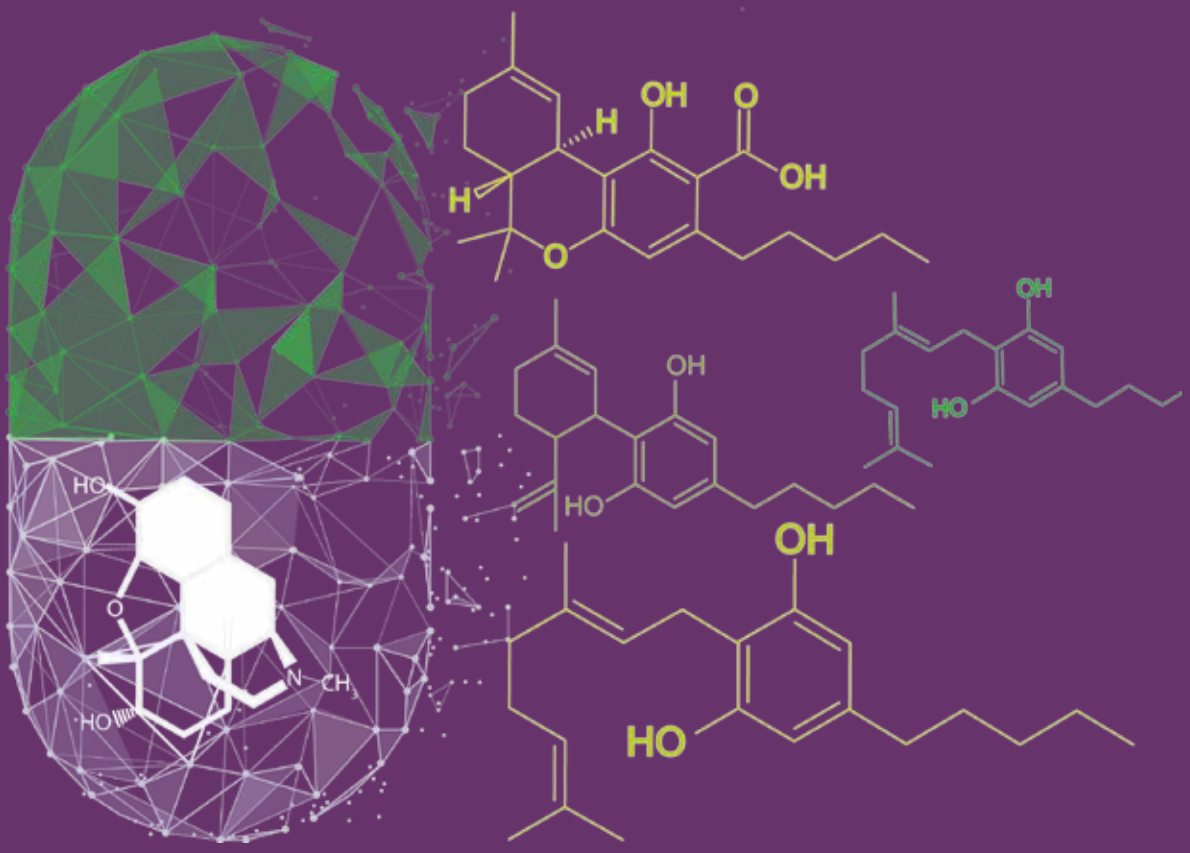
American Journal of Endocannabinoid Medicine

science • knowledge • research

Volume 2 • Issue 1



Opioid Wean With Medical Cannabis:
A Case Report

Liposomal Cannabidiol Delivery:
A Pilot Study

Medical Cannabis Reduces Opioid Use in TOPS

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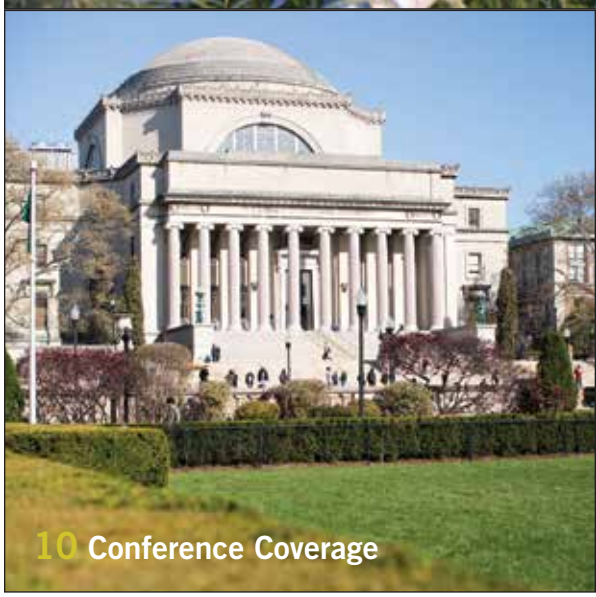
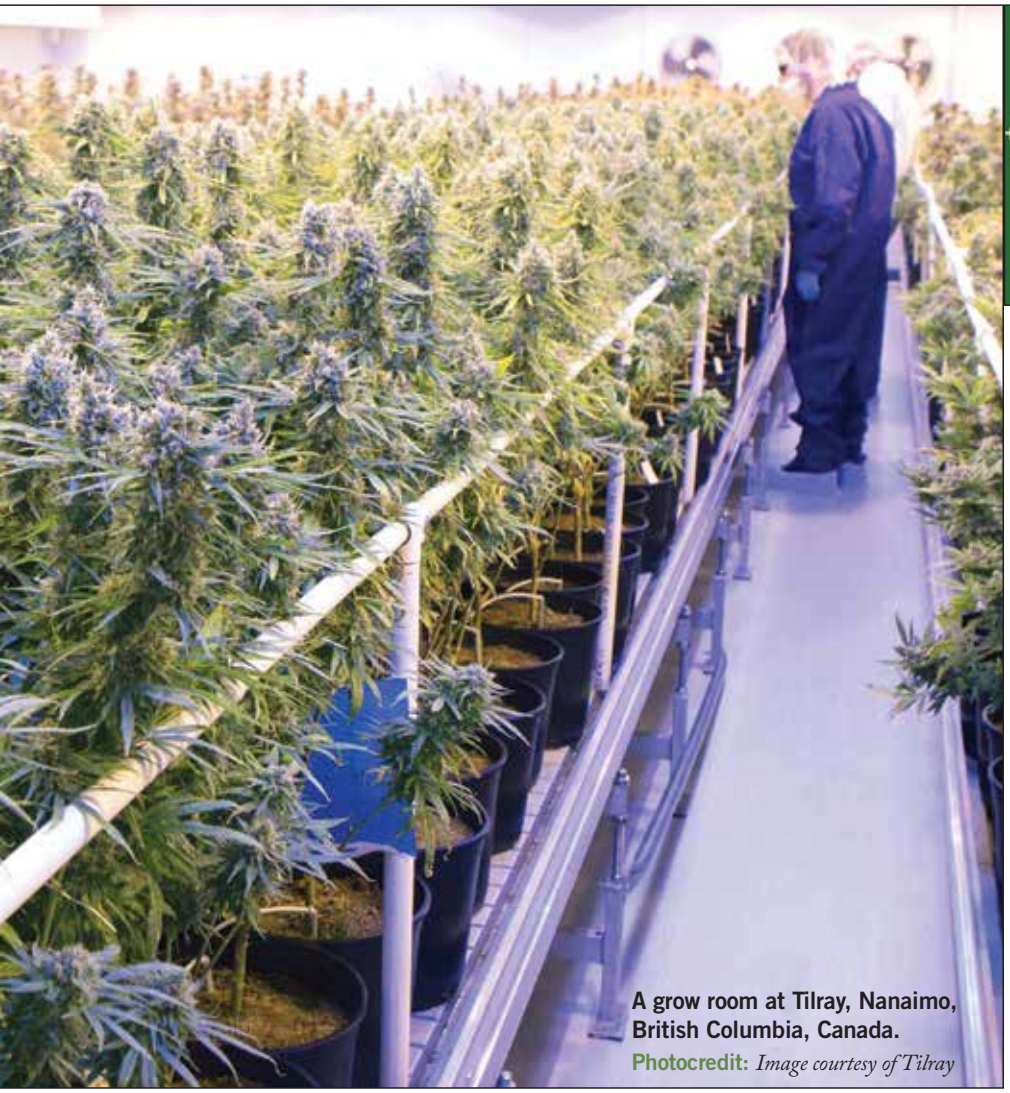
Conference Coverage

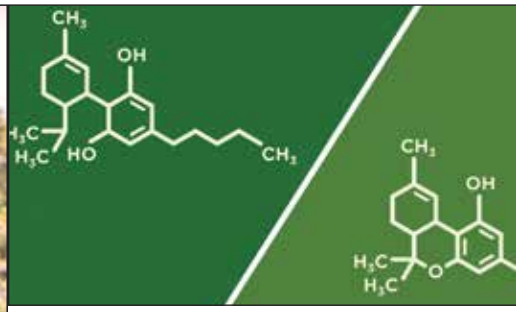
Original Research

Clinical Distillation





A grow room at Tilray, Nanaimo, British Columbia, Canada.
Photocredit: *Image courtesy of Tilray*



In the Issue

Did you know there has been a **23% decrease** in opioid use disorder-related hospitalizations associated with implementation of medical marijuana policy? Discover more fascinating facts in this issue's Cannabis by the Numbers.

Cannabis Policy

Practice Spotlight

Q&A

By Jahan Marcu, PhD

Our second issue of the *American Journal of Endocannabinoid Medicine (AJEM)* examines the role of medical cannabis in chronic pain management and its relationship to opioid use. The cover art shows an opioid molecule interacting with compounds found in the cannabis plant. The image represents the heart of the current issue and can be interpreted to reflect the role that cannabis and opioids may play in chronic pain management.

Additionally, you will find coverage of drug interactions associated with cannabis and cannabidiol-related products, articles on cannabis policy, and a department called Practice Spotlight.

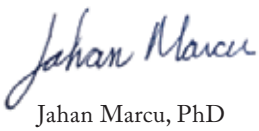
Practice Spotlight focuses on medical cannabis practices around the country that have an on-site physician. Our first article spotlights the work of Leslie Apgar, MD, in Ellicott City, Maryland. *AJEM* welcomes Dr. Apgar to our peer review board and we recommend reading the Practice Spotlight article as well as the case report she authored on opioid weaning.

Additionally, we have some new faces in this issue, including heavy hitters from the research field—Margaret Haney, PhD, and Phillipe Lucas, PhD(c). If you don't know where to start, I encourage you to read articles by Drs. Apgar, Haney, and Lucas' for high-quality, thought-provoking discussions.

Although Drs. Haney and Lucas are both involved with clinical research, they provide different perspectives on cannabis and its relation to substance use—the therapeutic benefits as well as the risk for substance use disorders. Thanks to the hard work of researchers like them, we may see cannabis products being developed into pharmaceutical standard therapies. However, that pathway to drug development of cannabis is fraught with concerns.

The legal and policy issues surrounding cannabis are causing considerable delays in research advances. *AJEM* reports on this topic, examining potential pathways for cannabis market approvals. If cannabis is rescheduled or descheduled, research activities could expand and the FDA may be able to exert greater regulation and oversight. However, there does not seem to be a viable approval pathway for the vast majority of the products in the cannabis and hemp market today. Rob Dhoble of HAVAS-ECS jumps on his hemp box and makes a case for a dual-path federal regulatory framework for prescription and nonprescription cannabis. Mr. Dhoble's article peers into a turbid crystal ball, where a cannabis rescheduling hearing and federal legalization are inevitable.

A quote from Shakespeare's Hamlet sums it up: "*there is nothing either good or bad, but thinking makes it so*" or *cannabis is neither good or bad, but thinking about the data makes it so.* As a peer-reviewed medical education journal, we must be able to discuss the good and the bad. This discussion is ongoing and must be conducted with equal passion and consideration so that medical cannabis policies and drug development can move forward. There is a lot of data out there to address the good and the bad. Some is old, much is new.



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Contributing Authors

Jahan Marcu, PhD, Editor in Chief

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 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, founder and past-chair of the Cannabis Chemistry Subdivision of the American Chemical Society. He serves 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).

Leslie Apgar, MD

Leslie Apgar is a physician born and raised in the Pacific Northwest. She graduated from the Honors Program at Washington State University with a BS in Zoology, then attended medical school at Penn State University. Dr. Apgar completed her OBGYN residency at Penn State University, Milton S. Hershey Medical Center. Dr. Apgar has more than 20 years of experience in direct patient care, and routinely counsels patients and sees the various, sometimes devastating conditions, that can cause the need for alternative therapies. A skilled minimally invasive surgeon, she has been on numerous hospital committees helping to educate, train new surgeons and students, change policies and embrace, emerging technologies. She has been board certified since 2002. As a serial entrepreneur, and having cared for so many women with wellness complaints, she decided to fill an obvious void in the community by expanding into the aesthetics field. Her new company, Pura Vida, was born in 2008 and she became the sole owner of the wellness facility in 2013. Her business continues to thrive well into its 12th year of operation. She and her best friend won a Maryland Medical Cannabis Commission dispensary award in 2016 and their award-winning medically focused dispensary, Greenhouse Wellness, opened in 2017. After seeing an obvious void in the market, they then founded Blissiva, a cannabis line of products directed toward women. Presently, she focuses her energy on continued education on cannabis, aesthetics, and women's health and wellness.

Margaret Haney, PhD

Dr. Margaret (Meg) Haney is a Professor of Neurobiology (in Psychiatry) at Columbia University Irving Medical Center. As the Director of the Cannabis Research Laboratory and Co-Director of the Substance Use Research Center, Dr. Haney is internationally recognized for her expertise in cannabis and cannabinoids.

Her current work focuses on (1) conducting placebo-controlled studies testing the efficacy of potential treatment medications for cannabis use disorder, and (2) testing the potential therapeutic effects of cannabis and its constituents for a range of indications, including appetite-enhancement and pain. Dr. Haney's research has been continuously supported by the National Institute of Health since 1999.

She has authored more than 145 articles in peer-reviewed journals, 12 book chapters, is an Associate Editor for *Cannabis and Cannabinoid Research*, is an Advisory Editor for *Psychopharmacology*, and recently co-edited *Neuropsychopharmacology Reviews* 2018, Cannabis and Cannabinoids: From Synapse to Society. Dr. Haney is a longstanding participant in NIH review groups, is an elected Fellow at the American College of Neuropsychopharmacology, and is the recent past President of the College on Problems of Drug Dependence (2019).

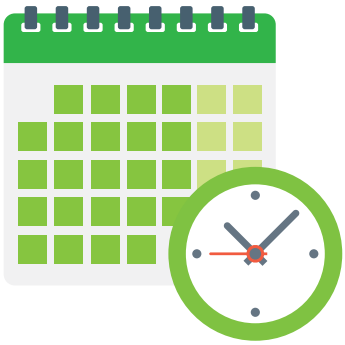
Philippe Lucas, PhD(c)

Philippe Lucas is Vice President, Global Patient Research & Access at Tilray (www.tilray.ca), a federally authorized medical cannabis production, research and distribution company based in Nanaimo, BC; and a Graduate Researcher with the Canadian Institute for Substance Use Research. Dr. Lucas' scientific research includes the therapeutic use of cannabis in the treatment of pain, mental health conditions, and addiction, and he has been invited to provide expert testimony before the Canadian House of Commons, the Canadian Senate, and the BC Supreme Court.

Dr. Lucas first became involved with medical cannabis as a patient, and founded the Vancouver Island Compassion Society in 1999 to serve the needs of patients who might benefit from the medical use of cannabis. He is extremely community involved, and served as a Victoria City Councillor and Regional Director from 2008 to 2011.

Dr. Lucas has received a number of accolades and awards for his work, including the Queen Elizabeth II Diamond Jubilee Medal (2013) for his work and research on medical cannabis, and a Lifetime Achievement Award from the Cannabis Canada Council (2018).

2020 Meeting Calendar



March

National Medical Cannabis Unity Conference 2020
March 25-29, 2020
Washington DC
www.asaunity.org

3rd Annual 2020 Cannabis Sciences Virtual Event
March 25, 2020
https://www.labroots.com/ms/virtual-event/cannabis-sciences-2020

April

2020 Cannabis Science Conference East
April 6-8, 2020
Baltimore, Maryland
www.cannabisscienceconference.com

4th International Conference on Cannabis and Medicinal Research
April 8-9, 2020
Sydney, Australia
cannabis-marijuana.neurologyconference.com

Scientific, Clinical and Regulatory Cannabinoid Conference
April 16-17, 2020
London, UK
www.cmcresearchconference.co.uk

May

3rd International Annual Congress on Controversies in Cannabis-Based Medicines
May 21-22, 2020
Copenhagen, Denmark
www.med-cannabis2020.com/

14th National Clinical Conference on Cannabis Therapeutics
May 28-30, 2020
Rockville, Maryland
www.medicalcannabis.com

Cannabinoid Derived Pharmaceuticals Summit Europe
May 26-28, 2020
London, UK
www.international-cdp.com

July

30th Annual International Cannabinoid Research Society Symposium on the Cannabinoids
July 4-9, 2020
Galway, Ireland
www.new.icrs.co/ICRS2020/ICRS2020/

August

2020 Cannabis Science Conference West
August 31-September 2, 2020
Portland, Oregon
www.cannabisscienceconference.com/

September

CannMed 2020
September 20-22, 2020
Pasadena, California
www.cannmedevents.com

October

11th International Association for Cannabinoid Medicines Conference on Cannabinoid in Medicine
November 7-9, 2020
Mexico City, Mexico
www.cannabis-med.org

November

Medcann World Forum 2020
November 4-6, 2020
Malta
www.medcannworldforum.com

AJEM Cannabinoid Medicine Capital Conference
November 6, 2020
Boston, Massachusetts

Medical Cannabis Reduces Opioid Use in the Tilray Observational Patient Study

Philippe Lucas, PhD(c) speaks to conference attendees at Columbia University in New York City

New York, NY—Patients who initiate medical cannabis significantly decrease their use of opioids as well as other prescription medications at 6 months, according to data from TOPS (Tilray Observational Patient Study), presented at the inaugural meeting of Medical Cannabis: The Science. The Research. The Risks, held at Columbia University in November.[1]

TOPS is the largest national longitudinal study of medical cannabis patients to date in Canada. The study enrolled more than 2100 participants at 21 clinics. In addition to opioids, the use of non-opioid pain medications, antidepressants, antiepileptic drugs, benzodiazepines, and sleep aids/muscle relaxants significantly decreased after 6 months of medical cannabis use.

"Cannabis may be playing a role in reducing the personal public health and safety impacts of opioids, benzodiazepines, and other substances," said lead investigator Philippe Lucas, PhD(c), who is Vice President of Global Patient Research and Access at Tilray in Nanaimo, BC, Canada.

Patient Demographics

The final data set presented by Dr. Lucas is based on 1145 adult patients (57.5% women; mean age 51.2 years) who completed at least one post-baseline visit by October 15, 2018. Most of the patients (~55%) graduated from college or achieved a higher degree, and most (56%) were married or living as married.

"It was really encouraging as a cannabis researcher to see that this was a study with a mostly female population," Dr. Lucas said. "In 15 years of doing research on medical cannabis, this is the first study I've ever been part of that had more women than men participating in it," he said, adding that women are the fastest rising demographic of medical cannabis users.

"There are a lot of conditions with a higher prevalence in women, such as fibromyalgia, lupus, multiple sclerosis, headaches, migraines, anxiety, and depression that don't respond very well to many traditional pharmaceutical drugs, but do seem to respond well to medical cannabis," Dr. Lucas told attendees.

Table. Primary Symptoms Cited by Medical Cannabis Users in TOPS

Symptoms	n (%)
Chronic pain	915 (79.9)
Insomnia	384 (33.5)
Anxiety	327 (28.6)
Depression	219 (19.1)
Stress	219 (19.1)
Headache	166 (14.5)
Spasms	118 (10.3)
Appetite loss	105 (9.2)
Nausea	95 (8.3)
Gastrointestinal issues	60 (5.2)

TOPS, Tilray Observational Patient Study.

Source: Lucas P.[1]

Cannabis Use Patterns

Chronic pain topped the list of symptoms reported by medical cannabis users in this study (80%), followed by insomnia (34%), anxiety (29%), depression (19%), stress (19%), and headache (15%; Table). Of 10 of the primary symptoms cited by patients, 6 were either pain or mental health disorders, Dr. Lucas said, noting the reciprocal relationship between these conditions.

In contrast to the theory that patients may need increasingly higher doses of cannabis to maintain efficacy over time, the findings did not show a significant increase in cannabis use among those using flower cannabis from baseline to 6 months (6.2 and 6.9 g, respectively).

"In fact, it is not unusual to hear from patients who have been using medical cannabis for 10 or 15 years that their current dosage levels are actually lower than what they started out on," Dr. Lucas said. "What you do hear from patients is they develop a tolerance to the adverse effects of cannabis, including dizziness, disorientation, and even impairment associated with THC [delta-9-tetrahydrocannabinol]."

In terms of formulation, high cannabidiol (CBD) was preferred by 52% of patients, and oral ingestion by capsules or drops was preferred by 51%. These findings mark a notable change in medical cannabis use patterns over the past decade, Dr. Lucas told attendees.

"If we were holding this conference 5 years ago, we would really be talking about the inhalation of high THC products," Dr. Lucas said. "Now, we are talking about the oral ingestion of CBD products, and this marks a big shift in the way that we look, talk about, and consider medical cannabis."

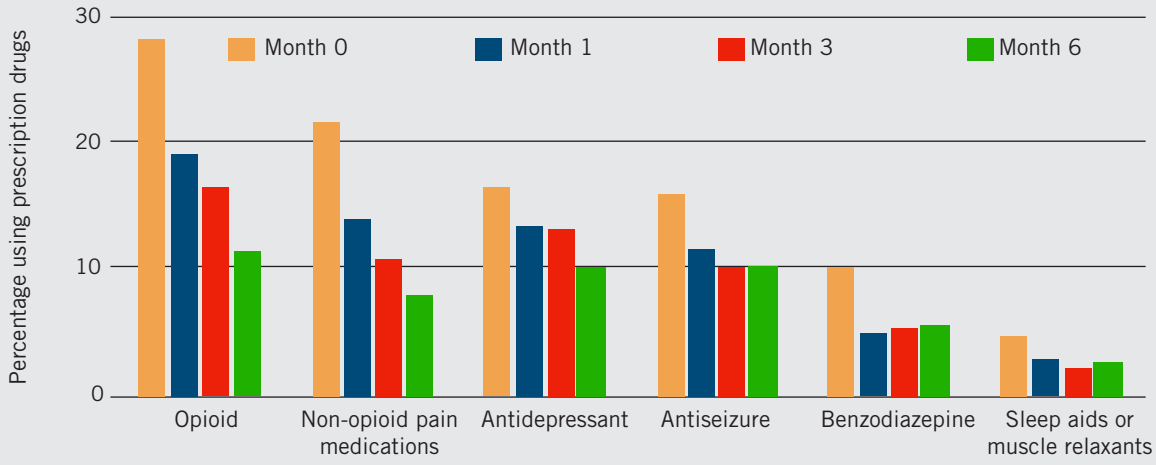


Figure. Percentage of patients initiating medical cannabis who used prescription drugs at baseline to 6-month follow-up in the Tilray Observational Patient Study.

Source: Lucas P.[1]

Patient preference for orally ingested CBD as opposed to inhaled high THC was largely mediated by age, with 50% of patients 18 to 25 years of age preferring high THC strains; whereas 80% of patients 55 years and older preferred high CBD strains ($P<0.001$). Although more research is needed to understand the mechanisms behind these age-related preferences, the differences may be related to impairment concerns among older adults or that certain conditions affecting older patients (eg, osteoarthritis) may benefit from CBD rather than THC, Dr. Lucas said.

