at the California Pacific Medical Center in San Francisco reported in the journal *Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders* that the administration of THC both before and after the onset of ALS symptoms staved disease progression and prolonged survival in animals compared to untreated controls.[2] University of Arkansas researchers reported that the administration of the cannabinoid agonist AM-1241 more than doubled survival rates compared to controls. "[T]he magnitude of effect produced by AM-1241 initiated at symptom onset rivals the best yet reported for any pharmaceutical agent, even those given pre-symptomatically," authors concluded.[3] A study of plant-derived cannabis extracts also documented delayed ALS progression during early stages of the disease.[4]

As a result, some experts are calling for clinical trials to assess the efficacy of cannabinoids in modulating the treatment of ALS progression. Writing in the *American Journal of Hospice & Palliative Medicine* in 2010, a team of investigators reported, "Based on the currently available scientific data, it is reasonable to think that cannabis might significantly slow the progression of ALS, potentially extending life expectancy and substantially reducing the overall burden of the disease." They concluded, "There is an overwhelming amount of preclinical and clinical evidence to warrant initiating a multicenter randomized, double-blind, placebo-controlled trial of cannabis as a disease-modifying compound in ALS."[5] Authors of a 2016 review in the journal *Neural Regeneration Research* echoed these findings, opining: "[T]here is a valid rationale to propose the use of cannabinoid compounds in the pharmacological management of ALS patients."[6]

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Chronic Pain

As many as one in five Americans lives with chronic pain.[1] Many of these people suffer from neuropathic pain (nerve-related pain) -- a condition that is associated with numerous diseases, including diabetes, cancer, multiple sclerosis, and HIV. In most cases, the use of standard analgesic medications such as opiates and NSAIDS (non-steroidal anti-inflammatory drugs) is ineffective at relieving neuropathic pain. Further, long-term use of most conventional pain relievers, including acetaminophen, opioids, and NSAIDs, is associated with a host of potential adverse side effects, including dependence, heart-attack, liver damage, and accidental overdose death.

Survey data indicates that the use of cannabis is common among patients with chronic pain[2] and patients who use it for this indication typically report it to be an effective treatment.[3] Majorities further report that cannabis possesses fewer side effects than conventional pain medications and that it provides greater symptom management than opioids.[4]

In addition to these anecdotal claims, numerous clinical trials report that inhaled marijuana alleviates neuropathic pain. A recent review identifies 35 controlled studies specific to the use of cannabis or cannabinoids in pain treatment, involving over 2,000 subjects.[5] These include a pair of randomized, placebo-controlled clinical trials demonstrating that smoking cannabis reduces neuropathy in patients with HIV by more than 30 percent compared to placebo.[6-7] (Additional details on these studies appear in the HIV section of this publication.) A University of California at San Diego double-blind, placebo-controlled trial reported that inhaled cannabis significantly reduced capsaicin-induced pain in healthy volunteers.[8] A University of California at Davis double-blind, randomized clinical trial reported both high and low doses of inhaled cannabis reduced neuropathic pain of diverse causes in subjects unresponsive to standard pain therapies.[9] A McGill University study reported that smoked cannabis significantly improved measures of pain, sleep quality and anxiety in participants with refractory pain for which conventional therapies had failed.[10] Another clinical trial reported that both inhaled cannabis and oral THC significantly decreased pain sensitivity and increased pain tolerance in healthy subjects exposed to experimental painful stimuli.[11]

Clinical trials also report that vaporized cannabis is effective at mitigating pain. A 2013 FDA-approved trial assessing the impact of vaporized cannabis on neuropathic pain reported that even low doses of THC (1.29 percent) "provided statistically significant 30% reductions in pain intensity when compared to placebo."[12] A 2014 Israeli open-label clinical trial reported that the administration of a single dose of whole-plant cannabis via a thermal-metered inhaler was effective and well tolerated among patients suffering from nerve pain.[13] Placebo-controlled data published in 2015 in *The Journal of Pain* further reported that vaporized cannabis provides "a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain."[14] A 2016 placebo-controlled trial in a cohort of 42 subjects with spinal injury neuropathy reported that vaporizing cannabis low to moderate levels of THC elicited a "significant analgesic response" in study participants.[15]

A review of these and other trials published in the *British Journal of Clinical Pharmacology* concluded, "[I]t is reasonable to consider cannabinoids as a treatment option for the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well."[16] A separate review published in *The Clinical Journal of Pain* further concluded, "Overall, based on the existing clinical trials database, cannabinergic pain medicines have been shown to be modestly effective and safe treatments in patients with a variety of chronic pain conditions. ... Incorporating cannabinergic medicine topics into pain medicine education seems warranted and continuing clinical research and empiric treatment trials are appropriate."[17] Another review of the data similarly reports, "[C]annabinoids are safe [and] demonstrate a modest analgesic effect and provide a reasonable treatment option for treatment chronic non-cancer pain."[18] Most recently, a review of over 10,000 scientific studies by the National Academies of Sciences, Engineering, and Medicine concluded that whole-plant cannabis is effective for the treatment of chronic pain in adults. "In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms," they determined.[19]

Longitudinal trials have also shown cannabis therapy to be safe and effective for pain treatment. A one-year assessment of Canadian chronic pain patients reported that daily use of herbal cannabis was associated with sufficient safety and efficacy. Compared to controls, patients in the cannabis use group experienced a significant reduction in average pain intensity while reporting no increased risk of adverse cognitive or pulmonary events. Authors concluded: "[T]his study suggests that the adverse effects of medical cannabis are modest and comparable quantitatively and qualitatively to prescription cannabinoids. The results suggest that cannabis at average doses of 2.5g/d in current cannabis users may be safe as part of carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate."[20]

Preclinical data indicates that cannabinoids, when administered in concert with one another, are more effective at ameliorating neuropathic pain than the use of a single agent -- a phenomenon sometimes referred to as the entourage effect. Investigators at the University of Milan have reported that the administration of single cannabinoids such as THC or CBD produce limited relief compared to the administration of plant extracts containing multiple cannabinoids, terpenes (oils), and flavonoids (pigments). Researchers concluded: "[T]he use of a standardized extract of Cannabis sativa ... evoked a total relief of thermal hyperalgesia, in an experimental model of neuropathic pain, ... ameliorating the effect of single cannabinoids." ... "Collectively, these findings strongly support the idea that the combination of cannabinoid and non-cannabinoid compounds, as present in [plant-derived] extracts, provide significant advantages in the relief of neuropathic pain compared with pure cannabinoids alone."[21] Other studies have reported similar results.[22]

Cannabis dosing also permits some chronic pain patients to significantly reduce their use of opioids. A 2011 clinical trial assessing the administration of vaporized plant cannabis in chronic pain patients on a daily regimen of morphine or oxycodone reported that inhaled "cannabis augments the analgesic effect of opioids." Authors concluded, "The combination (of opioids and cannabinoids) may allow for opioid treatment at lower doses with fewer side effects."[23] A 2016 Israeli clinical trial of intractable pain patients similarly reported that inhaled cannabis reduced symptom severity and

also was associated with 44 percent overall reduction in subjects' use of opiates.[24] A separate University of Michigan study of 244 chronic pain subjects similarly reported that cannabis use led to a 64 percent decrease in opioid consumption.[25] Patient survey data published in 2017 reported that 97 percent of respondents "strongly agreed/agreed" that they are able to decrease the amount of opioids they consume when they also use cannabis."[26]

