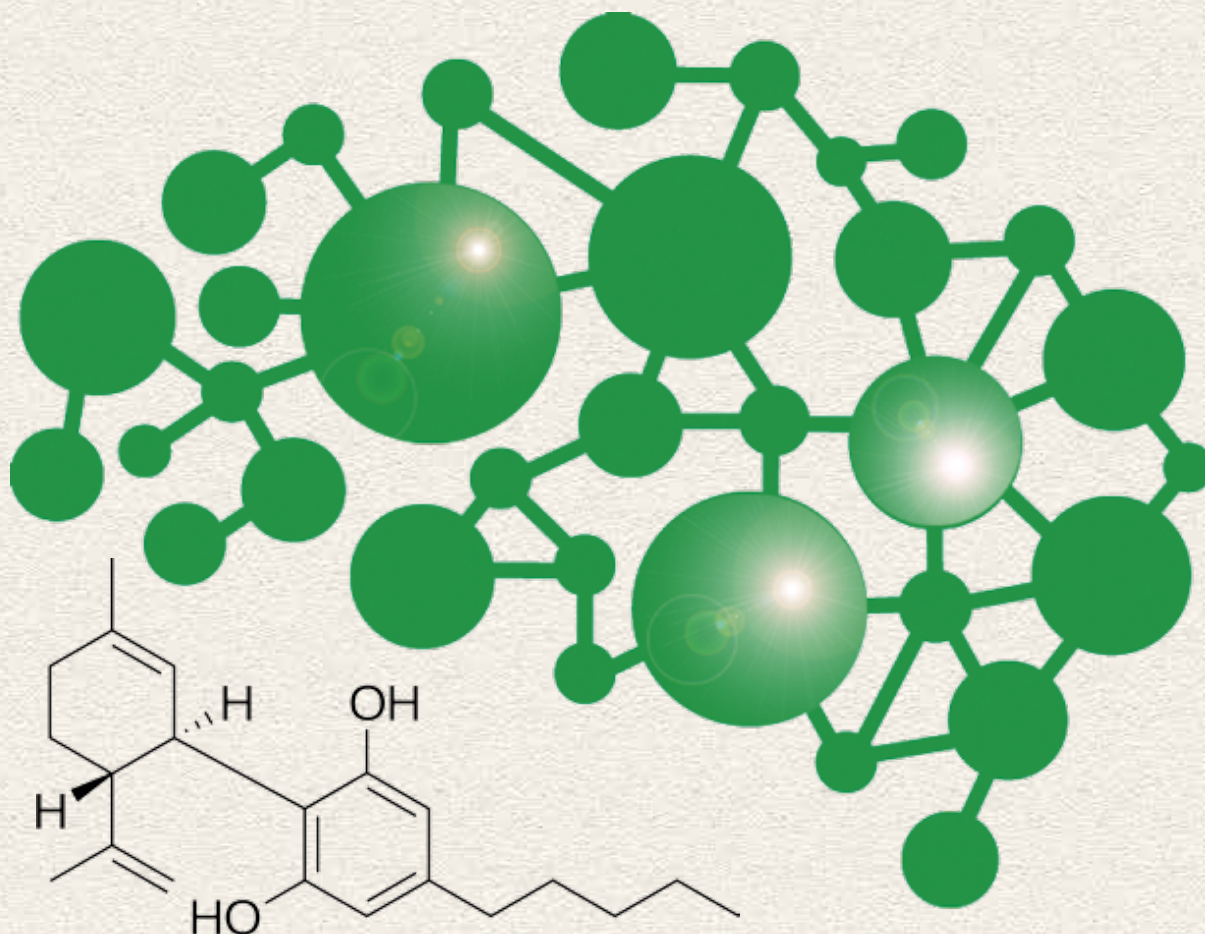


# American Journal of Endocannabinoid Medicine

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Volume 1 • Issue 1



## Positive Autism Intervention With Cannabidiol: A Case Study

**Next Generation of Liposomal  
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## By Jahan Marcu, PhD

Welcome to the *American Journal of Endocannabinoid Medicine*. Despite one-third of people in the United States living in a state where they can easily purchase cannabis products, awareness of the effects of various cannabis preparations and the endocannabinoid system is lacking among health care professionals.

In this inaugural issue, we present articles on several topics and include case reports, original research, and commentary on key publications in the field. Our Editorial Board of experts scoured the literature for articles to summarize and distill relevant information for clinical practice. There is no shortage of basic research journals, but the purpose of this journal is to provide information in a form that is easy for clinicians to read and apply in their practice. This is not a journal written for PhDs or basic researchers; it is written for clinicians.

This journal is focused on providing education and information, not receiving citation counts for the articles. This leaves the journal unfettered with weights that limit the type of information that many journals provide. The case reports offer perspectives from different medical disciplines and a chance to learn from the experience of medical colleagues. We hope that these case reports and other articles will become a part of a database, where the information can be mined to uncover vital health information.

Our experts represent a multidisciplinary Editorial Board consisting of practitioners from the fields of neurology, pediatrics, pharmacy, nursing, psychology, social work, and naturopathic medicine, as well as basic researchers and professors who study drug abuse and the endocannabinoid system. Michael Patterson, NHA, OTR/L, who has 25 years of experience operating nursing homes, provides commentary and practical considerations for medical cannabis use in this setting. Janet Galliard, EdS, provides a detailed case report on autism and cannabidiol (CBD), tracking a pediatric patient over a number of years. We also feature a research article on a pilot study involving a new liposomal delivery system for CBD molecules. Additionally, other content covers practical considerations for dosing and administering

cannabis products, useful information regarding the public health issue on vaping, and commentary on women's sexual health and cannabis use authored by a pharmacist with years of experience counseling medical cannabis

patients at dispensaries. I also hope you will enjoy *Cannabis by the Numbers*, statistics arranged for a thoughtful and contrasting effect, offering a unique distillation of information.

Because there is no shortage of inconclusive, or even conflicting, data surrounding the therapeutic potential of cannabinoids, we aim to present multiple perspectives. In this issue, we provide 2 views on pregnancy and cannabis use—a recent FDA article in *News Briefs* and a historical perspective in *A Look Back*.

It is our wish that the summaries of noteworthy studies, accompanying commentaries, case reports, and original research offer “pearls” of knowledge that may be applied in everyday clinical practice. Ultimately, we hope that the knowledge imparted by these important studies allows for improved outcomes and quality of life for patients using cannabis products through the initiation of optimal care based on the latest clinical evidence.

The format of *the American Journal of Endocannabinoid Medicine* is outstanding because it provides a concise, directed, and extra-filtered approach to development that emphasizes the collaboration between researchers and the many specialists who manage patients.

We hope you enjoy reading this issue!

Jahan Marcu, PhD  
Editor in Chief





**Editor in Chief****Jahan Marcu, PhD**

Chief Science Officer and co-founder of the International Research Center on Cannabis and Health, New York, New York

**Faculty****Karyemaître Aliffe, MD**

Teaching Faculty, Cannabis Clinical Pharmacology, Immuno-Oncology Wellness, University of Miami, Miller School of Medicine, Florida

**Ann Allworth, PhD**

Founder and CEO, Cannabis Education Solutions, Hyattsville, Maryland

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Master of Jurisprudence in Health Law, Park Ridge, Illinois

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Certified Integrative Nutrition Health Coach and Director of Research and Development, 101CBD.org

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Assistant Professor of Psychology, Department of Psychiatry at the University of Pennsylvania, Philadelphia, Pennsylvania

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On Point Medicine, Morganton, North Carolina

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Chief Marketing Officer, The Anthos Group, Los Angeles, California

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Attorney, Kight on Cannabis, Asheville, North Carolina

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US Cannabis Pharmaceutical Research and Development, Vero Beach, Florida

**Jonathan Psenka, NMD**

Longevity Medical Health Center, Phoenix, Arizona

**Jan Roberts, LCSW, CEO,**

International Research Center on Cannabis and Health, International Research Center on Cannabis and Health, New York, New York

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President, New Jersey CannaBusiness Association, Trenton, New Jersey

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Managing Director, International Cannabinoid Research Society, CEO, Cortical Systematics, Tucson, Arizona

**Christian Shaw, MD, PhD**

Halcyon Therapeutics LLC, Phoenix, Arizona

**Daniel P. Stein, MD**

Neurology of Cannabis, Sarasota, Florida, and Faculty Florida State University College of Medicine, Tallahassee, Florida

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**Staff****Publisher**

Ken Watkins III, GreenMeds Communications  
ken@ajendomed.com

**Associate Publisher**

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**Managing Editor**

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**Eloise Theisen, RN, MSN, AGPCNP-BC**

President, American Cannabis Nurses Association, Washington, DC

**Sara Jane Ward, PhD**

Assistant Professor, Center for Substance Abuse Research Department of Pharmacology, Temple University, Lewis Katz School of Medicine, Philadelphia, Pennsylvania

**Stacia Woodcock, PharmD**

Secretary, Association of Cannabis Specialists, New York, New York

**Ryan D. Zaklin, MD, MA, PC**

Integrative Medicine Physician  
Salem, Massachusetts

**About Jahan Marcu, PhD**

**D**r. Jahan Marcu has more than 15 years of experience in cannabis research, policy, and operations. He has been a passionate advocate of consumer safety and the medical benefits of cannabis. He is also among a selected group of professionals globally who has earned PhDs focused on the endocannabinoid system (ECS; with research on the structure and function of cannabinoid receptors, molecular pharmacology of the ECS, and the role of the ECS in bone).

He is the Chief Science Officer and co-founder of the International Research Center on Cannabis and Health, a community-based institute that collaborates with universities, researchers, foundations, state institutions, and others to leverage the highest caliber talent in the field. He is founder and past-chair of the Cannabis Chemistry Subdivision of the American Chemical Society, the world's largest and oldest professional scientific society. Further illustrating the recognition earned through his efforts, he has been asked to serve on multiple expert government advisory and trade association committees, as well as scientific organizations including ASTM International (D37 Subcommittee chair), American Herbal Products Association (AHPA) Cannabis Committee (past-chair), American Chemical Society Cannabis Chemistry Subdivision, American Oil Chemists' Society, AOAC International, International Association for Cannabinoid Medicines (past Board of Directors), and the International Medical Cannabis Patient Coalition (co-founder).

Dr. Marcu's work has been instrumental in facilitating and supporting fact-based, scientific approaches vital to industry and patients. This has included research focused on solving the structure and function of cannabinoid receptors and the anti-cancer properties of cannabis compounds, as well as method development and validation for analyzing complex formulations. Furthermore, his efforts include the development of international certification and training programs, co-authoring American Herbal Pharmacopeia's Cannabis

Quality Control and Therapeutic Monographs, and assisting in the creation of the first standards for industry as a chairman of the cannabis committee for the AHPA.

His dedication to consumer safety is further evident in his work to co-develop a biotech application to predict drug-drug interactions between cannabis and commonly prescribed pharmaceutical drugs (Navigator Genomics). Additionally, Dr. Marcu published one of the first product safety studies on CBD products.

Reflecting his dedication to the field, Dr. Marcu has received numerous awards including the Mahmoud Elsohly Award for Excellence in Cannabis Chemistry and the Billy Martin Research Achievement Award from the International Cannabinoid Research Society for his work on THC and CBD synergy in aggressive brain cancers. He is also a court-qualified synthetic cannabinoid and cannabis expert. His work has been published and covered in publications such as *Science*, *Nature*, *JAMA*, *The Washington Post*, *CNN*, and many other media outlets.

**Selected Publications**

Bonn-Miller MO, Loflin MJE, Thomas BF, **Marcu JP**, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA*. 2017;318(17):1708-1709. <http://doi.org/10.1001/jama.2017.11909>

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# Cannabis by the Numbers

*Did you know that 69% of CBD-containing products have inaccurate labels?*

*Discover more fascinating facts in AJEM's Cannabis by the Numbers, November 2019.*

**1992**

Year that the endocannabinoid system was discovered<sup>1</sup>

**1985**

Year that dronabinol was approved by the FDA as a prescription medicine<sup>2</sup>

**69%**

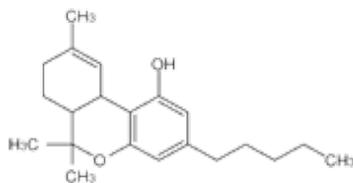
Estimated percentage of CBD-containing products that have inaccurate labels<sup>5</sup>

**9%**

Frequency of cannabis use disorder in adult cannabis users in 2017<sup>6</sup>



Dosages available of FDA-approved dronabinol, an encapsulated pure THC, in milligrams: **2.5 mg, 5 mg, and 10 mg**<sup>2</sup>



**6** Maximum number of doses of dronabinol recommend per day<sup>2</sup>



**18**

Number of clinical trials on the pharmacology of medical cannabis in oncology as of 2019<sup>3</sup>

Number of clinical trials on cannabis and cannabinoids for pain as of 2019<sup>4</sup>

**25**

**47** Minimum number of states that have enacted legislation to regulate industrial hemp cultivation and production<sup>8</sup>

**33** Number of states where medical use of cannabis is legal (+ District of Columbia, Guam, Puerto Rico, and the US Virgin Islands)<sup>9</sup>

**14** Number of states and territories that have approved adult-use cannabis<sup>9</sup>

*All images courtesy of Wikimedia Commons.*

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# Cannabis, Health Care, and Federal Law

By Rod Kight, Attorney at Kight on Cannabis,  
Asheville, North Carolina

Health care professionals are in the unique and difficult position of being increasingly pressed to give guidance about cannabis at a time when it is challenging to identify reliable information. Indeed, the discovery of the endocannabinoid system (ECS), and the fact that it can be modulated by exogenous phytocompounds called cannabinoids produced by the *Cannabis sativa* L. plant (cannabis), has sparked a revolution in health care. A primary aim of this journal is to help medical professionals sort through the disparate claims regarding cannabis and obtain reliable information.

Although the ECS was discovered in 1964,<sup>1</sup> studies about it were severely limited for many decades due to the Schedule I controlled status (the most restrictive) of cannabis under the federal Controlled Substances Act (CSA). Fortunately, several changes in the law over the past 20 years have created opportunities to study the health properties of cannabinoids. These changes include the legalization of cannabis under the laws of many states, the liberalization of cannabis laws in several countries, and the removal of hemp from the CSA. The result is a patchwork of legal options for studying cannabis. Consequently, there has been a rapid rise in the number of

cannabis studies in the past 2 decades, with many promising results.<sup>2</sup>

Advancements in understanding the ECS have not been overlooked by the general public, which has demanded both answers about cannabis as a medicine and access to it. On the one hand, cannabinoids produced by cannabis clearly have medicinal benefits.<sup>3-5</sup> This is evidenced by numerous clinical studies,<sup>1</sup> 2 recent World Health Organization reports,<sup>4,5</sup> and even a government patent.<sup>6</sup> On the other hand, it is easy to get overwhelmed by the spectrum of various claims regarding cannabis. In some circles “reefer madness” propaganda, which portrays cannabis as a threat to health and civil society, still reigns. In others, cannabis is presented as a cure-all elixir that will save the planet. The truth lies somewhere in between.

A significant problem facing the medical community regarding cannabis is the confusing legal framework within which clinicians must operate. Federal and state statutes and regulatory schemes are frequently in conflict and are rapidly evolving. There is much “grey” area. Additionally, despite a lack of significant botanical difference between marijuana and hemp, both of which are cannabis, the laws governing each are radically different.

For instance, federal law governs cannabis largely in 2 ways. The first is by virtue of its classification under the CSA. Cannabis that meets the legal definition of hemp is

**Table. Hemp vs Marijuana<sup>7</sup>**

	Hemp	Marijuana
Definition	“... the plant <i>Cannabis sativa</i> L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a <b>delta-9 THC concentration of not more than 0.3%</b> on a dry weight basis” <sup>8</sup>	“... all parts of the plant <i>Cannabis sativa</i> L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term <b>does not include the mature stalks</b> of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, <b>or the sterilized seed of such plant which is incapable of germination</b> ” <sup>9</sup>
Regulatory agency	USDA, FDA	DEA, FDA
Types of use	Ingredient in body products, cosmetics, and supplements; textiles and fabrics; and other manufactured and industrial products	Recreational and medicinal products

DEA, Drug Enforcement Administration; FDA, Food and Drug Administration; THC, tetrahydrocannabinol; USDA, US Department of Agriculture

Table adapted from Congressional Research Service. *Defining Hemp: A Fact Sheet*. March 22, 2019: R44742.



not controlled. (In this context *controlled* is a legal term of art, referring to a substance's listing on the CSA.) However, and with the exception of the mature stalks and nongerminating seeds of the plant, cannabis that does not meet the definition of hemp is marijuana, a Schedule I controlled substance (Table).<sup>7</sup> The sole difference between illegal marijuana and lawful hemp is the plant's concentrations of delta-9-tetrahydrocannabinol (THC). Thus, the source of a cannabinoid determines its legal status.

This concept is colloquially known as the "Source Rule," which I developed several years ago.<sup>10</sup> It informs the definition of hemp in the Agricultural Improvement Act of 2018, which holds that hemp-derived cannabinoids (and other extracts and compounds) are not controlled substances. Those same cannabinoids are a controlled substance when derived from marijuana. For instance, the cannabinoid cannabidiol (CBD) is a Schedule I controlled substance when derived from marijuana, a Schedule V controlled substance when in the form of the US Food and Drug Administration (FDA)-approved seizure drug Epidiolex (also derived from marijuana), or not a controlled substance when derived from hemp.

The second way that federal law regulates cannabis is through application of the federal Food, Drug, and Cosmetics Act (FDCA). In fact, one of the biggest developments for both the medical community and the cannabis industry is the emergence of the FDA as the primary federal agency regulating cannabis and all CBD that is marketed for use by humans and animals. This role is becoming increasingly important due to the rapidly expanding market in cannabis products.

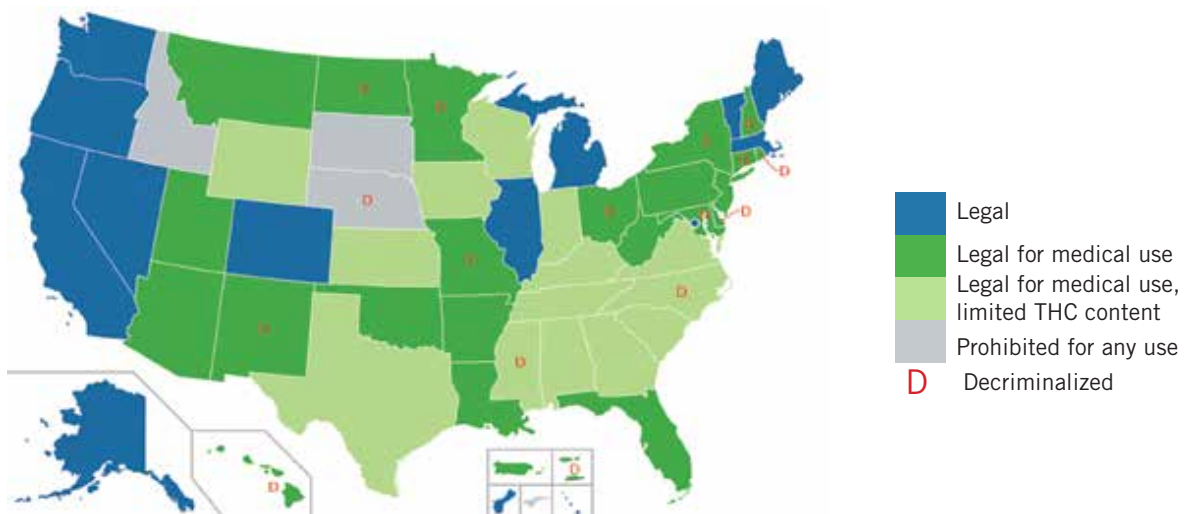
**"A significant problem facing the medical community regarding cannabis is the confusing legal framework within which clinicians must operate. Federal and state statutes and regulatory schemes are frequently in conflict and are rapidly evolving. There is much 'grey' area."**

**—Rod Kight**

The FDA held the first public hearing about cannabis on May 31, 2019.<sup>11</sup> In the hearing, the FDA solicited comments and information about cannabis from a diverse group of stakeholders across the industry, including representatives from pharmaceutical companies, media companies such as Consumer Reports, small consumer products companies, manufacturers, farmers, lawyers, physicians, cannabis advocates, and prohibitionists.

I testified at this historic event and noticed that the single thread uniting all of the disparate testimony was a call for clear regulations.<sup>12</sup> Although most of the testimony focused on CBD, it appears that the FDA intends to take a long view and will likely (hopefully) create a coherent regulatory framework that encompasses all consumer products formulated with cannabis and its hundreds of phytocompounds. We do not know when the FDA will issue its regulations

► continued on page 10



**Figure.** Map showing legal status of cannabis in the United States.

**Photo credit:** Image courtesy of Lokal Profil, Wikimedia Commons.

## Cannabis, Health Care, and Federal Law

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or what they will look like. In the meantime, the cannabis industry continues to grow apace, and consumers and medical providers alike are required to sort through a mounting array of products in order to separate snake oil from medicine. The FDA reopened the public comment period through September 30, 2019.<sup>13</sup>

With respect to CBD, the new darling of the natural products industry, the FDA's current position is that it may not be marketed as a food or dietary supplement and, aside from Epidiolex, therapeutic claims cannot be made about products containing CBD.<sup>14</sup> Importantly, this does not depend on the source of CBD, which only determines its controlled status under the CSA. Although the FDA has not taken an aggressive stance about the inclusion of CBD in food, it has enforced its position regarding therapeutic claims by sending dozens of warning letters to companies for making such claims on product labels and other marketing materials.<sup>15</sup> I expect that we will see more of this type of enforcement by the FDA in the coming months.