Decreased Use of Opioids

Statistically significant reductions in the percentage of patients using all major drug classes included in the analysis were found at 6 months (Figure). The mean cost of medication reduction decreased by 87%—from a mean of $106 to $18 per month between baseline and 6 months.

The percentage of patients taking opioids decreased from 28% at baseline to 11% at 6 months ($P<0.05$). This significant reduction in opioid use was found regardless of whether patients were cannabis naive or non-naive at baseline (see page **25** for more information). Additionally, the mean dose of opioid use decreased by 78%—from 152 to 32 morphine milligram equivalents per day at 6 months. These findings are based on prescription drug questionnaires completed by the patients' health care providers, to minimize recall bias among patients.

The findings suggest that patients commonly substitute medical cannabis for other opioids and other pharmaceuticals, Dr. Lucas concluded. "It is hard to look at data like this without thinking that medical cannabis can and is playing a role in reducing the personal and the public health impacts of opioids on individuals in society," Dr. Lucas said.

The TOPS findings confirm previous research showing that state implementation of medical cannabis laws is associated with a 5.88% lower rate of opioid prescribing among Medicaid enrollees.[2] Additionally, research links daily (at least) cannabis use with a 21% greater odds of retention in opioid agonist treatment (methadone or buprenorphine/naloxone-based) than patients with less-than-daily cannabis use.[3] Furthermore, a study using Medicaid State Drug Utilization Data from Washington DC and 8 states that legalized recreational marijuana found that legalization was associated with a 32% reduction in number of opioid prescriptions, a 30% reduction in total doses, and a 31% reduction in spending on Schedule III opioids.[4]

Quality-of-Life Improvements Found

"At the same time as we saw these reductions in prescription drug use, we saw statistically significant improvements in all 4 facets of the World Health Organization Quality of Life Short Form," Dr. Lucas said. The greatest changes were reported in physical health (26.4% increase), and psychological health (14.4% increase).

"In many ways, it is kind of a simple formula," Dr. Lucas explained. "You've got this patient population mostly affected by pain and mental health. You introduce medical cannabis in their course of treatment, and you get an associated reduction in prescription drug use overall and an associated improvement in QoL."

Reference

1. Lucas P. Medical cannabis in the treatment of pain and mental health, and substitution for opioids and other drugs; results from a large prospective study. Presented at: Medical Cannabis: The Science. The Research. The Risks.; November 15, 2019; New York, NY. Accessed February 23, 2020. www.medicalcannabis-science-research-risks.com
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4. Shi Y, Liang D, Bao Y, An R, Wallace MS, Grant I. Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug Alcohol Depend*. 2019;194:13-19.

Dr. Lucas *is Vice President, Global Patient Research and Access for Tilray, the sponsor of the Tilray Observational Patient Study (TOPS).*

Medical Cannabis: Bridging Science and Policy

Margaret Haney, PhD, speaks to conference attendees at Columbia University in New York City.

New York, NY—Vast changes in cannabis public policy have occurred over the past 20 years with little scientific input, Margaret Haney, PhD, told attendees at the inaugural meeting of Medical Cannabis: The Science. The Research. The Risks, held at Columbia University.[1]

"Putting medical cannabis decisions up to vote has led to this crazy patchwork across our country where in New Jersey you can use cannabis for migraines, but in New York you cannot. The decision is not based on science. It is based on who was lobbying in that particular state," said Dr. Haney, who is Director of the Cannabis Research Laboratory and Co-director of the Substance Use Research Center at NewYork-Presbyterian/Columbia University Irving Medical Center, and Professor of Neurobiology (in Psychiatry), at Columbia University in New York City. "While legalization of recreational use is perfectly within the purview of voters in a democracy, it is deeply troubling to have voters vote on what constitutes an efficacious medication," she added.

Although Dr. Haney noted that medical cannabis has shown "tremendous potential" in the treatment of a variety of conditions, including pain, obsessive compulsive disorder (OCD), and food intake in patients with HIV,[2] the current understanding of the therapeutic use of cannabis and cannabinoids is still in the early stage. "Cannabis has escaped the process required of every other prescribed medication, and that is randomized placebo-controlled evidence," Dr. Haney told meeting attendees.

Legal Barriers to Cannabis Research

Although randomized controlled trials using safely manufactured products of known composition are the key to closing the gap between science and policy, trials are difficult to conduct as statewide legalized recreational or medical cannabis legislation does not extend to scientific study. Dr. Haney emphasized the need to reclassify cannabis and its constituents to a Schedule II status to open the pathway for scientists to conduct more placebo-controlled trials.

Presently, cannabis and its constituents remain Schedule I substances according to the Drug Enforcement Administration (DEA) with the exception of Epidiolex (cannabidiol [CBD]), which is approved for the treatment of Lennox-Gastaut syndrome or Dravet syndrome.[3] "Currently, there is no US source of FDA-approved CBD for scientific research, so how can we test this drug?" Dr. Haney asked attendees.

Dr. Haney discussed the following regulatory hurdles:

- For scientists who would like to conduct federally funded clinical research, the DEA has only approved one source of cannabis from a farm at the University of Mississippi
- Each investigator needs federal/local DEA and state licenses as well as FDA approval (investigational new drug application) for each protocol
- Cannabinoids—including oral CBD—must be stored in a gun safe in a double-locked and alarmed room, and each Schedule I-licensed investigator needs a separate safe
- Cannabinoids/cannabis can only be administered on site, limiting research for chronic conditions that require ongoing use and longitudinal analysis

An additional issue is that cannabis "has morphed into this large-scale, for-profit industry and, in lieu of evidence, the medical benefit is really what the marketers are saying it is because the FDA has stayed remarkably silent for the most part on all of this," Dr. Haney said.

Cannabis Research Laboratory

At the Cannabis Research Laboratory at Columbia University, Dr. Haney collaborates with researchers from many different specialties including oncology, pain medicine, and psychiatry. Currently, she is enrolling patients in the laboratory's first randomized placebo-controlled trial using FDA-approved CBD:delta-9-tetrahydrocannabinol (THC) capsules imported from Canada.

"This is a well-powered, placebo-controlled trial," Dr. Haney said. "We have patients underway and are conducting biweekly measures of pain and functional impairment."

The researchers are evaluating the effects of cannabis capsules containing high CBD:low THC (n=48) compared with placebo (n=48) given for 8 weeks in women with taxane-induced peripheral neuropathy (TIPN). This side effect occurs in more than 65% of patients treated for breast cancer, and no effective treatment is currently available. As a result, TIPN causes a significant number of women to terminate chemotherapy. In animal models, CBD and THC given before paclitaxel prevented development of TIPN, and significantly reduced symptoms when given after onset of TIPN.[4,5] A proposed mechanism behind this effect is agonism at the serotonin 1A receptor.[5]

The laboratory provides a unique setting for clinical trials as it contains 4 bedrooms in addition to a recreational space, and allows for around-the-clock monitoring of mood and drug effects, sleep, cognitive performance, and other measures. "I bring in 4 people to live in the lab at a time, and I have them smoke controlled amounts of cannabis throughout the day and then placebo cannabis as well," said Dr. Haney.

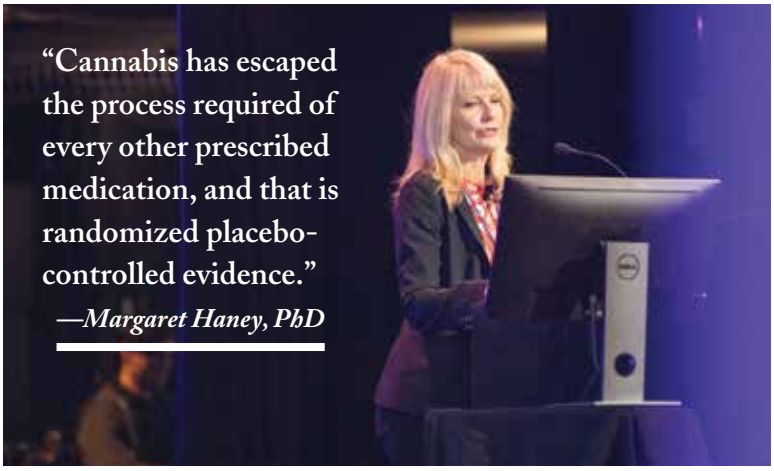
In a study at the laboratory using a cold presser task experimental pain model, researchers examined the analgesic effects of dronabinol versus cannabis among daily cannabis smokers. Study findings revealed that cannabis and dronabinol produced a comparable magnitude of analgesia compared with placebo in healthy male (n=15) and female (n=15) cannabis smokers.[6] However, dronabinol showed longer-lasting effects and only cannabis produced abuse-related effects, Dr. Haney noted.

In a more recent study of experimental pain in healthy cannabis smokers (N=18), neither cannabis nor a subtherapeutic dose of oxycodone (2.5 mg) produced an analgesic effect; however, when these agents were combined, a significant synergistic effect on pain threshold and tolerance was found ($P \leq 0.05$).[7]

"This suggests that a subtherapeutic dose of oxycodone paired with active cannabis could give a nice analgesic effect, supporting

the notion that you could tentatively use less opioids and get a significant analgesic effect," Dr. Haney said. This synergistic effect was not found with higher doses of oxycodone.[7]

However, the analgesic effect of cannabis may only be found in men, according to research by Dr. Haney and Ziva D. Cooper, PhD, Research Director of the UCLA Cannabis Research Initiative in the Jane and Terry Semel Institute for Neuroscience and Human Behavior, and the Department of Psychiatry and Biobehavioral Sciences at the University of California, Los Angeles.[8] In a study involving 21 male and 21 female cannabis smokers, an experimental model of pain showed that active cannabis significantly decreased pain sensitivity compared with inactive cannabis in men ($P<0.01$) but not in women. Men and women in this study were matched for current cannabis use, to rule out the potential effects of tolerance to cannabis.



"Women tended to be more sensitive to the abuse potential of cannabis, but less sensitive to the analgesic effect," Dr. Haney told the *American Journal of Endocannabinoid Medicine*.[8] The mechanism behind this difference is unclear, she said.

Future Research

Dr. Haney emphasized the need for future placebo-controlled trials of cannabis in the treatment of glioblastoma and post-traumatic stress disorder (PTSD). Additionally, Dr. Haney said that more research on the effects of the bioavailability of different routes of cannabis administration, dose, and sex on outcomes is urgently needed.

"We've shown in our small studies, evidence for efficacy of cannabis in pain, OCD, and food intake in patients with HIV, but our understanding of the therapeutic use of cannabis and cannabinoids is still in its infancy," Dr. Haney said.[9] "We have to consider the potential placebo effects of cannabis because the majority of data in the field is observational."

Current Knowledge on Cannabis Efficacy

Finally, Dr. Haney outlined current evidence-based research findings to meeting attendees. She cited a 2017 report from the National Academies of Science, Engineering, and Medicine showing conclusive or substantial evidence that cannabis or cannabinoids are effective for the following[2]:

- Treatment of chemotherapy-induced nausea and vomiting
- Improving patient-reported spasticity in multiple sclerosis
- Treatment of chronic pain in adults

A randomized placebo-controlled trial demonstrated efficacy of CBD as an adjunct to antiepileptic drugs in the treatment of drug-resistant seizures in children with Dravet syndrome, with a reduction in the median frequency of convulsive seizures from 12.4 to 5.9 per month.[10] A reduction in convulsive-seizure frequency of at least 50% was found in 43% of patients who received CBD compared with 27% of patients in the placebo group ($P=0.08$).

Dr. Haney said there was insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders, pointing to a 2019 meta-analysis of cannabis use in psychiatric disorders.[11] The study found "scarce evidence" that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit/hyperactivity disorder, Tourette syndrome, PTSD, or psychosis. Additionally, there was "very low-quality evidence" that THC use (with or without CBD) leads to a small improvement in symptoms of anxiety in patients with other medical conditions.

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The Science of the Endocannabinoid System

Monica Taing, PharmD, RPh, speaks to conference attendees at Columbia University in New York City.

New York, NY—"The endocannabinoid system [ECS] is a comprehensive and complex homeostatic balancing system with diverse potential therapeutic clinical implications in chronic conditions," said Monica Taing, PharmD, RPh, at the inaugural meeting of Medical Cannabis: The Science. The Research. The Risks, held at Columbia University.[1,2]

Dr. Taing, who is a Clinical Cannabis Consultant Specialist for hospital systems and academic medical institutions, spoke to meeting attendees about the pharmacokinetic and pharmacodynamic parameters of various cannabinoids and their effects on homeostasis, chronic disease states, dosing, formulation selection, and potential drug–drug interactions.

The Role of the ECS in Homeostasis

"The ultimate function of the ECS is homeostasis, which is returning balance in the body," Dr. Taing told attendes. "It is the internal biological balancing mechanism of the body and brain."[1]

Dr. Taing used the acronym PREFS to describe the key functions of the ECS in promoting homeostasis: protect, relax, eat, forget, and sleep (Table).[2-4]

"The ECS changes as we age," Dr. Taing continued. "It's different in every person based not only on age, but also on race, gender, and use of pharmacotherapies that can tip the balance away from or help restore homeostasis."

Basics of the ECS

Dr. Taing cited preclinical data showing that the ECS has a profound effect on stress, anxiety, and depressive states at the pharmacologic, biochemical, and genetic levels.[5,6]

Table. Functions of the ECS[2-4]

Function	Description
Protect	Protects the body by stimulating the immune system to mount a response to a foreign pathogen
Relax	Helps maintain balance in response to acute or long-term stress and breakthrough or persistent symptoms
Eat	Stimulating or suppressing the ECS can increase or decrease hunger. ECS stimulation is helpful in conditions like HIV/AIDS wasting syndrome or chemotherapy-induced nausea and vomiting
Forget	Disrupts short-term memory, which is important in conditions such as PTSD because it helps patients relax, potentially forget nightmares or flashbacks, and better process the trauma
Sleep	Restorative sleep can help reduce inflammation and pain

ECS, endocannabinoid system; **PTSD,** post-traumatic stress disorder.

The fundamental pillars of the ECS, consist of the following:

- **CB_1 and CB_2 receptors** are G protein-coupled receptors (upon which a majority of other pharmacologic therapies also impact) produced in the body as a result of human evolution. CB_1 receptors are ubiquitous throughout the body and are predominantly found in the central nervous system, with a high density in certain areas of the brain (eg, cerebellum, globus pallidus, hippocampus, and substantia nigra),[7] whereas CB_2 receptors are mainly limited to the periphery, including the immune system.
- **Endocannabinoids:** *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) are produced in the body on demand and act as partial agonists at CB_1 and CB_2 receptors. Activation of these receptors by anandamide and 2-AG has the potential to modulate anxiety/stress, inflammation, pain perception, and neuropathic pain, among other processes.[8,9]
- **Enzymes** produced in the cerebrospinal fluid drive the biosynthesis, degradation, and transport of endocannabinoids and other ligands that act on cannabinoid receptors.[10]

"It is interesting that CB_1 receptors are very minimally, if at all, located in the brainstem," Dr. Taing said.[6] "This is the pathophysiologic reason why it is not physically possible to induce cardiorespiratory depression [solely] with [botanical] cannabis."

Cannabinoid Pharmacology

Delta-9-tetrahydrocannabinol (THC) mimics the effects of anandamide and 2-AG and on CB_1 and CB_2 receptors, and CBD has multimodal activity at CB_1 and CB_2 receptors as well as at receptors beyond the ECS, Dr. Taing said.[11,12] She uses the lock-and-key metaphor for explaining the complex pharmacology of cannabis to patients, where CB_1 and CB_2 receptors are the locks and cannabinoids (either endogenously produced or exogenously introduced) are the keys.

Preclinical research suggests that anandamide and 2-AG exhibit local effects on cardiovascular physiology (eg, cardiac contractility, platelet activation, endothelial cell activation) as well as positive effects on other cells that contribute to cardiovascular/atherosclerotic pathologies (eg, monocytes, macrophages, lymphocytes, neutrophils, and other inflammatory cells).[13]

"Understanding the activity of CB_1 and CB_2 receptors in the ECS, ligands (concentration and duration), as well as enzyme synthesis, release, and degradation is needed to understand the diverse therapeutic clinical implications of medical cannabis use in the treatment of chronic conditions," said Dr. Taing, who is on the Board of Directors at Doctors for Cannabis Regulation, a non-profit health care provider advocacy organization based in Princeton, NJ.

Additionally, it is important to consider the entourage effect of cannabis, which is the theory that "terpenes, flavonoids, and cannabinoids all work together like a symphony," Dr. Taing said.

Monica Taing, PharmD, RPh

"These components all complement each other so that you can get the maximal effect of the plant," she added. Terpenes are essential oils that provide aroma and flavor to the plant, whereas flavonoids provide pigment and potentially antioxidants.[14]

"In practice, I meet patients who are prescribed the synthetic agent dronabinol and say that it didn't work for them, and this may be because they are not benefiting from the entourage effect," Dr. Taing noted. This prescription medication also has a narrow indication and may not address all the issues and symptoms that patients with chronic conditions have, she added.

Dosing and Safety

THC produces biphasic effects with low doses mimicking the effects of endocannabinoids in reducing hypothalamic–pituitary–adrenal (HPA) axis activity and anxiety, whereas high doses increase HPA axis function and are anxiolytic.[15]

"Biphasic dosing of THC is the pharmacological rationale behind 'start low, go slow' dosing for patients, regardless of whether the patient is using an adjustable or inhalation delivery method," Dr. Taing said.[16] Patient education is particularly important for those taking edible cannabis, as there is a lag in onset of action, and then an extended duration of action compared with inhaled cannabis.

"When the body is starting to digest and metabolize THC, it will convert it to 11-hydroxy THC, a metabolite that is more potent than the original THC and potentially lasts in the body longer," Dr. Taing noted.[15,17-19] "I have seen so many [reported incidents of] patients who took one bite of a cannabis brownie and they didn't feel any effect after 15 minutes, and then ate the entire brownie and wound up in the emergency room."

Even in a cannabis-experienced patient, Dr. Taing suggested starting treatment with a product that has less than 10% THC. Then, she suggests gradually dose titrating by monitoring for efficacy and the emergence of adverse events.[2,3]

Monitoring for drug–drug interactions also is essential to care. For example, "We need to monitor patients taking antidepressants or mood stabilizers for changes in terms of how they feel, their affect, their mood, and any short-term and long-term benefits of cannabis in order to manage the dosing of cannabis as well as dosing of the other prescription medications that they are taking," Dr. Taing explained.

Striking the right balance in terms of dosing also is important for patients with cardiovascular issues, as the risk for an acute cardiovascular attack is increased for 1 hour after using cannabis, Dr. Taing said.[20]

Additionally, Dr. Taing noted that patient counseling for those who are apprehensive is important to ensure that they are in an optimal environment and mindset to obtain benefit from cannabis treatment.

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Pharmacogenomic Testing and Drug–Drug Interactions With Cannabinoids

Jahan Marcu, PhD, speaks to conference attendees at Columbia University in New York City.

New York, NY—Pharmacogenomic testing is a promising strategy for predicting drug–drug interactions (DDIs) with cannabinoids, preventing addiction, lowering side-effect risk, informing dosage guidelines, and personalizing strategies for health care, Jahan Marcu, PhD, told attendees at the inaugural meeting of Medical Cannabis: The Science. The Research. The Risks, held at Columbia University.[1]

Genomic, genetic variability influences the efficacy and tolerability of the 2 major pharmacologically active cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD),[2] Dr. Marcu said. Pharmacogenomic influences may include variability in drug transporters (eg, P-glycoprotein), which may impact drug absorption and distribution. Additionally, variability in drug metabolizing enzymes, most commonly the cytochrome P450 (CYP450) family, resulting from genetics or drug interactions may affect cannabis metabolism and the risk for side effects.[3]

PHARMACOKINETIC	PHARMACODYNAMIC
Cannabinoid as "**victim**": • Cannabinoid levels are changed by another drug	• Both drugs contribute to **overlapping side effects** • Concepts of "victim" and "perpetrator" don't apply
Cannabinoid as "**perpetrator**": • Cannabinoid causes change in levels of another drug	

Figure. Types of drug–drug interactions with oral cannabinoids.

Image credit: M. Tagen

"The activity of these CYP450 enzymes, whether patients are ultra-rapid or ultra-slow metabolizers, can vary 10-fold between individuals due to genetic mutations or polymorphisms," Dr. Marcu told attendees.[3,4] Notably, this effect applies to oral administration of cannabis, which undergoes extensive first-pass metabolism. In contrast, inhaled administration has no significant first-pass metabolism and sublingual administration avoids first-pass metabolism with the exception of a small portion that is swallowed.[5]

For example, the CYP2C9*3 polymorphism, which is present in approximately 8% of the white population and leads to reduced enzyme activity, is associated with 3-fold higher plasma levels of THC with oral administration compared with the CYP2C9*1 polymorphism, Dr. Marcu explained.[6,7] Thus, what might be an effective dose for a patient with the CYP2C9*1/*1 polymorphism may be intolerable for a patient with the CYP2C9*3/*3 polymorphism. The clinical implication is that patients with the CYP2C9*3 polymorphism may require a 2- to 3-fold reduced oral THC dose, but do not require a dosing adjustment for inhaled THC, Dr. Marcu said.

If proven effective, "pharmacogenomics could speed up the trial-and-error period with cannabis therapy, improving therapy and lowering cost to patients," Dr. Marcu said.

Additionally, pharmacogenomics testing could identify patients at risk for cannabis or substance use disorders, in whom cannabis may not be the best option. The findings also have legal implications given that some patients taking medical cannabis may fail a roadside sobriety blood test because of genetic factors leading to high serum levels of THC, even when they are not actually impaired,[8] Dr. Marcu told attendees (see **DWIC,** page 42).

Are Cannabinoids Acting as Victims or Perpetrators of Drug–Drug Interactions

Dr. Marcu likened oral cannabinoids to either victims or perpetrators in DDIs (Figure). Cannabinoids are victims when administered with strong CYP3A4 inhibitors, including clarithromycin, telithromycin, itraconazole, ketoconazole, and protease inhibitors. When combined with these agents, THC and CBD levels increase 1.8-fold each and 11-OH-THC levels (the major metabolite of THC) increase 3.5-fold.[9]

An example of a cannabinoid acting as a perpetrator in a DDI is high-dose CBD (5–20 mg/kg/d) and the antiepileptic agent clobazam. Here, high-dose CBD significantly increases serum levels of the active metabolite of the antiepileptic agent (*N*-desmethylclobazam) with a 150% to 200% increase over baseline, according to a randomized safety trial of CBD in children with Dravet syndrome,[10] Dr. Marcu explained.

Unanswered Questions

"There are definitely are a lot of yellow lights when it comes to cannabis and pharmaceutical drug interactions when cannabinoids are taken orally," Dr. Marcu said.

"Unanswered questions remain around the extent that THC and CBD can be inhibitory or activating when combined with other drugs," Dr. Marcu told attendees. "There is insufficient evidence around CYPs contributing to bioavailability. And there is a lack of consistency of THC and CBD exposure in a lot of studies."

The Future of Pharmacogenomic Testing

Availability of noninvasive direct-to-consumer pharmacogenomic testing is increasing exponentially, Dr. Marcu explained. However, he warned that patients should make sure that these

tests are CLIA certified and FDA compliant, and also protect patient privacy.

Pharmacogenomic clinical trials of cannabis are currently underway, including those examining the effects of the catechol-*O*-methyltransferase (*COMT*) gene on the effects of CBD and THC.[11,12] Additionally, researchers are investigating the role of pharmacogenomic mechanisms associated with cannabis-associated psychosis.[13] Furthermore, researchers are examining genes related to dopamine, γ-aminobutyric acid, glutamate, and CB_1 receptors and their effects on cannabinoids, according to Dr. Marcu.