In jurisdictions that permit medical cannabis access, patients are using fewer opioids. According to the findings of a 2015 National Bureau of Economic Research study, "[S]tates permitting medical marijuana dispensaries experience a relative decrease in both opioid addictions and opioid overdose deaths compared to states that do not.[27] The NBER findings are similar to those published in 2014 in the *Journal of the American Medical Association (JAMA) Internal Medicine* which also reported that the enactment of statewide medicinal marijuana laws is associated with a 24.8 percent lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws.[28] A 2016 study produced by Castlight Health similarly reports that rates of unauthorized opiate use is significantly lower in medical cannabis jurisdictions. Incidences of opioid-related hospitalizations[29] and traffic-related fatalities[30] have also fallen, as have overall prescription drug spending.[31] (For a comprehensive summary of relevant studies finding that legal cannabis access is associated with decreases in opioid use, abuse, hospitalization, and mortality, please see NORML's fact-sheet, Relationship Between Marijuana and Opioids.) Consequently, some pain experts are now advising that physicians recommend cannabis therapy in addition to or in lieu of opiate medications to "reduce the morbidity and mortality rates associated with prescription pain medications."[32]

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Diabetes Mellitus

Diabetes mellitus is a group of autoimmune diseases characterized by defects in insulin secretion resulting in hyperglycemia (an abnormally high concentration of glucose in the blood). There are two primary types of diabetes. Individuals diagnosed with type 1 diabetes (also known as juvenile diabetes) are incapable of producing pancreatic insulin and must rely on insulin medication for survival. Individuals diagnosed with type 2 diabetes (also known as adult onset diabetes) produce inadequate amounts of insulin. Type 2 diabetes is a less serious condition that typically is controlled by diet. Over time, diabetes can lead to blindness, kidney failure, nerve damage, hardening of the arteries and death. The disease is the third leading cause of death in the United States after heart disease and cancer.

Preclinical and observational studies indicate that cannabinoids are inversely associated with diabetes,[1] may modify disease progression, and that they also may provide symptomatic relief to those suffering from the disease.[2-3] A 2006 study published in the journal *Autoimmunity* reported that injections of 5 mg per day of the non-psychoactive cannabinoid CBD significantly reduced the incidence of diabetes in mice. Investigators reported that 86 percent of untreated control mice in the study developed diabetes. By contrast, only 30 percent of CBD-treated mice developed the disease.[4] In a separate experiment by this same research team, investigators reported that control mice all developed diabetes at a median of 17 weeks (range 15-20 weeks), while a majority (60 percent) of CBD-treated mice remained diabetes-free at 26 weeks.[5] A 2013 study assessing the effect of THCV (tetrahydrocannabivarin) in genetically modified obese mice reported that the cannabinoid's administration produced several metabolically beneficial effects relative to diabetes, including reduced glucose intolerance, improved glucose tolerance, improved liver triglyceride levels, and increased insulin sensitivity. Authors concluded, "Based on these data, it can be suggested that THCV may be useful for the treatment of the metabolic syndrome and/or type 2 diabetes (adult onset diabetes), either alone or in combination with existing treatments."[6]

Other preclinical trials report that cannabinoids may mitigate various symptoms of the disease. Writing in the *American Journal of Pathology*, researchers at the Medical College of Virginia reported that rats treated with CBD for periods of one to four weeks experienced significant protection from diabetic retinopathy[7] -- one of the leading causes of blindness in working-age adults. Other preclinical studies show that cannabinoid administration reduces diabetic-related tactile allodynia (pain resulting from non-injurious stimulus to the skin)[8-9] and symptoms of diabetic cardiomyopathy (weakening of the heart muscle). Experts have concluded, "[T]hese results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications."[10]

Randomized placebo-controlled clinical data has replicated some of these preclinical results. For example, a 2015 study published in *The Journal of Pain* reported that vaporized, whole-plant cannabis significantly reduces diabetic neuropathy in subjects resistant to other analgesics. Authors reported: "This small, short-term, placebo-controlled trial of inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain. ...

Overall, our finding of an analgesic effect of cannabis is consistent with other trials of cannabis in diverse neuropathic pain syndromes."[11] A 2017 placebo-controlled clinical trial published in the journal *Diabetes Care* reported that the administration of THCV "significantly decreased fasting plasma glucose" levels and improved pancreatic cell function in type 2 diabetics.[12]

Several observational trials have reported that those with a history of cannabis use possess a lower risk of type 2 diabetes than do those with no history of use. For example, researchers at the University of California, Los Angeles assessed the association between diabetes mellitus and marijuana use among adults aged 20 to 59 in a nationally representative sample of the US population of 10,896 adults. They reported that past and present cannabis consumers possessed a lower prevalence of adult onset diabetes, even after authors adjusted for social variables (ethnicity, level of physical activity, etc.), despite all groups possessing a similar family history of diabetes. Researchers did not find an association between cannabis use and other chronic diseases, including hypertension, stroke, myocardial infarction, or heart failure compared to nonusers. Authors concluded, "Our analysis ... showed that participants who used marijuana had a lower prevalence of DM and lower odds of DM relative to non-marijuana users."[13]

Similar observational trial data appeared in the *American Journal of Medicine* in 2013. Researchers at Harvard Medical School and the Beth Israel Deaconess Medical Center in Boston assessed the relationship between marijuana use and fasting insulin, glucose, and insulin resistance in a sample of 4,657 male subjects. They concluded, "[S]ubjects who reported using marijuana in the past month had lower levels of fasting insulin and HOMA-IR [insulin resistance], as well as smaller waist circumference and higher levels of HDL-C [high-density lipoprotein or 'good' cholesterol]. These associations were attenuated among those who reported using marijuana at least once, but not in the past 30 days, suggesting that the impact of marijuana use on insulin and insulin resistance exists during periods of recent use."[14]

Commenting on this study, the journal's Editor-in-Chief wrote in an accompanying commentary: "These are indeed remarkable observations that are supported, as the authors note, by basic science experiments that came to similar conclusions. ... We desperately need a great deal more basic and clinical research into the short- and long-term effects of marijuana in a variety of clinical settings such as cancer, diabetes, and frailty of the elderly. I would like to call on the NIH and the DEA to collaborate in developing policies to implement solid scientific investigations that would lead to information assisting physicians in the proper use and prescription of THC in its synthetic or herbal form."[15]

More recently, investigators from the Conference of Quebec University Health Centers assessed cannabis use patterns and body mass index (BMI) in a cohort of 786 Inuit (Arctic aboriginal) adults ages 18 to 74. Researchers reported that subjects who consumed cannabis in the past year were more likely to possess a lower BMI, lower fasting insulin, and lower HOMA-IR (insulin resistance) as compared to those who did not use the substance.[16] Their findings are consistent with previous research showing an inverse relationship between cannabis use and diabetic markers and are supportive of previous population data showing that those who consume cannabis, typically possess

lower BMI,[17] lower odds of metabolic syndrome[18-19] and non-alcoholic fatty liver disease,[20] and are less likely to be obese as compared to those who do not.[21-22]

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Dystonia

Dystonia is a neurological movement disorder characterized by abnormal muscle tension and involuntary, painful muscle contractions. It is the third most common movement disorder after Parkinson's disease and tremor, affecting more than 300,000 people in North America.

A small number of case reports and preclinical studies[1] indicate that cannabinoids possess anti-dystonic activity.

A case study published in *The Journal of Pain and Symptom Management* reported improved symptoms of dystonia after inhaling cannabis in a 42-year-old chronic pain patient. Investigators reported that subject's subjective pain score fell from 9 to zero (on a zero-to-10 visual analog scale) following cannabis inhalation, and that the subject did not require any additional analgesic medication for the following 48 hours. "No other treatment intervention to date had resulted in such dramatic overall improvement in [the patient's] condition," investigators concluded.[2]

A second case study appeared in the journal *Movement Disorders* reporting "significant clinical improvement" following cannabis inhalation in a single 25-year-old patient with generalized dystonia due to Wilson's disease.[3]

A German research team at the Hannover Medical School reported successful treatment of musician's dystonia in a 38-year-old professional pianist following administration of 5 mg of THC in a placebo-controlled single-dose trial.[4] Investigators reported "clear improvement of motor control" in the subject's affected hand, and noted, "[Two] hours after THC intake, the patient was able to play technically demanding literature, which had not been possible before treatment." Prior to cannabinoid treatment, the subject had been unresponsive to standard medications and was no longer performing publicly. "The results provide evidence that … THC intake … significantly improves [symptoms of] … focal dystonia," investigators concluded.

