"Experience without memory is useless." —Martha Gellhorn

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Benefit too obvious to deny:

U.S. weighs rescheduling a molecule as CBD-rich cannabis proves helpful to children with epilepsy and others

By Fred Gardner

In August 2013, the widely respected neurosurgeon Sanjay Gupta, MD, documented on television the dramatic seizure relief that CBD-dominant cannabis oil was affording a little girl with Dravet Syndrome, a very severe form of epilepsy. Her name was Charlotte Figi.

In the two years that followed, reports from physicians treating pediatric epilepsy patients in various contexts —including "expanded access" programs authorized by the U.S. Food and Drug Administration— have confirmed that CBD is an effective anti-convulsant.

Bonni Goldstein, MD, in California and Margaret Gedde, MD, in Colorado have each monitored the progress of hundreds of pediatric epilepsy patients. *(See stories on pages 7 and 33.)* More than 600 patients have been treated in FDA-sanctioned programs using GW Pharmaceuticals' Epidiolex, a plant extract that is 99% CBD.

Slightly more than half the children using CBD-rich oil are having significantly fewer and less-severe seizures. Personalities and abilities emerge as children wean off debilitating synthetic anti-convulsants. The side effects of CBD are generally mild; drowsiness is foremost.

Why CBD-rich oil works for some patients but not for others is being pursued by researchers.

For a fortunate five to 10 percent of patients, CBD-rich oil eliminates seizures entirely. For an approximately equal number, it doesn't help at all, or exacerbates symptoms.

Why CBD-rich oil works for some patients but not for others is being pursued by researchers. In most pediatric epilepsy cases the conditions are caused by genetic mutations. Some but not all gene-based epilepsies are amenable to treatment with CBD, and some are proving amenable to treatment with CBD plus THC and other cannabinoids.

Doctors and patients are tracking which cannabinoid-terpenoid blends are most effective in treating various conditions.

Paige Figi's daughter Charlotte experienced dramatic seizure reduction after being given CBD-rich cannabis. Fifteen states have adopted bills legalizing CBD for medical use. Figi is lobbying Congress in support of a bill that would remove CBD from Schedule I, the category for dangerous drugs with no known medical use.

Diverse Sources of Cannabidiol

Sanjay Gupta, MD, interviewed Geoffrey Guy, MD, at a facility in England where Guy's GW Pharmaceuticals grows CBD-rich *Cannabis* plants and makes extracts for medical use. Epidiolex, a GW extract that is 99% CBD, is being given to children with severe epilepsy at research centers in the U.S. Graphic: CNN

"Mom-and-pop growers" in Nevada County, California, organized a plant giveaway featuring CBD strains ACDC, Harlequin, Medi-Haze and Cannatonic. Oil made from CBD-rich plants is distributed by dispensaries that are legal under state law. Physicians are monitoring the progress of pediatric epilepsy patients using CBD-rich oil.

Cannabis oil is made by treating harvested plants with a solvent that extracts beneficial compounds and leaves behind the cellulose. Like Charlotte Figi, many people who use CBD need large, sustained doses to deal with serious illness. The most efficient delivery vehicle is a cannabis extract —for example, 50 milligrams of CBD in a milliliter of olive or coconut oil— in droppers or tubes. Cannabis oil can be diluted to facilitate measured dosing.

Lower doses of CBD can be delivered in sprays for under-the-tongue application. Few patients who use cannabis in treating epilepsy smoke or inhale vapor from CBD-rich flowers, although some report that inhalation after a seizure can reduce the duration of a headache.

Inhaled cannabis goes through the lungs to the brain and exerts its effects almost immediately, but the effects tend to wear off within an hour. Ingested orally, the compounds in cannabis pass through the stomach and the liver on the way to the brain. They get metabolized into slightly different compounds whose effects may take close to an hour to come on, but can last eight or nine hours.

CBD counters the mood-altering effects of THC, but as a component of the *Cannabis* plant, it is defined by the U.S. government as harmful and without medical use, and it remains on Schedule I of the federal Controlled Substances Act. There is an obvious gap between federal law and reality. It can be fully closed by rescheduling or descheduling the plant, and partially closed by singling out cannabidiol for descheduling.

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For a slimmer waistline?

THCV plants being grown for medical use in California; Cannabinoid may counter metabolic-syndrome symptoms

By O'S News Service

Cannabis varieties containing unusually high amounts of THCV —tetrahydrocannabivarin— will become available to medical users in 2016, thanks to kind fate and propagators who chose not to hoard their unusual bounty.

The difference between THCV and THC is slight at the molecular level *(two fewer carbon atoms in the "tail" —see illustration on page 21)*, but susbtantial in terms of how they work and their impact on the body.

GW Pharmaceuticals began investigating THCV more than a decade ago in hopes that it could be useful in treating metabolic syndrome. The disorder is actually a set of symptoms —high blood pressure, increased abdominal fat, elevated blood sugar, and unhealthy cholesterol levels— that are associated with obesity, type II diabetes and heart disease.

Roger Pertwee and colleagues at the University of Aberdeen reported in 2005 that THCV blocked anandamide (the molecule made by our bodies that activates the CB1 receptor) while allowing THC to act almost unimpeded at CB1. John McPartland commented on Pertwee's finding: "It's as if cannabis was designed as a combination remedy that simultaneously gave our endogenous mechanism a rest (shutting down anandamide), and supplemented with an exogenous remedy (THC)."

Also in 2005 the pharmaceutical giant Sanofi-Aventis had begun marketing a drug called Rimonabant —which works by fully blocking the CB1 receptor— as a treatment for metabolic syndrome. The first-ever mention of the endocannabinoid system in the *Journal of the American Medical Association* was a paper entitled "Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients: RIO-North America: A Randomized Controlled Trial," published in February 2006 —about 14 years after the components of the system had been identified.

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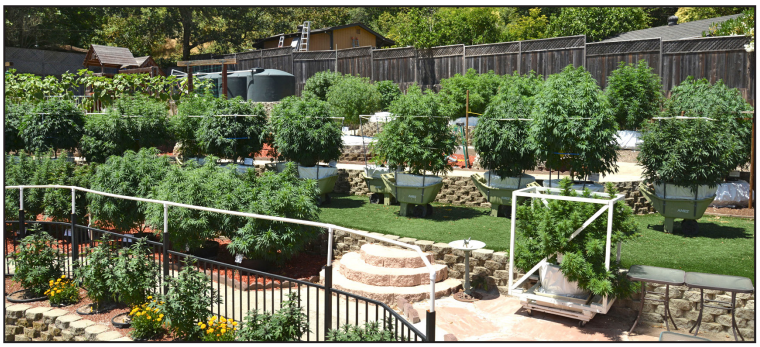

'Black Beauty' plants high in THCV were grown in western Marin County, California, in the summer of 2015. Elevated pots enable "wicking" of water (with fertilizer).

Commentary

Adding Cannabis to the Curriculum

Without fanfare, Temple University School of Medicine introduced cannabis to the curriculum in 2011. All it took was a faculty member —Ronald Tuma, PhD, a professor of physiology— proposing to add a one-hour lecture on the endocannabinoid system to the material he taught first-year medical students as part of "Block 3."

Temple organizes the curriculum into "blocks" according to body or organ systems. Classes are led by faculty from various departments. The blocks replaced the traditional set of courses administered by separate academic departments. Perhaps the "integrated curriculum," adopted by Temple a decade ago, made it easier for the endocannabinoid system —which is involved in almost every physiological process in the body— to find a niche.

Temple's Block 3 —"Body Systems 1"— provides "the fundamental facts and concepts necessary to understand the microscopic structure, embryological development and function of the cardiovascular system, the pulmonary system, the gastrointestinal system, and the kidneys."

When Tuma told Block 3 Director James Heckman, PhD, that he intended to devote a lecture to the endocannabinoid system. Heckman, who is also a physiology professor, approved unhesitatingly.

Tuma says the endocannabinoid lecture is "always very well received" by the more than 200 first-year medical students who attend it each year.

Ronald Tuma, PhD

Tuma does not consider himself the Jackie Robinson of medical education. "It was something I wanted to do and it was time," he says matter-of-factly.

Temple University School of Medicine has long been supportive of cannabinoid research, with labs run by Mary Abood and Sara Jane Ward doing cutting-edge studies. Jahan Marcu worked in Abood's lab en route to geitting his PhD, then as a postdoc.

Tuma's lab, according to the med school website, is investigating "inflammatory reactions that contribute to central nervous system injury following stroke, trauma, and autoimmune disease, and how modulation of the activity of specific cannabinoid receptors influences the progress of these diseases."

Tuma and colleagues at Temple were "first to demonstrate that modulation of the activation of cannabinoid 2 receptors has a significant impact on the development of a model of multiple sclerosis, as well as on the magnitude of damage in mouse models of stroke and spinal cord injury."

Unfortunately, Temple University School of Medicine —and McGill in Montreal, where pain specialist Mark Ware, MD, started teaching a class on the endocannabinoid system five years ago— are the exceptions that prove the rule. Virtually all med school graduates enter practice with no understanding of how cannabis works as medicine. They are unprepared to treat cannabis-using patients and know nothing about a treatment option that could help cannabis-naive patients. They may miss out on research opportunities over the course of their careers.

We suspect that some of the very doctors and scientists who until now ignored or disrespected Cannabinoid Medicine, will be teaching courses about it —or shaping their content

We expect a surge of medical schools adding introductions to the endocannabinoid system in the next few years. Whereas professors Tuma and Ware have real experience and expertise, we suspect that some of the very doctors and scientists who until now ignored or disrespected Cannabinoid Medicine, will be teaching courses about it —or shaping their content. Count on them to instill disinformation such as "9% percent of all longterm users become addicted."

Continuing Medical Education

Licensed physicians and nurses are required by state licensing boards to take a certain number of Continuing Medical Education courses annually to stay abreast of advances.

CME courses introducing doctors and nurses to cannabinoid medicine have been slowly proliferating. The Canadian Consortium for the Investigation of Can-

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WB O'Shaughnessy "at the bench."

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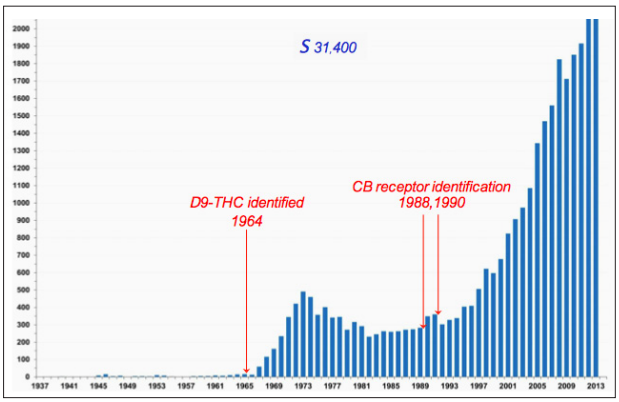
Fifty years of intensifying research



Graph prepared from PubMed data by Istvan Ujvary shows that peer-reviewed studies on cannabis and cannabinoids have accelerated dramatically since 1964, when Y. Gaoni and Raphael Mechoulam notified the *Journal of the American Chemical Society* that they had worked out the chemical structure of delta-9 tetrahydrocannabinol and cannabidiol —THC and CBD, the principal compounds in hashish.

Is Cannabis-Based Medicine a viable —and valid— specialty?

A spectre is haunting California physicians who have been practicing Cannabis-based Medicine: the likelihood of "legalization" in 2016. The economic viability of their specialty may depend on how the new law is worded.

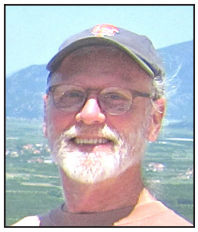
If legalization involves a steep tax on cannabis sold for recreational use, many people will continue visiting MDs to confirm that their use is medical. This is the situation in Colorado, where a doctor's authorization letter effectively confers a 25% price break from dispensaries, and cannabis-oriented medical practices are flourishing.

But what if the tax is not steep enough to induce cannabis users to get a doctor's approval? How many people using the herb to treat common conditions such as pain, depression and anxiety will feel the need to seek annual renewals?

We asked Jeffrey Hergenrather, MD, the president of the Society of Cannabis Clinicians (SCC), how he sees the future of the specialty.

Hergenrather's office is in Sebastopol, California, a small city some 60 miles north of San Francisco. His examinations are thorough —each new patient gets an hour and a half— and his expertise is exceptional. Hergenrather, 67, was in Emergency Medicine for 26 years and has never been in any kind of trouble with the medical board. He charges $250 for the initial visit, $120 for recheck visits.

Off the top, he estimates, "Fifty to 90 percent of my patients would not seek renewals if the legal and economic incentives were removed.



Jeffrey Hergenrather, MD

"The need for many patients to have a cannabis consultation is greater than ever."

"At the same time," he went on, "the need for many patients to have a cannabis consultation is greater than ever. Patients are presenting with cancers and a whole range of serious illnesses for which cannabis is capable of providing relief, but they need guidance in using it —how to optimize their treatment plan. They need doctors who stay informed about cannabis and cannabinoids and can share evidence-based information about strains, dosage, frequency of administration, methods of administration, and so forth."

Cannabis specialists also have an important role to play, Hergenrather says, countering "the constant stream of misinformation from the federal government" by collecting data conscientiously and publicizing their findings.

Hergenrather was a founding member of the SCC, which was launched 1999 by Tod Mikuriya, MD, the Berkeley-based psychiatrist who drafted the first sentence of the Compassionate Use Act of 1996 (Prop 215), allowing doctors to approve cannabis use by patients for "any... condition for which marijuana provides relief." Today the group has some 200 members nationwide.

"'Cannabis Clinician' is a valid specialty," Hergenrather asserts. "It doesn't fit in with the conventional categories such as Oncologist, Neurologist, Dermatologist, Rheumatologist, Gastroenterologist, Endocrinologist, Pediatrician, and so forth. It is a unique specialty that cuts across all the conventional divisions by virtue of the catholic nature of the endocannabinoid system. In the words of a recent paper by NIH researchers Pal Pacher and George Kunos, 'modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans.'

"Genetic variations in the endocannabinoid receptors are being revealed by the field of genomics, and shed light on the endocannabinoid deficiency diseases. Similarly, the 'natural' deterioration of the endocannabinoid system seems to give rise to diseases that we are resistant to in our youth. It isn't so-far fetched to imagine that the plant cannabinoids, like the essential fatty acids from which they are derived, are like essential nutrients in an increasingly poisonous world."

The treatment plan Hergenrather provides patients is individualized —"based on the person and their real-life situation —their age, diagnosis, condition, employment, aspirations, and obligations—like they'll be picking up the kids at 3 o'clock— everything needs to be considered. Tailoring the treatment plan to meet the needs of each patient can't be done with a 10 minute appointment and a prescription pad in your hand."

The availability of CBD-rich cannabis in recent years has been a boon to many in the workforce. "Typically people use CBD tincture in the morning or daytime to stop the anxiety and or reduce the pain without impairing their global ability to multi-task at work. With CBD and THC we're just scratching the surface of what cannabis-based

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An Introduction to the Endocannabinoid System

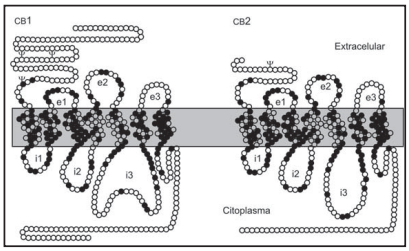
A description of the lipid signaling system essential to health, healing, and homeostasis, long excluded from the medical school curriculum

By Dustin Sulak, D.O.

Adapted from a class for doctors entering the field of Cannabis-based Medicine.

You may be wondering why, as a clinician, you've never learned about the endocannabinoid system (ECS) during any of your training. The discovery of this system is relatively new, but it's been around for 20 years, and a huge body of evidence and peer-reviewed research has been published on various aspects of the endocannabinoid system.

There are two different cannabinoid receptors, the CB1 and the CB2, which are very similar in structure. They follow the classic pattern of the G protein-coupled receptor with seven passes through the cell membrane.



CB1 and CB2 are 7-transmembrane G-coupled receptors. Lipophilic ligands outside the cell (top) activate structures within the hydrophobic layer of the membrane, leading to a response within the cell (bottom).

CB1 receptors are located primarily in the nervous system, but also found in reproductive tissues, connective tissues, adipose tissues, and other glands and organs. The CB2 receptors are found primarily in cells of the immune system, but during situations of injury or inflammation, the CB2 receptors can also be created and up-regulated in other tissues where they're not normally found.

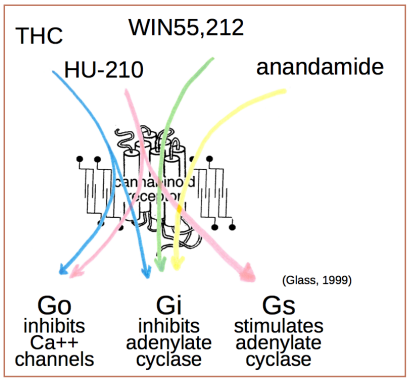
The cannabinoid system is extremely old. Phylogenetic studies suggest the cannabinoid receptors evolved some 600 million years ago. Insects don't have any cannabinoid receptors.

Very primitive animals like sea squirts and nematodes have a cannabinoid receptor that's almost identical to the human CB1 receptor. This high level of evolutionary conservation suggests that this receptor and receptor system is very important for the function of life.

G protein receptors

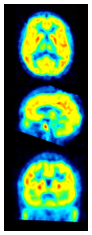
G protein-coupled receptors can open or close the ion channels and they can inhibit or stimulate the formation of adenylate cyclase, which will have other downstream effects in the cell.

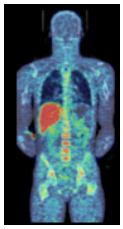
"Agonist trafficking" means that the function of the cannabinoid receptor depends on which agonist actually activates that receptor, which adds another layer of complexity to the ECS. This is analogous to an assortment of keys opening the same lock. But depending on which key is used, the door will open into different rooms.



different actions (bottom row) are triggered by the cannabinoid receptor (middle row), depending on the agonist activating it (top row). THC is from the plant. WIN55,212 and HU-210 are synthetics, and anandamide is made by the body.

Dustin Sulak, DO, is the founder and medical director of Maine Integrative Healthcare in Manchester, Maine, and Integr8 Health, LLC in Falmouth Maine. This article is based on Sulak's presentation for the Society of Cannabis Clinicians' CME course, which can be accessed via ***cannabisclinicians.org****.*





CB1 receptors *(scans at left)* are distributed throughout the central nervous system, with highest densities shown in red. CB2 receptors *(scan at right)* are found throughout the periphery, with especially high density in the liver.

Endogenous Cannabinoids and Their Targets

The endogenous (endo-) cannabinoids are molecules our bodies make to interact with the cannabinoid receptors. The two most well-known are anandamide and 2-arachidonoyl glycerol (2-AG). Anandamide is named after the Sanskrit word *ananda*, which means bliss.

The endocannabinoids are arachidonic acid derivatives synthesized on demand from precursors in the cell membrane. They act as "retrograde messengers." Elsewhere in the body these endocannabinoids function as autocrine (within cells) and paracrine (cell-to-cell) mediators.

When the endocannabinoids have finished their signaling role, they're degraded by enzyme hydrolysis; FAAH (fatty acid amide hydrolase) degrades anandamide and MAGL(monoaglycerol lipase) degrades 2-AG.

Several other endogenous cannabinoids, less well understood than anandamide and 2-AG, play a significant role in the function of the endocannabinoid system.

The endocannabinoids also have other targets in the body besides the CB1 and CB2 receptors. For example, G-protein receptor 55 (or GPR55) is a post-synaptic membrane receptor involved in hyperalgesia and endocannabinoid production. Stimulating this receptor likely signals the cell to cease the production of endocannabinoids.

The TRPV1 receptor (also know as the capsaicin receptor) is another target of endocannabinoids. It has implications in pain, inflammation, respiratory, and cardiovascular disorders.

Peroxisome proliferator-activated receptors (or PPARs) are nuclear membrane receptors located inside the cell that are also targets of endocannabinoids. They regulate the translation of genes that are involved in metabolism, energy homeostasis, cell differentiation, and inflammation. PPAR agonists tend to have anti-inflammatory, cardioprotective, and neuro-protective properties.

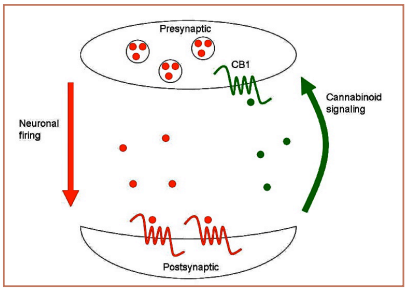
Furthermore, endocannabinoids can control voltage-gated ion channels and ligand-gated ion channels.

Canabinoid function in the nervous system

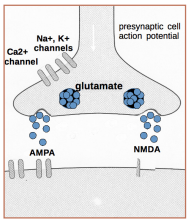
The CB1 receptor is the most common G-protein receptor found in the human brain. The highest densities of CB1 are found in the hippocampus, the cerebral cortex, the cerebellum, the amygdala nucleus, and the basal ganglia —areas of the brain involved with short-term memory, cognition, mood and emotion, motor function, and nociception.

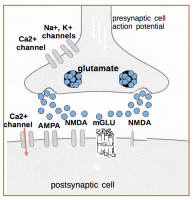
Cannabinoid receptors are virtually absent in brainstem cardiorespiratory centers. This is why that there is no lethal overdose of cannabinoids.

Below is a simplified diagram of the "retrograde signaling" activity of cannabinoids in the nervous system. At the top you see the presynaptic cell with neurotransmitters inside of vesicles. Upon nerve depolarization, these neurotransmitters are released, and they move across the synapse to stimulate a receptor on the post-synaptic cell. Cannabinoids follow the opposite path. They're produced on the cell membrane of the post-synaptic cell and travel retrograde across the synapse to interact with the CB1 receptor on the pre-synaptic nerve terminal.



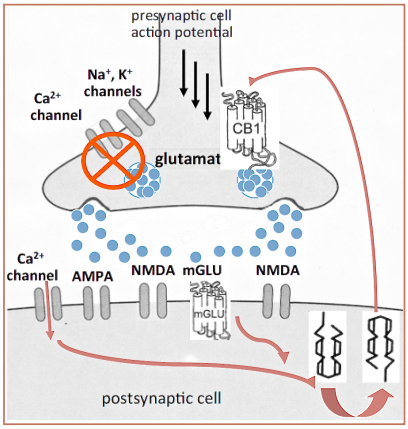
Retrograde signaling is the process by which cannabinoids made on a postsynaptic cell travel across the synapse (upwards in graphic) to modulate the neurotransmitter release of the presynaptic cell.





Let's look at the function of retrograde signaling in a little more depth, beginning with depolarization-induced suppression of excitation. In the illustrations at right we see an excitatory glutamatergic nerve releasing its glutamate neurotransmitter into the synapse. This occurs after an action potential arrives at the accent terminal and opens voltage-gated calcium channels. The glutamate diffuses across the synapse to interact with receptors in the post-synaptic cell. Cannabinoids are produced in the post synaptic membrane and act on the presynaptic cell to halt this excitatory process.

The same model applies to inhibitory GABAnergic neurons. In the illustration below we see 2-AG diffusing retrosynaptically to a presynaptic CB1 receptor, closing calcium channels and preventing the release of GABA into the synapse. This is called depolarization-induced suppression of inhibition.



Neuroplasticity

The function of the endocannabinoid system in the nervous system is more than just homeostatic prevention of too much excitation or too much inhibition. There is a significant protective and repair function, and the endocannabinoid system is heavily involved in neuroplasticity.

Neuroplasticity involves the sprouting and pruning of synapses, changes in dendritic spine density, and changes in neurotransmitter pathways. It gives rise to all types of adaptive learning, including recovering from a stroke, the conscious act of gaining a new skill, and the unconscious acquisition of a new emotional response. It is also involved in pathological processes such as central sensitization to pain.

There are multiple mechanisms by which cannabinoids modulate neural plasticity, including neurogenesis (the formation of new neurons), long-term potentiation and long-term depression.

Research in humans has shown that the administration of exogenous cannabinoids can cause neuroplastic changes. One study that looked at volunteers who were heavy cannabis users found neuroplastic changes in the nucleus accumbens and amygdala. These are two areas of the brain that are involved in the enjoyment of activities such as eating and sex, and also involved in addiction.

continued on next page

Endocannabinoid System *from previous page*

Other studies have shown that cannabinoids can enhance a process called fear extinction. Fear extinction is a neuroplastic event that's essential for preventing and recovering from post-traumatic stress.

Anandamide and 2-AG are also endogenous neuroprotective agents, produced by the nervous system in response to both chemical and mechanical trauma. Other phytocannabinoids and synthetic cannabinoids have been shown to decrease glutamate excitotoxicity in a situation of a seizure or a stroke.

When neurons become injured or ill, they tend to release their contents. Excitatory neurons release levels of glutamate that become toxic to the surrounding cells, and we see a domino effect of excitotoxicity. Cannabinoids have been shown to halt that process.

The United States Department of Health and Human Services actually owns a patent on the use of cannabinoids as anti-oxidants and neuroprotectants. The authors of this patent discuss the potential benefit of using cannabinoids in neurodegenerative conditions such as multiple sclerosis, Alzheimer's, Parkinson's, Huntington's, and more.

Cannabinoids also affect autonomic tone. In the sympathetic nervous system, CB1 receptor stimulation will inhibit noroepinephrine release. It will dampen sympathetically mediated pain and modulate the hypothalamic-pituitary-adrenal axis and the hypothalamic locus coerulius-norepinephrine axis.

Depending on the situation, stimulation of the CB1 receptors could increase or decrease heart rate and contractility.

Cannabioid receptors also have peripheral activities that affect autonomic tone: For example, myocardial CB1 receptors, when activated, cause vagally mediated biphasic effects in heart rate and cardiac contractility. Depending on the situation, stimulation of the CB1 receptors could increase or decrease heart rate and contractility.

In vascular tissues CB1 activation causes vasodilation, which leads to an anti-hypertensive effect that has been demonstrated in humans.

Some rodent studies suggest that cannabinoid receptor activation has a protective role in myocardial ischemia.

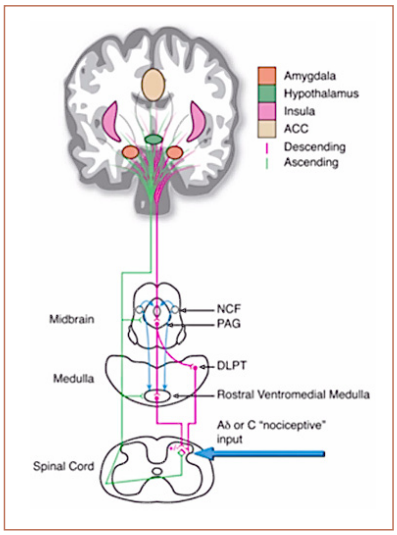
The parasympathetic nervous system also has CB1 receptors, which will reduce parasympathetic activity when stimulated. And this is likely providing the anti-emetic effect of cannabinoids.

Pain signaling

The endocannabinoid system is heavily involved in pain signaling. Pre-clinical models have shown that endocannabinoid activation causes antinociceptive effects in the three major types of pain: acute pain, persistent inflammatory pain, and neuropathic pain.

The antinociceptive effects of cannabinoids involve many mechanisms in different parts of the body, including the central nervous system's periaqueductal gray, ventroposterior lateral nucleus of the thalamus, and rostral ventromedial medulla), as well as the spinal cord, the peripheral nervous system, and the peripheral tissues.

One mechanism by which cannabinoids are able to decrease nociception and decrease the perception of pain involves the descending pain inhibitory pathway depicted below. This pathway has components in the mid-brain, the medulla, and the spinal cord that decrease the nociceptive signals that make it to pain areas in the brain.



'Descending pain inhibitory pathway' is enhanced by cannabinoids to decrease pain signaling to the brain.

In the dorsal horn of the spinal cord there are inhibitory interneurons that release GABA and actually suppress this descending pain inhibitory pathway. Cannabinoids will suppress these GABA-releasing interneurons, thus enabling the descending pain pathway to do its work in decreasing the amount of pain experienced.

Cannabinoids also decrease pain associated with injury via the homeostasis of activators and sensitizers. When we experience an injury, activators and sensitizers cause peripheral sensitization including hyperalgesia and eventually allodynia. These activators and sensitizers come from a variety of sources including the damaged tissue itself, the leukocytes, leukocyte-activated platelets, the neighboring autonomic nerves, and the nociceptive nerves themselves. All can release activators and sensitizers, leading to peripheral sensitization, which elicits a homeostatic response by the endocannabinoid system.

As peripheral sensitization begins after an injury, the function of the endocannabinoid system provides the first line of defense against pain. CB1 receptors will decrease the release of activators and sensitizers around the site of the tissue injury. CB1 receptors on the nociceptor will also open potassium channels and cause the nociceptor to hyperpolarize, making it less likely to fire. At the same time, CB2 receptor signaling decreases the release of activators and sensitizers from the neighboring immune cells.

As noted, CB2 receptors are found not only in immune cells but also in other tissues, especially during situations of injury. CB2 receptors have been found, for example, in painful neuromas. And CB2 agonists produce anti-nociceptive effects in pre-clinical models of inflammatory and nociceptive pain.

Cannabinoid-opioid interaction

Opioids and cannabinoids share several pharmacologic effects including antinociception. In animal studies, the crosstalk between these two signaling pathways has shown promise for combination pain therapy and novel treatments for opioid addiction and abuse.

The spinal administration of various cannabinoids with morphine produces a greater-than-additive anti-nociceptive effect in mice. The "tail-flick test" enables researchers to assess pain levels. The rodent is positioned with its tail on a hot plate and the heat is gradually increased until the animal feels the pain and flicks its tail.

Various doses of morphine can be given to rodents to plot the dose response curve of antinociception in the tail flick test. When very low doses of THC —doses that are marginally active in a tail-flick test— are added to morphine, the dose response curve of morphine shifts to the left by four-to-12-fold.

The same is true in the opposite experiment. When low doses of morphine are added to the THC trial, we see the dose response curve shifting to the left again. This points to an analgesic synergy beyond just the additive effects of morphine plus THC.

Adding cannabinoids to opioids will potentiate analgesia but will not increase the risk of cardio-respiratory suppression or fatal overdose.

THC has also been shown to trigger the release of endogenous opioids, which stimulate both the delta and kappa opioid receptors. Combination treatment with cannabinoids and opioids is surprisingly safe. The cannabinoid and opioid receptors are both found in areas of the brain and spinal cord that control pain signaling. But because the cannabinoid receptors have such low densities in the brainstem's cardio-respiratory center, adding cannabinoids to opioids will potentiate the analgesia but will not increase the risk of cardiorespiratory suppression or fatal overdose. Therefore, combination therapy actually increases the therapeutic index of opioids.

We all know that, clinically, treating chronic pain with opioids is a major problem due to tolerance building and the need for dose escalation. Cannabinoids, when co-administered with opioids, can prevent tolerance building to the opioids. Opioid receptor proteins are upregulated in the spinal cord of animals treated with both cannabinoids and opioids. Mice treated with low doses of THC and morphine in combination showed avoidance of tolerance to the opioids while retaining their anti-nociceptive effects.

CB1 and MU opioid receptors are also co-localized in the areas of the brain that are important for morphine abstinence, such as the nucleus accumbens.

Endocannabinoids and connective tissue

In bone, both osteoblasts and osteoclast produce anandamide and 2-AG, and both express the CB2 receptor. Stimulation of this receptor leads to decreased osteoclast activity and increased osteoblast activity, thus increasing bone formation.

There are CB1 receptors on the sympathetic nerve terminals close to the osteoblasts. These nerves release norepinephrine, which restrains bone formation. Retrograde CB1 signaling will inhibit the release of the norepinephrine and alleviate this tonic sympathetic restraint, thus allowing bone to form.

Cells in other connective tissues —fibroblasts, myofibroblasts, chondrocytes, and synoviocytes— express both CB1 and CB2 receptors, and the enzymes used to metabolize endocannabinoids.

CB1 receptors have been found to be upregulated after exposure to inflammatory cytokines and equiaxial stretching of fibroblasts in models of stress.

Cannabinoids also modulate fascia remodeling via fibroblast focal adhesions.

Cannabinoids have been shown to prevent cartilage destruction by inhibiting chondrocyte expression of cytokines and metalloproteinase enzymes.

Cannabinoids have also been shown to decrease connective tissue inflammation. Animal models of atherosclerosis demonstrate that CB2 receptor activation on macrophages within atherosclerotic plaques can decrease atherosclerosis.

ECBs in the immune system.

In contrast to the drug war propaganda that cannabinoids are immunosuppressive, researchers have found that cannabinoids modulate the immune system, just as they modulate other bodily systems. Cannabinoids have been shown to decrease Th1 cytokine levels, increase the levels of Th2 cytokines, and increase certain subsets of B, T, and NK (natural killer) cells.

Phytocannabinoids also have other immune-mediating mechanisms that are separate from cannabinoid receptors. For example, THCa, the acidic form of THC, can inhibit the release of tumor necrosis factor-alpha from macrophages.

Neoplasm

As clinicians, when we think of cannabinoids and cancer, we tend to think of the management of cancer symptoms and the side effects of chemotherapy. Many clinicians are surprised to discover that cannabinoids also have direct oncologic effects.

The animals treated with cannabinoids tend to have much slower growing tumors than the animals treated with a control vehicle.

Cannabinoids have been shown to inhibit tumor growth in multiple cell lines. This is a hot area of research. Numerous human cancer cells lines have been xenografted to immunosuppressed rodents and treated with cannabinoids.

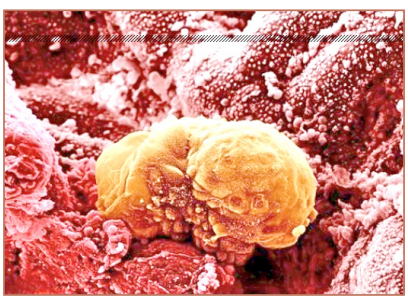
The animals treated with cannabinoids tend to have much slower growing tumors than the animals treated with a control vehicle. Cannabinoids affect neoplasm via multiple mechanisms of action, including cytostatis, apoptotis, antiangiogenesis, and antimetastesis.

Cannabinoids are selective anti-tumor compounds that can kill cancer cells without injuring healthy cells at the same dosage. This makes cannabinoids much less toxic than traditional chemotherapy agents.

Cannabinoids in embryology

Cannabinoids are also heavily involved in embryology and cell growth and differentiation. CB1 receptors have been detected in mouse embryos as early as the second day of gestation. Blastocyst implantation into the endometrium, which is thought of as the first suckling function, requires suitable levels of anandamide.

The proliferation and differentiation of neural stem cells are shaped by extracellular cues provided by endocannabinoids. Adult neurogenesis is regulated by many of these



Six-day-old human embryo, known as a blastocyst, implanting itself onto the wall of the mother's womb, a process mediated in part by the endocannabinoid system in mother and child. False colors show the blastocyst in orange and the womb (endometrium) in pink.

continued on next page

Endocannabinoid System *from previous page*

same embryonic endocannabinoid mechanisms.

Endocannabinoids in the Gastrointestinal System

In the digestive system, CB2 receptors are found in the lamina propria, the plasma cells, activated macrophages, and in the myenteric and submucosal plexus ganglia in the human ilium. CB2 receptor signaling likely involves the inhibition of inflammation, visceral pain, and intestinal motility in the inflamed gut.

The Endocannabinoid System In The Liver

The liver expresses both CB1 and CB2 receptors at low levels. The CB1 receptors are mostly found in endothelial cells and hepatocytes, and the CB2 receptors are mostly found in Kupffer cells.

Anandamide and 2-AG are present at substantial levels in the liver, along with the enzymes needed to break down the endocannabinoids.

Liver injury is associated with an increased endocannabinoid tone in several pathologic settings. During injury or inflammation, CB1 receptors are induced in hepatocytes, hepatic myofibroblasts, and endothelial cells. CB2 receptors are induced in Kupffer cells as well as the hepatic myofibroblasts. Levels of 2-AG also increase in hepatic stellate cells and hepatocytes during liver injury.

The Kupffer cells are involved in our response to early liver injury via the production of tumor necrosis factor-alpha. This signals the stellate cells to synthesize collagen and cause fibrosis. Fibrosis will eventually lead to cirrhosis or loss of liver function.

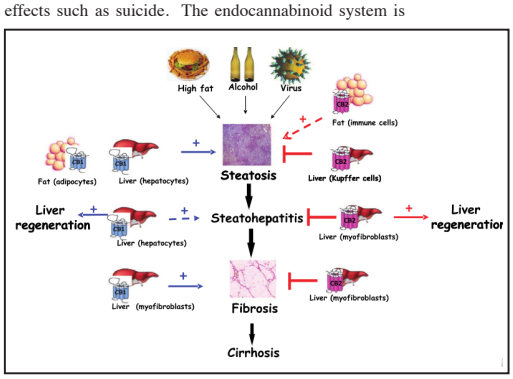
As we can expect from a signaling system that has homeostatic properties, the cannabinoid system can both increase and decrease liver fibrosis via different mechanisms of CB1 and CB2. It's been shown that stimulation of the CB1 receptor can enhance fibrogenesis, while stimulation of the CB2 receptor counteracts the progression of fibrosis. It's important to note that effective antifibrotic treatments are not available in humans yet. And numerous efforts are being directed at the development of liver-specific antifibrotic therapies to treat liver disease and prevent cirrhosis.