> **"There are definitely are a lot of yellow lights when it comes to cannabis and pharmaceutical drug interactions when cannabinoids are taken orally. Unanswered questions remain around the extent that THC and CBD can be inhibitory or activating when combined with other drugs."**
>
> ***—Jahan Marcu, PhD***

The vast majority of pharmacogenomics testing (90%) for medical cannabis is focused on CYP polymorphisms, which is limiting given that there are many other genetic factors that may affect response to cannabinoids, Dr. Marcu continued.

"Many of these factors are going to turn out to be more important than CYPs," Dr. Marcu concluded.

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Role of Cannabinoids in Brain Health of NFL Players

AJEM attends 2020 Vision Player Networking Event during Super Bowl week as NFL players learn more about the important role that cannabinoids may have on brain health.

Miami, FL—National Football League (NFL) players learned more about the important role that cannabinoids may play in chronic pain management and brain health at the Twenty Twenty Vision Annual Player Networking Event.[1] *AJEM* was on-site at the event, which was held during Super Bowl week in Miami, Florida.

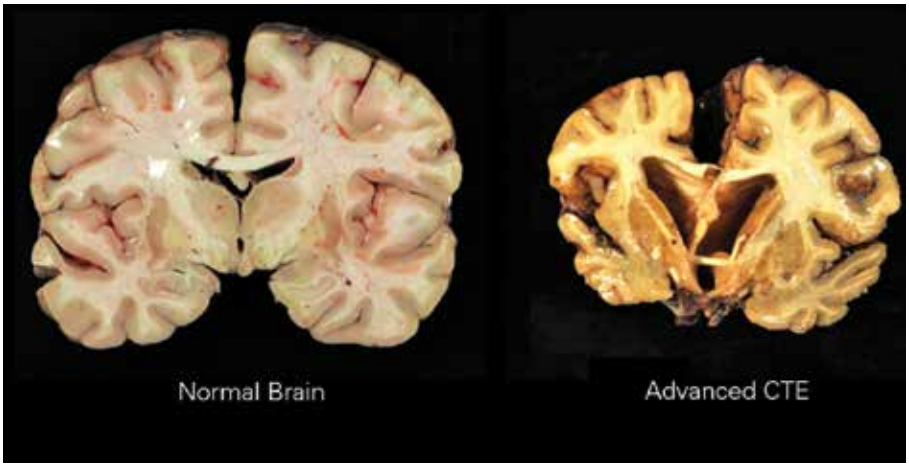

Image showing normal brain and brain with advanced chronic traumatic encephalopathy (CTE).

Photocredit: *Boston University Chronic Traumatic Encephalopathy Center, Wikimedia Commons.*

Softened Marijuana Policies for NFL Players

The focus on cannabinoids came on the heels of an announcement by Major League Baseball in December that marijuana will no longer be on its list of banned substances. The NFL may be following suit soon. Team owners have already approved a proposed collective bargaining agreement with players that would protect them from facing game suspension for testing positive for marijuana and will implement changes to testing protocols, including a 2-week testing window instead of 4 months.[2]

One thing is certain: Doctors across the country are in agreement that NFL players are at increased risk for chronic traumatic encephalopathy (CTE), after a seminal report on the topic was published in *the Journal of the American Medial Association* by Anne McKee, MD, Director of Boston University's CTE Center.[3] In the largest study of its kind, and a collaborative effort between the US Department of Veteran Affairs and Boston University's CTE Center, researchers examined the brains of deceased professional, semiprofessional, college, and high school football players. Of the 111 NFL player brains examined, 110 (99%) showed positive CTE pathology. The authors noted that accumulations of amyloid-β, α-synuclein, and TDP-43 were common in the brains of cases with severe CTE pathology.

Cannabis for Brain Injury

As former and current NFL players urge the league to allow cannabis to be used as a potential treatment for pain management and head trauma, research is getting a boost as major grants recently have been awarded to Harvard University's Phytomedicines and Medical Cannabis Institute, as well as others. Additionally, researchers like Sara Jane Ward, PhD, Assistant Professor of Pharmacology at Temple University's Lewis Katz School of Medicine in Philadelphia, are leading a research lab exploring the effects of cannabis on pain in animal studies.[4]

"Currently our research results in animal models of pain, stroke, and traumatic brain injury continue to excite us regarding the potential for CBD to alleviate brain inflammation and related behavioral consequences such as pain and cognitive impairment," Dr. Ward told *AJEM*. "Given these promising results and the relative safety of CBD, what is greatly needed now are trials in patients, including athletes, to determine how our laboratory results will translate to people," she added.

Mounting evidence from other animal studies suggest that CBD can act as a neuroprotective factor, thereby preventing damage to the brain. Japanese researchers found that stroke damage was lessened in mice who were treated with cannabidiol. Specifically, the authors hypothesized that the neuroprotective effect of cannabidiol may be related to increased blood flow through the serotonergic serotonin 5-hydroxytriptamine1A receptor.[5]

AJEM will continue to follow emerging research showing that professional athletes who experience concussion, acute pain, and chronic pain may benefit from cannabinoids.

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Liposomal Cannabidiol Delivery: A Pilot Study

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

Abstract

OBJECTIVE: The aim of this study was to measure the bioavailability of equivalent amounts of cannabidiol (CBD, 10 mg) as a stand-alone active ingredient compared with a liposomal preparation (CELLg8 Hemp).

METHODS: This pharmacokinetic pilot study included 15 healthy patients who were not taking a CBD product at baseline. A crossover study design was used to analyze peak blood CBD levels at baseline and 1 hour after ingesting the liposomal and nonliposomal preparations, with a 2-week washout period between each preparation.

RESULTS: CBD was detected in the blood of all 15 patients who ingested the liposomal preparation at 1 hour, whereas the stand-alone ingredient was only found in 40% of the individuals at the same time point. Serum levels of CBD were significantly higher ($P<0.0001$) in patients after use of the liposomal preparation compared with the stand-alone CBD.

CONCLUSION: The findings suggest that the bioavailability of oral CBD is higher in the liposomal preparation than the nonliposomal CBD preparation.

Introduction

Although oral cannabidiol (CBD) formulations are increasingly popular, studies show that oral CBD has a much lower bioavailability than inhaled CBD.[1] This study was designed to compare the bioavailability of 2 different preparations of oral CBD, with and without a liposomal delivery system.

Puffin Hemp (http://www.puffinhemp.com) has a patent-pending liposome manufacturing technology that is used to prepare CBD products with high bioavailability, using a proprietary CELLg8 delivery system. This natural liposomal preparation is designed to increase the amount of active ingredient that is absorbed into the bloodstream. We have previously published on a similar liposomal delivery system for vitamin C, where increased absorption was observed compared with a nonliposomal product.[2]

Methods

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

- Men and women 25 to 70 years of age
- Able 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.

Fifteen individuals met the inclusion criteria and were recruited for the pharmacokinetic pilot study. A crossover study design was used to analyze peak blood CBD levels at baseline and 1 hour after ingesting the liposomal and nonliposomal preparations, with a 2-week washout period between each preparation.

At the first study visit, participants completed the informed consent process and were randomized to either stand-alone CBD or liposomal CBD. Liposomal CELLg8 CBD, derived from industrial hemp, was provided by Puffin Hemp. Participants were instructed to wait at least 4 hours after eating before undergoing a blood draw to measure baseline CBD blood levels. Then, they ingested 10 mg of CBD either with or without the liposomal delivery system. At 1-hour post-ingestion, blood was collected to compare the concentration of CBD before and after ingestion.

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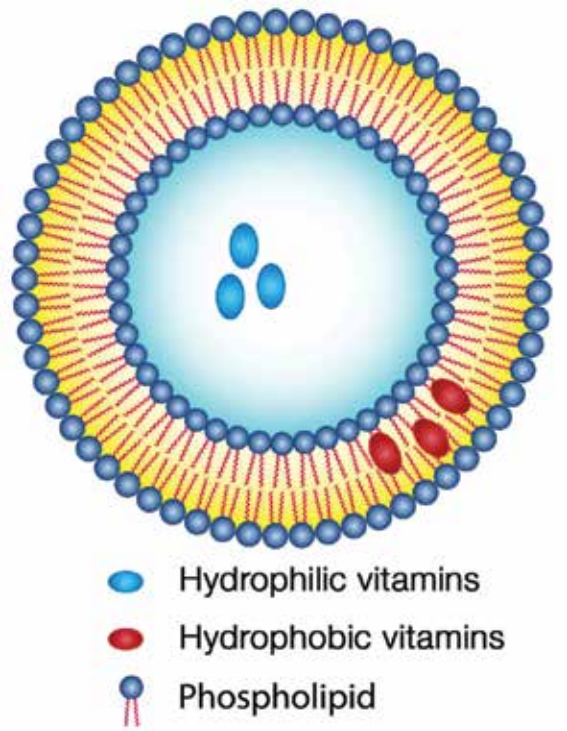

Figure. Liposomes are injected with vitamins, minerals or other active compounds to facilitate absorption through the digestive tract.

Image courtesy of Puffin Hemp.

Liposomal CBD
continued from page 19

At the second study visit (2 weeks later), the same procedure was repeated in all study participants with the alternate preparation. This 2-week dosing schedule was designed to allow for a washout period. The blood draws were completed at Any Lab Test Now where a clinical chemist was chaperoning study participants. Compensation for participation in the study included a bottle of liposomal CBD for each blood draw.

Results

All participants showed absorption of CBD in the bloodstream via liposomal delivery at 1 hour. In contrast, no CBD was detected in 9 of the 15 participants at 1 hour after ingestion of nonliposomal CBD. Table 1 shows CBD blood levels measured at baseline and 1-hour post-ingestion for both CBD preparations. Two participants demonstrated baseline CBD levels >0 (0.1 and 0.19 ng/mL) before ingesting the liposomal preparation but because they were already randomized, they were still included per intention to treat analysis (ITT).

Statistical analysis was performed to calculate the area under the curve (AUC) using the trapezoid method. The mean CBD level at 1-hour post-ingestion was significantly higher when participants received the liposomal preparation compared to the nonliposomal preparation (1.77 and 0.24, respectively; $P<0.0001$; Table 2). Results were not markedly altered by the 2 participants with baseline CBD levels.

> "The results of this study demonstrate that liposomal [CBD] has significantly greater bioavailability than stand-alone CBD."
>
> *—Emek Blair, PhD*

The highest concentration of CBD detected at 1 hour was 5.9 ng/mL in the liposomal CBD preparation compared with 1.3 ng/mL in the nonliposomal preparation. The mean area under the curve (AUC) for CBD concentration was significantly higher (0.89±0.75 ng/mL) in the liposomal preparation compared with the nonliposomal preparation (0.12±0.20 ng/mL; $P<0.0001$).

Participants were monitored for adverse events and were asked to report any form of discomfort or unusual effects including stomach upset, nausea, or headache. No issues were reported.

Discussion

The present study suggests that the bioavailability of oral CBD is higher in the liposomal preparation than in the nonliposomal preparation. To my knowledge, this is the first study to compare the bioavailability of 2 preparations of oral CBD in humans.

A review by Millar et al. states that "literature in humans is not sufficient" in regard to understanding CBD bioavailability.[1] A recent study by Tayor et al. investigated the metabolism of CBD in 8 individuals with varying degrees of renal impairment, finding that renal impairment had no effect on the metabolism of CBD.[3] Another pharmacokinetic study evaluated the safety and tolerability of oral CBD in 32 healthy individuals, finding support for twice-daily administration of CBD.[4] These recently published studies are

Table 1. CBD Levels Before and After Ingestion of 10 mg CBD as a Liposomal and Nonliposomal Preparation

	Nonliposomal CBD		Liposomal CBD	
Participant	Baseline (ng/mL)	1-hour post-ingestion (ng/mL)	Baseline (ng/mL)	1-hour post-ingestion (ng/mL)
1	0	0.87	0	5.9
2	0	0	0	0.87
3	0	0.14	0.1	2
4	0	0	0.19	2.4
5	0	0.45	0	1.6
6	0	0	0	0.35
7	0	1.3	0	2.7
8	0	0	0	0.43
9	0	0	0	0.13
10	0	0.17	0	1.7
11	0	0	0	0.65
12	0	0	0	3.4
13	0	0	0	2.5
14	0	0	0	0.86
15	0	0.65	0	1

CBD, cannabidiol.

Table 2. CBD Concentration 1 Hour After Ingestion of 10 mg CBD as a Liposomal and Nonliposomal Preparation

	Nonliposomal		Liposomal		
	Mean (SD)	95% CI	Mean (SD)	95% CI	*P* value
Post-ingestion, ng/mL	0.24 (0.40)	0.02-0.46	1.77 (1.50)	0.93-2.60	<0.0001
Change from baseline to 1 hour, ng/mL	0.24 (0.40)	0.02-0.46	1.75 (1.50)	0.92-2.58	<0.0001
AUC, ng/mL*h	0.12 (0.20)	0.01-0.23	0.89 (0.75)	0.47-1.31	<0.0001

AUC, area under the curve; **CBD,** cannabidiol.

critical contributions to this emerging area of research, but to my knowledge, none has investigated a liposomal delivery system.

With the rapidly expanding use of hemp extract and CBD products, a thorough understanding of the rate of absorption of CBD is critical to the development of CBD as a health food and supplement. In fact, Vandrey et al. reported on the mislabeling of CBD content in medical marijuana products. The authors found only 13 of 44 products containing CBD that accounted for the ingredient on the label.[5] Furthermore, 4 of the products were underlabeled and 9 were overlabeled for CBD content. These findings support the need for a more thorough understanding of CBD dosage in humans and improved quality control within the industry.

Results of this study show greater absorption of liposomal CBD than the stand-alone active ingredient and higher ratio per peak concentration. This demonstrates that the liposomal preparation may provide a more efficient delivery of CBD to the bloodstream than oral ingestion of the stand-alone ingredient.

Study limitations include the potential carryover effect that may occur with a crossover study design. Future studies with larger populations are needed to fully understand the crossover effect between the standard and liposomal preparations. The 2 participants who demonstrated baseline CBD levels before ingesting the liposomal preparation may be a confounding factor in the ITT. Finally, further studies with additional time points should be conducted in the future to measure duration and more closely compare the rate at which liposomal CBD and stand-alone CBD enter the bloodstream.

Liposomal delivery systems may help bypass the digestive system, where active ingredients are broken down or rejected via first-pass rejection.[6] Theoretically, liposomal preparations may allow for lower doses of CBD to be given to achieve the same effect as a nonliposomal product. For these reasons, a liposomal CBD preparation may be preferred.

A recent safety study on the same liposomal CBD preparation showed that 7 of 10 of blood measures (comprehensive metabolic panel or complete blood cell count measure) that were out of range at baseline normalized in all individuals after taking liposomal CBD daily for 30 days.[7] Additionally, all 5 individuals who were in the high range for baseline glucose level exhibited normalized values after taking liposomal CBD. Liposomal CBD appears to be safe and effective in healthy patients, although further research in larger studies is needed.

> **"Larger studies with more time points are needed to replicate results and validate that liposomal [CBD] is a more efficient and universal delivery system than nonliposomal preparations of [CBD]."**
>
> ***—Emek Blair, PhD***

Conclusion

The results of this study demonstrate that liposomal CBD has significantly greater bioavailability than stand-alone CBD. Larger studies with more time points are needed to replicate results and validate that liposomal CBD is a more efficient and universal delivery system than nonliposomal preparations of CBD.

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

Opioid Wean With Medical Cannabis: A Case Report

By Leslie Apgar, MD, Medical Director, Greenhouse Wellness, Ellicott City, Maryland.

We present a case report of a patient who was guided through 2 postsurgical opioid wean programs. The opioid wean after the first surgery did not include medical cannabis whereas the opioid wean after the second surgery did; the difference in symptoms is striking.

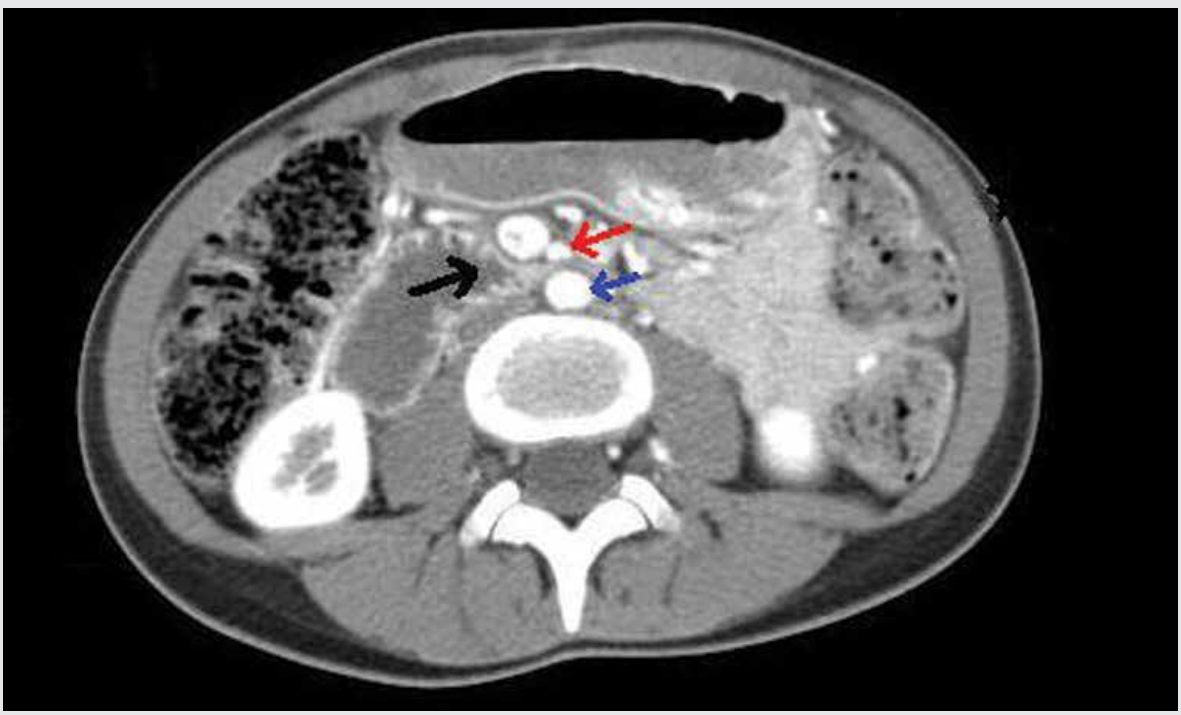
LM is a 30-year-old white woman who visited Greenhouse Wellness (GW)—a medical cannabis dispensary located in Maryland near Baltimore and Washington, DC—on January 5, 2018 for chronic pain management. The dispensary has a unique model of care, emphasizing the education and rigorous training of its wellness consultants by the on-site medical director, Leslie Apgar, MD (see **Practice Spotlight,** page 30).

Medical History

LM has a past medical history significant for common variable immune deficiency (CVID). She was diagnosed with CVID in 2014, but has experienced symptoms her entire life. Additionally, she experienced postural orthostatic tachycardia syndrome as a teenager and throughout college, acute viral parotitis (mumps) in 2012, Legionnaires' disease and Lyme disease in high school, and constant upper respiratory infections, all of which resulted in significant weight loss—at her lowest, LM weighed 98 lb. She has had constipation since childhood necessitating enemas, laxatives, medications, and special diets with no symptomatic relief. During high school, she took antidepressants and over-the-counter pain medications, and was registered as disabled upon entering college.

During college, LM experienced symptomatic relief of pain and nausea and intermittent appetite stimulation with smoked cannabis obtained from friends. Still in constant pain, LM consulted numerous specialists including a gastroenterologist, rheumatologist, cardiologist, electrophysiologist, neurologist, gynecologist, nephrologist, urologist, pulmonologist, vascular radiologist, and a vascular surgeon. Finally, LM was diagnosed with superior mesenteric artery syndrome (SMAS) and renal nutcracker syndrome in April 2015 by a gastroenterologist. Regular oral intake resulted in vomiting, dumping syndrome, and severe pain due to duodenum compression. Although her pain symptoms were initially associated with oral intake, they evolved to include constant left flank, lumbar, and pelvic pain.

> "The opioid wean after the first surgery did not include medical cannabis and the opioid wean after the second surgery did; the difference in symptoms is striking."
> *—Leslie Apgar, MD*



Case of superior mesenteric artery syndrome. Abdominal and pelvic computed tomography scan showing duodenal compression (emphasized by black arrow) by the abdominal aorta (blue arrow) and the superior mesenteric artery (red artery).

Photo credit: *Samantha S. Mina, Wikimedia Commons.*

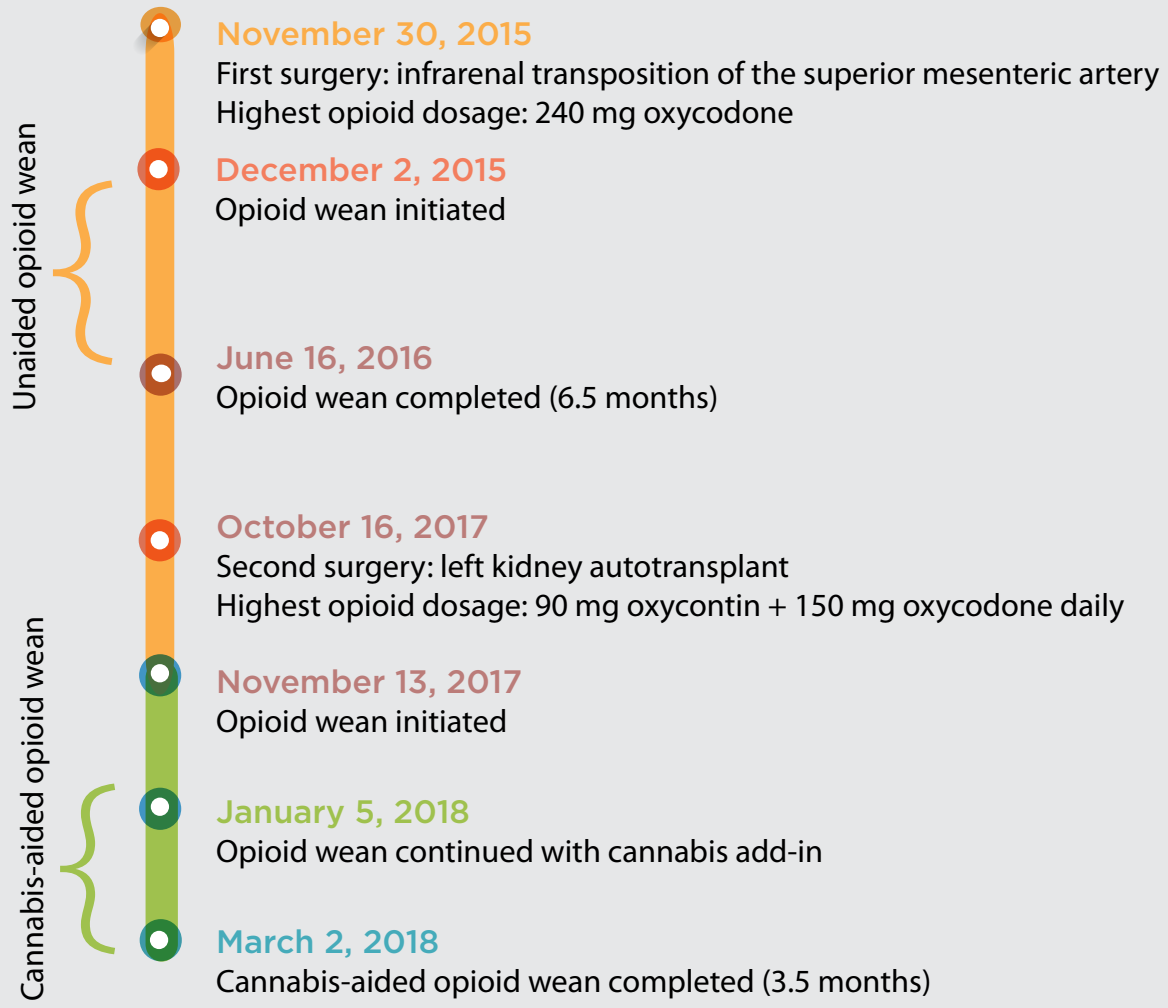


Figure. Timeline of 2 opioid weans with and without medical cannabis.