A 2002 randomized, placebo-controlled study investigating the use of the synthetic oral cannabinoid naboline (Cesamet) in 15 patients afflicted with generalized and segmental primary dystonia did not show a significant reduction in dystonic symptoms.[5] By contrast, a case report finds that the daily administration of dronabinol was associated with decreased symptoms of paroxysmal dystonia.[6]

A 2015 literature review opines that cannabis products likely possess a "promising role" for treating various movement disorders, including dystonia.[7]

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Epilepsy

Epilepsy is a central nervous system disorder characterized by uncontrollable twitching of the arms or legs and/or seizures. One in 26 Americans will develop epilepsy during their lifetime, according to statistics published by The Epilepsy Foundation. Conventional treatment to mitigate symptoms of this disorder includes medications or sometimes surgery. Nonetheless, even with conventional treatment, an estimated 30 percent of people with epilepsy continue to experience seizures.

Epileptics frequently report gaining subjective relief from cannabis-based interventions.[1] In recent years, increased focus has been paid to the use of cannabis-based therapies by adolescents with severe forms of pediatric epilepsy.

Parents of epileptic children have long advocated in favor of the therapeutic efficacy of cannabis, in particular the use of CBD-rich products, in media reports[2] and in scientific surveys.[3-4]

A growing number of studies are now available in the scientific literature acknowledging CBD's anti-seizure activity in adolescent patients. For example, a retrospective chart review of children and adolescents who were given oral cannabis extracts in a Colorado epilepsy center reported mitigation in seizure frequency in up to 57 percent of subjects.[5] Additional benefits reported included: improved behavior/alertness (33 percent), improved language (10 percent), and improved motor skills (10 percent).

Israeli researchers in 2016 retrospectively evaluated the effects of CBD oil in a multicenter cohort of 74 patients with intractable epilepsy. Participants in the trial were resistant to conventional epilepsy treatment and were treated with CBD extracts for a period of at least three months. Extracts in the study were provided by a pair of Israeli-licensed growers and were standardized to possess a CBD to THC ratio of 20 to 1. Investigators reported: "CBD treatment yielded a significant positive effect on seizure load. Most of the children (89 percent) reported reduction in seizure frequency. ... In addition, we observed improvement in behavior and alertness, language, communication, motor skills and sleep."[6]

They concluded, "The results of this multicenter study on CBD treatment for intractable epilepsy in a population of children and adolescents are highly promising. Further prospective, well-designed clinical trials using enriched CBD medical cannabis are warranted."

In the fall of 2013, the United States Food and Drug Administration granted orphan drug status to imported, pharmaceutically standardized, plant-derived CBD (aka Epidiolex) extracts for use in experimental pediatric treatment. Clinical trials assessing the safety and efficacy of the treatment in children with severe forms of the disease, such as Dravet syndrome, began in 2014.[7] Results from several of these trials have become available in recent years.

Clinical trial results publicized in April 2015 at the 67th Annual Meeting of the American Academy of Neurology reported that the administration of these extracts decreased seizure frequency by 54

percent over a 12-week period in children with treatment-resistant epilepsy.[8] Trial data reported in the fall of 2015 at the American Epilepsy Society's annual meeting further reported that the adjunctive use of Epidiolex was associated with long-term seizure relief in 40 percent of adolescent subjects.[9] Open-label trial data reported in the journal *Lancet Neurology* reported a median reduction in seizures in adolescent patients treated with Epidiolex that approached 40 percent. Authors concluded, "Our findings suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy."[10] Preliminary data provided from one such state-sponsored trial, provided by the University of Alabama at Birmingham in 2016, reported that an estimated 90 percent of subjects with pediatric epilepsy showed "some improvement" following CBD treatment.[11]

Clinical trial data has also shown Epidiolex treatment to mitigate seizure frequency and be well tolerated in the treatment of Lennox-Gastaut Syndrome, a rare and severe form of epilepsy.[12-13] Epidiolex/CBD treatment is also associated with improved symptoms and reduced prescription drug intake in pediatric patients with febrile infection-related epilepsy syndrome (FIRES), a devastating form of epilepsy affecting normal children after a febrile illness,[14] as well as with seizure reduction in patients with Tuberous sclerosis complex-induced epilepsy.[15]

Observational data published in the journal *Epilepsia* concludes that 70 percent of children administered Epidiolex adjunctively with clobazam experience a greater than 50 percent decrease in seizure frequency. "CBD is a safe and effective treatment of refractory epilepsy in patients receiving CLB treatment," authors reported.[16] Additional clinical trials of Epidiolex, along with several state-sponsored trials using CBD extracts, are ongoing.

Overall, "most studies suggest anticonvulsant effects of CBD, and consider most adverse effects to be mild," reviewers wrote in the *Journal of Epilepsy Research* in 2017.[17]

As a result of this growing body of evidence, the Epilepsy Foundation of America has resolved for "changes to state laws to increase access to medical marijuana as a treatment option for epilepsy, including pediatric use as supported by a treating physician."[18] An NDA submission to the US Food and Drug Administration for Epidiolex is pending.[19]

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Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome of unknown etiology. The disease is characterized by widespread musculoskeletal pain, fatigue and multiple tender points in the neck, spine, shoulders and hips. An estimated 3 to 6 million Americans are afflicted by fibromyalgia, which is often poorly controlled by standard pain medications.

Fibromyalgia patients frequently self-report using cannabis therapeutically to treat symptoms of the disease,[1-4] and physicians – in instances where it is legal for them do so – often recommend the use of cannabis to treat musculoskeletal disorders.[5-6] To date, however, there are few clinical trials assessing the use of cannabinoids to treat the disease.

Writing in the journal *Current Medical Research and Opinion*, investigators at Germany's University of Heidelberg evaluated the analgesic effects of oral THC in nine patients with fibromyalgia over a 3-month period. Subjects in the trial were administered daily doses of 2.5 to 15 mg of THC and received no other pain medication during the trial. Among those participants who completed the trial, all reported a significant reduction in daily recorded pain and electronically induced pain.[7]

Another study published in *The Journal of Pain* reported that the administration of the synthetic cannabinoid nabilone significantly decreased pain in 40 subjects with fibromylagia in a randomized, double-blind, placebo-controlled trial. "As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia," investigators concluded.[8] A separate 2010 trial performed at McGill University in Montreal reported that low doses of nabilone significantly improved sleep quality in patients diagnosed with the disease.[9] However, a recent literature review has criticized these papers as being relatively low quality.[10]

A 2011 observational, case-control trial reported that the use of whole-plant cannabis is associated with beneficial effects on various symptoms of fibromyalgia, including the relief of pain and muscle stiffness. Investigators at the Institut de Recerca Hospital del Mar in Barcelona, Spain assessed the associated benefits of cannabis in patients with fibromyalgia compared with FM patients who did not use the substance. Twenty-eight users and non-users participated in the study.

Authors reported: "Patients used cannabis not only to alleviate pain but for almost all symptoms associated to FM, and no one reported worsening of symptoms following cannabis use. ... Significant relief of pain, stiffness, relaxation, somnolence, and perception of well-being, evaluated by VAS (visual analogue scales) before and two hours after cannabis self-administration was observed." Cannabis users in the study also reported higher overall mental health summary scores than did non-users. Investigators concluded: "The present results together with previous evidence seem to confirm the beneficial effects of cannabinoids on FM symptoms."[11]

Literature reviews of various types of cannabis preparations report that cannabinoids are efficacious in alleviating various types of pain, including pain due to neuropathy, musculoskeletal disorders, fibromyalgia, and other chronic conditions.[12] (Please see the 'Chronic Pain' section of this book for

further details.) Further, cannabinoids' immune-modulating effect also make them promising agents for the treatment of fibromyalgia and other related conditions.[13-16]

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Gastrointestinal Disorders

Gastrointestinal (GI) disorders, including functional bowel diseases such as irritable bowel syndrome (IBS) and inflammatory bowel diseases such as Crohn's disease (CD) and colitis, afflict more than one in five Americans, particularly women. While some GI disorders may be controlled by diet and pharmaceutical medications, others are poorly moderated by conventional treatments. Symptoms of GI disorders often include cramping, abdominal pain, inflammation of the lining of the large and/or small intestine, chronic diarrhea, rectal bleeding and weight loss.