CB1 and CB2 receptors have opposite effects on liver fibrosis (see figure below). At the top of the figure we have three typical liver insults: a high fat diet, alcohol, and a virus such as hepatitis C. Early liver injury leads to steatosis, which is enhanced by CB1 receptor activation on hepatocytes and on adipocytes, but inhibited by CB2 receptor activation on the Kupffer cells. Prolonged steatosis will lead to liver inflammation and steatohepatitis. Again, this process is enhanced by CB1 signaling on the hepatocytes and this time inhibited by CB2 signaling on the myofibroblasts. Both CB1 signaling and CB2 signaling can promote liver regeneration at this step. Prolonged inflammation, however, will lead to fibrogenesis, as mentioned previously. This process is enhanced by CB1 signaling in myofibroblasts and inhibited by CB2 signaling in the same cells.

The endocannabinoid system also helps control both hunger and feeding. Human breast milk contains endocannabinoids, and newborn mice that are given a CB1 receptor antagonist stop suckling and die.

The endocannabinoid system modulates cellular metabolism via many other hormones include ghrelin, leptin, orexin, and adiponectin. In obesity, adipocytes produce excessive levels of endocannabinoids which can drive CB1 receptors into a feed-forward dysfunction, contributing to metabolic syndrome. Interestingly, long-term heavy recreational cannabis use is inversely associated with both obesity and Type 2 diabetes.

It has been suggested that blocking CB1 receptor activation could reduce hunger and be a treatment for obesity. A drug that blockes CB1 receptors, Rimonanbant, was approved in Europe, but was later withdrawn from the market because it was found to cause severe psychiatric side effects such as suicide. The endocannabinoid system is incredibly complex and simply blocking a CB receptor is unlikely to offer health benefits without significant side effects in other systems.



CB1 and CB2 play opposite roles play opposite roles during liver inflammation and injury. CB1 promotes fibrosis (scarring), while CB2 counteracts fibrosis. Both CB1 and CB2 can stimulate liver regeneration.

Potential Disregulations

Although cannabinoid deficiency syndromes have not yet been clearly defined in humans, there is some pre-clinical evidence and some human evidence that dysregulation of the endocannabinoid system is associated with several conditions. Endocannabinoid deficiencies have been implicated in schizophrenia, migraine, multiple sclerosis, Huntington's, and Parkinson's, irritable bowel syndrome, anorexia, motion sickness, fibromyalgia, menstrual symptoms, and other conditions that involve hyperalgesia and abnormal sensitization to pain. Several polymorphisms [differing forms] have been identified in the genes that code for the cannabinoid receptors. And some of these polymorphisms have been associated with clinical outcomes, such as a tendency towards happiness or depression, and the likelihood of developing a post-traumatic stress disorder.

Cannabinoid hyperemesis syndrome is an interesting example of endocannabinoid dysregulation. The precise mechanism of action is unknown, but it may involve endocannabinoid system dysfunction in both the central nervous system and the digestive system. It's a rare condition characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and hot bathing.

Cannabinoid hyperemesis syndrome shares several similarities with cyclic vomiting syndrome, and the two conditions are often confused. This occurs in individuals with long-term, high-dose cannabis use histories. And the onset of the hyperemesis syndrome is often years after initiating cannabis use. The acute treatment for cannabinoid hyperemesis syndrome is hot showers, and patients with this condition are often found compulsively bathing. The long-term solution to this syndrome is cannabis abstinence, which likely allows the endocannabinoid system to return to its homeostatic role in a more balanced manner.

Effects of Exogenous Cannabinoids

Delta-9 THC is the most well known phytocannabinoid. It mimics the activity of anandamide and 2-AG by acting as a partial agonist at CB1 and CB2 receptors. As a partial agonist, THC is usually stimulating the CB1 and CB2 receptors, but it may play the role of an antagonist at CB2 receptors and when the endocannabinoid system is down regulated. There may be advantages of cannabinoid receptor antagonism, for example in the situation of obesity, where the endocannabinoid system is dysregulated and hyperactive endocannabinoid synthesis is contributing to the problem via a feed-forward dysfunction at the CB1 receptor.

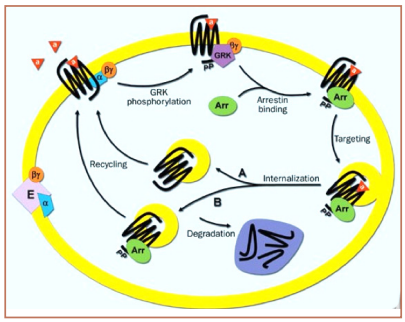
Low doses and acute doses of THC have been shown to cause upregulation within the endocannabinoid system. THC has been shown to increase the production of endocannabinoids, to upregulate CB1 receptors, to increase the receptor affinity, and to enhance the pain relief imparted by endocannabinoids. This suggests that cannabinoid treatments can actually widen their own therapeutic window by enhancing the endocannabinoid system and upregulating the receptor production and receptor sensitivity.

Tolerance to THC develops due to endocannabinoid system down regulation.

In the clinical setting, patients often find that when their cannabis use is below a certain dose threshold, they actually sensitize to cannabis over time and require a lower dose with greater therapeutic benefits. Once the patient exceeds a certain threshold dosage, they begin building tolerance to THC and other exogenous cannabinoids. Tolerance to THC develops due to endocannabinoid system downregulation.

When the cannabinoid receptors are persistently agonized they become phosphorylated, bound by arestin, and pulled into clatherin-coated pits inside the cell, making the receptors unavailable for stimulation. This CB receptor down-regulation and resulting drug tolerance occurs at varying rates and magnitudes in different brain regions. It occurs faster and more dramatically in the hippocampus, which regulates memory, than in the basal ganglia, which mediates the euphoric effect of THC. This difference may explain why memory loss decreases among frequent cannabis users, but the euphoric effect remains. The therapeutic window of cannabinoids can also be widened over time by faster tolerance-building to adverse effects than benefits

In most clinical situations, I recommend using the lowest dose of exogenous cannabinoids and keeping the endocannabinoid system finely tuned and sensitive. However, building tolerance with a cannabinoid receptor agonist —especially when it's needed at higher doses— can actually be advantageous because over time the user will experience less side effects.

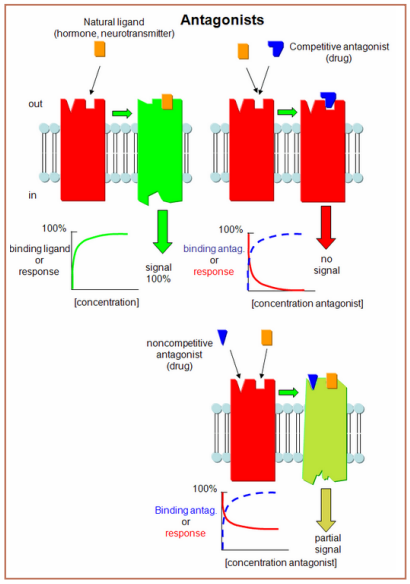


Over-stimulating the CB receptors will trigger the cell to internalize the receptor and prevent further activation, a mechanism of tolerance-building to cannabinoids.

Cannabidiol (CBD) is another plant cannabinoid that has been getting a lot of attention for its variety of therapeutic effects. CBD has very low affinity for both the CB1 and CB2 receptors and tends to antagonize other agonists of the CB1 and CB2 receptor. It has been described as "a non-competitive inverse agonist" that modulates the affinity of cannabinoid receptors for their other ligands.

But in addition to the effects on the cannabinoid receptors themselves, cannabidiol has several other mechanisms of action. It antagonizes GPR55, alpha-1 adrenergic receptors, and mu-opioid receptors while activating the 5HT serotonergic receptors and the TRPV1 and TRPV2 vanilloid receptors.

CBD can inhibit the uptake of a variety of neurotransmitters, including noradrenaline, dopamine, serotonin, GABA, and anandamide (the endocannabinoid) by inhibiting the activity of fatty acid amide hydrolase. CBD also has effects on the mitochondria, on voltage-gated calcium channels, and the inhibitory glycine receptor.



CBD has a very low affinity for CB1 and CB2 receptors. It is thought to act as a "non-competitive inverse agonist," de- creasing the receptors' affinity for agonists like THC without completely blocking the receptor's activity. This illustration compares the non-competitive activity of CBD (bottom) with the competitive antagonism of Rimonobant (top). In the bottom model, CBD is represented by the blue triangle, and THC by the orange rectangle.

Synthetic cannabinoids developed for use in animal research have had clinical application in humans for decades. Dronabinol (Marinol), a synthetic THC, was approved as a schedule 2 drug in 1986 and was moved to schedule 3 in 1999. Nabilone, a THC analog, was also approved by the FDA and finally marketed in the U.S. in 2006. Nabilone is approximately twice as strong as THC. Both these drugs are indicated for chemotherapy-induced nausea and

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vomiting, and as an appetite stimulant for AIDS patients.

Ultra-potent synthetic cannabinoids have much stronger psychoactive effects and a worse side effect profile compared to herbal cannabinoids. One of the disturbing results of cannabis prohibition has been the marketing of herbal products that look like cannabis and have been sprayed with synthetic cannabinoids. These products are sold over the counter —"K2," "Spice," et al— and can land patients in the emergency room with severe psychiatric side effects.

Other influences on the endocannabinoid system

Some common medications have endocannabinoid system activity. For example NSAIDS, both ibuprophen and ketorolac, block the hydrolysis of anandamide by inhibiting FAAH.

COX-2 inhibitors also have cannabinoid effects by potentiating synaptic 2-AG, release thus enhancing CB1 signaling.

Acetaminophen is deacetylated in the liver to its metabolite P aminophenol, which is then conjugated with arachidonic acid in the CNS to form N-arachidonoyl phenylamine, or NAP. NAP has several cannabinoid effects, including preventing the breakdown of anandamide by FAAH, inhibiting COX-1 and COX-2, and acting as a TRPV-1 receptor agonist. The analgesic activity of acetaminophen in rats has been blocked by CB1 and CB2 receptor antagonists, confirming a cannabinoid mechanism of action of acetaminophen for analgesia.

Glucocorticoids also have cannabinoid effects. Pre-clinical rodent studies have shown that acute glucocorticoid administration enhances the activity of endocannabinoids. Corticosteroid mania may have a cannabimimetic component. Chronic exposure to glucocorticoids down regulates the endocannabinoid system, which is scenario consistent with chronic stress. CB1 receptors have also shown to play a pivotal role in the anxiolytic action of benzodiazepines. And many antidepressant, antipsychotic, anxiolytic, and anesthetic agents have demonstrated effects on the endocannabinoid system.

Probiotics have been shown to upregulate CB2 receptor expression in colonic epithelium cells in mice. Administering probiotics can decrease pain behavior following colonic distension with butyrate, a model of Irritable Bowel Syndrome. This effect is reversed by CB2 antagonists, so we know that some of the benefits of priobiotics are due to a CB2 mechanism.

Ethanol can dampen the effects of the endocannabinoid system. Chronic alcohol consumption and binge drinking likely desensitize or down-regulate the CB1 receptor and impair endocannabinoid signaling, except perhaps in areas of the brain involved in reward and motivation to self-administer the substance of abuse.

Several herbal medicines also have endocannabinoid system activity. Curcumin, the active component of the yellow spice turmeric, for example, elevates endocannabinoid levels and brain nerve growth factor in a brain region specific fashion. Pre-treatment with a CB1 receptor antagonist blocks the effects of curcumin on endocannabinoids and brain nerve growth factor.

Echinacea, an herb well known for its use in balancing and stimulating the immune system, contains alkylamides which are potent agonists of the CB2 receptor. These do not interact with the CB1 receptor, and this is why Echinacea doesn't have psychoactive effects. Copal is in the Boswellia family, which has traditional uses for anti-inflammatory and analgesic purposes. Copal incense contains a pentacyclic triterpene that has high affinity for both CB1 and CB2 receptors. Beta-caryophyllene is the principal terpenoid in black pepper and is also found in cannabis and elsewhere in the plant kingdom. Beta-caryophyllene is a CB2 agonist and has demonstrated protective effects in colitis and cisplatin-induced nephrotoxicity via a CB2 mechanism.

Lifestyle Factors

Several lifestyle factors have also been shown to affect the endocannabinoid system. For example, medium to high intensity voluntary exercise increases endocannabinoid system signaling via increased levels of anandamide and potentially increased CB1 receptor expression. The "runner's high" —the euphoria after vigorous exercise that was previously attributed to endorphins— is most likely a cannabimimetic effect.

On the other hand, forced exercise doesn't increase anandamide levels and can actually decrease CB1 signaling! Forced exercise is seen by the endocannabinoid system as a type of stress.

Stress and social play have an impact on the endocannabinoid system. Chronic stress has been shown to impair the ECS via decreased levels of both anandamide and 2-AG. Social play in rats, on the other hand, increases CB1 phosphorylation, which is a marker of CB1 activation in the amygdala. It enhances anandamide levels in the amygdala and the nucleus accumbens, again, areas of the brain that are responsible for enjoyment of pleasurable activities.

Several non-pharmacologic therapeutic treatments have also been shown to work via cannabinoid mechanisms. Electro-acupuncture, for example, causes increased levels of anandamide in the skin via a CB2 receptor mechanism. It also upregulates the expression of the CB2 receptors in the skin, and may have central effects that are mediated by CB1 receptors.

Osteopathic manipulative treatment (OMT), one of my favorite healing modalities, can also have a cannabimimetic effect. In subjects receiving the OMT, serum levels of anandamide after the treatment more than doubled compared with the pre-OMT levels. No change was seen in the control subjects. Other studies have shown cannabinoid effects of other types of bodywork as well.

In summary, the endocannabinoid system is widely distributed throughout the body. The primary function of the endocannabinoid system is cellular homeostasis. Our understanding of the endocannabinoid system is currently incomplete, still emerging, and suggests significant complexity. Manipulation of the endocannabinoid system may provide effective treatments for a wide variety of conditions.

Dustin Sulak, DO, is the founder and medical director of Maine Integrative Healthcare in Manchester, Maine, and Integr8 Health, LLC in Falmouth Maine. This article is based on Sulak's presentation for the Society of Cannabis Clinicians' CME course, which can be accessed via ***cannabisclinicians.org.***

A Discovery By Inference

By Fred Gardner

While studies reported in journals help keep scientists and doctors abreast of recent developments, conferences offer a preview of ongoing research and a chance to question and network with the investigators. Scientists who attend meetings of researchers in other fields remark the unusually non-competitive, collegial openness at get-togethers of cannabinoid researchers.

The International Association for Cannabinoid Medicines grew out of a group founded in 1997 by a German physician, Franjo Grotenhermen, the "Association for Cannabis as Medicine." (Similarly, the C-word in the International Cannabinoid Research Society's name has been changed from "Cannabis.")

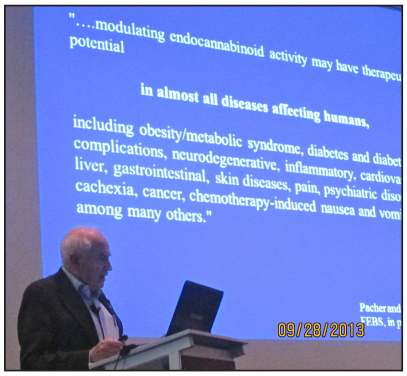
At the September 2013 IACM meeting in Cologne, Raphael Mechoulam recounted a hypothesis published by Pal Pacher and George Kunos in *FEBS (The Journal of the Federation of European Biochemical Societies)*: "modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans."

Tod Mikuriya, MD, had posited essentially the same hypothesis in 1996, based on his reading of the medical literature and histories he'd taken from patients at the San Francisco Cannabis Buyers Club.

Mikuriya, who died in 2007, was a psychiatrist with a practice in the East Bay, and a scholar who had compiled an anthology of the pre-prohibition medical literature devoted to cannabis. It was he, with the support of organizer Dennis Peron, who insisted that California's medical marijuana initiative legalize its use in treating not just a short list of grave illnesses, but also "any other condition for which marijuana provides relief.

Mikuriya's finding that cannabis alleviates a very wide range of symptoms —and his inference that compounds in the plant act on many physiological systems— were met with contempt by federal officials. At a press conference in December 1996, Drug Czar Barry McCaffrey scoffed that Mikuriya practiced "Cheech and Chong medicine," and Attorney General Janet Reno threatened to revoke the licenses of physicians who approved marijuana use by patients.

Hearing Mechoulam refer matter-of-factly in 2013 to "endocannabinoid involvement in a myriad of bodily processes," I couldn't help thinking that Tod (co-founder of *O'Shaughnessy's*) had reached the same conclusion from a different direction. An insightful doctor can discern things about a drug's mechanism of action. Pharmacology is not the only route to the truth, although as "hard science," it commands more respect than the clinician's craft.



Professor Raphael Mechoulam, at the 2013 meeting of the IACM, admiringly quoted a statement by Pacher and Kunos, "modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans." A slide provided a partial list of conditions involving the endocannabinoid system.

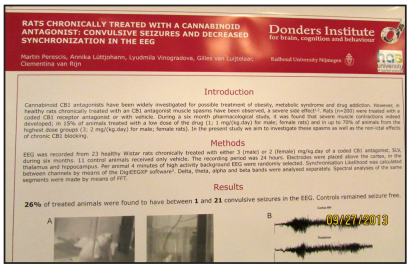
Drug Czar Barry McCaffrey, at a press conference in December 1996, ridiculed Dr. Tod Mikuriya's finding that marijuana provides relief for a very wide range of conditions. A partial list of treatable conditions, culled from a website and attributed to Mikuriya, was blown up for display on an easel.

Pharmacology is not the only route to the truth, although as "hard science," it commands more respect than the clinician's craft.

Another IACM presentation that Tod anticipated, in a sense, linked Rimonabant to epileptic seizures. Rimonabant is a cannabinoid-antagonist drug that Sanofi-Aventis marketed for treating metabolic syndrome. It was approved by European regulatory authorities in 2006 but had to be withdrawn when it led to a spate of suicides.

Tod had written a letter to the U.S. Food and Drug Administration urging that Rimonabant be rejected because any drug blocking the CB1 receptor would very likely cause a wide range of adverse effects —not just mood-related ones. This is an important point because drug manufacturers still dream of marketing synthetic cannabinoid antagonist drugs, and some would have us believe that suicidality was the one and only problem with Rimonabant.

An IACM poster by Dutch researcher Martin Perescis described a study in which he and his team treated 200 rats with either an antagonist drug or placebo for six months. "Severe muscle contractions developed in 15% of animals treated with a low dose of the drug... and in up to 70% of animals from the highest dose groups." Video recordings showed that over the course of 24 hours, "26% of animals treated with this CB1 antagonist were found to have between 1 and 21 convulsive seizures in the EEG, whereas controls remain seizure free."



Cannabinoid antagonist drugs can induce seizures in rats, according to an IACM poster by Martin Perescis and colleagues in the Netherlands. Their findings put the lie to the oft-repeated assertion that the only adverse effect of the antagonist drug Rimonabant was suicidal ideation.

Cannabis in the Treatment of Pediatric Epilepsy

By Bonni Goldstein, MD

The author documents the progress of more than 100 patients using CBD-rich cannabis oil to treat seizure disorders.

I have been a medical cannabis physician seeing adult patients in California for the past six years. Occasionally I would be approached by parents who knew of my background and asked me to monitor their children's use of cannabis. (As a doctor who trained in pediatrics and practiced pediatrics and emergency medicine for 12 years, I have considerable experience taking care of children.)

In the summer of 2013 I evaluated a few adolescents for use of cannabis: a teenage boy with cancer; a teenage girl who went through a horrific trauma and was suffering with PTSD, anxiety and depression and had failed all conventional treatment; a teenage boy with Tourette Syndrome; another teenager with epilepsy.

The nature of my practice changed dramatically after Dr. Sanjay Gupta's documentary aired on CNN in August 2013. Parents of children with intractable epilepsy wanted to know about CBD and cannabis as a possible treatment. They learned about my background on the Internet and asked if I'd be willing to treat their children. Many of the parents are connected on a pediatric epilepsy Facebook page, through which most of my current patients found my practice.

Epilepsy is not a rare disorder. In the United States, according to the Centers for Disease Control, some 2.3 million adults and 468,000 children (under 17) have epilepsy. Epilepsy in children is often a genetic or congenital condition. Epilepsy can result at any time in life from head trauma, infections, or tumors.

About one-third of epilepsy cases are "intractable" —meaning available pharmaceutical drugs do not control the seizures.

Many patients who get seizure relief from pharmaceutical anticonvulsants suffer intolerable side effects. About one-third of epilepsy cases are "intractable"—meaning available pharmaceutical drugs do not control the seizures.

Between August 2013 and April 2014, I became the medical cannabis consultant to 93 children with intractable epilepsy. Their parents had, in the past, authorized various interventions —surgery, vagus-nerve-stimulator implant, the ketagenic diet. Some had left the country for stem-cell treatment. These are families that are desperately searching.

My first pediatric epilepsy patient was a 14-year-old girl with Lennox-Gastaut Syndrome. Her parents had learned about CBD and signed up to be on the waiting list of Realm of Caring, the Colorado non-profit run by the Stanley Brothers, whose "Charlotte Web" strain was shown to be very effective in the case featured by Dr. Gupta.

Procedures

Prior to coming into my office, parents are required to fax over their child's medical records for review. They fill out a questionnaire and sign an informed consent form. We talk about which medications they've tried, what has helped and what has not helped. Is there is a typical pattern to the child's seizures? Do they occur more when the child is awake or asleep? What kinds of seizures does the child have? How are the medications and seizures affecting their child's development? Have they tried cannabis medication yet?

After this evaluation, I decide if the patient qualifies for medical cannabis based on California law and if I think the child may benefit from medical cannabis. If the answers to these two questions are yes, the child is approved and receives a letter of recommendation to use medical cannabis. The parents receive caregiver letters.

I educate the parents about what we know so far about CBD and the endocannabinoid system. It's important that they understand that although clinical trials are lacking, there's a scientific basis for what we're doing.

I explain that I have very high standards for the medication they are going to give their child. They cannot give untested preparations of CBD. In the world of western medicine we have a sense, as consumers, of being protected when we walk into a pharmacy and pick up a medication. We rely on the pharmacist and the companies that make and distribute drugs to produce a clean, consistent product that contains exactly what the label says it does.

Unfortunately, the state of California hasn't done much to regulate who can produce and distribute marijuana as medicine. It is definitely a "buyer-beware" situation. I insist they only use tested preparations, and I explain to them how to read the results of a cannabis lab test report.

For various reasons my edict sometimes gets ignored. I had one family that had obtained medication from a local cannabis dispensary. It had not been tested and I insisted that before giving another dose, they have it evaluated by a cannabis testing facility. The test results showed that the oil contained 9% rubbing alcohol! Not all oils are contaminated but the only way to be sure is to have the oil tested prior to use.

The oil made from Charlotte's Web has a CBD-to-THC ratio of about 25-to-1. The Stanley brothers authorized Ray Mirzabegian of Los Angeles to grow Charlotte's Web plants and produce oil for distribution in California. As of November, 2014, Mirzabegian was providing oil for 81patients. Another 1175 were on his waiting list.

Some of my patients learned online about other California collectives providing CBD-rich oil from a strain called "ACDC," which has a similar CBD:THC ratio to Charlotte's Web and is equally effective. But in my experience, its producers have not been meticulous and patients have reported occasional inconsistencies. One week I had numerous phone calls from parents reporting that their children were acting "high." This is just not acceptable.

Parents ask if they should test every bottle. This is difficult because in addition to paying out of pocket for the oil, the added expense of testing every bottle becomes prohibitive.

Dosing

Realm of Caring developed a dosing protocol for children on Charlotte's Web that parents are following. For most epilepsy patients, starting dose is 0.5 milligrams per pound per day, divided into three doses to be given at eight-hour intervals (ideally). Thus a 40-pound child would start at 20 milligrams per day divided into three doses. (In pediatric medicine, everything is based on weight because children can outgrow their dose as they gain weight.)

After starting on CBD oil, the children are observed for one or two weeks. Patients whose seizures are less frequent —for example only three seizures a month— may be observed for a longer period without increasing the dose. Most of the patients I see have daily seizures, which enables parents to tell quite quickly if there is any benefit from the oil. Parents are asked to keep a diary or calendar of seizures and improvements and to check in every one to two weeks

If the child is doing well, after a week or two the dose is titrated up by increments of 0.5 milligrams per pound per day. It appears from the data collected in Colorado that the therapeutic range is 2 – 6 mg per pound per day for many of the children that respond well to CBD treatment.

Some patients do need higher doses to achieve good results. One little boy was still having about 20 seizures a month on three anti-epileptic drugs. With Charlotte's Web oil he became seizure free for six months at a dose of 7.5 milligrams per pound per day, and he has been weaned off almost all of the seizure medications.

In Colorado one patient has gone as high as 8 milligrams per pound per day.

Doctors using GW Pharmaceuticals' Epidiolex reportedly have gone as high as 24 milligrams per kilogram per day in an FDA-approved context.

continued on next page

About Epilepsy

Epilepsy is a condition of recurrent, unprovoked seizures. The seizures may result from a hereditary tendency or a brain injury, but often the cause is unknown. Many use the term "seizure disorder" instead because "epilepsy" seems more serious or stigmatized. However, almost all seizure disorders are epilepsy. A person with epilepsy has had two or more unprovoked seizures, regardless of seizure type.

An estimated 65 million people worldwide are afflicted with epilepsy —some 2.2 million in the U.S. When seizures cannot be eliminated by medication, epilepsy is said to be "refractory" or "intractable" or "treatment-resistant" or "catastrophic." Approximately one-third of all epilepsy cases are refractory.

Many types of epilepsy have been defined in terms of age of onset, seizure types and where they arise in the brain, EEG findings, family history, and neurological history, among other factors.

Seizures are characterized as "generalized" or "partial."

Generalized seizures begin with a widespread, excessive electrical discharge involving most or all of the brain.

Absence Seizure: A brief space-out —an episode usually lasting a few seconds, sometimes associated with automatic movements of the hands or mouth, formerly called "petit mal" seizures.

Atypical Absence Seizure: A staring episode that usually lasts longer than 10 seconds and occurs in children who have other types of seizure, lower than average intelligence and difficult to control epilepsy.

Myoclonic Seizure: A brief jerk or series of jerks that may involve a small part of the body such as a finger, hand or foot, or the shoulders or upper arms.

Atonic Seizure: A sudden loss of muscle tone throughout most or all of the body which may cause the head to drop suddenly, objects to fall from the hands, or the person to fall to the ground.

Clonic Seizure: Rhythmic jerking movements of body parts such as the arms or legs.

Tonic Seizure: A stiffening of the body and/or limb, often resulting in a fall if the patient is standing.

Tonic-Clonic Seizure: Whole body stiffening with simultaneous rhythmic jerking of the arms and legs, usually lasting at least one minute and also incuding loss of consciousness. After this type of seizure, the patient typically enters a state of confusion and fatigue lasting 30 minutes or longer. Also known as a "grand mal" seizure.

Partial seizures begin with an abnormal electrical discharge restricted to one region of the brain.

Simple partial seizure: An episode of altered sensation, cognitive function, or motor activity during which the patient is fully alert. Patients usually call these seizures "auras" and symptoms vary depending on the brain region involved.

Complex partial seizure: An episode altered behavior, sensation or motor activity during which alertness and responsiveness are also compromised. The motor activity may consist of repetitive automatic movements of the face or limbs, or "automatisms." Often patients are unaware of these seizures.

A partial seizure can develop into a tonic-clonic or "grand mal" seizure.

Types of Epilepsy

Temporal Lobe Epilepsy
Frontal Lobe Epilepsy
Parietal Lobe Epilepsy
Occipital Lobe Epilepsy
Primary Generalized Epilepsy
Idiopathic Partial Epilepsy
Symptomatic Generalized Epilepsy
Progressive Myoclonic Epilepsy
Reflex Epilepsy
Febrile Seizures
Benign Rolandic Epilepsy
Juvenile Myoclonic Epilepsy
Infantile Spasms
Lennox-Gastaut Syndrome
Childhood Absence Epilepsy
Benign Occipital Epilepsy
Mitochondrial Disorders
Landau-Kleffner Syndrome
Rasmussen Syndrome
Hypothalamic Hamartoma & Epilepsy

Source: NYU Langone Medical Center Comprehensive Epilepsy Center

Bonni Goldstein, MD, sees patients in an office in Lawndale (Los Angeles County) and is the director of the Canna-Centers chain of clinics, with five offices in California. She graduated from the Robert Wood Johnson Medical School in New Jersey and did her internship, residency and Chief Residency at Childrens Hospital Los Angeles. She worked in Critical Care Transport and Pediatric Emergency Medicine for 12 years before becoming a medical cannabis specialist.

Treating Pediatric Epilepsy *from previous page*

THC free preparation

Concentrated oil is the formulation easiest for the parent giving a dose. When you're giving close to four milligrams per pound per day to a 50-pound child, you're giving up to 200 milligrams. If the oil only has 15 milligrams per milliliter, you're giving that child a lot of oil. In large quantities, even healthful olive oil or coconut oil can cause diarrhea.

Many people think that seizure reduction is the goal of treatment, but it's only part of the goal.

Many people think that seizure reduction is the goal of treatment, but it's only part of the goal. The effects of the conventional anti-epileptic drugs (AEDs) can be debilitating —lethargy, developmental delay, liver damage and more. The ultimate goal for pediatric epilepsy patients is freedom from seizure and the side effects of the AEDs. Interestingly, many parents whose children are having success with CBD oil to treat epilepsy are also reporting that their children have improved sleep, improved appetite, more alertness, and developmental progression. It is these other beneficial effects that make CBD a wonderful option for children suffering with seizures.

Drug Interactions

CBD has not been shown to be a pro-convulsant in 21 preclinical and laboratory studies (see below). If a patient using CBD has an increase in seizure activity, it is likely from an interaction with other AEDs that the patient is taking.

Drug interactions are very complex. Each patient is on a different drug regimen and/or special diet. There are many variables: the patient's metabolism, the other medications, the patient's endocannabinoid system, and the profile of the particular cannabis product.

CBD is an inhibitor of the P450 enzyme system, and affects the rate at which other drugs are metabolized. Unfortunately, research is lacking on how CBD interacts with most of the other anti-epilepsy drugs in the liver but there are researchers who have started looking at these very important reactions.

A reassuring fact has been reported by G.W. Pharmaceuticals, the British company that makes Epidiolex and also makes Sativex, which is 50% CBD and has been approved for use in 27 countries to treat pain and spasticity from Multiple Sclerosis. Sativex has been used for 30,000 patient-years by people taking concommitant drugs and there have been no confirmed adverse consequences due to drug-drug interactions.

A journal article from 1977 suggested that CBD potentiated the effects of phenytoin (Dilantin) and phenobarbital, but reduced the anticonvulsant potency of Librium, Clonazepam, Trimethadione, and Ethosuximide.

Laboratory testing has shown that some but not all patients on CBD oil can have decreased Depakote levels and decreased felbamate levels with CBD. It appears that CBD interacts to increase Onfi (clobazam) levels.

Some parents using THCA

THCA is the raw, unheated, non-psychoactive phytocannabinoid that converts to THC when heated. THCA has been shown to be a significant anti-inflammatory. There are tested THCA preparations that have become available and have been claimed to have anticonvulsant properties. There are at least five patients in my practice who added THCA to the CBD treatment regimen and had improved seizure reduction.

Treating pediatric epilepsy patients is very complicated. Treatment varies case-by-case, day-by-day and week-by-week. Weaning a child off an anti-epileptic drug involves an act of faith on the part of the parents who have to deal with the withdrawal symptoms. For example, one of my patients achieved an 80% reduction in seizures. When the parents started to wean one of the AEDs that she was on, she had an increase in number of seizures. After about one week, she improved and seizures reduced again. Parents reported that after this difficult week, she was much more alert and responsive. And now the hope is that seizure reduction due to CBD will resume.

Preliminary Findings

In June 2014 I reported on what I had learned about cannabis in the treatment of pediatric epilepsy at events put on by the Realm of Caring Foundation and the Epilepsy Foundation of Los Angeles. I reviewed the charts of the 93 patients that I approved to use CBD oil for epilepsy and who had been on the oil for at least three months.

Twelve of the children were on oil from Realm of Caring Foundation (Charlotte's Web oil). Nine of the 12 had reduction in severity and frequency of seizures, and some were in the process of weaning off other medications.

Forty-one children were on AC/DC oil and the success rate was very similar —31 out of 41 reporting reduction in frequency of seizures. One child in this group was seizure free.

Ten children were using other CBD-rich oils, obtained from small collectives. Six experienced seizure reduction.

Twenty-two of the families had not started oil and were waiting for Charlotte's Web to become available.

Eight patients had started taking CBD-rich oil from other sources but had stopped, six for financial reasons.

Some patients do not show up as seizure-reduction statistics because the frequency of seizures hasn't gone down —but severity and recovery time have gone down.

On average, the patients had been put on 10 anticonvulsants over the course of their young lives. At present they were on between one and four AEDs. Only one out of the 93 patients was not taking pharmaceuticals at the time I collated my data.

A point worth repeating: some patients do not show up as seizure-reduction statistics because the frequency of seizures hasn't gone down —but severity and recovery time have gone down. Parents may report, "When he has a seizure he's not wiped out for three hours." Each case is so individual.

Report to the Society of Cannabis Clinicians

In September 2014 I described my work with pediatric epilepsy patients to colleagues in the Society of Cannabis Clinicians at a meeting in San Francisco. I had by then seen some 200 children with almost every type of Epilepsy diagnosis .

My patients are concurrently being treated by a pediatrician and a neurologist and may be seeing other specialists such as geneticists. Almost all have been categorized as "refractory" or "intractable" cases, meaning anti-epileptic drugs have not eliminated their seizures. Almost all have been on multiple medications with no improvement.

A study published in the New England Journal of Medicine in 2000 showed that the chances of achieving freedom from seizures diminishes sharply with each drug tried. Whereas 47% responded to the first-line drug they were treated with, the response to a second drug —either substituted or added— went down to 13%. The third drug helped only 4% of patients.

The burdens of refractory epilepsy include poor quality of life, the debilitating side-effects of medications, cognitive decline, physical injuries from falling, psychosocial dysfunction, a restricted lifestyle —adults can't drive, which makes living in our society very difficult— and increased mortality: the idea that you're going to drop dead any day now.

SUDEP —Sudden Unexpected Death in Epilepsy— has been explained to my patients by their neurologists. Those who are teenagers and young adults live with this possibility. One patient in her early twenties said to me, "I could have a seizure tonight and not wake up tomorrow."

With cannabis medicine you can offer hope that patients who have failed all other options that they may get some control over their seizures and possibly lead a normal life.

The chances of achieving freedom from seizures diminishes sharply with each drug tried.

The side effects of the anti-epilepsy drugs described by my patients and their families include lethargy and somnolence, loss of focus, learning and memory problems, loss of speech, loss of social skills and motor skills, incontinence, insomnia, anorexia, and failure to thrive. Felbamate can cause aplastic anemia and or liver failure. Vigabatrin can cause permanent loss of vision.

Parents have reported that their child seemed to be tolerating the first one or two drugs, but then they'll add another drug and they stop talking and stop walking, it just shuts them down.

Endocannabinoids and Epilepsy

Epilepsy —like any given medical problem— will remain "treatment resistant" if the prescribed medications are not targeting the appropriate metabolic system(s). There is ample evidence that the endocannabinoid system plays an important role in modulating excitatory signals in the brain.

To cite but a few examples, in 2008 Hungarian researchers compared tissue from epileptic patients who had decided to undergo brain surgery to tissue from the brains of people who died naturally. Controlling for age and health status, they found that the level of endocannabinoids in tissue removed from the epileptics was 60% lower than in brain tissue from the cadavers. The strong implication is that a lack of endocannabinoids is associated with loss of neurotransmitter control.

In 2010 Andrea Romigi and colleagues at the University of Rome tested spinal fluid from patients with newly diagnosed temporal-lobe epilepsy and found lower-than-normal endocannabinoid levels. These studies and others suggest that some types of epilepsy are associated with an "endocannabinoid deficiency syndrome." (The concept of an endocannabinoid deficiency syndrome underlying many disorders was introduced by Ethan Russo, MD, himself a pediatric neurologist.)

Because CBD can enhance endocannabinoid tone without inducing psychoactivity, it became a compound of interest to far-sighted medical researchers. In the 1970s and '80s, in addition to animal studies, there were several small, promising studies in Brazil of CBD as a treatment for people with seizure disorders.

A 1978 paper co-authored by Raphael Mechoulam described the treatment of nine patients —four with CBD (200 milligrams/day) and five with placebo. Two of the four CBD patients were seizure-free during the test period and suffered no toxic side effects. None on placebo reported improvement.

In 1980 J.M. Cunha et al treated 16 refractory tonic-clonic seizure patients. Eight received 200-300 milligrams of CBD per day. Of these, three became seizure free, four had seizure reduction, and one was unchanged. In the placebo group, one patient had seizure reduction, seven were unchanged.

"It seemed very promising," said Mechoulam looking back decades later, "but unfortunately, nothing has been done ever since. To the best of my knowledge, nobody has done any work on cannabidiol in the clinic on epilepsy, and I just wonder why?"

At the 2005 meeting of the International Association for Cannnabinoid Medicine, Italian researchers led by A. Pelliccia described an open study ("modulating administration and titration schedules on a case-by-case basis, according to clinical response") in which 18 children with intractable epilepsy were treated with a low dose of CBD in corn oil.