The FDA's current position on CBD raises many issues. For example, is there a legal distinction between products formulated with the purified CBD molecule (known in the industry as "CBD isolate") and products formulated with cannabis extract, which contains CBD among other phytonutrients, such as cannabinoids, terpenes, and sesquiterpenes? Most legal commentators, including myself, contend that there is a legal distinction. (This was the subject of my testimony to the FDA.) However, to date, the FDA has not made this distinction and no courts have ruled on it.

Additionally, to what degree can medical professionals recommend CBD to their patients? Does the answer to that question change if the medical professional owns an interest in a company that makes CBD products? What if the medical professional's products are sold in the waiting room? Although I contend that medical professionals are free to discuss CBD and to recommend it to their patients (subject, of course, to the laws of their respective states and the source of the CBD), my position changes if the medical professional also sells CBD products in the office. Can the average patient distinguish between representations about CBD made by the provider while acting in the role of medical advisor vs when the provider is acting as salesperson? Answers to these questions, and many more, are an urgent national priority to protect the public's health.

Unfortunately, regulators are struggling to keep pace with the rapid development of the cannabis industry and to provide coherent answers to important questions. As a lawyer advising clients in the industry and writing about it for a medical journal, my primary role is to identify and discuss legal issues that emerge during the rise of cannabis as a force in medicine. I intend to explore cannabis-related legal questions and issues in the *American Journal of Endocannabinoid Medicine*.


Thank you for reading this issue. I look forward to taking this exciting journey with you.

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# American Journal of Endocannabinoid Medicine

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Original research,  
expert opinion, and  
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# Medical Cannabis Intervention Improves Symptoms, Quality of Life Among Skilled Nursing Home Residents

*A commentary on Palace ZJ et al. Medical Cannabis in the Skilled Nursing Facility: A Novel Approach to Improving Symptom Management and Quality of Life. J Am Med Dir Assoc. 2019;20(1):94-98.*

By Michael Patterson, NHA, OTR/L, Chief Executive Officer,  
US Cannabis Pharmaceutical Research and Development

A study recently published by Palace et al. in the *Journal of the American Medical Directors Association*, is the first to describe a medical policy and procedure for legally obtaining and using medical cannabis for symptom management in a skilled nursing facility (SNF).<sup>1</sup> Although the study was exploratory in nature (N=10), it provides other SNFs across the United States with a framework within which to use medical cannabis in their facilities.

In 2016, the Compassionate Care Act of New York legalized the use of medical cannabis in New York State

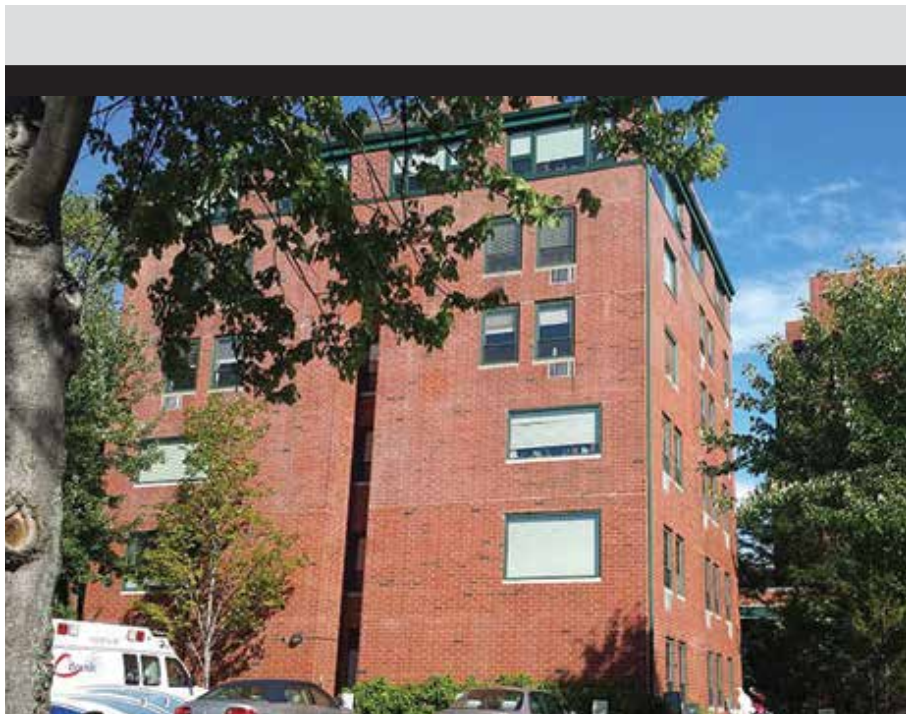
for patients with cancer, HIV, AIDS, amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, Huntington's disease, spinal cord damage with neurologic sequelae, seizure disorder, inflammatory bowel disease, neuropathy, chronic pain, opioid use, and post-traumatic stress disorder. However, because SNFs receive Medicare and Medicaid funding, they are unable to purchase/store medical cannabis or administer it to residents.

## Medical Cannabis Intervention

The authors of the study, Zachary J. Palace, MD, CMD, Medical Director, Hebrew Home at Riverdale, and Daniel A. Reingold MSW, JD, President and CEO of Hebrew Home at Riverdale, created a program at their SNF that would allow the residents to legally obtain and use medical cannabis for symptom management within the SNF.

As part of the program, residents participating in the New York State Medical Marijuana Program could purchase cannabis directly from a state-certified dispensary. The patients are required to secure the product in a lockbox provided by the facility. The medical cannabis must be self-administered or administered by a caregiver who is not a staff member. Cannabis administration was limited to oral forms (capsules or cannabis oil drops) because of the facility's no smoking/vaping policy.

Of the 10 residents (62–100 years



Hebrew Home at Riverdale, New York.

Photo credit: PointsofNoReturn, Wikimedia Commons.



**Table. Resident Comments and Observations of Medical Cannabis by Diagnosis in a Skilled Nursing Facility**

Diagnosis	Comments/Observation
Pain	Less discomfort, coming out of room more
	Improved appetite, reduced opioid dose by 50%
	Participating more in activities
	Improved sense of well-being, reduced opioid dose by 50%
	Feels better overall
	Pain improved, opioid changed to prn
Parkinson's disease	Minimal effect
	Mild reduction in stiffness
Parkinson's disease/pain	Mild improvement in pain
Seizure	Resident nonverbal due to advanced dementia Staff observing significant reduction in seizures

Table adapted from Palace and Reingold.<sup>1</sup>

of age) who participated in the program, eligible diagnoses included chronic pain (n=6), Parkinson's disease (n=2), comorbid chronic pain and Parkinson's disease (n=1), and seizure disorder (n=1). Three patients withdrew from the program because of financial reasons, and the remaining 7 received medical cannabis for more than 1 year. Additionally, other residents cited expense as a factor limiting their participation in the program.

### Promising Results

Study findings revealed improvements in quality-of-life measures among the residents who participated in the medical cannabis program. Residents reported sustained improvement in chronic pain severity resulting in reduced use of opioids and improved sense of well-being, improved rigidity complaints in the 2 patients with Parkinson's disease, and marked reduction in seizure activity (down from twice weekly to 1 to 2 episodes per month on average) in the patient with seizure disorder (Table).

### Clinical Implications

As a 25-year veteran of the SNF industry and former chief operating officer of a 20 SNF chain in multiple states, I believe this study represents a large step forward in an otherwise conservative industry. The findings demonstrate that it is possible for SNFs to provide medical cannabis for patients without violating federal law.

One of the limitations of this study was the lack of discussion about adjusting the dosage of medical cannabis in order to decrease unwanted side effects mentioned (poor concentration and sedation) or increase

positive aspects of the treatment (decrease seizures, decreased pain). Because patients are required to self-medicate, there is no way to determine what time of day the patient used the cannabis or what dosage was given. Set timetables for administration of the treat-

ment would allow for a better analysis of benefits. Furthermore, the study did not mention any decrease in use of prescription medications, other than opiates, once medical cannabis was implemented into the resident's treatment regimen.

Although the majority of SNF operators cite federal law as the reason they are unable to use medical cannabis in their facilities, this study serves as a framework for other SNFs who wish to conduct medical cannabis research. Additionally, it will decrease the stigma of cannabis among SNF patients and the fear of SNFs losing their federal funding. Finally, the use of medical cannabis will give physicians another tool for improving the quality of life for SNF residents.

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1. Palace ZJ, Reingold DA. Medical cannabis in the skilled nursing facility: a novel approach to improving symptom management and quality of life. *J Am Med Dir Assoc*. 2019;20(1):94-98.

# Cannabidiol in the Management of Comorbid Rheumatoid Arthritis, Lupus, and Raynaud's Disease

By Christian Shaw, MD, PhD, Halcyon Therapeutics LLC, Phoenix, Arizona  
and Jahan Marcu, PhD, Editor in Chief

## Introduction

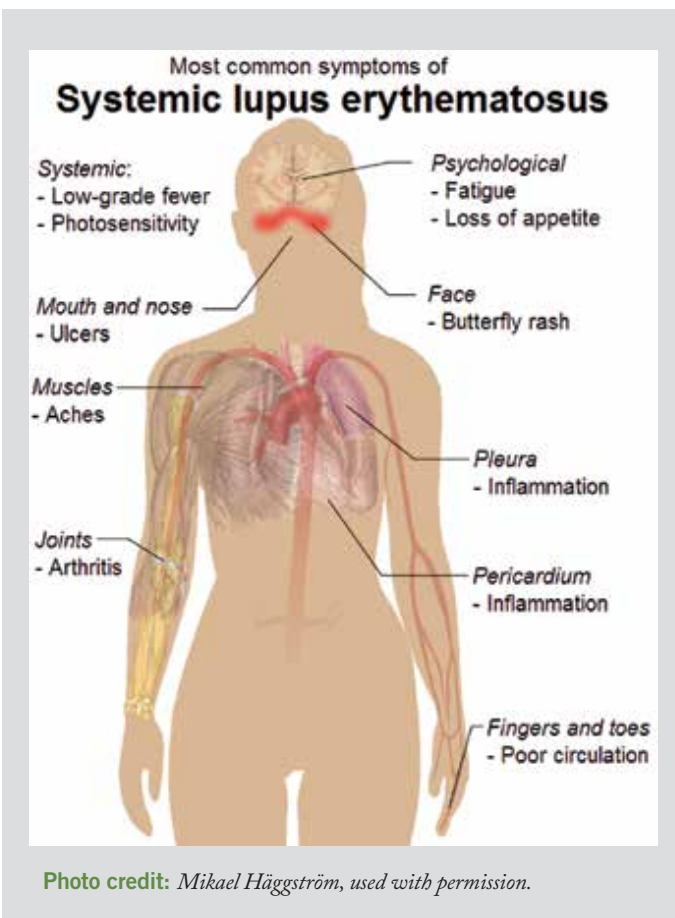
Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Raynaud's disease, are chronic inflammatory autoimmune diseases characterized by pain, inflammation, and fatigue.<sup>1-3</sup> Treatment presents a clinical challenge for several reasons, including the progressively degenerative nature of autoimmune diseases, the involvement of multiple pain mechanisms, and the adverse side effects of pain medications. Even pain treatments with low addiction profiles may pose an implicit risk, such as liver or kidney toxicity.

Presently, there are limited, if any, modern studies examining the effects of cannabidiol (CBD) products on pain and other outcomes in RA, SLE, or Raynaud's disease.<sup>4</sup> This case

report describes the potential efficacy and safety of a daily, high-dose, medical grade CBD product (ie, "Hemp CBD") in the treatment of persistent pain and inflammation in a patient with multiple autoimmune disorders.

In autoimmune disorders such as RA, SLE, and Raynaud's disease, an abnormal and chronic inflammatory response occurs in various tissues that over time results in the observed degenerative features and symptoms of the conditions. For many patients with these diseases, pain and accompanying loss of mobility are the most common and debilitating daily symptoms.

Currently, use of cannabinoids in the treatment of autoimmune conditions in the United States presents both clinicians and patients with considerable challenges, including the lack of conformity between individual state and federal cannabis/hemp laws, minimal funding to support the clinical study of hemp- and cannabis-derived products, heterogeneity of patient symptomology (particularly in elderly patients), and quality inconsistency of cannabis/hemp-derived products.<sup>4-6</sup> Multiple substantiated sources suggest that CBD's anti-inflammatory properties are significant.<sup>7,8</sup> There also are anecdotal patient reports of symptom relief when using CBD products for inflammatory conditions. However, there currently is a lack of general knowledge about the effect of cannabinoids in autoimmune diseases and potential dosing regimens. The authors of a recent meta-analysis stated that, "There are no clinical trials of medical cannabis in rheumatology arthritis."<sup>9</sup> A few studies have investigated the effects of cannabis obtained outside of a state program (ie, illicitly) in RA, but to our knowledge, no previously published clinical data or case reports exist on the efficacy of CBD-containing products compliant with state and federal regulations outlined in the 2018 Farm Bill in patients suffering from advanced autoimmune disorders.<sup>6,10</sup> The aim of this article is to provide clinicians and patients with new insights on treatment and dosing applications of CBD for inflammatory disorders.



**Table 1. Medication History**

Medication	Dosage	Condition	Provider	Duration, Year
Gabapentin	300 mg daily	Pain	Primary Care 1	30 days, 2015
Gabapentin	600 mg daily	Pain	Primary Care 1	60 days, 2015
Gabapentin	1200 mg daily	Pain	Primary Care 1	90 days, 2015
Prednisone	20 mg daily	Inflammation	Primary Care 2	30 days, 2016
Methocarbamol	500 mg PO, 4x daily	Pain	Primary Care 2	30 days, 2016
Potassium	1500 mg (20 mEq) daily	Muscle cramping	Primary Care 2	30 days, 2016
Tramadol	50 mg as needed, but not to exceed 150 mg daily	Pain	Primary Care 2	30 days, 2016
Prednisone	20 mg daily	Inflammation	Primary Care 2	90 days, 2017
Tizanidine	4 mg PO x 8 h	Pain	Primary Care 2	30 days, 2017
Prednisone	10 mg daily	Swelling	Rheumatologist	1 year, 2018
Leflunomide	20 mg daily	Inflammation	Rheumatologist	1 year, 2018
Amlodipine	10 mg daily	Finger ulcers	Rheumatologist	1 year, 2018
Nitro paste	25 mg nightly	Finger ulcers	Rheumatologist	1 year, 2018
CBD isolate medium-chain triacylglyceride oil tincture	600 mg daily	Pain	Preventive Medicine Physician	60 days, 2019
CBD isolate medium-chain triacylglyceride oil tincture	400 mg daily	Pain	Preventive Medicine Physician	60 days, 2019
CBD isolate medium-chain triacylglyceride oil tincture	200 mg daily	Pain	Preventive Medicine Physician	Present

## Medical History

The patient is a 50-year-old woman with pain and mobility-related symptoms of multiple autoimmune disorders. She was diagnosed with Raynaud's disease in 2015, RA in 2016, and SLE as well as scleroderma in 2017. She has been managed by conventional treatments (eg, gabapentin, prednisone, tramadol, tizanidine, and leflunomide) on and off for many years, achieving only intermittent alleviation of her pain, inflammation, and joint swelling (Table 1). Moreover, prolonged use of prednisone (at doses of 10–20 mg/d) and nonsteroidal anti-inflammatory drugs resulted in significant adverse events that now prevent the patient from safely tolerating the ongoing use of these agents.

## Assessment

The patient presents with subjective complaints including pain and swelling of the hands, low back, hips, right knee, and feet, with exacerbations of low back and hip pain. The patient reports that the pain limits her ability to sit or walk. She reports enduring daily pain at work and a typical pain score of 7/8 out of 10. On an average of 2 out of every 20 work days, when the pain reached a 10 and her

“feet were so swollen she couldn't wear any shoes or walk at all,” she had to call in sick. Objective assessment indicated decreased range of motion in the cervical, thoracic, and lumbar spine; decreased range of motion and strength in shoulders bilaterally; and decreased strength of the right lower limb. With the exception of bilateral pedal edema, no other significant swelling was found. Laboratory evaluation revealed significantly elevated levels of the inflammatory biomarkers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR; Westergren method).

## Management

The patient discontinued all disease modifying anti-rheumatic drugs (DMARDs) 2 weeks prior to start of study to ensure an extended washout period occurred. She was started on a 28-day regimen of highly purified (99.9%) CBD isolate medium-chain triacylglyceride oil tincture (Figure 1 provides potency analysis). The CBD was administered sublingually at a dose of 200 mg (by 1-mL dropper), 3 times daily. The patient completed the McGill Pain Questionnaire and 36-Item Short Form Survey 1.0 (SF-36) immediately

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**CASE REPORT**

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before treatment and on day 28. Confirmatory urine drug testing and blood analysis were performed on the final day of treatment by independent third-party laboratories (Quest Diagnostics and TriCore Laboratories, respectively).

**Follow-Up**

Significant improvement of pain and mobility-related symptoms was reported within 72 hours of treatment, reaching a maximum therapeutic effect by day 10. Symptoms related to mood (decreased anxiety, increased sense of well-being) continued to improve up to day 21 of treatment and remained increased until day 28. McGill Pain score decreased from 52 of 78 pretreatment to 25 of 78 on day 28 (Tables 2–4). SF-36 scores improved considerably across all 9 health domains (Table 4).

Pretreatment CRP and ESR values were 4.4 and

**“Laboratory blood analysis demonstrated decreased inflammatory markers by day 28, further substantiating the patient’s self-reported improvement from a biochemical perspective.”**  
**—Christian Shaw, MD, PhD**

**Table 2. McGill Pain Questionnaire, Section 1: What Does Your Pain Feel Like?**

Group #	Descriptor	Pre treatment	Day 28	Net difference
1	Temporal	4	1	3
2	Spatial	1	1	0
3	Punctate pressure	4	2	2
4	Incisive pressure	1	1	0
5	Constrictive pressure	4	2	2
6	Traction pressure	3	1	2
7	Thermal	2	1	1
8	Brightness	4	3	1
9	Dullness	4	1	3
10	Sensory, miscellaneous	4	1	3
11	Tension	3	1	2
12	Autonomic	1	1	0
13	Fear	2	1	1
14	Punishment	2	1	1
15	Affective-evaluative-sensory	2	1	1
16	Evaluative	3	1	2
17	Sensory, miscellaneous	3	1	2
18	Sensory, miscellaneous	2	2	0
19	Sensory	2	1	1
20	Affective-evaluative-sensory	2	1	1

**Table 3. McGill Pain Questionnaire, Section 2: How Does Your Pain Change With Time?**

Question	Pretreatment		Day 28	
	Response	Points	Response	Points
Which word or words would you use to describe the pattern of your pain?	Continuous, steady, constant	1	Brief, momentary, transient	3

**Table 4. McGill Pain Questionnaire, Section 3: How Strong Is Your Pain?**

Question	Pretreatment		Day 28	
	Response	Points	Response	Points
Which word describes pain right now?	Excruciating	5	Mild	1
Which word describes it at its worst?	Excruciating	5	Distressing	3
Which word describes it when it is least?	Discomforting	2	Mild	1





**Figure 1.** Laboratory testing result of the cannabidiol product.

% = % (w/w) = Percent (Weight of Analyte / Weight of Product)

\* Total Cannabinoids results reflects the absolute sum of all cannabinoids detected.

\*\* Total Potential THC/CBD is calculated using the following formulas to take into account the loss of a carboxyl group during decarboxylation step.

Total THC = THC + (THCa \* (0.877)) and Total CBD = CBD + (CBDa \* (0.877))

**CBD**, cannabidiol; **CBG**, cannabigerol; **THC**, delta-9-tetrahydrocannabinol.

For the complete laboratory report, please visit [www.ajendomed.com](http://www.ajendomed.com).

**Table 5.** Scores on the SF-36

Scale	Pretreatment, %	Day 28, %
Physical functioning	15	50
Role limitations due to physical health	0	75
Role limitations due to emotional problems	0	67
Energy/Fatigue	0	70
Emotional well-being	36	76
Social functioning	0	88
Pain	23	90
General health	15	15
Health change	0	100

SF-36, 36-Item Short Form Survey 1.0.

48 mg/dL, respectively. At day 28, these values were 2.2 and 39 mg/dL, respectively. Adverse effects of treatment were mild and transient, and were limited to esophageal and stomach irritation after swallowing the CBD tincture.

### Conclusion

Since completion of the 28-day CBD trial at the end of December 2018, the patient has been using nothing but CBD for her conditions with much success. Her CBD dose was titrated from 600 mg daily for 2 months, to 400 mg daily for 2 months, and 200 mg daily thereafter. The patient discontinued DMARDs 2 weeks prior to start of study and has not resumed any prescribed medications for rheumatic diseases since that time nor does she have any interest in doing so.

She no longer feels it necessary to see her

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rheumatologist. Notably, prior to participating in the CBD trial, the patient's rheumatologist intended to start her on a biologic due to her lack of response with conventional DMARDs.

This case demonstrates that a highly purified (99.9%) CBD isolate tincture of 600 mg daily was well tolerated and appeared highly effective in decreasing systemic inflammation while improving quality of life and pain scores on highly validated assessment tools. CBD did not appear to affect the kinetics of existing medications or lead to significant drug–drug interactions.

## Discussion

An increasing number of reports and articles on individuals with RA using cannabis to treat their symptoms is available, although systematic studies regarding efficacy in conditions such as RA, and in patients facing multiple autoimmune conditions, are lacking.<sup>1,7–12</sup> In this case study, the patient reported experiencing significant pain relief after 72 hours of high-dose CBD treatment. The patient reported greatly improved mobility and mood experienced by approximately day 10. Multidomain quality-of-life metrics reinforced the findings, indicating marked improvement between assessments taken pretreatment and on day 28 of treatment. Laboratory blood analysis demonstrated decreased inflammatory markers by day 28, further substantiating the patient's self-reported improvement from a biochemical perspective. Finally, confirmatory urine drug testing proved absent for any detectable tetrahydrocannabinol, a considerable finding within itself, as many patients suffering from inflammatory pain disorders are reluctant to use CBD products due to workplace drug testing concerns.<sup>13</sup>

Although this study is limited in its generalizability as an N=1 case report, the results are encouraging and highlight the need for future well-controlled clinical trials to investigate the efficacy of commercially available, federal and state regulatory-compliant CBD products as additional therapeutic options for inflammatory and autoimmune conditions.