Patients with these disorders frequently report using cannabis therapeutically to address a variety of symptoms, including abdominal pain, abdominal cramping, and diarrhea.[1-9] According to survey data published in 2011 in the *European Journal of Gastroenterology & Hepatology*, "Cannabis use is common amongst patients with IBD for symptom relief, particularly amongst those with a history of abdominal surgery, chronic abdominal pain and/or a low quality of life index."[10] More recent survey data of IBD patients affirms: "[A] significant number of patients with IBD currently use marijuana. Most patients find it very helpful for symptom control."[11]

Preclinical studies demonstrate that activation of the CB1 and CB2 cannabinoid receptors exert biological functions on the gastrointestinal tract.[12] Effects of their activation in animals include suppression of gastrointestinal motility,[13] inhibition of intestinal secretion,[14] reduced acid reflux,[15] and protection from inflammation,[16] as well as the promotion of epithelial wound healing in human tissue.[17] Experts suggest the endogenous cannabinoid system plays "a key role in the pathogenesis of IBD,"[18] and that "cannabinoids may, therefore, be beneficial in inflammatory disorders" such as colitis and other digestive diseases.[19]

Observational trial data reports that whole-plant cannabis therapy is associated with a reduction in Crohn's disease activity and disease-related hospitalizations. Investigators at the Meir Medical Center, Institute of Gastroenterology and Hepatology assessed 'disease activity, use of medication, need for surgery, and hospitalization' before and after cannabis use in 30 patients with CD. Authors reported, "All patients stated that consuming cannabis had a positive effect on their disease activity" and documented "significant improvement" in 21 subjects.

Specifically, researchers found that subjects who consumed cannabis "significantly reduced" their need for other medications. Participants in the trial also reported requiring fewer surgeries following their use of cannabis. "Fifteen of the patients had 19 surgeries during an average period of nine years before cannabis use, but only two required surgery during an average period of three years of cannabis use," authors reported. They concluded: "The results indicate that cannabis may have a positive effect on disease activity, as reflected by a reduction in disease activity index and in the need for other drugs and surgery."[20]

In a follow up, randomized placebo-controlled trial, inhaled cannabis was reported to decrease Crohn's disease symptoms in subjects with a treatment-resistant form of the disease. Nearly half of the patients in the trial achieved disease remission.[21] By contrast, the administration of oral CBD was

not found to have a beneficial therapeutic effect in Crohn's disease patients in a controlled trial setting.[22]

Based on the available evidence to date, some experts now opine that modulation of the ECS represents a novel therapeutic approach for the treatment of numerous GI disorders — including inflammatory bowel disease, functional bowel diseases, gastro-oesophagael reflux conditions, secretory diarrhea, gastric ulcers and colon cancer.[23-25]

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Gliomas/Cancer

Gliomas (tumors in the brain) are especially aggressive malignant forms of cancer, often resulting in the death of affected patients within one to two years following diagnosis. There is no cure for gliomas and most available treatments provide only minor symptomatic relief.

A review of the modern scientific literature reveals numerous preclinical studies, some case reports, and one controlled clinical study demonstrating cannabinoids' ability to act as antineoplastic agents, particularly on glioma cell lines.

Writing in the September 1998 issue of the journal *FEBS Letters*, investigators at Madrid's Complutense University, School of Biology, first reported that delta-9-THC induced apoptosis (programmed cell death) in glioma cells in culture.[1] Investigators followed up their initial findings in 2000, reporting that the administration of both THC and the synthetic cannabinoid agonist WIN 55,212-2 "induced a considerable regression of malignant gliomas" in animals.[2] Researchers again confirmed cannabinoids' ability to inhibit glioma tumor growth in animals in 2003.[3]

Italian investigators that same year similarly reported that the non-psychoactive cannabinoid, cannabidiol (CBD), inhibited the growth of various human glioma cell lines *in vivo* and *in vitro* in a dose dependent manner. Writing in the November 2003 issue of the *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, researchers concluded, "Non-psychoactive CBD ... produce[s] a significant anti-tumor activity both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as an antineoplastic agent."[4]

In 2004, Guzman and colleagues reported that cannabinoids inhibited glioma tumor growth in animals and in human glioblastoma multiforme (GBM) tumor samples by altering blood vessel morphology (e.g., VEGF pathways). Writing in the August 2004 issue of *Cancer Research*, investigators concluded, "The present laboratory and clinical findings provide a novel pharmacological target for cannabinoid-based therapies."[5]

Investigators at the California Pacific Medical Center Research Institute reported that the administration of THC on human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced cell death more rapidly than did the administration of the synthetic cannabinoid agonist WIN 55,212-2. Researchers also noted that THC selectively targeted malignant cells while ignoring healthy ones in a more profound manner than the synthetic alternative.[6] A separate preclinical trial reported that the combined administration of THC and the pharmaceutical agent temozolomide (TMZ) "enhanced autophagy" (programmed cell death) in brain tumors resistant to conventional anti-cancer treatments.[7]

Guzman and colleagues have also reported that THC administration decreases recurrent glioblastoma multiforme tumor growth in some patients diagnosed with recurrent GBM. In the first ever pilot clinical trial assessing the use of cannabinoids and GBM, investigators found that the intratumoral administration of THC was associated with reduced tumor cell proliferation in two of

nine subjects. "The fair safety profile of THC, together with its possible anti-proliferative action on tumor cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids," investigators concluded.[8] Several additional investigators have also recently called for further exploration of cannabis-based therapies for the treatment of glioma.[9-11] A case report, published in 2011 in the journal of the *International Society for Pediatric Neurosurgery*, also documents the spontaneous regression of residual brain tumors in two children coinciding with the subjects use of cannabis.[12]

In addition to cannabinoids' ability to moderate glioma cells, separate preclinical studies demonstrate that cannabinoids and endocannabinoids can also inhibit the proliferation of other various cancer cell lines,[13-14] including breast carcinoma,[15-19] prostate carcinoma,[20-24] colorectal carcinoma,[25-26] gastric adenocarcinoma,[27] skin carcinoma,[28] leukemia cells,[29-33] neuroblastoma,[34-35] lung carcinoma,[36-37] uterus carcinoma,[38] thyroid epithelioma,[39] pancreatic adenocarcinoma,[40-41] cervical carcinoma,[42-44] oral cancer,[45] biliary tract cancer (cholangiocarcinoma)[46] urological cancers,[47] and lymphoma,[48-49] among others. In some instances, improved anti-cancer activity has been reported when cannabinoids are administered in concert with one another, rather than in isolation.[50-51] A 2013 case report published in the journal *Case Reports in Oncology* also reports successful treatment with cannabis extracts in a 14-year-old patient diagnosed with an aggressive form of acute lymphoblastic leukemia.[52] Population studies also report an inverse relationship between cannabis use and the prevalence of various types of cancer, including lung cancer,[53] head and neck cancer,[54] and bladder cancer.[55]

Experts acknowledge that there exists "solid scientific evidences supporting that cannabinoids exhibit a remarkable anticancer activity in preclinical models of cancer,"[56] and that cannabinoids may one day "represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis and the metastatic spreading of cancer cells."[57-58] Presently, medical cannabis use is prevalent among patients with various types of cancer, though many say that they "desire but are not receiving information about cannabis use during their treatment from oncology providers."[59] Despite an absence of clinical trials, "abundant anecdotal reports describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate. … Human studies should be conducted to address critical questions related to the foregoing effects."[60]

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Hepatitis C

Hepatitis C is a viral disease of the liver that afflicts an estimated four million Americans. Chronic hepatitis C is typically associated with fatigue, depression, joint pain and liver impairment, including cirrhosis and liver cancer.