The results were very promising. No patients discontinued due to side effects. Most obtained seizure reduction of 25% or more. And, according to Pelliccia: "in all CBD-

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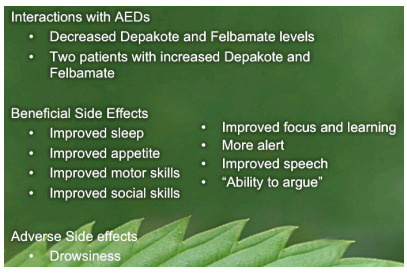
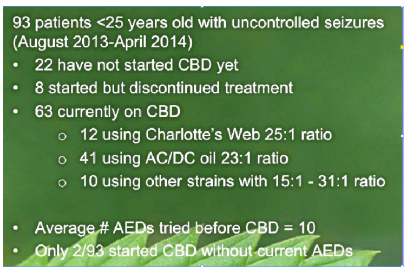
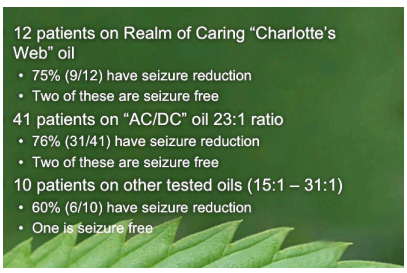


Slides summarizing Dr. Goldstein's unpublished results were part of her presentation to the Epilepsy Foundation of



Los Angeles and the Realm of Caring Foundation in June. Approximately two-thirds of the pediatric epilepsy patients



whose cannabis use she has been monitoring have experienced seizure reduction.

Treating Pediatric Epilepsy *from previous page*

treated children, a clear improvement of consciousness and spasticity (whenever present) was observed.

"However, only nine out of these are currently on treatment, since the parents of the remaining children, although appreciating the improvement of their offspring, not only concerning the fits but also the awareness and the muscular tone, preferred to discontinue due to the economic overcharge induced by the treatment (approximately 300 Euros per month)."

This heartbreaking situation —parents unable to afford a helpful medication— is one I have encountered in my practice. As noted, the issue of affordability should not be ignored by clinicians.

When G.W. Pharmaceuticals got approval from the British government to develop cannabis-based extracts for clinical trials in 1998, the company began funding lab studies to establish the safety of cannabidiol and other so-called "minor" cannabinoids. G.W. provided purified CBD and CBD extracts to many labs, where scientists studied the effects on cell lines and mice, and the mechanism of action.

In 2013 one of the G.W.-supported researchers, Ben Walley of the University of Reading, reviewed the preclinical data (see graphic at top of page) and found no evidence — zero—that CBD acts as a pro-convulsant. To a physician helping patients figure out appropriate dosing levels, this is important information.

G.W.'s interest in CBD and other possibly beneficial cannabinoids inspired U.S. activists to study the contents of marijuana being grown for distribution by dispensaries. O'Shaughnessy's reported in 2010 that about one in 700 varieties being tested by analytic chemistry labs in California and Colorado contained four percent or more CBD. A few plant breeders crossed these "CBD-rich" strains to create increasingly high CBD-to-THC ratios.

By 2013 there were enough epilepsy patients using CBD to inspire a data-collection effort by Stanford University neurologists B.E. Porter and C. Jacobsen that was published in Epilepsy & Behavior in December 2013.

They looked at results from 19 Colorado patients using oil from Charlotte's Web. Thirteen were Dravet's patients, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy (meaning of uncertain origin). The average number of anti-epileptic drugs tried before CBD was 12.

Sixteen of 19 families reported a reduction in their child's seizure frequency while taking CBD-rich cannabis. Two reported complete seizure freedom. Eight reported a greater than 80% reduction in seizure frequency. (Interestingly, this corresponds to what Walley found in reviewing the animal studies.) Six patients in the Stanford survey experienced a 25-60% reduction.

Beneficial effects included increased alertness, better mood and improved sleep. Adverse effects included drowsiness and fatigue (which may have been brought on in part by AEDs. The authors didn't specify which child was on which pharmaceuticals.)

Also in December 2013, Drs. Margaret Gedde and Edward Maa, at a meeting of the American Epilepsy Society reported very promising results from 11 patients who had used oil from Charlotte's Web for three months. All the children experienced at least 20% seizure reduction. Nine had at least 75% reduction. Eight had at least 98% reduction. And five had 100% reduction. (Gedde notes that the patients in the study "were selected by the provider of the extract.")

CBD's Anticonvulsant Mechanism of Action

CBD does not act directly on the CB1 receptor. It works by multiple actions —what has been termed "polypharmacology," exerting various effects within different parts of the brain that might defuse seizures. I explain it in comparison to the AEDs that parents are all familiar with.

CBD blocks NMDA receptors, which are involved in excitation. Felbamate acts similarly.

CBD binds to GABA receptors, enhancing the inhibition of excitation —as do Felbamate, Depakote, Tegratol, Onfi, and Phenobarbital.

CBD stabilizes ion channels —as do Banzel, Lamictal, Dilantin, Keppra, and Trileptal.

CBD modulates calcium release in neurons, blocking the uptake of endocannabinoids in order to normalize endocannabinoid tone.

CBD counters inflammatory reactions that appear to increase neuronal excitability and impair cell survival. This is why the National Football League is reviewing a proposal that CBD be provided to players suffering head injuries. CBD is neuroprotective; it reduces oxidative stress and glutamate toxicity.

Obtaining Medicine

The question of where to get their oil and what to use is a family decision. It's hard to find consistent CBD growers in Southern California at this time [September 2014]. There are only a few suppliers of oil that seem to be consistent bottle to bottle. There have been instances of CBD oil products having similar CBD content but having different effects, as they are prepared from different CBD strains.

Having a producer who makes oil from one specific strain increases the likelihood of obtaining consistent medication from month to month. Certain terpenes (essential oils in the cannabis plant) are known to have beneficial medicinal effects. Beta caryophyllene, a terpene that binds to the CB2 receptor, is a potent anti-inflammatory that appears to work synergistically with CBD. Both Charlotte's Web and AC/DC strains contain high amounts of this terpene.

Anybody who is making oil should know that parents get it tested and share the lab results on websites. Some of these parents will get it tested at two or three different labs so they know what is in the oil that they are giving to their child.

Having a reliable supply, one that is available and won't be "out of stock," is also crucial. Patients who start CBD oil treatment may wean their children off other medications. It could be catastrophic if a child is weaned off their anti-epileptic drugs and the CBD oil supplier did not continue to provide the oil that had been working.

Affordability

Affordability is a major concern for most families. They are paying anywhere from $150/month for a small child and up to $1800/ month for an adult-sized teenager.

One oil provider in Southern California is trying to be consistent with concentrated oil made from AC/DC plants. Their oil costs nine cents per mg, which is relatively affordable. Other CBD-rich oils used by my patients cost between 17 cents and 33 cents per milligram.

Realm of Caring is subsidized by the Stanley Brothers Social Enterprises so they can make their oil available for five cents a milligram.

I have had five patients who have had to discontinue treatment because they could not afford the oil. These patients have remained on AEDs and are on the waiting list for more affordable oil from Realm of Caring.

Other patients are using lower-than-ideal doses because they're at their limits financially

CBD use by Diagnosis

Lennox-Gastaut Syndrome: Of 10 patients with LGS, ages two to 14, the parents all reported > 25% seizure reduction. Parents also reported that their children were more alert, more interactive, happier, and had quicker recovery from seizure. Eight of the 10 were able to wean AEDs, two got off the ketogenic diet. There were no reports of negative side effects.

There were eight Dravet patients, ages four to 20. Four of reported 75-90% seizure reduction. One reports 35% reduction. Three report no change. All parents report improved alertness, behaviors, memory, ability to learn, better speech, improved social and motor skills, improved appetite and sleep. One parent reported "better sense of humor." Half have been able to wean AEDs. There were no reports of negative side effects.

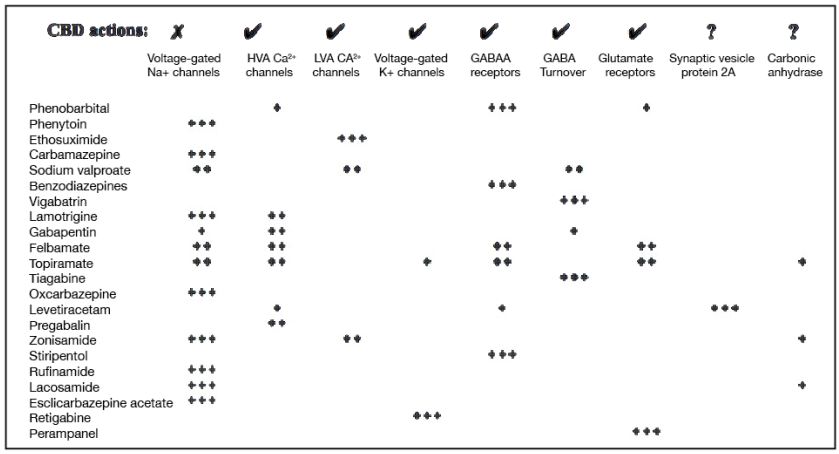
Of nine patients with other genetic syndromes, ages two to 17 years, one was seizure free. Four reported 75-90% reduction in frequency. Three reported 50% reduction. One reported no change. Most reported improved alertness, better sleep and appetite. One parent reported side effect of fatigue. Six of nine weaned at least one AED.

Of four patients with Infantile Spasms (West's Syndrome), ages nine to 18 months, one was seizure free, two had 80-90% reduction, one reported no effect from CBD. All parents reported improved development and better eye contact. All reported no negative side effects. Significant development takes place in the first year of life. Many parents state that development is arrested when their very young child has frequent seizures. With reduction of seizures with CBD, development can continue to move forward.

Tuberous Sclerosis: one patient soon after starting CBD was able to wean off Onfi, reduce trileptal, and had 75% fewer seizures. She improved in that she began trying to vocalize and interact with her caregivers.

Compound	Species	Studies	Dose	Anticonvulsant	No effect	Proconvulsant
THC	6	31	0.25-200 mg/kg	61%	29%	10% [1]
CBD	2	21	1-400 mg/kg	81%	19%	0%
Other plant cannabinoids	2	7	N/A	100%	0%	0%
CB1 agonists	2	55	N/A	73%	18%	2%

Summary of preclinical evidence was presented by University of Reading pharmacologist Ben Walley at the October, 2013, conference on Cannabidiols and Epilepsy at NYU. "Studies" refers to the separate conditions, models, and designs reviewed. In none of the 21 projects involving CBD or CBDV did researchers see a proconvulsant effect.



CBD acts in ways similar to various Anti-Epilepsy Drugs listed at left. In this chart developed by AJ Hill and colleagues, + signs indicate the relative strength of the interactions (row at top) that have been observed in the lab. "This is a slide that parents find very useful," according to Goldstein. "Instead of having to take all these different drugs, they can get many of the benefits with one medication."

P.S. 3/22/15: As of December 2014 there was no longer a waiting list for the CBD-rich oil made from the Charlotte's Web strain by the Realm of Caring Foundation. Good quality CBD rich oil from the ACDC strain has also become readily available in Southern California. I have seen an additional 100+ pediatric patients with refractory epilepsy since reviewing my files for this article and will be reporting on their results after three months of treatment and observation. Interestingly, a few patients who have reported excellent results have found, after 9 months or so, an increase of seizures or lethargy that appears to be unrelated to any other cause. Parents in Colorado also noticed this phenomena and found that stopping CBD for a few days, then restarting at a slightly lower dose (10-15% less) completely resolved the issues. It might be that there may be a point at which the endocannabinoid system is "full" and does not need as much cannabinoid medicine. This makes sense as the endocannabinoids are produced "on demand" in response to a trigger. Presumably by taking a break from the CBD oil or decreasing the dose, the endocannabinoid system can reset itself. Research into this phenomenon is greatly needed. —*B.G.*

CBD-Drug Interactions: the role of Cytochrome px450

By Adrian Devitt-Lee

With cannabidiol (CBD) poised to become widely available in pharmaceutical, nutraceutical, and herbal preparations, medical scientists are taking a closer look at CBD-drug interactions.

CBD and other plant cannabinoids can potentially interact with many pharmaceuticals by inhibiting the activity of cytochrome P450, a family of liver enzymes. This key enzyme group metabolizes most of the drugs we consume, including more than 60 percent of marketed meds.

Metabolizing THC

When THC or any other foreign compound enters the body, it is metabolized. Metabolizing something properly can involve multiple molecular pathways and various enzymes that enable the body to get rid of the compound (often done by adding something to the original compound). Or metabolism can entail breaking down a compound into a more basic molecule that the body then uses.

Products of a drug's metabolism are called its metabolites. These metabolites can have very different properties than the initial drug. Ethanol, for example, owes some of its effects, including much of the hangover, to its two-step metabolism.

The buildup of acetaldehyde in the liver—while ethanol is converted first to acetaldehyde and then to acetic acid—is a major reason for ethanol's liver toxicity and the nausea and vomiting caused by excessive consumption.

THC metabolites contribute significantly to the effects of cannabis consumption. Eleven-hydroxy-THC (11-OH-THC), for example, is a THC metabolite that activates the CB1 cannabinoid receptor in the brain and induces a high more potently than THC itself. This means that the body's metabolism of THC can make it more potent.

Cytochrome P450 enzymes contribute to the metabolism of drugs by oxidizing them, which generally means incorporating an oxygen atom into the drug's molecular structure. Oxidation will usually make a compound more water soluble and therefore easier for the kidneys to filter out. Both steps in the metabolism of ethanol, mentioned above, and the conversion of THC into 11-OH-THC involve oxidation (though ethanol is not oxidized specifically by cytochrome P450).

Different routes of cannabinoid administration have different effects. Inhaled THC enters capillaries in the lungs, passes into the general circulation, and quickly crosses the blood-brain barrier. When ingested orally, however, THC is absorbed in the small intestine and then carried to the liver, where it is metabolized by subclasses of cytochrome P450 (abbreviated CYP), specifically the CYP2C and CYP3A enzymes.

These liver enzymes also metabolize CBD, converting it into 7-OH-CBD and 6-OH-CBD. But there has been relatively little research into the properties of these CBD metabolites.

Metabolizing CBD

The way CBD interacts with cytochrome P450 is pivotal; in essence, they deactivate each other. Preclinical research shows that CBD is metabolized by cytochrome P450 enzymes while functioning as a "competitive inhibitor" of the same liver enzymes. By occupying the site of enzymatic activity, CBD displaces its chemical competitors and prevents cytochrome P450 from metabolizing other compounds.

The extent to which cannabidiol behaves as a competitive inhibitor of cytochrome P450 depends on how tightly CBD binds to the active site of the metabolic enzyme before and after oxidation. This can change greatly, depending on how—and how much—CBD is administered, the unique attributes of the individual taking this medication, and whether isolated CBD or a whole plant remedy is used.

If the dose of cannabidiol is low enough, it will have no noticeable effect on CYP activity, but CBD may still exert other effects. There is no clearly established cut-off dose below which CBD does not interact with other drugs.

A 2013 report on a clinical trial using GW Pharmaceutical's Sativex, a whole plant CBD-rich sublingual spray, found no interactions with CYP enzymes when approximately 40mg of CBD were administered. A subsequent clinical trial, however, found that 25mg of orally administered CBD significantly blocked the metabolism of an anti-epileptic drug.

How do CBD-generated changes in cytochrome P450 activity impact the metabolic breakdown of THC? Animal studies indicate that CBD pretreatment increases brain levels of THC. That's because CBD, functioning as a competitive inhibitor of cytochrome P450, slows down the conversion of THC into its more potent metabolite, 11-OH-THC. Consequently, THC remains active for a longer duration, but the peak of the extended buzz is blunted somewhat under the influence of cannabidiol.

Other factors figure prominently in CBD's ability to lessen or neutralize the THC high.

Grapefruit and Ganja

Lester Bornheim, a research pharmacologist at the University of California San Francisco, was awarded a NIDA grant in 1987 to investigate the effects of phytocannabinoids on cytochrome P450 enzymes. THC and cannabinol (CBN) also inhibit CYP activity, but CBD, of all the plant cannabinoids studied, is the strongest cytochrome P450 deactivator.

"It's a very unusual enzyme. Almost all other enzymes are designed to fit a single substrate and carry out a single chemical process resulting in a single product," Bornheim noted, whereas numerous drugs are substrates for cytochrome P450, which seems to function like a generic breakdown mechanism for a wide range of exogenous and endogenous substances.

In a 1999 presentation to the International Cannabinoid Research Society, Bornheim drew attention to the possibility that CBD could interfere with the metabolism of many medications.

A year earlier, Canadian scientists had identified certain compounds in grapefruit that inhibit the expression of some cytochrome P450 enzymes—which is why physicians often warn patients not to eat grapefruit before taking their meds. CBD, it turns out, is a more potent inhibitor of cytochrome P450 enzymes than Bergapten (the strongest of several grapefruit components that inhibit CYPs).

What does this mean in practical terms for a medical marijuana patient on a CBD-rich treatment regimen who takes a prescription blood-thinner like warfarin, for example? CBD reduces the enzymatic degradation of warfarin, thereby increasing its duration of action and effect. A person taking a CBD-rich product should pay close attention to changes in blood levels of warfarin, and adjust dosage accordingly, as instructed by their doctor.

Cancer and Epilepsy

In cancer treatment, the precise dosing of chemotherapy is extremely important; doctors often struggle to find the maximum dose that will not be catastrophically toxic. Many chemotherapy agents are oxidized by CYPs before their inactivation or excretion. This means that for patients using CBD, the same dose of chemotherapy may produce higher blood concentrations. If CBD inhibits the cytochrome-mediated metabolism of the chemotherapy and dosage adjustments aren't made, the chemotherapy agent could accumulate within the body to toxic levels.

By and large, however, there have been few reported adverse cannabinoid-drug interactions among the many cancer patients who use cannabis to cope with the wrenching side effects of chemotherapy.

It is possible that whole plant cannabis, with its compensatory synergies, interacts differently than the isolated CBD that is administered in most research settings. As well, the cytoprotective effects of the cannabinoids may mitigate some of the chemotherapeutic toxicity.

Some epileptic patients have encountered issues with how CBD interacts with their anti-seizure medication. A small clinical study at Massachusetts General Hospital involving children with refractory epilepsy found that CBD elevated the plasma levels and increased the long-term blood concentrations of clobazam, an anticonvulsant, and norclobazam, an active metabolite of this medication.

A majority of these children needed to have their dose of clobazam reduced due to side effects. Given that both clobazam and CBD are metabolized by cytochrome P450 enzymes, a drug-drug interaction is not surprising. Published in May 2015, the study concluded that "CBD is a safe and effective treatment of refractory epilepsy in patients receiving [clobazam]." But the report also emphasized the importance of monitoring blood levels for clobazam and norclobazam in patients using both CBD and clobazam.

Dr. Bonni Goldstein has observed cases in which small doses of high-CBD/low-THC cannabis oil concentrate seemed to aggravate seizure disorders rather than quell them. How could this happen, given CBD's renown anti-epileptic properties?

A 1992 review by Bornheim and his colleagues indicated that CBD inhibits some cytochrome P450 enzymes at smaller doses than what is required for CBD to exert an anti-epileptic effect. This means that a certain dose of CBD could alter the processing of an anti-epileptic drug taken by the patient, but this amount of CBD might not be enough to provide any anti-epileptic relief itself.

The advice some physicians offer in this situation may seem counterintuitive: Increase the dose of CBD—perhaps even add a little more THC (or THCA, the raw, unheated, non-psychoactive version of THC)—and this may be more effective for seizure control.

Enigmatic Enzymes

But why would preventing the breakdown of an anti-epileptic drug reduce its effect? The answer depends on the drug in question. The active component of the drug (the chemical that exerts an anti-epileptic effect) may be a breakdown product of the actual drug taken. So, by slowing the metabolism of the original drug, CBD would make that drug less active.

Other explanations are conceivable. For example, if the activity of certain CYPs is slowed, the drug may be broken down by another metabolic pathway, the products of which could then interfere with the drug's activity. Or perhaps the inhibition of CYPs is not the predominant way that CBD interacts with certain anti-epileptic medications.

To complicate matters even further, a presentation by Dr. Kazuhito Watanabe at the 2015 International Cannabinoid Research Society meeting in Nova Scotia disclosed preliminary evidence that cannabidiol may "induce"—meaning amplify the activity of—some cytochrome P450 enzymes. (Induction of a protein involves increasing the transcription of its corresponding mRNA, which leads to greater synthesis of the protein.) This suggests that CBD can either increase or decrease the breakdown of other drugs. Again, it depends on the drug in question and the dosages used.

Any pharmaceutical, nutraceutical or green rush scheme to exploit the therapeutic potential of CBD must reckon with the fact that cannabidiol can both inactivate and enhance various cytochrome P450 enzymes in the liver—and this can potentially impact a wide range of medications.

Drug interactions are especially important to consider when using life-saving or sense-saving drugs, drugs with narrow therapeutic windows, or medications with major adverse side effects. In particular, those who utilize high doses of CBD concentrates and isolates should keep this in mind when mixing remedies.

Sources

Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. 1998. Br J Clin Pharmacol. 2004.

Bland TM, Haining RL, Tracy TS, Callery PS. CYP2C-catalyzed delta9-tetrahydrocannabinol metabolism: kinetics, pharmacogenetics and interaction with phenytoin. Biochem Pharmacol. 2005.

Bornheim LM, Everhart ET, Li J, Correia MA. Characterization of cannabidiol-mediated cytochrome P450 inactivation. Biochem Pharmacol. 1993.

Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015.

Jiang R, Yamaori S, Takeda S, Yamamoto I, Watanabe K. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. Life Sci. 2011.

Klein C, Karanges E, Spiro A, Wong A, Spencer J, Huynh T, et al. Cannabidiol potentiates Delta(9)-tetrahydrocannabinol (THC) behavioural effects and alters THC pharmacokinetics during acute and chronic treatment in adolescent rats. Psychopharmacology. 2011.

Stott C, White L, Wright S, Wibraham D, Guy G. A phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the phamacokinetics of THC/CBD oromucosal spray in healthy volunteers. SpringerPlus. 2013.

Watanabe K, Yamaori S, Funahashi T, Kimura T, Yamamoto I. Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. Life Sci. 2007.

Yamaori S, Ebisawa J, Okushima Y, Yamamoto I, Watanabe K. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety. Life Sci. 2011.

Yamaori S, Kinugasa Y, Takeda S, Yamamoto I, Watanabe K. Cannabidiol induces expression of human cytochrome P450 1A1 that is possibly mediated through aryl hydrocarbon receptor signaling in HepG2 cells. Life Sci. 2015.

Yamaori S, Kushihara M, Yamamoto I, Watanabe K. Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. Biochem Pharmacol. 2010.

Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. Drug Metab Dispos. 2011.

Yamaori S, Okushima Y, Masuda K, Kushihara M, Katsu T, Narimatsu S, et al. Structural requirements for potent direct inhibition of human cytochrome P450 1A1 by cannabidiol: role of pentylresorcinol moiety. Biol Pharm Bull. 2013.

Adrian Devitt-Lee is a senior at Tufts University, studying mathematics and chemistry.

"I have always loved things like seashells or litle bits of coloured rock —all the odd treeasures one picks up as a child. A bright bird's feather, a variegated leaf —these things, I sometimes feel, are the true treasures of life, and one enjoys them better than topazes, emeralds, or expensive little boxes by Fabergé."

—Agatha Christie

Dr. Abrams' recruitment problem: patients already know treatment helps

The University of California San Francisco's Donald Abrams, MD, is seeking people with Sickle Cell Disease to take part in a study of cannabis as a treatment for pain, now underway at San Francisco General Hospital (SFGH).

The cannabis, being supplied by the National Institute on Drug Abuse, is 5% THC and 5% CBD. Patients vaporize three times a day during two five-day stints at SFGH's historic Clinical Research Center. During one stint they'll be vaporizing placebo.

Kalpna Gupta

Eleven patients have taken part so far. The goal is to enroll a total of 35.

Sickle Cell Disease is a genetic blood disorder that causes intense pain and is generally treated with opioids. It afflicts African Americans and a smaller percentage of African Latinos. *(See story below at right).*

The study was generated by the findings of Kalpna Gupta, MDPhD, a professor of medicine at the University of Minnesota. Working with a mouse model of sickle cell disease, Gupta showed that synthetic cannabinoids decreased pain, inflammation and "markers of disease progression." She hypothesized that cannabinoid medicine would enable patients to reduce opioid use and achieve better pain control.

Gupta got a large grant from the National Heart, Lung and Blood Institute (part of NIH) to study cannabinoids in the treatment for of Sickle Cell Disease. She asked Abrams to conduct a human "proof of principle" study consisting of two arms, one of which had to be a placebo. He chose to test NIDA's variety with equal amounts of CBD and THC.

Work on the project was stalled for several months in the winter of 2013-14 when federal spending was "sequestered" by Congress. Funding was released in April 2014 and Abrams then began seeking the approvals necessary to conduct the research —from SFGH Clinical Research Center Medical Advisory Committee, UCSF Institutional Review Board, the Research Advisory Panel of California, DEA (local and federal), FDA, NIDA and the NIH funding Institute (NHLBI in this case).

Donald Abrams

"In general the FDA has been very cooperative and supportive of everything that I've done," says Abrams, "but when we submitted the IND to study this CBD-THC cannabis, they said I couldn't proceed until I gave them two animal pulmonary histopathology studies showing the effects of inhaling CBD on the lungs. They said that cannabidiol was an NME – a novel molecular entity that had not yet been given to people. I said '*What?*'"

FDA also gave Abrams the option of enrolling patients previously exposed to CBD "'so you're not putting them at any greater risks than they've put themselves,'" he was told. "And then they made us add that CBD could cause sterility in men!"

What patients know

"Many patients with Sickle Cell have already discovered that cannabis is useful for pain," says Abrams. "We hear from some of them that their friends don't want to come in because they don't want to risk five days vaporizing placebo.

"We recently had a patient admitted who felt that she was getting placebo, and on day three she experienced a painful crisis. She needed to be transferred to the emergency room and did not complete the five day segment of the study." She will come back and do the second five day period, says Abrams, who is still blinded.

UCSF's IRB asked Abrams to change the consent form to say that patients randomized to the placebo may experience an increase in pain, even a crisis.

Abrams originally planned to study the effects of cannabis on Sickle Cell patients who were using opioids, but modified the protocol after learning that "many sickle cell patients don't need opiates... Now we're just looking at the effects of adding CBD-THC or placebo to their baseline pain regimen. They can be on opioids but they don't have to be."

It's ironic that Gupta originally involved Abrams because he is a DEA-approved researcher in a DEA-approved setting —San Francisco General Hospital has a locked and alarmed refrigerator to store the NIDA cannabis and a ward from which no fumes escape— only to encounter a new obstacle: patients who already know the answer to the question.

Clinical Trial of Vaporized Cannabis

For Chronic Pain Caused By Sickle Cell Disease

This UCSF study at San Francisco General Hospital (SFGH) will evaluate whether using vaporized cannabis reduces pain in people who are taking opioid medications for chronic pain associated with sickle cell disease.

To join this study you must

- Have a diagnosis of sickle cell disease
- Be taking a stable regimen of pain medications, including an opioid (such as morphine, oxycodone, hydromorphone, etc.) for chronic sickle cell disease-associated pain.
- Be able and willing to spend two separate periods of 5 days and 4 nights in the Clinical Research Center at SFGH.
- Have smoked cannabis on at least 6 occasions in your lifetime
- NOT use cannabis for one week prior to starting the study.
- Agree to use adequate birth control during this study.
- NOT be pregnant or breast-feeding, if you are a women who can become pregnant. You will be tested for pregnancy at screening.
- Be able to read and speak English.
- NOT have any severe heart, lung, kidney, or liver problems.
- NOT currently be using smoked tobacco products.
- NOT test positive for alcohol or injection drugs, as determined by urine screening.
- Meet certain other criteria.

If you are eligible you will:

- Spend two 5-day periods in a clinical research center at SFGH
- Have blood tests and other measurements done
- Inhale cannabis three times a day, using the Volcano™ vaporizer.
- Keep a pain diary for 5 days prior to both hospitalizations to track your pain and medication use.

You can receive up to $560 for participating.

For more information call (415) 476-4082 ext. 146

Black Lives Matter

From Sister Somayah Kambui to O'Shaughnessy's in 2007

Though the list says it was put together by Dr. Mikuriya, and although Thallasemia is a genetic variant of sickle cell, Sickle Cell Disease was ignored in the article.

Fir niore than 20 years, the Crescent Alliance Self Help for Sickle Cell, founded by Sister Somayah Moore-Kambui, has been on the front line advocating for cannabis to be included in sickle cell research.

People living with Sickle Cell Disease have found Cannabis to be most beneficial in their lives. Using all parts of the plant, for both therapeutic and nutritional support has been the primary work and study of of peer research within the Crescent Alliance.

The people at O'Shaughnessy's should be well familiar with Sister Somayah and her struggle to get the City of Los Angeles to apply the CUA 1996 instead of defying and refusing to apply the CUA 1996 to her as well as to all citizenry of the City of Los Angeles.

Can anyone give me a sound reason why Sickle Cell Disease should be excluded from O'Shaughnessy's published "Chronic Conditions Treated With Cannabis?" Certainly, between 1990 and 2005 it is well known that people living with Sickle Cell Disease get therapeutic and curative benefits from consuming cannabis from its seed oil, plant concentrates and extracts as well as overall optimum health in people living with sickle cell disease.

Cannabis addresses the violent episodes of pain, and overall comfort for sickle cell sufferers, but the primary benefit is in eating healthy foods enhanced with cannabis, so as to allow the body to heal itself, produce healthier bloodcells allowing longevity of life and quality of life enhanced. We should also be linking our sites together, shouldn't we?

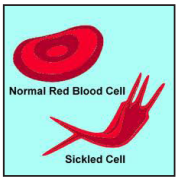
Chris Conrad, Sister Somayah, Mikki Norris. Photo by Brenda Kershenbaum.

Sickle Cell Disease and Cannabis

By Jay Cavanaugh, PhD

Some 70,000 Americans suffer from Sickle Cell Disease —a genetic blood disorder that primarily affects African Americans, Latinos, and those of Mediterranean origin. One African American in 650 will be born with the disease.

Normal red blood cells are made of two types of hemoglobin and have a round shape that allows the blood cells to move through capillaries. A mutation of one type of hemoglobin can produce malformed hemoglobin that causes the red blood cells to adopt a sickle shape which causes the red blood cells to clog capillaries.



Sickle cell disease is a recessive genetic trait. Carrying just one sickle gene actually confers a greater ability to fight malarial infections while carrying two sickle cell genes results in defective red blood cells responsible for the symptoms of the disease.

Routinely genetic screening (a blood test and/or DNA) should be done if any relatives have the disease. If one of the parents is a carrier and the other not then there is no chance that offspring will have the disease but they will have a 50% of being a carrier. If both parents are carriers the chances are 1⁄4 that the child will have Sickle Cell and 3⁄4 chance of being a carrier of the mutant gene.

Those with the disease usually have lives shortened by their bodies' reduced ability to fight infection, organ damage from "crises," strokes and heart attacks. Most patients experience an average of one "crisis" each year. These attacks often result in hospitalization. Some patients have several episodes of severe illness each year. Each episode can cause organ and nerve damage that may persist after the attack.

Episodes can be mild or severe. In more severe attacks, life-threatening problems can occur, such as a stroke or breathing problems due to fluid in the lungs. Potential complications include:

Anemia caused by splenic breakdown of sickle cell RBC's.
Blood clots (thrombosis)
Pain in various parts of the body, especially the joints.
Stroke
Eye problems (proliferative retinopathy)
Infections, such as pneumonia
Fluid in the lungs during severe attacks
Enlarged heart or heart murmur
Liver problems, such as jaundice and gallstones
Blockage of the spleen/loss of spleen function
Kidney damage
Painful erections (priapism)
Bone problems (osteomyelitis and avascular necrosis)
Leg ulcers
Delayed growth

The primary treatment of Sickle Cell "crises" is rehydration and pain control. Pain can be of excruciating severity and may require both non-steroidal anti-inflammatory agents and major narcotics of the opiate class.

Cannabis does not cure Sickle Cell but is a highly effective agent in managing pain. Patients utilizing medical cannabis can expect better pain relief with lower doses of major narcotics. Cannabis also acts as a powerful anti-inflammatory without NSAID side effects. Cannabis acts both centrally in the brain and directly in the periphery. Further, cannabis provides neuroprotective effects that may reduce the incidence of retinopathy and neuropathy.

The above information from pharmacist Jay Cavanaugh was posted on the American Alliance for Medical Cannabis website in 2006.

The letter at left from Sister Somayah Moore-Kambui is another example of patients' advanced awareness. In 2006 Tod Mikuriya, MD, published his master list of "Chronic Conditions Treated With Cannabis as reported to California physicians, 1990-2005" in O'Shaughnessy's *—and omitted Sickle Cell Disease, which prompted Sister Somayah's letter.*

PTSD associated with cannabinoid deficits

By Martin A Lee

A recent article in the journal *Neuroendocrinology* highlights the crucial role of the endocannabinoid system in protecting against post-traumatic stress disorder (PTSD), a debilitating chronic condition involving horrific memories that can't be erased.

In an effort to understand the neurobiological mechanisms that underlie the onset and development of PTSD, a team of U.S. and Canadian scientists analyzed 46 subjects who were near the World Trade Center in New York City during the September 11 terrorist attacks. Twenty-four of these subjects suffered from PTSD following the attacks; 22 did not.

The researchers found that people with PTSD had lower serum levels of anandamide, an endogenous cannabinoid compound, compared to those who did not show signs of PTSD after 911. Innate to all mammals, anandamide triggers the same brain receptors that are activated by THC (tetrahydrocannabinol, The High Causer) and other components of the marijuana plant.

CB1 receptor signaling deactivates traumatic memories and endows us with the gift of forgetting.

Concentrated in the brain and central nervous system, the cannabinoid receptor known as CB1 mediates a broad range of physiological functions, including emotional learning, stress adaption, and fear extinction. Scientists have determined that normal CB1 receptor signaling deactivates traumatic memories and endows us with the gift of forgetting.

But CB1 signaling that is skewed due to endocannabinoid deficits (such as low serum levels of anandamide), results in impaired fear extinction, aversive memory consolidation, and chronic anxiety, the hallmarks of PTSD.

PTSD is one of many enigmatic conditions that may be associated with a dysfunctional endocannabinoid system. A 2009 report by Virginia Commonwealth University scientists discerned a link between the dysregulation of the endocannabinoid system and the development of epilepsy. Researchers at the University of Rome in Italy have documented low levels of anandamide in the cerebrospinal fluid in patients with untreated newly diagnosed temporal lobe epilepsy.

Dr. Ethan Russo postulates that "clinical endocannabinoid deficiency" underlies migraines, fibromyalgia, irritable bowel disease, and a cluster of related degenerative conditions – which may respond favorably to cannabinoid therapies.

Alcoholism induces endocannabinoid deficits. So does lack of exercise and a diet laden with corn syrup and artificial sweeteners.

Individuals have different congenital endocannabinoid levels and sensitivities that factor into how one responds to stress and trauma. Alcoholism induces endocannabinoid deficits. So does lack of exercise and a diet laden with corn syrup and artificial sweeteners.

Additional research has established that clinical depression is associated with endocannabinoid-deficits. Canadian scientist Matthew Hill analyzed the "serum endocannabinoid content" in depressed women and found that it was "significantly reduced" compared with controls.

Animal studies show that chronic stress is associated with decreased endocannabinoid levels. Cannabinoid receptor signaling has been identified as a key modulator of adaptation to stress.

Chronic stress has a different effect than acute stress.

In healthy individuals, acute stress triggers a spike in endocannabinoid levels. Scientists view this as a protective response – the fleeting uptick of anandamide eases stress and facilitates homeostasis (a return to baseline) by dialing down the production of stress hormones.

But chronic stress has a different effect than acute stress. Chronic stress depletes endocannabinoid tone and sets the stage for all manner of illness. Chronically elevated stress levels boost anxiety and significantly hasten the progression of Alzheimer's dementia. Emotional stress has been shown to accelerate the spread of cancer. Stress alters how we assimilate fats.

In 2012, a team of Brazilian scientists found that chronic stress decreases CB-1 receptor binding and expression in the hippocampus, an area of the brain that plays a major role in short and long-term memory consolidation. This has major implications for treating PTSD.

Chronic stress impairs endocannabinoid signaling and impedes fear extinction, according to NYU Medical Center professor Alexander Neumeister. In a 2013 paper in *Depression and Anxiety* Neumeister argued for PTSD treatments that target the endocannabinoid system.

The Role of FAAH

Neumeister notes that "chronic stress produces an upregulation" of a crucial metabolic enzyme –Fatty Acid Amide Hydrolase, otherwise known as FAAH– which decisively influences endocannabinoid signaling.

It's the aberrant up-regulation and/or down-regulation of genes – more so than the genes themselves – that drives disease vectors. Stress messes with gene expression.

Various enzymes are involved in the biosynthesis and creation of anandamide; other enzymes break down endogenous cannabinoid compounds. The FAAH enzyme figures prominently in the metabolic breakdown of anandamide and several other fatty acid messenger molecules. FAAH degrades these endogenous compounds; this is part of the normal, fleeting life cycle of anandamide and its fatty acid cousins.

Polymorphisms —unusual amino acid sequence repeats— in the genes that encode FAAH are associated with a propensity for drug addiction and predisposition toward various afflictions. But it's the aberrant up-regulation and/or down-regulation of genes – more so than the genes themselves – that drives disease vectors. Stress messes with gene expression.

Chronic stress upregulates FAAH. And more FAAH results in lower endocannabinoid levels. Conversely, less FAAH means more anandamide, and more anandamide means elevated cannabinoid receptor signaling.

Cannabidiol –CBD– is a nonpsychoactive component of marijuana and hemp that enhances endocannabinoid tone by inhibiting the FAAH enzyme. And this is just one of the ways that CBD shows promise as a treatment for PTSD.

Brazilian scientists report that CBD reduces anxiety in animal models by binding directly to the 5HT1A serotonin receptor; activating this receptor confers an anxiolytic and anti-depressant effect. Preclinical research in Brazil indicates that "CBD has beneficial potential for PTSD treatment and the 5HT1A receptors could be a therapeutic target in this disorder."