Additionally, we call for the implementation of a publicly available database for cataloging clinical outcome data on commercially available and regulatory-compliant

CBD products used for medical conditions. This would enable such information to be systematically mined for therapeutically relevant insights, especially in the absence of much needed evidence-based research, to guide clinical decisions on CBD and cannabinoid-based treatment options until the appropriate randomized control trials are completed.

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*Dr. Marcu provides consulting, advising, and education services to licensed cannabis operators, private companies, regulatory bodies, and universities. He serves on PAX' health advisory board and as an advisor to Navigator Genomics.*

*Dr. Shaw has no financial information to disclose.*

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# Association Is Not Causation in Cannabis Research

By Jahan Marcu, PhD, Editor in Chief

“There is no research on cannabis” is a myth conception frequently encountered. Yet, while stating there is no research on cannabis, many sources are still willing to infer causality and contend that cannabis is both the cause of and answer to various health problems.

A search for “cannabis” on the Web of Science yields more than 100,000 articles; thus, the first part of our mythic tale is a nuanced misconception. Although it is true that cannabis research in the United States is restricted, it would take a lifetime to read all the studies published over the past 100 years. The studies that have been approved are largely observational studies and case reports (Figure). Thus, they are limited due to lack of control and the potential influence of confounding variables, and typically are not appropriate for the purposes of inferring causation.<sup>1</sup> However, these studies are useful as foundational information, hypothesis generation, and when enough of them exist around a particular subject, the data can be mined to shed light on potential causal relationships.

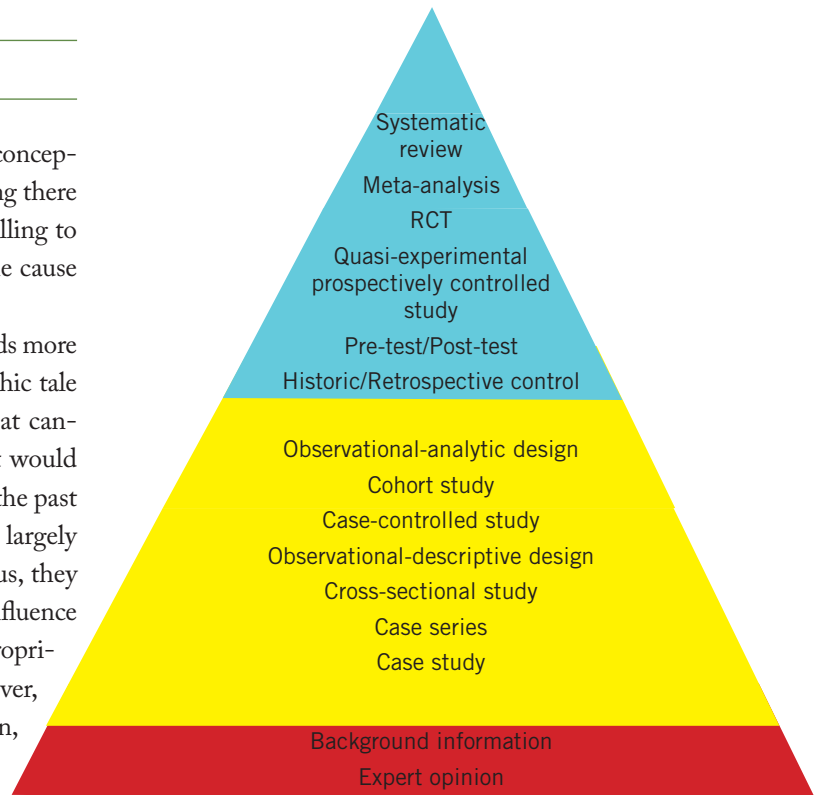
**“A handy strategy for navigating cannabis and hemp claims is to mentally replace all references to causal effects with references to associations.”**

**—Jahan Marcu, PhD**

Due to the nature of observational studies, much of the data presents as associations or correlations with cannabis. So, event A and event B can be linked to each other, but not causally. For example:

*“Case in point: Are you aware that there’s a 95% correlation between cheese sales and the number of people who’ve strangled themselves by their own bed sheets in the past 10 or 20 years? There’s also the classic example that links ice cream sales and drowning. These examples may demonstrate an association or link but perhaps are better explained by secondary correlations. ...*

*One can say that coffee causes people to be jittery if they drink too much. But no one contends that drinking a cup of coffee will give you attention-deficit hyperactivity disorder (ADHD). Similarly, too much THC, while not fatal, can trigger transitory*



**Figure. Studies on cannabis are primarily observational; limitations include lack of control and confounding variables.**

*anxiety or paranoia, but that doesn’t mean THC causes mental illness. If a drug immediately triggers an experience or has an effect that mimics the symptom of a disease, it doesn’t necessarily mean that the drug causes that disease.”<sup>2</sup>*

Many sources confuse association with causation when assessing the risks and benefits of cannabis. A handy strategy for navigating cannabis and hemp claims is to mentally replace all references to causal effects with references to associations. Causal questions in an observation study are difficult to formulate; hence, randomized controlled trials provide more experimental control and can infer causality. An observational study cannot prove causation unless painstakingly designed to do so.

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# Next Generation of Liposomal Delivery for Cannabidiol From a Hemp Extract: A Safety Study

By Emek Blair, PhD, CELLg8 and Valimenta Labs, Fort Collins, Colorado

## Abstract

A human clinical safety study examined the alterations in the blood profiles of 10 healthy adults before and after taking CELLg8™ Hemp—an advanced liposomal cannabinoid preparation standardized for cannabidiol—daily for 30 days. Primary outcome measures were the comprehensive metabolic panel and complete blood count. Results showed that of 340 blood tests administered, 339 improved or remained the same at day 30. One patient showed an increase in absolute eosinophil or neutrophil count from 319 to 573 cells/ $\mu$ L (normal range, 15–500 cells/ $\mu$ L). Furthermore, all 5 individuals who had high glucose levels at baseline showed normal levels on day 30 of liposomal cannabidiol treatment. In conclusion, this study demonstrated the safety of CELLg8™ Hemp and the potential efficacy of this preparation to lower fasting blood glucose levels.

**“Our results are very promising and additional work is in the planning stages to further delineate the mechanism of action of CBD on glucose levels, and to confirm the present findings.”**

—Emek Blair, PhD

## Introduction

Although there are numerous mouse and animal studies on cannabidiol (CBD), there are limited human studies and no credible randomized controlled human safety studies in the literature.<sup>1</sup> To our knowledge, this is the first human study to assess the safety of CBD in a liposomal CBD preparation. The purpose of the study was to investigate the safety (ie, lack of negative effects on blood profiles) of taking a liposomal CBD product for 30 days. Puffin Hemp (<http://www.puffinhemp.com>) has a patent-pending proprietary liposome manufacturing technology, CELLg8™, that is used to make highly bioavailable CBD preparations. Additionally, this product uses natural liposomes to

increase the amount of hemp actives that quickly enter the bloodstream, which is the subject of a paper to be published in the next issue of *American Journal of Endocannabinoid Medicine*.

## Methods

### Materials

Liposomal CELLg8 CBD, derived from industrial hemp, was provided from Puffin Hemp's stock production. Each 1 mL contains 10 mg of CBD from full-spectrum hemp extract, lipids derived from non-GMO sunflowers, tetrahydrocannabinol <0.05%, water <1 microS/cm, with natural plant extracts used to mask the hemp flavor for compliance.

### Study Population

Participants were recruited from the general population in Colorado using the following inclusion criteria:

- 25 to 70 years of age
- Ability to read and sign the informed consent and complete the protocol
- Ability to comply with study requirements and study schedule
- Not taking a CBD product at baseline
- In good general health

Exclusion criteria included the inability to complete the protocol and the presence of a terminal illness.

### Study Design

The study included 10 healthy individuals. At the first visit, the participants were given a 1-month supply of liposomal CBD, and after fasting for 8 hours, completed a baseline blood draw to assess comprehensive metabolic panel (CMP; 16 measures) and a complete blood count (CBC; 18 measures). After taking 10 mg of liposomal CBD daily for 30 days without any lifestyle changes, participants returned for a repeat blood draw. CMP and CBC measures from both time points were compared.

## Results

Of 340 blood tests that were administered (on the CMP and CBC combined), 339 remained relatively the same or



**Table 1. Excerpt of Comprehensive Metabolic Panel From Baseline to Day 30 of Taking Liposomal CBD**

Participant	Test	Baseline value	Day 30 value	Normal range	Change from baseline
2	BUN	28 mg/dL	28 mg/dL	7–25 mg/dL	H to H
3	Glucose	100 mg/dL	88 mg/dL	65–99 mg/dL	H to N
3	ALT	30 U/L	20 U/L	6–29 U/L	H to N
4	Glucose	103 mg/dL	87 mg/dL	65–99 mg/dL	H to N
4	CO <sub>2</sub>	30 mmol/L	31 mmol/L	18–30 mmol/L	N to H
5	Glucose	106 mg/dL	94 mg/dL	65–99 mg/dL	H to N
7	Glucose	109 mg/dL	91 mg/dL	65–99 mg/dL	H to N
8	Glucose	141 mg/dL	99 mg/dL	65–99 mg/dL	H to N
10	Creatinine	1.12 mg/dL	1.17 mg/dL	0.5–99 mg/dL	H to H
10	Bilirubin	1.3 mg/dL	1.2 mg/dL	0.5–1.2 mg/dL	H to N

ALT, alanine transaminase; BUN, blood urea nitrogen; CBD, cannabidiol; CO<sub>2</sub>, carbon dioxide; H, high; L, low; N, normal.

**Table 2. Complete Blood Cell Count Measures From Baseline to Day 30 of Taking Liposomal CBD**

Participant	Test	Baseline value	Day 30 value	Normal range	Change from baseline
1	RBC count	3.95 million/ $\mu$ L	4.28 million/ $\mu$ L	3.96–5.31 million/ $\mu$ L	L to N
2	Hematocrit	39%	45.6%	41.5%–53.8%	L to N
2	Absolute EOC or absolute neutrophils	319 cells/ $\mu$ L	573 cells/ $\mu$ L	15–500 cells/ $\mu$ L	N to H
4	Hb	18.5 g/dL	18.4 g/dL	13.7–17.7 g/dL	H to H
4	MPV	13.2 fL	13.5 fL	7.5–12.5 fL	H to H
6	Hb	11.7 g/dL	11.6 g/d	13.7–17.7 g/dL	L to L
6	Hematocrit	36%	35.9%	41.5%–53.8%	L to L
6	MCH	26.52 pg	26.6 pg	27–33 pg	L to L
6	RDW	15.6%	15.9%	11%–15%	H to H
9	Absolute lymphocytes	617 cells/ $\mu$ L	536 cells/ $\mu$ L	850–3900 cells/ $\mu$ L	L to L
9	Absolute EOC	9 cells/ $\mu$ L	8 cells/ $\mu$ L	15–500 cells/ $\mu$ L	L to L

EOC, eosinophil count; H, high; Hb, hemoglobin; L, low; MCH, mean corpuscular hemoglobin; MPV, mean plasma volume; N, normal; RBC, red blood cell; RDW, red cell distribution width.

improved after 30 days of daily consumption of liposomal CBD. Additionally, 7 of the 10 participants in this study who had at least 1 CMP or CBC measure that was above or below the reference range at baseline showed normal levels after taking liposomal CBD for 30 days.

Two participants had a measure that changed from normal to high at day 30. Participant 4 showed a small increase in blood carbon dioxide that was not considered clinically significant (ie, an increase from 30 to 31 mmol/L that was 1 mmol/L over the normal range; see Table 1). Participant 2 experienced an increase in absolute eosinophil or neutrophil count to 73 cells/ $\mu$ L higher than the normal range (Table 2).

On the CMP measures, 7 of 10 of the measures that were above or below the normal range at baseline normalized after taking liposomal CBD for 30 days (Table 1). A striking improvement in fasting glucose levels was observed in all 5 participants who had above-average glucose levels at baseline. Additionally, 1 of the participants initially had out-of-range alanine transaminase and bilirubin assay values that were normalized after taking liposomal CBD for 30 days. Two of the participants who had higher-than-normal creatinine levels at baseline remained in the high range at day 30, and 1 participant with a high range blood urea nitrogen level at baseline remained in the high range at day 30.

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## SAFETY

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On the CBC measure, 5 participants had out-of-range values at baseline (Table 2). The red blood cell count for 1 participant and the hematocrit value for 1 participant normalized. The other values that were out of range did not normalize, but did not worsen.

## Discussion

Results of this study demonstrated that no deleterious effects of liposomal CBD on CMP or CBC measures were found in any of the 10 participants after taking this product on a daily basis for 30 days. Additionally, 10 measures were normalized at day 30. The findings suggest that liposomal CBD, when used in this healthy population, is safe.

Additionally, all participants reported satisfaction with the liposomal CBD formulation and said that they would like to continue taking this product in the future.

It is believed that CBD and other cannabinoids are nontoxic, with no known fatal overdose levels reported.<sup>1</sup> Results of this study further substantiate this idea.

In the present study, 8 of 10 participants maintained normal bilirubin levels; whereas 1 had their bilirubin normalize over the 30-day period. In contrast, a recent study found hepatotoxicity of CBD in a mouse model.<sup>2</sup> The present findings are in line with other research suggesting that CBD may protect the liver from alcohol-induced damage<sup>3</sup> and ischemia reperfusion injury.<sup>4</sup>

Although all the markers remained relatively constant over time, blood glucose was the exception. All 5 participants who exhibited a high glucose level at baseline showed normal levels after taking liposomal CBD for 30 days. Mouse studies have shown that CBD reduced pancreatic inflammation in a mouse model.<sup>5</sup> Data from the National Health and Nutrition Examination Survey found that current marijuana users had lower fasting insulin levels and lower homeostasis model assessment of insulin resistance than non- or past users.<sup>7</sup> Our results are very promising and additional work is in the planning stages to further delineate the mechanism of action of CBD on glucose levels, and to confirm the present findings.

Additionally, data from a mouse model of nonobese diabetic mice suggests a positive or neutral effect of cannabinoid ingestion on diabetes markers.<sup>7</sup> Furthermore, a small number of controlled clinical trials in humans suggests that cannabinoids may be beneficial in controlling blood sugar,

pain, or other symptoms associated with diabetes, but more studies are required to confirm these findings.<sup>7</sup> Based on the current animal research, CBD; peripheral blockade of the CB<sub>1</sub> receptor; and increased activity of CB<sub>2</sub>, GPR55, or GPR119 have shown promise in the treatment of diabetes, but require further testing in humans. Many studies have demonstrated a connection between chronic inflammation and insulin resistance, indicating a potential role for CBD in affecting these markers. Future work in this area is recommended.

For the normalization in blood urea nitrogen and creatinine, the sample size is too small to draw any conclusions as there was no significant and obvious change. For the blood measures that remained in the high or low range, these measures were not significantly out of range or not markedly altered after consuming liposomal CBD.

## Conclusion

Liposomal CBD was well tolerated in this small case series, improved blood measures in some cases, and was considered safe. It is recommended that the beneficial effects of liposomal CBD on blood glucose levels be explored further in future studies.

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*Dr. Blair is the owner of Puffin Hemp and funded the research.*

Please visit [www.ajendomed.com](http://www.ajendomed.com) for supplemental data related to this article.

# Dosing Strategies for Medical Cannabis

*A commentary on MacCallum CA, et al. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12-19.*

**By Cohin Kakar, PharmD, MBA, The Anthos Group, Los Angeles, California**

The key takeaway from the review article by MacCallum and Russo<sup>1</sup> is that there is a space for cannabis in medicine, but more training and educational opportunities are needed. Although cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are well known, many other cannabinoids that contribute to the benefits of cannabis are being discovered daily. Starting with a low dosage is always the best approach, and the dosage can be titrated up as provider and patients feel more comfortable. Qualifying sources for patients is absolutely imperative to avoid any setbacks with new therapies being introduced into regimens.

## Introduction

The article begins with a brief history of cannabis and its different uses through hundreds of years, dating back to 1840. The endocannabinoid system is a relatively recent discovery, and education around cannabis has been limited. As the review authors note, survey findings show that 89.5% of medical residents and fellows do not feel prepared to prescribe cannabis-based products (like the FDA-approved agent nabiximols), and only 9% of US medical schools cover clinical cannabis in their curricula.<sup>2</sup>

It is well known that double-blind and controlled studies of cannabis are lacking, and the authors, therefore, suggest the use of individual patient case studies to begin accumulating evidence-based data. MacCallum and Russo suggest that all cannabis-based products come from facilities that are Good Agricultural Practice (GAP) certified and extracted under certified Good Manufacturing Practice (GMP). Additionally, consumers should be provided with full access to information highlighting the cannabinoid and terpene profile as well as confirmation of absence

of heavy metals, pesticides, and other contaminants, the authors wrote.

## Mechanism of Action

A brief pharmacology review in the article underlines the strong phytocannabinoid presence in cannabis, particularly within the unfertilized female flowers. THC is, of course, known for its psychoactive effects and is a weak partial agonist of CB<sub>1</sub> and CB<sub>2</sub> receptors. Evidence suggests that THC has effects on pain, appetite, digestion, emotions, and mental health.<sup>3,4</sup> Depending on the dose, it can have euphoric effects through its psychoactivity.

CBD, on the other hand, actually has a low affinity for the CB<sub>1</sub> and CB<sub>2</sub> receptors directly, but has pharmacologic effects on other families of receptors, including 5-HT<sub>1A</sub> and adenosine A2A. CBD is also known for its activity in nonreceptor mechanisms, which has led to positive effects on pain, inflammation, anxiety, and mental health.<sup>4,5</sup>

Cannabis comes in thousands of different “chemovars,” which can vary in different phytocannabinoid profiles, the review authors noted. This phytocannabinoid diversity is what can lead to different portfolios of benefits, and ideally reduce the need for prescription drugs.

## Pharmacokinetics

Absorption of cannabis-based products is variable and depends on the products’ lipophilicity, bioavailability, and organ tissue differences, according to MacCallum and Russo. Cannabinoids are lipophilic and are best absorbed in the presence of fats, oils, and polar solvents both topically and orally. Recent meals, depth of inhalation, and temperature can affect absorption both orally (20%–30%) and in inhalation (10%–60%).<sup>6</sup>

Dosing is one of the biggest challenges that both providers and patients face. The general approach is to start

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**“Dosing is one of the biggest challenges that both providers and patients face. The general approach is to start low and go slow.”**

**—Cohin Kakar, PharmD, MBA**

## Dosing Strategies

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**Table. Efficacy of Cannabis-Based Treatment in Various Conditions**

Level of evidence	Benefits
<b>Conclusive/Substantial</b>	<ul style="list-style-type: none"> <li>• Adult chronic pain</li> <li>• MS spasticity</li> <li>• Chemotherapy-induced nausea and vomiting</li> <li>• Seizures in Dravet and Lennox-Gastaut syndromes (CBD)</li> </ul>
<b>Moderate evidence</b>	<ul style="list-style-type: none"> <li>• Sleep disturbance from chronic pain, MS, fibromyalgia, obstructive sleep apnea</li> <li>• Decreasing intraocular pressure in glaucoma</li> </ul>
<b>Limited evidence</b>	<ul style="list-style-type: none"> <li>• Symptoms of dementia</li> <li>• Symptoms of Parkinson's disease</li> <li>• Schizophrenia</li> <li>• PTSD</li> <li>• Appetite and decreasing weight loss associated with HIV/AIDS</li> <li>• MS spasticity</li> <li>• Anxiety (CBD)</li> <li>• Tourette syndrome</li> <li>• Depressive symptoms in patients with chronic pain or MS</li> </ul>
<b>Insufficient evidence</b>	<ul style="list-style-type: none"> <li>• Addiction abstinence</li> <li>• IBS</li> <li>• Cancer</li> <li>• Lateral sclerosis</li> <li>• Chorea</li> <li>• Dystonia</li> </ul>

**CBD**, cannabidiol; **IBS**, irritable bowel syndrome; **MS**, multiple sclerosis; **PTSD**, post-traumatic stress disorder.

Table adapted from MacCallum et al.<sup>1</sup>

low and go slow. Other recommendations from MacCallum and Russo include the following:

- Inhalation should be spaced in 15-minute intervals until desired symptom control is achieved
- Higher THC concentrations generally allow for lower dosage amounts
- THC-mediated side effects are better controlled when starting with a lower dose
- Medical cannabis patients prefer chemovars with lower THC to gain full symptom control with the least amount of adverse events
- Long-acting, oral preparations are better received for chronic conditions
- Vaporization can be used as an add-on therapy as needed for symptom exacerbation
- Physicians must clearly communicate potential risks and safety considerations of cannabis
- Patients must keep a symptom inventory chart to

document response and efficacy

- THC oral preparation should be uptitrated starting at 2.5 mg once daily in the first 2 days and then twice daily on days 3 and 4; uptitrated to 15 mg THC-equivalent daily over 3 doses in 1 day as needed

Cannabis should not be used in patients who are pregnant or nursing, the authors noted. It has a relatively good safety profile overall, with no reported deaths due to overdose. THC side effects can be controlled with low dosing and are further controlled in CBD and THC combinations. The most commonly reported side effects of cannabis-based medications include the following:

- Drowsiness
- Dizziness
- Dry mouth
- Cough
- Anxiety
- Nausea
- Cognitive effects

The article briefly mentions drug interactions and that cannabis is metabolized by cytochrome P450: 2C9, 2C19,



and 3A4, yet there seems to be no drugs that have been reported specifically as contraindicated, with the exception of concomitant treatment with clobazam.<sup>7</sup> Patients should be followed every 1 to 6 months, depending on their familiarity with cannabis.

The authors presented levels of efficacy of cannabis-based treatment in various conditions (Table 1). The authors also highlighted the following special cases in which cannabis has shown efficacy.