Scientists theorize that the endocannabinoid system may moderate aspects of chronic liver disease.[1-2] Population data shows that adults with a history of cannabis use are less likely to suffer from specific liver problems, such as non-alcoholic fatty liver disease (NAFLD), than non-users. Specifically, a 2017 University of Massachusetts study reported that frequent consumers of cannabis were 52 percent less likely to be diagnosed with NAFLD as compared to non-users, while occasional consumers were 15 percent less likely to suffer from the disease.[3] A Stanford University study similarly reported that cannabis use independently predicted a lower risk of suspected NAFLD in a dose-dependent manner. "Active marijuana use provided a protective effect against NAFLD independent of known metabolic risk factors," authors concluded.[4]

Patients diagnosed with hepatitis C frequently report using cannabis to treat both symptoms of the disease as well as the nausea associated with antiviral therapy.[5-6] An observational study by investigators at the University of California at San Francisco (UCSF) reports that hepatitis C patients who used cannabis were significantly more likely to adhere to their treatment regimen than patients who didn't use it.[7]

While some older observational studies cautioned that heavy cannabis use among hepatitis C patients may adversely impact the liver,[8-10] more recent studies report that cannabis inhalation is not associated with the promotion of liver disease in hepatitis C subjects,[11] and, in some cases, may even act as a protective agent against steatosis.[12] Separate longitudinal data finds that patients co-infected with hepatitis C and HIV who consume cannabis are also less likely to suffer from insulin resistance as compared to non-users.[13]

Experts in the field offer divergent opinions regarding the therapeutic use of cannabinoids for hepatitis C treatment. While some experts opine that cannabis' "potential benefits of a higher likelihood of treatment success [for hepatitis C patients] appear to outweigh [its] risks"[14] others discourage the use of cannabis in patients with chronic hepatitis until further studies are performed.[15-19]

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Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus is a retrovirus that invades cells in the human immune system, making it highly susceptible to infectious diseases. According to the World Health Organization, over 500,000 Americans have died from HIV/AIDS and over one million US citizens are living with the disease.

Survey data indicates that cannabis is used by as many as one in three North American patients with HIV/AIDS to treat symptoms of the disease as well as the side-effects of various antiretroviral medications.[1-4] One recent study reported that more than 60 percent of HIV/AIDS patients self-identify as "medical cannabis users."[5] Patients living with HIV/AIDS most frequently report using cannabis to counter symptoms of anxiety, appetite loss and nausea, and at least one study has reported that patients who use cannabis therapeutically are more than three times more likely to adhere to their antiretroviral therapy regimens than non-cannabis users.[6]

A 2008 longitudinal analysis of both HIV positive and HIV negative men reported that cannabis use does not adversely impact CD4 and CD8 T cell counts,[7] while more recent papers find that cannabis exposure is linked to higher lymphocyte counts[8-9] and may improve immune function.[10-11] Cannabis prevalence is not associated with any negative effects on mortality risk.[12] In patients co-infected with HIV and hepatitis C, daily cannabis use is "independently associated with a reduced prevalence of steatosis (fatty liver disease)".[13] Co-infected patients are less likely to suffer from insulin resistance as compared to non-users.[14]

Clinical trial data has reported that HIV/AIDS patients who inhaled cannabis four times daily experienced "substantial ... increases in food intake ... with little evidence of discomfort and no impairment of cognitive performance." Investigators concluded, "Smoked marijuana ... has a clear medical benefit in HIV-positive [subjects]."[15]

Separate clinical data has reported that inhaling cannabis significantly reduced HIV-associated neuropathy compared to placebo. Researchers reported that inhaling cannabis three times daily reduced patients' pain by 34 percent. They concluded, "Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated neuropathy [in a manner] similar to oral drugs used for chronic neuropathic pain."[16]

Researchers at the University of California at San Diego have reported similar findings. Writing in the journal *Neuropsychopharmacology*, they concluded: "Smoked cannabis … significantly reduced neuropathic pain intensity in HIV-associated … polyneuropathy compared to placebo, when added to stable concomitant analgesics. … Mood disturbance, physical disability and quality of life all improved significantly during study treatment. … Our findings suggest that cannabinoid therapy may be an effective option for pain relief in patients with medically intractable pain due to HIV."[17]

Most recently, cannabis inhalation has been demonstrated in clinical trial to be associated with increased levels of appetite hormones in the blood of subjects with HIV infection.[18] In animal

models, delta-9-THC administration is associated with decreased mortality and ameliorated disease progression."[19] In preclinical models, cannabinoids have also been shown to decrease HIV replication.[20]

Some experts now believe that "marijuana represents another treatment option in [the] health management" of patients with HIV/AIDS[21] and that cannabinoids "could potentially be used in tandem with existing antiretroviral drugs, opening the door to the generation of new drug therapies for HIV/AIDS."[22]

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Huntington's Disease

Huntington's Disease (HD) is an inherited degenerative brain disorder characterized by motor abnormalities and dementia produced by selective lesions in the cerebral cortex and, in particular, the striatum. There are presently no known conventional therapies available to alleviate HD symptoms or delay HD-associated striatal degeneration.

Cannabinoids possess various properties that make it attractive in the potential treatment of neurodegenerative disorders like Huntington's disease,[1-3] and cannabinoid administration has shown efficacy in the treatment of HD in preclinical models[4-6] as well as in case studies.[7] As a result, scientists have called for clinical trials evaluating the effect of cannabinoid pharmacology in HD patients.[8-9] To date, however, no controlled human trials exist assessing cannabis for this clinical condition.

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Hypertension

High blood pressure, or hypertension, afflicts an estimated one in four American adults. This condition puts a strain on the heart and blood vessels and greatly increases the risk of stroke and heart disease.

Emerging research indicates that the endogenous cannabinoid system plays a role in regulating blood pressure, though its mechanism of action is not well understood.[1] Animal studies demonstrate that anandamide and other endocannabinoids profoundly suppress cardiac contractility in hypertension and can normalize blood pressure,[2-3] leading some experts to speculate that the manipulation of the endocannabinoid system "may offer novel therapeutic approaches in a variety of cardiovascular disorders."[4]

The administration of exogenous cannabinoids has yielded conflicting cardiovascular effects on humans and laboratory animals.[5-9] The vascular response in humans administered cannabis in experimental conditions is typically characterized by a mild increase in heart rate and blood pressure. However, complete tolerance to these effects develops quickly and potential health risks appear minimal.[10-11]

Cannabinoid administration in animals has been associated with vasodilation, transient bradycardia and hypotension,[12] as well as an inhibition of atherosclerosis (hardening of the arteries) progression.[13-15] The administration of synthetic cannabinoids have also been shown to lower blood pressure in animals and have not been associated with cardiotoxicity in humans.[16]

At this time, research assessing the clinical use of cannabinoids for hypertension is in its infancy[17] and potentially higher-risk populations are largely cautioned by experts to refrain from cannabis smoking.[18]

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Incontinence

Urinary incontinence is defined as a loss of bladder control. Incontinence can result from several biological factors, including weak bladder muscles and inflammation, as well as from nerve damage associated with diseases such as multiple sclerosis (MS) and Parkinson's disease. More than one in ten Americans over age 65 is estimated to suffer from incontinence, particularly women.