CBD and other therapeutic interventions that enhance cannabinoid receptor signaling could become breakthrough treatments for PTSD. CB1 receptor transmission, in particular, has emerged as a target of novel cannabinoid-based remedies for anxiety and other mood disorders tied to stressful life events.

Smoking marijuana is one method of augmenting CB1 receptor transmission. Numerous combat veterans and other PTSD patients claim that nothing can calm the storm that rages in their heads like a few puffs of pot. A 2011 observational study by Israeli scientists found that smoked cannabis, which directly activates the CB1 receptor, improved symptoms of PTSD.

Some scientists aren't optimistic about-marijuana as a PTSD treatment option. NYU's Neumeister contends that despite "their potential therapeutic value, direct-acting cannabinoid receptor compounds [such as THC] have very limited medical applications, mainly because of their undesirable psychotropic side effects and ability to cause addiction."

This assertion reflects political assumptions rather than scientific fact. The premise –that the marijuana high is an adverse side effect– is biased.

Cannabis doesn't cause addiction any more than food causes a person to become a compulsive eater.

Cannabis doesn't cause addiction any more than food causes a person to become a compulsive eater.

Dissing smoked cannabis as "an appealing short-term 'solution' that will more likely create longer term problems," Neumeister favors "blocking endocannabinoid deactivation" by inhibiting FAAH, which "may lead to a more circumscribed and beneficial spectrum of biological responses than those produced by direct CB-1 receptor activation."

PTSD sufferers can't afford to wait for whatever benefits synthetic FAAH-inhibitors may offer.

Big Pharma has its sights set on developing and patenting synthetic FAAH-inhibitors to treat PTSD, depression, and other pathological conditions –the very same conditions for which whole plant cannabis provides relief.

But PTSD sufferers can't afford to wait for whatever benefits synthetic FAAH-inhibitors may offer in the years ahead. They need help now. Many self-medicate with THC-dominant strains to deal with anxiety, insomnia, nightmares and other symptoms of post-traumatic stress. Others have begun using CBD-rich extracts and flowers.

Sources

Campos AC, et al, "Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors," Journal of Psychiatric Research, 2012 Nov4; 46(11):12501-10

Campos, et al, "Predator threat stress promotes long-lasting anxiety-like behaviors and modulates synaptophysin and CB1 receptors expression in brain areas associated with PTSD symptoms," Neuroscience Letters (2012) http://dx.doi.org/10.10.16/j.neulet 2012.11.016

Ganon-Elazar E, Akirav I, "Cannabinoids and traumatic stress modulation of contextual fear extinction and GR expression in the amygdala-hippocampal, prefrontal circuit," Psychoneuroendocrinology, 2013 Feb 20.

Gorzalka BB, et al, "Regulation of endocannabinoid signaling by stress: implications for stress-related affective disorders," Neuroscience Biobehavioral Review, 2008 Aug.

Hill, MN, et al, "Reductions in circulating endocannabijoid levels in individuals with post-traumatic stress disorder following exposure to the world trade center attacks," Psychoneuroendocrinology, 2013 Sept 10.

Hill, MN, et al, "Endogenous cannabinoid signaling is essential for stress adaptation," Proceedings of the National Academy of Science USA, 2010 May 18.

Hill, MN, et al, "Downregulation of endocannabinoid signaling in the hippocampus following chronic unpredictable stress," Neuropsychopharmacology, 2005 March

Mikuriya, Tod, MD, "Cannabis Eases Post-Traumatic Stress," O'Shaughnessy's, Spring 2006.

Neumeister, Alexander, "The endocannabinoid system provides an avenue for evidence-based treatment development for PTSD," Depression and Anxiety, 30:93-96 (2013).

Guernica, a mural by Pablo Picasso expressed the shock and horror people felt when aerial bombing of civilian populations was adopted as a tactic by the fascists during the Spanish Civil War. Now it's acceptable "collateral damage."

Findings and Observations

From Robert Sullivan, MD

What do you tell patients re dabbing? What have they told you?

I tell them that it's like a concentrate of a concentrate, very potent. Some of my patients who've developed a tolerance say they like it, usually because they don't need to smoke much of it and it still works. It is sort of faddish.

I also tell them that having to use a tungsten nail and a torch reminds me too much of hard drugs. That it apparently can be useful for people using it as a treatment for various cancers. And that the butane extraction method is criticized by some people who don't believe it evaporates completely, thus leaving a possible toxic residue that, if present, would definitely be a big concern, and that I couldn't give them a definitive answer to that question.

What feedback are you getting re CBD?

Some patients who have adopted it find it has improved their lives very much and they resonate much happiness. Some others aren't interested because they like the high THC and don't think the varieties they're using lack medical effect, so why change? Most haven't tried it but are very interested in doing so. They like the idea of remaining more functional, more clear-headed. I've been explaining it to every patient I see for the last two years so they can explore it if they wish.

For what conditions, if any, are patients using cannabis concentrates ("oil," etc.) With what results?

For any of the usual conditions they want. I'm not aware of concentrates being especially good for any certain conditions. It seems to work fine. Most prefer it because they're smoking less cellulose (plant matter) and have to inhale less to get good results. And, of course, you can make good concentrates from the trimmed material ("shake"), so that's a nice practical use of material some people would otherise throw away

How many patients have you authorized to use cannabis over the years?

I'd estimate about 12-15,000 different people over 10 years, most having returned many times now for annual renewals, so I've gotten to know them fairly well.

With what medical conditions have they presented? List top five and approximate percentage (total can exceed 100%).

The medical conditions are very many and wide ranging in systems. Here's an incomplete list by diagnosis or symptom:

- Arthritis of many kinds —20%
- Pain of diverse causes —40%
- Insomnia of many causes —50%
- Anxiety/Depression —14%
- GI conditions of diverse causes (IBS, Crohn's, GERD, Anorexia, etc.)—25%.

Also: Migraines, Bipolar Disorder, Multiple Sclerosis, Nausea, HIV/AIDS,

Less common: many Skin diseases (Psoriasis, Eczema, Urticaria [Itching], etc), Asthma, PTSD, ADD, ADHD, Restless Leg Syndrome, Menopause, Premenstrual Symptoms, Autism, Seizures, Spasms, Renal Failure, Cancer, Chemo, CRPS, Diabetes, Neuropathy, Addiction, Hypertension, Glaucoma, Fibromyalgia, Chronic Fatigue Syndrome, Tinnitus.

Have you noticed any trends in terms of your patients?

Not so much in diagnosis or symptoms, but more people who are cannabis naïve, including a few young children with bad Seizures or Autism.

Which rare conditions have you encountered?

Wolfram Syndrome (Diabetes, Blind [optic atrophy], demyelination, general pain and numbness)

Morgellon's Disease (unusual skin lesions with colored fine fibers hanging out, black skin spots, Chronic Fatigue, Fibromyalgia, joint pain, problems with concentration and memory, "crawling" skin sensations)

Have you compiled demographic data or can you estimate the breakdown with respect to patients' age, gender, race, economic status? Any trends discernible?

Too much to tackle now.

How many of your patients are consciously substituting cannabis for alcohol? For hard drugs? For prescription meds? For seizure disorders?

A few percent for alcohol. Same for hard drugs. Almost all using it to get off Rx drugs. A few percent for seizures, including some children.

How many pediatric epilepsy cases have you encountered?

I recall only 2 pediatric seizure patients I've seen:

- A 16 y/o girl with several daily mixed type (Focal & PM) seizures without a satisfactory response to the many conventional (and unconventional) drugs tried. Improved greatly when cannabis added to the last two Rxs she was on, and no significant side effects noted by mother. (As opposed to "horrible" ones on the other Rxs.)
- A 4-5 y/o boy with 40-50 absent type seizures daily, also pretty resistant to conventional Rxs, on cannabis down to a few a day. Conventional Rx side effects also described as terrible, intolerable.

Have you observed or had reports of adverse effects from cannabis? If so, please describe?

Nothing beyond the common red eyes, dry mouth, sleepy, and an occasional complaint of Sativa keeping a fellow awake at night.

Please include any insights or observations you consider worth sharing with colleagues, patients and the community at large.

My patients are just trying to live a "normal" life, to function (a job, family, fun, etc.) but have a health problem that is in the way. Almost to a man/woman they have tried the conventional drugs with either little effect or intolerable side effects. They are so happy to find that cannabis significantly tones down their symptoms without making them a zombie or suffering other big-time side-effects. They can still function, and that's what we all want. I'm sure my colleagues get the same immense satisfaction I do in helping these people significantly improve their lives.

I believe the genie is really out of the bottle now. Too many people now get it that cannabis really works (on themselves or someone in their circle of contacts) and friends tell friends about things that really work. A state or two every election legalizes medical use. Recreational approval is now starting to happen.

While significant monied and corrupt corporate, bureaucratic, and propagandized political resistance remains, I perceive some cracks in the wall. Their propaganda doesn't work nearly as well any more. We must continue to push to get cannabis rescheduled. I believe that will break the dam.

Any special cases to report?

There are certain patients you find especially moving... A 37-year-old man, had a horrible accident in the Air Force five years ago. He was severely injured around the face. His face had to be "rebuilt,"which took several operations. He didn't tell me how it happened and I didn't need to know. They gave him a new jaw and he looks surprisingly good. He's lean and tan —the manager of a peach orchard. A cheerful, smiling polite young man from the Deep South. And he's had this horrible experience protecting our country, and he's come through it.

His symptoms are chronic pain around his jaw and neuropathy in all four extremities, every day, off and on. He has muscle spasms, generalized, during the day but especially at night, so his sleep is disturbed. He was on 10 different pills. They would decrease in effectiveness and the adverse effects would increase. He was stupefied. He was not functioning, didn't feel at all himself.

On his own he withdrew from all the pills because a friend, another military guy, said "You should try cannabis."

He says he remembers when he first tried it —relaxation going through his whole body. He says he felt comfortable for the first time in a long time. He said the pain didn't go away but it didn't bother him. And he was able to function, his life picked up. He's managing this orchard and he's all positive thoughts.

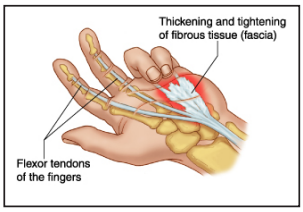
He was a moving guy to meet. A hero to me. But the VA doctor was very hostile. She said you can use the cannabis, but no pills from me. He was on Vicodin and other addictive stuff, and she was willing to cut him off cold turkey!

Robert Sullivan, MD, with Anna Boyce, RN and Philip A. Denney, MD. Boyce was a leading proponent of Proposition 215, which legalized cannabis for medical use in California in 1996. For years there were very few doctors in the southern part of the state willing to approve cannabis use. When Sullivan and Denney opened their office in Lake Forest, activists thanked them for "lifting the Orange (County) Curtain."

Case report

Dupuytren's Contracture resolves with topical cannabis salve

By John Lovejoy, D.O.



Dupuytren's contracture involves thickening of fibrous bands (cords) of skin and underlying tissue in the palm (palmar fascia) that can result in the band shortening. As the bands contract, the fingers pull down into the palm (flexion contracture). The bands are so strong that the individual becomes unable to straighten his or her involved fingers.

Dupuytren's contracture is a hereditary disorder with a prevalence of 4% in the US. Most common in Norway, where it affects 30% of males >60 years. Severity varies, with some individuals developing only nodules (bumps in palm) without the flexion contractures. —The Reed Group

Diagnosis

Medical condition: Arthritis

Specific condition: Dupuytren's Contracture

Symptoms

Painful finger contracture deformity with palmar fascia and flexor tendon deformity. Pain Scale (before treatment): 6

Abstract

46-year-old male carpenter with slowly progressing Dupuytren's contacture of his right 3rd finger was advised to try using a home made concentrated cannabis salve with an occlusive barrier (nitrile glove) at bedtime in order to reduce daytime pain. Patient returned one year later for his medical cannabis recommendation with near complete resolution of the contracture.

Pain Scale (after treatment): 1

Patient information

Otherwise healthy non-smoker.

History & Symptomatology

Several-year progression of palmar fascia and flexor tendon contracture of the right third finger was making it more and more difficult for this patient to swing a hammer on the job. He was looking for a non-psychoactive alternative for daytime pain relief. Exam found a classic thickened and deformed palmar fascia with firm bead deformities of the flexor tendon.

Previous Therapies

Massage, splinting.

Cannabis Therapy

Method of administration: Topical cannabis cream was applied liberally to the entire palmar surface of the affected hand which was then covered by a single rubber glove and worn overnight then removed and washed in the morning. He was not ingesting or smoking/vaporizing cannabis.

Frequency of Usage

Times per day 1, days per week 7

Cannabis strain highTHC/low CBD strain by description, but not tested.

Clinical Response

Patient reported that after several weeks of bedtime cannabis salve and a glove the contracture had nearly entirely resolved. When seen by me one year later he had near normal extensor range of motion, preserved flexor range of motion, normal appearance and no palpable deformity.

Comments

Dupuytre's contractures may in part be due to upregulation of myofibroblasts. This article [http://www.ncbi.nlm.nih.gov/pubmed/24312195] describes the endocannabinoid system as a mediator of mesenchymal stromal cell immunosuppressive properties.

Here is the only other case [http://www.ncbi.nlm.nih.gov/pubmed/1402277] of non-surgical resolution that I could find, this with continuous passive traction. Interestingly, it calls for "further .... pharmacological studies."

He used a homemade salve. I always advise using coconut oil plus DMSO He was uninsured at the time and couldn't afford surgery though he wanted to. Lucky guy**!**

Dr. Lovejoy is a member of the Society of Cannabis Clinicians.

"It is easier to fight for principles than to live up to them." —Alfred Adler

The PPAR-gamma receptor is involved

How Does CBD Regulate Gene Expression?

By Adrian Devitt-Lee and Martin A Lee

There is growing interest among medical scientists in the gene-regulating properties of cannabidiol (CBD), the non-psychoactive plant cannabinoid. Researchers at the California Pacific Medical Center have shown that CBD reduces brain cancer and breast cancer cell proliferation and metastasis by inhibiting the expression of the ID-1 gene. ID-1 expression is implicated in several kinds of aggressive cancer.

In 2012, Israeli scientists identified more than 1,200 genes affected by CBD. Some 680 "gene transcripts" were upregulated ("turned on") by CBD and 524 were downregulated ("turned off"). The probe focused on CBD's role in maintaining the right amount of zinc within cells (zinc homeostasis).

In the same study, THC was found to regulate 94 genes. "The results show that CBD, but much less so THC, affects the expression of genes involved in zinc homeostasis and suggest that the regulation of zinc levels could have an important role through which CBD may exert its antioxidant and anti-inflammatory effects," the researchers concluded.

Mechanism of action

It is well accepted among cannabinoid scientists that CBD has little binding affinity for either the CB1 or CB2 receptor, both of which are activated by THC. Instead, cannabidiol works its magic primarily through receptor-independent channels and by binding with various non-cannabinoid receptors.

Recent studies indicate that CBD influences the expression of some genes by directly activating PPAR-gamma, a non-cannabinoid receptor situated on the cell's nucleus. (The scientists pronounce it "pea-par.") CBD's ability to activate PPAR-gamma has promising therapeutic implications, particularly with respect to cancer and metabolic disorders.

When activated, PPARs bind to certain segments of DNA to promote or prevent transcription of specific genes.

What are PPARs?

Peroxisome proliferator-activated receptors (PPARs) are a group of three proteins inside cells—PPAR-alpha, PPAR-gamma, and PPAR-delta (the latter is not yet well-characterized). PPARs are triggered by hormones, endogenous fatty acids, and various nutritional compounds. When activated, PPARs bind to certain segments of DNA to promote or prevent transcription of specific genes. Many of the genes regulated by PPARs are involved in energy homeostasis, lipid uptake and metabolism, insulin sensitivity, and other metabolic functions.

Big Pharma recognizes the importance of these nuclear receptors. Two classes of pharmaceutical PPAR activators —fibrates and thiazolidinediones— have been approved by the U.S. Food and Drug Administration.

PPAR agonists

Several studies have documented CBD's role as a PPAR-gamma agonist (activator). Cannabidiol also promotes PPAR-alpha activity by inhibiting fatty acid amide hydrolase (FAAH). FAAH is a metabolic enzyme that breaks down several endogenous fatty acid compounds known as N-acylethanolamides. This important family of endogenous fatty acid molecules includes anandamide, the endocannabinoid that binds directly to the CB1 receptor (which is concentrated in the mammalian brain and central nervous system).

Two other N-acylethanolamides —N-palmitoylethanolamide (PEA) and N-oleoylethanolamide (OEA)— bind directly to PPAR alpha. By suppressing the FAAH enzyme and thereby increasing PEA and OEA levels, cannabidiol indirectly activates PPAR-alpha. Higher levels of PEA and OEA result in enhanced PPAR-alpha transmission. Deficient PPAR-alpha signaling has been linked to schizophrenia.

Omega-3s and CBD

Nutritional factors also influence PPAR signaling. The omega-3 fatty acid derivatives docosahexaenoyl ethanolamine (DHEA) and eicosapentaenoyl ethanolamine (EPEA) directly activate PPAR-gamma. DHEA and EPEA can be created in the body from the fish oil constituents docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

At the 2013 International Cannabinoid Research Society conference in Vancouver, Jocelijn Meijerink from Wageningen University in the Netherlands reported that DHEA acts as an inhibitor of the COX-2 enzyme. So does CBD; this is one of the major reasons why cannabidiol has potent anti-inflammatory properties.

COX-2 is an enzyme that creates prostaglandins, a class of inflammatory compounds. Asprin and all the other non-steroidal anti-inflammatory drugs are COX inhibitors.

Regulating angiongenesis

According to a 2008 report by Italian scientists at the University of Rome, both PPAR-alpha and PPAR-gamma regulate angiogenesis, which entails the creation of new blood vessels, particularly capillaries. In cancerous tumors, dysregulated angiogenesis leads to new blood vessels, which provide tumors with nutrients, helping them to grow and metastasize. By directly activating PPAR-gamma and indirectly promoting PPAR-alpha activity, CBD may inhibit tumor angiogenesis.

Three major complications associated with Diabetes Mellitus —retinopathy, neuropathy, and nephropathy — are all worsened by aberrant angiogenesis. Among medical scientists there is great interest in using PPAR agonists to prevent many diabetic complications.

However, there is conflicting data regarding the effect of PPAR signaling on angiogenesis. Although numerous PPAR agonists have shown efficacy in preventing retinal angiogenesis, some studies report that activating PPARs can amplify angiogenesis. The overall scientific consensus seems to be that PPAR-alpha and PPAR-gamma agonists prevent angiogenesis.

PPAR activation is a promising approach to treating type II diabetes and obesity, cancer, Alzheimer's disease and schizophrenia

Clinical applications

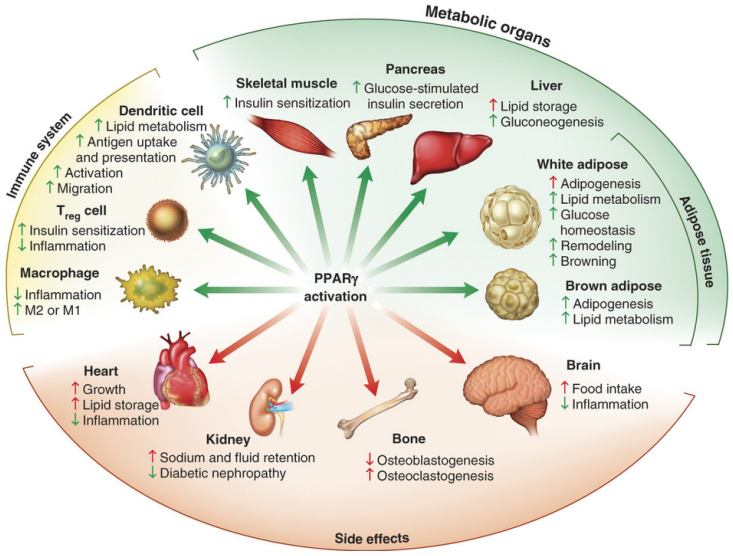
Obesity and metabolic syndrome, cancer, Alzheimer's disease, and schizophrenia are conditions that researchers think might prove amenable to treatment by PPAR activation.

Most genes regulated by PPARs are involved with lipid metabolism and energy storage. PPAR activation typically promotes glycolysis (glucose breakdown), lipolysis (lipid breakdown), and insulin sensitivity, These properties make PPAR activation a promising approach to treating type II diabetes and obesity. The PPAR-activating drugs fibrates and thiazolidinediones (PPAR-alpha agonists and PPAR-gamma agonists, respectively) have been approved to treat dyslipidemia (obesity) and insulin insensitivity in type II diabetics.

PPAR-gamma activation has demonstrated an anti-proliferative effect as well as an ability to induce tumor regression in human lung cancer cell lines. But in some cases PPAR activation can also have an opposite result. In clinical trials, fibrates and thiazolidinediones, as well as some drugs that activate multiple PPARs, often have a side effect of increasing the risk of cancer. These contradictory findings need to be examined further.

In 2011, an Italian research team reported that PPAR-gamma activation degrades amyloid-beta plaque, a key molecule in the development of Alzheimer's disease. This is one of the reasons why cannabidiol, a PPAR-gamma agonist, may be a useful remedy for Alzheimer's patients.

PPAR-alpha agonists in particular are indicated as an adjunct treatment for schizophrenia. Polymorphisms or mutations in the gene encoding PPAR-alpha are associated with schizophrenia. Furthermore, PPAR-alpha activation is both anti-inflammatory and can decrease dopamine release, thereby minimizing schizophrenic symptoms. This may help to explain how and why CBD has anti-psychotic effects.



PPARs are involved in a wide variety of cellular functions and disease pathogeneses. CBD can modulate some G-protein coupled receptors, such as GPR55, or diffuse into the cell to directly activate PPAR-alpha or PPAR-gamma. These PPARs then promote or prevent the transcription of genes involved in insulin sensitivity, metabolic syndrome, cancer pathogenesis, and schizophrenia.

Sources:

Ament Z, et al, "Applications of metabolomics for understanding the action of peroxisome proliferator-activated receptors (PPARs) in diabetes, obesity and cancer," Genome Medicine," 2012.

Biscetti F, et al, "Peroxisome proliferator-activated receptors and angiogenesis," Nutrition, Metabolism & Cardiovascular Diseases, 2009.

Chearwae W and Bright JJ, "PPAR-gamma agonists inhibit growth and expansion of CD133+ brain tumour stem cells," British Journal of Cancer, 2008.

Costa M, et al, "Investigation of endocannabinoid system genes suggests association between peroxisome proliferator activator receptor-alpha gene (PPARA) and schizophrenia.," European Psychopharmacology, 2012.

Esposito G, et al, "Cannabidiol reduces amyloid beta-induced neuroinflammation and promotes hippocampal neurogenesis through PPAR-gamma involvement," PLOS One, 2011.

Juknat, A, et al, "Cannabidiol affects the expressions of genes involved in zinc homeostasis in BV-2 microglial cells," Neurochemical International, 2011.

Ramer R, et al. "COX-2 and PPAR-gamma confer cannabidiol-induced apoptosis of human lung cancer cells," American Association for Cancer Research (AARC), 2012.

Rovito D, et al, "Omega-3 PUFA ethanolamides DHEA and EPEA induce autophagy through PPAR activation in MCF-7 breast cancer cells," Journal of Cellular Physiology, 2013.

Song M, et al, "Modulation of diabetic retinopathy oathiohysiology by natural medicines through PPAR--related pharmacology," British Journal of Pharmacology, 2012.

Sugden M, et al, "PPAR control: it's SIRTainly as easy as PCG," Journal of Endocrinology, 2010.

Treacy, MP and Hurst, TP, "The case for intraocular delivery of PPAR agonists in the treatment of diabetic retinopathy," BMC Opthalmology, 2012.

Adrian Devitt-Lee is studying biology and math at Tufts University. His father, Martin A Lee, is the director of Project CBD and the author of Smoke Signals.

Appendino's Advice to Cannabinoid Researchers: Consider 'New Targets, Chemistry, and Plant Sources'

By Ryan Lee and O'S News Service

The International Cannabinoid Research Society held its 24th annual meeting at a lakeside hotel in Baveno, Italy, in June 2014. ICRS members are mainly —but not exclusively— university-connected biochemists and pharmacologists investigating how things work at the sub-cellular level.

Baveno is a resort town on big, beautiful Lake Maggioro, with the Alps visible to the north. There were four days of talks describing recent studies, and sessions at which investigators answered questions about their findings as summarized on posters.

When the ICRS was founded in 1990, its original name was "International *Cannabis* Research Society." In 1995 —after the body's own cannabinoid receptor system had been discovered and elucidated by ICRS members— the group changed the *C*-word in its name to "Cannabinoid." As pharmacologist Dale Deutsch explained in 1998, "The field is moving away from the plant."

The 2014 ICRS meeting marked the return of the plant to the forefront of the field. Neurologist Ethan Russo was serving as ICRS president (the job is held for a year), and he invited the Italian natural product chemist Giovanni Appendino to give the featured talk at the meeting in Baveno.

Appendino, a professor at the Università del Piemonte Orientale, noted proudly that he is from Carmagnola, a northern Italian town renowned for its fiber hemp variety of the same name.

Appendino first published research in the cannabinoid field in 2002, when he was co-author of a paper on "Noladin ether —a putative endocannabinoid." (The lead authors were Raphael Mechoulam and Vincenzo DiMarzo.) But Appendino's "relationship with cannabis as fiber hemp" goes much further back: "My grandfather was growing it and the odor of hemp retting tanks was filling the air around Carmagnola during the Fall."

By defining cannabinoids as drugs that work at the CB1 and CB2 receptors, researchers may be overlooking beneficial compounds in Cannabis *that work by other mechanisms.*

Researchers have focused almost exclusively on THC, CBD, CBC (cannabichromene) and CBG (cannabigerol, precursor to the other three), Appendino said, while not investigating the therapeutic potential of related molecules present in *Cannabis* —and other plants as well.

Similarly, by defining cannabinoids as drugs that work at the CB1 and CB2 receptors, researchers may be overlooking beneficial compounds in *Cannabis* that work by other mechanisms. "Nature has varied on the cannabinoid structure," Appendino reminded his ICRS audience.

HELICHRYSUM UMBRACULIGERUM, a daisy native to South Africa, produces cannabigerol (CBG). It was identified by Ferdinand Bohlmann and Evelynn Hoffmann in 1978.

"Natural Selection Works Like a Tinkerer..."

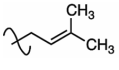
LEAVES THAT RESEMBLE *CANNABIS SATIVA* are (top row, left to right): *Acer japonicus, Aconitum vulparia, Geranium pratense*. Bottom row, left to right: *Hibiscus cannabinum, Vitex agnus-castus, Cannabis sativa*. Graphic from *"Plantes interdites. Une histoire des plantes politiquement incorrectes,"* by Jean-Michel Groult. Appendino quoted the French scientist Francois Jacob in connection with this slide:: "Natural selection works like a tinkerer who does not know exactly what he is going to produce, but uses whatever he finds around him to produce some kind of workable object. None of the material at the tinkerer's disposal has a precise and definite function. Each can be used in different ways. Novelty comes from previously unseen association of old material. To create is to recombine."

In the course of screening more than 200 varieties of fiber hemp, Appendino and colleagues have found significant quantities of obscure compounds whose medical potential he considers "worthy of investigation."

Cannabinoids are not unique to Cannabis *—they have been found in other plants.*

He touched briefly on canniprene, the cannflavins, cannabinoid esters, and "sesqui-CBG," which Appendino's group isolated from a fiber hemp variety.

Appendino has encountered a hemp variety containing two percent canniprene —a compound he called "the *Cannabis* version of resveratrol" (a beneficial compound present in red grapes).



From others varieties he isolated the prenylated version of cannabigerol —meaning CBG attached to a prenyl group *(illustration at left)*. There is no reason, Appendino said, that marijuana should not also produce the prenylated version of THC —which would have distinct biological activity.

Cannabinoids not unique to Cannabis

Cannabinoids are not unique to cannabis —they have been found in other plants. Appendino reported that a large amount of CBG and its carboxylic precursor had been isolated from a specific *Helichrysum* variety found only in South Africa.

Studying how *Helichrysum* makes "non-cannabis" CBG and its related compounds has been difficult for Appendino and his colleagues, because strict South African bio-piracy laws prohibit the collection and export of native species or their seeds. These laws, designed to prevent foreign corporate exploitation of the country's unique genetic resources, also impede legitimate scientific research. After two years of bureaucratic red tape, Appendino was only able to obtain a small vial of extract from the plant. Being unable to obtain seeds themselves has limited his ability to investigate the biosynthetic pathways by which *Helichrysum* produces cannabinoids.

Appendino discovered that cannabinoid-like compounds are made by plants "apart from the normal cannabinoid biosynthetic route. There is a new pathway that starts from an aromatic acid." Referred to as the "*Helichrysum* cannabinoids," these compounds also have been detected in liverwort.

Helichrysum is used in African ethnopharmacology, Appendino explains, "like hemp, to make fumes in ritual ceremonies" and that a "psychotropic effect... similar to cannabinoids," might ensue.

Beta-caryophyllene

Terpenoids, the largest class of naturally occurring compounds on the planet, are the chemicals that give plants their unique smells and flavors. Found in high concentrations in many culinary herbs and spices, terpenes not only provide flavor and scent, they are also important signaling chemicals that plants use to communicate with insects.

Terpenes are synthesized by the plant from five-carbon isoprene units, two of which come together in specialized cellular compartments to form the 10-carbon monoterpenes (limonene, pinene, linalool, terpinolene, et al).

The 15-carbon sesquiterpenes such as beta-caryophyllene, differ from the monoterpenes by the incorporation of an extra isoprene unit. (β is the Greek letter *beta.)*

When Cannabis is dried, stored for periods of time, or made into extracts, the monoterpenes are generally first to evaporate. The sesquiterpenes like β-caryophyllene are more likely to remain.

Monoterpenes are more volatile —they evaporate at lower temperatures— so when *Cannabis* is dried, or stored for periods of time, or made into extracts, the monoterpenes are generally first to evaporate. The sesquiterpenes like β-caryophyllene are more likely to remain.

β-caryophyllene seems like the *Cannabis* plant's own perfect key for nature's CB2 lock. Plants use β-caryophyllene to defend themselves against predators. Some species up-regulate specific terpenes when attacked by herbivores to render the plant less palatable to the attacking insect.

In a beautiful demonstration of the web that Mother Nature has created, these same terpenes have been shown to recruit parasitic bugs that themselves attack the herbivores that are eating the plant!

The drive to breed high-yielding varieties of corn for intensive commercial agriculture sacrificed the ability of the plant to produce β-caryophyllene .

Appendino recounted how the wild, ancestral relative of corn, *teosinte,* grown by the Mayan and Incan farmers in pre-European Central and South America, produced significant amounts of β-caryophyllene before modern breeders selected towards high yielding corn with an increased sugar content. The drive to breed high-yielding varieties of corn for intensive commercial agriculture sacrificed the ability of the plant to produce β-caryophyllene .

That β-caryophyllene binds specifically to the CB2 receptor (which is found mainly outside the central nervous system) was reported by Jürg Gertsch at the 2007 ICRS meeting.

The CB2 receptor

The CB2 receptor has yet to be successfully exploited by the pharmaceutical industry, Appendino said. "If drug discovery is a sea, then CB2 is a rock that is surrounded by shipwrecked-projects," he commented poetically.

Pharmaceutical companies have spent

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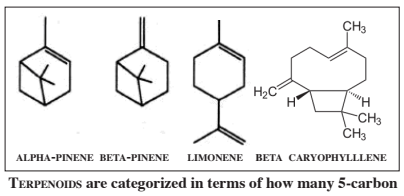


TERPENOIDS are categorized in terms of how many 5-carbon units they contain. Three molecules at left are monoterpenes —each contains 10 carbon atoms. Larger molecule at right, β-caryophyllene, is a sesquiterpene with 15 carbon atoms. Because β-caryophyllene is heavier than the monoterpenes, it evaporates less readily and is often present in relatively large amounts in dried *Cannabis*. (But not all *Cannabis* produces large amounts of β-caryophyllene.)

***TEOSINTE*, THE ANCESTOR OF CORN was tiny but rich in beta-caryophyllene. The cob in this photo is two inches tall.**

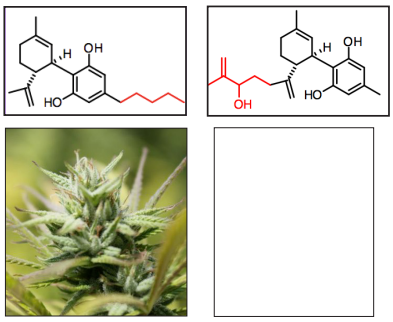
***ICRS** from previous page*

large sums investigating proprietary synthetic CB2-selective compounds that end up showing little clinical efficacy. "But β-caryophyllene is a special lottery ticket," said Appendino.

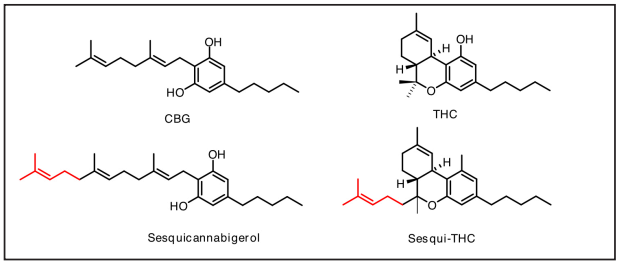
β-caryophyllene is known to be anti-inflammatory and easy on the stomach lining. A special lottery ticket, indeed! So grind some black pepper on your next salad, and order those Echinacea and marigold seeds now —they all contain β-caryophyllene.

Appendino described how the β-caryophyllene molecule interacts with the CB2 receptor. It's an unusual physical relationship for cannabinoid-type agonists. β-caryophyllene does not look like any other molecule that binds to the cannabinoid receptors.

Extracts from plants high in β-caryophyllene have shown some analgesic effect in clinical trials. "Maybe the interaction of β-caryophyllene with CB2 is an echo of an ancient dialog between plants and insects," Appendino said.



CBD *(top left)* and Ferruginene C (top right) have similar molecular structures. Ferruginene C is produced by *Rhododendron ferrugineum*, an Alpine evergreen shrub (photo at right). Photo at left is of a CBD-rich variety called "ACDC," grown and photographed by Lawrence Ringo.



Cannabigerol (CBG, top left) is the compound in *Cannabis* from which other plant cannabinoids are synthesized. Molecule at bottom left is sesqui-CBG, which has been identified in fiber hemp It consists of CBG plus a five-carbon pentyl tail (at right in illustration). Appendino posits the existence of Sesqui-THC, a plant compound consisting of THC plus a pentyl group.

Expanded-Definition Cannabinoids

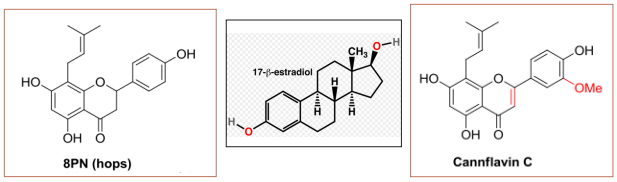
Just as natural selection tinkers with compounds, so do scientists, hoping to find a useful modification that evolutionary pressure hasn't induced nature to come up with. Research is underway into some of the unorthodox cannabinoids Appendino discussed.

For example, a Spanish biotech company called VivaCell has developed a drug, VCE-003, which outperforms CBG in activating PPAR receptors. VCE has shown efficacy in studies using mouse models of Multiple Sclerosis and Encephalomyelitis.

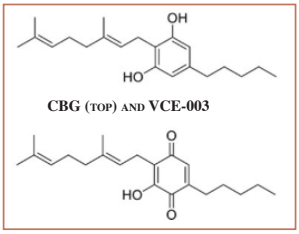
Drugs like VCE-003, made by adding side chains to naturally occurring molecules, are known as "semi-synthetics."

Hydrocodone and bupenorphine, which have replaced codeine and morphine and most opioid analgesics now sold in the U.S., are well-known semi-synthetics.

Appendino's expanded definition of cannabinoid drugs involves an expanded concept of the endocannabinoid system. In addition to CB1 and CB2, the biological targets of the expanded-definition cannabinoids include the GPR55 receptor; TRPs (pronounced "trips"), which are tiny ion channels with gates that open and close to transmit signals; and transcription factors in the mitochondria that switch genes on and off.



8PN (8-Prenylnaringenin, left), a flavonoid prevalent in hops, is the most potent estrogenic compound found in plants. Its effects are similar to, but weaker than the hormone estradiol (center). Pointing out the similar structure of flavonoids found in *Cannabis*, Appendino asked, "Could Cannflavin be the estrogenic principle of *Cannabis*?" Chemist Matt Giese adds, "These type of flavonoids can form isomers, where the methoxy (OMe) and hydroxy(OH) groups have switched positions. This can greatly affect binding and functionality, which is why A and B have such different activities."



ICRS coverage continued on next page.

The Flavonoids Unique to *Cannabis*

Flavonoids are compounds produced by many plants that influence the color of flowers, among other things. Flavonoids are defined by a 15-carbon backbone that includes two phenyl groups. Like terpenoids, they are "secondary metabolites," advantageous to the plant (attracting a pollinator, inhibiting growth of a mold, etc.) but not "primary" components like the proteins, lipids, and carboydrates needed for life itself.

In the 1980s, Dr. Marilyn Barrett identified two diprenylated flavonoids in *Cannabis* which were previously unknown. She named them "Cannflavin" A and B.

In 2013 Mahmoud ElSohly and colleagues at the University of Mississippi identified a third, Cannflavin C.