Postoperative Pain Control

LM underwent her first SMAS surgery—infrarenal transposition of the superior mesenteric artery—in November 2015. For postoperative pain control, she was prescribed 240 mg oxycodone daily in divided doses. She was also taking clonidine, alprazolam, lansoprazole, ondansetron, bupropion, acetaminophen, aspirin, stool softeners, and weekly saline enemas. She underwent a successful opioid taper over approximately 6.5 months.

Her left flank, pelvic, and lumbar pain returned, and LM underwent a second surgery—a left kidney autotransplant—on October 16, 2017. Prior to this second surgery, she was placed back on oxycodone 180 mg daily for pain. To manage pain postoperatively, her dosage was increased to oxycontin 90 mg and oxycodone 150 mg daily. By October 25, 2017, she was taking a slightly lower dosage—oxycontin 90 mg and oxycodone 120 mg per day.

Opioid Tapers

To taper opioid prescriptions after her first surgery, LM was placed on a 12-week opioid weaning schedule that proved to be too aggressive. She started the weaning schedule on December 2, 2015 and did not fully wean off of opioids until June 16, 2016, instead of the February 29 goal proposed by her surgical pain management team. During the weaning process, LM experienced significant withdrawal symptoms including emesis, diarrhea, cold sweats, restless legs, racing thoughts, insomnia, and depression. She experienced severe anxiety on the days that the dose was decreased. For the first 3 months of her weaning program, LM was bed bound and unable to exercise until 5 months after surgery. She does not recall being offered psychosocial support or any supportive medications to manage withdrawal symptoms.

> "The opioid wean time with medical cannabis was cut in half after her first postoperative opioid wean."
> *—Leslie Apgar, MD*

▶ continued on page 24

Opioid Wean

continued from page 23

By June 16, 2016, she was taking only ondansetron, baby aspirin 81 mg, bupropion, and over-the-counter pain medicine as needed. She was able return to normal activities of daily living and to travel to Europe for 10 days. LM was able to resume a normal diet and her SMAS symptoms resolved. She was in good spirits and was pain free for approximately 1 year.

To taper opioids after her second surgery, LM began a formal opioid wean program with her pain management specialist on November 13, 2017. She was initially weaned soley off oxycontin and then began her oxycodone wean on January 2, 2018, with medical cannabis (which was now legal in her state) started soon after, and ultimately tapered off all opioids by March 2, 2018.

LM first visited GW dispensary on January 5, 2018. She met with the medical director on site and learned how cannabis would potentiate the effects of the opioids and minimize her withdrawal symptoms. During her consultation with the medical director, LW reported "using black market cannabis whenever I could get my hands on it, but that was so unpredictable and often terrible quality."

LM opted to use medical cannabis as part of her wean program. At that time, the Maryland market was limited to flower, assorted vape cartridges, and a few edible options, as there were not as many product options as there are currently. Based on LM's high opioid burden and her need for immediate relief, the medical director at GW directed her toward vape pens high in delta-9-tetrahydrocannabinol. LM found that she benefited from chemovars that had higher percentages of limonene and myrcene, which she reported helped treat her nausea, pain, and other symptoms.[1] She almost exclusively used vape pens to treat her opioid withdrawal symptoms, weaning from 90 mg of oxycontin per day to none in 46 days. On January 2, 2018, she started her oxycodone wean and tapered from 120 mg per day to none on March 2, 2018.

Compared with the opioid taper subsequent to her first surgery, LM experienced significantly improved symptoms during the taper with medical cannabis after her second surgery. She described postoperative pain relief within weeks after her second surgery as opposed to months after the first surgery. The opioid wean time with medical cannabis was nearly cut in half after her first postoperative opioid wean (Figure, page 23).

Additionally, LM reported experiencing 75% less withdrawal symptoms when using medical cannabis. Medical cannabis allowed her to use fewer supportive medications to manage her withdrawal. She did not use clonidine, bupropion, lansoprazole, ondansetron, or acetaminophen, and was on much less alprazolam and aspirin than during the first wean.

From a psychological standpoint, LM reported less anxiety and depression and was able to return to normal mental function much faster than after the first wean. Unlike the first wean, LM reported no anxiety associated with scheduled opioid dose tapering with medical cannabis. As documented by her caregivers, her mood was much better, absent the negative thoughts that were prevalent during her first wean.

Her gastroenterologic function normalized with the addition of cannabis—she was able to eat regular food and she experienced reduced nausea and constipation, no longer requiring stool softeners, laxatives, or enemas. Within 2 months of surgery, she was able to exercise. Her current weight is 113 lb with an upward trend.

Quality Assurance

Because Maryland has rigorous testing requirements for all medical cannabis products, the medical cannabis LM obtained from GW dispensary was tested for quality assurance, including screening for terpenes and cannabinoids, as well as testing for the presence of pesticides; heavy metals; residual solvents; microbiologics including aerobic microbials, total yeast, and mold; *Escherichia coli* and Salmonella; water content; and mycotoxin. Additionally, stability studies are required at to ensure the potency and purity of medical cannabis products at 6- and 12-month intervals.[2]

> **"LM is able to draw from her experience as a chronically ill young adult and her successful wean from opioids using medical cannabis. She is a true asset for the medical cannabis patients of Maryland."**
>
> ***—Leslie Apgar, MD***

Unique Model of Care

Because of the true medical nature of the GW dispensary, it has received numerous accolades and remains a referral center for many practitioners throughout the state. Patients report excellent reviews and often travel great distances to visit GW when they have found their experiences at other dispensaries to be inadequate.

LM has continued to use cannabis to manage her pain and nausea on a daily basis and reports much milder symptoms. She now works in the cannabis industry and counsels others as a wellness consultant at GW. LM is able to draw from her experience as a chronically ill young adult and her successful wean from opioids using medical cannabis. She is a true asset for the medical cannabis patients of Maryland.

Study Limitations

Study limitations included the potentially different postoperative pain symptoms following infrarenal transposition of the superior mesenteric artery surgery vs left kidney autotransplant surgery. However, because the doses of opioids LM was prescribed after the 2 surgeries were identical, this suggests the potential role of medical cannabis in weaning from high doses of postoperative opioids.

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Dr. Apgar *is co-owner of Greenhouse Wellness and Blissiva, and is co-author of* High Heals.

What Is the Role of Medical Cannabis in Substance Use Disorders?

A Q&A With Philippe Lucas, PhD(c)

To better understand the potential role of medical cannabis as a treatment for substance use disorders, Jahan Marcu, PhD, Editor in Chief, *American Journal of Endocannabinoid Medicine*, sat down with prolific researcher Philippe Lucas, PhD(c), Vice President, Global Patient Research and Access, Tilray, Nanaimo, BC, Graduate Researcher, Canadian Institute for Substance Use Research, and Doctoral Candidate, Social Dimensions of Health, University of Victoria, BC. The duo spoke about emerging research and the impact of cannabis substitutions from a public health perspective.

Dr. Marcu: Does current evidence support the efficacy of cannabis in treating substance use disorders?

Dr. Lucas: Cannabis has been shown to be as effective as opioids in the treatment of chronic pain in some patients, and patients on medical cannabis self-report ad hoc reductions in opioid use.[1-3] In addition, a growing number of medical cannabis users, and also in some cases recreational users, report that cannabis and cannabinoids seem to reduce not only their use of opioids but also the cravings and other symptoms associated with opioid withdrawal.[4-7] Furthermore, data from a randomized controlled trial demonstrated positive effects of cannabidiol (CBD) in the treatment of tobacco dependence, and research suggests that CBD may aid in the treatment of stimulant use disorders.[8,9]

More recently, findings from the 2017 Tilray Patient Survey suggested that use of medical cannabis leads to reduced use of opioids and other prescription drugs as well as alcohol, tobacco, and illicit substances.[10] In this study, a high percentage of study participants (N=2032) who were registered in Canada's federal medical cannabis program reported substituting medical cannabis for prescription drugs (69%), alcohol (45%), tobacco (31%), and illicit substances (26%).

Philippe Lucas, PhD(c)

The most commonly substituted prescription drugs were opioids (35%) and antidepressants medications (22%; Table).[10] Of the 610 patients who reported substituting cannabis for opioids, 59% completely stopped using opioids and an additional 18% reduced their use by 75%.

Table. Breakdown of Drugs Substituted With Cannabis[10]

Prescription drugs*	n (%)
1. Opiates/Opioids	610 (35.3)
2. Antidepressant	371 (21.5)
3. Non-opioid pain medications	189 (10.9)
4. Antiseizure medications	149 (8.6)
5. Muscle relaxant/Sleep aids	140 (8.1)
6. Benzodiazepines	75 (4.3)
7. Stimulants	59 (3.4)
8. Antiemetics	24 (1.4)
9. Antipsychotics	18 (1)
Illicit drugs†	
1. Cocaine/Crack	89 (17.4)
2. Psychedelics	60 (11.7)
3. Nonprescription opioids	29 (5.7)
4. Stimulants	14 (2.7)
5. Depressants	8 (1.6)

*Of 1730 specific prescription drugs substituted by cannabis.
†Of 511 illicit drugs substituted by cannabis.
Adapted from Lucas P, et al. *Harm Reduct J.* 2019;16(1):9.

Dr. Marcu: If we extrapolate from this recent study of more than 2000 individuals, what seems to be the potential impact cannabis may have on the opioid epidemic from a public health perspective?

Dr. Lucas: From an objective perspective, when we look at the harms to society of opioids, alcohol, tobacco, and a number of illicit substances, cannabis ends up potentially being the least harmful agent as it leads to the fewest health care-related costs and impact on society. The relative risk for addiction to cannabis is mild compared with that of opioids. Additionally, there is no risk for fatal overdose associated with cannabis and cannabinoid use. Thus, in terms of harm reduction, shifting away from the use of potentially more dangerous or highly addictive substances and toward a more benign substance like cannabis offers a net public health benefit.

For 70 years, policymakers, regulators, and governments have suggested that cannabis may be a gateway drug—meaning that people who start using cannabis progress to more dangerous drugs of abuse. Over the past 25 years, the gateway theory has been disproven by academic research.[11-13] Additionally, for at least a percentage of the population, research suggests that cannabis is an effective exit drug for substances of abuse.[14-17]

In addition to opioids, the United States and Canada have a rather invisible yet deleterious benzodiazepine crisis. Benzodiazepines are among the most overprescribed medications, are linked to an incredibly high risk for dependency, are dangerous when combined with alcohol, and may lead to long-term side effects such as memory loss.[18] Thus, cannabis and any other agents that can help patients manage anxiety or sleeplessness with a lower risk for dependence and a lower side-effect profile than what is found with benzodiazepines will lead to public health benefits.

▶ continued on page 26

Dr. Lucas Q&A

continued from page 25

Dr. Marcu: Do you have any updates you can share on clinical research studies that are in the pipeline regarding cannabis as a treatment for alcohol or substance use disorders?

Dr. Lucas: Researchers at the British Columbia Centre on Substance Use are currently planning randomized controlled trials to evaluate cannabis as a substitute for opioids in patients with opioid use disorder.[19]

Additionally, Tilray is currently engaged in 2 randomized, double-blind clinical trials of CBD as a treatment for alcohol use disorder (AUD) at New York University. The first is a proof-of-concept study (N=40) designed to assess feasibility and contrast effects of extended (8 weeks) treatment with oral CBD to those of placebo in 40 patients with AUD. The second is a 6-week study of oral CBD use compared with placebo in 48 healthy adults with moderate or severe AUD and comorbid post-traumatic stress disorder.[20,21]

Tilray has become an international leader in gathering real-world evidence regarding cannabis use via large-scale observational studies, with much of this research suggesting that medical cannabis use can lead to reduction or cessation of prescription drug use, alcohol, tobacco, and illicit substance use.[10,22]

Dr. Marcu: Some research has linked cannabis use to increased use of alcohol or tobacco, but this seems to be linked to products that are not standardized.[23-25] What role does product consistency play in the efficacy and safety of cannabis substitutions found in clinical trials of medical cannabis?

Dr. Lucas: Consistency of product supply is essential when using medical cannabis. If a patient finds a cannabis product that is effective for their symptoms, there is no guarantee of consistency when purchasing products from illicit or unregulated markets. This can lead to widely varying effects of treatment. In fact, a tremendous amount of research suggests that the highly unregulated CBD supply in the United States is leading to inaccurate product labeling regarding CBD and delta-9-tetrahydrocannabinol content.[26,27] Additionally, products claiming to be purified may contain heavy metals, polycyclic aromatic hydrocarbons, pesticides, or other contaminants. Thus, having a safe and dependable cannabis supply is important, particularly for medicinal cannabis use.

Longitudinal data from the Tilray Observational Patient Study (TOPS; pre-publication results), which tracked the effects of a legally regulated cannabis supply on quality of life and prescription drug use, also found a significant reduction in opioid use over a 6-month period in both cannabis-naive and non-naive patients (see **TOPS,** page 10). Cannabis non-naive was defined using cannabis 5 or more times in the past year, whereas cannabis-naive was defined using cannabis less than 5 times in the same time frame.

Thus, non-naive cannabis users, who might have used cannabis on a regular basis at study entry, experienced the same reduction in opioid use at 6 months as cannabis-naive patients. This suggests that it is not just access to cannabis that is having this impact, but rather access to a standardized supply that is consistent from one batch or product to the next.

> "The findings suggest that patients who are deliberately using cannabis to taper off tobacco, alcohol, or opioids, have greater success in reducing use of these agents. Thus, intentionality seems to be directly related to cannabis substitution."
>
> *—Philippe Lucas, PhD(c)*

Dr. Marcu: What role can intentionality play in the efficacy of cannabis substitutions? And how does the support of a patient's health care practitioner factor into the potential substitution effect?

Dr. Lucas: The question of intentionality in regard to cannabis substitutions is an area of interest for me. A January 2019 survey (prepublished data) called the Canadian Cannabis Patient Survey (CCPS2019) conducted by Tilray and developed in cooperation with other international cannabis researchers interested in substitution effect, incorporated the following questions regarding intentionality in a submodule called the Comprehensive Cannabis Substitution Questionnaire (CCSQ):

- If you saw a change in your substance use, were you pleasantly surprised?
- Did you specifically use cannabis to reduce your use of opioids, tobacco, or alcohol?
- Did you work with your physician on using cannabis to reduce your substance use?
- Did your physician design a tapering program for you?

Not surprisingly, we found a very low percentage of patients who were working deliberately with their physicians on substitution programs. However, a high percentage of patients (~50%) initiated medical cannabis with the intention of reducing use of other substances.

Importantly, the greater the patient intentionality, the greater the rates of substitution effect. Maybe it is no surprise, but the findings suggest that patients who are deliberately using cannabis to taper off tobacco, alcohol, or opioids, have greater success in reducing use of these agents. Thus, intentionality seems to be directly related to cannabis substitution.

Although the intentionality rate was relatively high in this group, a gap in support and awareness of substitution from the health care practitioner perspective also was observed. The findings are encouraging in that they suggest that if physicians developed a more deliberate, public health-centered strategy of reducing use of opioids or other addictive substances through deliberate cannabis substitution, a greater level of substitution may occur.

Dr. Marcu: In your study, antidepressants medications were the second most commonly substituted prescription medications. Can you comment on the significance of those findings?

Dr. Lucas: We have different concerns regarding use of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). These agents do not pose

a risk for fatal overdose and are not dependence-forming medications. However, antidepressants are not particularly effective for a large percentage of the population, with mostly modest effect sizes found in a recent meta-analysis of placebo-controlled trials of first- and second-generation antidepressants.[28] Additionally, when used in the management of chronic neuropathic pain, the number needed to treat for SSRIs is 6.8 compared with 3.4 for cannabinoids.[29]

Thus, we need different solutions when it comes to treating patients with depression and other mental health conditions such as trauma, anxiety, and stress. I believe that cannabis and cannabinoids can play a role in treating these conditions.

Dr. Marcu: Is there anything else you would like to tell our readers about the emerging science on cannabis substitutions?

Dr. Lucas: It has become apparent that along with the legalization and regulation of medical and recreational cannabis use has come a very welcomed renaissance of cannabis research. I'm optimistic that as more funding becomes available to examine the therapeutic potential of cannabinoids, entirely new modalities will develop in regards to cancer care, and the treatment of Alzheimer's disease/dementia, arthritis, anxiety and many other serious conditions.

I'm honored to be working with Tilray and international academic partners to spearhead many of these cutting-edge cannabis studies, while also improving access to pharmaceutical-grade cannabis products to critically and chronically ill patients around the globe.

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Dr. Lucas *is Vice President, Global Patient Research & Access for Tilray, the sponsor of the 2017 Tilray Patient Survey, the Canadian Cannabis Patient Survey 2019, Tilray Observational Patient Study (TOPS), and some of the clinical trials mentioned in the article.*

Cannabis Substitution Reduces Opioid Use in Patients With Chronic Pain

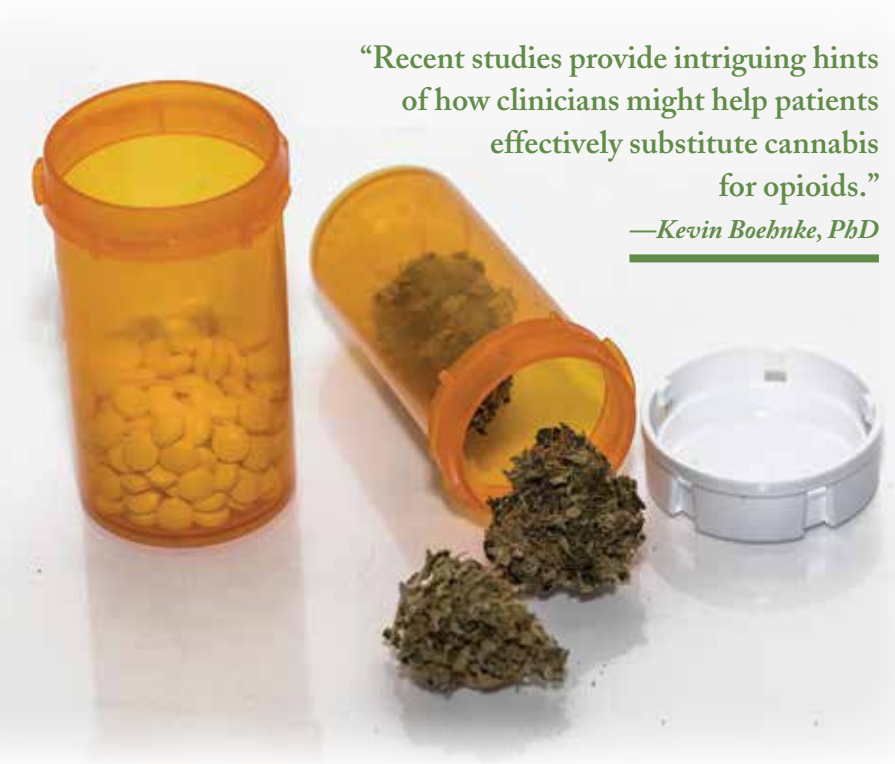
Pain researcher discusses findings from his latest study: Boehnke KF, et al. Pills to Pot: Observational Analyses of Cannabis Substitution Among Medical Cannabis Users With Chronic Pain. *J Pain.* 2019;20(7):830-841.

By Kevin Boehnke, PhD, Research Investigator, Department of Anesthesiology and the Chronic Pain and Fatigue Research Center, University of Michigan Medical School, Ann Arbor, Michigan

In a large nationwide survey study (N=1321), my colleagues and I found that individuals using cannabis for chronic pain management reported reductions in the use of opioids and other pain medications.[1] In our retrospective study, 53% (n=691) of participants substituted cannabis for opioids and 22% (n=287) for benzodiazepines, with more than 65% of substitutors reporting discontinued use of these medications due to better symptom management and fewer side effects.

These results corroborate our 2016 pilot study (N=185), which showed a 64% decrease in opioid consumption among patients using medical cannabis for chronic pain management.[2] The rationale and effect size are consistent with studies conducted in Canada that similarly gauge substituting cannabis for other medications.[3]

Our study population was 59% female with a mean age of 49.8 years (SD±13.8), reflecting the population demographic in which chronic pain is common—older adults and women.[4]



"Recent studies provide intriguing hints of how clinicians might help patients effectively substitute cannabis for opioids."
—Kevin Boehnke, PhD

Cannabis as an Opioid Alternative

The poor performance of many pain medications, including high numbers needed to treat (NNT) and challenging side-effect profiles, have many looking for alternatives that have greater analgesic efficacy.[5,6] Additionally, the ongoing opioid crisis has made it more difficult to obtain opioid prescriptions, and the increasing social acceptance of cannabis as a safe, alternative medication may be driving people toward opioid alternatives.[7,8] Although our data are observational and retrospective, the pattern emerging from these and numerous similar studies makes it clear that some individuals derive benefit from cannabis-based medicines—enough so that they discontinue traditional pain medications.

Strategies for Effectively Substituting Cannabis for Opioids

Despite this pattern, however, we must proceed cautiously, as other studies report that cannabis use is associated with worse clinical pain symptoms and prescription medication misuse.[9,10] Although some may frame these incongruent findings as conflicting, we believe that they instead suggest that there are subsets of individuals for whom cannabis is unhelpful (or even harmful), and others for whom substitution is possible and clinically useful. Thus, the pressing questions moving forward are how and in which clinical populations this substitution can be done most effectively.

Although we did not examine whether participants modified their medication regimen under the guidance of medical professionals, some recent studies provide intriguing hints of how clinicians might help patients effectively substitute cannabis for opioids. For example, Sagy et al. reported that patients with fibromyalgia (N=367) were guided by a certified nurse through a slow, methodical titration regimen of delta-9-tetrahydrocannabinol (THC) oil and/or cannabis flower. After 6 months, participants reported significant improvements in pain and quality of life, as well as decreased opioid and benzodiazepine use.[11]

Similar effects were found in a study examining patients with chronic pain (N=600; unspecified conditions) who were undergoing an opioid taper. Participants were given access to sublingual, oral, and/or vaporized cannabis products with appropriate education on dose titration, as well as online psychological support tools. Eighty-one percent of participants discontinued or reduced their opioid dose and all but one participant reported satisfaction with sleep, pain control, and quality of life.[12]

Additionally, 2 recent clinical trials shed light on important mechanisms by which cannabidiol (CBD) and THC may alleviate opioid withdrawal or reduce opioid consumption. In the first study, Hurd et al. showed that CBD reduced cue-related anxiety and craving among individuals in recovery from heroin use disorder, suggesting that CBD may assist in quelling symptoms related to opioid addiction or dependence (and perhaps other substance use disorders as well).[13]

In the second study, Cooper et al. found that smoked THC-dominant cannabis combined with subthreshold doses of oxycodone provided similar pain relief as a higher dose of oxycodone, providing plausibility that individuals could reduce opioid consumption by adding cannabis into their treatment regimen.[14]

Taken together with the observational studies mentioned above, these findings highlight several important factors for substituting effectively: flexible dosing regimens (both in terms of cannabinoids and administration routes), educational supports for both cannabis titration and pain-related symptoms, and psychological services.