Several clinical trials show that the administration of cannabis-derived extracts improves bladder control. For example, investigators at Oxford's Centre for Enablement in Britain reported that self-administered doses of whole-plant cannabinoid extracts improved incontinence compared to placebo in patients suffering from MS and spinal cord injury.[1] In a follow up study of 15 patients with advanced multiple sclerosis, investigators at London's Institute for Neurology reported that cannabis extract therapy significantly decreased urinary urgency, frequency, and nocturia (urination at night). They concluded, "Cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS."[2]

These findings were replicated in a multi-center, randomized placebo-controlled trial involving 630 patients. Researchers reported that subjects administered cannabis extracts experienced a 38 percent reduction in incontinence episodes from baseline to the end of treatment, while patients administered THC alone experienced a 33 percent reduction, suggesting a "clinical effect of cannabis on incontinence episodes."[3] Extracts have also been shown to reduce overactive bladder symptoms in subjects with previously treatment resistant OAB.[4]

In light of these clinical trial findings, some experts have recommended the use of cannabinoids as potential 'second-line' agents for treating incontinence.[5] However, similar trials assessing the use of whole-plant cannabis on bladder control have yet to be conducted.

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Methicillin-resistant Staphyloccus aureus (MRSA)

Many bacterial infections possess multi-drug resistance. Arguably the most significant of these bacteria is methicillin-resistant *Staphyloccus aureus*, more commonly known as MRSA or 'the superbug.' This bacterium is resistant to standard antibiotics, including penicillin. According to the *Journal of the American Medical Association*, MRSA is responsible for nearly 20,000 hospital-stay related deaths annually in the United States.[1]

Cannabinoids are acknowledged to possess antibacterial and antifungal properties.[2-3] In 2008, investigators at Italy's Universita del Piemonte Orientale and Britain's University of London, School of Pharmacy assessed the germ-fighting properties of five separate cannabinoids against various strains of multidrug-resistant bacteria, including MRSA. They reported that all of the compounds tested showed "potent antibacterial activity" and that cannabinoids were "exceptional" at halting the spread of MRSA.[4]

Other studies have reported that non-cannabinoid constituents in the plant, such as terpenoids, also possess antibacterial properties against MRSA and malaria.[5-7]

Clinical trials regarding the use of cannabinoids for MRSA have been recommended, but not yet conducted. Experts opine, "Cannabis sativa ... represents an interesting source of antibacterial agents to address the problem of multidrug resistance in MRSA and other pathogenic bacteria."[8]

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Migraine

Migraine is a reoccurring headache syndrome that can last for up to 72 hours if left untreated. About 14 percent of Americans, primarily women, suffer from migraine. Migraine effects include pulsing cranial pain, nausea, light sensitivity, dizziness, difficulty speaking, and confusion, among other symptoms.

The endogenous cannabinoid system is suspected to play a significant role in migraine pathophysiology[1-3] and several studies have identified differences in ECS functioning and the production of endocannabinoids in migraine sufferers versus controls.[4-7]

Cannabis possesses a long history of human use in the treatment of migraine.[8] Literature reviews[9-10] and case reports[11-12] suggest that cannabis is effective for both the treatment of and the prevention of headache. Among patients recommended medical cannabis, as many as two-thirds report decreasing their use of conventional medications to treat migraine.[13-14] However, others anecdotally report gaining no therapeutic relief from cannabis.[15]

A recent retrospective assessment of 121 adults with the primary diagnosis of migraine headache reported, "Migraine headache frequency decreased from 10.4 to 4.6 headaches per month with the use of medical marijuana." Inhaling cannabis was also reported by many patients to abort the onset of migraine.[16] Clinical trial data presented in 2017 at the 3rd Congress of the European Academy of Neurology reported that the daily administration of cannabinoid extracts resulted in a 40 percent reduction in migraine frequency in a cohort of 79 chronic migraine patients.[17]

While clinical trial data remains at this time insufficient to definitively demonstrate the efficacy of cannabis or cannabinoids for migraine treatment "there are sufficient anecdotal and preliminary results, as well as plausible neurobiological mechanisms" to warrant further study, and "it appears likely that cannabis will emerge as a potential treatment for some headache sufferers."[18]

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Multiple Sclerosis

Reports of cannabinoids' ability to reduce MS-related symptoms such as pain, spasticity, depression, fatigue, and incontinence are plentiful in the scientific literature.[1-14] Cannabis' efficacy is further supported in randomized placebo-controlled trials. Investigators at the University of California at San Diego report that inhaled cannabis significantly reduces objective measures of pain intensity compared to placebo in patients with MS. They concluded that "smoked cannabis was superior to placebo in reducing spasticity and pain in patients with multiple sclerosis and provided some benefit beyond currently prescribed treatment."[15] These results were later published in the *Journal of the Canadian Medical Association*. Investigators concluded, "Smoked cannabis was superior to placebo in symptom and pain reduction in patients with treatment-resistant spasticity."[16] Not surprisingly, patients with multiple sclerosis typically report engaging in cannabis therapy,[17-19] with one survey indicating that nearly one in two MS patients use it therapeutically.[20]

Preclinical models suggest that cannabinoids may also inhibit MS progression in addition to providing symptom management. Writing in the journal *Brain*, investigators at the University College of London's Institute of Neurology reported that administration of the synthetic cannabinoid agonist WIN 55,212-2 provided "significant neuroprotection" in an animal model of multiple sclerosis. "The results of this study are important because they suggest that in addition to symptom management, ... cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in multiple sclerosis and probably other disease," researchers concluded.[21] Spanish researchers have reported similar findings, documenting that "the treatment of EAE mice with the cannabinoid agonist WIN55,512-2 reduced their neurological disability and the progression of the disease."[22] Purified CBD has also been shown to possess an anti-apoptotic power against the neurodegenerative processes underlying MS development in animals.[23] Clinical data reports that the administration of oral THC can boost immune function in patients with multiple sclerosis, suggesting "pro-inflammatory disease-modifying potential of cannabinoids [for] MS."[24] Results from a 2016 trial of children with treatment-resistant MS also demonstrated that that dronabinol reduced spasticity in the majority of patients.[25]

A small number of controlled trials suggest that cannabis therapy may slow down the clinical progression of MS in humans.[26] Observational data from an extended open-label study of 167 multiple sclerosis patients found that use of whole plant cannabinoid extracts relieves symptoms of pain, spasticity and bladder incontinence for an extended period of treatment (mean duration of study participants was 434 days) without requiring subjects to increase their dose.[27] Results from another two-year open label extension trial report that the administration of cannabis extracts is associated with long-term reductions in neuropathic pain in select MS patients. On average, patients in that study required fewer daily doses of the drug and reported lower median pain scores the longer they took it.[28] These results would be unlikely in patients suffering from a progressive disease like MS unless the cannabinoid therapy was halting its progression, investigators suggested.

In recent years, health regulators in numerous countries – including Canada, Denmark, Germany, New Zealand, Spain and the United Kingdom -- have approved the prescription use of plant

cannabis extracts to treat symptoms of multiple sclerosis. Longitudinal data finds that daily use of these extracts are typically effective and well-tolerated in patients, including those with treatment-resistant MS.[29] In some instances, patients who have failed to respond to these extracts have ultimately exhibited therapeutic benefits from whole-plant cannabis.[30]

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Osteoporosis

Osteoporosis is a degenerative skeletal disease characterized by a deterioration of bone tissue. Patients with osteoporosis are at risk of suffering multiple fractures and other serious disabilities. Approximately 10 million Americans over age 50 suffer from osteoporosis, according to the US Surgeon General's office, and another 34 million are at risk of developing the disease.

Initial references to the potential role of cannabinoids in the protection against the onset of osteoporosis appear in the scientific literature beginning in the early 1990s.[1] To date, however, no controlled clinical trials exist assessing the administration of cannabis or cannabinoids for this indication.