- Epilepsy: CBD shows anticonvulsant properties, as Epidiolex is an FDA-approved medication
- Cancer: THC has accumulating data supporting its use in cancer and diverse phytocannabinoid preparations can help with malignancies
- Pain: Strong data has accumulated to support the use of cannabis in chronic pain
- Geriatrics: THC can treat agitation in dementia
- Parkinson's disease: CB<sub>1</sub> saturation in the basal ganglia can be supportive
- Pediatrics: Data is building to support the use of CBD in mental health
- Opioid: Cannabis may be helpful for patients with chronic pain who are tapering off opioids

Furthermore, the authors presented tables delineating administration factors in various cannabis delivery methods as well as routes of administration.

**“A key aspect of the cannabis market that is overlooked is the qualification of material. All plants should be organically grown with no presence of contaminants.”**

**—Cobin Kakar, PharmD, MBA**

## Commentary

This review article is a good introduction to cannabis and its forms of administration in the medical setting. However, it lacks strong data to support the claims and disease states that are mentioned. The dosing guidance is general and hard to follow without a clear description of specific products available. Clinicians can benefit from education on the effects of specific products (as opposed to general cannabinoid formulations) on specific symptoms. As the science advances, clinicians could further benefit from the

## Clinical Takeaways

- Cannabis education is in severe shortage in the US medical field, and must be qualified from advanced professionals familiar in the space
- THC- and CBD-dominant formulations can be effective in symptom control if managed carefully
- Cultivation, extraction, manufacturing, and packaging of sources must always be verified to assure a safe cannabis-based product
- Data is accumulating to support the use of cannabis in epilepsy, stress, anxiety, PTSD, pain, inflammation, and cancer
- Dosing should always start low and titrate up slowly
- Routes of administration include inhalation, oral, oromucosal, and topical

ability to match chemovars to diseases and prescribe/advise accordingly.

I agree with MacCallum and Russo's belief that cannabis can be an effective alternative to prescription drugs. THC formulations should be dosed low and slow to control any risk for adverse events. The most effective formulations combine a variety of cannabinoids, addressing different receptors and mechanisms that can achieve relief.

In addition, a key aspect of the cannabis market that is overlooked is the qualification of material. All plants should be organically grown with no presence of contaminants. Finished products should be created under stringent quality guidelines and facilities must have all certifications in place.

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# The Dangers of Vaping and Propylene Glycol

*Dr. Marcu presents his 2015 report on the hidden dangers of propylene glycol and vape pens and provides a commentary with recent updates on this topic.*

By Jahan Marcu, PhD, Editor in Chief

## How Safe Is Your Vape Pen

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### Hidden Dangers of Propylene Glycol

Portable electronic devices, known as “vape pens,” are increasingly popular among medical marijuana patients and others because they provide a convenient, discreet, and presumably benign way to administer cannabis. But how safe are vape pens and the liquid solutions inside the cartridges that attach to these devices? Who knows what’s actually being inhaled?

It’s generally assumed that vaping is a healthier method of administration than inhaling marijuana smoke, which contains noxious substances that may irritate the lungs. Since a vaporizer heats the cannabis flower or oil concentrate without burning it, the active ingredients are inhaled but no smoke is involved. At least that’s how it’s supposed to work.

But there may be a hidden downside to vape pens, which are manufactured (typically in China), marketed, and utilized without regulatory controls. Available online and in medical marijuana dispensaries, vape pens contain a battery-operated heating mechanism, which at high temperatures can transform solvents, flavoring agents, and various vape oil additives into carcinogens and other dangerous toxins.

### Propylene Glycol in Vape Pens

Of particular concern: Propylene glycol, a widely used chemical that is mixed with cannabis or hemp oil in many vape pen cartridges. A syrupy, thinning compound, propylene glycol is also the primary ingredient in a majority of nicotine-infused e-cigarette solutions. At high temperatures, propylene glycol converts into tiny polymers that can wreak havoc on lung tissue.

Scientists know a great deal about propylene glycol. It is found in a plethora of common household items—cosmetics, baby wipes, pharmaceuticals, pet food, antifreeze, etc. The

U.S. Food and Drug Administration and Health Canada have deemed propylene glycol safe for human ingestion and topical application. But exposure by inhalation is another matter. Many things are safe to eat but dangerous to breathe.

A 2010 study published in the *International Journal of Environmental Research and Public Health* (<http://www.mdpi.com/1660-4601/7/12/4213>) concluded that air-borne propylene glycol circulating indoors can induce or exacerbate asthma, eczema, and many allergic symptoms. Children were said to be particularly sensitive to these air-borne toxins. An earlier toxicology review warned that propylene glycol, ubiquitous in hairsprays, could be harmful because aerosol particles lodge deep in the lungs and are not respirable.

When propylene glycol is heated by a red-hot metal coil, the potential harm from inhalation exposure increases. High voltage heat can transform propylene glycol and other vaping additives into carbonyls. Carbonyls are a group of cancer-causing chemicals that includes formaldehyde, which has been linked to spontaneous abortions and low birth weight. A known thermal breakdown product of propylene glycol, formaldehyde is an International Agency for Research on Cancer group 1 carcinogen.

Because of low oral toxicity, propylene glycol is classified by the FDA as “generally recognized as safe” (GRAS) for use as a food additive, but this assessment was based on toxicity studies that did not involve heating and breathing propylene glycol.

### Flavoring Compounds

Prevalent in nicotine e-cig products and present in some vape oil cartridges, FDA-approved flavoring agents pose additional risks when inhaled rather than eaten. The flavoring compounds smooth and creamy (diacetyl and acetyl propionyl) are associated with respiratory illness when inhaled in tobacco e-cigarette devices. Another hazardous when-inhaled-but-safe-to-eat flavoring compound is *cinnamon ceylon*, which becomes cytotoxic when aerosolized.

## Safe Vaping

Currently, there is no conclusive evidence that frequent users will develop cancer or another illness if they inhale the contents of vape oil cartridges. That's because little is actually known about the short or long-term health effects of inhaling propylene glycol and other ingredients that are present in flavored vape pen cartridges. Many of these pre-filled cartridges are poorly labeled with little or no meaningful information on their contents.

The possibility that vape pens might expose people to unknown health hazards underscores the importance of adequate safety testing for these products, which thus far has been lacking.

Scientists face several challenges as they try to gather relevant safety data. As yet, no one has determined how much e-cig vapor the typical user breathes in, so different studies assume different amounts of vapor as their standard, making it difficult to compare results. Tracing what happens to the vapor once it is inhaled is equally problematic.

## Heating Up

The biggest variable is the device itself. The performance of each vape pen can vary greatly between different devices and sometimes there is considerable variance when comparing two devices of the same model.

Some vape pens require pressing a button to charge the heating coil; others are buttonless and one activates the battery simply by sucking on the pen. The surface area of the vape pen's heating element and its electrical resistance play a large role in converting ingestible solvents into inhalable toxins.

Another confounding factor is the scant information on when and how long the user pushes the button or inhales on average, how long the coil heats up, or the voltage used during the heating process. A five-volt setting yielded higher levels of formaldehyde in a controlled



Photo credit: Rachel Carson Council

propylene glycol study cited in the *New England Journal of Medicine* (<https://www.nejm.org/doi/full/10.1056/NEJMc1413069>).

In the case of vape pens, there's a great need for specific research on how people actually use these products in the real world in order to understand potential benefits or harms.

Such studies have been conducted using the Volcano vaporizer, a first generation vaping device that differs from a vape pen, a more recent innovation, in several ways. Utilized in clinical trials as a medical delivery device, the Volcano is not a portable contraption. The Volcano only heats raw cannabis flower, not oil extract solutions, and it doesn't combust the bud.

Vape pen manufacturers don't like to admit it, but when the heating element gets red hot in a vape pen, the solution inside the prefilled cartridges undergoes a process called "smoldering," a technical term for what is tantamount to "burning." While much of the vape oil liquid

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## Commentary

# An Update on Vaping Safety

By Jahan Marcu, PhD, Editor in Chief

Millions of people regularly vape cannabis products. My original 2015 article (page 26) was written as the vape pen market began to increase dramatically. At the time, the significant issues were hardware that was prone to overheating, cutting agents that released formaldehyde-releasing agents when heated, and inaccurate labels. The problems remain largely the same, with additives being the most likely cause of safety issues, rather than cannabis oil itself. It may not be propylene glycol on the hot seat this time, but rather additives flowing through cheap devices that can heat over 900°C. The legal and unregulated markets are flooded with inexpensive, disposable hardware, which can heat material well above the vaporizing threshold; in fact, many “vape pens” are not vaporizers—they burn the material.

Cannabis product safety has been a passion of mine, and for years I have written and spoken about the potential dangers of cannabis products, especially those produced outside of regulated markets. The purpose of this commentary is to provide context to the current public health crisis, as well as recent information that could be useful for health care professionals who may need to discuss vaping with their patients. What follows is a brief discussion on some of the origins of this issue; how many of the factors remain the same; what have we learned; and the potential opportunities to create vital public health data in front of researchers, regulators, and doctors.

## Multistate Outbreak of Lung Injury

After years on the market and hundreds of

millions of vape pens sold without significant issues, suddenly in 2019, increases in hospital visits related to e-cigarette use dramatically increased over the summer (if filled with cannabis/hemp extracts, these devices often are referred to as vape pens).<sup>1</sup> Major media outlets began heavily reporting on the tragic and unnecessary deaths and illnesses in multiple states that are believed to be tied to inhalation of diluted cannabis extracts in e-cigarette devices. The US Centers for Disease Control and Prevention (CDC), state health departments, research institutes, and private companies in the cannabis industry have begun investigations or issued warnings.<sup>1,2</sup>

What is clear today about cannabis and hemp, is that the issues surrounding the public health crisis and the regulated vs unregulated market dynamics are even more important to consider, given that regulated markets have track and trace requirements, and basic product testing services are usually required by state law. The lack of regulation provides opportunities for products to be developed without oversight for the quality, and safety of products. Products being distributed in unregulated markets, including cannabidiol products that can be purchased easily online, have a proven record of unreliability, according to data from the FDA and other research groups.<sup>1,2</sup>

## Practical Considerations

Health issues are associated with using low-quality cannabis and nicotine vape products due to the inclusion of pesticides, thinning agents, thickening agents, and other dangerous additives. Cannabis flowers that are vaporized are not associated with this epidemic. However, the dilution of cannabis extracts is challenging to do safely, and even cannabis sold in legal markets can have additives.



## Vaping Statistics and CDC Recommendations

- As of October 15, 2019, 1,479 lung injuries associated with the use of e-cigarette, or vaping, products have been reported from 49 states (all except Alaska), the District of Columbia, and 1 US territory
- Thirty-three deaths from these injuries have been confirmed in 24 states
- The FDA and the CDC have not identified the cause or causes of the lung injuries in these cases
- Delta-9-tetrahydrocannabinol (THC) is present in most of the samples tested by the FDA to date, and most patients report a history of using THC-containing products

## The CDC recommends that patients should not:

- Use e-cigarette, or vaping, products that contain THC
- Buy any e-cigarette, or vaping products, particularly those containing THC, off the street
- Modify or add any substances to e-cigarette, or vaping, products that are not intended by the manufacturer, including products purchased through retailers

Source: US Centers for Disease Control and Prevention.<sup>1</sup>

**Don't buy cheap.** Not all vapes are created equally. Many portable, e-cigarette-type hardware will burn the material. If it is an inexpensive device, it is probably not a vaporizer. For example, herbal cannabis vaporizers retail for as much several hundred dollars. Building quality hardware with safe materials is difficult,

and costly. If they're giving it away for free, make sure you trust the source. Look for devices that state their vaporization temperature—not just the wattage and resistance.

**Don't ban all vaporizers.** Well-intentioned leaders may be inadvertently be making the situation worse by placing bans on all vaporizers, as this can drive consumer demand to illicit markets.

**Do buy from regulated retailers.** When purchasing cannabis vape cartridges (or any cannabis product), it is essential to purchase products made by licensed manufacturers and that are tested and comply with relevant state regulations. With the rise of counterfeit vapes being sold under the name of legal and trusted brands, it is equally important to purchase from a licensed dispensary.

**Do read the label.** It is important to know what ingredients are in those products. Most states require ingredients to be listed on the packaging of cannabis products, with some requiring manufacturers and dispensaries to share laboratory results with consumers upon request. Buy from a different dispensary if ingredients are not listed.

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[ecigarettereviewed.com](http://ecigarettereviewed.com)

## Vaping

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is vaporized and atomized, a portion of the vape oil blend undergoes pyrolysis or combustion. In that sense, most of the vape pens that have flooded the commercial market may not be true vaporizers.

Unlike vape pen devices, the Volcano vaporizer has been tested for safety and pharmacokinetics (a measurement of what's in the blood and how long it stays there). Collectively, the data indicate that vaporizing whole plant cannabis exposes the user to lower amounts of carcinogens compared to smoke and decreases side effects (such as reactions to the harshness of smoke).

But nonportable vaporizers like the Volcano may still pose health concerns if the vaporized cannabis flower is below acceptable botanical safety standards. A recent article in the *Journal of Analytical Methods* notes that high levels of ammonia are produced from vaporizing cannabis grown incorrectly, perhaps due to the lack of flushing during hydroponic cultivation. There is a growing body of data suggesting that the chemicals used to push the plant towards unnaturally high THC concentrations stay in the finished product.

## CBD HEMP OIL VAPE CARTRIDGES WITH PROPYLENE GLYCOL

Project CBD research associate Eric Geisterfer conducted a limited survey of cannabis vape oil and CBD hemp vape oil cartridges. Several of these products were found to include propylene glycol as an additive. The list below is incomplete—vape oil products are continually being introduced and in some cases rebranded.

Hemp oil vape cartridges that contain propylene glycol include:

- Alternate Vape
- Bluebird Botanicals
- CannaVape CBD Oil
- Cloud 9 CBD
- Delta Liquids
- Entourage Hemp Products (also known as Cannoid LLC)
- Hemp Life Today (also known as Cannazall)
- Hemp Pure Vape
- HempVap
- KanaVape
- Miracle Smoke

- Michigan Hemp Company (also known as Bluegrass Naturals)
- Pure CBD Vapors
- Pure Hemp Vape
- Tasty Hemp Oil
- Zamnesia CBD Smart Liquid

Some cannabis vape oil cartridges also include propylene glycol or polyethylene glycol (<https://www.sciencedirect.com/science/article/pii/S037851739400221P>) as a thinning agent. Both compounds may have adverse health effects when heated and inhaled. Neither has been safety tested by the FDA for inhalation when heated. Cannabis consumers should carefully scrutinize cannabis product labels.

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# Atypical Presentation of Cannabinoid Hyperemesis Syndrome: Two Case Reports

By Dustin Sulak, DO, Healer, Society of Cannabis Clinicians  
and Eloise Theisen, RN, MSN, AGPCNP-BC, Radicle Health, American Cannabis Nurses Association

## Introduction

The clinical use of herbal cannabis and cannabinoid compounds in the treatment of a wide variety of conditions is becoming more common as compelling evidence grows, standardized products reach the market, and laws change. In states that have legalized medical cannabis, about 1% of the population use cannabis with the recommendation of a medical provider.<sup>1</sup> Cannabinoid hyperemesis syndrome (CHS), a rare side effect of long-term cannabis use, is a newly recognized disorder characterized by abdominal pain, cyclic episodes of vomiting, and compulsive hot bathing. First described in a series of cases in Australia in 2004,<sup>2</sup> numerous case reports have since been published around the world that describe a similar clinical presentation, and improvement in symptoms with cannabis abstinence.

Although the exact pathophysiology of CHS is unknown, several contributing factors have been hypothesized or explored, including genetic polymorphisms,<sup>3</sup> delayed gastric emptying,<sup>4</sup> splanchnic vasodilation,<sup>5</sup> abnormal allostatic regulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system,<sup>6</sup> and endocannabinoid system dysregulation.

The diagnostic criteria of CHS include: long-term cannabis use, severe cyclic nausea and vomiting, resolution with cannabis cessation, relief of symptoms with hot showers or baths, abdominal pain, and at least weekly use of cannabis in the context of negative workup for other etiology.<sup>4</sup> The following cases describe atypical presentations of CHS, or a similar phenomenon, in patients using herbal cannabis to treat chronic pain under medical supervision.

## Case Report 1

In 2010, a 53-year-old man presented with chronic back pain and left lower extremity radiculopathy since experiencing a work-related injury in 2004. He was diagnosed with degenerative disc disease. Medical history included left shoulder rotator cuff repair in 1980. Family history included mother

deceased at age 48 from breast cancer and father with coronary artery disease, diabetes, and glaucoma.

In the 2 years after the work-related injury, the patient experienced abdominal pain, nausea, vomiting, and weight loss, and was eventually diagnosed with celiac disease. The abdominal symptoms responded to avoidance of gluten.

## Medication History

At presentation, he was taking up to 30 mg of hydrocodone with acetaminophen daily to treat back pain, with a trend of opioid-tolerance and dose

escalation. He described nausea and dissociated feelings as side effects of the hydrocodone/acetaminophen. He had tried smoking herbal cannabis and found that it provided analgesic benefits and relieved nausea.

Other medications included atenolol 50 mg daily, dextlan-soprazole 60 mg daily, and vardenafil 10 mg as needed for coitus. The patient reported no medical or environmental allergies besides gluten.

## Management

The patient was transitioned from hydrocodone to extended-release morphine 15 mg 3 times daily, with a plan to gradually taper and discontinue opioid therapy. He was certified to use medical cannabis in accordance with state law, and was encouraged to use it in conjunction with morphine to

**“... It is important to note that while cannabis did cause significant adverse effects in both patients, they were also both able to modify their cannabis use, under the guidance of an experienced clinician, to successfully continue using cannabis for pain relief with little to no GI side effects.”**

**—Dustin Sulak, DO, and Eloise Theisen, RN, MSN, AGPCNP-BC**

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**CHS**

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potentiate analgesia and to prevent opioid tolerance.<sup>1</sup> He also received regular osteopathic manipulation treatments for back pain.

The patient smoked an average 1 oz of cannabis per week. Over time, he transitioned to using a homemade cannabis tincture administered sublingually 2 to 3 times daily, prepared by making an ethanol extraction that was concentrated using evaporation and then dissolved in vegetable glycerin. He continued to smoke or vaporize cannabis for breakthrough pain. His total weekly consumption for both tincture and inhalation remained at approximately 1 oz of cannabis flower.

**Emergence of CHS**

In early 2012, the patient had surgery for an inguinal hernia with sequelae of inguinal and testicular pain, which setback the opioid taper. By the end of 2012, he was stable on 22.5 mg dose of morphine daily and reported no gluten exposures or celiac symptoms in more than 6 months. Previous intermittent gluten exposures resulted in 2 days of nausea, vomiting, diarrhea, abdominal cramping, sweating, and chills, followed by 3 to 4 months of feeling minor residual gastrointestinal (GI) symptoms (eg, early satiety and mild nausea.)

In September 2013, the patient experienced another episode of GI symptoms, which he attributed to an unknown gluten exposure. Although he was more careful with his diet, he continued to experience episodes every 2 to 4 weeks in early 2014. After losing approximately 30 lb over 9 months, a GI workup revealed that the patient's celiac disease was well controlled and the diagnosis of CHS was considered.

The patient discontinued cannabis for 7 days and his GI symptoms resolved. He then took 3 inhalations of cannabis vapor, and the symptoms quickly returned. Hot showers did not ameliorate the symptoms. The patient then abstained from cannabis for 2 months with no recurrence of symptoms. After the period of abstinence, he found that he was able to tolerate 2 to 3 inhalations of cannabis vapor 2 to 3 times daily for 1 to 2 consecutive days without triggering a GI episode, although he did experience a mild prodrome of decreased appetite. If he used cannabis for 3 or more days in a row, he began experiencing a stronger prodrome of sleep disturbance and persistent nausea, which would progress to a full episode if he continued the cannabis or would resolve with cannabis abstinence.

The patient tried smoking and vaporizing a cannabidiol (CBD)-dominant cannabis chemovar, "ACDC," (~14% by weight) with low levels of tetrahydrocannabinol (THC; ~1% by weight), and experienced the same pattern of symptomatology after 2 to 3 days of use. Additionally, he reported that the CBD-dominant cannabis was less effective for analgesia than the THC-dominant variety. The patient continued to use cannabis intermittently on nonconsecutive days for analgesia.

In December 2014, the patient travelled to Jamaica and acquired Chikungunya virus infection. After this illness, his sensitivity to cannabis increased, and he would feel ill for a week after a single inhalation of cannabis. By June 2015, his ability to tolerate cannabis had improved and he experienced no prodrome unless he used cannabis for 5 to 7 consecutive days. During 2015, the patient completed tapering morphine and did not use opioid medications to treat the chronic pain. Over time, the patient's ability to tolerate cannabis gradually improved. At his most recent follow-up visit, he reported being able to use low-dose inhaled and oromucosal THC-dominant cannabis to treat chronic pain without triggering episodes of GI symptoms. He occasionally experiences mild anorexia and/or nausea; when this occurs, he abstains from cannabis for 1 to 3 days and then restarts the treatment without adverse effects.

**Case Report 2**

In 2019, a 66-year-old woman presented with widespread diverse pain due to fibromyalgia (diagnosed in 1980) and chronic Lyme disease (diagnosed in 2009). Additional medical history included hypothyroidism and migraines. Family history included a mother with unknown cancer, and a sibling with possible arthritis. Her father's medical history is unknown.