Tips for Providing Clinician Oversight in Cannabis Treatment

Although federal restrictions present challenging barriers to conducting rigorous cannabis studies (especially randomized clinical trials), cannabis is becoming increasingly available. States have continued to pass both medical and adult-use cannabis legislation, and hemp-derived CBD products are available in nearly all states.[15]

In this context, patients can and will use cannabis for symptom management. Despite the lack of strong clinical trials that give explicit dosing guidance, clinicians can still provide sound clinical oversight by:

- Developing treatment plans that take into account patient expectations/goals (eg, substitution) and that include symptom tracking;
- Employing harm-reduction strategies (eg, avoid smoking, "start low, go slow"); and
- Ensuring patients know the limits of both the evidence and the regulatory system in place—especially for CBD products, which often are inaccurately labeled and do not undergo stringent safety testing.[15]

In so doing, clinicians can embody the practice of evidence-based medicine by synergizing the best available scientific evidence with compassionate clinical expertise that accounts for the preferences and rights of patients with whom they are making clinical decisions.[16] This is not yielding to a health fad, but taking a step toward demystifying cannabis so it can be judiciously used as medicine.

"... clinicians can embody the practice of evidence-based medicine by synergizing the best available scientific evidence with compassionate clinical expertise that accounts for the preferences and rights of patients with whom they are making clinical decisions."

—Kevin Boehnke, PhD

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Dr. Boehnke *has no financial conflicts of interest to disclose.*

Spotlight on
Medical Cannabis Wellness Center

In this installment of Practice Spotlight, we shine a light on the unique model of care created by medical cannabis trailblazers Leslie Apgar, MD, and Gina Dubbé at Greenhouse Wellness in Ellicott City, Maryland.

The medical cannabis dispensary Greenhouse Wellness (GW) in Ellicott City, Maryland, practices like a residency program and includes an on-staff physician, nurses, and wellness consultants who receive formalized training using best practices.

"If you want to take cannabis seriously, then it needs to be approached as medicine, and we just didn't see anybody else doing that," said Leslie Apgar, MD, Medical Director of GW, who co-founded the medical cannabis dispensary in 2017 with Gina Dubbé, a venture capitalist and entrepreneur with a master's degree in engineering.

Unique Model of Care

GW's unique model of care is what sets it apart. It seamlessly blends aspects of conventional Western medicine—such as a residency model of training and an on-site medical director—with Eastern medicine—a focus on wellness and prevention.

In the short time since GW opened, it has received numerous accolades and is already considered a physician referral center for pain management specialists in the area, as well as for physicians nationwide. In fact, the medical cannabis practice saw 24,000 patients in 2019, with an average of 70 patients per day. Pain is the main reason that patients present to GW, followed by anxiety, depression, and sleep disorders. Other conditions include sexual dysfunction, multiple sclerosis, tremors, and seizure disorders. The patient population is slightly more women than men, with the average age of approximately 50 years.

"Typically, we are known as the place where physicians send their patients to be cared for," Dr. Apgar said. Interestingly, Dr. Apgar did not initially receive support from her physician friends and colleagues when she sought to open the dispensary, underscoring the stigma surrounds cannabis medicine. "I would get comments like, 'You're throwing your career away. What are you doing?' Now these physicians are either coming in as patients or sending me their loved ones."

Training and Education

The practice functions as a residency program with Dr. Apgar serving as the attending physician and training "chief residents," who then train the "junior residents, interns, and medical students," otherwise known as cannabis wellness consultants. Questions or concerns from staff members are directed to GW's nurses or senior staff members, and ultimately Dr. Apgar.

Inside the medical dispensary at Greenhouse Wellness in Ellicott City, Maryland.

"Our dispensary has a very collegiate, collaborative environment," explained Dr. Apgar. All GW staff receive formalized training in the medicine behind cannabis and best practices.

"We have an employee training manual that goes over the basics, including what cannabis is and its medicinal qualities, how to conduct a patient interview, dosing strategies, pharmacology, etc," Dr. Apgar said.

Additionally, all staff read *The Medical Marijuana Guide: Cannabis and Your Health* by Patricia Frye, MD, and take a quiz afterward. Each month, the team is given reading assignments, much like a journal club, followed by a quiz. New hires shadow Dr. Apgar in practice, followed by other senior consultants. The learning curve is steep, Dr. Apgar noted, but the emphasis on education results in highly trained staff.

Leslie Apgar, MD (left), Medical Director and on-site physician, opened Greenhouse Wellness in 2017 with Gina Dubbé (right), venture capitalist, entrepreneur, and licensed professional engineer.

"I do consults, but when it comes to recommending the products, the wellness consultants outshine me every day," Dr. Apgar said.

"Sometimes, I will go in, much as in residency, and start pimping, putting the consultants on the spot," Dr. Apgar said. "Sometimes we do role playing, where I pretend to be a patient and I have them tell me what they would do in a certain situation."

> **"If you want to take cannabis seriously, then it needs to be approached as medicine."**
>
> ***—Leslie Apgar, MD***

Women's Health and Cannabis Medicine

Dr. Apgar's 17-year practice as a board-certified obstetrician and gynecologist (OB/GYN) prepared her for the trial-and-error approach that is typically needed in cannabis medicine. "OB/GYNs don't necessarily wait to enact change because they've got 2 lives at stake. Nothing in the practice of obstetrics was ever FDA approved for babies, so I was trained to make the best decisions and to take care of the patient's best interest at all times."

Her clinical worlds often intersect when women with complicated gynecology cases present to her seeking cannabis treatment for chronic pain.

"The cross-section of my career path has been strange," Dr. Apgar said. She often feels that "there is not a single person on the planet earth who could have been better equipped to deal with these complicated gynecology patients at this particular moment."

This career intersection led Dr. Apgar and Ms. Dubbé to develop their proprietary brand Blissiva, which is directed toward women and has various cannabidiol (CBD) to low delta-9-tetrahydrocannabinol (THC) ratios. Dr. Apgar noted that many products on the market are off-putting toward women. Other products in the Blissiva line are popular with both men and women and offer a 1:1 CBD:THC ratio for anxiety and sleep with terpene ratios to give a relaxing effect. Another product for pain has a 3:1 ratio with a different terpene blend to reduce sedating effects so patients can function during the day.

Compared with a conventional doctor's office, Dr. Apgar finds that GW's dispensary setting allows patients to be more honest about their previous or current cannabis use and with transparency, better healing can occur.

"Sometimes, they tell me their deepest, darkest feelings, or information that they don't want put in their chart, but that helps me individualize their treatment," she said.

Individualized Treatment

Start low and go slow is the typical focus of medical treatment at GW, particularly in elderly patients. Dosage is individualized based on patient age, medical history, cannabis experience, and route of administration.

Although some literature suggests an initial THC dose of 2.5 or 5 mg,[1] Dr. Apgar suggests initiating treatment at an even lower dose—such as one drop of a tincture—in an elderly patient who is cannabis-naive. She then titrates up "cautiously and carefully."

On the other end of the spectrum is a 60-year-old patient who has smoked cannabis every day for years. "I'm going to start him at a

▶ continued on page 32

Greenhouse Wellness

continued from page 31

higher dose depending on route of administration," Dr. Apgar said. "He could probably tolerate a higher concentration of THC and a flower, but maybe in an edible. I would definitely start him at 5 mg and then may go up higher to treat a pain condition, for example."

In terms of drug–drug interactions, "the safest advice I give patients and my staff is to separate the cannabis dose by 2 hours from any other medications [patients] are taking," Dr. Apgar said. The staff are educated on important drug–drug interactions, such as use of cannabis in combination with blood thinners.

"Our focus is on quality and safety first and foremost," Dr. Apgar said, adding that stringent testing regulations in Maryland ensure product safety. Products are tested at the grow level, at the processor, and at dispensaries.

Advice on Starting a Medical Dispensary

"The key to starting a medical dispensary is surrounding yourself with people who know what they're doing to fill in where your inadequacies might be in terms of running a business, because doctors are not typically good business people," Dr. Apgar told *AJEM*. Medical school does not readily prepare physicians to run their own business, "which is a complete oversight and needs to change," she said.

Gina Dubbé (left) and Leslie Apgar, MD (right)

Even in states where medical cannabis is legal, many banks steer clear of cannabis businesses because of the fear of violating federal law regarding cannabis.[1] Fortunately, this was not an obstacle for Greenhouse Wellness.

"We were really lucky because Severn Bank agreed to let a certain number of cannabis businesses bank with them," Dr. Apgar said. "The fees are high, there is no interest, and we can't write checks, but we have a safe and secure place to deposit the money, and we are grateful for that."

Finding physical space for the dispensary was much more challenging, as many potential landlords were distrustful, and many large leasing companies are headquartered across the state line or use banks with branches across the state line, Dr. Apgar said.

Ultimately, Dr. Apgar advised health care practitioners interested in entering the medical cannabis field to "be passionate and as long as you have a clear goal in mind about what you want to do, you'll get there. … Wake up every day with that goal in your mind."

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CBD Shortage Affects Treatment

Dr. Apgar worries about the growing market in Maryland, where there is currently a shortage of plants that are high in CBD, with most growers focusing on plants that are higher in THC.

The lack of access to high CBD products "is a problem already, and we are in a medical state. Can you imagine what's going to happen when our state approves recreational use?" Dr. Apgar said more growers are needed in Maryland as the current 15 growers are not able to meet the demand.

> **Dr. Apgar's 17-year practice as a board-certified obstetrician and gynecologist prepared her for the trial-and-error approach that is typically needed in cannabis medicine.**

"I know that growers are trying to increase their square footage, and they are actively working toward that end," she said, adding that she has great relationships with most of these growers. "Theoretically, we will have another 4 growers coming online at some point, but as in many states, these grower and processor awards are fraught with lawsuits and are difficult to get up and running. It is depressing that CBD has to be a niche grow or a boutique grow but, maybe that is what it's going to take."

The Patient Experience

New patients who present to GW with medical cannabis cards are asked to complete a state-mandated form on diversion, and then are able to access the dispensary where wellness consultants will take a medical history, including previous cannabis use and current pharmacotherapies, and ask patients what they hope to gain from cannabis treatment. New patients also have the option of booking a complementary 30-minute appointment with Dr. Apgar or a wellness consultant in a private conference room. Patients are educated on the various forms of cannabis that are available and are given patient education, if needed, to dispel any misconceptions regarding cannabis treatment.

▶ continued on page **33**

Would you like to nominate a trailblazing physician who opened a medical cannabis practice?

Email the Editor: drjahan@ajendomed.com to nominate a physician for our next installment of Practice Spotlight.

Can Medical Cannabis Dispensaries Be Saved in Canada?

In light of recent policy changes, a Canadian researcher discusses findings from her study: Capler R, et al. Are dispensaries indispensable? Patient experiences of access to cannabis from medical cannabis dispensaries in Canada. *Int J Drug Policy.* 2017;47:1-8.

By Rielle Capler, MHA, PhD, Postdoctoral Research Fellow, British Columbia Centre on Substance Use and Faculty of Medicine, University of British Columbia

Medical dispensaries in Canada have served a valuable role in securing patient access to high-quality cannabis over the past several decades, filling the gaps in access to Health Canada's medical cannabis program. However, recent legislative changes have excluded dispensaries from the federal regulatory framework for medical cannabis, despite the important role they have played in providing access and the high levels of utilization by patients.

Before recent policy changes, the key barriers to legal medical cannabis access included physician support for required documentation, affordability, and availability of strains and products.[1] An article published in 2017, entitled *Are Dispensaries Indispensable?*, concluded that based on the strong endorsement of dispensaries by patients, future regulations should consider including dispensaries as a legal source of medical cannabis.[2] In 2018, new legislation in Canada legalizing cannabis for nonmedical purposes included provisions for storefront sales of nonmedical cannabis.[3] However, such provisions were not extended to the medical cannabis program, and dispensaries remain an unauthorized source.

> "Health care practitioners' comfort with medical cannabis may grow with the inclusion of pharmacies as a source of cannabis."
>
> *—Rielle Capler, MHA, PhD*

Since the legalization of cannabis for nonmedical purposes in Canada, the number of medical dispensaries has dwindled considerably, and it is unclear how long these dispensaries will be tolerated. It is also yet to be determined how the barriers to accessing legal medical cannabis have been impacted by the recent legislative changes. The question is: Are dispensaries still indispensable, and if so, can they be saved?

The Federal Medical Cannabis Program

Under the current medical cannabis regulations in Canada, patients who have authorization from their health care practitioner can legally access cannabis online through a federally licensed cannabis producer or through personal/designated cultivation.[4] Currently, there is no legal storefront option for patients seeking medical cannabis in Canada.

A 2019 population survey found that only 23% of medical users were accessing cannabis from licensed producers in the federal medical cannabis program.[5] Despite physician associations issuing statements suggesting that with the legalization of nonmedical cannabis there is no longer a need for a separate medical stream, the number of health care practitioners providing documents for patients to register with a licensed producer has increased steadily.[6] As of September 2019, there were 369,614 actively registered clients in the medical cannabis program.[7]

Although there has been a steady increase in the number of people registered in the program since its inception, after the legalization of nonmedical cannabis in October 2018, the sales of dried cannabis in the medical stream has dropped substantially.[7] Potential reasons for the decrease in legal medical sales follow:

- An increase in the cost of medical cannabis resulting from a new excise tax that was applied to cannabis produced in both the medical and nonmedical streams may have led

▶ continued on page 34

Greenhouse Wellness

continued from page 32

Advancing the Field

Dr. Apgar hopes to capture outcomes data at the dispensary for clinical research in the future. Currently, she and other dispensaries across the country are participating in a Stanford Medicine study on cannabis and sexual health (study link: https://stanforduniversity.qualtrics.com/jfe/form/SV_2mkzODLAGoHCvGt). Dr. Apgar is also interested in future studies as they arise.

Dr. Apgar and Ms. Dubbé detail how they started the dispensary and overcame regulatory hurdles in their book *High Heals*. "The whole point of opening this dispensary, which has been an uphill battle every single day, is that we want to make the industry better," Dr. Apgar said. "We'll never improve this field or achieve legitimacy unless we make it better."

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Dr. Apgar and Ms. Dubbé *are co-owners of Greenhouse Wellness and Blissiva and are authors of* High Heals.

Dispensaries
continued from page 33

patients to seek cannabis outside the program, including from unregulated sources that have comparatively lower prices.[8,9] These elevated costs also may have led to an increase in personal and designated production within the program.[7] Some insurance companies have started to include cannabis in their drug plans, and patients are advocating for cost coverage from provincial health insurance plans. Additionally, some licensed producers are offering discounted priced on their medical lines.

- A new legal storefront retail source in the nonmedical stream, although not less costly, may be preferable to some patients than the option of mail order provided through the medical stream.
- Shortages of cannabis in the medical stream, possibly due to diversion to the nonmedical stream, may have led patients to use other legal and illegal sources.[10]

An additional legal source of medical cannabis has recently become available through the large pharmacy chain Shoppers Drug Mart, which was recently licensed by Health Canada to sell medical cannabis online to residents of Canada.[11] The retail chain offers telemedicine consultations to receive authorization for medical cannabis use. One benefit of this source is the ability of patients to access products from various licensed producers from one source; this previously required the patient to order separately from each producer and to obtain separate documentation from their health care practitioner for each order.

This new source of medical cannabis also will offer pharmacist oversight regarding drug interactions, which is not available with online mail order directly from licensed producers. Some skepticism has been voiced about the ability of pharmacists to provide this oversight and support with their current knowledge base.[12] It is yet to be seen how this source might impact the support of health care practitioners, cost, and the sales of cannabis within the medical stream.[13]

It is possible that clinicians' comfort with medical cannabis may grow with the inclusion of pharmacies as a source of cannabis, as well as with the recent additional of new cannabis products in the program.[14] Additionally, the legalization of nonmedical cannabis has resulted in more public and private funding for cannabis research, which also may increase the comfort of health care practitioners with use of this medicine. To address gaps in clinicians' knowledge, which has been a barrier to their participation in the program, it is vital to provide education about cannabis and the endocannabinoid system within school medical curricula.[15]

Medical Access From Legal Nonmedical Retailers

Under the Cannabis Act of 2018, cannabis for nonmedical purposes is legally available to adults in Canada (18 or 19 years of age depending on province/territory) from provincially licensed public and private retailers, including online and storefront sales (the specific retail options vary by province/territory).[13]

Although staff at nonmedical retail stores are not permitted to discuss medical efficacy or medical use of cannabis with customers, there is nothing preventing individuals from using the cannabis they purchase from these stores for medical purposes. Many medical cannabis users indeed do access cannabis from these legal nonmedical retailers. Data from a large population survey indicate that in 2019, whether registered in the federal medical program or not, 29% of medical cannabis users were accessing cannabis from legal nonmedical retail storefronts.[5]

The number of individuals accessing cannabis for medical use from nonmedical retailers may increase as more retail stores are licensed across the country, particularly in the highly populated provinces of British Columbia and Ontario, which both have experienced a slow rollout of their retail licensing programs.[13] The addition of new cannabis products, including edibles and concentrates, which became legal at the end of 2019, may result in even higher numbers of medical patients accessing nonmedical retailers.[14]

> **"Individuals accessing cannabis from the nonmedical stream will not have the benefit of physician oversight when taking cannabis for medical purposes and will not have a clinician monitoring for drug–drug interactions."**
>
> ***—Rielle Capler, MHA, PhD***

Notably, health and wellness are among the top reasons why Canadian consumers use recreational cannabis post-legalization, according to a recent survey.[16] In fact, according to that survey, the motivation to use cannabis as a health/medical product rose from 32% to 42% between the first quarter of 2018 and the first quarter of 2019. As the use of cannabis for medical purposes is increasing, it must be considered whether nonmedical stores are the ideal source for medical cannabis. Individuals accessing cannabis from the nonmedical stream will not have the benefit of physician oversight when taking cannabis for medical purposes and will not have a clinician monitoring for drug–drug interactions. They also will not have support from retail staff for the selection of strains and products to address their symptoms and conditions.

Where Does This Leave Dispensaries and Patients?

Dispensaries have been one of most highly accessed and highly rated source of medical cannabis in Canada. A study of Canadian patients using cannabis for medical purposes in 2011–2012 found that only 7% of patients authorized to use medical cannabis under the federal program exclusively accessed cannabis from legal sources available at the time,[1] with as many as 80% obtaining cannabis from medical dispensaries.[17] Another study demonstrated the high ratings given to dispensaries, with dispensaries being rated equally to or more favorably than other sources of cannabis, both legal and illegal, for quality, safety, availability, efficiency, and feeling respected; they were rated less favorably than self-production and accessing from other producers in terms of cost.[2]

Before the legalization of recreational cannabis in Canada, unregulated dispensaries flourished across the country, particularly

Remedy, a medical cannabis dispensary in Halifax, Nova Scotia, was considered illegal by the province and closed a few days before Canada legalized recreational cannabis nationwide on October 17, 2018.
Photocredit: *Coastal Elite, Wikimedia Commons.*

in major cities. Although illegal, the activities of these dispensaries were tolerated in several major cities and smaller municipalities across the country in recognition of the shortcomings of the federal government's medical cannabis program. In 2016, approximately 175 dispensaries were serving an estimated 100,000 to 200,000 clients.[18,19]

However, since the 2018 legalization of nonmedical cannabis, very few dispensaries have remained open. Most of the dispensaries have either transitioned to licensed nonmedical retailers or have shut down by choice or by force.[20] The provinces and territories, which regulate sales of nonmedical cannabis, no longer tolerate these dispensaries operating without a license and selling unregulated product regardless of whether the needs of patients are being met through the medical or nonmedical legal channels.[21]

Thus, in the context of legal nonmedical cannabis, it has become even more challenging for unregulated medical cannabis dispensaries to operate. The closure of these shops is reflected in the substantial drop in the use of dispensaries by medical cannabis users in the general population from 28% in 2018 pre-legalization, to 12% in 2019 post-legalization.[5,22] It is unknown to what degree patient needs are currently met through the legal medical and nonmedical sources, or through illegal sources.

The loss of this source of cannabis may disproportionately impact some medical cannabis users. Previous research found differences in patient demographic and use patterns between people

> **"It must be considered whether nonmedical stores are the ideal source for medical cannabis."**
> ***—Rielle Capler, MHA, PhD***

using storefront dispensaries and those using other sources.[2] For example, individuals using storefront dispensaries were found to be older than patients who used other sources. In terms of patterns of use, patients using dispensaries purchased larger quantities of cannabis and placed a higher value on access to specific strains than patients obtaining cannabis elsewhere. It is possible that the new legal sources may address the needs of some of these individuals.

Some of the few remaining strictly medical dispensaries are attempting to find avenues to continue providing the products and services that patients have valued for the past 2 decades. One of first dispensaries in Canada has garnered the support of its municipal government to petition the British Columbia provincial government to grant it a temporary exemption from the province's Cannabis Control and Licensing Act,[23] so it can continue providing "responsible access and a safe, welcoming community space for medical cannabis users."[24] It is unclear whether this dispensary, or the other remaining medical dispensaries, will continue to be tolerated until such a time when there are provisions for legal storefront retail for medical access.

▶ continued on page **36**

Dispensaries
continued from page 35

Lessons From Canada: The Impact of Nonmedical Cannabis Regulation

An unintended consequence of nonmedical cannabis regulation may be that the needs of medical patients are overlooked. If the price of medical cannabis is too high, or products are not earmarked for the medical stream, patients will forego using the legal medical sources and will seek recreational or illegal sources. A review of the medical program is scheduled to take place within 5 years of the enactment of the 2018 Cannabis Act.[25] It will be vital to assess the impact of the new medical and nonmedical sources of cannabis on patient access and whether patient needs are being met through current legal channels. It is unclear what the outcome of that review will be, and how long it will take to implement any changes. It remains to be seen whether storefront access will finally be included in the legal medical stream, and, in the meantime, if dispensaries will continue to fill the gaps in this new regulatory climate.

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Prescription and Nonprescription Cannabinoids: A Dual-Path Regulatory Framework

By Rob Dhoble, Managing Director, Havas ECS, New York, New York.

Scientific understanding of the human endocannabinoid system (ECS) has grown to include clinical outcomes data on the benefit of exogenous cannabinoids, specifically *Cannabis sativa L.*—the plant's component cannabinoids, terpenes, and synthetic counterparts.[1] As research mounts and the medical community begins to view cannabis as a legitimate therapy, there has been a shift toward an emerging standard of care (SOC).[2] A dual-path federal regulatory framework is needed to support this SOC in order to ensure patient safety, product quality, and market access.

All humans have an ECS, comprised of receptors throughout the body that together uniquely support homeostasis.[3,4] *Cannabis sativa L.* is a hardy plant species comprising numerous cannabis cultivars and chemovars, each with wide-ranging concentrations of delta-9-tetrahydrocannabinol (THC; the psychoactive component of cannabis); cannabinoids such as cannabidiol (CBD), cannabigerol (CBG), and cannabinol (CBN); as well as terpenes such as myrcene and linalool.[1] Evolving clinical evidence on the impact of cannabinoids, flavonoids, and terpenes on ECS receptors and body systems can serve as a common denominator for local, state, and international laws regarding access to prescription and nonprescription products containing natural or synthetic analog cannabinoids.