Preclinical data indicates that cannabinoid administration slows the development of osteoporosis, stimulates bone building, and reduces bone loss in animal models.[2] Follow up research published in the *Annals of the New York Academy of Sciences* reported that the activation of the CB2 cannabinoid receptor reduces experimentally-induced bone loss and stimulated bone formation.[3] Investigators have also reported that mice deficient in the CB2 cannabinoid receptor experienced age-accelerated bone loss reminiscent of human osteoporosis.[4] More recently, Israeli investigators at Hebrew University Bone Laboratory assessed the ability of CBD administration to promote healing in rats with mid-femoral fractures. Researchers reported, "CBD markedly enhanced the biomechanical properties of the healing femora after 8 weeks."[5]

A 2017 population study reported "no association" between cannabis use and bone mineral density, even among subjects at higher risk for the condition.[6]

Scientists speculate that one of the primary roles of the endocannabinoid system is to maintain "bone remodeling at balance, thus protecting the skeleton against age-related bone loss,"[7] leading some experts to believe that cannabinoids may be "a promising target novel target for anti-osteoporotic drug development."[8]

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Parkinson's Disease

Parkinson's disease is a progressive disorder of the central nervous system that results in tremor, slowed movement, and muscle rigidity. There is no cure for PD, but some conventional medications are available to treat symptoms of the disease.

In surveys, patients with Parkinson's report cannabis to be highly efficacious at mitigating disease symptoms, particularly in the treatment of non-motor symptoms.[1-3] Observational trial data supports these claims. Investigators at Tel Aviv University, Department of Neurology evaluated Parkinson's disease symptoms in subjects at baseline and 30-minutes after inhaling cannabis. In one trial, researchers reported that inhaled cannabis was associated with "significant improvement after treatment in tremor, rigidity, and bradykinsea (slowness of movement). No significant adverse effects of the drug were observed."[4] In another trial, investigators reported that cannabis inhalation – both short-term and long-term – was associated with improved pain relief.[5]

In a separate, retrospective observational trial, researchers assessed the daily use of cannabis in 47 patients with Parkinson's disease over a period of several months (ranging from three months to 84 months). Most (82 percent) of the patients reported that medical cannabis "improved their overall symptoms." Specifically, cannabis administration was associated with reductions in pain, stiffness, and tremor as well as with improvements in mood and sleep quality. Participants were also less likely to report suffering from falls after initiating cannabis use. Authors concluded, "[T]he results of our study demonstrate that most of the users had found MC (medical cannabis) to improve their condition, and that MC treatment was safe, without major side effects."[6]

The administration of isolated cannabinoids also likely addresses various PD symptoms. According to a series of case summaries published in the *Journal of Clinical Pharmacy and Therapeutics* in 2014, daily cannabidiol treatment reduced symptoms REM sleep behavior disorder (RBD) in patients with Parkinson's.[7] Placebo-controlled clinical data further reports that CBD administration is associated with improved "quality of life" and "well being" in PD patients.[8] The compound has also been shown to mitigate symptoms of psychosis in patients with the disease.[9]

As a result, some experts in the field now speculate that "various cannabinoids or other compounds targeting the endogenous cannabinoid system might be useful in the treatment of PD symptoms."[10]

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Post-Traumatic Stress

Post-traumatic stress disorder (PTSD) is a psychiatric health response to a traumatic event. Symptoms of post-traumatic stress may include flashbacks, nightmares, and severe anxiety, as well as uncontrollable thoughts about the event. These symptoms may persist long after the triggering event and may be unresponsive to conventional therapeutic treatments. An estimated one in ten Americans suffers from post-traumatic stress.

The endogenous cannabinoid system is believed to play a "critical role ... in the etiology of PTSD in humans."[1] Researchers theorize, "Cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and to feel less anxious and less involved with flashback memories. ... Evidence is increasingly accumulating that cannabinoids might play a role in fear extinction and anti-depressive effects."[2] Studies show that cannabinoid administration can facilitate fear extinction memory recall in both animals and in humans.[3-4]

Small clinical trials assessing the use of individual cannabinoids have shown success in PTS treatment. A 2014 Israeli trial reported that the adjunctive administration of orally absorbable THC "caused a statistically significant improvement in global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms" in a cohort of ten subjects.[5] Separate trials report that the administration of nabilone, a synthetic cannabinoid, safely mitigates various symptoms of post-traumatic stress, including insomnia, chronic pain, and treatment-resistant nightmare.[6-7]

Observational trial data provides inconsistent results. A retrospective review of PTSD patients' symptoms published in 2014 in the *Journal of Psychoactive Drugs* reported a greater than 75 percent reduction CAPS (Clinician Administered Posttraumatic Scale) symptom scores following cannabis therapy.[8] But a larger observational study of PTS subjects reported that "those who never used marijuana had significantly lower symptom severity four months later than those who continued or started use after treatment."[9] Similarly, a 2015 case-control study found no association between self-reported cannabis use and mental health symptom severity in a cohort of veterans with probable PTSD.[10] A separate study similarly reported "no significant positive nor negative associations between baseline cannabis use and end-of-treatment PTSD symptom severity and days of primary substance use."[11] A 2017 literature review by the Canadian Agency for Drugs and Technologies in Health concudes, "[T]here is evidence from very low quality studies to support the efficacy of smoked marijuana, oral THC, and nabilone in reducing some symptoms of PTSD."[12] As a result, experts presently advise physicians to "use their own clinical judgment when weighing the potential risks and benefits for a particular patient."[13] Two military veterans advocacy organizations, The American Legion and AMVETS, have expressed support for veterans' access to cannabis therapy.

As of this writing, placebo-controlled randomized clinical data assessing cannabis' impact on PTS are underway in both the United States and Canada.[14-15]

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Pruritus

Itching (pruritus) is a common symptom associated with numerous skin diseases, as well as a secondary symptom of numerous serious conditions such as renal failure and liver disease. Itching, unlike other skin sensations, is generally a result of CNS activities and typically goes untreated by standard medical therapies.

The endocannabinoid system is acknowledged to play an important role in maintaining skin health[1] and cannabinoids have been regarded as "promising" agents for the treatment of itch.[2]

A review of the scientific literature identifies at least three clinical trials investigating the use of cannabinoids in the treatment of pruritus. Writing in the August 2002 issue of the *American Journal of Gastroentrology*, investigators from the University of Miami Department of Medicine reported successful treatment of pruritus with 5 mg of THC in three patients with cholestatic liver disease.[3] Prior to cannabinoid therapy, subjects had failed to respond to standard medications and had lost their ability to work. Following evening cannabinoid administration, all three patients reported a decrease in pruritus, as well as "marked improvement" in sleep and were eventually able to return to work. Resolution of depression was also reported in two out of three subjects. "Delta-9-tetrahydrocannabinol may be an effective alternative in patients with intractable cholestatic pruritus," investigators concluded.

The following year, British researchers reported in the journal *Inflammation Research* that the peripheral administration of the synthetic cannabinoid agonist HU-211 significantly reduced experimentally-induced itch in 12 subjects.[4] Investigators had previously reported that topical application of HU-210 on human skin reduced experimentally-induced pain and acute burning sensations.[5]

More recently, Polish researchers reported that application of an endocannabinoid-based topical cream reduced uremic pruritus and xerosis (abnormal dryness of the skin) in hemodialysis patients.[6] Three weeks of twice-daily application of the cream "completely eliminated" pruritus in 38 percent of trial subjects and "significantly reduced" itching in others. Eighty-one percent of patients reported a "complete reduction" in xerosis following cannabinoid therapy.

As a result, some dermatology experts opine that cannabinoids may represent "promising new avenues for managing itch more effectively"[7] and that the use of cannabinoids, particularly non-psychotropic topical preparations, may be a viable option for patients.[8]

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory disease of the joints characterized by pain, stiffness, and swelling, as well as an eventual loss of limb function. Rheumatoid arthritis affects about one percent of the population, primarily women.