The patient had used cannabis for 2 years to manage widespread chronic pain. The cannabis formulation consisted of a 1:1 CBD/THC tincture 500 mg total cannabinoids in a 1-oz organic sugar cane alcohol base. The producer used a frozen organic ethanol wash for extraction. Certificate of analysis was negative for pesticides, heavy metals, bacteria, mold, and residual solvents (Figures, page 33-34). At the time of the consultation, the patient reported using 1500 to 2000 mg per month of total cannabinoids (given orally), which averaged about 50 to 75 mg of CBD and THC combined daily. The pain had improved with cannabis, but she was still averaging a 7 out of 10



Cannabinoid Profile			
Cannabinoids	Wt. %	mg/gram	mg/mL
<b>Δ9-THC Max.</b>	<b>0.23</b>	<b>2.27</b>	<b>2.07</b>
<b>CBD Max.</b>	<b>5.82</b>	<b>58.22</b>	<b>53.09</b>
<b>CBG Max.</b>	<b>0.15</b>	<b>1.53</b>	<b>1.39</b>
Δ9-THC	0.23	2.27	2.07
Δ9-THCA	ND	ND	ND
CBD	5.82	58.22	53.09
CBDA	ND	ND	ND
CBG	0.13	1.30	1.19
CBGA	0.03	0.25	0.23
CBN	0.00	0.05	0.05
CBC	0.72	7.21	6.58
Δ8-THC	ND	ND	ND

Microbial Impurities		
Contaminant	Action Level (cfu/g)	Pass/Fail
<i>E. coli</i> (STEC)	LLOD	NT
<i>Salmonella</i> spp.	LLOD	NT
<i>A. fumigatus, niger flavus, &amp; terreus</i>	LLOD	NT

Moisture Content and Water Activity			
Analysis	Action Level	Amount Present	Pass/Fail
Moisture Content	0.65 A <sub>w</sub>	NT	NT
Water Activity	13.00%	NT	NT

Foreign Material Analysis	
Pass or Fail:	NT

Residual Solvent Detection			
Category 1 or 3 Residual Solvent or Processing Chemical	Action Level (ug/g)		Amount Detected (ug/g)
	Inhalable Cannabis & Cannabis Products	Other Cannabis & Cannabis Products	
Acetone II	3100	5000	NT
Acetonitrile	6	410	NT
Benzene I	LLOD	LLOD	NT
Butane II	5000	5000	NT
Chloroform I	LLOD	LLOD	NT
1,2-Dichloroethane I	LLOD	LLOD	NT
Ethanol II	5000	5000	NT
Ethyl Acetate II	5000	5000	NT
Ethyl Ether II	5000	5000	NT
Ethylene Oxide I	LLOD	LLOD	NT
Heptane II	5000	5000	NT
Hexane II	70	290	NT
Isopropyl Alcohol II	320	5000	NT
Methanol II	400	3000	NT
Methylene Chloride I	LLOD	LLOD	NT
Pentane II	5000	5000	NT
Propane II	5000	5000	NT
Toluene II	30	890	NT
Total xylenes II	10	2170	NT
Trichloroethylene I	LLOD	LLOD	NT
Residual Solvent Results (Pass/Fail)			
Inhalable Cannabis & Cannabis Products		Not Tested	
Other Cannabis & Cannabis Products		Not Tested	

Residual Solvent Detection is determined by GC/FID

D= Detected ND=Not Detected NT=Not Tested

LLOD= lower level of detection in parts/million

Potency test is determined by UPLC

Microbial is determined by qPCR

I Category I Residual Solvent (required July 2018)

II Category II Residual Solvent

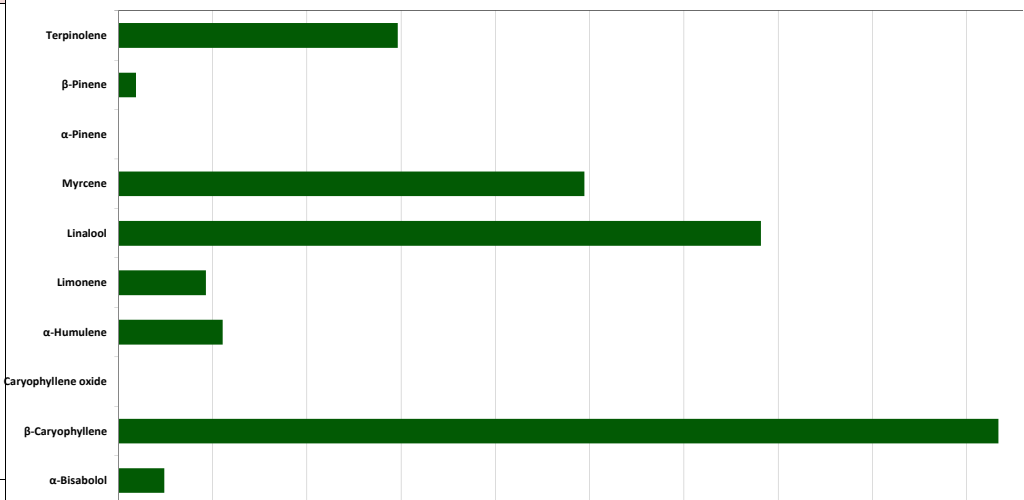
(required Jan 2018)

per California Code of Regulations

Title 16 Division

42. Bureau of Cannabis Control §5719.

Terpenes	mg/g
α-Bisabolol	0.10
β-Caryophyllene	1.87
Caryophyllene oxide	<LLOQ
α-Humulene	0.22
Limonene	0.19
Linalool	1.36
Myrcene	0.99
α-Pinene	<LLOQ
β-Pinene	0.04
Terpinolene	0.59
<b>Sum of Terpenes</b>	<b>5.35</b>



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## CHS

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pain score, with constant severe pain mostly located in the shoulders, knees, joints, and muscles. The patient was seeking further pain control with cannabis.

## Presentation of CHS Symptoms

Upon review of systems, it was reported that the patient also was experiencing GI issues such as nausea, loss of appetite, weight loss of 10 lb, and diarrhea for 2 months. A full GI workup included blood tests, stool tests, and abdominal x-ray, computed tomography scan of the abdomen and pelvis, colonoscopy, and endoscopy. No formal diagnosis

Residual Pesticide Detection			
Category 1 or 2 Residual Pesticide	Action Level (ug/g)		Amount Detected (ug/g)
	Inhalable Cannabis & Cannabis Products	Other Cannabis & Cannabis Products	
Acephate II	0.100	5.000	ND
Acequinocyl II	0.100	4.000	ND
Acetamiprid II	0.100	5.000	ND
Aldicarb I II	LLOD	LLOD	ND
Abamectin II	0.100	0.300	ND
Azoxystrobin II	0.100	40.000	ND
Bifenazate II	0.100	5.000	ND
Bifenthrin II	3.000	0.500	ND
Boscalid II	0.100	10.000	ND
Captan II	0.700	5.000	ND
Carbaryl II	0.500	0.500	ND
Carbofuran I	LLOD	LLOD	ND
Chlorantraniliprole II	10.000	40.000	ND
Chlordane I	LLOD	LLOD	ND
Chlorfenapyr I	LLOD	LLOD	ND
Chlorpyrifos I	LLOD	LLOD	ND
Clofentezine II	0.100	0.500	ND
Coumaphos I	LLOD	LLOD	ND
Cyfluthrin II	2.000	1.000	ND
Cypermethrin II	1.000	1.000	ND
Daminozide I	LLOD	LLOD	ND
Diazinon II	0.100	0.200	ND
Dichlorvos I	LLOD	LLOD	ND
Dimethoate I	LLOD	LLOD	ND
Dimethomorph II	2.000	20.000	ND
Ethoprop(hos) I	LLOD	LLOD	ND
Etofenprox I	LLOD	LLOD	ND
Etiozazole II	0.100	1.500	ND
Fenhexamid II	0.100	10.000	ND
Fenoxycarb I	LLOD	LLOD	ND
Fenpyroximate II	0.100	2.000	ND
Fipronil I	LLOD	LLOD	ND
Flonicamid II	0.100	2.000	ND
Fludioxonil II	0.100	30.000	ND
Hexythiazox II	0.100	2.000	ND
Imazalil I	LLOD	LLOD	ND
Imidacloprid II	5.000	3.000	ND
Kresoxim-methyl II	0.100	1.000	ND
Malathion II	0.500	5.000	ND
Metalaxyl II	2.000	15.000	ND
Methiocarb I	LLOD	LLOD	ND
Methomyl II	1.000	0.100	ND
Mevinphos I	LLOD	LLOD	ND

Pesticide detection is determined by LCMSMS

I Category I Pesticide (required Jan 2018) II Category II Pesticide (required Jun 2018) per California Regulations Title 16, Division 42 Bureau of Cannabis Control §5719.

Date Analyzed	
6/7/2018	
Sample Name	
DAILY 50	
Description	
Pesticide Results (Pass/Fail)	
Inhalable Cannabis & Cannabis Products	PASS
Other Cannabis & Cannabis Products	PASS

T&amp;T #: 180607-144-JC-2

Batch #: 0

Residual Pesticide Detection			
Category 1 or 2 Residual Pesticide	Action Level (ug/g)		Amount Detected (ug/g)
	Inhalable Cannabis & Cannabis Products	Other Cannabis & Cannabis Products	
Myclobutanil II	0.100	9.000	ND
Naled II	0.100	0.500	ND
Oxamyl II	0.500	0.200	ND
Paclobutrazol I	LLOD	LLOD	ND
Parathion methyl I	LLOD	LLOD	ND
PCNB II	0.100	0.200	ND
Permethrin II	0.500	20.000	ND
Phosmet II	0.100	0.200	ND
Piperonyl butoxide II	3.000	8.000	ND
Prallethrin II	0.100	0.400	ND
Propiconazole II	0.100	20.000	ND
Propoxure I	LLOD	LLOD	ND
Pyrethrins II	0.500	1.000	ND
Pyridaben II	0.100	3.000	ND
Spinosad II	0.100	3.000	ND
Spinetoram II	0.100	3.000	ND
Spiromesifen II	0.100	12.000	ND
Spirotetramat II	0.100	13.000	ND
Spiroxamine I	LLOD	LLOD	ND
Tebuconazole II	0.100	2.000	ND
Thiacloprid I	LLOD	LLOD	ND
Thiamethoxam II	5.000	4.500	ND
Trifloxystrobin II	0.100	30.000	ND

LLOD= lower level of detection in parts/million

was made. The patient was given pancrelipase 12,000 units before meals and ondansetron 4 mg 3 times daily for nausea. Additional medications included the following:

- Cevimeline HCl 30 mg as needed
- Estradiol
- Gabapentin 100 mg at bedtime
- Levothyroxine tablets daily
- Omeprazole 30 mg daily
- Sumatriptan 100 mg prn
- Fesoterodine fumarate ER 4 mg daily
- Tramadol 25 mg daily as needed for pain
- Multiple vitamin injection daily
- Fish oil 1200 mg daily
- Aspirin 81 mg daily

The patient reported discontinuing the cannabis tincture for 1 week to see if GI symptoms resolved. No history of compulsive hot showers was reported. After 1 week of abstinence, the symptoms did not resolve, and the patient resumed her 1:1 tincture at the previous dosages.

## Management

The patient agreed to stop the cannabis for 3 weeks to determine if the GI symptoms would improve. The patient also agreed to take tramadol 25 mg 3 times daily for pain. Previously when the patient discontinued the tincture, she did not observe any withdrawal symptoms so it was decided that she could abruptly stop the tincture and notify the clinician if she experienced any adverse events such as headaches, diarrhea, increased pain, and/or insomnia.

At day 10 after cessation of the cannabis, the patient reported having some days with no nausea and improved appetite. She stayed off of cannabis for the full 3 weeks. At that time, her GI symptoms had almost entirely resolved. There was only mild nausea after her third meal of the day. Additionally, she was able to discontinue ondansetron.

The patient wanted to explore other cannabinoid profiles for pain relief. Although tramadol was effectively managing her pain, it was her goal to use a more natural approach to pain. After the 3-week break from her 1:1 tincture, the patient tried 5 drops and reported a resurgence of her GI symptoms. She was started on a 25:1 CBD/THC (50 mg/mL CBD and 2 mg/mL THC) tincture in olive oil. The cultivar was “ACDC” and the producer used organic ethanol extraction. Certificate of analysis was negative for pesticides, heavy metals, bacteria, mold, and residual solvents (Figure). The initial dose was 12.5 mg CBD twice daily with a plan to increase to 25 mg CBD twice a day after 1 week.

After 5 days on the 12.5 mg CBD twice-daily dosage, the patient reported that her GI symptoms had returned. She was instructed to stop the 25:1 CBD/THC tincture and her symptoms dissipated within 24 hours.

Finally, the patient was placed on a cannabigerol-rich (CBG) tincture with 21 mg/mL CBG and 0.22 mg/mL THC to address the pain. The CBG tincture was administered twice daily at 0.5 mL per dose. After 3 weeks on CBG, the patient did not report any GI symptoms. Her pain level continues to be 5 out of 10, and she has been able to discontinue the use of tramadol again.

## Conclusion

Both cases demonstrate patients with episodes of cannabis-induced GI symptoms that do not fit the classical presentation or diagnostic criteria of CHS. Although both patients experienced nausea, vomiting did not occur. Hot bathing did not relieve symptoms, and complete abstinence of cannabis was not required to prevent symptoms. Similarities with CHS include the following: GI workups that ruled out other etiology; resolution and recurrence of symptoms directly correlated with cannabis abstinence and use, respectively; and similar prodrome characterized by nausea, anorexia, and vague abdominal discomfort. The first patient experienced distinct episodes of severe GI symptoms, similar to the hyperemetic phase of CHS; the second patient may have had more ongoing symptoms. The biggest distinguishing factor is the predominance of lower GI symptoms.

The pathophysiology of CHS is likely multifactorial, and may include physiologic derangements related to long-term overstimulation and/or downregulation of cannabinoid receptors in pathways that control the function of the GI tract. The 6 months of increased sensitivity to cannabis after an infectious illness in case report 1, and the chronic borrelia infection in case report 2, may indicate that immune activity is another contributing factor.

Both cases were sensitive to CBD-dominant cannabis with very low levels of THC, a phenomenon not previously reported for CHS. THC is a partial agonist of CB<sub>1</sub> and CB<sub>2</sub> receptors, but CBD does not directly agonize either CB<sub>1</sub> or CB<sub>2</sub>. By decreasing the reuptake and hydrolysis of the endogenous CB<sub>1</sub>/CB<sub>2</sub> ligand anandamide, CBD can act indirectly at these receptors.<sup>8</sup> Additionally, they also were able to modify their cannabis use, under guidance, to successfully continue using cannabis for pain relief with little to no GI side effects.

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## CHS

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Although CHS is a distinct clinical entity with clear diagnostic criteria, a spectrum of cannabis-related GI adverse effects may exist that share clinical and physiologic features with CHS, including lower GI symptoms (eg, diarrhea), and failure to respond to hot bathing.

Other components of cannabis, besides THC, may be responsible for triggering episodes and other conditions (eg acute infections and chronic GI conditions) may complicate the presentation. With increasing use of cannabis medically and recreationally, clinicians must be aware of the potential for less well-defined episodic GI side effects in certain patients. Patients may not fit into the current CHS diagnostic criteria, and atypical cases may become more prevalent.

These 2 case reports demonstrate that even lower levels of THC can lead to GI side effects. More research is needed to improve the timely diagnosis and management of CHS.

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Dr. Sulak and Ms. Theisen have no financial information to disclose.

## Cannabis May Lower Cancer Risk in Crohn's Disease

Adults hospitalized with Crohn's disease (CD) or ulcerative colitis (UC) who reported cannabis use had a lower frequency of colorectal cancer, parenteral nutrition, and anemia compared to nonusers, according to a retrospective analysis reported in the June issue of *Annals of Translational Medicine*.

The study included data from the Nationwide Inpatient Sample on 6,002 patients with CD (2,999 cannabis users) and 1,481 with UC (742 cannabis users) who were hospitalized between 2010 and 2014. In patients with CD, cannabis use was linked to a significantly lower prevalence of colorectal cancer (0.3% vs 1.2%,  $P<0.001$ ), need for parenteral nutrition (3.0% vs 4.7%,  $P=0.001$ ) and anemia (25.6% vs 30.1%,  $P<0.001$ ), but a significantly higher risk of active fistulizing

disease or intraabdominal abscess formation (8.6% vs 5.9%,  $P<0.001$ ), unspecified lower gastrointestinal (GI) hemorrhage (4.0% vs 2.7%,  $P=0.004$ ) and hypovolemia (1.2% vs 0.5%,  $P=0.004$ ).

Patients with UC who used cannabis had a significantly lower frequency of postoperative infections ( $<0.1\%$  vs 3.4%,  $P=0.010$ ), but a higher

frequency of fluid and electrolyte disorders (45.1% vs 29.6%,  $P<0.001$ ) and hypovolemia (2.7% vs  $<0.1\%$ ). In both groups, cannabis use was linked to a significantly shorter length of hospital stay and reduced costs per stay ( $P<0.001$  for all comparisons).

In a second analysis of Nationwide Inpatient Sample data, researchers reported that CUD was linked to an increased likelihood of hospitalizations for CD or UC, after controlling for demographics, psychiatric and medical comorbidities, and other substance use disorders.



CT scan of patient with Crohn's disease in the fundus of the stomach.

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## FDA Advises Against Cannabis Use During Pregnancy and Breastfeeding

The FDA strongly advised pregnant and breastfeeding women not to use cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC), or marijuana in any form, according to a Consumer Update released October 16, 2019.<sup>1</sup>

“There is no comprehensive research studying the effects of CBD on the developing fetus, pregnant mother, or breastfed baby,” according to the report. “FDA is continuing to collect and study the data on the possible harmful effects of CBD during pregnancy and while breastfeeding. However, based on what we do know, there is significant cause for concern.”

Research suggests that THC during pregnancy may affect brain development and increase the risk for a newborn with low birth weight, premature birth, and potentially stillbirth. Breast-milk may contain THC for up to 6 days after use, and may affect a newborn’s brain development and other long-term consequences (eg, hyperactivity, poor cognitive function). Additionally, CBD products may contain contaminants, including pesticides, heavy metals, and bacteria or fungus, the FDA stated.

### Use on the Rise in Pregnancy

A separate study found that the number of women using cannabis in the year before their pregnancy and in early pregnancy is on the rise, as reported in *JAMA Network Open*.<sup>2</sup>

This survey of more than 277,000 pregnant women in California found that the adjusted prevalence of self-reported cannabis use in the year

before pregnancy increased from 6.8% to 12.5% between 2009 and 2017, and the adjusted prevalence of self-reported cannabis use during pregnancy increased from 1.9% to 3.4% during this period. Annual rates of change in self-reported daily, weekly, and monthly-or-less cannabis use increased significantly, although daily use increased most rapidly. The authors’ previous work published in *JAMA Internal Medicine* in 2018 found that women with severe nausea and vomiting in pregnancy were nearly 4 times more likely to use cannabis during the first trimester of pregnancy.<sup>3</sup>

“These findings should alert women’s health clinicians to be aware of potential increases in daily and weekly cannabis use among their patients,” lead author Kelly Young-Wolff, PhD, MPH, a research scientist with the Kaiser Permanente Division of Research, said in a press release. “The actual numbers are likely higher, as women may be unwilling to disclose their substance use to a medical professional.”<sup>4</sup>

The study was supported by a National Institute on Drug Abuse K01 Award (DA043604) from the National Institutes of Health.

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“These findings should alert women’s health clinicians to be aware of potential increases in daily and weekly cannabis use among their patient. ... The actual numbers are likely higher, as women may be unwilling to disclose their substance use to a medical professional.”

—Kelly Young-Wolff, PhD, MPH

# Cannabis/Marijuana Use Linked to Decreased Use of Opioids

**M**arijuana use was linked to cessation or decreased opioid use in more than 40% of adults using opioids for pain, according to a nationwide survey reported in *PLoS One*.<sup>1</sup>

Researchers analyzed internet survey responses from 9,003 adults (mean age 48 years; 52% female; 64% white) who reported using opioids for pain in the previous 12 months. Of this group, 486 respondents (5%) reported ever using marijuana in the last year, 43% of whom use opioids daily and 23% of whom reported using marijuana in the previous 30 days (Table).

Overall, 187 of the 486 respondents linked marijuana use to a decrease (21%) or cessation (20%) of opioid use, and the remaining patients reported no change (46%) or an increase in opioid use (8%). The most common reason for substituting marijuana for opioids was better pain management (36%), followed by fewer side effects (32%) and fewer withdrawal symptoms (26%; Table).

The study was funded by the National Heart, Lung, and Blood Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases.

In a related study of 60 patients with chronic pain, an opioid reduction program that involved use of medical cannabis was linked to opioid cessation or a marked reduction in opioid use in 82% by 6 months, as reported in *American Journal of Psychiatry and Neuroscience*.<sup>2</sup>

The single-site pilot study involved 600 patients taking daily opioid doses ranging from 90 to 240 mg morphine

**Table. Substitution of Marijuana for Opioids Among Adults Taking Opioids for Pain in a National Survey of US Adults**

Characteristic	Ever Marijuana Users with Opioid Use in the Past 12 Months (n=486) n (%)*
<b>Frequency of opioid use</b>	
Daily	197 (43)
Weekly	95 (18)
Monthly	42 (9)
Less than monthly	150 (29)
Refused	2 (0)
<b>Frequency of marijuana use</b>	
Current (within the past 30 days)	113 (23)
Past year (more than 30 days but within the past 12 months)	80 (15)
More than past year	293 (62)
<b>Change in opioid requirement due to marijuana use</b>	
A lot more opioid needed	14 (4)
Slightly more opioid needed	18 (4)
No change in opioid use	244 (46)
Slightly less opioid needed	31 (8)
A lot less opioid needed	63 (13)
Stopped opioid use	93 (20)
Refused	23 (5)
<b>Reasons for decrease or cessation of opioid use</b>	
Better pain management with marijuana	71 (36)
Fewer side effects from marijuana	63 (32)

\*Numbers are unweighted, and percentages are weighted to approximate the US population. We used weights provided by GfK to approximate the US population based on socio-demographic factors (eg, age, gender, race, ethnicity, education, household income, home ownership, and metropolitan area).