Emerging Standard of Care for Cannabis

In recent years, literature on the therapeutic benefits associated with cannabis and cannabinoids has grown, reaching 568 systematic reviews and 2282 primary studies between 1999 and 2016, according to a comprehensive review conducted by the Committee on the Health Effects of Marijuna.[5] As research studies become more rigorous and access to cannabis increases, there has been a shift toward an emerging SOC across many medical conditions.[2] The combined list of qualifying medical conditions among 38 US states and territories with medical marijuana programs now exceeds 75, not including hospice care and terminal illness qualifications. Such qualifying acute and chronic conditions include amyotrophic lateral sclerosis, ulcerative colitis, multiple sclerosis, fibromyalgia, post-traumatic stress disorder, chemotherapy-induced nausea and vomiting, severe and intractable pain, parkinsonism, rheumatoid arthritis, epilepsy, seizures, psoriatic arthritis, obsessive-compulsive disorder, and opioid use disorder, as well as rarer qualifying conditions such as Tourette syndrome, Huntington's disease, lupus, and muscular dystrophy.[6] Importantly, many cannabis components such as CBD, CBG, CBN, and terpenes, have demonstrated beneficial clinical and preclinical activity across many of these same conditions.[1] Importantly, shifts toward an SOC for medical cannabis are being driven by off-label use of prescription cannabinoids, especially by physicians in states without medical marijuana programs. Additionally, clinical trials suggest efficacy of off-label use of these agents for conditions ranging from severe chronic obstructive sleep apnea to chronic neuropathic pain, and adjuvant treatment of chronic pain in patients receiving opioid therapy.[7-9]

> "A dual-path federal regulatory framework is needed to support the [standard of care] in order to ensure patient safety, product quality, and market access."
>
> —*Rob Dhoble*

Although strides are being made regarding the consistency of care and patient safety in the prescription market, the wide variety and availability of nonprescription cannabinoid products is left largely unregulated. To date, the FDA has not established labeling requirements or ingredient analysis standards for nonprescription cannabinoids, but instead has focused on enforcement actions related to unsubstantiated medical claims and quality issues of manufacturers of these products.[10]

Limitations of Current Pharmacotherapy

Cannabis medicine may fill the gaps in the efficacy and tolerability of many FDA-approved treatments for chronic conditions as well as the lack of safe and effective treatments for many rare diseases.[11-13] Nearly one-third of patients recently surveyed said they stopped taking a prescription medication without consulting a health care practitioner, most commonly because of side effects (29%) or they felt the drug was not working (15%).[14]

Additionally, the current health care landscape is limited by the cost of health insurance, high deductibles, and the high cost of prescription medications.[15] As a result, many Americans postpone or delay needed medical treatment, with 1 in 5 having to liquidate their savings to pay a medical bill.[15] In fact, 31% of surveyed adults

▶ continued on page 38

Dual Path
continued from page 37

reported that they or a family member have relied on home remedies or over-the-counter (OTC) drugs instead of seeing a doctor, and approximately 18% reported not filling a prescription due to cost, thus taking an OTC product instead.[16]

Only 3 cannabinoid products are FDA-approved in the United States—cannabidiol (Epidiolex), dronabinol (Marinol, Syndros), and nabilone (Cesamet)—and these agents are narrowly labeled.[17-20] Although there are more than 10 new prescription cannabinoids in clinical development, most of these compounds are likely many years from potential FDA approval, and many are expected to have indications representing relatively small treatment populations, such as fragile X syndrome, intraocular hypertension, and cystic fibrosis.[11-13]

> **"There needs to be product consistency and accurate labeling, which has been plaguing the field. Properly designed studies with appropriate controls are needed."**
>
> ***—Mark Green, MD, former FDA Panel Member of the Peripheral and Central Neurological Drugs Advisory Committee***

Thus, the health care marketplace urgently requires a dual-path approach to ensure affordability and market access to quality prescription and nonprescription cannabinoids for use under the direction of medical professionals, with nonprescription cannabinoids comprising "self-care."

A Dual-Path Approach to Federal Policy

To better ensure access to quality cannabinoids that may benefit underserved medical populations, we should consider priorities for a dual-path federal regulatory framework including:

- Prescription Cannabinoid Path 1:
  - Accelerated FDA priority review and approval of qualifying cannabinoid New Drug Applications, and supplemental applications, due to expanding medical science supporting the need for safe products that selectively engage the ECS
  - Medicaid, Medicare, Military, and Veterans Administration (VA) reimbursement coverage of on- and off-label use of FDA-approved prescription cannabinoids, especially when prescribed by ECS-trained medical professionals who are able to individualize treatment based on medical condition, adjunctive therapies, and patient needs. Off-label use of FDA-approved prescription cannabinoids provides clinicians with "first-choice" products that are federally monitored for manufacturing consistency, each with rigorously defined profiles in pharmacokinetics, bioavailability, adverse events, drug interactions, and dose responsiveness
  - Federal and state incentives to educate medical professionals on the dynamics of the ECS, to better understand and support the role of cannabinoids and cannabis as part of individualized, condition-specific treatment regimens
- Nonprescription Cannabinoid Path 2: A "brief summary" requirement for health professional and consumer awareness, uniformly depicted on product packaging and within product advertising, to summarize the presence or absence of:
  1) Independent laboratory-assessed listing of product ingredients including CBD, THC, and other cannabinoids; linalool, myrcene, and other terpenes; inert ingredients; and the absence of contaminants
  2) Identification of ingredients as being botanical, synthetic, or biosynthetic
  3) Current Good Manufacturing Practice FDA compliance in manufacturing and packaging, including package expiration
  4) Bioavailability data regarding how dose/serving size relates to absorption and blood levels

Ideally, these dual-path approaches would align with a Drug Enforcement Administration (DEA) re-scheduling of THC-containing cannabis as either a Schedule II or III controlled substance, coinciding with the scheduling class of synthetic THC analogs dronabinol (III) and nabilone (II). Such DEA re-scheduling would increase opportunities for clinical research of THC-containing cannabis among the greater medical community.

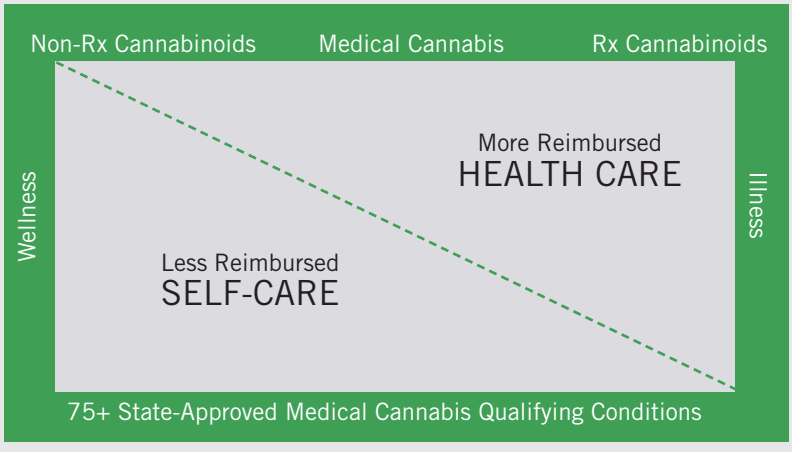

Figure. Self-care to health care cannabinoid ecosystem.

Activating a Dual Path Forward

The FDA is part of the U.S. Department of Health and Human Services (HSS), which is part of the executive branch of the federal government. Executive branch leadership is needed to establish a new framework that bridges relevant gaps existing between the FDA, DEA, U.S. Department of Agriculture, VA, and HSS.

The dual-path framework proposed here would ensure expanded access to both prescription and nonprescription cannabinoid

products, with federal quality standards for each. For example, such a framework could allow some CBD and other cannabinoids (eg, CBG and CBN) to exist as nonprescription products comprised of generally recognized as safe (GRAS) ingredients. Additionally, more rigorously studied prescription cannabinoid agents would be considered worthy of public- and private-sector medical insurance reimbursement. Such a framework may require a new kind of cannabinoid label, which would require legislation to amend the Dietary Supplement Health and Education Act.

What is important is that we recognize the need for new ways to advance both research and regulatory science and encourage them."

—Peter Pitts, Former FDA Associate Commissioner

"There needs to be product consistency and accurate labelling, which has been plaguing the field," Mark Green, MD, former FDA Panel Member of the Peripheral and Central Neurological Drugs Advisory Committee, told *American Journal of Endocannabinoid Medicine.* "Properly designed studies with appropriate controls are needed. All of this is needed in order to go beyond 'proof of concept studies' to approvable products," added Dr. Green who is Director of Headache and Pain Medicine at the Icahn School of Medicine at Mount Sinai in New York.

Former FDA Associate Commissioner Peter Pitts, spoke to *American Journal of Endocannabinoid Medicine* about the legal and policy considerations surrounding prescription and nonprescription cannabinoid products. "It's not about whether more and more robust research into cannabinoids awaits more comprehensive FDA regulation, it's how to ensure that both advance together—with all due speed—in order to best serve the public health," said Mr. Pitts, who is President of the Center for Medicine in the Public Interest. "At present there are more questions than answers. This is always the case with innovative therapies. What is important is that we recognize the need for new ways to advance both research and regulatory science and encourage them," said Mr. Pitts.

The following are instances where we need federal nonprescription cannabinoid regulatory standards:

- When prescription cannabinoids are unavailable to ECS-trained medical professionals and/or are not reimbursed for ECS-related medical conditions
- When ECS-related medical conditions have no corresponding FDA-approved prescription cannabinoid indication
- When prescription cannabinoid ingredients result in potential warnings or precautions, such as for product ingredients representing patient allergies
- When having both prescription and nonprescription cannabinoid product standards will increase treatment options for conditions in which the ECS is the clinical target, and will promote reproducibility of results across the practice of medicine

An Opportunity for Self-Regulation

There is a benefit to adopting nonprescription cannabinoid quality standards for research reported within this journal. By only publishing research conducted with products incorporating quality assurance standards, findings from clinical research studies or case reports can be more easily compared. It is further suggested that the *American Journal of Endocannabinoid Medicine* require that advertisers include a "brief summary" labeling requirement for nonprescription cannabinoid products to increase brand transparency and product quality for clinicians.

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Mr. Dhoble *has no financial conflicts of interest to disclose.*

First Congressional Hearing on Cannabis Policy Reform

House Subcommittee debates and explores proposed legislation.

The U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health held its first legislative cannabis hearing on January 15, 2020. The 3.5-hour hearing included testimonials from congressional representatives and key witnesses from the National Institute on Drug Abuse (NIDA), the FDA and the Drug Enforcement Administration (DEA). Although no policy changes were enacted and no voting took place, subcommittee members debated and explored proposals to lessen restrictions in order to advance cannabis research. The congressional representatives discussed issues related to 6 bills that offer a range of solutions for federal cannabis policy reform (Table).[1]

> "[Researchers] can't conduct cannabis research until they show that cannabis has a medical use, but they can't show that cannabis has a medical use until they can conduct research."
>
> *—Anna Eshoo, Chair, Subcommittee on Health*

Barriers to Cannabis Research

Anna Eshoo, Chair of the Subcommittee on Health, discussed the current catch-22 situation regarding cannabis research given the Schedule I classification of this agent. Researchers "can't conduct cannabis research until they show that cannabis has a medical use, but they can't show that cannabis has a medical use until they can conduct research," she said.[1]

Currently, the only provider of cannabis for FDA-approved clinical research is a government-authorized farm at the University of Mississippi. This supply has been criticized by scientists as lacking the properties and potency of commercially available cannabis, thereby limiting research.

The current supply "does not have the capacity to manufacture a broad array of cannabis-derived formulations for research or to supply these cannabis products for commercial development," said Nora Volkow, MD, Director of NIDA at the National Institutes of Health.[1] "Moreover, it is not clear how entities seeking to develop these products for commercial purposes would demonstrate equivalency between the University of Mississippi cannabis used in clinical trials and the drug product that would ultimately be approved by the FDA for marketing and sale."

DEA May Expand List of Growers

The DEA hopes to expand the number of registrants approved to grow cannabis for research purposes, and as of August 2019 has begun to review applications from other cannabis growers for use in federally authorized research.[2] The DEA anticipates that registering additional qualified marijuana growers will increase the variety of marijuana available for research purposes.[2]

Matthew J. Strait, Senior Policy Advisor, Diversion Control Division at the DEA outlined the agency's regulatory plans. "In

Table. Proposed Legislation for Cannabis Policy Reform

Bill	Resolution	Proposal
H.R. 171	Legitimate Use of Medicinal Marijuana Act	To provide for the legitimate use of medicinal marijuana in accordance with the laws of the various states; moves marijuana to Schedule I
H.R. 601	Medical Cannabis Research Act of 2019	To increase the number of manufacturers registered under the CSA to manufacture cannabis for legitimate research purposes, to authorize health care providers of the Department of Veterans Affairs to provide recommendations to veterans regarding participation in federally approved cannabis clinical trials, and for other purposes
H.R. 1151	Veterans Medical Marijuana Safe Harbor Act	To allow veterans to use, possess, or transport medical marijuana and to discuss the use of medical marijuana with a physician of the Department of Veterans Affairs as authorized by a state or Indian tribe, and for other purposes
H.R. 2843	Marijuana Freedom and Opportunity Act	To decriminalize marijuana, and for other purposes
H.R. 3797	Medical Marijuana Research Act of 2019	To amend the CSA to make marijuana accessible for use by qualified marijuana researchers for medical purposes, and for other purposes
H.R. 3884	Marijuana Opportunity Reinvestment and Expungement Act of 2019	To decriminalize and deschedule cannabis, to provide for reinvestment in certain persons adversely impacted by the War on Drugs, to provide for expungement of certain cannabis offenses, and for other purposes

CSA, Controlled Substances Act.

Source: Committee on Energy and Commerce.[1]

the near future, DEA intends to propose regulations that would govern persons seeking to become registered with DEA to grow marijuana as bulk manufacturers, consistent with applicable law, taking into account recent changes in the Controlled Substances Act [CSA]. At present, a notice of proposed rulemaking is under review by the Office of Management and Budget," he said.[1]

Next Steps

Dr. Volkow pointed out that obtaining or modifying a Schedule I registration for research can take up to 1 year and adding new substances to an existing registration is a lengthy process.[1] To remedy this situation, Dr. Volkow called for clarification of the CSA to allow "one individual to hold a Schedule I registration under which colleagues from the same institution may work even if those colleagues do not work directly for the registrant (eg, as members of their laboratory); that registered researchers may store, administer, and work with any substances for which they hold a researcher registration at multiple practice sites on a single contiguous campus; and that if a person is registered to conduct research with a controlled substance and applies to conduct research with a second controlled substance that is in the same schedule or in a schedule with a higher numerical designation, an inspection that was performed for purposes of the existing registration shall be sufficient to support the application."[1]

Dr. Volkow also noted that registered researchers do not need to obtain a separate manufacturing registration to create specific dosage formulations that are consistent with their research protocol. She added that this is particularly true when researchers need to create dosage formulations from cannabis products supplied through the NIDA Drug Supply Program.[1] She also called for changes to federal law restricting research supported by NIDA and other federal agencies on marketed cannabis products available through state marijuana dispensaries, resulting in a "significant gap in our understanding of their impact on health," Dr. Volkow said.[1]

Pathways for Nondrug CBD Products

The FDA is actively working to determine the safety and efficacy of nondrug products containing cannabidiol (CBD), including safe manufacturing processes, and is considering the possibility of establishing new legal pathways for the safe marketing of certain dietary supplements and/or food products containing CBD, explained Douglas Throckmorton, MD, Deputy Director for Regulatory Programs at the FDA's Center for Drug Evaluation and Research.[1]

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The full Subcommittee on Health hearing of "Cannabis Policies for the New Decade" is available at https://energycommerce.house.gov/committee-activity/hearings/hearing-on-cannabis-policies-for-the-new-decade

Medical Marijuana and DWIC: Medical and Legal Considerations

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Driving while impaired by cannabis (DWIC) is not a new issue. However, in the wake of the current marijuana revival, in which patients have more access than at any time in recent history, the issue of DWIC is rapidly coming to the forefront. As health care providers increasingly care for patients who may be using medical cannabis, it is important to understand the legal and medical considerations surrounding DWIC.

Legal Considerations

All US states and the federal government have laws prohibiting DWIC. As with most things in the cannabis sector, the laws addressing DWIC differ widely between jurisdictions.

Broadly speaking, regulations regarding DWIC can be divided into 4 categories:

1. Zero tolerance: Driving with any detectable amount of delta-9-tetrahydrocannabinol (THC), the primary intoxicating compound in cannabis, or its metabolites, in the body is a criminal act. Twelve states have zero tolerance laws.[1]
2. Per se: This law prohibits driving with a detectable amount of THC that exceeds a defined legal limit. Six states have per se laws, although the legal limits vary between them, from 1 to 5 ng/mL.[1,2]
3. Driving under the influence of drugs (DUID) regulations: These regulations prohibit driving while actually impaired by THC. Thirty-two states and the federal government have adopted DUID laws.[1]
4. Reasonable inference: This is a rebuttable inference of criminally sufficient impairment if a driver's blood contains THC exceeding 5 ng/mL. Only Colorado has adopted reasonable inference regulations.[1]

Before discussing the efficacy of these various regulatory approaches, a threshold issue to consider is whether cannabis use actually functionally impairs driving ability. Surprisingly, this issue is not settled. According to Sewell et al. "most marijuana-intoxicated drivers show only modest impairments on actual road tests. Experienced smokers who drive on a set course show almost no functional impairment under the influence of marijuana, except when it is combined with alcohol."[3] Unlike alcohol, which causes predictable functional impairment among all drivers, cannabis does not impair all drivers, nor does it impair all drivers equally.[4-11] A National Highway Traffic Safety Administration report submitted to Congress indicated "Subjects dosed on marijuana showed reduced mean speeds, increased time driving below the speed limit and increased following distance during a car following task."[12] This and other studies reveal that "after smoking marijuana, subjects in most of the simulator and instrumented vehicle studies on marijuana and driving typically drive slower, follow other cars at greater distances, and take fewer risks than when sober."[12]

> "Current evidence suggests that regulatory approaches to DWIC should be geared toward removing impaired drivers from the road while not unnecessarily criminalizing nonimpaired drivers who use cannabis legally.
>
> *— Rod Kight, Esq*

THC Blood Levels Are Insufficient to Measure Impairment

Because of the complex ways in which cannabis interacts in the body, it affects individuals differently based on a number of factors.[13] Conceptually, this means an experienced cannabis user may not be impaired at all by cannabis use, whereas an inexperienced user may be impaired by using a relatively small amount. Evidence shows that not all drivers with THC in their blood plasma, even at per se impairment levels, are functionally impaired.[14,15] Teri Moore and Adrian T. Moore, PhD, stated that "Unlike alcohol, which is 'hydrophilic,' cannabis is 'lipophilic,' meaning that it is stored in the fatty tissues of the body. This characteristic means that cannabis compounds, including the psychoactive THC, store and are detectable long term, up to a month or longer of abstinence, as THC leaches into the bloodstream from fatty tissues. Blood plasma levels and impairment vary greatly in subjects given the same dose."[16]

Also problematic is the converse, namely, that not all impaired drivers test positive for THC. This is due to the fact that peak impairment, which typically occurs 90 minutes after smoking, coincides with an 80% drop in THC levels in blood plasma. Thus, low THC levels may not be a reliable indicator of recent cannabis use.[3,6,17-20] In other words, per se THC blood levels do not track with impairment. This means that states that rely on per se levels are likely to release drivers with below per se levels who are still impaired.[16]

Recent advances in other testing methods, including a breathalyzer developed by Hound Labs, Inc., claim the ability to determine if an individual has smoked THC in the past 2 to 3 hours. That system collects 5 minutes of exhalation onto a silicon bead module, dissolves it in pure ethyl alcohol, and sends it to a fluorescent-based chemical assay for analysis. Readout is in picograms/liter of breath. Although this may be a useful tool for law enforcement, it still does not prove impairment, and no state laws currently set limits for THC on the breath or use a time-based

determination to confirm impairment. Colorado, as the first state to legalize cannabis for recreational use, defines DUI for an individual when they are "substantially incapable, either mentally or physically, or both mentally and physically, to exercise clear judgment, sufficient physical control, or due care in the safe operation of a vehicle."[21] This is a useful definition of impairment, but it has no correlation to specific quantities consumed or how recent the consumption occurred, and fully supports the argument that impairment testing is the most useful method for determining THC influence.[21]

For these reasons, the notion that impairment can be assumed or not based solely on specific concentrations of THC or its metabolites in a driver's blood or urine is plainly wrong. As a result of an extensive study, the American Automobile Association Foundation for Traffic Safety concluded that, "a quantitative threshold for per se laws for THC following cannabis use cannot be scientifically supported."[22] Furthermore, postmortem analysis for THC has been found to have a fatal flaw. After death, the body begins to break down and the cumulative THC stored in fat cells is released into body. For this reason, every postmortem analysis of THC shows hyper-elevated levels of THC and are meaningless for developing DWIC policy generally, and per se limits specifically.[23]

> **"No state laws currently set limits for THC on the breath or use a time-based determination to confirm impairment."**
> ***—Russ Phifer***

Criminalizing Nonimpaired Drivers

Together, current evidence suggests that regulatory approaches to DWIC should be geared toward removing impaired drivers from the road while not unnecessarily criminalizing nonimpaired drivers who use cannabis legally. Zero tolerance and per se regulatory approaches are ill-suited to supporting this policy goal, as they are not reliable measures.[11] Additionally, both approaches have a great capacity to criminalize individuals who are not impaired, but who have THC or its metabolites in their blood or urine. In fact, both approaches almost certainly violate the Due Process Clause of the Fourteenth Amendment of the US Constitution because they "subject drivers to criminal prosecutions without any real culpability. …"[24] And, although Colorado's permissible inference approach does not violate the Due Process Clause, the fact that it places the burden on the driver to prove that he or she was not impaired is overly burdensome (if not philosophically impossible) and unsupported by relevant data.

On the other hand, the DUID approach, which does not rely exclusively on blood or urine tests to determine impairment, is best suited for removing impaired drivers from the road while ensuring that the Constitutional rights and arrest records of unimpaired drivers remain intact. The problem posed by the DUID approach is determining impairment by the use of nonqualitative field sobriety tests (FSTs). Although training can greatly improve one's skill at judging impairment in the field, doing so is more of an art than a science.

Because FSTs evaluate divided attention skills, they provide fairly accurate assessments of driving impairment, no matter what substance the driver may have ingested. In the case of cannabis, a driver's failure to perform an FST as demonstrated, combined with a THC-positive reading on a roadside testing device, provides adequate reasonable suspicion for further investigation or, more typically, probable cause for DUI arrest.[17]

This description of FST may be overly optimistic. The most important question is whether there is objective data supporting the same (or similar) level of confidence for FST in determining

▶ continued on page 44

DWIC
continued from page 43

cannabis impairment as there is for FST in determining alcohol impairment. The answer appears to be "no," or at least, "not always," which is why FSTs in development specifically measure symptoms of cannabis intoxication, such as slow reaction time, misperception of time passage, and inability to handle divided attention tasks.[11,25] In short, there is currently no parity between alcohol and cannabis intoxication, at least in terms of reliable methods for determining functional driving impairment. Whereas alcohol impairment can be reliably determined by the driver's blood alcohol levels and/or FST, the same is not true for cannabis.

> **"We conclude that impairment is the issue, not the concentration of THC and its metabolites in the human body.**
>
> ***— Jahan Marcu, PhD***

Future Implications

Currently, there is sparse and contradictory evidence regarding THC concentrations and their correlation with cannabis intoxication and driving habits.[26] We conclude that impairment is the issue, not the concentration of THC and its metabolites in the human body. The use of THC concentrations alone, or the presence of metabolites in any fluid sample, to equate to an acute cannabis intoxication will continue to result in inappropriate arrest, prosecution, and civil liability.[26] Although far from perfect, field sobriety testing for impairment is currently the best and fairest option for determining whether a driver (or worker in the workplace) can safely navigate the road or be safely productive in the workplace.[3,11,18] To this end, the DUID regulatory approach, which focuses on impairment rather than the presence of THC in the body, is the most appropriate one to achieve the dual policy goals of removing impaired drivers from the road, while not criminalizing nonintoxicated drivers who lawfully use cannabis.