The cannabis plant is acknowledged to possess anti-inflammatory, anti-arthritic, and anti-rheumatic properties,[1] and the endocannabinoid system has been proposed as modulator of RA.[2]

The use of cannabis to treat symptoms of RA is frequently self-reported by patients. In a 2005 anonymous questionnaire survey of medicinal cannabis patients in Australia, 25 percent reported using cannabinoids to treat RA.[3] A survey of British medical cannabis patients found that more than 20 percent of respondents reported using cannabis for symptoms of arthritis.[4] A review of state-registered medical cannabis pain patients reported that 27 percent used it to treat arthritis.[5] Nevertheless, there exists limited clinical data with respect to the use of cannabinoids on RA in the literature at this time.

In January 2006, investigators at the British Royal National Hospital for Rheumatic Disease reported successful treatment of arthritis with cannabinoids in the first-ever controlled trial assessing the efficacy of natural cannabis extracts on RA.[6] Investigators reported that the administration of cannabis extracts over a five week period produced statistically significant improvements in pain on movement, pain at rest, quality of sleep, inflammation and intensity of pain compared to placebo. No serious adverse effects were observed. Similar results had been reported in smaller trials investigating the use of orally administered cannabis extracts on symptoms of RA.[7] A randomized, placebo-controlled trial assessing the use of vaporized cannabis in osteoarthritis patients began in Canada in 2016.[8] Nonetheless, the limited number of studies and their short-term duration "allows for only limited conclusions for the effects of cannabinoids in rheumatic conditions."[9]

Preclinical data indicates that cannabinoids moderate RA progression. Writing in the *Journal of the Proceedings of the National Academy of Sciences*, investigators at London's Kennedy Institute for Rheumatology reported that cannabidiol administration suppressed the progression of arthritis *in vitro* and in animals.[10] Administration of CBD after the onset of clinical symptoms protected joints against severe damage and "effectively blocked [the] progression of arthritis," investigators concluded. Daily administration of the synthetic cannabinoid agonist HU-320 has also been reported to protect joints from damage and to ameliorate arthritis in preclinical models,[11] as has the administration of the cannabinoid agonist HU-444.[12]

Summarizing the available literature in the *Journal of Neuroimmunology*, researchers at Tokyo's National Institute for Neuroscience concluded, "Cannabinoid therapy of RA could provide symptomatic relief of joint pain and swelling as well as suppressing joint destruction and disease progression."[13] More recently, experts in the field have opined that "specific activation of CB2 (receptor) may relieve RA"[14] and that "a selective CB(2) agonist could be a new therapy for RA."[15]

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Sleep Apnea

Sleep apnea is a medical disorder characterized by frequent interruptions in breathing of up to ten seconds or more during sleep. The condition is associated with numerous physiological disorders, including fatigue, headaches, high blood pressure, irregular heartbeat, heart attack and stroke. Though sleep apnea often goes undiagnosed, it is estimated that approximately four percent of men and two percent of women ages 30 to 60 years old suffer from the disease.

Limited data shows that cannabinoids may hold promise in addressing sleep apnea. Writing in the June 2002 issue of the journal of the *American Academy of Sleep Medicine*, researchers at the University of Illinois (at Chicago) Department of Medicine reported "potent suppression" of sleep-related apnea in rats administered either exogenous or endogenous cannabinoids.[1] Another animal trial reported that injected doses of synthetic THC mitigates apnea and augments upper airway muscles in rats.[2]

In a clinical settings, the administration of dronabinol mitigates apnea in adults. Writing in the journal *Frontiers in Psychiatry* in 2013, investigators concluded that THC administration significantly mitigated symptoms of the disorder in patients with Obstructive Sleep Apnea over a three-week period. "Dronabinol treatment may be a viable alternative or adjunctive therapy in selected patients with OSA," authors concluded.[3]

A 2017 clinical trial of 73 subjects with moderate to severe obstructive sleep apnea reported that the administration of dronabinol prior to bedtime reduced symptom severity and improved subjective sleepiness.[4]

A 2017 review of the literature concludes: "Novel studies investigating cannabinoids and obstructive sleep apnea suggest that synthetic cannabinoids such as nabilone and dronabinol may have short-term benefit for sleep apnea due to their modulatory effects on serotonin-mediated apneas. CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while nabilone may reduce nightmares associated with PTSD and may improve sleep among patients with chronic pain. Research on cannabis and sleep is in its infancy and has yielded mixed results. Additional controlled and longitudinal research is critical to advance our understanding of research and clinical implications."[5]

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Tourette Syndrome

Tourette syndrome (TS) is a complex neuropsychiatric disorder of unknown etiology that is characterized by involuntary vocal tics. Severity of this condition varies widely among patients. Though there is no cure for Tourette syndrome, the condition often improves with age. Experts estimate that 100,000 Americans are afflicted with TS.

A review of the scientific literature reveals several case reports and a small number of clinical trials specific to the use of cannabinoids for the treatment of TS. One of the first appears in the *American Journal of Psychiatry* in 1999. Investigators at Germany's Medical School of Hanover, Department of Clinical Psychiatry and Psychotherapy, reported successful treatment of Tourette syndrome with a single dose of 10 mg of delta-9-THC in a 25-year-old male patient in an uncontrolled open clinical trial.[1] Investigators reported that the subject's total tic severity score fell from 41 to 7 within two hours following cannabinoid therapy, and that improvement was observed for a total of seven hours. "For the first time, patients' subjective experiences when smoking marijuana were confirmed by using a valid and reliable rating scale," authors concluded.

Investigators confirmed these preliminary results in a randomized, double-blind, placebo-controlled, crossover, single dose trial of THC in 12 adult TS patients. Researchers reported a "significant improvement of tics and obsessive-compulsive behavior (OCB) after treatment with delta-9-THC compared to placebo."[2] Investigators reported no cognitive impairment in subjects following THC administration[3] and concluded, "THC is effective and safe in treating tics and OCB in TS."[4]

Investigators later conducted a second randomized, double-blind, placebo-controlled trial involving 24 patients administered daily doses of up to 10 mg of THC over a six-week period. Researchers reported that subjects experienced a significant reduction in tics following long-term cannabinoid treatment,[5] and suffered no detrimental effects on learning, recall or verbal memory.[6] A trend toward significant improvement of verbal memory span during and after therapy was also observed.

A 2003 review of the data published in the journal *Expert Opinions in Pharmacotherapy* reported that in adult TS patients, "Therapy with delta-9-THC should be tried ... if well established drugs either fail to improve tics or cause significant adverse effects."[7] Another scientific review similarly concluded: "[B]y many experts THC is recommended for the treatment of TS in adult patients, when first line treatments failed to improve the tics. In treatment resistant adult patients, therefore, treatment with THC should be taken into consideration."[8]

A 2016 case study reported that the twice daily administration of cannabinoid extracts in a patient with treatment-resistant TS was associated with an 85 percent reduction in the subject's motor tics and a 90 percent reduction in vocal tics. Authors concluded, "Our results support previous research suggesting that cannabinoids are a safe and effective treatment for TS and should be considered in treatment-resistant cases."[9] Another recent pair of case reports acknowledged that the daily administration of cannabis-based therapy "provided significant symptom improvement" in patients with treatment resistant TS.[10]

Most recently, University of Toronto investigators retrospectively assessed the safety and efficacy of inhaled cannabis in 19 patients with TS. Researchers reported, "All study participants experienced clinically significant symptom relief," including reductions in obsessive-compulsive symptoms, impulsivity, anxiety, irritability, and rage outbursts. Eighteen of 19 patients experienced decreased tic severity. Cannabis was "generally well tolerated" by study subjects. They concluded: "Overall, these study participants experienced substantial improvements in their symptoms. This is particularly striking given that almost all participants had failed at least one anti-tic medication trial. ... In conclusion, cannabis seems to be a promising treatment option for tics and associated symptoms."[11]

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