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equivalent doses who indicated that they were prepared to reduced their opioid use. An individualized tapering plan was developed for each patient, with the tapering rate typically at approximately 10% every 1 to 2 weeks. Medical cannabis (via sublingual, oral, or vaporization) was given at a rate of 0.5 g/day for each 10% reduction in opioid dose. The patients also received psychological support via a web-based mental health and wellness tool.

At 6 months, 156 patients (26%) had stopped using opioids and 329 (55%) had reduced their opioid use

by an average of 30%. No withdrawal symptoms were reported. The remaining 114 patients (19%) showed no change in opioid use and 1 patient had an increased opioid dose owing to poorly controlled pain and an aggravated pain condition.

The study was not funded.

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2. Rod K. A pilot study of a Medical Cannabis—Opioid Reduction Program. *Am J Psych Neuroscience*. 2019;7(3):74-77.



## Patients With Epilepsy Commonly Use Cannabis

Nearly 9 of 10 patients with epilepsy surveyed at a single epilepsy center in Oregon reported using cannabis for medicinal use, according to data published in *Epilepsy & Behavior*.

Of 39 respondents, 34 (87%) reported using cannabis for the purpose of treating epilepsy, and most strongly agreed (54%) or agreed (28%) that cannabis improved their seizure control. The most common cannabis strains used had high cannabidiol (CBD) concentrations, and smoking was the most common method of administration (67%), followed by edibles (50%), and concentrates (44%).

The most common sources of cannabis were medical and recreational dispensaries, followed by home grown and family/friends.

Kerr A, Walston V, Wong VSS, Kellogg M, Ernst L. Marijuana use among patients with epilepsy at a tertiary care center. *Epilepsy Behav.* 2019;97:144-148.

## CBD May Increase Life Expectancy in Glioblastoma Multiforme

Adjunctive use of plant-derived cannabidiol was associated with improved life expectancy in patients with glioblastoma multiforme, according to a case series published in *Anticancer Research*.

The study included 9 patients who were given a daily CBD dose of 400 mg in addition to standard treatment with maximal resection followed by radiochemotherapy.

At the time of article submission, the median survival time was 22.3 months (range 7 to 47 months), and all but one patient was alive. In comparison, the authors noted that median survival is typically 14 to 16 months in patients with this form of brain cancer.

Likar R, Koestenberger M, Stultschnig M, Nahler G. Concomitant treatment of malignant brain tumours with CBD - a case series and review of the literature. *Anticancer Res.* 2019;39(10):5797-5801.

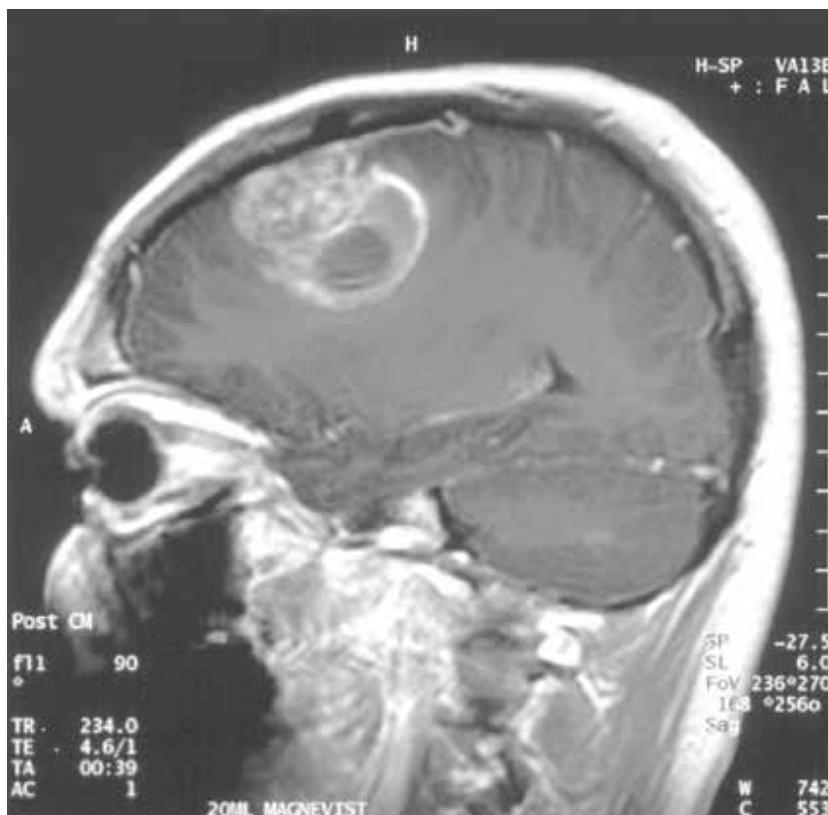


Photo credit: Christaras A, Wikimedia Commons.



## Medical Cannabis Is Associated With Improved IBD Disease Activity

Use of medical cannabis in patients with inflammatory bowel disease (IBD) was linked to significantly reduced disease activity and increased patient weight in a prospective, observational study reported in the *European Journal of Gastroenterology and Hepatology*.

The study included 127 patients with IBD treated with medical cannabis using an average dose  $31 \pm 15$  g/month, or 21 mg delta-9-tetrahydrocannabinol and 170 mg cannabidiol per day. During a median follow-up of 44 months, patients showed significant improvement in disease activity on the Harvey-Bradshaw Index with scores decreasing from  $14 \pm 6.7$  to  $7 \pm 4.7$  ( $P < 0.001$ ).

An average weight gain of 2 kg was found at 1 year ( $P < 0.05$ ), and the need for use of IBD medication was significantly reduced.

Additionally, employment status increased from 65% to 74% ( $P < 0.05$ ), and no negative effects of cannabis use on social or occupational status were reported.

Naftali T, Bar-Lev Schleider L, Sklerovsky Benjaminov F, Lish I, Konikoff FM, Ringel Y. Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects. *Eur J Gastroenterol Hepatol*. 2019;31(11):1376-1381.

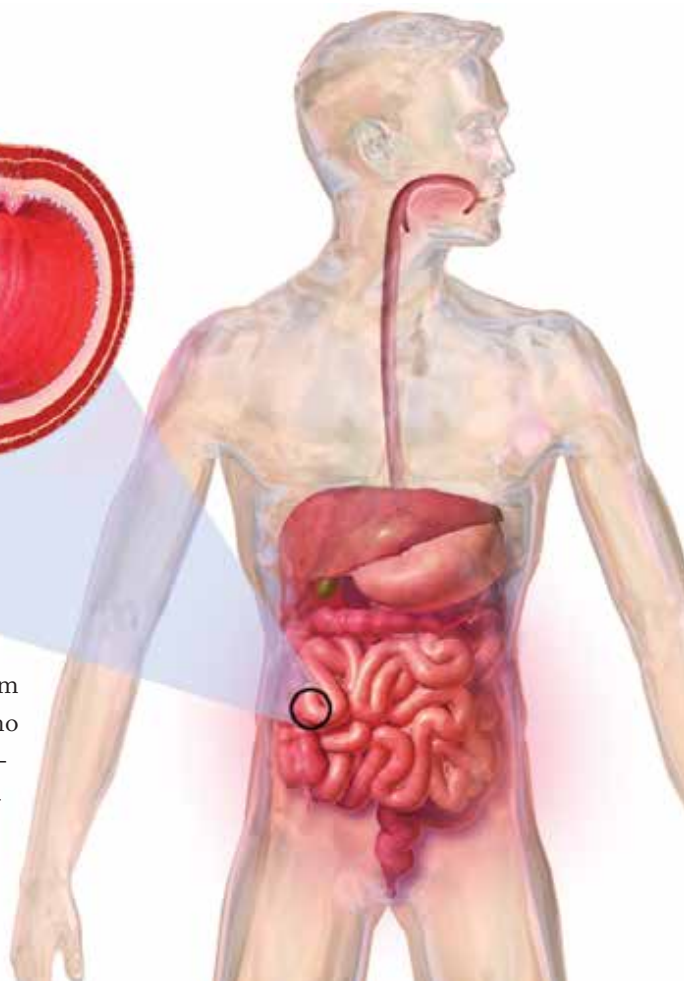
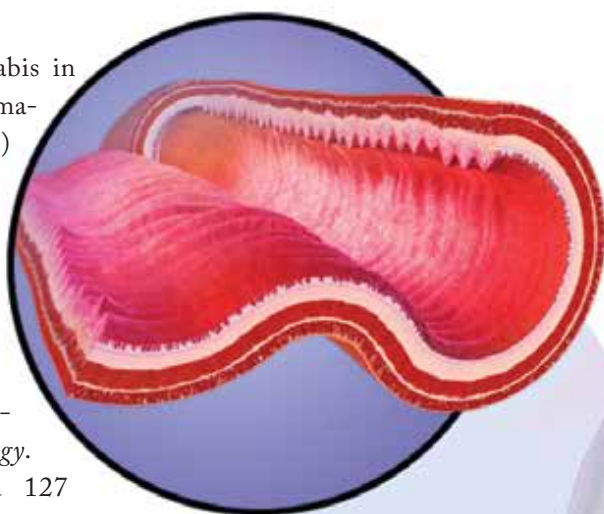


Photo credit: BruceBlaus, Wikimedia Commons.

## Medical Cannabis Improves Pain in Palliative Care

In a survey of 101 patients from a single ambulatory palliative care practice in Georgia with medical cannabis cards, 96% believed that cannabis was important for pain management, researchers reported in the *Journal of Palliative Medicine*.

In addition, a majority of those patients with cancer reported cannabis as being important for cancer cure (59%).

A majority of the patients had cancer (76%) and were married (61%), disabled or

retired (75%), older than 50 years of age (64%), and male (56%). The most common administration of cannabis was ingestion (61%) or vaporization (49%). Side effects were reportedly “minimally bothersome,” with drowsiness being the most common adverse effects (28%).

Zarrabi AJ, Welsh JW, Sniecinski R, et al. Perception of benefits and harms of medical cannabis among seriously ill patients in an outpatient palliative care practice [Epub ahead of print]. *J Palliat Med*. 2019 Sep 20. doi: 10.1089/jpm.2019.0211.



Photo credit: © O'Dea at Wikimedia Commons, CC BY-SA 4.0



## Marijuana May Improve Metabolic Status in Adults With Obesity

**M**arijuana use was associated with better metabolic status, including lower insulin resistance and fasting insulin levels, in a study involving 129,509 adults with obesity 18 to 59 years of age. The findings, which are based on data from the 2009 to 2016 National Health and Nutrition Examination Survey, were reported in the *Journal of Diabetes*.

Current marijuana users with less than 4 uses per month had a 52% lower mean fasting insulin level than never-users. Even former marijuana users with 8 uses per month (> 12 months previously) had a 47% lower mean fasting insulin level than never-users. The association between marijuana use and fasting insulin level was not found in nonobese adults.

The study was funded by the Canadian Institutes of Health Research.



Ngueta G, Ndjaboue R. Lifetime marijuana use in relation to insulin resistance in lean, overweight, and obese US adults [Epub ahead of print]. *J Diabetes*. 2019 doi: 10.1111/1753-0407.12958.

## Cannabis Linked to Reduced Risk for Hospital-Acquired Intestinal Infection

**P**atients who used cannabis were at significantly reduced risk for hospital-acquired *Clostridioides difficile* infection (CDI) compared with nonusers, according to a large study published in *Anaerobe*.

Researchers analyzed data from nearly 60,000 hospitalizations the Nationwide Inpatient Sample 2014 to compare outcomes in patients with and without cannabis use disorder (CUD) as documented in ICD-9-CM codes. Patients with CUD were matched to those without CUD in a 1:1 ratio.

Overall, cannabis use was linked to a 28% reduced risk for CDI (prevalence: 455.5 vs 636.4 per 100,000 hospitalizations) compared with nonuse ( $P=0002$ ). The greatest benefit was found in patients with dependent CUD who had an 80% reduced likelihood of CDI compared with nonusers. In comparison, non-dependent CUD users had a 23% reduced risk for CUD compared with users.

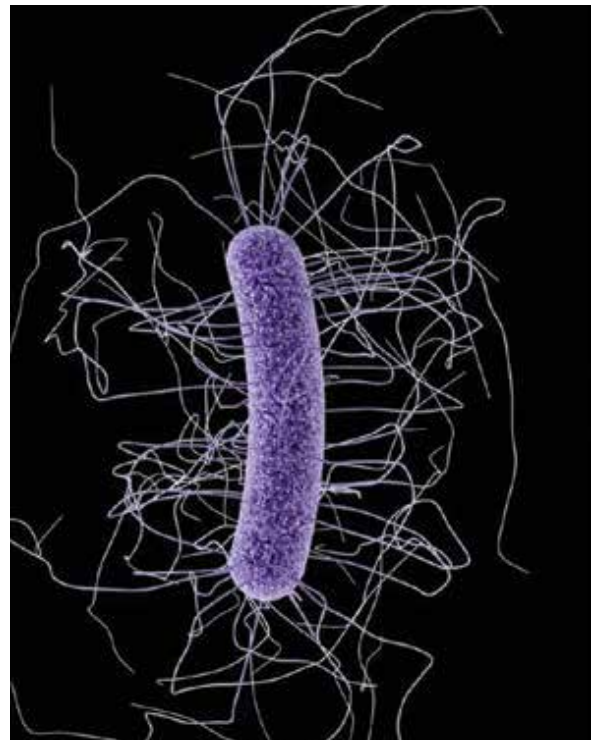


Photo credit: CDC/James Archer.

Adejumo AC, Bukong TN. Cannabis use and risk of *Clostridioides difficile* infection: analysis of 59,824 hospitalizations [Epub ahead of print]. *Anaerobe*. 2019 Sep 4:102095. doi: 10.1016/j.anaerobe.2019.102095.

# The Biochemical System Controlling the Effects of Cannabis: An Introduction

Jahan Marcu, PhD, presents his 2015 article on the endocannabinoid system as it appeared in *HerbalEGram*. 2015;12(6).

In every human there are complex biological systems working to keep physiological functions in order. When these biochemical systems are functioning optimally, they maintain optimal mood and help maintain appropriate levels of immunity, proper digestion, regular sleep, and brain function. The housekeeping properties of these systems have an important role in modulating health and disease. One of these systems is the endocannabinoid system (ECS). The system is built out of G protein-coupled receptors called (CB<sub>1</sub> and CB<sub>2</sub> receptors) and the endocannabinoids that bind to them. The ECS maintains normal cerebral and physiologic function.<sup>1</sup>

Human clinical trials and animal studies show that stimulating this biochemical system can have both highly beneficial health effects and few negative side effects.<sup>2,3</sup> Basic research experiments with genetically modified mice, which are created without CB<sub>1</sub> or CB<sub>2</sub> receptors, have shown that without this biochemical system, the animals (and presumably, humans) would probably die at birth.<sup>4-7</sup> Studies in both humans and animals demonstrate that blocking this biochemical system can result in dreadful consequences, including, but not limited to, depression, stress, nausea, vomiting, diarrhea, anxiety, and even increased tendency for suicide.<sup>8-11</sup> The only antagonist drug ever to be marketed to humans that blocked the cannabinoid receptors—Acomplia® (rimonabant; Sanofi-Aventis; Paris, France)—was quickly withdrawn from the market due to its negative health consequences.<sup>12</sup>

## How Medical Cannabis Works

Cannabis (*Cannabis sativa*, Cannabaceae; common name marijuana, among others) has been used for centuries to treat neurologic and neurodegenerative disorders such as epilepsy or spastic disorders. The medieval Arab writer Ibn al-Badri documented the use of hashish or a cannabis concentrate to cure a neurodegenerative disorder (probably epilepsy) afflicting the son of the chamberlain of the Caliphate Council in Baghdad.<sup>2</sup> Centuries later, Western physicians, including

W.B. O'Shaughnessy and other British neurologists of the 19th century, confirmed the benefits of cannabis concentrates (hashish, hash oil, and tinctures) in the treatment of spasticity, convulsions, and related neurodegenerative disorders.<sup>13,14</sup> However, it was not until the discovery of the ECS in 1994 that scientists could explain these observations.

The progression of diseases such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and other neurodegenerative diseases is affected by neuroinflammation and neurodegeneration (brain cell death).<sup>15</sup> Cannabis can have a positive effect on these and related disorders in a number of ways. Delta-9-tetrahydrocannabinol (THC) from the cannabis plant stimulates CB<sub>2</sub> receptors, which decreases neuroinflammation by inhibiting the movement, growth, and activity of immune cells. Basically, the stimulation of the ECS by constituents from the cannabis plant results in decreasing the migration and activation of the immune cells that maintain the environment of neurodegenerative disorders, thereby disrupting the signals that sustain inflammation and cell death.<sup>16</sup>

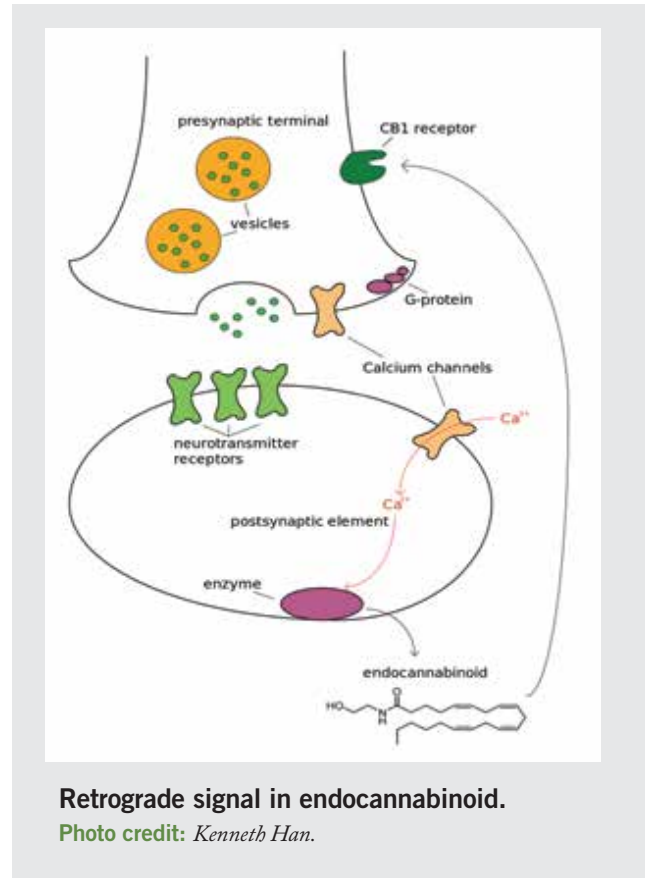
Another important aspect of neurodegenerative disorders is the irreversible death of neurons leading to progressive dysfunction. Excessive glutamate receptor activity is known to cause neuronal cell death by damaging cells and creating reactive oxygen species. The CB<sub>1</sub> receptors found in the brain have a direct effect on neurons by limiting glutamate release when stimulated at the presynaptic nerve terminals. (Glutamate is a key neurotransmitter, derived from glutamic acid, an amino acid.) Cannabis compounds are also potent antioxidants, reducing oxidative damage and blocking the activities of inflammatory signaling molecules like tumor necrosis factor- $\alpha$ . Stimulation of the ECS also has pro-survival effects on brain cells.<sup>17,18</sup>

At the present time, the evidence of the ECS as an appropriate target to treat neurodegenerative and other diseases does not come solely from the limited approved studies on marijuana from the US National Institute on Drug Abuse. The information comes from a wealth of new information about stimulating this biological system and the mechanisms explaining the central role of this system in health. The ECS is inherent to proper human functioning; in fact,

every physiologic system that has ever been studied is positively modulated by it.<sup>19</sup> Recent reports suggest that cannabis, cannabis extracts, and mixtures of the plant's active ingredients are useful for treating epilepsy (ie, Dravet syndrome), traumatic brain injury, cancers, post-traumatic stress disorder, HIV, wasting, glaucoma, Crohn's disease, multiple sclerosis, autism, and other diseases and symptoms.<sup>20</sup>

Since the isolation and structure elucidation of the main ingredient found in cannabis (THC) in the 1960s, several research groups have explored THC and other cannabinoids for therapeutic effects (anti-epileptic effects, palliative care) in adults and children.<sup>21-23</sup> Also, since the elucidation of THC's structure, more than 100 other plant cannabinoids have been documented.<sup>24-29</sup> The efficacy of THC can be increased with other phytocannabinoids and plant compounds such as cannabidiol (CBD) and various terpenes, respectively.<sup>30-34</sup> THC and CBD are both psychoactive but have very different therapeutic mechanisms of action; THC directly stimulates CB<sub>1</sub> and CB<sub>2</sub> receptors, whereas CBD appears to interact with receptors of other important neurotransmitters, serotonin and adenosine.<sup>33,35</sup> When the distinct mechanisms of THC and CBD are combined, they can trigger an enhancement of activity. For example, experimentally derived combinations of THC and CBD have been documented to synergistically inhibit cancer cell growth in Petri dish experiments on human grade IV glioma cells by increasing activity in a specific molecular pathway when co-applied.<sup>34</sup> When a 1:1 combination is used clinically, it proves effective at treating multiple sclerosis without causing intoxication.<sup>36-38</sup>

In mammals, the ECS is modulated during disease or injury; for example, CB<sub>2</sub> receptor density is increased during inflammation or bone injury.<sup>39-42</sup> This upregulation or modulation during disease or injury is associated with increases in both levels of endocannabinoids and the expression of the cannabinoid receptors on the cell membrane.<sup>1,43,44</sup> Modulation of the ECS may be an attempt by the body to reduce or abolish unwanted effects or to slow the progression of various disorders. There is evidence supporting a modulation of this biochemical system in a number of disease models.<sup>2</sup> Additionally, a number of genetic mutations and polymorphisms of the ECS (eg, CB<sub>1</sub> and/or CB<sub>2</sub> receptor mutations) in the human genome are associated with diseases in human populations, such as anorexia, bulimia, migraines, chronic pain, gastrointestinal disorders, mental disorders, alcoholism, and other treatment-resistant conditions.<sup>45-50</sup> A mutation or fault



in the ECS that may underlie a disease or condition has been termed the clinical endocannabinoid deficiency syndrome.<sup>47</sup>

## Conclusion

In addition to anecdotal reports and more than 30,000 basic scientific studies with cannabinoids, there are also more than 100 published clinical studies that have looked at the effect of a variety of cannabis-based medicines (including inhaled whole-plant material, oral THC capsules, and cannabis extracts) on the treatment of a wide range of disorders.<sup>3,36,51</sup>

The data generated from these clinical trials suggest that cannabis and its various preparations interact with the ECS to result in improvements in spasticity, muscle spasms, pain, sleep quality, tremors, appetite, and the patient's general condition.<sup>3,51</sup> Most of these clinical trials have focused on either THC as the primary therapeutic ingredient or a 1:1 ratio of THC to CBD, but there is a paucity of clinical studies examining pure CBD for a therapeutic outcome.