As noted by Giovanni Appendino at the 2014 ICRS meeting, Cannflavins are now being studied for anti-inflammatory activity, and hemp cultivars with unusually high cannflavin content (c. 2%) are being grown in Italy.

We sought some background info from Barrett, who is based in Mill Valley.

Barrett describes her discovery as "classic pharmacognosy." She was a PhD student at the School of Pharmacy, University of London, looking for compounds that would counter the activity of an inflammatory mediator, prostaglandin E2 (PGE2), present in synovial cells cultured from the knee joints of patients undergoing surgery for rheumatoid arthritis.

Barrett and her co-workers found that a cannabinoid-free alcohol extract of *Cannabis* was inhibiting the release of these inflammatory prostaglandins from the cultured cells. To determine which component of the extract was having the anti-inflammatory effect, they divided the extract into fractions (using preparative thin layer chromatography) and measured the activity of each fraction in the cell culture assay. The most active fraction, in turn, was divided into fractions and its most active fraction selected, and the process repeated until a pure compound was isolated.

"Once you get down to a pure compound," Barrett explains, "then you can work on identifying the structure of that compound. We used mass spectrometry (MS) to measure the molecular weight along with proton- and carbon- nuclear magnetic spectroscopy to get a picture of the structure. Ultraviolet spectroscopy confirmed we were working with a flavonoid, belonging to the class of flavones

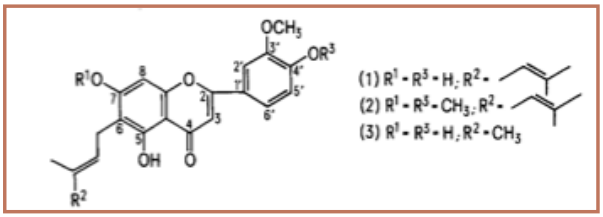
Previous work by Barrett's colleagues (Fairbairn and Pickens) at the School of Pharmacy used a model of catalepsy in mice to measure the psychoactive properties of the cannabinoids, particularly THC. They were extracting the cannabinoids from dried plant material using petroleum spirit until the remaining plant material was cannabinoid-free. The spent plant material was then extracted with alcohol.

Fairbairn and Pickens determined that this alcoholic extract of *Cannabis*, which was free of cannabinoids, had the ability to counteract the cataleptic activity of THC in mice. They suspected that the inhibition of prostaglandins was important to this effect, and in confirmation of this idea, inhibitors of cyclooxygenase also demonstrated this activity in mice. It was this work that led to Barrett's search for an anti-inflammatory agent in the alcoholic extract.

Barrett first published her account of isolating Cannflavin in Biochemical Pharmacology, June 1985. Details of the structure elucidation were published in a second paper in Experientia 42, April 1986.

Although Barrett's team found Cannflavin to be 30 times more potent than aspirin as an anti-inflammatory in the cell culture assay, it was 18 times weaker than Indomethacin —which is perhaps why no effort was made to develop Cannflavin as a drug.

"Especially interesting, from a scientific point of view," Barrett notes, "might be that the *Cannabis* plant contains substances that both cause and reduce a cataleptic effect in mice." This finding was duplicated in the synovial cell assay, in which the cannabinoids stimulated the production of PGE2 and Cannflavin had an inhibitory effect. —***O'S News Service***



Cannflavin A (structure 1) and cannflavin B (structure 3) were isolated from *Cannabis* in the 1980s by Barrett et al. These are prenylated flavones—compounds that have a prenyl group (3-methyl-but-2-en-1-yl) attached to their flavonoid backbone. Cannflavin B is different from A, lacking the five carbon alkyl unit at C-4. (Structure 2 was included for purposes of structure identification; it is not a compound found in *Cannabis*.)

ISOLATION FROM *CANNABIS SATIVA* L. OF CANNFLAVIN—A NOVEL INHIBITOR OF PROSTAGLANDIN PRODUCTION

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(*Received* 15 *October* 1984; *accepted* 20 *December* 1984)

Abstract—The isolation from *Cannabis sativa* L. of an inhibitor of prostaglandin (PG) E_2 production by cultured rheumatoid synovial cells is described. This agent, for which the name Cannflavin has been coined, is distinct from cannabinoids on the basis of isolation procedure, preliminary structural analysis and biological properties. The activity of Cannflavin has been compared with several established anti-inflammatory drugs and the major cannabinoids.

Paper by Marilyn Barrett and colleagues in "Biochemical Pharmacology," June 1985 described the isolation of Cannflavin, the first in a new group of diprenylated flavones.

Table 3. Comparison of Cannflavin with established anti-inflammatory drugs in inhibiting TPA-induced PGE_2 release from cultured synovial cells

Drug	IC 50 (ng/ml) mean (range)	Relative potency
Cannflavin	31 (4.4–58)	1
Aspirin	840 (460–1500)	0.037
Indomethacin	1.7 (0.3–4.0)	18
Dexamethasone	0.27 (0.036–0.5)	115

The IC 50 values are the means of four assays of each drug; the range of values observed in the assays is also given. Cannflavin was arbitrarily assigned a potency of 1 for comparison of potency with other drugs.

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The 2014 ICRS meeting was attended by 328 people —a record. Major pharmaceutical companies that used to send scientists to present papers and monitor the latest research—Abbott, Allergan, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmith-Kline, Merck, Pfizer, Eli Lilly and Sanofi-Aventis—were not represented in Baveno. At least for now, Big PhRMA seems to have surrendered to the plant itself as a source of cannabinoid drugs.

The one exception was Hoffman-La-Roche. Researchers employed by the Basel-based giant have synthesized a drug with an extra-strong affinity for the CB2 receptor. It was found to greatly reduce the build-up of collagen (which obstructs the ureter) in a mouse model of kidney disease. "CB2 agonists might have beneficial effects in both acute and chronic kidney disease," the presentation by Jean-Michel Adam concluded.

The trend towards studying plant compounds and their possible therapeutic applications is largely attributable to GW Pharmaceuticals, a British company, founded in 1998, that has been developing plant-based medicines to treat various conditions.

The ICRS scientists' Holy Grail —even GW Pharmaceuticals'— is a drug that exerts the beneficial effects of cannabis without psychoactivity.

Thanks to GW providing materials and funding for studies of cannabidiol (CBD) and other so-called "minor cannabinoids," the virtual monopoly of the U.S. National Institute on Drug Abuse as sponsor of cannabinoid research has ended. But NIDA is still the biggest ICRS backer, and quite a few presentations in Baveno were devoted to "abuse potential" and other elusive adverse effects.

NIDA funds basic research

Mostly, NIDA provides funding for scientists doing important basic research in physiology and pharmacology. Over the years NIDA-funded scientists have figured out the mechanisms of action by which plant cannabinoids and endocannabinoids (made in the body) exert their effects and get metabolized (broken down).

This research continues in ever-finer detail at the molecular level. For example, in the late 1990s Dale Deutsch and colleagues at Stony Brook University identified fatty acid amide hydrolase (FAAH) as the enzyme that breaks down the endogenous cannabinoid anandamide within the cell. In recent years Deutsch's lab has focused on the fatty acid binding proteins (FABPs) that bring endocannabinoids from the cell membrane to the endoplasmic reticulum (where FAAH does its stuff).

Dale Deutsch reported that the molecules that transport anandamide and 2-AG from the receptor to the nucleus of brain cells — certain fatty-acid binding proteins— perform the same function for THC and CBD.
PHOTO BY Istvan Ujvary

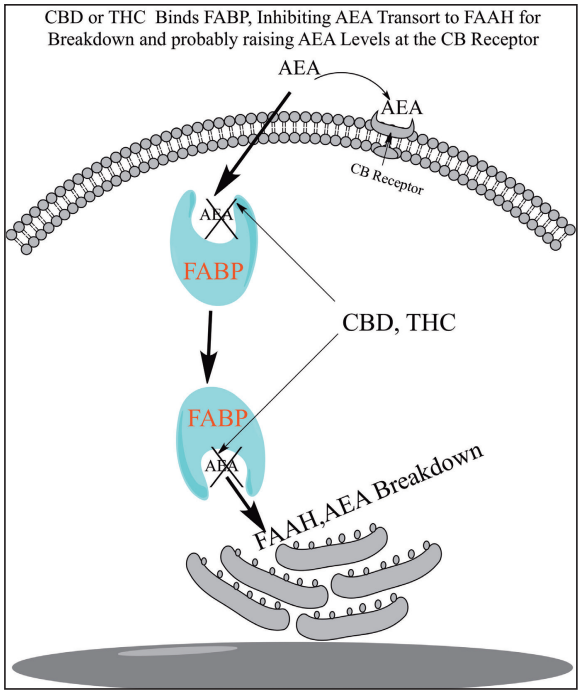
When plant cannabinoids are ingested by people smoking or eating marijuana, THC and CBD molecules are carried in the blood into the brain, "presumably by albumin and lipoproteins, which carry fats," says Deutsch. "But there's no albumin inside those cells in the brain."

In 2012 Deutsch's lab identified the molecules that transport anandamide (and perhaps 2-AG) in cells inside the brain: fatty-acid binding proteins —FABPs 3, 5, and 7 to be precise.

To determine if these very same fatty-acid binding proteins transport the plant cannabinoids THC and CBD, Deutsch reported this year in Baveno, his team did three kinds of experiments.

Simulations of molecular shapes, done by computational analysis, showed that THC and CBD "fit very nicely inside the fatty-acid-binding-protein carriers."

Binding studies using FABPs synthesized and purified in the lab showed that THC and CBD bind to these molecules as readily as anandamide and 2-AG do.



ANANDAMIDE (AEA) INACTIVATION results when CBD or THC targets fatty-acid binding proteins within the cell. At top, anandamide crosses the membrane by diffusion at the cannabinoid (CB) receptor. Once inside the cell, AEA requires fatty-acid binding proteins (FABPs) for transport through the cytoplasm to the endoplasmic reticulum (canoe-shaped structures), where it gets broken down by fatty acid amide hydrolase (FAAH). FABP inhibitors prevent anandamide from being delivered to FAAH for breakdown, resulting in increased anandamide levels at the receptor. Dale Deutsch and collaborators at Stony Brook University have identified the enzyme SB-FI-26 as a potent inhibitor of the FABP transporters.

Cell cultures confirmed that adding THC and CBD inhibited the uptake of anandamide and 2-AG —meaning they were binding to the same transporter molecules.

Deutsch also cited two human studies in which ingestion of THC or CBD was shown to increase anandamide levels in the blood because they act as anandamide -transport inhibitors. (See illustration above).

Deutsch's identification of FAAH as the enzyme that metabolizes anandamide inspired drug developers to create compounds that inhibit production of FAAH, resulting in elevated cannabinoid levels without ingestion of exogenous ("from without") THC. Fatty-acid binding proteins could also be drug targets, and their efficacy the topic of future ICRS talks.

Gender Distinctions

Cannabinoids are more potent analgesics in female rats than in male rats.

Rebecca Craft and MD Leitl reported in 2008 that the sex hormone estradiol enhances the analgesic effects of THC in females whose ovaries had been removed, whereas testosterone blocks the motion-reducing effects of THC in males.

At the 2013 meeting Aaron Haas, a post-doc in Craft's lab at Washington State University, presented a poster showing that estradiol increases sensitivity to THC's anti-pain effects, but testosterone does not.

A team of Israeli researchers led by Sharon Anavi-Goffer found a marked difference in the way male and female mice respond to postnatal administration of HU-267, a cannabinoid drug developed by co-author Raphael Mechoulam. ("HU" stands for "Hebrew University.") HU-267 is described as "a novel synthetic compound whose structure resembles that of ajulemic acid." The researchers gave the drug to mice of both sexes 24 hours after birth. They found that by 25 days of age, the males were more hyperactive while the females where more hypoactive compared with their control litter mates.

Now the researchers' goal is to figure out why this drug exerted gender-related effects. Its pharmacology is being elucidated in collaboration with Roger Pertwee.

Sexist Science Surpassed

At the 2014 meeting, Chris Breivogel, a pharmacologist at Campbell University in North Carolina, presented a paper called "Beta-arrestin2 appears to mediate the activity of cannabinoids in female mice in a manner that differs from males."

Beta-arrestin2 is a protein inside the cell that interacts with an activated cannabinoid receptor, and —it was thought by the scientists who isolated the molecule and put arrest in its name— blocks or dampens the signal.

Breivogel had previously shown that male beta-arrestin2 knockout mice (bred to lack the gene that encodes for beta-arrestin2) respond to THC more strongly than wild-type males.

Traditionally, experiments with rodents have been conducted with males.

His more recent studies, using female mice, "have shown very different effects from what was seen in males. The antinocieptive (but not rectal temperature) effects of THC obtained in wild-type females were nearly absent in beta-arrestin2 knockouts."

Traditionally, experiments with rodents

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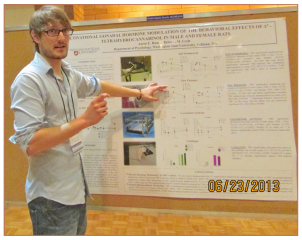
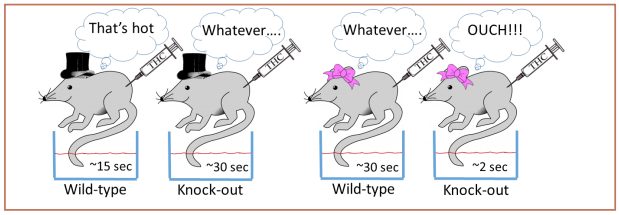


Aaron Haas at his 2013 ICRS poster showing that estradiol increases sensitivity to THC but testosterone does not.

Changing of the Guard among ICRS sponsors is reflected on page from the conference abstract book, although the U.S. National Institute on Drug Abuse remained the biggest backer of the organization (and of sanctioned cannabinoid research). A decade ago ICRS sponsors included major pharmaceutical companies. In 2014 GW Pharmaceuticals and Otsuka (a Japanese company allied with GW) were next, followed by Tilray, one of 13 Canadian companies licensed to cultivate.

ICRS *from previous page*



Different responses to pain are seen in wild-type and beta-arrestin2 knock-out mice on THC. In the tail-flick test, mice are treated and held with the tip of the tail in a warm water bath. Untreated mice will remove their tails in about two seconds, but THC will dull the uncomfortable sensation so that they leave their tails in the water longer —about 15 seconds for wild-type males, and up to 30 seconds, the limit of the test, for the knock-out males.

Knocking out beta-arrestin2 in female mice practically eliminates the effect of THC. Wild-type females typically endured close to 30 seconds; the knockouts flicked out after about two seconds.

have been conducted with males. Researchers have known that "there are slight differences" in test results from male and female animals, according to Breivogel, but these were attributed to differences in rates of metabolism by the liver, differences in the amount of muscle mass and/or body fat, or perhaps changes in receptor level or sensitivity during the estrus cycle.

It was assumed that at the receptor level, there were no differences in mechanism of action.

Breivogel explains, "Males are simpler [to use in experiments] because researchers don't have to worry about changes during the estrus cycle, and how that would affect your results... And so it just got to be the habit where everybody just looked at males.

In the experiments Breivogel described in Baveno, male and female beta-arrestin2 knockout mice, and male and female wild-type mice were given THC by intraperitoneal injection (the most common route used in rodents).

In the wild types, the males and females showed classic symptoms of cannabinoid activation: a drop in body temperature, and greater tolerance for pain as measured by a tail-flick test.

Deleting beta-arrestin2 in the males increased the effect of THC, so the knock-out males showed a greater response.

"What was so surprising when we did the females," Breivogel recounted, "was that it went in the opposite direction. Instead of enhancing the effect of THC, knocking out beta-arrestin2 decreased it to practically nothing.

In female mice, beta-arrestin2 might be involved in helping to mediate the signal instead of blocking the signal.

"The implication is that in a male when THC activates the cannabinoid receptor, beta-arrestin2 will bind to the receptor on the inside of the cell, and interact with other proteins to actually block the signal. It decreases the effect of THC on the cell.

"In the knock-out males, when you remove the beta-arrestin2, you get an enhanced effect.

'In the knock-out females, at least in one kind of assay, the effect practically goes away. This suggests that the beta-arrestin2 might be involved in helping to mediate the signal instead of blocking the signal."

Beta-arrestin knockout mice had been engineered/created and bred by Robert Lefkowitz, a Nobel Prize-winning scientist at Duke University, who supplied Breivogel with 12 animals to start breeding for his experiments in 2003.

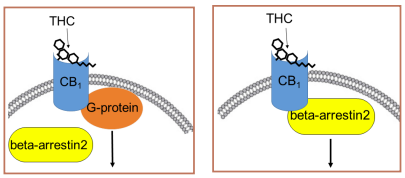
The Lefkowitz lab —working only with males—had determined that beta-arrestin2 knockout mice had a stronger response to morphine's anti-pain effect than wild-types.

Breivogel recently tested the response to morphine of beta-arrestin2 knockout females and attempted to reproduce the effects previously seen in males. "There was no difference between males and females in the effect of morphine upon deletion of beta-arrestin2," he reports, which implies that the sex-differences for beta-arrestin2 seen with THC may not be universal, and may occur only with some drugs and their receptors, and may even be limited to only a few receptor systems. That all still needs to be investigated.

The differences in activation of beta-arrestin2 by THC in male and female mice are probably also present for anandamide, Breivogel says, because the differences are also brought on by a FAAH inhibitor, URB597, which works by augmenting anandamide.

"We just sort of stumbled on it one day. We were doing an experiment with a lab course, and I always do something I haven't done yet that might be interesting. 'You know we've never looked at the female mice...'"

The National Institutes of Health announced a policy in May, 2014, mandating that researchers state the sex of the animals (including people) used in their experiments, or the sex of the animal the tissue or cells came from when publishing data. Basic, pre-clinical research grant applications must "address the influence of sex in the design and analysis of biomedical research with animals and cells."



Possible Explanation of different responses to THC by male and female mice observed by Breivogel is illustrated. In both males (cell at left) and females (cell at right) THC activates the CB1 receptor on the outside of the cell membrane. CB1 can couple to *either* a G-protein *or* a beta-arrestin at any given time. Both molecules couple to the same part of the receptor, so when one is there, the other is blocked.

Male CB1 receptors activated by THC produce an antinociceptive (and temperature depressing) effect via G-proteins. When beta-arrestin2 is removed, THC is more effective. In females, Breivogel proposes, "THC may activate CB1 to couple beta-arrestin2 to produce antinociception, so when you knock out beta-arrestin2, you lose the effect of THC."

"Biased Signaling"

Drug developers hope to exploit the discovery that different ligands activate signaling pathways inside the cell with varying efficacy. Drugs (like THC) that activate the same receptor in males and females but then activate different signaling pathways inside the cell are said to exhibit "biased signaling." Such drugs might have different effects in males and females, or at least might vary in the ability to cause certain effects (therapeutic and/or side effects). "Differences in signaling, mediated by beta-arrestin2 and possibly other proteins, may be why certain drugs have somewhat different effects in men and women," says Breivogel.

An olive orchard in Crete.

All About EVOO

People in Greece, Southern Italy, and Spain have lower rates of colon, breast, prostate, and ovarian cancer than Northern Europeans. This is attributed to differences in diet. In the Mediterranean diet, the primary source of fat is extra-virgin olive oil (EVOO); the Northerners use butter and lard.

Extra-virginity is important because the polyphenols in freshly pressed olive oil degrade with aging and refining.

The EVOO benefit is dramatic —an almost 50% lower rate of colon cancer, for example. Extra-virginity is important because the polyphenols in freshly pressed olive oil degrade with aging and re-processing.

Andrea Di Francesco and colleagues in Mauro Maccarrone's lab have been studying EVOO's mechanism of action. Exposing colon cancer cells (Caco-2) to EVOO or an extract of its phenolic compounds resulted in "a selective increase in CB1 gene expression" and "inhibited proliferation of Caco-2 cells and arrested their cycle."

The researchers also fed healthy rats with a standard diet and an EVOO supplement, then looked for changes in cells lining the colon. Ten days of EVOO supplement led to "a significant increase in CB1 gene expression levels in colon."

This was due to "epigentic mechanisms." As explained by Maccarrone, "We found that CB1 is less expressed in cancer cells because it is more methylated at the promoter level. The gene is there, but it is not expressed."

A "promoter" is a region of DNA that initiates transcription of a particular gene. It's where DNA is turned into RNA. Methylation refers to the addition of methyl groups (CH_3) to a molecule.

Catalyzed by specific enzymes, methylation is involved in regulating gene expression and protein function. In normal cells, the promoter region is not highly methylated and the gene is expressed. But in cancer cells, the promoter region is highly methylated and the gene is silenced. More methylation of the gene means less CB1 expression and weaker endocannabinoid tone.

Aberrant methylation appears to be a precipitating factor in the development of cancer. But methylation doesn't just happen on its own. If a gene is inappropriately methylated, then some process in the body is causing this to happen.

Psychological trauma and high level activation of the body's stress system, especially in early childhood, are known to trigger abnormal methylation that changes DNA and disables genes. So, too, in animals. There have been studies that show differences in maternal care during the first six days of a rat's life result in different methylation patterns in promoter regions, thereby influencing gene expression.

Poor diet and exposure to environmental toxins can also skew gene expression.

What's in a Name?

A presentation by Dr. John McPartland challenged the widespread notion that there are three species of Cannabis —indica, sativa, and ruderalis.

McPartland used a novel approach involving "DNA barcodes."

There are 10 chromosome pairs in the nucleus of every typical cannabis cell. In every generation mutations occur.

Unlike human or plant 'nuclear' genomes, which are inherited from both an individual's male and female parents, chloroplast genomes are inherited only from the mother. Thus chloroplast genomes experience fewer mutations and evolve much more slowly

By focusing on regions of the chloroplast genome that are present in all plants, McPartland and co-author Geoffrey Guy were able to calculate the degree of relatedness between 'indica' and 'sativa' genetic sequences described in the academic literature.

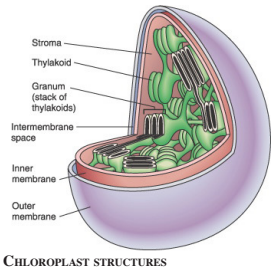
McPartland was able to create baselines that expressed the genetic differences as a numerical value.

Chloroplasts contain the genes responsible for key pieces of the photosynthetic machinery of the plant, in addition to other genes required for the plant to survive. Because these genes are so crucial for proper plant development and function, they mutate or "evolve" at a much slower rate than nuclear DNA. Comparing these conserved genetic sequences between both related and unrelated species, in addition to varieties or cultivars of the same species, McPartland was able to create baselines that expressed the genetic differences as a numerical value.

McPartland selected genetic sequences from *Cannabis* chloroplasts published in the academic literature, and used these same methods to calculate the degree of relatedness between the plants from which the samples were derived. The genetic differences show that the degree of variation between sequences was far less than those between unrelated species. In fact, they resembled the distance between different varieties as seen in other species.

The conclusion, therefore: *Cannabis sativa* and *indica* belong to different varieties of the same species. The evidence is corroborated by the ability of all varieties of cannabis —indica, sativa, and ruderalis— to inter-mate and produce fertile offspring.

McPartland also called on his audience to use correct terminology when referring to *Cannabis indica* (misnamed *"sativa"* in the current vernacular), *Afghanica* (misnamed *"indica"*), and *sativa* (misnamed *"ruderalis"*).



Chloroplast structures

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Exome Sequencing

It's unusual for a single case study to represent a breakthrough, but that was how Kevin McKernan's presentation — "Exome Sequencing of Familial Atrial Fibrillation Informs Positive Treatment With Cannabidiol"—was received by the ICRS.

McKernan was the lead researcher behind Medicinal Genomic's draft sequence of the *Cannabis sativa* genome in 2011. With co-workers at Courtagen Life Sciences in Woburn, Massachusetts, he has been using a sophisticated exome sequencing technique —targeting the "panel" of genes that encode for proteins, about 1% of the whole genome— to determine if certain disorders may be treatable by cannabinoids.

McKernan described a patient with an inherited form of atrial fibrillation who had not been helped by the conventional pharmaceutical treatments —beta blockers and calcium channel blockers. By comparing the exome sequences of six family members, it was determined that the patient inherited rare mutations in calcium-channel genes *RYR2* and *CACNA1C*. Knowing that cannabidiol regulates intracellular calcium homeostasis led to treatment with CBD. And sure enough, sprayed in the mouth, 75mg once a day, CBD promoted a regular heartbeat.

Atrial fibrillation returned with doses below 25mg given three times a day. "This case presents a private scenario," McKernan aptly noted. But targeting gene panels to identify underlying disorders treatable by cannabinoids is widely applicable.

McKernan's team has been exome sequencing the DNA of pediatric epilepsy patients involved in the clinical trial of G.W. Pharmaceuticals' Epidiolex.

The family with A-Fib was sequenced in two steps. First 500 genes, then all 18,000 genes —"and even this 18,000 genes represents only 1% of the genome," McKernan notes.

As of June 2015, he adds, "For GW we are still in the 500 gene phase, and even though there is some exciting data starting to emerge, the IRBs may not approve sequencing the whole exomes of the children without substantial increases to the genetic counseling budget. Genes like APOE and BRCA1 (associated with Alzheimers and breast cancer risks, respectively) are unrelated to pediatric epilepsy but present an ethical dilemma sequencing children with Epilepsy. Discovery of variants in these genes can produce stress and harm to the family and our study is designed to have no harm to the family. But even with the 500 genes, we are seeing some impressive signals. We need more patients sequenced to improve the signal."

G.W. Pharmaceuticals' Strategy

G.W.'s drug development strategy was outlined in a talk by James Brodie. The prevailing approach in the pharmaceutical industry involves "screening synthesized molecular libraries to identify those most potent and selective at a single receptor/disease target."

G.W.'s approach involves figuring out the mechanism of the disease and deciding which cannabis extract is best suited to treating it. "Disease causation is multifactorial," Brodie said, "and a 'broadside' approach may be more successful in overcoming the redundancy and multifunctionality that are inherent compensatory mechanisms in biological systems. "In other words, hitting one mechanism of a neurodegenerative disease or a cancer is less likely to work than a multipronged attack on the physiology of the disorder.

G.W.'s flagship product, Sativex, a plant extract formulated for spraying under the tongue, has been approved by regulators in 27 countries (starting with Canada in 2005) for treating pain and spasticity in Multiple Sclerosis. Sativex is in phase 3 clinical trials in the U.S. as a treatment for intractable cancer pain.

G.W.'s Epidiolex, an almost-pure-CBD extract, is in clinical trials as a treatment for two rare pediatric epilepsy syndromes *(See story on page 1)*.

Brodie said that advances in high-throughput screening, ever-declining sequencing costs, and the profusion of online databases —plus "proprietary in-house data"— enables G.W. to assess the role of "receptors, enzymes, genes, organelles and more" in a disease of interest.

One such disease is Duchenne Muscular Dystrophy (DMD), a hereditary condition that causes irreversible degeneration of muscle tissue and is usually fatal before age 15 due to respiratory failure.

Earlier in the conference it had been reported by F.A. Ianotti that in a mouse model of DMD, certain genes belonging to the endocannabinoid system were upregulated at the time of disease onset.

Treating the mice with Rimonabant to reverse the effect of CBD resulted in "a marked increase in locomotor activity... These findings indicate a novel role for CB1 in the development of dengerative muscle disease, perhaps by affecting muscle differentiation and repair processses, thus making this receptor a potential therapeutic target for the treatment of such disorders."

Presumably the extract GW would deploy as a treatment for DMD would be high in CBDV, which —like synthetic Rimonabant — is an inverse agonist at the CB1 receptor.

DMD is one of the so-called "orphan diseases" —defined by the Food and Drug Administration as affecting fewer than 200,000 Americans— that G.W. is focused on developing drugs to treat. Others include Dravet Syndrome and Lennox-Gastaut Syndrome.

A drug that is beneficial in treating the most severe forms of epilepsy is likely to be beneficial in treating most seizure disorders.

By developing extracts and natural compounds with specified ratios, Brodie said, "you can form a matrix of intellectual property that will be safe... It is our belief and the belief of our commercial partners that you cannot genericize Sativex."

Help for Acute Pancreatitis?

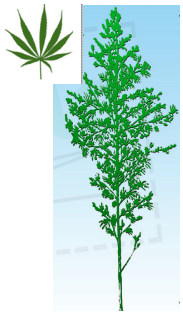
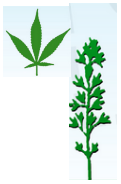
• Acute pancreatitis is a very painful disease in which digestive cells created by acinar cells in the pancreas for use in the small intestine start digesting the pancreas itself. There are no drugs to treat it —only painkillers.

Cannabinoid receptors are expressed in the pancreas and appear to prevent acinar cell pathogenesis (possibly by modulating interacellular calcium-ion signals). Using a mouse model, Huang et al tested GW 13542, an extract that targets CB2, as a treatment for acute pancreatitis and concluded that it "eliminates intracellular Ca2+ signaling in pancreatic acinar cells, which may provide a new therapeutic strategy."

continued on next page

From John McPartland's ICRS Presentation

Correct(ed) Vernacular Nomenclature

	Indica (formerly "Sativa")	**Afghanica (formerly "Indica")**	**Sativa (formerly "Ruderalis")**
			
Original provenance:	India	Central Asia (Afghanistan, Turkestan, Pakistan)	Usually feral or wild *C. sativa* from Europe, but sometimes of Asian provenance.
Morphology:	Relatively tall (ca. ≥1.5 m), laxly branched, with narrowly lanceolate leaflets, and relatively sparse flowering tops.	Relatively short (ca. 0.6-1.5 m), densely branched, with broad leaflets often oblanceolate, and dense flowering tops.	Variable, depending on provenance.
Physiology:	Flowering time (seed germination to intiation of reproduction structures under natural conditions) long, 9-14 weeks; no frost tolerance, moderate resin production.	Flowering time short, 7-9 weeks; frost tolerance, high resin production, susceptible to mold.	Flowering time relatively short but variable, sometimes autoflowering; moderate frost tolerance, relatively low resin production.
Chemistry:	THC much greater than CBD; uniquely prominent terpenoids: sabinene, α-terpinolene, trans-β-ocimene, trans-β-farnesene, imparting a flowery fragrance.	Cannabinoid profile variable (THC greater than or roughly equal to CBD); uniquely prominent terpenoids: camphene, β-myrcene, guaiol, β- and γ-eudesmol, imparting an acrid fragrance.	CBD>THC; prominent terpenoids: β-caryophyllene, myrcene, imparting a flowery fragrance.
Psychoactivity:	"Stimulating."	"Sedating."	Usually lacking.
Medical indications:	Lethargic depression, nausea, appetite stimulation, migraine headaches, and chronic pain. Relative contraindications: insomnia, anxiety, and schizophrenia.	Insomnia, anxiety, chronic pain, joint stiffness and inflammation, muscle spasms, tremors (from multiple sclerosis and Parkinson's disease), and epilepsy. Relative contraindications: lethargic depression, somnolence, and schizophrenia.	Chronic pain, joint stiffness and inflammation, epilepsy. Relative contraindications: allergy to cannabis.

Revised nomenclature was proposed by John McPartland at the 2014 meeting of the International Cannabinoid Research Society. His paper, co-authored by Geoffrey Guy, used "DNA barcodes" to determine whether or not *Cannabis indica* and *Cannabis sativa* are separate species. The answer was not. *C. indica* and *C. sativa* are subspecies —separate varieties of one *Cannabis* species. McPartland traced the confusion that prevails today among plant breeders and the pot-loving masses to the 1970s, when a *C. afghanica* plant collected by botanist Richard Evans Schultes was incorrectly identified as *C. indica*.

***ICRS** from previous page*

Cannabis, the anti-drug

Ever since he started running a cannabis dispensary in Vancouver, B.C. in 2002, Philippe Lucas realized that many people were using the herb as a substitute for alcohol and other drugs.

In the spirit of Tod Mikuriya's "Marijuana as a Substitute for Alcohol" (O'Shaughnessy's 2003), Lucas continued collecting data from patients who used cannabis as an alternative to harder drugs. He has been updating his findings at ICRS meetings since 2005, in ever more impressive posters.

In Baveno he gave a talk based on a survey to which 628 Canadians had responded. Consisting of 414 questions [that's a lot of questions], it was distributed online and in hardcopy to patients. Lucas found:

"Overall, 86.6% of patients reported substituting cannabis for at least one other substance: 80.3% (n=504) of patients stated that they used cannabis as a substitute for prescription drugs, 51.7% used it as a substitute for alcohol, and 32.6% used it as a substitute for illicit substances.

"The main reasons cited included 'better symptom management' and 'less adverse side effects.' Patients who listed a greater number of symptoms were more likely to report cannabis substitution, and younger patients (below 30) were far more likely to substitute cannabis for prescription drugs, alcohol and illicit substances than older patients (50 and over)."

Lucas ended with a call for "research into cannabis as a treatment for problematic substance use in non-patient populations."

Bringing it all back home

The 80th and final oral presentation in Baveno was by Jahan Marcu, PhD, who has gone from lab research to auditing cannabis production and distribution by U.S. growers and dispensaries as Senior Scientist for Americans for Safe Access.

The U.S. contingent included California practioners (Jeffrey Hergenrather, Michelle Sexton, William Courtney, R. Stephen Ellis), lab directors (Jeffrey Raber, Justin Hartzell), and political organizers (Steph Sherer, Martin Lee, Kristen Peskuski). There were also about a dozen entrepreneurs seeking out scientists with products to market and/or expertise to tap.

"With popularity of a name," Raber noted, "comes the greater potential for its abuse by those simply seeking to capitalize on a transaction involving the cultivar."

Raber gave an oral presentation, showing with data from his lab, the Werc Shop, the extent to which cannabis sold in California and Washington dispensaries is inaccurately named. "With popularity of a name," Raber noted, "comes the greater potential for its abuse by those simply seeking to capitalize on a transaction involving the cultivar."

Raber also found lamentable inconsistency in the way cultivars were dubbed *indica* and *sativa*. "A specifically named cultivar at one disepnsary is not necessarily the same product in the package at another dispensary simply because it posesses the same name. This may also be the case even week to week at the same dispensary, leading towards many different reports of the physiological impacts for a specific name and considerable numbers of frustrated patients seeking to find relief with a specific varietal."

Raber foresees more accurate identification of cultivars based on terpene content.

CBD Activates Serotonin

The evidence now seems conclusive that CBD works in part by activating the 5HT1A (serotonin) receptors, as suggested by Ethan Russo in a 2005 poster. Spanish researchers reported that CBD administered in the first six hours after hypoxic-ischemia had been induced in newborn piglets had strong neuroprotective effects. But if given along with a compound that blocks 5HT1A, there is no beneficial effect.

CBD Protects the RPE

Macular degeneration is a leading cause of blindness in the elderly. It is caused by accumulation in the retinal pigment epithelium (RPE) of a compound called A2E, which down-regulates a compound produced in the RPE called MCP-1

Shimon Ben-Shabat and colleagues at the University of the Negev have determined that cannabinoids (HU-210, HU-308 and CBD) counter the down-regulation of MCP-1 and provide neuroprotection.

THREE DISCOVERERS

IN ORDER OF THEIR LANDMARK FINDINGS: WILLIAM ANTHONY DEVANE (RIGHT), molecular pharmacologist. Working in the lab of Allyn Howlett at St. Louis University in 1988, he discovered the cannabinoid receptor (dubbed the CB1 receptor when a second one was found in 1992). LUMÍR ONDŘEJ HANUŠ (LEFT) analytical chemist. Working with Devane in the lab of Raphael Mechoulam at Hebrew University in Jerusalem, he isolated the first endocannabinoid on March 24, 1992. Devane named it "anandamide," incorporating the Sanskrit word for "bliss." SHIMON BEN-SHABAT (CENTER), medicinal chemist. Working in Mechoulam's lab in 1994, he was the first to isolate the endocannabinoid 2-arachidonoyl glycerol (2-AG).

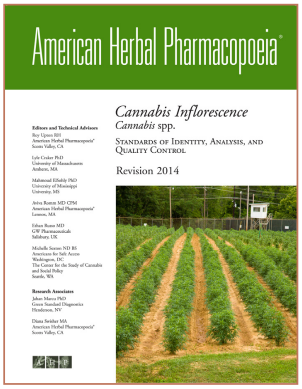
This photo was taken at the 2014 ICRS meeting with Dr. Ben-Shabat's cellphone by a passerby. Hanuš describes it as "a unique picture," the first of the three discoverers together. "It is for us pleasant to see how these three discoveries influenced science," he says. "This ICRS conference is basically on cannabinoid receptors and endocannabinoids. Around the world there are whole laboratories on this subject."

Will the industry accept?

ASA's Audacious Audit Offer

As the cannabis industry burgeoned in recent years, naturopath Michelle Sexton urged ASA's executive director, Steph Sherer, to push for safety standards that would protect patients' interests. Sexton suggested involving the American Herbal Products Association —AHPA, a trade association for the natural-products industry— and the American Herbal Pharmacopeia —AHP, which publishes monographs defining "standards of identity, purity, and analysis for botanicals."

Sherer pursued them. AHPA agreed to create guidelines on proper manufacturing, processing, dispensing, and lab procedures.



AHP MONOGRAPH COVER features a photo of the garden at the University of Mississippi where *Cannabis* is grown legally under federal law (surrounded by a 10-foot tall barbed wire fence, with cameras and a guard tower for extra security). The herb is for distribution by NIDA to government-sanctioned researchers. The grower, Mahmoud ElSohly, is one of the Monograph editors.

The AHP set to work on a monograph establishing standards of purity for cannabis that could be incorporated into regulations by state legislators. (AHP standards are widely used by companies that make and distribute licensed herbal supplements.)

Sherer raised funds for the mongraph's publication in December, 2013, a revised edition issued in the fall of 2014, and a second volume —a "Therpaeutic Compendium" citing all the medical literature, coming soon.