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Medical Marijuana Neuroimaging Study Shows Improved Executive Function

A commentary on Gruber SA, et al. The grass might be greener: medical marijuana patients exhibit altered brain activity and improved executive function after 3 months of treatment. *Front Pharmacol.* 2018;8:983.

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

In the first neuroimaging study focused on examining the effects of medicinal marijuana, Gruber et al. found improved executive function and changes in brain activation patterns within the cingulate cortex and frontal regions after 3 months of use.[1] These changes were accompanied by decreased use of conventional pharmacotherapy, including opioids and benzodiazepines, as well as positive changes in measures of clinical state, impulsivity, sleep, and quality of life.

The study included 22 patients (11 women; mean age, 50.6 years) using medical marijuana for a variety of conditions, most commonly pain, anxiety (post-traumatic stress disorder), sleep, and mood. Patients were required to be marijuana-naive or to have been marijuana-free for 2 years at baseline in order to minimize the effects of previous marijuana exposure on outcomes.

Patients either had medical marijuana cards or described a plan to use industrial hemp-derived products. They selected their own treatment regimens and were assigned a monitoring schedule. Patients provided a sample of their most frequently used product to an outside laboratory, which quantified levels of 10 major cannabinoids, data from which will be provided in a future study, according to the researchers.

Patients used medical marijuana an average of 5.3 days per week and 1.8 times per day. The most common modes of administration were vaporized flower (n=9) and smoked flower (n=8). Executive function and cognitive control were measured using the Multi-Source Interference Test (MSIT) while patients simultaneously underwent functional magnetic resonance imaging pretreatment and at 3 months after treatment initiation.[1]

Changes in Brain Function and Activation

At 3 months, patients showed significantly improved task performance on the MSIT (Table), accompanied by significant changes in brain activation patterns within the cingulate cortex and frontal regions (Figure, page 46). Brain activation patterns of the patients more closely resembled those of healthy controls in previous studies than did their pretreatment patterns, according to Gruber et al.[2,3]

These changes were accompanied by significant improvements in self-reported measures of depression, motor impulsivity, sleep

▶ continued on page 46

Table. Multi-Source Interference Test Performance at Pretreatment and After 3 Months of Medical Marijuana Use (Post-Treatment)[1]

MSIT variable	Visit 1 pretreatment Mean (SD)	Visit 2 post-treatment Mean (SD)	Wilcoxon Z	Wilcoxon *P* (r)
Control condition				
Response time (ms)	608.90 (97.20)	582.62 (64.97)	2.062	0.020 (0.500)*
Percent accuracy	97.40 (2.57)	98.82 (1.74)	2.282	0.011 (0.553)*
Omission errors†	1.73 (2.25)	0.68 (1.09)	1.974	0.024 (0.479)*
Commission errors†	0.77 (0.97)	0.46 (0.86)	1.461	0.072 (0.354)
Interference condition				
Response time (ms)	914.23 (76.56)	886.62 (82.76)	2.743	0.003 (0.665)*
Percent accuracy	79.03 (18.87)	86.55 (11.88)	2.858	0.002 (0.693)
Omission errors†	11.96 (12.01)	7.27 (7.92)	2.750	0.003 (0.667)
Commission errors†	8.18 (9.11)	5.77 (5.57)	1.718	0.043 (0.417)‡

MSIT, Multi-Source Interference Test.

df=1,21

*Results significant at $P \leq 0.05$ when $\alpha=0.05$ or, for Bonferroni corrected analyses, at $P \leq 0.025$ when $\alpha=0.025$.

†Corrected for multiple comparisons using Bonferroni method.

‡Results trending toward significance at $P \leq 0.10$ when $\alpha=0.05$ or, for Bonferroni corrected analyses, at $P \leq 0.05$ when $\alpha=0.025$.

Table adapted from Gruber et al. *Front Pharmacol.* 2018;8:983.[1]

Neuroimaging
continued from page 45

quality, and Short Form-36 role limitations due to physical health and energy/fatigue scores. No significant worsening of clinical state or quality of life was found.

Medical Marijuana vs Recreational Marijuana

The findings were surprising in that they conflict with previous studies linking recreational marijuana to decreased cognitive performance and atypical neural alterations.[4-6] Importantly, many of these recreational marijuana studies included adolescents and young adults, groups that are still at critical stages of neurodevelopment and may be more vulnerable to the potentially adverse cognitive effects of delta-9-tetrahydrocannabinol (THC), as Gruber et al. noted.[5,7,8] Additionally, recreational cannabis may have higher levels of THC than medical marijuana.

In the present study, patients were between 28 and 74 years of age. Adults may be less susceptible to cognitive deficits associated with THC use, and are more likely to have been exposed to some type of marijuana in the past than adolescents and young adults. Additionally, 59% of patients were taking products high in cannabidiol (CBD), which may play a role in the findings; however, this is purely speculative given the small sample size and further analysis of cannabinoid constituent profiling are forthcoming.[1]

It is also important to consider that natural endocannabinoid levels may decrease with age based on genetics, metabolism, and diet. Thus, younger patients may not need exogenous cannabinoids to balance their endocannabinoid system as much as older patients..

Additionally, the conflicting findings may result from the improved quality of product used in the medical marijuana study. Patients reported frequency and magnitude of use on a monthly basis. This might have prevented inadvertent use of high levels of product that possibly resulted in cognitive deficits similar to recreational use. Additionally, given that there was a 3-month follow-up assessment, patients may have been more likely to take the product as advised knowing that they would be asked to answer questions about their use at follow-up.

Thus, use of a well-controlled marijuana regimen to treat anxiety, sleep, or stress in adolescents and young adults, in combination with constant health care provider monitoring, may have different results on cognitive function than what has been found in previous trials using unregulated recreational marijuana in the same age group.

The Role of Agriculture in Product Quality

Importantly, *medical marijuana* is a generalized term and the specific mechanism of action behind each cannabinoid involved in this therapy is often overlooked. In the CBD world, broad-spectrum, zero-THC products are popular. However, it is important to consider the potential ramifications of extractions that alter the ratio of CBD to THC. Removing THC, for example, removes other cannabinoids as well. This extra processing can alter the most natural composition of the plant and its extracted cannabinoids, which can diminish the sought-after "entourage effect."[9]

It is also important to consider that the foundation of product quality is agriculture. If we can grasp the science behind the

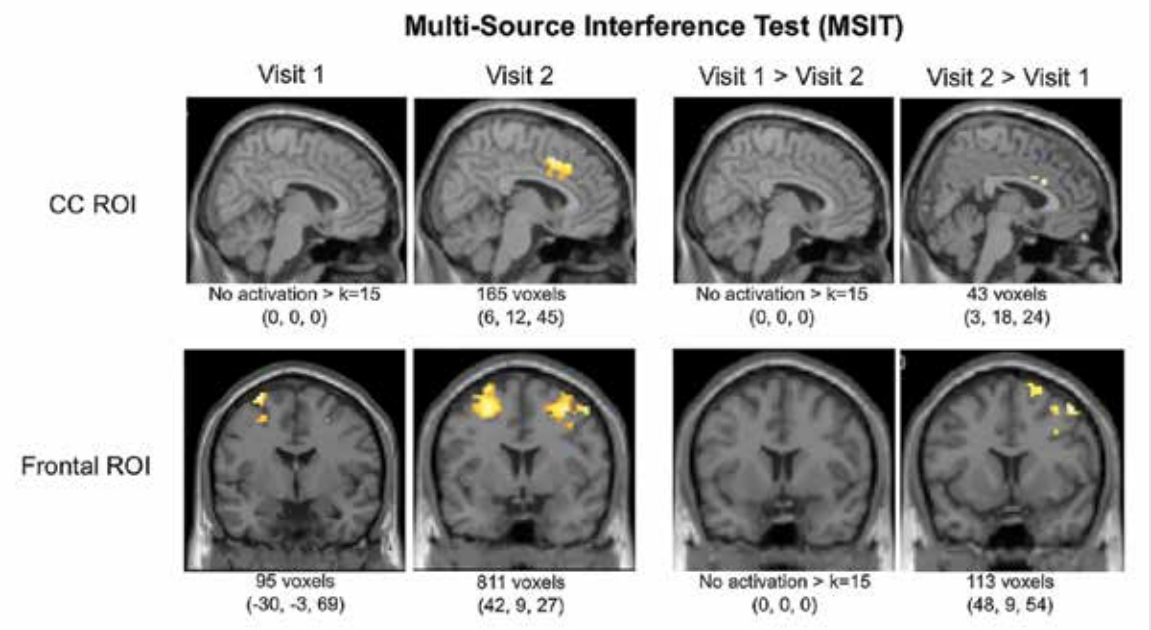

Figure. Functional magnetic resonance imaging (fMRI) activation in cingulate cortex (CC) and frontal regions of interest (ROIs) during the MSIT (Interference-Control).

Local maxima and total k (voxels activated within ROIs per contrast) are displayed below images.

Image credit: Gruber et al. *Front Pharmacol.* 2018;8:983.[1]

phytocannabinoids that are produced by the best organic agriculture, including but not limited to THC and CBD, we will be able to formulate and identify more therapeutic uses and the potential of these cannabis-based products.

As more research emerges to support various indications of medical marijuana and CBD, it becomes even more important to determine the role of agriculture in product efficacy. Studies that tie the science of agriculture with the efficacy of cannabis found in clinical trials will provide much needed clarity.

CBD vs THC: Which Improves Cognitive Function?

It is unclear what component of cannabis is responsible for the cognitive benefits found in this study. Interestingly, the study authors point to research on recreational marijuana use showing an association between high THC levels and poorer cognitive performance.[9,10] Other studies have shown that administration of CBD before THC may decrease cognitive deficits.[6,11]

What is known is that cognitive function relates to the brain, and the brain is heavily concentrated with cannabinoid-1 (CB_1) receptors, which THC has a high affinity for[12] and CBD actually has a lower affinity for CB_1 and CB_2 receptors.[13] CBD also modulates different receptors outside of the endocannabinoid system (eg, serotonin receptors).[14] Thus, because there is heavy concentration of CB_1 receptors in the brain and THC has a high affinity toward those CB_1 receptors, THC may be responsible, along with CBD, for the neurologic benefits of cannabis as research is developed on Alzheimer's disease, Parkinson's disease, and Lennox-Gastaut and Dravet syndromes.[15,16]

Decreased Opioid and Benzodiazepine Use Found

Patients in the Gruber et al. study reported a 48% reduction in opioid use and a 47% reduction in benzodiazepine use at 3 months. Additionally, a 22% reduction in antidepressant use and a 29% reduction in mood stabilizer use was reported.

There are 2 theoretical reasons why medical marijuana is linked to reduced opioid use. The first is that cannabinoids in medical marijuana with an affinity toward CB_1 can be an option for pain relief.[17] The second is that medical marijuana may have a similar therapeutic effect as opioids by affecting CB_1 receptors located in the same area of the brain where opioid receptors are located.[18] Lastly, medical cannabis may decrease the rewarding properties of opioids or decrease opioid craving or withdrawal signs.[19] Working together, cannabis and opioids may have a more powerful, relaxing, and pain-relieving effect than use of either agent alone. The clinical implications of these findings are that use of medical marijuana may give patients and clinicians more confidence in tapering opioid doses.

This study had a number of limitations. First, the study was limited by its small patient population (N=22). Second, more detail on the cannabis products and formulations used in the study is needed to determine which phytocannabinoids are attributed to the improvements in cognitive function.

Third, the study lacked a placebo arm. Ideally, a 3-armed study that randomized patients to placebo, recreational marijuana, or medical marijuana with a clear description of dosing regimen and the phytocannabinoid profiles of all products would be useful.

Conclusion

This is an exciting time for medical marijuana. Studies such as the present one by Gruber et al. will continue to strengthen the message that there is therapeutic value behind medical marijuana.

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Updates on the Pharmacokinetics and Pharmacodynamics of Cannabis

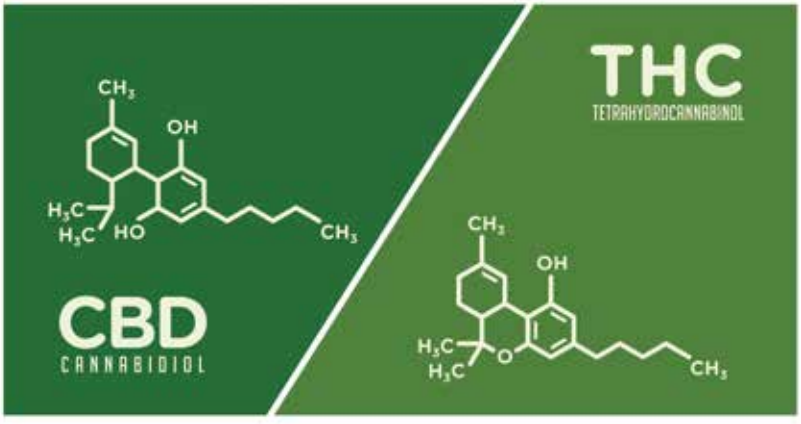
A Q&A with Linda E. Klumpers, PhD

Linda E. Klumpers, PhD

Research is rapidly emerging on the effects and metabolism of delta-9-tetrahydrocannabinol (THC), as well as the individual and combined pharmacokinetics and pharmacodynamics of cannabinoids and terpenes. To update readers on this topic, *American Journal of Endocannabinoid Medicine* spoke with Linda E. Klumpers, PhD, who is Founder and Director at Tomori Pharmacology Inc, and a consultant at Verdient Science, LLC, in Denver, Colorado.

AJEM: What should *AJEM* readers know about potential drug–drug interactions with cannabis use?

Dr. Klumpers: Cannabinoids are metabolized by enzymatic systems in the body, including the cytochrome P450 (CYP) system where pharmacokinetic drug–drug and food–drug interactions typically occur. Physicians should be aware of potentially dangerous interactions between cannabis and pharmacotherapy that induces or inhibits the CYP system, and especially in patients taking polypharmacy. For example, cannabis use may increase plasma concentrations of warfarin and, therefore, increase the risk for bleeding.[1]



In addition to anticoagulants, a number of other agents may interact with cannabis, including antiplatelet agents, clobazam, valproate, diazepam, phenytoin, and bupropion.[1-3] These potential interactions illustrate the need for physicians to oversee cannabis use in the context of health care in general.

AJEM readers can use the Cannify tool (http://cannify.us), which includes an extensive list of drugs that can cause potential drug–drug interactions with cannabis, as well a list of scientific literature that physicians can refer to for more information.

AJEM: What are the most exciting recent discoveries about cannabis and the endocannabinoid system?

Dr. Klumpers: Many of the therapeutic properties of the cannabis plant have been known since ancient history. Recent discoveries include refinement of what was previously known, and additional mechanistic understanding.

For example, we now understand more about the various elements of the endocannabinoid system, as well as potential modification by mainly synthetic compounds. Although research has led to many disappointing results—eg, the failed studies of synthetic inhibitors of a breakdown enzyme of endocannabinoids called fatty acid amide hydrolase (FAAH) to relieve pain—there are exciting new areas that include (endo)cannabinoid transporters.[4]

These transporters are needed to move hydrophilic compounds through fatty environments, as well as to transport lipophilic compounds through watery environments, such as cannabinoids through the blood or through the interior of a cell. Furthermore, there are theories about potential pathologies associated with a naturally occurring endocannabinoid "tone" disorder, including that patients with low levels of endocannabinoids might need exogenous cannabinoid supplements to treat their symptoms.[5] This theory can be compared with the effects for which monoamine oxidase inhibitors are used to manipulate amines such as serotonin and dopamine. More research in this area is needed.

> "Cannabis may have the added variability of inconsistency of the plant product. Physicians should be aware of the need for long-term availability of products for patients who respond to a particular variety of medicinal cannabis."
> —*Linda E. Klumpers, PhD*

Personally, I am excited to better understand how the widespread endocannabinoid system interacts with other physiologic systems in the human body, as well as the predictability of effects in patients. The latter aspect is a passion of mine, and I am working on better understanding the predictability of cannabis efficacy by analyzing survey data with Cannify, as well as working on clinical studies that aim to give us more answers.

AJEM: What are the key clinical pearls regarding the pharmacokinetics and pharmacodynamics of cannabis that clinicians should know?

Dr. Klumpers: In addition to drug–drug interactions, clinicians should understand issues surrounding the route of administration of cannabis. In Western medicine, cannabis has more recently

been administered by inhalation. For patients and clinicians who prefer different administration methods (eg, oral, patch, cream, suppository), it is important to understand the impact of different formulations on the onset and the duration of efficacy, as well as potency.

For example, oral cannabis administration is more likely to cause systemic effects than a cannabis patch. In fact, no peer-reviewed study to date has demonstrated systemic absorption by a patch. Additionally, THC is metabolized into a few metabolites, one of which is 11-hydroxy-THC (11-OH-THC), which may have more potent psychoactive effects than THC. The first-pass metabolism that occurs with oral administration is likely why oral THC is associated with greater psychotropic effects than the same dose of THC administered by inhalation (smoking or vaporizing).[7,8]

Additionally, cannabis can have both beneficial therapeutic effects as well as negative side effects.[7] Awareness of the individualized responses or sensitivities to cannabis should be taken into consideration in the risk–benefit assessment for each patient, as well as when adjusting pharmacotherapy based on treatment response.

> "Terpenes are interesting molecules because they are able to influence the way that other molecules such as cannabinoids behave in the body. On a broader level, terpenes might be able to improve the bioavailability of drugs."
>
> *—Linda E. Klumpers, PhD*

AJEM: Can you explain the entourage effect of cannabis and how it applies to clinical practice?

Dr. Klumpers: When we discuss the clinical implications of the *entourage effect*, we should first agree on the definition of the term. In the late 1990s, the entourage effect was proposed when researchers discovered that endogenous cannabinoids in combination have an effect that is greater than the sum of the individual effects of each cannabinoid.[6] The interpretation of the entourage effect has changed over time and now is used by the general public to describe the interaction among phytocannabinoids, terpenes, and other constitutes of the cannabis plant that in totality produce a "more beneficial" effect than taking the individual components alone.[9]

However, there is no scientific proof for this theory. The few studies on this matter contradict each other and are inconclusive. The claims that are generally made on effects by cannabis terpenes are generally based on animal studies, whereby the dosages are incomparable (eg, sometimes in the mg/kg range) to the terpene quantities in cannabis.[10] In reality, cannabis contains around 2% terpenes, and terpenes may be lost through volatilization due to processing or extraction.[11,12] Thus, it is unknown how many of these terpenes actually end up in the body as these volatile compounds might have evaporated from a given product before ingestion.

In summary, although terpenes have shown promising effects in animals and have interesting mechanisms of action (eg, the terpene β-caryophyllene binds to CB_2 receptors to act as an agonist),[13] clinicians need to be aware of the many unknowns regarding the added value of these compounds, as well as their variability in the finished product as, to date, there are no validated methods to standardize the amount of the terpenes in cannabis flower.

Using the new interpretation of the entourage effect, there are many examples of cannabinoids interacting with each other to produce a specific effect. Cannabidiol (CBD) is known to decrease the anxiety-inducing effects of THC, as well as other (psychotropic) effects; however, it seems as if the symptom-relieving effects of THC are not affected by CBD. For example, nabiximols—which is approved outside of the United States for the treatment of spasticity due to multiple sclerosis—contains THC and CBD in a close to 1:1 ratio, exemplifying that the combination of these cannabinoids does not necessarily level out the pharmacotherapeutic effects of each agent.[14]

However, the outcomes of various studies examining the interaction effect between THC and CBD using different administration methods, formulae, dosages, and THC-to-CBD ratios are variable. I am currently part of a research group that is working to secure a grant to study the effects of various THC-to-CBD ratios in a structural manner. If the grant is awarded, the study will begin this year.

Physicians work with compound interactions every day, as pharmaceutical compounds can interact with each other in a variety of ways (eg, induction, inhibition, influencing absorption). However, because cannabis is a plant product, it can be hard to produce in a consistent way.

Some growers prefer to grow plants with different chemovars. This also means that a grower may not always be able to supply the same plant throughout the entire year or to keep the genetics of the plant consistent for decades. Manufacturers or dispensaries can run out of a particular plant product, which may have negative consequences for the patient.

Thus, in addition to the general variables in taking medications—including time of day, taken with or without food, types of foods eaten, and symptom severity—cannabis may have the added variability of inconsistency of the plant product. Physicians should be aware of the need for long-term availability of products for patients who respond to a particular variety of medicinal cannabis.

AJEM: How can terpenes help cannabinoids cross the blood–brain barrier? What impact might this effect have on clinical practice?

Dr. Klumpers: Terpenes are interesting molecules because they are able to influence the way that other molecules such as cannabinoids behave in the body. For example, there are terpenes that can change absorption and distribution by influencing permeability of the skin or the blood–brain barrier.[15,16] Thus, on a broader level, cannabis terpenes might be able to improve the bioavailability of drugs.

Thus far, the only studies showing a drug–drug interaction that increases the bioavailability of a traditional pharmacologic therapy is with antiepileptic drugs. For example, CBD increases plasma levels of clobazam and, in particular, produces a 3- to 6-fold increase in the active metabolite of clobazam *N*-desmethylclobazam.[17,18] As

▶ continued on page 50

Pharmacokinetics

continued from page 49

a result, doses of clobazam may need to be reduced in patients with epilepsy who are also using cannabis or CBD.[17,18]

More studies are needed to understand how this effect of cannabinoids and terpenes could be applied effectively to other pharmacotherapies. I am currently applying for grants to study potential drug–drug interaction of cannabinoids with pain medications that inhibit common CYP enzymes in patients with neuropathic pain.

An animal study has demonstrated that the metabolite 11-OH-THC is able to more easily penetrate the blood–brain barrier than THC.[19] Future research is needed to determine the role of cannabinoids in increasing delivery of medications to the brain.

AJEM: What are the most common myths regarding cannabis that you address with health professionals?

Dr. Klumpers: What is very interesting about the cannabinoid space, as opposed to compounds from any other physiologic system, is that there are a lot of emotions and opinion about cannabis that do not always reflect the scientific validity of what scientists have found in this space.

That is why it is important to give the scientist's view on what we know, but also what we don't know about cannabis, which was the goal of our recent paper in the *Journal of AOAC International*.[20]

> **"There are theories about potential pathologies associated with a naturally occurring endocannabinoid 'tone' disorder. This theory can be compared with the effects for which monoamine oxidase inhibitors are used to manipulate amines such as serotonin and dopamine. More research in this area is needed."**
>
> ***—Linda E. Klumpers, PhD***

One common misconception is that there are indica and sativa cultivars of cannabis that have different effects. There has been so much interbreeding that the distinction at this point in time is almost negligible.

Although CBD generally has few side effects, another misconception is that CBD products are safe: Various studies have shown that CBD products can be mislabeled or contain contaminants.[21] Mislabeling not only leads to under- or overdosing, but some products have even been found to contain significant amounts of the psychotropic THC. Finding trustworthy sources is very important when patients are considering the use of CBD products.

AJEM: Is there anything else you would like to tell our readers about this topic?

Dr. Klumpers: We need to take individual responsibility and be critical about cannabis research. The cannabis space has expanded into various dimensions, and not always for the better. Many product companies that advertise their "science" or "quality" do not care about these aspects at all. Cannabis education is widely available, loaded with "facts," but which of these sources can actually give you the references that they refer to and how many are accurate?

Additionally, which researchers and companies are receptive to critical feedback about their research or education? From my own experience, not many are receptive to questions regarding the accuracy of information. The key to exploring the cannabis field is to be critical and ask questions.