Animal and human research also demonstrates a potential for synergizing or enhancing certain therapeutic effects when cannabinoids and/or terpenes are applied in an appropriate

► continued on page 44



## Biochemical

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combination. The therapeutic rationale for combining THC and CBD, and other cannabis plant components in fixed ratios, can result in a decrease in unwanted side effects and an enhancement of therapeutic benefits.<sup>33,37</sup>

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# Book Review:

## *Cannabis sativa* L.: Botany and Biotechnology

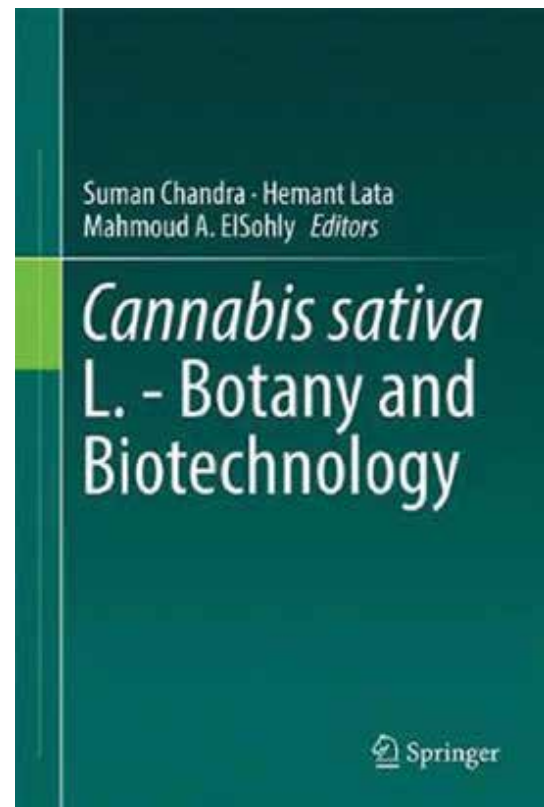
Jahan Marcu, PhD, reviews *Cannabis sativa* L.: Botany and Biotechnology, edited by Suman Chandra, Hemant Lata, and Mahmoud A. ElSohly. Springer. [http://doi.org/10.1007/978-3-319-54564-6\\_3](http://doi.org/10.1007/978-3-319-54564-6_3). Hardcover 479 pages ISBN 978-3-319-54563-9. for HerbalEGram.

What does it take to make a difference in the cannabis research field or in its industry? Given the state of things the question can be too paralyzing to ask. With research roadblocks that take years to navigate, the only protection for the industry from the Drug Enforcement Agency is an annually reviewed CJS amendment,<sup>1</sup> a lack of consistent regulations, and a ton of myth-information about products and their consistency, efficacy and legality. The state of things is a very clear grey area for hemp and cannabis-based medicines. The cloudiness of the lens and resources to accelerate solutions is an essential part of what the authors have to show.

Over the last 15 years, growing cannabis (aka hemp, marijuana) has become a major agricultural industry in many countries. Unfortunately, detailed knowledge of the various aspects of cannabis botany and biotechnology seems to be beyond the field experience of many growers and we continue to see medical cannabis sold without details as regards to contents or even different varieties, extracts and mixtures sold under the same commercial name. “It is unbelievable that neither government agencies nor private foundations have gone ahead or encouraged clinical trials—but this is a fact!,” pointed out Raphael Mechoulam in his section.

The book attracts quite the cast of characters, authors that seem to have been around as long as the plant itself, as well as innovative-rising stars from the industry and academia. No other cannabis science book can boast such a broad range of disciplines under one binding. For example, the book is edited and co-authored by one of the most published natural products researchers in history, and another author is the director of a lab that specializes in genetic testing for the cannabis industry. This blend of curiosity and outcome driven experts is a potent tonic, made with data that is difficult to summarize due to the widely dispersed nature of literature on the topics presented.

At the beginning, it seems like any other carefree academic book. But the innovative interests of the authors



become clearer as the reader proceeds through the sections on ancient history to state-of-the-art research applications. I immediately began implementing it as a source in my own research proposals and businesses strategies. Biotechnology plays an important role in propagation, conservation of varieties, and improvement in medicinal plants. Chapters 13-21 focus on this role, and an entire chapter is devoted to comparing state-of-the-art methods for cannabis micropropagation.

The book covers existing knowledge and identifies areas for further research in botany and horticulture, pharmacology and methods of analysis, chemical and morphological phenotypes in breeding, morpho-anatomy of marijuana,

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## Book Review

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biosynthesis and biotechnological applications, allergenicity to cannabis and methods to assess personal exposure, genomics and molecular markers, micropropagation, hairy root culture as a biotechnological tool, cannabis endophytes and their application in breeding and fitness, and contaminants of concern in cannabis. The reader can achieve a purposeful view of cannabis science.

Aside from the botanical and biotechnology aspects of the plant, the book ends with a chapter on product safety and contaminants. While academia and industry seem to be hitting their stride with the plant, there has been serious issues due to sloppy, unethical, dubious and unscrupulous operators in the cannabis space. The book shows a number of surprising lessons the global cannabis industry has hopefully learned from. While the plant is innocuous and non-toxic, humans find an endless combination of ways to make it less safe, as with any mass-produced commodity. Such as spraying plants with fertilizer made from human dung (Europe) or untreated manure (North America), or a company that was caught repacking a product targeted at cannabis growers as “Guardian” as “100% Natural,” when it was an illegal pesticides. The impact of these behaviors leads to costly fines, recalls, and influences policy and regulatory decisions.

The book also discusses aspects of cultivation to enhance or inhibit different aspects of the plant. Not only genetics and nutrients, but the microbiome, the friendly bacteria and fungus the plant needs to either be a great hemp or a potent medicinal plant. If you are growing the plant for cannabidiol (CBD), you shouldn't be growing it for fiber, and there are many reasons. Hemp appears across 22 genera of plants, it is a name bestowed to plants used to make textiles like rope, clothing, and industrial products; *Cannabis* produces a hemp variety. Hemp varieties may be more susceptible to heavy metals and contamination because of the increased fiber content and lower standards for the cultivation of products that are not grown for human consumption.

The compiled information on hemp is useful, for anyone that works across disciplines, in research, regulations,

and the industry. The book's chapters clarify every botanical aspect to concrete the organizational family of cannabis. This is important as hemp plants are grown differently from medicinal plants, in most respects to improve fiber production over resin production. The tools and resources exist to improve cannabis agriculture, but we need the academics and the industry to work closer together to leverage the knowledge base to truly create a resurgence of cannabis' place in the global economy.

This book succeeds because it combines basic sciences such as botany, with applied sciences such as biotechnology. This combination of curiosity and outcome driven research has proven powerful enough to have solved many issues, such

as how to decontaminate dried flower tops or apply genetic testing to breed specific drug chemo-vars (chemical varieties; dominant for a specific cannabinoid. But also identified a number of research projects the could truly make cannabis have a significant economic resurgence as a hemp or medicinal plant. The book is also useful for the student looking for a project to keep her busy for years, or the industry entrepreneur trying to earn licenses or increase funding opportunities by utilizing innovative research technology. Personally,

the book has been a useful guide for my partners in the cannabis industry to help choose and focus on projects at various cultivation operations.

I'd recommend this book to many people especially cannabis growers in the hopes that it would encourage cultivation operations to work with agricultural specialists, biochemists, and analytical chemists to make possible a consistent and global supply of standardized medical cannabis for patients and researchers. This book will be of considerable importance not only in summarizing present day knowledge but also in advancing innovations in the cultivation and use of cannabis.

**“This book will be of considerable importance not only in summarizing present day knowledge, but also in advancing innovations in the cultivation and use of cannabis.”**

***Jaban Marcu, PhD***

## Reference

1. The Rohrabacher–Farr amendment (also known as the Rohrabacher–Blumenauer amendment) is legislation first introduced by U.S. Rep. Maurice Hinchey in 2001, prohibiting the Justice Department from spending funds to interfere with the implementation of state medical cannabis laws. It passed the House in May 2014 after six previously failed attempts, becoming law in December 2014 as part of an omnibus spending bill. The amendment does not change the legal status of cannabis however, and must be renewed each fiscal year in order to remain in effect.

# Tales From the Clinic: Cannabis' Impact on a Case of PTSD

By Jan L. Roberts, DSW, LCSW, International Research Center on Cannabis and Health, New York University, New York, New York

Kim is a 68-year-old white woman referred to a psychotherapy clinic specializing in treating trauma-related mental health conditions. Kim had no experience with psychotherapy and had only reluctantly decided to seek help. At intake, Kim reported that it had been 13 months since her husband of 43 years committed suicide by hanging. Kim had found his already decomposing body in their basement.

## History and Initial Treatment

Kim said she was repeatedly reliving that moment of finding her husband and was unable to stop these memories from intruding into her daily life. She reported difficulty sleeping, with overwhelming nightmares when she was able to get any significant sleep. Kim had multiple flashbacks of the event throughout a typical day, and the intrusive thoughts were accompanied by noted hypervigilance, increased startle reflex, and feelings of both guilt and hopelessness. Kim reported a lack of motivation and withdrawal from her friends and family. She felt irritable and endorsed passive suicidal ideation. Based on the initial intake, Kim was diagnosed with post-traumatic stress disorder (PTSD). Her symptoms were severe, and she was asked to sign a contract for safety, to ward off imminent suicidality concerns.

Kim had no psychiatric history before the event, but given the severity of her symptoms and passive suicidality, she was referred to a psychiatrist for immediate assessment. The psychiatrist prescribed 50 mg sertraline, with a slow titration schedule from 25 to 50 mg. Kim reported having difficulty tolerating the sertraline due to stomach upset and “feeling really weird, like I’m out of my body.” Against the advice of both her psychiatrist and therapist, Kim ceased taking

sertraline cold turkey and immediately reported “feeling better.”

Nonetheless, her depression continued to increase with time, as did concern over her continued suicidality. She reported “feeling desperate” and said that she had started drinking alcohol more often at night. During her weekly therapy sessions, which were primarily focused on symptom improvement, she reported that her mood was too fragile to feel motivated to complete (reasonably small) assigned behavioral goals. At this point, I suggested cannabis as a potential direction for treatment.<sup>1-4</sup>

## Cannabis Use for PTSD

Kim used cannabis when she was younger but had not taken any form of cannabinoid for more than 30 years. After a discussion about how her state-run medical cannabis program functioned, Kim agreed to try medical cannabis. However, at her next session, she reported that she had procured “some marijuana from her friend’s son” who had received it illicitly. Kim was told that her state’s program would be able to provide safer cannabinoid-based medicine, as it is tested for purity and contamination. Kim’s primary care physician was unable to sign a recommendation as the provider’s health system strictly prohibited it. Thus, I strongly

**“In light of these findings—as a clinician, cannabis researcher, and educator—I believe that far more funding needs to go toward rigorous research so that we might truly determine if the various cultivars of cannabis are as promising as they seem in the treatment of mood disorders.”**

**—Jan Roberts, DSW, LCSW**

encouraged Kim to call a state-approved doctor who is certified to recommend medical cannabis. Kim was assisted with securing an appointment with a certified physician at the only functional cannabis dispensary in the northern part of the state, and in obtaining a legal medical cannabis card.

At the appointment, Kim obtained both flower- and vape cartridge-based cannabis derived from a strain that has shown positive results (according to the manufacturer) in people with sleeplessness, hypervigilance, and depression.

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## PTSD

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Kim began taking both formulations and reported that she was immediately sleeping better and felt less agitated. She noticed that she felt “less angry around others” and was able to return to playing golf—one of her favorite pastimes—with her friends. Over time, Kim’s quality of life began to improve with the medicinal use of cannabinoids. Her feelings of hypervigilance eased, she started feeling motivated to spend more time with her friends, and her mood significantly improved. Kim also reported that she was experiencing fewer nightmares, and flashbacks of the event were reduced considerably. Kim was stable and, eventually, became motivated enough for us to begin working on her traumatic experience. We were able to look at both her cognition and behaviors, to reframe and rework her thoughts concerning the event, and remodel her behaviors in the absence of prior anxiety.

### Effects of Cannabis Cessation

Kim made significant progress until issues arose with supply at the providing dispensary. The primary dispensary suffered shortfalls in production, negatively affecting their ability to meet patient demands. The particular

variety of cannabis flower (and extracted oil) that Kim had used was no longer available, and other similar varieties also were unavailable. As a result, Kim was no longer able to procure the cannabis that had successfully and significantly reduced her symptoms of PTSD. Slowly, the same difficulties with sleeping and arousal states eventually returned at the same level of severity, increasing the frequency of flashbacks of the event, and finally resulting in a pronounced dysthymia. There was an apparent correlation between the reduction of Kim’s cannabis use (due to the unavailability of a specific variety) and the increase in her PTSD-derived symptoms.

At this point, Kim’s primary care physician prescribed zolpidem, which she eventually stopped taking because of significant side effects. Psychotherapy had to revert to more basic therapeutic work centered around ensuring safety and support.

### Resumption of Cannabis Use and Follow-Up

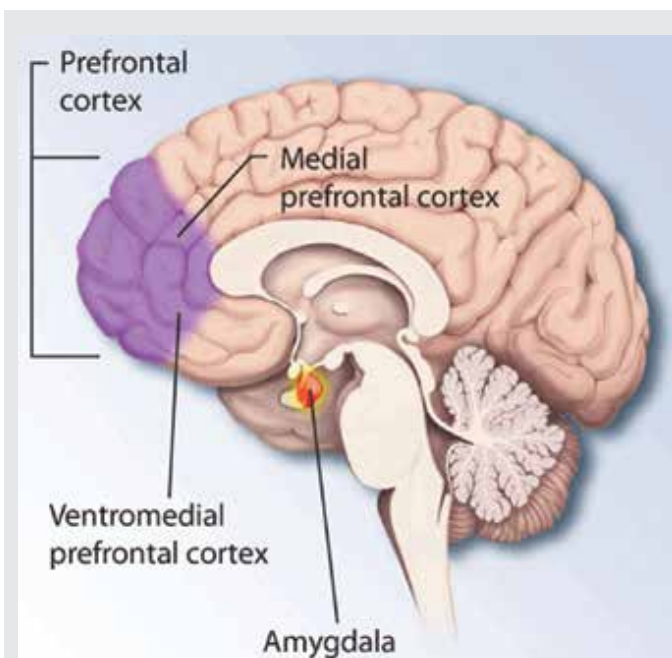
After a few months, the dispensary began stocking the same variety of cannabis that Kim had previously used. She began to use cannabis daily in low dosages with similar improvement in symptoms.

Kim reported that cannabis administration assisted in improving the quality of her sleep, reduced the severity and frequency of her flashbacks, improved her motivation, and elevated her mood. She began “re-engaging in the world” and working on her cognitive understanding of the traumatic event that brought her to therapy originally. It has been 3 years now since her husband’s death, and Kim is finally starting to feel like herself again. Her quality of life has returned.

### Commentary

As a clinician, it is my job to advocate for my clients. Kim is a typical example of one of the fastest growing patient demographics in the United States (ie, the older population). Kim’s lack of understanding about the differences between the illicit “marijuana” market and the legal and regulated cannabis market led her to make inadvertently risky decisions concerning her own medication. Additionally, issues regarding insufficient state supplies of safe and standardized cannabis are of vital concern to anyone using cannabis medicinally.<sup>5,6</sup>

Notably, I had called a local dispensary asking for a detailed account of what products were in stock.



**Brain structures involved in dealing with fear and stress.**

**Photo credit:** *The National Institute of Mental Health, Wikimedia Commons.*





PTSD

anxiety

flashbacks

trauma

stress

symptoms

diagnosis

treatment

coping

avoidance

hyperarousal

negative affect

intrusive thoughts

hypervigilance

startle response

social withdrawal

concentration difficulties

sleep disturbances

irritability

aggression

substance use

suicidal thoughts

self-harm

depression

anxiety disorders

PTSD

As has been demonstrated in similar preclinical trials, Kim's use of cannabis seemed to help reduce both her startle reflex and flashbacks.<sup>2,7-9</sup> In this particular case, Kim's use of cannabis provided significantly less adverse reactions than were reported from zolpidem use. In light of these findings—as a clinician, cannabis researcher, and educator—I believe that far more funding needs to go toward rigorous research so that we might truly determine if the various cultivars of cannabis are as promising as they seem in the treatment of mood disorders. The apparent correlation between Kim's cannabis therapy cessation and her increased PTSD

symptoms appears to provide provocative anecdotal evidence that merits further study.

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*Dr. Roberts has no financial information to disclose.*

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# A History of Cannabis Use in Women's Health

By Jahan Marcu, PhD, Editor in Chief

Source: Russo E. *J Cannabis Ther.* 2002;5-35.

Cannabis has played a role in women's health for thousands of years, as described in a historical review by Ethan Russo, MD.<sup>1</sup> The earliest references of cannabis use for female medical conditions date back as early as the 7th century BCE from Mesopotamia. These early manuscripts describe use of azallû—a mixture of hemp seed and other agents in beer—for difficult childbirth, menses (when mixed with saffron and mint), and other unspecified female ailments.<sup>2,3</sup>

Additionally, ancient texts from Egypt, China, Persia, Israel/Palestine, Syria, and other countries describe a wide range of cannabis uses, including for menstrual disorders and cramps, childbirth, anal fissures, migraine, postpartum hemorrhage, lactation, and breast swelling and pain.

In the 1800s, use of cannabis oral extracts and tinctures was described in Western medicine to treat uterine hemorrhage, menorrhagia, dysmenorrhea, and gonorrhea, as well as to increase labor contractions. Interestingly, Queen Victoria was known to receive monthly doses of *Cannabis indica* for menstrual pain.

Cannabis continued to be recommended in the early 1900s, with the authors of *Pharmacotherapeutics, Materia Medica and Drug Action* describing its use to counteract “painful cramps” and its “particular influence over visceral pain.”<sup>4</sup> Additionally, cannabis was listed as a treatment for dysmenorrhea in *The British Pharmaceutical Codex* in 1934.<sup>5</sup> Cannabis was dropped from the National Formulary in 1941; however, the editor of the *Journal of the American Medical Association*, Morris Fishbein, continued to recommend cannabis for menstrual migraines the following year.<sup>6</sup>

The FDA recently issued a strong warning against use of cannabidiol, delta-9-tetrahydrocannabinol, or marijuana during pregnancy or breastfeeding (see page 37). Although some research suggests that use of cannabis in pregnancies is



Cannabis fluid extract bottle.

Photo credit: Courtesy of [www.AntiqueCannabisBook.com](http://www.AntiqueCannabisBook.com), Wikimedia Commons.

## Historical Uses of Cannabis in Women's Health<sup>1</sup>

- Abortifacient
- Childbirth aid
- Decreased libido
- Dysmenorrhea
- Dysuria
- Gonorrhea
- Hyperemesis gravidarum
- Menorrhagia
- Menstrual irregularity
- Menopausal symptoms
- Postpartum hemorrhage
- Toxemic seizures
- Urinary frequency
- Urinary retention

linked to decreased birth weight and malformations, the largest study to date (N=12,424 pregnancies) found no significant association between cannabis use and low birth weight, shortened gestation, or malformations after controlling for other potentially confounding factors.<sup>7</sup> More research is needed.

Russo concluded that “the long history of cannabis in women's medicine supports further therapeutic investigation and application to a large variety of difficult clinical conditions. Cannabis as a logical medical alternative in obstetrics and gynecology may yet prove to be, in the words of Robson, a phoenix whose time it is to rise once more.”<sup>1</sup>

Cannabis as a logical medical alternative in obstetrics and gynecology may yet prove to be, in the words of Robson, a phoenix whose time it is to rise once more.”<sup>1</sup>

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# Effects of Marijuana Use on Sexual Function in Women

*A commentary on Lynn et al. "The Relationship Between Marijuana Use Prior to Sex and Sexual Function in Women." Sex Med. 2019;7(2):192-197.*

**By Stacia Woodcock, PharmD, Secretary,  
Association of Cannabis Specialists  
New York, New York**

Currently, there is a huge divide between the resources allocated to sexual health in men and women.<sup>1</sup> There are a vast number of erectile dysfunction medications on the market for men vs only 2 medications approved for low libido in premenopausal women. Interestingly, of the 2 medications for women, 1 must be taken every day, and the other is an injection administered 45 minutes before sexual activity.<sup>2,3</sup>

The use of cannabis as a sexual wellness medication represents a much-needed breakthrough in female sexual enhancement. This retrospective review by Lynn et al. represents a great initial general assessment into the effectiveness of cannabis as a sexual arousal and satisfaction tool.<sup>4</sup>

## Study Design and Key Findings

Lynn et al. analyzed survey data from 373 women, including 127 (34%) who reported using marijuana before sexual activity and 49 (13%) who used marijuana but not before sex. Among marijuana users, 68% of those who used it before sex reported satisfying orgasms vs 53% of those who did not use marijuana before sex (adjusted odds ratio [aOR], 2.13;  $P=0.04$ ). Additionally, the effect on orgasms was associated with the frequency of marijuana use, with 71% of frequent users reporting satisfying orgasms vs 58% of infrequent marijuana users (aOR, 2.10;  $P=0.02$ ). Furthermore, a majority of women who used marijuana before sex reported that its use improved the overall sexual experience (69%), increased their sex drive (61%), and increased the number of satisfying orgasms (52.8%).