Auditing the producers

At the 2014 ICRS meeting, ASA's Jahan Marcu described how an "audit" is conducted to confirm that a facility —a farm, dispensary, or lab— meets AHP standards, complies with state and local regulations, and qualifies for "Patient-Focused Certification."

"I go to the site," says Marcu. "I make sure that the place is clean. I go through all their paperwork —staff training manuals, documentation. Is there a logbook? Do they have policies and procedures stating how they do things? When was the last time they applied a pest-management product? How much do they apply? What batch number of what pesticide product did you use? When was the last test on the water you're using from your well? When was your last soil test? Where did the last batch you cultivated go and could you initiate a recall? Is the facility processing on site? Are solvents stored properly and labeled? Are fertilizers and fuels stored properly and labeled?"

Marcu typically sees problems that can be readily resolved. Most common at the dispensary level, he says, is "the lack of a plan to record and report adverse events."

Waste disposal by labs and dispensaries

Marijuana prohibition can be seen as part of a broader war on botanical medicine.

is another area that often calls for improvement. "The rules and requirements differ from state to state," Marcu says, "but you don't throw away moldy cannabis or outdated products into an easily accessible trash can." Marcu says AHP standards are not costly to comply with.

Facilities that pass the audit get a label vouching for the quality of their operation, be it cultivation, manufacturing, dispensing, or lab reports. "Doctors can't tell people where to get cannabis," Marcu notes, "but they *can* remind patients to look for the PFC seal. If you have this seal on your product, you know that it's following basic safety and handling protocols for botanical medicine, or that the readings from the lab are going to be within acceptable limits of accuracy."

Certification by a third party is common in U.S. industries. "FDA does not certify manufacturing facilities and labs," Marcu points out. "They punt it to third parties that are often established by the very industry they're trying to regulate." Marcu compares his role to that of a rabbi certifying a food product as kosher.

Marcu's presentation to the ICRS in July 2014 framed the ASA audit as an experiment, and as this issue goes to press in December, 2015, the results are inconclusive. "Everyone really seems to like the audit and certification except for businesses," he said. "The patients like it, regulators, researchers love it... We'll just have to see about the industry."

Steph Sherer had come to Baveno for the ICRS meeting and gave us the back story on the audit project. Researching the origins of marijuana prohibition, she came to see it in the context of "scientific medicine" wiping out alternative approaches —including herbal medicine— in the first part of the 20th century.

In 1910 the Carnegie Foundation funded a crtique of U.S. medical schools by a layman named Abraham Flexner (who also had connections to the Rockefeller family and Johns Hopkins University). It was a blueprint for transforming the profession.

The American Medical Association became the mechanism for driving out competition from herbalists, homeopaths, and all other practitioners who had not been trained at elite medical schools (whose labs and hospitals required underwriting by the wealthy, and whose tuition fees effectively excluded working-class students).

'Scientific medicine' glorified technology and research. Historian Richard Brown attributes its credibility to the work of European bacteriologists who had "identified discrete, external, and specific agents of disease. This perspective encouraged the idea of specific therapies to cure specific pathological conditions, and it diverted attention from the social and economic causes of disease."

Scientific medicine made possible the cannabis prohibition of 1937 (and its continuation to this day) by disrespecting "crude" herbs. Scientific medicine recognizes that certain plants contain specific active ingredients that can be isolated, synthesized, and marketed as medicine.

Marijuana prohibition can be seen as part of a broader war on botanical medicine.

Treatment With Cannabis and Cannabinoids: Some Practical Aspects and Controversies

By Ethan Russo, MD

Ethan Russo, MD, resigned as senior medical advisor at GW Pharmaceuticals at the end of 2014. During his decade with the company, Russo was somewhat constrained in his public comments about cannabis use, research, and politics. Steph Sherer of Americans for Safe Access invited him to speak his mind at ASA's 2015 conference, which was held in Washington, DC, in late March. This article is based on his talk.

To talk about some of the confusion surrounding cannabis, first we have to introduce the endocannabinoid system —an internal homeostatic regulatory system that is involved in almost every physiological process. It has three components: the receptors CB1 and CB2, their biosynthetic and degradative enzymes, and the endocannabinoids themselves – anandamide and 2AG. There are active and inactive components that work in concert to achieve what Dr. Raphael Mechoulam has described as "the entourage effect."

There are cannabinoid receptors throughout the body. CB1 is the most abundant G-protein-coupled receptor in the central nervous system, with a major neuromodulatory function. It is found in the periphery as well. Its role has been characterized by Vincenzo DiMarzo as "relax, eat, sleep, forget and protect." CB2 is an immunomodulatory receptor found mainly in the periphery. It plays an important role in pain and inflammation.

This slide *(bottom left)* illustrates the biosynthetic pathways of cannabinoids in the plant. These are produced as carboxylic acids that are then customarily decarboxylated by heat to produce the familiar pentyl cannabinoids (with five-carbon side chains), tetrahydrocannabinol (THC), cannabidiol (CBD) *et al*.

Cannabis is also capable of producing propyl cannabinoids with three-carbon side chains, depending on the enzymes available. *(Slide at bottom right.)* Professor Mechoulam has called this an example of "Nature's Law of Stinginess," but I call it "enzymatic-substrate promiscuity," or ESP. Cannabis has ESP.

Below is a breakdown of cannabinoid content in a pharmaceutical plant analyzed by David Potter. Note that cannabinoids are not present at all in the roots or seeds (which both contain other beneficial compounds).

Seeds	**0%**
Roots	**0%**
Stem	**0.3%**
Leaves	**0.8%**
Seeded female buds	**6.3%**
Unseeded female buds	**15.2%**

Cannabinoid distribution in a pharmaceutical plant is highly concentrated in unseeded female flowers (also known as ganja, sinsemilla and other terms of endearment).

One thing that is *not* misunderstood: the unfertilized female flower is the most important medicinal portion of the plant. "Sinsemilla" buds contain 18 times the amount of THC and other cannabinoids present on the leaves.

There are many people who juice leaves and report medical benefit. If this benefit derives from cannabinoids, whether raw or decarboxylated, it's from a very small amount.

Trichomes are glands that produce cannabinoids and terpenoids. Sessile trichome (above) is much flatter and smaller (20 microns in diameter) than the capitate trichome at right (100 microns). Sessile trichomes sit directly on leaves. Capitate trichomes are globular and sit on stalks that keep their acidic contents away from the flowers. Juicing leaves is an inefficient way to ingest cannabinoids. Photos by David Potter

The true production facility for cannabinoids in the plant are the glandular trichomes. There are two main kinds: capitate trichomes, are found on the flowers. They are globular and sit on stalks that keep them away from the flowers. Sessile trichomes are flatter and sit directly on the leaves.

Applying the formula for the volume of a sphere, we see that there's about 100 times more volume in the capitate glandular trichomes.

Additionally, the biochemistry is different. In the leaves there are a lot of bitter sessile terpenoids that are there to prevent grazing by deer and other animals that will try to eat the plant. This may be why people occasionally get sick from juicing leaves of cannabis.

It is true certain cannabis plants that have cannabidiol in them will be sedating, but it's not because of the cannabidiol. It's because those plants tend to be myrcene-dominant.

Cannabidiol —CBD— is a molecule that some of us have been trying to call attention to for 20 years. The structure was elucidated by Professor Mechoulam in 1963, a year earlier than THC. But it got lost in the shuffle because it doesn't have the sexiness of being psychoactive.

One myth is that a little bit of CBD will have a significant impact and counter the effects of THC. In general, to get a real medicinal effect, there has to be a substantial amount of CBD.

The best ratios are probably 1:1, which is akin to what we'd see in a plant in Afghanistan and Morocco in the olden days, before selective breeding changed it to be all about THC.

There is a persistent myth that cannabidiol is sedating.

What CBD does do with regular usage is increase the amount of anandamide, the best-known endogenous cannabinoid in the body.

It is not. It has been clearly shown with EEGs and other methods that CBD is a very stimulating molecule at low and moderate doses.

Sedation may occur at very high doses, particularly in association with the smorgasbord of pharmacological agents that kids get put on, there can be drug-drug interactions that produce sedation. But in general, CBD is not a sedative.

It is true certain cannabis plants that have cannabidiol in them will be sedating, but it's not because of the cannabidiol. It's because those plants tend to be myrcene-dominant. Myrcene is a terpenoid with sedating, narcotic-type properties. In combination with THC, myrcene is responsible for couch lock.

There also is a prevalent myth that CBD turns into THC in the body. This is based on outdated research. It was once thought that the biosynthetic pathway to THC went through CBD. That is not true. When pure CBD has been ingested and pharmacokinetics are done to look at what's in the blood afterwards, no THC has been produced.

There is also a myth involving THCA. The plant does not produce THC acid to get people high once it's been dried and decarboxylated. It's there because it's insecticidal. Additionally, THCA has been shown to be a very strong anti-inflammatory without being altered to THC. .It also affects tumor necrosis factor alpha, which plays a role in a number of diseases.

Many families have added THCA to their child's regimen to treat seizures. We have to analyze why it provides benefit. Back in 1978 the anti-convulsive properties of THCA were tested by Karler and Turkanis, and it was found that a very high dose was required to produce an effect —up to 400 milligrams per kilogram of body weight per day, whereas CBD requires 100mg/kg.

If somebody used leaves to get THCA, they'd need about 2,200 leaves a day to get the anticonvulsant dose. Clearly, if THCA is needed, it should come from the flower and not from the leaves, which make good compost or could be used otherwise.

CBDA —cannabidiol acid— which is present in fresh hemp, is a natural pesticide. It was noted hundreds of years ago when hemp was being retted in ponds, it killed the fish.

It has also been shown that CBDA prevents vomiting. It is a very powerful anti-emetic —much more powerful than CBD or THC. It works through stimulation of the Serotonin 5-HT1A receptor, which is one of the main mechanisms involved in other beneficial effects.

CBDA also has a strong effect on tumors, but this use is really not new. It was described by Renaissance herbalists quite extensively. It's only now that we have the chance to study CBDA in a lab.

There are many other cannabinoids, most of which haven't come to public attention yet, but all of which have weird and wonderful pharmacological properties.

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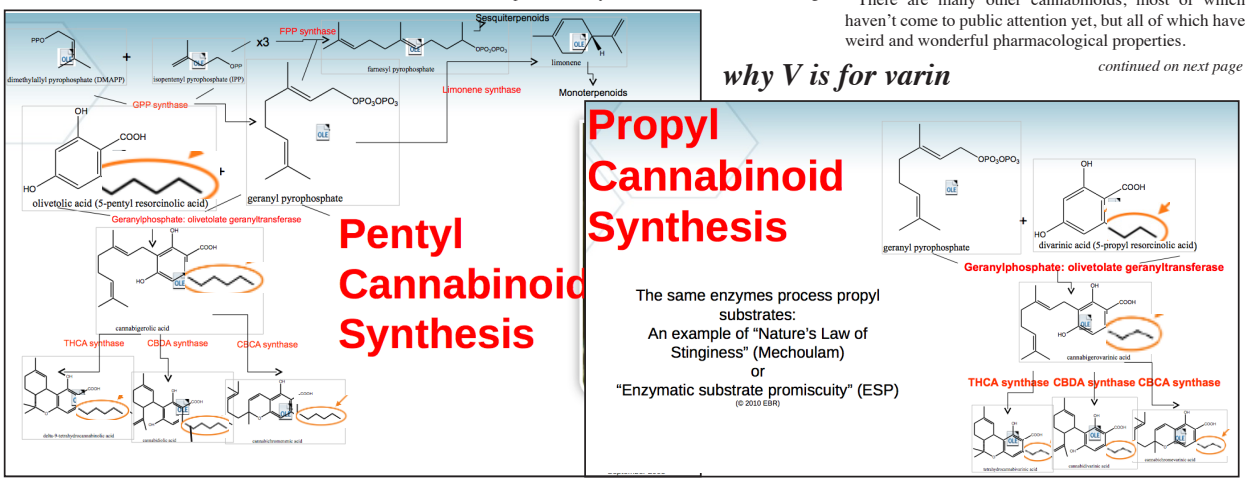
why V is for varin



The *Cannabis* plant synthesizes THC acid and CBD acid by combining geranyl phosphate with olivetolic acid (which has a five-carbon 'tail' that gets retained in the process). Cannabis employs the same enzymes —THCA synthase and CBDA synthase— when combining geranyl phosphate and di*varin*ic acid (which has a three-carbon tail that similarly gets retained) to synthesize THCV and CBDV. Thus THC and CBD each have a five-carbon pentyl group attached where CBDV and THCV each have a three-carbon propyl group in their tails, and *varin* in their names. The varinic acid form of cannabichrome (CBCVA) is the third propyl cannabinoid in these graphics from Russo's power point.

Russo's Keynote *from previous page*

What misleads people about the importance of terpenoids is that they're present in very tiny concentrations in the plant.

Some of us have been trying to convince people for a long time that the terpenoids in Cannabis are important. Many are analgesic and anti-inflammatory in their own right. And many have psychoactive properties. What misleads people about their importance is that they're present in very tiny concentrations in the plant. But they're extremely potent molecules, and in combination with the cannabinoids they make a big difference in a plant's medicinal properties.

The species controversy. You'll hear a lot about sativas and indicas, most of which is nonsense, because even the taxonomists can't agree. Taxonomists are the people who define what species is what in botany—and they are constantly changing their minds. There's no uniformity of opinion at all. They're worse than neurologists.

The prevailing notion is that Cannabis is one species with varieties. *(See John McPartland's take on page 17.)* Ernest Small in Canada has identified three basic types. Type 1 is a high-THC plant. Type 2 is mixed THC and CBD, the way cannabis frequently was in the past. And Type 3 is CBD predominant.

Some years ago, Karl Hillig did a series of articles showing that what really distinguished one *Cannabis* variety from another was their terpenoid content. This has been demonstrated subsequently by Jeffrey Raber in his survey of plants grown in California.

Very rarely do cannabis dispensaries provide medical consumers with relevant information about their products. What's its specific cannabinoid content? What's its specific terpenoid content? How does it taste when vaporized? And how should it be used? What conditions is it good for? What have patients reported in terms of benefits? What might be in there that shouldn't be in there?

A format developed by Mark Lewis and Matt Giese of Napro Research provides a great deal of useful information (*See illustration at bottom of page.)*

A brief comment on Marinol, which I find problematic. Synthetic THC was approved as a medicine, dronabinol, in 1985; Marinol is the trade name. When it was downscheduled from Schedule 1 to Schedule 3 in 1999, I used it extensively in my practice. Over the course of four years, I found that even people who are accustomed to cannabis had trouble with Marinol. It's very quirky. It tends to produce dysphoria rather than euphoria. The dose is often too high. People are fine and they're suddenly too high. It's very expensive. And it lacks all those accoutrements, the synergistic components of whole cannabis.

Typically, about 15 percent of the THC is actually drawn into the lungs.

Smoking cannabis —the most common method of application— is problematic. It remains illegal in most jurisdictions, and even where it's legal, you're not supposed to do it publicly. Smoking is very wasteful of THC. Typically, about 15 percent of the THC is actually drawn into the lungs.

Contrary to the wishes of many people, smoked cannabis just cannot get through the FDA approval process.

Although smoking cannabis alone, without tobacco, has not been linked to the development of lung cancer, it does produce polyaromatic hydrocarbons, which are carcinogens. The body has to process them, which puts an unnecessary metabolic demand on the liver. Irritants in the smoke cause bronchitis.

Vape pen heating element (left) turns red-hot in seconds. "This is burning, not vaporizing," said Russo. Vape pens using propylene glycol as a propellant have been shown to produce cancer-causing formaldehyde. Photos by Ethan Russo

As much as we'd like to demarcate ourselves from insects, if a substance kills an insect, there's a good chance that it's not good for you, either.

There is also the real danger of inhaling toxic pesticide residues when cannabis is smoked. Jeff Raber and colleagues at the Werc Shop, a lab in California, applied pesticides —Diazinon, Paclobutrazol, Bifenthrin, Permethrin— to cannabis and then measured how much came through when the material was "smoked" by bong (with and without filters) and glass pipe. The result was an ominous 40 to 70 percent.

I queried labs in California and was told that between 15 and 35 percent of their samples from growers and dispensaries had pesticide residues.

Abamectin and other pesticides that are cholisterase-inhibitors, if present in cannabis used by someone with epilepsy, can induce seizures. Even someone who doesn't have seizure tendency can have a seizure if they're exposed to neurotoxic pesticides in sufficient amounts. As much as we'd like to demarcate ourselves from insects, if a substance kills an insect, there's a good chance that it's not good for you, either

Vaporization is preferable to smoking as a delivery system for cannabis, but it's not perfect. The idea is to vaporize cannabinoids and terpenoids at a lower temperature that does not burn the material to produce smoke. Unfortunately, there has not been a study to date with the Volcano —a very good machine— or any other vaporizer that showed a total absence of polyaromatic hydrocarbons. Again, we can't say that they will cause cancer if somebody's not smoking tobacco. But we can say that the FDA is never going to approve a device that produces any amount of these.

Arno Hazekamp did a survey of consumer preferences in the Netherlands in 2013 and reported that only 27% of medical users were vaporizing. Smoking still predominated, which is really suboptimal in terms of harm reduction.

Edibles are reportedly gaining popularity, and consumers are being offered extracts in a variety of formats. But the industry has serious quality control problems. The American Herbal Pharmacopeia and other organizations are trying to develop standards that I think will be a boon to consumers, whether recreational or medicinal.

Confections, particularly ones packaged to look like real candy with catchy names, are attractive to children, and you can understand that the DEA would look askance at this kind of thing.

Particularly for patients with chronic conditions, oral administration could be a big advantage because it doesn't require frequent dosing throughout the day. With modern hash-making techniques and a good chemovar, it's possible to get the THC level of a concentrate up to about 60 percent. I would seriously question why people need any more than that. How high does a patient need to be to have symptom relief?

Recreationally, people will take what they want to take, but for the medical user, what's important is proper administration with maximum harm reduction.

"Dosing is a crucial issue therapeutically. Dosing should be to the point of symptom relief rather than psychoactivity. Two point five milligrams of THC is a threshold dose for most patients. Five milligrams is usually effective and tolerated. Ten milligrams is too much for many people, but not for those with tolerance.

But the quest for higher levels of THC continues, and "dabs" keep gaining popularity.

Cannabinoids and terpenoids are sticky substances. Polar solvents —either a fat or alcohol— are required to extract them. But many of those same solvents are flammable or explosive. Not a week goes by in this country that somebody doesn't blow themselves up trying to do a butane extraction at home. Butane and naphthalene can leave toxic residues. Not just cannabinoids but contaminants, too, are highly concentrated by the process.

It just mystifies me how people can be environmentalist vegans, so fastidious in their habits otherwise, and yet accept this kind of solvent in the material that they're inhaling. People who use dabs acknowledge that they suffer onset of tolerance and even withdrawal symptoms when they refrain. So, I don't think that dabs are ideal at all for medical users.

Again, I would ask the question, how high does a patient really need to be to get relief? Development of tolerance should be avoided. There is a sweet spot in therapeutics that is achievable and desirable where symptoms are treated without intoxication.

Just a little more about wax. We now have these devices called "vape pens," which are a misnomer in most instances. An unheated heating element *(photo at left, above)* will turn red hot with seconds of the device being turned on *(photo at right)*. I guarantee you this temperature is way above the vaporization point of THC and terpenoids.

text continued on bottom page 24

Ethan Russo, MD, addressing the Americans for Safe Access "Unity Conference" in Washington, DC, March 2015. When asked if O'S could run a print version of his talk, Russo expressed concern about being perceived as "a scold." Russo is not a scold, he's a doctor — a neurologist. He's also an ethnobotanist, a novelist, a historian, an educator, and a Grateful Dead fan.

With John McPartland in 2001, Russo challenged the medical establishment's assumption that single-molecule, "silver bullet" medicines are superior to herbal medicines with their "shotgun" full of active compounds.

It was Russo who first proposed that a "Clinical Endocannabinoid Deficiency" was associated with various ailments. His 2004 paper in Neuroendocrinology Letters asked "Can this concept explain therapeutic benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?"

Over the years no one has done more than Russo (and McPartland, David Watson and Rob Clarke) to publicize the role of terpenoids in determining the effects of cannabis.

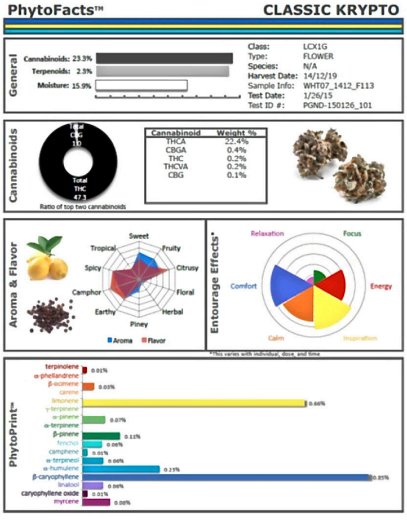
Useful Info

Russo praised the format devised by Mark Lewis and Matt Giese of Napro Research to provide "the information that a consumer would really need in helping to select a strain to use for their condition: cannabinoid content and terpenoid content, a picture of the actual plant, what the notes are in terms of its scent and taste, the effects that people get from it..."

With reference to a slide *(graphic at right)*, Russo said, "Here we see a very high degree of limonene. *(yellow bar, 'Phytoprint' at bottom)*. This might be a chemovar that's very good for treatment of depression, because limonene has that effect. It also is very high in beta-caryophyllene *(blue bar)*. Beta-caryophyllene is a CB2 agonist, a very powerful anti-inflammatory. It also is very low in myrcene, the couch lock compound, so this would be a non-sedating strain that people could use if they have to work or study.

"I think this level of information would be a boon to future consumers."

The essential-oil patterns displayed in "PhytoPrints" suggest a way to define cannabis into classes the way wine is categorized as Merlot, Zinfandel, Pinot, etc.



Phytecs' Plants of Interest

Artemesia Members of the daisy family and noted for their high essential oil production, including wormwood, mugwort and sagebrush. Thujone produced by wormwood was once thought to act as a cannabinoid, but has recently been shown to have a rather weak affinity for cannabinoid receptors, though it is active at other receptors.

Camellia A genus of Asian flowering plants. Contains many ornamental varieties and also Camellia sinensis, the tea plant. C. sinensis produces catechins and flavonoids that interact with the ECS.

Cannabis Cannabis produces a wide range of phytocannabinoid compounds that interact with the endocannabinoid system and associated receptors. Cannabis also produces entourages of compounds that are of great interest, because of their synergistic effects.

Catha A small genus containing three species. The most famous is *Catha edulis,* a stimulant herb used in Africa and the Middle East. At least one alkaloid produced by the plant has been shown to elevate endocannabinoid levels in animal tissue studies.

Desmodium This is a large group of plants, including the tick-trefoils, many of whom produce very active essential oils.

Echinacea A genus of nine plants called coneflowers within the daisy family. Echinacea purpurea is a popular herbal remedy, though large controlled studies supporting its efficacy are lacking. This species appears to produce alkamides and other constituents that interact with CB receptors.

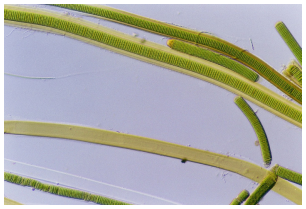
Glycine Members of the bean family, noted for Glycine max, the soybean. Some flavonoids in this genus appear to inhibit ECS enzymes.

Helichrysum A genus of over 600 plants in the sunflower family. Some members produce compounds with striking chemical similarities to cannabinoids.

Heliopsis A small genus in the sunflower family, that includes the oxeyes, common across the central US and Canada.

Laminaria A genus of over thirty species of brown algae commonly called kelp. Some of this genus produces polyunsaturated fatty acids that are chemically similar to endocannabinoids.

Lepidium A genus of the mustard family. Noted for the "superfood" called maca, and garden cress.



Lyngbya Not a plant genus, but one of cyanobacteria. Some of these produce interesting polyunsaturated fatty acids.

Morinda A genus of eighty or so species in the madder family, some of which have been used for centuries in traditional Asian medicine. Also, a city in Contra Costa County.

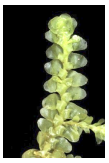
Pinus The subgenus that includes many European species of pine. It is believed that some species of pine produce analogs of endocannabinoids.

Piper An enormous genus containing over 2,000 species of pepper plants. Piper nigrum is commonly known as black pepper and produces the terpenoid b-caryophyllene that functions as CB2 agonist. The kava plant, also of the Piper genus, produces a kavalactone that has significant CB1 affinity.

Pistacia A genus of shrubs and small trees in the cashew family. Besides the well known pistachio tree, other members of this genus produce medicinal resins which have been used since antiquity.

"No person should succumb to brutality without putting up a resistance. Individually it can save one's life; en masse it can change the course of history." —Shalom Yaron

Protium A genus of ,more than 100 flowering plants, primarily trees, many of which are native to Central and South America.



Radula Members of the liverwort family. Radula marginata, native to Tasmania and New Zealand, was one of the first and only plants, beyond Cannabis, found to produce a phytocannabinoid.

Rhodiola A genus in the stonecrop family noted for sedums. Rhodolia rosea known as goldenseal root is a popular herbal medicine.

Ruta A genus of evergreen shrubs noted for production of intensely aromatic oils, several of which are of potential interest.

Salvia The largest genus of the mint family. It includes common sage and also Salvia divinorum, a potent psychoactive.

Syzygium A genus belonging to the myrtle family, mostly consisting of evergreen shrubs and trees. The most well-known may be *Syzygium aromaticum* known as clove, which contains beta-caryophyllene, a CB2 receptor agonist.

Trifolium A genus of three-hundred plants in the pea family, noted for clover or trefoil.

Tuber A genus in the Tuberceae family of fungi that includes the black truffle. Recently, an analysis of black truffles found traces of anandamide, a principal endocannabinoid.

THE LAUNCH OF PHYTECS

Russo's new employer aims to develop natural products (some cannabis-based)

Ethan Russo was on the agenda twice at the ASA meeting. One talk, drawing on his experience at GW Pharmaceuticals, explained the steps involved in getting U.S. Food and Drug Administration approval for Cannabis-based medicines. Russo expects Epidiolex to "sail through" the FDA approval process. "If you have the right preparation with the right ingredients," he said, "you can make this a very acceptable medicine." Clearly he did not leave the UK company because of misgivings about the practicality of their research agenda.

In Russo's keynote address there were hints of the approach he plans to pursue in his new role as medical director of a start-up called Phytecs. (The name is synthesized from *phyto,* which is Greek for "plant," plus *e*ndocannabinoid *s*ystem.)

According to its website, launched quietly in late February, Phytecs will evaluate beneficial plants other than *Cannabis* that "produce compounds that interact with the endocannabinoid system in many different ways, from mimicking endocannabinoids to slowing or accelerating the enzymes that metabolize them."

Initially, the company plans to develop cosmetics, skincare products, nutraceuticals, and food supplements — "natural products" that can be marketed to consumers after an FDA approval process that does not involve clinical trials. Although it cannot be claimed that natural products are medicines, consumers may discover, for example, that a CBD-rich skin cream is a better (not to mention safer) treatment for acne than FDA-approved Accutane.

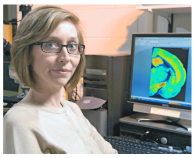
Phytecs, according to Gary Hiller, the Los Angeles attorney who launched it, was inspired by a speech to the International Cannabinoid Research Society by Raphael Mechoulam entitled "Planning Research for the Next Half a Century." Mechoulam suggested that investigators explore new applications for CBD, the uses of the CB-2 receptor, and the role of numerous fatty acids that are close chemical relatives of the body's own cannabinoids.

Hiller engaged Mechoulam as Phytecs' Director of Global Research, and will support trials of semi-synthetic cannabinoids developed in Mechoulam's lab at Hebrew University in Jerusalem.

Phytecs's advisory board includes scientists Heather Bradshaw, Andrea Hohmann and Jürg Gertsch, ethnbotanist James A. Duke, and former Congressman Tony Coelho, who introduced the Americans with Disabilities Act.

Bradshaw runs a lab at Indiana University that has been trying to determine the cause, at the receptor level, of endometriosis and other disorders affecting female reproductive function.

Hohmann also directs a lab at IU that has been focused on the role of the endocannabinoid system in processing pain. "Her laboratory first demonstrated that activation of



ANDREA HOHMANN

CB2 receptors suppresses the processing of nociceptive information," says her Phytecs resume. "Her lab also demonstrated that endogenous cannabinoids are mobilized in the brain underlying a phenomenon known as stress-induced analgesia. This work identified the enzyme monoacylglycerol lipase as a previously unrecognized analgesic target."

Gertsch, now a professor at the University of Bern in Switzerland, determined that beta-caryophyllene in Echinacea exerts effects through the CB-2 receptor. His current research, according to the Phytecs site, "focuses on molecular pharmacology of the endocannabinoid system and drug discovery."

JÜRG GERTSCH

The site provides an intriguing list of plants known to contain beneficial compounds that might be incorporated into balms of various kinds. *(See next page.)* We know that at least one of them makes beneficial compounds, and that cosmetics and nutraceuticals derived from it will be available in Costco sooner rather than later.

"Phytecs is focused not on the arrow, cannabis, but on the target —the endocannabinoid system and other lipid mediators throughout the body and into the microbiome in the gut, where we now know there is interaction between our bodies and the microbes that inhabit us through lipid signaling mechanisms!"
—Michael Backes

"Phytecs is focused not on the arrow, cannabis, but on the target," said Michael Backes, auteur of the Phytecs website at a Society of Cannabis Clinicians meeting in March. He defined the target as "the endocannabinoid system and other lipid mediators throughout the body and into the microbiome in the gut, where we now know there is interaction between our bodies and the microbes that inhabit us through lipid signaling mechanisms!"

Phytecs, said Backes, is "going to cast a very wide net that extends beyond cannabis. We've identified more than 20 genera of plants that have species within them that exhibit endocannabinoid-system activity —not just activating receptors, but interfering with any part of the process of synthesis and metabolism.

Common Name	Terpene Super Class	Secondary Terpene	Tertiary Terpene
Big Sky	Caryophyllene	Humulene	Limonene
Bubba Kush	Limonene	Caryophyllene	Linalool
OG Kush	Limonene	Caryophyllene	Myrcene
Purple Urkle	Myrcene	Caryophyllene	Pinene
Jack Herer	Terpinolene	Caryophyllene	Humulene
Trainwreck	Terpinolene	Myrcene	Limonene
Blue Dream	Pinene	Myrcene	Caryophyllene

Characterizing California Cannabis Strains

By Mark Lewis

Cannabis medicines are currently described by common names, such as "OG Kush, "Purple Urkle," "Trainwreck" et al. Although colorful, these names tell a patient nothing about the chemistry of the plant, and rarely do they convey the anticipated entourage effects.

Names can be meaningless and inconsistencies in naming and production are a major concern in the unregulated medical cannabis industry. In my lab, NaPro Research, the solution was to create a shorthand system of nomenclature to describe cannabis medicines based on their chemistry instead of a common name.

Since 2011 we have analzyed thousands of cannabis samples by gas chromatography for growers and plant breeders in California. (*Giese et al*., submitted for publication 2014 *JAOAC)*. It soon became clear that these connoisseurs relied heavily on their sense of smell when determining the "most correct" common name.

Knowing that smell and entourage effects are related, we looked at the relative essential oil content of each cannabis sample. In due course, classes began to emerge in a continuum of relative phytochemical concentrations. In many cases, the classes aligned with what connoisseurs have traditionally defined as an "OG," a "Purp" or a "Trainwreck."

Contrary to conventional wisdom, common names can be used to distinguish different cultivars, but only when they have been named correctly by cultivators and dispensaries savvy enough to elucidate chemical differences based on aroma and morphology. This isn't always the case, unfortunately, and incorrect names are often applied to samples.

The bottom line is that *Cannabis* genotyping based on secondary-metabolite concentration is a plausible solution to finally ending the naming game.

Product variability is inevitable.

Bear in mind that Grower Andrew's OG might not be the same as Grower Betsy's OG —even if their clones were from the same mother plant. Environment impacts phenotype, and plants with identical genotypes can produce drastically different phenotypes and chemotypes (finished products) when grown or processed in different settings. Cannabis is an agricultural crop and product variability is inevitable.

Keynote *from previous page*

But the problem is worse than that, I'm afraid. A recent paper by R.P. Jensen in the *New England Journal of Medicine* reported that some e-cigarettes using propylene glycol and glycerol as propellants get hot enough to produce large quantities of formaldehyde —a Group 1 carcinogen. This could result in a cancer risk 15 times greater than posed by smoking cigarettes

The researchers were using nicotine in e-cigarettes, but cannabis in a vape pen using propylene glycol as the propellant would pose the same risk. Propylene glycol is nontoxic for humans taken orally in small amounts, but not when it is heated and inhaled.

Cannabis does have side effects. Any time somebody starts an argument by saying, "Cannabis has no side effects," they've already lost. This is something you should never say because it's just simply not true. The truth is that it has some side effects but they're largely avoidable.

According to a tabulation put together by Mark Ware and his colleagues some years ago, neurologic and psychiatric side effects are not uncommon. High-THC preparations cause anxiety, euphoria, decreased muscle tone (which can be useful if spasticity is present), effects on movement, heightened sensory perception, decreased short-term memory, possible sedation, and decreased body temperature. Some people get cold because the set point in the hypothalamus goes down.

People who aren't used to cannabis can easily get too high on a single dose, particularly with a vape pen. Some people take one inhalation on a vape pen and instantly lose consciousness due to orthostatic hypotension. The heart rate slows down so much that there's no oxygen to the brain.

Again, although, cannabis does not cause cancer when smoked, it is inarguable that it produces cough and symptoms of bronchitis.

In the early stages of the Sativex development program, very high doses and very rapid titrations were allowed. What was found was, after a certain number of sprays per day, maybe 10 to 12, there wasn't a big improvement in efficacy, but there was a big increase in side effects.

"The best dose is the lowest dose that improves symptoms… Remember, for proper dosing, 'Start low and go slow.'"

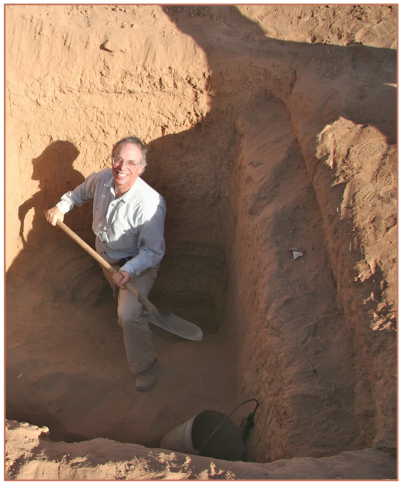
What we know now is that the best dose is the lowest dose that improves symptoms. If you get to the point of overt psychoactivity, it's not necessarily going to be more effective therapeutically. GW Pharmaceuticals found that giving lower doses of Sativex with lower titration reduced dizziness from 32 percent to 14 percent.

Other side effects such as fatigue, somnolence, sleepiness, nausea, dry mouth, all almost disappear. The bottom line is, you got a much better safety profile and efficacy – improvement – by using lower doses and moving slowly. So we will amend the prior statement: Cannabis does have side effects, but they are better than those of any medicine that you see advertised on TV.

Remember, for proper dosing, "start low and go slow."

Finally, in closing: It is critical to understand that cannabis is a plant that modulates the endocannabinoid system (ECS), an innate homeostatic regulator of human physiology. The ECS can also be influenced by lifestyle and dietary factors beyond cannabis. Paramount among these would be low-impact aerobic exercise, and an anti-inflammatory/antioxidant diet.

Thank you!



ETHAN RUSSO AT YANGHAI TOMBS in 2008, near Turpan, Xinjiang, in western China. He assisted in the re-excavation of the tomb of a Gushi shaman who had been buried with a massive stash of cannabis. Photo by Hong-En Jiang, PhD.

From Tel Aviv To Sonoma County

Nursing home staffers document a versatile boon for the elderly

Hadarim by Zach Klein

The option of using cannabis for medicinal purposes in Israel was publicized in *"Prescribed Grass,"* a documentary I produced that was released in September 2009. A few months later I received an unexpected phone call:

"Hi. my name is Inbal Sikorin and I'm the head nurse of the Hadarim nursing home. One of our patients got a license for using cannabis and I don't know what to do with it. I want you to come and help us."

"Why me?" I asked.

"A family member of the patient saw your movie, applied for a license, and now we have it here and we don't know what to do with it. You made that documentary and you probably know something about it."

So I went to Kibbutz Na'an for a visit to the Hadarim nursing home —a 36-bed skilled nursing facility. Patients admitted to Hadarim have difficulties coping with the required activities of daily living. Inbal introduced me to the patients and I became their cannabis consultant.

1ST Case: Mrs. A.

She was a 75-year-old lady, sitting on her wheelchair, groaning. She had been diagnosed with severe dementia. Not responding to anything. Just groaning. Inbal said she had been that way for months. She had no appetite and had been losing weight rapidly. The nursing team called her, not without affection, "the tiger."

At that time patients in Israel received cannabis only as dried flowers for smoking. But smoking a cigarette was not physically possible for Mrs A. So I had to hold the cigarette an inch from her mouth and puff some smoke towards her. It did the trick.

A few minutes after she inhaled she stopped groaning. Her eyes stopped running around unfocused. She responded when we spoke to her. And for the first time since she was admitted at Hadarim, she smiled and laughed. That was the first time anyone at the ward had seen her laughing or smiling.

That experience led to another license in the nursing home and a few months later another one.

Methods of administration

A lot of improvisation was needed at the beginning. A member of the kibbutz built a simple smoke machine, so the nurses could use the herb.