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The Use of Cannabis for Endometriosis Symptom Management

A commentary on Sinclair et al. Cannabis use, a self-management strategy among Australian women with endometriosis: Results from a national online survey. *J Obstet Gynaecol Can*. 2019; Nov 7 [Epub ahead of print].

By Stacia Woodcock, PharmD, Director of Education, International Research Center on Cannabis and Health, New York, New York

Endometriosis occurs when the lining of the uterus (the endometrium) grows outside of the uterine cavity in other areas of the body, most frequently involving the ovaries, fallopian tubes, and pelvic lining.[1] The primary symptoms of endometriosis are pelvic pain before and during menstruation (including painful urination and defecation), pain during sexual intercourse, nausea, fatigue, and infertility (Figure).[2] Treatment most commonly includes nonsteroidal anti-inflammatory drugs and oral contraceptive therapy, which have been shown to be most effective for only mild to moderate endometriosis symptoms.[3,4]

> "Continuing to classify cannabis in this manner undermines efforts to legitimize cannabis use as a clinical treatment option as opposed to a recreational lifestyle intervention."
> *--Stacia Woodcock, PharmD*

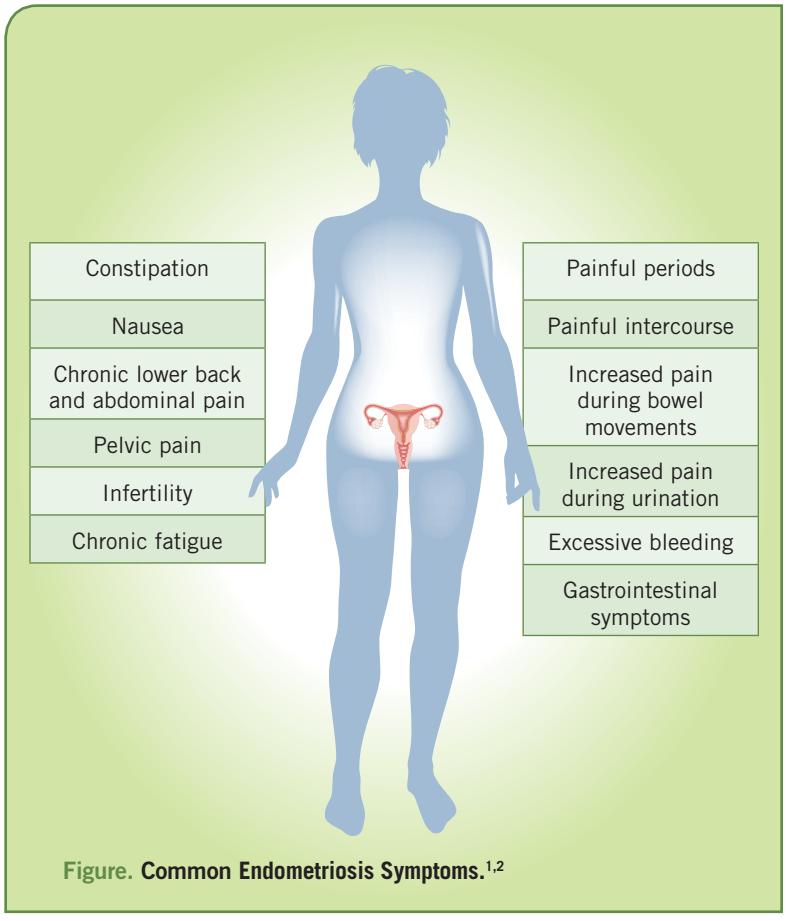

Figure. Common Endometriosis Symptoms.[1,2]

The high incidence of pain associated with endometriosis and the limited treatment options currently available make cannabis an attractive option for many women looking for symptom relief. This national survey of women with endometriosis in Australia provides an interesting insight into the use of cannabis for the self-management of endometriosis symptoms.[5]

Sinclair et al. conducted a 3-month online survey of Australian women (N=484; 18–45 years of age) with a surgically confirmed diagnosis of endometriosis to assess the use of self-management treatment modalities for endometriosis symptoms, including the use of cannabis. Among the 76% of women who reported using some form of self-management treatment for endometriosis, 13% reported using cannabis for symptom control.[5]

Study participants rated the effectiveness of cannabis for pain reduction as 7.6 on a 10-point scale, with 56% of patients also reporting a decrease in pharmaceutical treatment by at least 50%. In terms of pain relief, cannabis was found to be the most effective treatment modality, showing greater efficacy than other self-management interventions such as heat or dietary changes. The greatest alleviation of symptoms with cannabis use, secondary to pelvic pain, were seen in insomnia and nausea/vomiting. Adverse effects associated with cannabis were reported at 10% compared with higher rates seen in alcohol (52.8%), exercise (34.2%), yoga/Pilates or heat packs (15.9%).[5]

Limitations

This survey opens the door to some very interesting questions regarding both the use of cannabis medicinally as well as the way

▶ continued on page 52

Endometriosis
continued from page 51

cannabis is viewed as a treatment modality. The inclusion of cannabis in the survey as a "self-management tool" alongside lifestyle interventions, such as exercise or yoga, or recreational substances such as alcohol rather than as a pharmaceutical intervention is counterintuitive to the understanding of how cannabis works within the body. Continuing to classify cannabis in this manner undermines efforts to legitimize its use as a clinical treatment option rather than a recreational lifestyle intervention.

"Until further studies can investigate the role this plays in the progression of endometriosis, caution should be used with high-THC ratios of cannabis so as to prevent the possible exacerbation of disease."

--Stacia Woodcock, PharmD

Additionally, the survey limited participation to patients with a surgical diagnosis of endometriosis. This is significant in that endometriosis is historically challenging to diagnose, with estimated incidence of undiagnosed endometriosis at 11% of the population,[6] and time from presentation of symptoms to a definitive diagnosis averages 6 to 11 years for most patients.[7,8] This means there is likely a large population of undiagnosed patients self-managing endometrial symptoms, as the delayed diagnosis can result in significant deterioration in patient quality of life and disease progression.[9,10] The use of cannabis within this study population is likely much higher than the survey indicated, as patients with a surgical diagnosis are much more likely to have been given pharmaceutical interventions than those without a definitive diagnosis.

Cannabis use within the surveyed patients is very poorly defined, which presents another challenging factor in evaluating its effects.[5] The primary dosage form of cannabis used was inhalation via smoking, which is the shortest-acting dosage form available for cannabis administration and does not represent the ideal duration of action for symptom relief of a disease associated with chronic symptoms. Additionally, the amount of delta-9-tetrahydrocannabinol (THC) and cannabidiol present in the cannabis used by survey participants was not quantified, which also affects patient outcomes based on the variable pharmacology of different cannabinoid ratios within the body.

The reporting of tachycardia, drowsiness, and anxiety as the most common side effects of cannabis use indicates high THC cannabis as likely for the majority of patients, as these side effects are typically associated with increased levels of THC.[11] This presents an additional concern as THC activates GPR18 receptors, which have been associated with an increase in the migration of endometrial tissue when stimulated,[12] meaning that until further studies can investigate the role this plays in the progression of endometriosis, caution should be used with high THC ratios of cannabis so as to prevent the possible exacerbation of disease.

Finally, it is important to note that only 13% of surveyed patients who used self-management treatment options reported cannabis use.[5] Australia legalized medical cannabis in 2016, but did not include chronic pain as a qualifying symptom for treatment.[5] This means that physicians cannot recommend medical cannabis to patients with endometriosis through the existing legal program in Australia, which limits patient access to illicit market products that have not been tested and regulated. It also indicates a huge knowledge gap for both patients and health caer practitioners when it comes to the use of cannabis for the management of endometriosis symptoms.

Clinician Oversight Needed to Incorporate Medical Cannabis Into Endometriosis Treatment

In conclusion, the use of cannabis for endometriosis symptom management appears to be an effective alternative to traditional self-management treatment options, especially when it comes to decreasing pain, nausea, and insomnia. However, the lack of education and clinical studies surrounding the different cannabinoid ratios and their possible effect on endometrial tissue presents a challenge for patients and practitioners seeking to incorporate medical cannabis into endometriosis treatment in a safe and effective way. Patients are largely flying blind and potentially putting themselves at risk for worsened disease progression when they choose to use illicit cannabis for the self-management of their endometriosis symptoms.

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Dr. Woodcock *has no financial conflicts of interest to disclose.*

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Integrating Medical Cannabis Into Palliative Care

A commentary on Briscoe J, et al. Top ten tips palliative care clinicians should know about medical cannabis. *J Palliat Med.* 2019;22(3):319-325.

By Luba Andrus, RPh, Master of Jurisprudence in Health Law, Park Ridge, Illinois

As the silver tsunami approaches and palliative care experts prepare for the rise in older patients, cannabis is poised to play a larger role in end-of-life care. With a growing number of states recently enacting medical marijuana and adult-use cannabis legislation, many patients entering palliative care may already be using cannabis or may request use of cannabis for symptom management.

The review article by Briscoe et al. presents an excellent overview of current evidence on the benefits and risks of cannabis use in the palliative care population, as well as the unknowns.[1]

Barriers to Medical Cannabis

The authors begin the review by discussing the legal issues surrounding cannabis, which is a primary concern regarding cannabis expressed by health care providers.[2-5] It is important to know state law as a first step before integrating cannabis use in clinical practice.

Whether I am educating a hospital practice, fellows, or a concierge group, the first barrier to medical cannabis use always is legality. Physicians are reluctant to sign their name recommending medical cannabis because of its Schedule I designation.

Perhaps, the second most common barrier for physicians is lack of knowledge about efficacy, data, research, potency/dosage information, titration, allergic reactions, adverse drug reactions, and potential drug–drug interactions.[2,6,7] However, medical literature is available to guide decisions on each of these topics.

In the palliative care setting, as well as in long-term care facilities and hospitals, providers are concerned about policy, storage, diversion, delivery systems, and cannabis disposal.[8] Additionally, in sick populations receiving palliative care, it is important to consider the impact of cannabis use on blood sugar in patients with diabetes and on blood pressure in patients with hypertension. Antidiabetic agents and antihypertensives may need to be re-dosed in patients initiating cannabis. Increased monitoring is recommended in these cases.

Benefits of Cannabis in Palliative Care

I have seen a number of advantages of cannabis use in patients with cancer in the palliative care setting. From personal experience these benefits seem to include reduced side effects of chemotherapy (eg, vomiting and pain), reduced need to increase chemotherapy dosing, improvements in physical/mental stress, as well as reduced anxiety or stress levels, particularly before chemotherapy sessions.[9-12] For example, a patient scheduled for chemotherapy on Friday may begin to feel anxious on Tuesday or Wednesday in anticipation of the side effects of treatment. Thus, by lessening this anxiety, cannabis use can change a patient's approach to the disease.

In addition to chemotherapy-induced nausea and vomiting, evidence also supports efficacy of cannabis use in neuropathic pain and anorexia associated with AIDS, according to Briscoe et al.[1] More research is needed on the efficacy of cannabis in the treatment of psychological conditions (such as anxiety and depression) and cancer-associated cachexia and anorexia. Clinically focused research in these areas could make medical cannabis products more reliable and predictable when used in the palliative care setting.

Importantly, cannabis patches and suppositories are available and may be a beneficial form of administration in the palliative care setting, particularly when used in cancer patients for pain management. For example, properly formulated suppositories bypass the first round of metabolism in the liver, helping to avoid potential drug–drug interactions, and exert systemic effects when entering the rectal mucosa. The result is greater bioavailability compared with oral administration as healing compounds spread quickly through nearby organs and into the bloodstream.[13] Additionally, suppositories that are formulated properly could be an effective way of potentially bypassing the "head high" psychoactive effects of delta-9-tetrahydrocannabinol (THC).

Policy Considerations at Long-Term Care Facilities

Patients whose symptoms are stable on cannabis and are receiving palliative care in the home setting, may have issues continuing their treatment when entering a long-term care facility or hospital that does not have a cannabis policy. Even if a physician at an inpatient facility is pro-cannabis, nurses may not want to sign off on dispensing cannabis because it is a Schedule I agent.[1]

Thus, it is important to find a palliative care group in which the entire care team has received training and education on cannabis and its uses, as well as the legal status of various products. All members of the interdisciplinary team must be educated on cannabis,

including the side effects, dosing, and delivery systems. Caregivers also play an important role in obtaining cannabis for the patient, as well as keeping a diary documenting which cannabis varieties and products were or were not effective, route of administration, and doses given to better individualize treatment decisions.

Palliative care providers seeking to integrate cannabis use into practice should work with their legal department to establish a written policy regarding cannabis use that includes information regarding storage, tracking, dispensing, and discarding of cannabis to prevent diversion. Also, facilities need to consider finding a cannabis-friendly hospital that also has a cannabis policy in case patients require a hospital transfer.

"Cannabis patches and suppositories are available and may be a beneficial form of administration in the palliative care setting, particularly when used in cancer patients for pain management."

—Luba Andrus, RPh, MJ

I ran into policy issues when conducting a small study on medical cannabis use at a memory care unit, where nurses initially refused to give cannabis to the patients. Fortunately, the director of nursing took full responsibility of the cannabis product at the facility, and kept the product locked in her office. Policy and procedure regarding cannabis use was written for staff, and cannabis products were given to patients by the director of nursing and nurses who volunteered to be a part of the study. The product could not be kept in a medication cart or in the patients' rooms freely.

Conclusion

The review article by Briscoe and colleagues presents a concise overview of medical cannabis as part of symptom-directed treatment regimens in the palliative care setting. Limitations of the review include a lack of information on the effects of cannabis on the cytochrome P450 system and avoiding drug–drug interactions in patients taking cannabis. While a recent review of drug–drug interactions was published by Cox et al, it may lack actionable information for many health care professionals.[14] Additionally, the review does not present information on cannabis patches or suppositories as alternative routes of administration in the palliative care population.

HELPFUL TIPS

Tips on Cannabis Use in Palliative Care[1]

1. Check with local laws and regulations regarding medical cannabis
2. Ask about cannabis use when conducting a comprehensive pain assessment
3. Medical cannabis may be useful to treat
   - Neuropathic pain
   - Chemotherapy-induced nausea and vomiting
   - Anorexia associated with AIDS
4. Evidence on cannabis use is limited and/or varied for
   - Psychiatric conditions
   - Cancer-associated cachexia and anorexia
5. Smoking medical cannabis is not linked to lung cancer or chronic lung disease risk, but may have side effects
6. Evidence supporting use of cannabis for treating seizures is growing, particularly in pediatric epilepsy
7. Driving under the influence of cannabis is linked to increased risk for motor vehicle collisions
   - Whether this risk extends to medical cannabis is unclear
   - Check state laws on what legally constitutes impairment (eg, presence of THC or THC metabolite)
   - It is unclear how long to wait to drive after taking medical cannabis; a period of at least several hours may be warranted

Source: Briscoe J, et al. *J Palliat Med.* 2019;22(3):319-325.

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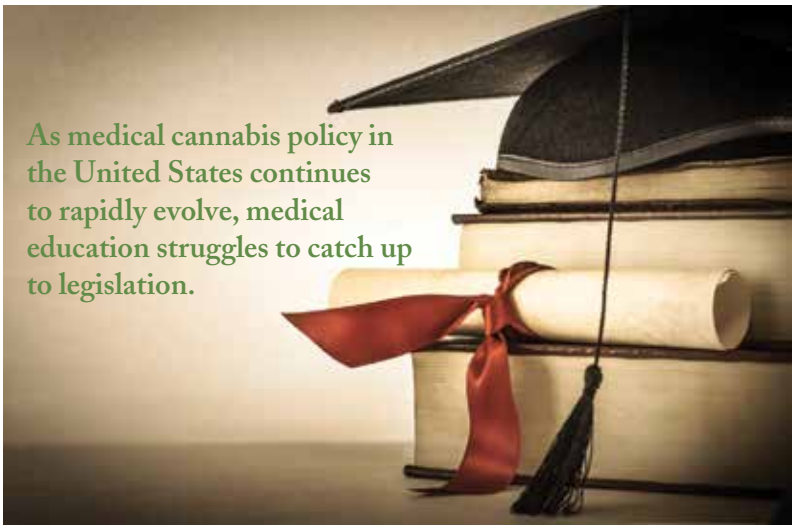
Luba Andrus RPh, MJ, *declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings.*

Cannabis Curricula: Two Universities Pave the Way in Graduate-Level Education

As medical cannabis policy in the United States continues to rapidly evolve, medical education struggles to catch up to legislation. To address these disparities, 2 universities are leading the way in developing graduate-level programs on medical cannabis.



University of Maryland School of Pharmacy

The University of Maryland School of Pharmacy in Baltimore launched the first 2-year graduate-level program on medical cannabis in the United States. The 2019–2020 inaugural class was initially set at 50 students, but after receiving more than 500 applications, the university increased the class size to 150.

The Master of Science in Medical Cannabis Science and Therapeutics program is ultimately designed to improve patient care, Program Director Leah Sera, PharmD, MA, BCPS, told the *American Journal of Endocannabinoid Medicine*.

"The comprehensive education we provide in this program will prepare students to improve patient care both directly (for those working in clinical environments) and indirectly (for those interested in research or policy development)," said Dr. Sera, who is an Assistant Professor at the university.

"We anticipate that our graduates will be able to leapfrog over entry-level positions in the industry, and we also expect that our students will be trailblazers in creating new positions in the medical cannabis field, including clinical practice, research and development, regulatory affairs, and patient advocacy," Dr. Sera added.

Students enrolling in the program have a variety of different academic and professional backgrounds, including science, health care, law, and public health. "Approximately half of the students have a background in science or medicine—we have pharmacists, physicians, and nurses in the program. Other students come to us with a background in law, public health, communications, business, education, and other fields."

The graduate program primarily involves online instruction with in-person symposia held once per semester. The curriculum includes a variety of core courses and electives (see Table). Instead of a thesis, students complete a capstone course that features a selection of expert seminars, case studies, and discussions. Dr. Sera noted that the program will be accepting another 150 students for the Fall 2020 semester.

Table. Curriculum for the Master's Program in Medical Cannabis at the University of Maryland School of Pharmacy

Core courses	Introduction to Medical Cannabis History, Culture, and Policy
	Principles of Drug Action and Cannabinoid Pharmacology
	Basic Cannabinoid Chemistry and Drug Delivery
	The Clinical Effects of Medical Cannabis
	Negative Physical, Psychiatric, and Social Effects of Cannabis
	Research Design and Medical Cannabis
	Expert Seminars and Case Studies
Electives	Advanced Cannabis Therapeutics I
	Advanced Cannabis Therapeutics II
	Cannabis Genomics and Pharmacognosy
	Advanced Cannabinoid Chemistry and Analytic Testing Methodology
	State and Federal Cannabis Laws and Policies

Thomas Jefferson University

The Institute of Emerging Health Professions at Thomas Jefferson University in Philadelphia now offers 3 graduate-level certificates in cannabis education for health care and industry professionals:

1. Cannabis Medicine: This program is designed for clinicians seeking to incorporate medicinal cannabis into their practices and will cover pharmacologic and pathologic concepts as well as evidence-based research on disease states for which cannabinoids have demonstrated efficacy as an adjunct or replacement for conventional therapies
2. Cannabinoid Pharmacology Certificate: Targeting scientists and researchers, this program explores the mechanisms of drug action, and pharmacokinetics of cannabis and cannabinoids
3. Cannabinoid Chemistry and Toxicology: Geared toward those working in and regulating the legal cannabis industry and scientists,

this program provides students with an understanding of cannabis botany and propagation, products and biological samples, and principles of quality control for cannabis-containing products

The Cannabis Medicine program is open to applicants with clinical degrees including physicians, nurses, physician assistants, and pharmacists. The other 2 programs are open to applicants with a Bachelor of Science degree. A nonmatriculation option is also available for students with a Bachelor degree in any area of study. The primarily online graduate certificates span 1 to 2 years in length and include four 3-credit courses focused on evidence-based medicine.

> "… Our students will be trailblazers in creating new positions in the medical cannabis field, including in clinical practice, research and development, regulatory affairs, and patient advocacy."
>
> *—Leah Sera, PharmD, MA, BCPS*

Certificate and CME Programs

Other universities are offering shorter certificate programs on medical cannabis. For example, the University of Vermont, in Burlington, offers a 7-week, online professional certificate in cannabis and medicine that includes education on cannabis history, business, law and policy, plant biology, biological effects on humans, production and safety, pharmacology, and clinical research. The program is designed for physicians, dispensary personnel, nurse practitioners, pharmacists, physician assistants, and regulators.

Clark University in Worcester, MA, launched the first Certificate in Regulatory Affairs for Cannabis Control in fall 2019. The online 3-course graduate-level certificate program details public policy issues related to the cultivation, distribution, sales, and regulation of adult-use and medicinal cannabis.

Additionally, private education companies—such as Cannabis Career Institute, Cannabis Training Institute, Oaksterdam University, and The Medical Cannabis Institute—offer online continuing medical education programs on cannabis medicine for health care providers.[1]

Agriculture and Law

Because the field of medical cannabis closely intersects with agriculture and law, several universities are responding by creating educational programs in these areas. The University of Washington School of Medicine and The University of Southern Illinois are offering graduate-level programs on cannabis agriculture, while the University of Denver Sturm College of Law, The Ohio State University Moritz College of Law, and Vanderbilt University offer law and policy cannabis education programs.[1]

American Journal of Endocannabinoid Medicine will keep readers informed as more universities and institutes develop new programs to fill educational gaps in cannabis medicine.

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February 2020

Cannabis by the Numbers

Percent of prescribing clinicians interested in receiving more **formal training related to cannabis** for the treatment of anxiety and PTSD[1]

89%

Percent decrease in **opioid use disorder-related hospitalizations** associated with implementation of medical marijuana policy[2]

23%

Percent decrease in **opioid overdose-related hospitalizations** associated with implementation of medical marijuana policy[2]

13%

Percent decrease in opioid prescriptions by the 5 largest physician specialties since the passage of medical cannabis laws[3]

2%

Number of controlled clinical trials on cannabis and cannabinoids across 10 pathologies published between 1975 and 2005[4]

72

Number of randomized, blinded, placebo-controlled studies of cannabis and cannabinoids published between 2010 and 2014[5]

32

Percent decrease in opioid prescriptions by the 5 largest physician specialties since the passage of recreational cannabis laws[3]

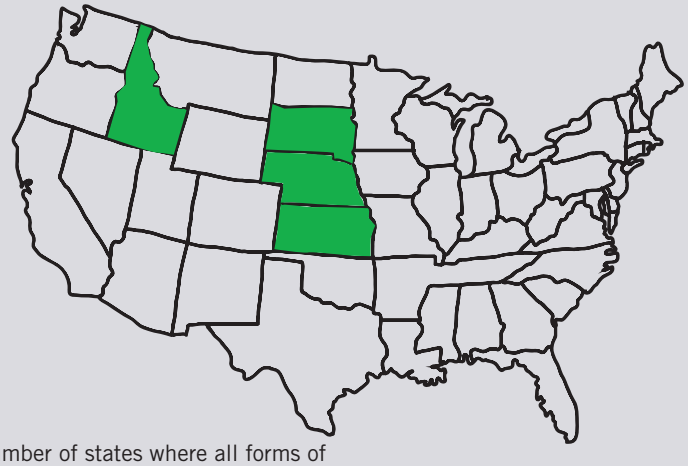
10.6%

Percent decrease in opioid prescriptions among highest prescriber specialties since the passage of medical cannabis laws[3]

6.9%

Percent decrease in opioid prescriptions among highest opioid prescriber specialties since the passage of recreational cannabis laws[3]

28.3%



Number of states where all forms of cannabis, including CBD, are illegal[7]

4

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