Cannabis' ability to decrease stress and inhibition, increase confidence and sensation, decrease pain, and prolong the perception of time all directly apply to the most common causes of sexual dysfunction in women.<sup>5</sup> A positive effect on

sex drive, orgasm, and overall sexual experience was reported in women who use cannabis—interestingly, the same effect was seen whether or not cannabis use was initiated directly before sexual activity, which bears further investigation.

## Study Limitations

A majority of women in the study who used marijuana before sex did not report a positive effect on lubrication. As opposed to the other measures, which all had a clear moderate to large increase with cannabis use, lubrication outcomes were clearly divided into "a lot" and "a little," with no in-between margin. It would be interesting to know if there was an underlying contributing factor to this division (ie, menopausal status, underlying medical conditions, etc).

In addition, the majority of patients in this study smoked cannabis, as opposed to using a topical or vaginal form of administration, which would also be an interesting topic for further research, as local administration may have a more measurable effect on lubrication and pain outcomes than inhaled administration.

## Conclusion

This study represents a significant shift in the application of medical cannabis specifically for women's health and wellness, which is a much needed and welcome change in the previous trend of the primarily male-focused sexual wellness space.

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**"There is a huge divide  
between the resources  
allocated to sexual health  
in men and women."**

**—Stacia Woodcock, PharmD**



# Low Levels of Endocannabinoids Found in Children With Autism

*A commentary on Aran et al. Lower circulating endocannabinoid levels in children with autism spectrum disorder. Mol Autism. 2019;10:2.*

By Daniel P. Stein, MD, Neurology of Cannabis, Sarasota, Florida, and Faculty Florida State University College of Medicine, Tallahassee, Florida

Aran et al.<sup>1</sup> assessed the circulating levels of several endocannabinoids in children with autism spectrum disorder (ASD; n=93) and matched controls (n=93), and found significantly lower levels of *N*-arachidonylethanolamine (AEA), *N*-palmitoylethanolamine, and *N*-oleoylethanolamine in children with ASD (Figure). Additionally, Aran et al. delineated the correlations between levels of these endocannabinoids.

## The Endocannabinoid System and Autism

The findings add to a recent study by Karhson et al.<sup>2</sup> Both studies carefully defined the study population and used sophisticated laboratory techniques. The results allowed

both research groups to posit a correlation between patients with ASD and lowered serum AEA (or anandamide) and controls. This correlation is attractive as a validation of what many cannabis clinicians have observed in case studies.<sup>3</sup> However, although some of the study population may have had systemic deficiency of AEA metabolism, the suggestion that circulating serum levels of AEA represent a clinically

useful measure of central nervous system (CNS) function is premature.

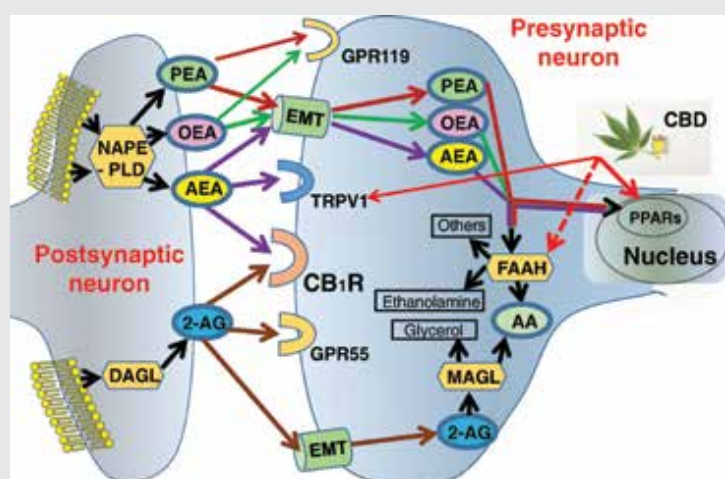
ASD is a disorder of the CNS, as are Parkinson's disease and depression, for example. Serum biomarkers for CNS disorders are rarely available for analysis. Neurons are not bathed in blood, but rather are bathed in clear spinal fluid.

Chemical messengers in the CNS, such as dopamine and serotonin do not communicate with the bloodstream because of the blood-brain barrier.<sup>4</sup> In the CNS, AEA is synthesized on demand and rapidly degrades after production. Thus, a purported insufficiency in AEA production within the CNS cannot be directly reflected in the peripheral circulation.

Aran and Karhson both realize the importance of connecting CNS changes and peripheral serum analysis. They both cited the work of Lerner et al.<sup>5</sup> as de facto support for how peripheral cannabinoid concentrations reflect CNS disease. However, Lerner's study was performed with mice that were subjected to chemically induced seizures. Levels in certain serum lipids following seizure were correlated with changes in CNS lipid profiles. This information, although contributing to our understanding of

**“The studies by Aran and Karhson add to this body of knowledge, and provide support for the theory that disruption of the endocannabinoid system may play a role in ASD.”**

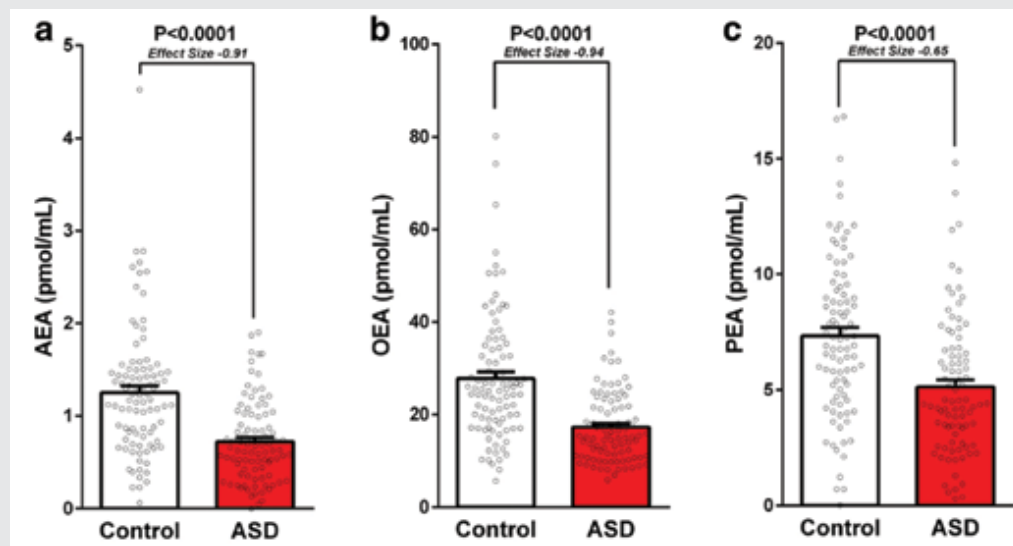
**—Daniel P. Stein, MD**



**Schematic diagram of the endocannabinoid system.**

Copyright Aran et al.<sup>1</sup> (<http://creativecommons.org/licenses/by/4.0/>)





**Figure.** Endocannabinoid levels in children with and without ASD.

Copyright Aran et al.<sup>1</sup> (<http://creativecommons.org/licenses/by/4.0/>).

AEA, N-arachidonylethanolamine; ASD, autism spectrum disorder; OEA, N-oleylethanolamine; PEA, N-palmitoylethanolamine

lipid science, remains highly speculative in terms of pathologic causation and application to humans.

The endocannabinoid system clearly plays a role in nearly all bodily functions, from bones to brain. A convulsive seizure, in mice or humans, has widespread effects on cardiac, pulmonary, circulatory, and musculoskeletal systems. Lerner appreciated this and included reference to multisystem effects on serum cannabinoid levels.

### Elucidating the Relationship

For serum analysis of cannabinoids to be clinically useful, we must continue the work of measuring these compounds in many individuals, under many conditions. Serum AEA levels in patients with various medical conditions have been reported.<sup>6-9</sup> The studies by Aran and Karhson add to this body of knowledge, and provide support for the theory that disruption of the endocannabinoid system may play a role in ASD. For now, however, the usefulness of measuring serum AEA levels in clinical practice remains unclear.

The blood-brain barrier will continue to challenge serum analysis of CNS diseases. Advanced imaging techniques and spinal fluid analysis remain the best ways to study brain function. However, routine analysis of spinal fluid, especially in children, is not practical. Perhaps,

in the future, serum AEA measurements will provide insights into genetically programmed endocannabinoid processes, which also may be applied to the CNS.

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# Positive Autism Intervention With Cannabidiol: A Case Study

By Janet Benton Gaillard, EdS, School Psychologist (Retired), Certified Integrative Nutrition Health Coach, and Director of Research and Development at 101CBD.org

## Introduction

Nearly 1 in 59 children in the United States has been identified with autism spectrum disorder (ASD), according to the latest estimates from the Centers for Disease Control and Prevention.<sup>1</sup> As a complex neurologic and developmental disorder, there are few proven educational or medical interventions for ASD that significantly decrease symptoms and increase social and language skills, as defined by the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5) ASD criteria.<sup>2</sup>

This case describes success with daily use of hemp-extracted cannabidiol (CBD) with low psychoactive delta-9-tetrahydrocannabinol (THC) in a young boy diagnosed with DSM-5 ASD. The child was diagnosed with level 2 severity, global developmental delays, significant language delays, and showed only limited improvement with traditional interventions.

## Background Information

Sam was a friendly, happy toddler who, at almost 2 years of age, was reading and writing a few words, playing songs on his toy piano, and enjoying playing with his older sister and parents.

After severe regression in all skill areas was noted in April, 2014, just before his second birthday in May. His formal diagnosis was precipitated in May 2014 when Sam escaped his home and couldn't be found. He was found by police and firemen hours later, 40 feet down a gorge, sitting without emotion, and unresponsive to his name or the presence of the officers. Observations at the time showed a child who stared into space and rarely spoke or responded

to others. He would often flap his arms, especially when upset. He lacked social and environmental awareness, and basic social, language, self-care, and play skills. Sam would impulsively try to escape his family home or elope his family in the community, seemingly unaware of danger. He was evaluated and began receiving support services in August 2014. He was diagnosed with DSM-5 ASD with a level 2 severity requiring substantial support. Additionally, he was diagnosed with related global developmental delays and speech/language delays.

**“The addition of the CBD had a quick and far-reaching impact on the desired goals of improved social language and interaction skills for relationship development, increased flexibility, less anxiety and avoidance, increased participation in school and family activities, and the skills needed to attend first grade at a public school without any support services.”**

**—Janet Benton Gaillard, EdS**

## Initial Treatment Interventions

Sam began receiving in-home services subsequent to his DSM-5 ASD diagnosis. Little progress was documented during the first year of in-home services.

In 2015, when Sam was 3 years of age, I implemented an in-home daily intervention using Treatment and Education of Autistic and Communication related handicapped CHildren (TEACCH)-based structured teaching principles.<sup>3</sup> His local school district recommended placement in a special education preschool classroom for children with global developmental delays. His parents disagreed, and he began attending a regular preschool 3 mornings a week with one-

on-one applied behavior analysis (ABA) support from trained behavior interventionists.<sup>4</sup> ABA training by a behavior interventionist was added at home, working in coordination with the structured teaching program. Speech/language services and parental training also were provided.

Initial interventions at age 3 also included dietary changes to an organic, gluten-free, casein-free, low-sugar

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**Table. Sam's ATEC Scale Summary Results, 2015–2019**

Administrator	Administration date: 10/15	Administration date: 5/16	Administration date: 5/16	Administration date: 7/19
<b>Mother</b>	Communication 12 Sociability 22 Sensory/Cognitive 27 Physical/Behavior 35 Scale total <b>96/179</b>	Communication 8 Sociability 11 Sensory/Cognitive 6 Physical/Behavior 21 Scale total <b>46/179</b>		Communication 2 Sociability 4 Sensory/Cognitive 1 Physical/Behavior 6 Scale total <b>13/179</b>
<b>Grandparent</b> School psychologist, (retired) Structured teaching—TEACCH	Communication 24 Sociability 35 Sensory/Cognitive 27 Physical/Behavior 34 Scale total <b>120/179</b>	Communication 10 Sociability 19 Sensory/Cognitive 5 Physical/Behavior 11 Scale total <b>45/179</b>		Communication 7 Sociability 7 Sensory/Cognitive 3 Physical/Behavior 7 Scale total <b>20/179</b>
<b>In-home BIs 5/2016</b> <b>ABA and TEACCH</b> 2 adults, child seated <b>In-home BIs 7/2019</b> <b>ABA</b> , 1 BI not seated; child no restrictions	Home support only	Communication 6 Sociability 9 Sensory/Cognitive 6 Physical/Behavior 8 Scale total <b>29/179</b>	Communication 3 Sociability 6 Sensory/Cognitive 6 Physical/Behavior 10 Scale total <b>25/179</b>	Communication 1 Sociability 8 Sensory/Cognitive 3 Physical/Behavior 9 Scale total <b>21/179</b>
School-based BI Teacher consultation In kindergarten <b>School setting 7/2019</b> 1 teacher:20 children	No school after recommendation for placement with children with global developmental delays	No school response provided	No school response provided	Communication 0 Sociability 8 Sensory/Cognitive 6 Physical/Behavior 7 Scale total <b>21/179</b>
<b>Priority needs</b>	Responds to “No” In a shell Aware of danger Says 2 words Anxious/Fearful	Responds to “No” In a shell Aware of danger Limited diet Anxious/Fearful		Carries on good conversations Limited diet Initiates activities Explores/adventuresome
<b>Strengths</b>	Does not injure others Is not destructive Uses 1 word	Uses 3 words together Responds to praise Reads/spells some words Follows some directions		Shows affection Completes full day of school following rules Math and reading skills

**ABA**, applied behavior analysis; **ATEC**, Autism Treatment Effectiveness Checklist; **BI**, behavior interventionist; **TEACCH**, Treatment and Education of Autistic and Communication related handicapped Children.

diet with added probiotics, fruits, vegetables, and dark greens juicing. Traditional Chinese plant-based foods and herbal supplement combinations—such as ginger root, licorice root, and dandelion root—and avoidance of heavy metals and environmental toxins were used for cleansing, nourishment, and inflammation. A simple screen was originally positive for heavy metals before treatment began.<sup>5</sup>

With Sam's continued problems, his physician recommended additional in-depth testing and identified high levels of candida markers, glyphosate, and heavy metals.

He diagnosed Sam with regressive autism, sensorimotor integration delays, a language disorder, abnormal stools, constipation, and candida. He recommended continuing probiotics, dietary supplements, dietary restrictions, and limiting environmental exposure to heavy metals and glyphosate, and added the antioxidant dimethylglycine (DMG) and vitamin B<sub>12</sub> injections. These recommendations were implemented, with discontinuation of the DMG and vitamin B<sub>12</sub> injections after a 12-month trial did not show significant improvements.



Psychological testing at the end of 2016 showed some progress, with test scores in the borderline range for adaptive skills and in the average range for motor and academic skills. Sam showed average receptive language, with significant problems with all aspects of social communication and peer social interactions. He continued to have problems focusing on classmates and teachers. He was inattentive, restless, displayed poor play skills, could not tolerate changes in routine, and demonstrated anxiety. He maintained his DSM-5 ASD diagnosis with level 2 functioning. Recommendations included direct one-on-one staff instruction 50% of his day, with continued one-on-one ABA intervention and supervision at school and at home. The initial interventions of dietary changes and supplements and the use of one-on-one ABA behavioral interventionists in the home and preschool settings continued through August 2017.

Results of these interventions did show gains in academic, communication, and self-care skills. Sam showed increased task participation and an increase in his ability to follow his teacher's directions with the one-on-one staff support. However, progress was slow, required adult support, and he was not on the desired trajectory to be able to attend regular school without assistance and meet age-appropriate developmental goals.

### Intervention With Hemp-Extracted CBD

Sam's parents were concerned that he was not making enough progress to meet the social language development and interaction skills needed to develop social skills and friendships, as well as to participate more fully in school and family activities. He was still anxious, avoided people and activities, and overreacted to new situations and noises. His parents' main goals for him were to be happier and to attend kindergarten at public school.

His parents began research on CBD in general, and then a CBD extracted from the hemp plant with low amounts of psychoactive delta-9-tetrahydrocannabinol (THC). CBD research documented its effectiveness with a range of neurologic conditions, including reports of controlling seizures in children.<sup>6-8</sup> After his parents failed to find the ideal CBD product for Sam, his parents developed a hemp-extracted CBD product with less than 0.3% THC based on holistic principles of a raw, whole plant, and organic approach. The CBD was extracted to keep it raw (processed below 105°) to maintain high levels of cannabidiolic acid (CBDA), the acidic precursor of CBD. Additionally, the oil was extracted

to maintain whole plant full-spectrum cannabinoids, terpenes, enzymes, and flavonoids in a base of certified organic, cold-pressed hemp seed oil. Third-party laboratory testing showed no pesticides, herbicides, molds, bacteria, or heavy metals, and a high percentage of CBDA with a very low (0.005%) THC content.

The CBD sublingual oil was added to Sam's daily supplements and was placed in his freshly juiced fruit and vegetable juice. Starting in August 2017, he was given 3 mg of CBD twice a day and was increased to 10 mg twice a day after 2 weeks. His dosage was increased to and maintained at 20 mg of CBD 3 times a day. It should be noted that when the CBD oil is given orally, only 5% to 20% is absorbed by the body. As there is little definitive research or consensus on CBD oral administration absorption rates reported,<sup>9</sup> an average of 15% absorption rate was chosen. Actual amounts of CBD in his juice were higher to reach the desired mg levels.

Subjective improvements were noticeable within 2 weeks, with less social anxiety and improved sleep observed. Observation after a 3-month period showed increased focus and attention, compliance with instructions, work completion, transitioning between activities, peer interactions, and a decrease in social anxiety. His doctor, Eric G. Sletten, MD, was supportive of the addition of CBD, stating, "In our integrative medicine practice, hemp-derived CBD oil has become a useful adjunct in the treatment of our patients with anxiety and hyperactivity."

By February 2018, Sam was able to visit the kindergarten classroom with other parents and children and calmly tried a variety of activities, responded to the teacher, and played blocks with 3 other children. This was a significant change from his past behavior in novel group settings. In March 2018, he was able to go on his own with an unfamiliar teacher to a computer lab for 40 minutes of online placement testing and a school admission interview. Soon, Sam was eligible to attend kindergarten at public school, and started full-day kindergarten in August 2018, with 6 hours a week of staff support to observe and assist the teacher with strategies when needed. This assistance was removed before the completion of the school year. He began first grade in August 2019, continuing without any support services.

Although the goal of working with Sam was not to create a research project, data was collected from ongoing observations, educational, and psychological assessments;

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ABA goal reports; daily skill training; and repeated measurement with the Autism Treatment Effectiveness Checklist (ATEC).<sup>10</sup> This free online tool was created to measure ongoing autism intervention effectiveness and can be completed by parents and professional staff. The ATEC measures autism symptoms, with lower scores showing fewer ASD symptoms. Total scores of 104 or higher indicate that the child would fall into the 90th percentile and would be considered severely autistic. He or she will likely need continuous care, perhaps at an institution, and may be unable to achieve any degree of independence from others. Scores below 20 indicate a neurotypical developing child.<sup>11</sup>

The ATEC was completed at ages 3, 4, and 7 by parents, this investigator, and the kindergarten interventionist. Sam made progress with the first set of one-on-one teaching, dietary changes, and supplements as shown in the May 2016 ATEC results. Many skills were dependent of one-on-one adult support. He continued to make slow, but unremarkable progress until the introduction of the CBD in August 2017. Current ATEC results show positive gains across all settings. This is particularly impressive as his level of staff support changed from 2 to 1 adult ratio in a classroom setting, to attending a regular kindergarten with all diagnoses and support phased out.

## Conclusion

Sam continues to take his CBD daily. When asked how he feels when he drinks his juice, he replied, "Happy!" He attended a daily summer sports camp on his own in 2018 and enjoyed group sports. Sam demonstrated his growth recently by leading a group of children he met at a park in a loud and fun game of Hot Lava.

Although Sam's success is based on the foundation of diet, supplements, ABA, and structured teaching, he had plateaued with these interventions. A projection of his rate of growth at that time would have resulted in special

education services as well as continuous adult support or institutional care. The addition of the CBD had a quick and far-reaching impact on the desired goals of improved social language and interaction skills for relationship development, increased flexibility, less anxiety and avoidance, increased participation in school and family activities, and the skills needed to attend first grade at a public school without any support services.

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Questions? Comments?

Email the editor: [jahan@ajemcan.com](mailto:jahan@ajemcan.com)





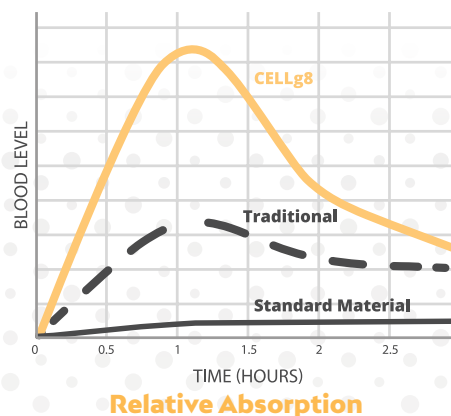
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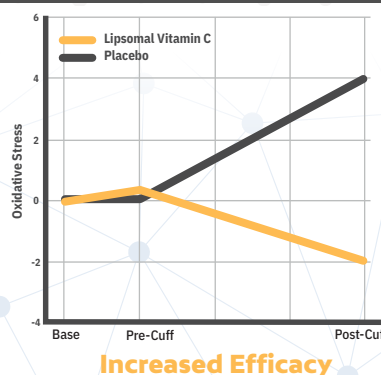


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