Later on we established more convenient ways for treating the disabled patients. Vaporizing and ingesting decarboxilated dried cannabis were introduced. Buds were finely ground and mixed with porridge. The starting dose was 0.08 grams, which was raised to 0.12 grams and then 0.25 grams three times a day.

The Ministry of Health issued a special license enabling the nursing home to use cannabis to treat patients.

The small, obscure facility became a pilgrimage site for journalists from all over the world as it was the first officially government-approved cannabis-friendly nursing home.

Return to Hadarim

In 2013, three years after my first visit, as a master's candidate at Tel Aviv University's Porter School of Environmental Studies, I came back to Hadarim to conduct research for my thesis. At this time 27 of the 36 patients were being treated with cannabis.

What is the connection, you may wonder, between environmental studies and cannabis use at a nursing home? The answer lies in the reduction of pharmaceutical drugs polluting the water supply. Thus my main goal was to assess whether cannabis could substitute for prescription medications.

To determine how cannabis use affects patients' well-being and their use of other medications, I reviewed the files of the 27 patients using cannabis for various conditions. Quality of life as described by the Hadarim staff was essential data.

Cannabis was precribed for:

Pain (18 patients), Appetite (9), Spasticity (7), Agitation (3) Parkinson's (2), Tremor, Ataxia, Insomnia, and Mood (1 each). Some patients were prescribed cannabis for more than one medical condition.

Four types of cannabis were used at Hadarim:

- Flowers of a high-THC strain with more than 20% THC and no CBD
- A mixture of flowers and trim that contained 8 % THC and no CBD.
- A balanced strain that contained 12% THC and 12% CBD
- A CBD-rich strain with 16% CBD and 1% THC

All were provided by Tikun Olam (a company licenced by the Israeli Ministry of Health to grow cannabis for medicinal use) and analysed at Hebrew University by professor Lumir Hanus.

Most of the patients (22) received cannabis mixed with porridge. Others smoked or vaporized. Most of those who inhaled moved on to digesting cannabis in edible form.

Mrs. A revisited

The first patient, Mrs. A, continued with treatment, inhaling 0.3 grams of Cannabis flowers in our smoke machine and later on with a vaporizer

Her weight loss was halted when she started using cannabis and remained stable for one year. The next year she even started gaining some weight.

continued on next page

Spasticity (clenched fists in photo at left) in a Hadarim patient with Multiple Sclerosis was relieved within minutes of Cannabis inhalation.

Primrose by Jeffrey Hergenrather

Philip Grob, MD, a geriatric psychiatrist in Santa Rosa, California, who had been referring patients to me to evaluate for cannabis use, began to take on that role himself a few years ago. Dr. Grob told me he had approved cannabis for several Alzheimer's dementia patients who had been admitted to an assisted living facility and the effects were visibly beneficial. He suggested that we collaborate on a formal study to measure the impact of cannabis on the symptoms of Alzheimer's, which include tremors, pain, and agitated behaviors.

In an assisted living facility patients are able to get a cannabis recommendation from their doctor. The doctor then writes the orders to the nursing staff so that they can administer the medicine.

Primrose is a privately owned residential care facility for the elderly (RCFE). It is licensed under California's Department of Social Services —unlike nursing homes and skilled nursing facilities, which are licensed under Health and Human Services and have more rigorous rules covering how medicine is administered.

In an assisted living facility patients are able to get a cannabis recommendation from their doctor. The doctor then writes the orders to the nursing staff so that they can administer the medicine in such and such a way. Thus Dr. Grob and the nurses at Primrose were able to use cannabis in the treatment of Alzheimer's disease.

The incidence of Alzheimer's is growing exponentially worldwide. The disease is progressive and irreversible. It slowly destroys memory, thinking skills, reasoning, and eventually the ability to carry out the simplest of tasks. It's the leading cause of dementia in the elderly, affecting approximately 5.1 million Americans. Dr. Grob says the incidence is really much higher than that and I would tend to believe him from what I'm seeing in practice as well.

In the mild form, memory worsens. Problems include getting lost, trouble handling money and paying bills, repeating questions, taking longer to complete normal tasks, using poor judgment, and having mood and personality changes.

We all know of people with mild forms of dementia. In the moderate form confusion worsens and there's difficulty in recognizing family members and friends. The patient may start having hallucinations or delusions, paranoia, and they become impulsive. The patients wander off, they're confused, they don't recognize people. There is a break point in many cases when a working family can no longer cope.

So with great grief they bring their family members to a place like Primrose, and the guilt they feel in doing this is huge. If we can make patients and families feel better, it's very important. In the severe form of Alzheimer's people can no longer communicate, they're completely dependent on others for care. At Primrose there are many patients who fall into this category.

The facility is beautiful. It's a large campus that has lots of grassy lawns, there's play areas for kids who are brought on visits and places for people to sit outside and enjoy the environment. There are flower gardens and a day club for activities so the more able patients can get involved in games or movies.

Despite its placid appearance, Primrose is a locked-down facility.There are fences around the perimeter, there are walls that are too high to climb, the gates are monitored 24 hours a day by cameras so that no one gets in or out without being buzzed in. So patients are not getting lost, even though they can wander out the doors. The staff keeps track of them and they do a great job at that.

A black-box warning means that the use of these drugs is associated with an increased risk of death in elderly patients with dementia.

Agitated behaviors are common in dementias. The allopathic response is the "chemical restraints of medications," but the FDA has no approved medications for agitation, which is a hallmark of dementia. Conventional medications include antidepressants, anxiolytics, antipsychotics, sleep meds, pain meds —all the usual suspects. They are ineffective. Behaviors worsen, the amount of medicine goes up.

Many of the meds being used have black-box warnings. If you pull out the package insert you'll see a black box in the tiny-font description of the drug. A black-box warning means that the use of these drugs is associated with an increased risk of death in elderly patients with dementia.

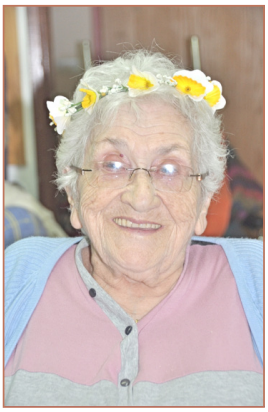
Some nurses have been traumatized by administering these drugs on orders from doctors and then having unexplained deaths among their patients. I've had it happen to my own patients prescribed these drugs by their other doctors. It's very sad when people who you think have a chance to do better, and seem well otherwise, suddenly, unexpectedly die under the influence of these black-box-warning medications.

Primrose facility president, John Wotring,

continued on page 27

Philip Grob, MD, writes cannabis approvals for patients and orders for nurses at Primrose

Hadarim Nursing Home *from previous page*



During the first few months of her treatment the use of her other medications was discontinued. These included Clonex (Clonazepam) as an anxiolytic, phenergan as a sedative, Ebixa (Memantine) for Alzheimer's, and Seroquel as an antipsychotic.

2ND Case: Mr. G.

Mr. G. was born in 1920 and admitted at age of 89.

He was diagnosed with Parkinson's. Five years before arrival he had a stroke and was confined to a wheelchair. He suffered from spasticity and pain. Excess saliva dripped from his mouth. He had repeated flare-ups of arthritis. He was deeply depressed and crying a lot.

He was treated with different medications for Parkinson's, pain, gastrointestinal problems and gout. He was given an enema once a week. The medical team wanted to find a solution for his constant pains.

The treatment for Mr. G. was 0.5 grams of shredded cannabis flowers from a high THC strain, inhaled from a Volcano vaporizer three times a day.

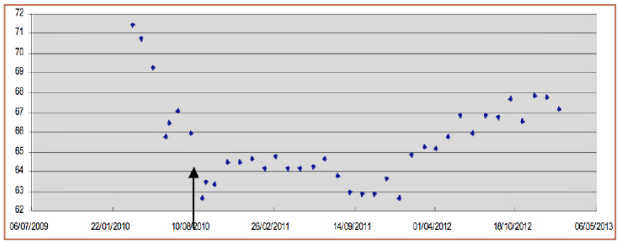
Almost immediately after treatment, Mr. G was free of pains, sitting upright in a chair, alert, and in good spirits. His salivation was significantly reduced, his muscles became less rigid and less cramped, his appetite improved and he ate better, no flare-ups of arthritis occurred, and his recurrent infections were reduced to zero.

The first medications Mr. G discontinued were painkillers, Lyrica and tramadex. Later on he was able to get off dopicar and comtan for the Parkinson's. And finally the use of colchicine for gout was discontinued.

These two cases, though dramatic, were typical of the 27 I reviewed. Collectively the patients experienced:

• Pain relief —and discontinuation of prescription painkillers.

• Improvement of appetite and weight gain.



WEIGHT LOSS BY MRS. A reversed after cannabis use began in August 2010 (arrow). Vertical scale gives weight in kilograms. Horizontal scale shows time from July 2009 through June 2013.

• Improved eating ability (discontinued feeding tubes).

• Decreased muscle contraction (spasticity).

• Improved sleep and decreased use of sleeping pills

• Enema treatments that were part of the ward's routine were almost completely halted for these patients after their constipation-inducing pharmaceuticals were discontinued.

Patients reported more than one benefit from using cannabis.

All 18 who had been prescribed cannabis for pain achieved relief of pain.

Fifteen patients experienced improved appetite.

Six patients slept better after cannabis treatment. (Only one had been given cannabis to treat insomnia.)

Two of the patients were holocaust survivors who suffered post-traumatic stress with nightmares and daytime anxiety. Cannabis prescribed for pain and appetite coincidentally alleviated their PTSD symptoms.

Two patients receiving cannabis to reduce pain and stimulate appetite experienced relief from arthritic inflammation.

Staff reponse

When cannabis was first introduced at Hadarim, the nursing staff expressed considerable skepticism about its usefulness. As time passed, however, and more patients received cannabis and responded well, healthcare workers have changed their minds about the treatment. The ability of the staff to provide care improved markedly in cases of spasticity, and loss of appetite.

As the patients' quality of life improved so did the quality of life for the nursing team. The department was calmer and less noisy as the patients suffered less.

Families of the patients reported that they had better visits

Families of the patients reported that they had better visits —contact with the hospitalized family member improved. Some patients were emotionally and intellectually reconnected with their relatives after a period of separation.

A total of 39 medications were discontinued by the 27 patients followed in my survey:12 painkillers, 10 anxiolytics, three drugs for Alzheimer's, three antipsychotics, two drugs for parkinson's, two for gout, two anticonvulsants, three sedatives, one laxative and one anti-diabetic.

Environmental impact

Recently, scientists in a hydrochemistry lab at Tel Aviv University documented severe water contamination caused by pharmaceutical residues from human excretion or thrown-away pills. Decreasing consumption of these compounds will protect our water resources. Increased use of cannabis will help us achieve this goal.

My next research project, to be conducted at Reut Rehabilitation Hospital, will test the effectiveness of cannabis treatment in oro-pharyngeal dysphagic patients and elderly patients with eating (swallowing) problems. I will also evaluate the cognitive effects of cannabis treatment on these patients.

Zach Klein thanks his Tel Aviv University advisors: Professor Dror Avisar, Hydrochemistry Laboratory: Professor Naama Friedman, School of Education:and Dr. Yehuda Baruch, Faculty of Medicine and Director of the Abarbanel Mental Health Center.

Clopixol	Lorivan	Ebixa	Percocet	Ameryl
Laxadin	Halidol	Clonex	Lyrica	Colchicine
Memorit	Oxycodin	Phenergan	Dopicar	Depalept
Cipralex	Xanax	Seroquel	Vaben	Durajesic
Exelon	Recital	Bondormin	Acamol	Tramadex

The Nurse as Organizer

By Karen Mankins, RN

I work at a Residential Care for the Elderly facility, a "life care community" which involves three levels of care: Independent, Assisted, and Skilled Nursing. I am the administrator for Assisted Living.

In the fall of 2012 a resident's daughter asked me to talk to her mother's physician about medical marijuana to treat her severe chronic back pain. (Three compression fractures to her low back despite numerous medical procedures.)

So the following day I talked with her physician and without hesitation he took out his script pad and wrote a recornmendation for Cannabis for her pain!

I was completely surprised, I didn't think he would. I expressed that to him and he stated, "Karen, I'd much rather have my patients on this then all the other crap they are taking!"

I returned to my desk and I'm holding in my hand an order for cannabis for chronic pain. How do I order this? Who do I call?

The first thing I did was call the California Department of Social Services (DSS). I asked if there were any regulations for cannabis use in an assisted living facility? I could hear a faint chuckle and was told they had received many calls lately (remember, this was almost 3 years ago) and that there were no regulations, but to treat it like a Schedule II substance even though it's still considered a Schedule I by the federal government.

Okay, so now what do I do? Where do I get this filled? Was she supposed to smoke it? This is a non-smoking community! In order to monitor dosage do I count the number of joints or hits she takes?

In a local weekly newspaper, on the back page are advertisements for dispensaries (none in our area) and delivery services. Nervous but in need of information, I called a delivery service asked what is best for an 84-year-old lady with chronic back pain?

As a nurse, you never give a medication to a patient without knowing how the medication works in the body and the side effects associated with it.

They suggested a CBD-rich tincture, which would be easy to administer. The following day a very nice young man arrived at my facility and delivered to my office a dark brown bottle with an eye dropper and on the label it read "CBD Rich tincture. 3/4 of a tsp =1 dose."

As a nurse, you never give a medication to a patient without knowing how the medication works in the body and the side effects associated with it. I tried calling different facilities asking if anyone was using a tincture in their facility and I couldn't get anyone to talk to me. At the time I did not know Dr. Deborah Malka, a cannabis specialist with an office in Santa Cruz.

So, there I was holding a dark brown bottle (50cc) in my hand with an eyedropper. No measurements on the dropper. How do I know how much to give? I called my pharmacy and asked if they could send me some empty Roxanol containers which are measurable.

KAREN MANKINS, RN

Nurses will appreciate the fact that in our medication cart we have no narcotics to count each shift, no sleeping pills or anti-anxiety meds!

The resident and her daughter were getting anxious to try the new medication. At the time the patient was getting two Norco every four hours around the clock. She was constipated and on multiple bowel meds. She was nauseated from the narcotics and was getting anti-emetic meds. She had no appetite, was depressed and anxious and taking anti-anxiety meds. She had no energy and she couldn't sleep! What kind of quality of life is that?

I've learned when giving a new medication to an elderly patient to always give "low and slow." So instead of giving the ¾ teaspoon, I gave her two milliliters and asked her to remain in her chair. I called a half hour later and asked how she was feeling? She said "Well, I'm hungry!" Then I asked her about her pain. She replied "What pain?"

I couldn't believe it. This has to be a placebo effect. I went to her room and asked, "What do you mean 'what pain'?" She said, "Karen, I know the pain is still there but the edge is off so much better than those damn pain pills!"

continued on page 67

Sonoma elderly *from page 27*

Sr. and his son and CEO, John Wotring, Jr. have special compassion for elders with severe dementia. They, too, have been traumatized by unexpected deaths following use of black-box warning drugs.

Among the drugs being used at Primrose to treat Alzheimer's Disease are acetylcholinesterase inhibitors. Acetylcholine is a neurotransmitter involved in memory and thinking; acetylcholine esterase is the enzyme that breaks it down, which increases the acetylcholine level at the synapse. It also prevents the acetylcholinesterase-induced beta-ameloid "plaque" aggregation and deposition, which are the key pathological markers of Alzhemer's Disease.

Although promising in theory, synthetic acetycholine esterase inhibitors don't seem to work very well —and they're expensive..

THC also inhibits acetylcholinesterase. In a paper that came out of Scripps Research Institute in 2006, Eubanks, et al concluded: "Compared to currently approved drugs prescribed for the treatment of Alzheimer's disease, THC is a considerably superior inhibitor of A beta aggregation... cannabinoid molecules may directly impact the progression of this debilitating disease."

This raises the question of whether or not use of cannabis and high-THC medicine may not only slow or stop the progression of the disease, but may even improve cognition and aspects of the patients' care.

The role of nurses

The stars of the show are the nurses who do the observing, the advocating, and the administering of cannabis.

Their patients are on black-box-warning drugs, shuffling down the hallways, drooling, chemically sedated. They're making switches to cannabis products. They're observing them for how much they need. They're advocating for patients who don't have cannabis as an adjunct to their other medicines. And they're administering it appropriately to get the most advantage.

The nurses are setting up care conferences with the physicians, staff and families to discuss cannabis therapy. As of now the facility is not asking for a written informed consent, although when we gt into a more formal study this will be required.

The nursing staff assists families in product options and sources. Thanks to California law, family members can grow cannabis as caregivers for patients. In some cases family members are baking cookies or brownies and bringing them to Primrose. There are also cannabis dispensaries' staff delivering products for patients. Cannabis-infused products are locked up in the narcotic lock box and taken out according to the doctor's orders to be given to the patients.

Nurses and doctors collaborate on treatment plans. For example, the nurse says, "Doctor, may I have an order for 'Give one cannabis brownie or chocolate orally three times a day with a feature to hold if too sleepy?'"

Another order might be, "Give 15 drops of cannabis tincture sublingually every four hours, or increase to one dropperful —30 drops—if agitation persists. Hold order if the patient is too sleepy."

If the patient is getting too much cannabis, they're sleeping. If they're not getting enough and they're still agitated, then give some more. The nurse is the one who will know.

It's as simple as that. If the patient is getting too much cannabis, they're sleeping. If they're not getting enough and they're still agitated, then give some more. The nurse is the one who will know.

It's a simple way to write an order and it gives the nurses a lot of latitude. As changes are made in the administration of cannabis, they'll go back to the doctor and ask for an update in the order to accommodate whatever is needed.

What consitutes an "effective dosage" is a very important question. Some patients are getting a good response with 5 or 10 milligrams of cannabinoids per day. Others are getting as much as 30 milligram doses as much as four times daily. The dose is managed by the nursing staff to meet the needs of their patients.

Oral formulations at this time include THC-rich and CBD-rich cannabis products, typically in tinctures, cookies, candies and brownies. I want to put a plug in for THC. I think the euphoria and the change of mind that people experience with THC —and not with CBD— is very helpful to patients with dementia. It gives them a different view of the world. It does seem to make a difference. Why withhold THC from these patients? Who has a greater need for its mood-altering effects?

The Cohen-Mansfield inventory of agitated behaviors in dementia lists "pacing, aimless wandering, inappropriate dress or disrobing, spitting, cursing, constant unwarranted request for attention or help, repetitive sentence or questions, hitting, kicking, grabbing onto people, pushing, throwing things, strange noises (weird laughter or crying), screaming, biting, scratching, trying to get to a different place, intentional falling, complaining, negativism, eating/drinking inappropriate substances, hurting self or others, handling things inappropriately, hiding things, hoarding things, tearing things or destroying property, performing repetitious mannerisms, making verbal sexual advances, making physical sexual advances, and general restlessness."

The symptoms that we're using cannabis for in this population include: agitation, anxiety, psychosis, restlessness (which can be extreme), anorexia, and aggression. Sometimes patients are taken away by the police when they start punching people. They may be introduced to a roommate but an hour later they don't know who the person is and they're fearful and they can get quite aggressive. They're depressed, they have pain, and muscle spasms, and insomnia.

Cannabis can alleviate each of these symptoms —and provide neuroprotection. My view is: smell the flowers before you push up the daisies. Let 'em have some THC!

Case Report Excerpts

• Patient has exhausted regular medications, now using cannabis has stopped her loud crying and agitation.

• Horrible hallucinations delusions and aggression... using cannabis only and stopped using haldol.

• Alpha male with aggression and agitation got off a drug cocktail with multiple black box drugs... refused all other medicines except cannabis chocolates.

• A very petite woman receiving full care had exhausted her behavioral medications, now she's thriving on cannabis, it spiked her appetite and there's a smile on her face.

• A fully immobile agitated woman on antipsychotics to the point of oversedation now on cannabis and is quiet and contented. The antipsychotics have been discontinued.

• A patient with severe aggression and agitation had a big problem with constantly picking at the skin and bleeding. Under the influence of cannabis the skin-picking and aggression have ended.

• Alpha female kicked out of another facility because of pushing and kicking other residents, on cannabis has calmed down and has pleasant affect.

•A hardworking gentleman with insomnia, agitation, and aggression, constantly restless. Cannabis has allowed him to slow down, stop his movement, and sleep.

•A patient who had been taken away from the facility with a 5150 hold for being dangerous to himself and others has now returned. On cannabis his hallucinations and rages have subsided. He's now transitioning off of his other medications to cannabis only.

• A patient with advanced Parkinson's disease and aggression. His family made cookies and brought them in. This has dramatically lowered his aggression and improved his sleep.

• A severe opiate-dependent patient obsessively needing to go to the toilet. She was out of bed every three minutes through the night. (They put a monitor on the bed.) With cannabis she's up once a night to the toilet and experiencing no breakthrough pain, no need for additional opiates.

• Three patients have been using Marinol at the average expense to the families of $675/month. It has resulted in mood stabilization and increased appetite. The staff is encouraging these patients to transition onto cannabis, which will likely be more cost effective.

• Two residents that are Kaiser patients in this facility have been refused cannabis therapy by their admitting Kaiser physicians, despite requests from families and staff. There are influential Kaiser physicians who do not recognize cannabis as medicine; they stay with the addictive and dangerous conventional medications that we are taught to use in medical school and residency programs. A few Kaiser oncologists have accepted cannabis as an adjunct to chemotherapy, but in general Kaiser treats cannabis as a drug of abuse without real value.

We've made a little breakthrough at Primrose: the primary doctor from Kaiser is going to come for a site visit to get a better feeling for how cannabis is working for the other patients.

Conducting a study

Dr. Grob and I want to look at cannabis use with accurately measured medicine. So we are designing a study where we will administer fixed-dosage, lab-verified amounts of cannabinoids. We are trying to get funding so that we can analyze the medications that the patients will receive. We expect to document the diminished use of conventional medicines and behavioral changes in the Cohen-Mansfield agitation inventory that grades 29 agitated behaviors.

Our experience at Primrose just might be the start of a trend. There was a recent report of a family bringing a loved one to another Sonoma County assisted living facility and, upon learning that they wouldn't support the medicinal use of cannabis, packing up and going across town to Primrose.

One of the nurses who worked closely with Dr. Grob was subsequently hired at a neighboring nursing facility where a condition of her hire was that she will introduce cannabis therapy. Perhaps the owners anticipate increasing demand by the families of Alzheimer's patients for cannabis-friendly care.

Jeffrey Hergenrather, MD, has been a cannabis consultant since 1998, with an office in Sebastopol, California. He would like to thank the nurses involved by name, but they have requested anonymity due to licensing concerns and uncertainty about future employment options.

WARNING

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis [see WARNINGS AND PRECAUTIONS and PATIENT INFORMATION].

When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.

"Black-box Warning" on Zyprexa label acknowledges "Increased mortality in elderly patients with dementia-related psychosis." Other dangerous drugs commonly prescribed to elderly patients with dementia include Seroquel, Geodon, Abilifym Desyrel (trazadone), Navane, Haldol, Clozaril (clozapine), Risperdal, Celexa, Cymbalta.

Fences around the perimeter are part of the security system at Primrose to prevent patients from wandering off.

Israeli study unambiguous:

CBD-rich cannabis (whole plant extract) is better medicine than single-molecule CBD

By Martin A. Lee

The claims of Big Pharma that pure, single-molecule compounds are inherently more effective than "crude" botanicals are being soundly disproved.

Researchers at Hebrew University in Jerusalem have documented the superior therapeutic properties of whole plant CBD-rich *Cannabis* extract as compared to synthetic, single-molecule cannabidiol (CBD).

The definitive paper, "Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using *Cannabis* Extract Enriched in Cannabidiol" by Ruth Gallily, Zhannah Yekhtin, and Lumír Ondřej Hanuš (the co-discoverer of anandamide), was published in the prestigious journal *Pharmacology and Pharmacy* (February 2015).

The authors surveyed the scientific literature and noted that during the past 15 years, numerous preclinical studies had focused on the anti-inflammatory effects of pure, single-molecule CBD in animal models of various pathologies, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and diabetes. (For a compilation of preclinical data regarding CBD, visit ProjectCBD.org.)

"Healing was only observed when CBD was given within a very limited dose range, whereas no beneficial effect was achieved at either lower or higher doses,"

These studies showed that administration of pure, single-molecule CBD resulted in a bell-shaped dose-response curve, meaning that when the amount of CBD exceeded a certain point its therapeutic impact declined dramatically.

"Healing was only observed when CBD was given within a very limited dose range, whereas no beneficial effect was achieved at either lower or higher doses," the authors observed. This characteristic of single-molecule CBD —manifested as a bell-shaped dose response— limits its usefulness as a medicine.

The Israeli team sought to determine whether the administration of a whole plant CBD-rich extract would also generate a bell-shaped dose-response curve when administered to mice. Or would cannabidiol extracted from CBD-rich *Cannabis* avoid this liability? "The aim of the present study," the authors explained, "was to find a CBD source that could eliminate the bell-shaped dose-response of purified CBD."

The scientists obtained a CBD-rich strain called "Avidekel" from Tikkun Olam, an Israeli medical marijuana producer. Referred to as "clone 202" in this study, Avidekel has hardly any THC and therefore is not inebriating.

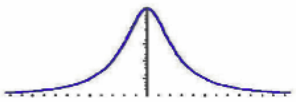
The origins of Avidekel can be traced to Spain, where breeders developed several phenotypes of "Cannatonic" (as in "cannabis tonic"), including a strain that measures close to 20 percent CBD by dry weight with almost no intoxicating ingredients. (The same high-yielding CBD-dominant strain is known as "ACDC" in California.)

The Israeli researchers extracted CBD-rich oil from clone 202. The extract —consisting of 17.9 percent CBD, 1.1 percent THC, 1.1 percent cannabichromene (CBC), 0.2 percent cannabigerol (CBG), and "traces" of cannabinol (CBN) and cannabivarol (CBDV)— was given to mice to evaluate its anti-inflammatory and pain-killing effect.

For comparative purposes, the scientists administered pure, synthetic CBD to another group of mice and assessed its anti-inflammatory and analgesic properties. They also compared the extent to which single-molecule CBD and whole plant CBD inhibited the production of tumor necrosis factor alpha (TNFa), a systemic inflammatory signaling molecule. Dysregulation of TNF-alpha production has been implicated in several diseases including cancer, Alzheimer's, clinical depression, and irritable bowel syndrome.

The pure CBD tests confirmed the findings of earlier preclinical research. Once again, singe-molecule CBD administration generated a bell-shaped dose-response curve with a narrow therapeutic window.

But a different dose response pattern was observed when the clone 202 extract was administered to mice. Rather than showing a bell-shaped curve, where a therapeutic effect could only be achieved at a certain concentration of pure CBD, the whole plant CBD-rich extract caused a direct, dose-dependent inhibition of pain, inflammation, and TNFa production. "In stark contrast to purified CBD," the Israeli team reported, "the clone extract... provided a clear correlation between the anti-inflammatory and anti-nociceptive responses and the dose, with increasing responses upon increasing doses, which makes this plant medicine ideal for clinical uses."



More Bang for the Buck

The Israeli researchers found that a much smaller amount of CBD in the clone extract was needed for significant pain relief compared to the amount of pure CBD required to achieve the same analgesic effect.

And whereas a dramatic drop in efficacy occurred if more than a specific dosage of pure CBD was administered, an "overdose" of whole plant CBD-rich extract did not reduce its therapeutic potency.

When a greater-than-optimal dose of the clone 202 oil was administered, its effectiveness leveled off, suggesting that a medicinal plateau had been reached.

The Israeli researchers found that *Cannabis* clone 202 extract "is superior over CBD for the treatment of inflammatory conditions."

The greater efficiency of the whole plant extract might be explained by additive or synergistic interactions between CBD and dozens of minor phytocannabinoids and hundreds of non-cannabinoid plant compounds. "It is likely that other components in the extract synergize with CBD to achieve the desired anti-inflammatory action that may contribute to overcoming the bell-shaped dose-response of purified CBD," the authors surmised.

Comparison to pharmaceuticals

The scientists also felt it was important to examine how the CBD-rich *Cannabis* extract compared with commercial pain-killers and anti-inflammatory drugs. They found that both pure CBD and the clone 202 extract exhibited greater anti-inflammatory potency than aspirin. Aspirin, but not tramadol, registered a slight inhibitory effect on TNFa production, which was negligible in comparison to the strong inhibitory effect of pure CBD and clone 202.

The key finding that CBD in the presence of other Cannabis components improves the dose-response is supported by recent reports documenting the anti-proliferative effect of cannabidiol on tumor cells and the inhibitory effect of CBD on bladder contractility.

"A lot of research has been [conducted] to isolate and characterize isolated single constituents of traditional herbal medicine to find their rationale for therapeutic uses," the authors concluded. "However, our data together with those of others provide legitimation to introduce a new generation of phyto-pharmaceuticals to treat diseases that have hitherto been treated using synthetic drugs alone. The therapeutic synergy observed with plant extracts results in the requirement for a lower amount of active components, with consequent reduced adverse effects."

Martin A. Lee is the director of Project CBD and the author of Smoke Signals: A Social History of Marijuana —Medical, Recreational, and Scientific.

Project CBD on Dosing

• Decide how you want to take cannabis. Cannabis oil is available in sprays, capsules, edibles and other products.

• Find your ratio. Cannabis products have varying amounts of CBD and THC. A high CBD product (with little THC) is not necessarily superior to a strain with a balanced ratio. Find the proper combination to optimize your therapeutic use of cannabis.

• Begin with a low dose especially if you have little or no experience with cannabis.

• Take a few small doses over the course of the day rather than one big dose.

• Use the same dose and ratio for several days. Observe the effects and if necessary adjust the ratio or amount.

• Don't overdo it. "Less is more" is often the case with cannabis therapeutics. Before using a cannabis product, consult your health counselor. Proceed cautiously, particularly if you have a history of alcohol or drug abuse, mental illness, or are pregnant or breast-feeding.

• Be aware of possible side effects. Cannabis is a safe and forgiving medicine. But depending upon delivery method and individual tolerance, it can amplify anxiety and mood disorders. Other possible side effects: dry mouth, dizziness, faintness. Fresh air, hydration, and food can help.

Dosage Guidelines

For anxiety, depression, spasms, and pediatric seizure disorders, many patients (at least initially) find they do best with a moderate dose of a CBD-dominant remedy. By "CBD-dominant," we mean a CBD:THC ratio of more than 14:1.

But a CBD-dominant remedy with little THC, while not intoxicating, is not necessarily the most effective therapeutic option.

A combination of CBD and THC will likely have a greater therapeutic effect for a wider range of conditions than CBD or THC alone.

For many conditions, including cancer and neurological ailments, patients may benefit from a balanced ratio of CBD and THC. Extensive clinical research has shown that a 1:1 CBD:THC ratio is effective for neuropathic pain.

Optimizing one's therapeutic use of cannabis may entail a careful, step-by-step process, whereby a patient starts with small doses of a non-intoxicating CBD-dominant remedy, observes the results, and gradually increases the amount of THC. In essence, the goal is to self-administer consistent, measurable doses of a CBD-rich remedy that includes as much THC as a person is comfortable with.

Find Your Ratio!

The Biphasic Effect

Cannabis compounds have biphasic properties, which means that low and high doses of the same substance can produce opposite effects.

Small doses of cannabis tend to stimulate; large doses sedate.

Too much THC, while not lethal, can amplify anxiety and mood disorders.

CBD has no known adverse side effects at any dose. But an excessive amount of CBD could be less effective therapeutically than a moderate dose.

"Less is more" is often the case with respect to cannabis therapeutics.

Although banned by federal law, dosed cannabis medicine is currently available in the form of concentrated oil extracts.

Infused in sublingual sprays, capsules, edibles, and other products, potent cannabis oil extracts have varying ratios of CBD and THC that are calibrated to suit the needs and sensitivities of each patient.

"Dosage is everything" —Paracelsus

Personalized Medicine

Cannabis therapeutics is personalized medicine. The right treatment regimen depends on the person and condition being treated.

For maximum therapeutic benefit, choose cannabis products that include both cannabidiol (CBD), a non-intoxicating compound, and tetrahydrocannabinol (THC), the psychoactive component of cannabis.

CBD and THC interact to enhance each other's therapeutic effects. They work best together.

A patient's sensitivity to THC is a key factor to determining the ratio and dosage of their CBD-rich medicine.

Many people enjoy the cannabis high and can consume reasonable doses of any cannabis product without feeling too high or dysphoric. Others find THC unpleasant.

CBD can lessen or neutralize the intoxicating effects of THC. So a greater ratio of CBD-to-THC means less of a "high."

O'Shaughnessy's Available Here

CBDevelopments *from page 1*

The Road to FDA Approval

In 1998 GW Pharmaceuticals received approval from the British Home Office to develop medicines from *Cannabis* plant extracts featuring cannabinoids other than THC and delivered by means other than smoking. In numerous lab studies CBD has been shown to exert various beneficial effects, and GW has been developing medicines designed to treat a wide range of illnesses.

GW's flagship product Sativex —which contains an equal mix of CBD and THC— was the first plant-derived cannabinoid medicine to win approval from regulatory authorities. An extract formulated for spraying under the tongue, it has been approved in 27 countries (starting with Canada in 2005) for treating pain and spasticity in Multiple Sclerosis.

In recent years GW has been testing various formulations and providing CBD to scientists conducting preclinical studies in animals. GW supplied Ben Whalley and colleagues at the Center for Integrative Neuroscience and Neurodynamics, University of Reading, who used mouse models of epilepsy to establish safety and show that CBD and another cannabinoid, CBDV, exert anti-seizure and anti-inflammatory effects. This research came to the attention of families in the U.S. who had loved ones with epilepsy.

In late 2012 some American parents contacted GW in hopes of obtaining CBD.

"Expanded Access"

Physicians, patients, and parents know that currently used anti-epilepsy drugs (AEDs) are detrimental to cognition and longterm development. CBD is way, way milder than conventional anti-convulsants in terms of side effects.

In late 2012 some American parents contacted GW in hopes of obtaining CBD. They asked if the company could provide CBD to the physicians treating their children under the Food and Drug Administration's "Expanded Access" IND program.

GW, which had been working closely with the FDA in connection with Sativex, looked into the IND option and decided the expanded access regulations might indeed allow the company to provide Epidiolex to the parents, even though it was an investigational medicine.

Back in 1978 —the Jimmy Carter era— the FDA had established a so-called "compassionate IND program" through which a few patients received marijuana grown at the University of Mississippi for the National Institute on Drug Abuse. The program was closed to new patients in 1990 —the George H.W. Bush era— as AIDS patients began applying en masse, thanks to the organizing efforts of Robert and Alice O'Leary Randall. The IND program existed in bureaucratic limbo until 1997, when Congress passed the Food and Drug Administration Modernization Act.

The FDA then developed regulations covering IND studies for unapproved drugs. These were revised over the years, and in August 2009 FDA issued its "final rule" on "Expanded Access to Investigational Drugs for Treatment Use." The summary states:

"Expanded access to investigational drugs for treatment use is available to individual patients, including emergencies; intermediate-size patient populations; and larger populations under a treatment protocol or treatment investigational new drug application (IND). The final rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies."

The FDA regulations spell out criteria for INDs. The would-be investigator must submit, among other things: "Chemistry, manufacturing, and controls information adequate to ensure proper identification, quality, purity, and strength of the investigational drug."

In other words, FDA wants to see a highly standardized, tested, "Good-Manufacturing-Practices" medication —which Epidiolex is. NIDA is still providing Mississippi-grown cannabis cigarettes to four surviving beneficiaries of the old, informal IND program. Those cigarettes would not be approved as a treatment under the current FDA regulations.

The FDA requires "Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for the treatment use."

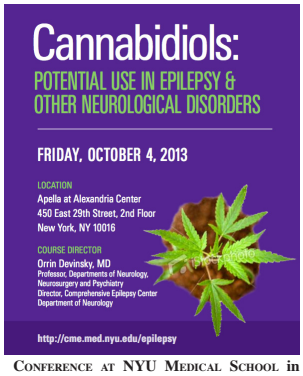
When GW was approached by the parents of epilepsy patients in late 2012, the company already possessed extensive preclinical data —five-and-a-half years' worth— establishing the safety of its CBD product, as well as information the FDA would require concerning its chemistry, manufacturing, controls, pharmacology, and toxicology.

In December 2012 GW agreed to provide purified CBD and the requisite data for single-patient INDs conducted by epileptologists Roberta Cilio, MD at UC San Francisco, and Orrin Devinsky, MD at NYU School of Medicine

In October 2013 GW supported and NYU sponsored a meeting in New York of epilepsy specialists interested in conducting clinical research with purified CBD in the United States. Devinsky described dramatic benefit provided to his initial patient by CBD treatment, and his plans to conduct an IND treatment program at NYU. Many of the doctors at the conference asked to sponsor INDs at their institutions. GW agreed to provide them with Epidiolex.

By January, 2014, INDs conducted by Devinsky at NYU (60 patients) and Roberta Cilio at UCSF (25 patients) were underway. The patients were children and young adults with various forms of Treatment Resistant Epilepsy. Each patient's frequency of seizures had been determined by parents keeping detailed diaries for a month to establish baselines prior to treatment with Epidiolex. Patients continued taking the anti-epilepsy drugs they'd been on. They were started on Epidiolex doses of five milligrams per kilogram of body weight per day, divided into morning and evening portions. The dose was increased weekly by five mg/kg/day up to 25 mg/kg/day.

In June 2014 GW announced efficacy and safety data on the first 27 patients to have been treated for 12 weeks (the minimum amount of time determined to offer accurate effectiveness measure). Epidiolex had enabled 48% to achieve at least a 50% reduction in seizure frequency compared to baseline.



Conference at NYU Medical School in October 2013 featured a report by Orrin Devinsky, MD, on a Dravet Syndrome patient achieving dramatic seizure reduction by medicating with a 99%-CBD plant extract from GW Pharmaceuticals. Other epilepsy specialists at US research centers are now using GW's "Epidiolex" in Investigational New Drug studies. Some 400 children were being treated at 17 sites as of October 2014.

Epidiolex enabled 48% to achieve at least a 50% reduction in seizure frequency compared to baseline.

Over the course of 2014, physicians would conduct Treatment-Resistant Epilepsy INDs at The Children's Hospital of Philadelphia, Lurie Children's Hospital in Miami, Pediatric and Adolescent Neurodevelopmental Associates in Atlanta, Texas Children's Hospital, MassGeneral Hospital for Children, the University of Utah Medical Center, Wake Forest School of Medicine, and Nationwide Children's Hospital in Columbus, Ohio.

Thanks to organizing efforts led by Paige Figi, a dozen states enacted laws in 2014 that legalized the medical use of CBD; some even provided money for research. By 2015 health departments in four states —Georgia, New York, Alabama, and Florida— were funding INDs, picking up the tab for physician visits, lab tests, data collection, and Epidiolex (which GW donated to hospital-funded INDs). More than 200 patients would soon be enrolled in state-sponsored INDs.

Efficacy documented

In April, 2015, at a meeting of the American Academy of Neurology, Devinsky was lead author on a poster presenting efficacy data on 137 patients who had completed 12 weeks of treatment with Epidiolex. There were 25 Dravet Syndrome and 22 Lennox-Gastaut Syndrome (LGS) patients among them, and patients with 10 other rare and severe types of epilepsy, some involving congenital abnormalities.

"Overall seizure frequency was reduced by 54% in all patients and by 63% in Dravet Syndrome patients," Devinsky et al reported. Nine percent of all patients and 16% of Dravet patients were seizure-free after 12 weeks. Those patients who were on Epidiolex for 24 weeks showed no fall-off in effectiveness.

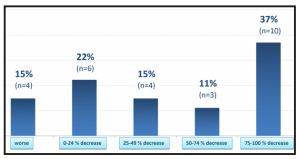
"Randomized controlled trials are warranted," the researchers concluded, "and we are pleased to report that these are now ongoing."

In the spring of 2015 GW commenced two placebo-controlled clinical programs, one in Dravet syndrome and one in Lennox-Gastaut syndrome (LGS). Both of these "pivotal" trials are designed to support a New Drug Application with the FDA by mid-2016.

Conditions such as Dravet Syndrome and Lennox-Gastaut Syndrome that affect a very small subset of the population —under 200,000 in the U.S.— are designated "orphan diseases," and treatments developed for them are referred to as "orphan drugs." Most orphan diseases are the result of genetic mutations.

The Orphan Drug Act of 1983 conferred tax breaks and market exclusivity protections on pharmaceutical companies willing to develop drugs for which the market is minuscule.

GW Pharmaceuticals sought and was granted orphan-drug status for Epidiolex as a treatment for Dravet and LGS. One of the benefits conferred is the right to combine phase 2 and 3 clinical trials. The two phase 3 studies —clinical trials— are taking place at various institutions around the US and in other countries. These studies involve patients adding Epidiolex to their regimen of anti-epilepsy drugs for a 14-week randomized, double-blinded treatment period. Results will be reported in early 2016.



worse 0-24% 25-49% 50-74% 75-100%

Levels of improvement experienced by first 27 patients in Epidiolex IND. Bars show percentage of patients achieving various levels of seizure reduction. Four patients (15% were deemed to have gotten worse.)

Assuming the doctors find a statistically significant reduction in seizure frequency—and an unthreatening adverse event profile— GW would submit the data to FDA. A priority review would take eight months, and if all goes well, Epidiolex could become the first FDA-approved medication for Dravet and LGS syndromes after the middle of 2017.

If approved by FDA, CBD will automatically be rescheduled. The schedule will depend on a body of preclinical and clinical (human) data that indicate whether the substance has abuse liability. It is likely that the Schedule will be somewhere between III and V, since CBD does not seem to have the abuse potential of products like opioids, which are generally schedule II.

Insurance companies are expected to reimburse for an FDA-approved Epidiolex. The level of reimbursement will be worked out between GW and the payors.

A drug that is beneficial in treating the most severe forms of epilepsy is likely to be beneficial in treating most seizure disorders.

The company also plans a clinical trial of Epidiolex in other pediatric epilepsies, starting with Tuberous Sclerosis Complex (TSC), a genetic disorder that causes non-malignant tumors in the brain and other organs, and affects some 50,000 patients in the US. Approximately 60% of TSC patients have treatment-resistant seizures. All five such patients in the expanded access program were helped by Epidiolex, it was reported at the American Epilepsy Society's annual meeting in December 2014.

Another condition for which CBD has proved beneficial in animal studies —and for which Epidiolex has been given orphan drug status— is Neonatal Hypoxic-Ischemic Encephatopathy, or NHIE (brain damage caused by oxygen deprivation during delivery).

"In neonatal hypoxic-ischemia," says GW chairman Geoffrey Guy, MD, "you've got an underlying inflammatory process which is massively exaggerated by excitotoxicity after each seizure, which is setting up the next seizure in a way. It's not enough to treat just the seizures without treating the underlying inflammatory encephalitis and the damage to neuroplasticity.

"Children's brains are very plastic and can usually work around issues, but if you're having continuing seizures and continuing inflammation, that ability will be dampened. We're hoping from the preclinical work that cannabidiol will address a number of these different issues, not just one."

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CBDevelopments *from previous page*

Bear in mind that a drug that is beneficial in treating the most severe forms of epilepsy is likely to be beneficial in treating most seizure disorders.

In March 2015 GW was issued a US patent for CBDV in the treatment of epilepsy

In 2014 GW completed a Phase 1 clinical trial of its CBDV product candidate, GWP4200. Having established safety and tolerability, they conducted a study of CBDV in people with focal seizures (vs placebo). Next came a Phase 2 study in adult patients with epilepsy. In March 2015 GW was issued a U.S. patent for CBDV in the treatment of epilepsy —"specifically for the control of generalised or temporal lobe seizures," according to a statement by the company.

James Brodie had laid out GW's commercial strategy in an ICRS presentation. By developing extracts and natural compounds with specified ratios, he said, "you can form a matrix of intellectual property that will be safe. It is our belief and the belief of our commercial partners that you cannot genericize Sativex."

In May 2015 GW moved its corporate headquarters from the UK to San Diego, signifying a focus on the US market and heightening the fears of many small-scale cultivators and their activist allies that GW will move against them in due course. Alice O'Leary Randall asks, "Will the feds use the inevitable approval of Epidiolex as a chance to crack down on growers in legal states, all to protect the copyrights and patents that GW Pharmaceuticals and the federal government hold on CBD?"

O'Shaughnessy's posed her question to GW officials: how and under what circumstances might they assert the company's intellectual property (IP) rights? Nobody wanted to be quoted by name. The responses included:

- Patenting products is standard procedure in developing pharmaceuticals, necessary for "freedom to operate" conferred by regulators.
- IP rights would most likely be asserted by requesting a licensing fee.
- If "a major commercial player, not just a mom and pop, was clearly violating GW's patent rights... we would look at our options."

Insys Therapeutics, Inc. has developed a synthetic CBD product for use by patients with Dravet and Lennox-Gastaut Syndromes, obviously taking advantage of GW's research. To date GW hasn't moved to curtail Insys —but Insys hasn't moved to market its product.

A transdermal CBD gel is being developed by a comany called Zynerba Pharmaceuticals in Devon, Pennsylvania. What will transpire in the period ahead depends on many factors, including who is in the White House and what actions the regulatory agencies take.

Rescheduling broached in the *NEJM*

The topic of rescheduling specific cannabinoids was carefully broached in a review article in the *New England Journal of Medicine* (September 10, 2015) by Samuel Friedman and Orrin Devinsky, two of the epileptologists treating patients with Epidiolex. "Relaxation of the regulatory status of cannabinoid-derived drugs, especially those containing a high proportion of non-psychoactive cannabinoids, for which the potential for abuse is low, could help to accelerate scientific study," they wrote.

They describe the work that has been done to date with Epidiolex, which they describe as 99% cannabidiol and less than 0.1% THC. They note that randomized clinical trials are underway for the treatment of Dravet's syndrome and Lennox-Gastaut syndrome. "No evidence suggests that the antiseizure effects of cannabidiol are limited to the treatment of these conditions," they add.

While acknowledging the evidence that THC has anti-convulsant effects, Friedman and Devinsky state that "Cannabis-based treatment with THC may have irreversible effects on brain development," and, as if it were a proven fact: "With longterm use there is a risk of addiction, which occurs in approximately 9% of longterm users."

Friedman gets consulting fees from Marinus Pharmaceuticals, Elsai, SK Biopharmaceuticals, Upsher-Smith Laboratories, and Pfizer. Devinsky gets grants from GW Pharmaceuticals and Novartis. Their *NEJM* article concludes with an oath of allegance to the FDA approval system and a swipe at an alternative approach to CBD distribution as a dietary supplement.

"Despite the power of anecdote and the approval of medical cannabis by many state legislatures, only double-blind, placebo-controlled, randomized clinical trials in which consistent preparations of one or more cannabinoids are used can provide reliable information on safety and efficacy. The use of medical cannabis for the treatment of epilepsy could go the way of vitamin and nutritional supplements, for which the science never caught up to the hype and was drowned out by unverified claims, sensational testimonials, and clever marketing. If randomized clinical trials show that specific cannabinoids are unsafe or ineffective, those preparations should not be available. If studies show that specific cannabinoids are safe and effective, those preparations should be approved and made readily available."

The image of CBD getting distributed as a nutraceutical was not hypothetical. It was a reference to the Charlotte's Web phenomenon.

Sanjay Gupta was shown CBD-dominant "Charlotte's Web" plants by Josh Stanley on a CNN report that aired in August, 2013. Stanley said, misleadingly, "There is nothing like this plant in the world. It is 21 percent CBD and less than one percent THC." He and his brothers were soon inundated with requests from parents of epileptic children seeking Charlotte's Web oil extracts. A non-profit, Realm of Caring, was created to counsel patients and their families, hundreds of whom moved to Colorado to expedite access to the promising new treatment.

'Charlotte's Web'

GW Pharmaceuticals' research into the medical benefits of cannabidiol was reported in *O'Shaughnessy's*, starting with the first issue in 2003. For years pro-cannabis doctors and their patients followed the news covetously, wishing that they, too, could investigate the medical uses of CBD. But without an analytic lab testing the contents of *Cannabis* plants, none containing CBD could be identified. Experts predicted that no appreciable amount of CBD would remain in a plant population which, for many generations in California, had been bred to maximize psychoactivity.

In late 2008 an Oakland start-up, Steep Hill Lab, began testing cannabis brought by growers to Harborside Health Center for mold and THC and CBD content (also for CBN, cannabinol, a breakdown product of THC that was thought to indicate time in storage).

From 2009 through 2012, very few dispensary operators were willing to stock cannabis that was not psychoactive.

Martin Lee and I arranged with Addison Demoura and David Lampach at Steep Hill —and Harborside's buyers— to be put in contact with the growers if and when any samples were found to contain 4% or more CBD. About one in 650 samples turned out to be CBD-rich by our arbitrary defintion.

Martin and I shared with the growers what we had learned about cannabidiol from GW Pharmaceuticals' presentations at meetings of cannabinoid researchers. This was the start of Project CBD.

It seems hard to believe, now that the CBD bandwagon is so big and has so much momentum, but from 2009 through 2012, very few dispensary operators were willing to stock cannabis that was not psychoactive. Harborside's buyers —Rick Pfrommer, Rachael Szmajda, and Caroline Francese— did their best to assure growers and producers of CBD-rich plants that they would have a market.

In the winter of 2011/12, when Paige Figi and her husband Matt (then deployed to Iraq with Special Forces) were researching epilepsy treatments on the internet, they were encouraged by an episode of a Discovery Channel "reality show" in which Jason David, father of a little boy named Jayden, describes his son's first seizure-free day to Harborside's Andrew DeAngelo, the supplier of Jayden's CBD-rich oil: "I heard him humming," the dad reported.

Paige Figi connected with Jason David, through a social media group dedicated to cannabis and epilepsy. Seven parents "chatted, shared info, looked into research together," is how she describes it. At this point, Paige says, she had "bought and lab tested thousands of dollars of medical cannabis. Oil from the high-THC strains helped with some ailments and comorbidities (sleep, appetite, autism, rage, etc.) but increased her seizures. One strain I found was working but they only had a few weeks' worth of supply. When abruptly stopped, seizures increased."

In February 2012 Paige gave Charlotte a dropper of oil that was effective. It had been made by the Stanley brothers of Colorado Springs. The Stanleys had launched their "Indispensary" in 2009 and added a second outlet in 2011. They were not pro-cannabis activists. They knew that marijuana was safe and effective medicine, having seen a family member get significant relief from it as he was dying from cancer. And, as happens at every dispensary, the more feedback the Stanleys got from people with various ailments, the more convinced they became that cannabis has a vast range of

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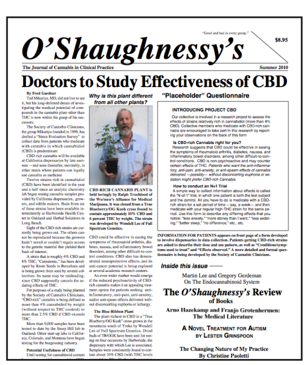
Project CBD



O'Shaughnessy's front pages reflect the progress of Project CBD. In 2008 (left), the lead story described work done in Europe by GW Pharmaceuticals. By 2009 a California lab had begun finding CBD-rich strains, and Sean McAllister had reported on the ability of CBD to kill certain cancer cells. By 2010 the Society of Cannabis Clinicians and Harborside Health Center were planning to collect data on the efficacy of CBD-rich cannabis in treating various symptoms —a complicated, longterm process we are still just at the start of. Among the growers to develop or come across CBD-rich plants in 2008-09, most gave clones to Project CBD to distribute (no money involved). The donors of Harlequin, Omrita, Jamaican Lion, and a few other CBD-rich varieties —not to mention Lawrence Ringo— expedited the introduction of CBD to medical cannabis users in California by two years.

CBDevelopments *from previous page*

became that cannabis has a vast range of applications. But they hadn't seen anything like Charlotte Figi's sudden and sustained improvement.

The Stanleys guaranteed Paige a regular supply of oil from the super-effective plant, which they renamed "Charlotte's Web." It typically grew to a height of four feet and had a CBD-to-THC ratio greater than 20-to-1. Some in Colorado assumed it had been bred from a CBD-rich strain called R4.

Word of Charlotte Figi's progress circulated online and parents of epileptic children began contacting the Stanleys with urgent requests for oil from Charlotte's Web. In July 2012, Paige, Mandy Stanley (Joel's wife), and Heather Jackson —whose son Zaki was the second child to benefit greatly from Charlotte's Web— formed a 501(c)3 foundation called "Realm of Caring" to interface with other families. The RoC organizers would work as volunteers (unpaid) for two years.

Demand Takes Off

Sanjay Gupta's "Weed" show in August, 2013, led to a flood of families contacting Realm of Caring. "It was a 180-degree turnaround for us," Paige says. "We knew we'd have to ramp up for an influx of patients, but didn't realize how many."

Colorado's medical marijuana program allowed them to grow only six plants per patient, and Charlotte's Web was a small plant.

The number of calls from families seeking information about Charlotte's Web jumped from 150 to several thousand a month. Heather Jackson functioned as executive director, maintaining the rapidly growing waiting list for oil made from Charlotte's Web. Families began moving to Colorado to expedite access. The Stanley brothers ramped up production in their greenhouses, but Colorado's medical marijuana program allowed them to grow only six plants per patient, and Charlotte's Web was a small plant. Paige Figi began lobbying for bills that would allow CBD oil to be made and used in other states.

Sanjay Gupta's second "Weed" special, which aired in March 2015, focused on families moving to Colorado to get Charlotte's Web. The show had been taped when Josh Stanley was still the brothers' spokesman. Gupta asked him to confirm that CBD does not cause a high, and Josh smirked: "You can set the whole hippie population of Colorado loose on this plant and you're just gonna be looking at a bunch of disappointed hippies."

As if hippies' kids don't come down with epilepsy! As if hippies don't get cancer! As if Josh Stanley didn't owe his livelihood to a gay, anti-war, Air-Force-vet hippie named Dennis Peron who cared for his friends with AIDS and wouldn't let anyone stop them from medicating with marijuana!

But Josh's smarmy pitch did not and does not detract from the real benefit that Charlotte's Web oil was and is providing to pediatric epilepsy patients and others. Physicians monitoring its use —notably Drs. Bonni Goldstein and Margaret Gedde— attest to its quality and consistency, and there could be no heavier endorsement. Goldstein credits Realm of Caring with keeping the price low —5¢ per milligram— and with reducing to zero a waiting list that reached 12,692 by the start of 2015.

This remarkable achievement was made possible by two political developments. The first was the passage by Colorado voters in November 2012 of Amendment 64. Best known for legalizing adult use of marijuana, Amendment 64 also created regulations for growing industrial hemp, defined as cannabis containing no more than 0.3% THC when dried, for research purposes.

In February 2014 President Barack Obama signed into law a federal Farm Act allowing Americans to grow industrial hemp for research purposes.

Then in February 2014 President Barack Obama signed into law a federal Farm Act allowing Americans to grow industrial hemp, similarly defined.

Assessing the market for hemp products is a valid research purpose, so virtually unlimited numbers of Charlotte's Web and other plants containing 0.3% THC and, say, 8% CBD, could be grown in Colorado as hemp. Oil extracted from such plants cannot be labeled or advertised as a medical product, but it can be marketed as a dietary supplement. So it was under the hemp rubric that the Stanley Brothers chose to proceed.

There are seven Stanley bros, six in the company called Stanley Brothers Social Enterprises, which is doing business as CW Botanicals —Joel, Jesse, Jon, Jared, Jordan and J. (Just the initial. "My parents ran out of J names," Joel jives.) There are four sisters, too, one of whom, Julie, works at the company's call center in Colorado Springs. Josh Stanley left "to pursue other opportunities" in March 2014.

Realm of Caring California

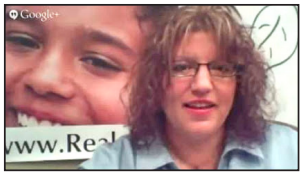
Among the parents of epileptic children who contacted Realm of Caring after the first Gupta show was Ray Mirzabegian of Los Angeles. Mirzabegian, 40, rejected the suggestion that he move to Colorado because it would mean leaving his supportive extended family in Southern California. He started a Facebook group that soon had 200 participants. Impressed, the Stanley Brothers authorized Mirzabegian in February 2014 to grow Charlotte's Web for distribution under the auspices of RoC California. Mirzabegian and his two brothers dropped their careers to become cultivators.

In addition to lining up three greenhouses and planting a crop, Mirzabegian organized forums at which parents waiting for Charlotte's Web could get detailed updates on the grow. The program included a talk by pediatrician Bonni Goldstein, MD. Your correspondent attended an RoC California forum in Milpitas.

Transcribing the talks I could hear the steady singsong of infants in strollers and the occasional moan of a teenager in a wheelchair. The audience could not have been more empathetic. They were people who, when their kids became seriously ill, curtailed everything else and devoted their lives to caregiving. Ray Mirzabegian was telling his version of their own story.

"I wanted this oil because my daughter was having many, many seizures," said Ray. "She had tried 13 medications that did not work. The ketogenic diet [an anti-seizure diet low in carbs, high in fats] worked for about six months and then seizures slowly started coming back...

"At a very well known epilepsy center in Southern California they casually pulled us aside and said 'There's really nothing else we can do for you guys, we suggest that you go home and enjoy your daughter as best you can.' So we went home very disappointed and upset.



Heather Jackson moderated the Realm of Caring Google Hangout in late May. In background, a graphic of her son Zaki, who had been seizure-free for 19 months.

"We saw about eight or nine neurologists after that until we found one at UCLA who was willing to sit down and listen to us and communicate and have a conversation. Our neurologist is very supportive of the parents' right to try something like CBD, especially since we've tried everything else. I talk to him frequently and he's interested in the feedback about the patients, about my daughter..."

"We want to do this whole thing legally, so we're creating a collective and resource center so I can have all of you as my patients and we'll do it as legally as possible… I am allowed to grow 99 plants in a facility —and that's all I'm doing, because I'm not planning on going to jail for years and years. But that makes it very tough and forces us to have several facilities to meet the demand...

"It's so hard for me to tell all 400 people to just hang in there and wait. I wish there was something I could do to make these plants grow faster —and there is, but I'm not going to do it. Because I want to grow organically, no extra hormones or… *(Applause.)"*

Charlotte's Web Grown as Hemp

In May 2014, Joel Stanley explained to a "Google hangout" for Realm of Caring members —a video conference call—that the company was growing 36,000 Charlotte's Web plants on 17 acres, thanks to the legalization of industrial hemp. Also taking part were Paige Figi, Heather Jackson, Jesse and Jared Stanley (Googling in from the grow site), and Ray Mirzabegian in Los Angeles. Questions from viewers were sent to Heather, who read them aloud.

"Someday there will be no waiting list," Joel promised.

"Someday there will be no waiting list," Joel promised. "But right now, for those of you who are on the waiting list, I understand that's got to be torture. As a parent… We really wish there was no such thing as a waiting list. We're doing everything we can to bring production to a scale where there won't be a waiting list."

One purpose of the Google hangout was to respond to detractors. The Stanley brothers and Paige Figi were being criticized for pushing so-called "CBD-only" legislation in other states.

Paige described her organizing efforts. "Some of these states are so conservative," she said, "they're not going to allow the best bill, which is a full medical marijuana bill. To go in and say it should be for this type of patient only, and this kind of oil, non-smokable, for these syndromes only, to play God, I think the whole thing is totally ridiculous. But if people want a bill, and they're told by the people who can oppose it and can trashcan it that they won't get anything…

"Minnesota is just passing a bill that is leaving post-traumatic stress and chronic pain patients behind, and people who want to smoke it. They were assured that nothing else would pass. No one is for CBD-only. It's tough...

"This trend started after the CNN show came out and pushed this new medicine for seizures. So some of the states, that's all they're willing to do. I can't step away. If I can't support all the patients, I can support some of them, whoever the state will allow.

"We're just pushing and pushing and pushing, and we're not going to stop until Charlotte's Web is available everywhere. We care about all of these patients. I travel every week and I'm for everybody. This isn't about a business plan that we're trying to push, this is about a socialized medicine."

[Paige Figi was too young to know, I gleaned in a later conversation, that the politicians whose support she seeks would find the term "socialized medicine" slightly more offensive than motherf---er. Paige had combined those two words, logically, to describe her and Realm of Caring's principle that "no one should be denied Charlotte's Web because they can't afford it." I should have warned her not to use the political obscenity in earshot of Mitch McConnell.]

Paige reminded her RoC audience that there was a real threat of Child Protective Services getting involved whenever a child was being given a Schedule I substance. The fear, said Paige, "isn't you going to prison, it's CPS taking your child from you. Until the scheduling is changed or descheduled, we have to live with that."

Heather Jackson added that after "almost every piece of press we do, someone calls the Department of Human Services on that family. There are counselors in hospitals who feel it's their obligation to mandatory report."

• A question was asked about shipping to other states. "It's still a gray area," Joel said. He was hopeful because "Charlotte's Web qualifies as hemp and the Colorado Department of Agriculture allows the shipment of processed hemp products." The Stanleys have been breeding for a higher CBD-to-THC ratio and are building out their lab facilities, he said.

September '14: list reaches 9,000

In September, 2014, Realm of Caring and the Epilepsy Foundation of Colorado held a get-together to discuss their progress with some of the doctors and others who were attending a "Marijuana for Medical Professionals" conference in Denver. The harvest was weeks away.

"It's the first time that hemp has been grown on a crop circle under center-pivot irrigation, which didn't exist in 1937," Joel said. "Completely open, like corn. It took us a while to find a field that hadn't been sprayed with pesticides the last couple of years. But we were able to find one."

The processed product —"CW Hemp Oil"— would be distributed as a dietary supplement. "We're standardizing our plant extract at 30-to-1 CBD-to-THC," Joel said. "That will be the only thing that's standardized about this product. The terpenes and minor cannabinoids will vary slightly based on the plants they came from.

"In 2007 the FDA passed a final rule on dietary supplements and the quality standards that must be met in terms of levels of microbiological contamination, residual solvents and heavy metals....We are going for full GMP —good manufacturing practices.

Joel described the production cycle. "The dried plants go through an alcohol extraction and then a roto-vac is used to pull that solvent off and we're left with our concentrate, which usually comes out at 500 milli-

continued on page 34

Ray Mirzabegian, director of Realm of Caring California, spoke to parents of pediatric epilepsy patients in Milpitas in February 2014, soon after he had begun growing Charlotte's Web plants. The number of patients waiting for oil from RoC California was then about 400. As of November 2014, the waiting list was 1,175 and Mirzabegian was supplying a total of 81 patients.

Treating Colorado's 'Medical Refugees' —Margaret Gedde, MD

Margaret Gedde, MD, is the Colorado Springs physician to whom Paige Figi brought five-year-old Charlotte for approval to medicate with cannabis in February 2012. (Colorado law required two approvals; the other was provided by Allan Shackleford, MD, of Denver.)

As families began moving to Colorado to obtain oil made from Charlotte's Web, Margaret Gedde became their go-to doctor. Gedde shared her findings and observations —based on a review of files of 107 pediatric epilepsy patients— at the "Marijuana for Medical Professionals" conference in Denver Sept. 10, 2014.

"After the CNN special," Gedde explained, "CBD oil was in short supply. So patients come to Colorado, we see them in clinics, and then they can't get the oil that they came for. They get the oil on their own and try different things." Gedde tells patients, "'I will work with you on any type of cannabis you have as long as you can get some information about its composition. We need to get a lab report."

"Clinical experience suggests cannabinoids have a bell-shaped dose response curve with respect to seizure control. Less may work better than more."

A slight majority of the patients surveyed by Gedde (55%) had been able to get Charlotte's Web from the Stanley Brothers. Others (8%) used high-ratio CBD:THC oil made by Colorado producers from plants called Haleigh's Hope, R4, and "Ballantine" (evidently a patient's mis-hearing of "Valentine").

Six percent of Gedde's patients were using medicaments made from imported hemp available from Amazon (Bluebird Botanicals, Cibidex, DixieDewDrops). Some used transdermal patches and gels from a Colorado manufacturer called Mary's Medicinals.

Fourteen percent of Gedde's patients had been using THCacid (which is non-psychoactive); seven percent were using THCA in combination with a high CBD:THC oil. Ten percent were using low ratio CBD:THC.

Gedde never advises a patient to change their pharmaceutical meds, but she urges them to keep their neurologists informed about the effects of the drugs they are prescribing and the effects of cannabinoids.

Gedde recommends that patients stay at a given dose level for three weeks before increasing the dose. "They may see a response in the third week that they won't see in the second," she said.

"Clinical experience suggests cannabinoids have a bell-shaped dose response curve with respect to seizure control. Less may work better than more. Sometimes patients have gone up fast on the dose and are not getting much seizure control. I tell them to go down instead."

About one-third of Gedde's patients experienced better seizure control after reducing cannabinoid dose. "They had gotten to the other side of the curve," she said.

Gedde's study was self-funded. She reviewed the records of all patients with pediatric-onset, treatment-resistant epilepsy seen in her two offices from February, 2012 through March, 2014. She assessed seizure reduction (relative to baseline) during two four-week spans, one during the first four months of treatment, and one prior to the patient's most recent visit or report.

Margaret Gedde, MD, presented findings at the 'Marijuana for medical professionals' conference, Denver, September 2014.

She assessed adverse and beneficial side effects, and changes in use of other drugs.

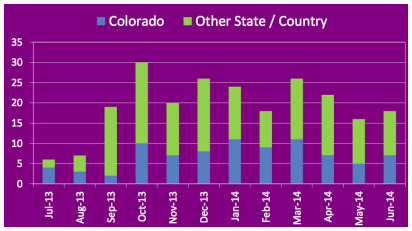
The average therapeutic dose for patients using high ratio CBD:THC medicine was found to be 2.2 milligrams per pound of body weight. For patients using low ratio CBD:THC it was 1.8 mg/pound.

Gedde employs the terminology developed by the International League Against Epilepsy, which categorize seizures by their etiologies (causes). All four etiologies were represented in her cohort:

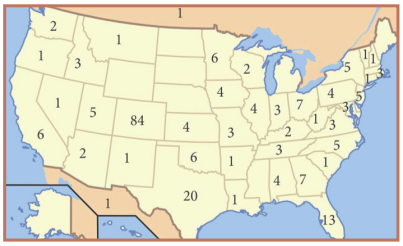
• Genetic (in which a mutation disables a structure needed for neurotransmission; Dravet Syndrome and Storage Diseases have genetic etiologies) 39%

• Structural (caused by neonatal brain damage such as cortical dysplasia and microcephy) 15%

• Secondary (caused by trauma, infection, toxic exposure, or hypoxia —lack of oxygen) 14%



Patients from outside Colorado accounted for most of Dr. Margaret Gedde's pediatric epilepsy patients. Chart shows patients per month making initial visit from July 2013 to June 2014. Colorado patients (lower half of each bar) are outnumbered by those from out of state (upper portion of bar). As of September 2014 Gedde was seeing "between four to six families per week, about two-thirds from out-of-state" at her offices in Colorado Springs and Buena Vista. Map shows patients' original states of residence.



• Unknown 36%

Gedde reviewed patients' records to compare seizure frequency during three four-week periods: baseline (the four weeks prior to starting treatment); within 16 weeks of starting cannabinoid treatment; and at the most recent office visit or report.

The outcome measure was divided into six categories:

Worse: an increase of 25% or more.

Same: between 25% increase and 25% decrease in seizure number.

Some fewer: at least 25%, up to 50% reduction in seizures.

A lot fewer: at least 50%, up to 80% reduction in seizures.

Greatly reduced: At least 80%, up to 100% reduction in seizures.

Gone: 100% reduction; patient was seizure free for at least 4 weeks.

Gedde defined "responder" as a patient having 50% or greater seizure reduction.

Gedde found that all seizure types were reduced by cannabinoids at roughly the same response rate. And all groups had a net reduction of other AEDs during the study.

Seizures in patients with storage diseases responded especially well to cannabinoids

Adverse effects reported for CBD at therapeutic doses were sleepiness and increased drooling that resolved. At above optimal doses there were reports of excessive sleepiness, increased seizures or new seizure types.

THCA at therapeutic doses caused no adverse effects. At above optimal doses parents reported excessive sleepiness, increased seizures or new seizure types

The benefits of CBD listed by Gedde: Improved cognition and interactions. Better sleep and appetite. Better gut function (relief of chronic constipation).Improved immune resistance. Better muscle tone –improvements in both hypertonia and hypotonia. Better fine and gross motor control. Relief of anxiety. Faster recovery after seizures. Shorter, less severe seizures

THCA was reported to promote improved alertness, cognition, language, sleep.

Each group was able to reduce or eliminate concomitant pharmaceuticals. Most commonly reduced were clobazam, clonazepam, levetiracetam, valproic acid, and zonisamide.

Gedde's "Take Aways"

• About 10% doing worse and 10% seizure free.

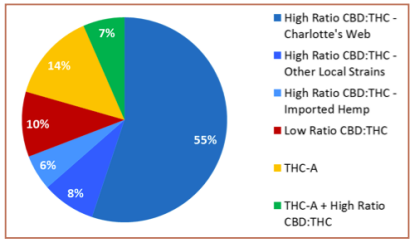
• All groups reduced AEDS while, largely maintaining seizure control.

• Many patients benefit from lower doses.

•All four cannabinoid combinations were associated with reduction of seizures.

• Patients having difficulty using cannabis products may be more likely to present to emergency departments than those who are doing well.

Gedde said she would like to hear from clinicians who might want to aggregate data. She she looked forward to the day when doctors can prescribe standardized cannabis preparations. She foresees "Compounding pharmacies will stock standardized preparations of cannabinoids and other cannabis compounds. Physicians will order customized ratios and combinations of cannabis compounds. Specialized pharmacists will compound customized cannabinoid medications.



Varieties of cannabis oil used by Gedde's patients are listed by percent. High ratio CBD:THC Charlotte's Web was available to 55%. "All four cannabinoid combinations were associated with reduction of seizures" in the cohort she studied.

Update April 2015

O'Shaughnessy's: How has your practice changed in the six months since you presented your results?

Gedde: Now that Charlotte's Web is available to all, we start with the Charlotte's Web. If we haven't gotten the full results we were looking for, we can bump it up a bit until we see a little more seizure and then we really can't go higher. That's when we bring in the THCA to try to get full control.

Another thing you can do is to change the ratio of THC—basically add THC to the CBD oil to get, say, a 10-to-1 ratio or even a 4-to-1.

There are a couple of patients who have added a lot of THC because of another issue. Like one child is very, very sensitive to light; it triggers the seizures. And the parents found that adding a significant amount of THC stops that. So that child is actually taking more THC than CBD.

O'S: That's very interesting. Have you seen any other specific cases where one cannabinoid or terpenoid seems to have a specific advantage or disadvantage?

Gedde: There was one other who added a lot of THC also —it might have been for the gut. Those kids who are getting mostly THC, they're going to be high, really. We'll have parents say "we added more THC but she was high so we didn't want to do that." So we shift our ratio again.

O'S: What are the adverse symptoms of THC? Wouldn't it have an anti-depressant effect for the suffering children. Why do the parents pull them off it? What do the kids do?

Gedde: It depends on how severe their condition is. For kids who go to school – most of our kids, especially once they're school-age – they're going to school, usually a regular school with a special program in place, an IEP (independent educational program). With too much THC, they can't focus. They're not cognitively as smart. You'll see the cognitive deficit of them being high, if you will. We need more scientific terms to talk about the effects.

There definitely is a motivation to just use the CBD if possible because so many people want to go home and now they've got laws in their home states. So some people say, let's just get off the THCA because we're not going to be able to use it in Utah or wherever.

O'S: What percentage of your patients are Charlotte's Web users?

Gedde: About two-thirds. Many are on another oil, Haleigh's Hope. Just about everybody has come back off of the others like Bluebird Botanical, made from imported hemp. Everybody who was on that basically has switched over to the Charlotte's Web.

O'S: Why is that? Is it more effective? Is it cheaper?

Gedde: There is a perception and probably a reality that the Bluebird, up until now, has been from imported hemp. So there's more of a question of quality. And the Charlotte's Web is batch tested, you get the lab report with it, whereas with the Bluebird, whatever is on the label is what we're going by.

Also, in cents per milligram it is less with the Charlotte's Web. So it is probably all of those. Patients will say, "we want to try the one that we came here for." And it does seem like they do well when they switch over... I am more comfortable, too, having locally grown, we know it's organic, and it does seem more consistent and we can dose up higher more easily because of the costs...

Some kids who would become a little high —so THC wasn't working during the day—the parents maybe add a little bit of THC at bedtime when it's less of an issue.

Now, for children who are severely impaired —not going to school, and they're really not even talking or even paying much attention— then the parents will talk about "I think he was a little high but he was happy so what's the problem?" They'll say things like that.

So if a child is not trying to perform or do anything specific, if THC brings more alertness and interaction and smiling and giggling, the parents say "Fine, he was a little high and it was good, no problem.

CBDevelopments *from page 32*

grams per milliliter (mg/ml) and is 30-to-1 CBD-to-THC. We test it to get the precise ratio and for residual solvents. That oil is diluted with organic, food-grade olive oil down to 50 mg per milliliter."

November 2014: The Shipping News

The harvest in Wray turned out to be a bumper crop, but in early November, citing the advice of counsel, the Stanleys announced that they would not be shipping CW oil to patients residing in states other than Colorado or California. Paige Figi, interviewed at the time, said "We're trying to pass the federal bill so we can ship this, and trying to pass state laws so patients can receive it."

Nothing in Figi's background prepared her to become a political organizer (although she did take a few pre-med courses at Colorado State). "Ten thousand bills are introduced and 1% get passed. Many are just to get media attention for their cause. This is different. We are in this for passing it, not just for attention."

Charlotte, at age eight, has osteoporosis from longterm use of pharmaceutical AEDs has broken each of her legs in the past year. Her mother attributes her frail bones to "permanent side effects of seizure drugs that never worked for her."

Charlotte's twin sister Chase has handled the family tragedy "in the most stand-up way," says Figi. "*She* is Charlotte's caregiver. She's a natural caregiver —a very strong kid who has had to deal with a lot. And she has gotten to see Charlotte improve."

The siblings of seriously ill children "have more responsibility," Figi observes. "They have loss of innocence at a young age. They watch you to see how you [parents] handle it."

Matt Figi now works in Afghanistan as a contractor for the U.S. military. Paige says that "getting called back home all the time on emergency leave" made a career in Special Forces impossible. "He didn't want to go into the Regular Army so he got out and now he's a contractor. He's deployed more now than when he was in the military."

"If we have any legal leg to stand on, how can we not?"

January 2015: the waiting list vanishes

The decision to not ship CW oil to other states was deeply disappointing to families waiting to be supplied, and the Stanley brothers soon reversed course. "It was not unanimous," Joel Stanley recounts. "But with legal opinions coming down on every side of the question, and children on the waiting list dying, we felt, 'If we have any legal leg to stand on, how can we not?'"

"Many want to try it but are still afraid because the DEA considers hemp illegal."

The national waiting list was 12,662 on in January 2015 when RoC headquarters notified everyone that their oil was ready to ship. The response was very surprising — "anti-climactic," to use Heather Jackson's word: only 100 orders were received right away. Over the next six months the number rose by "about 3,000," according to Jackson.

Why did so many people on the waiting list not order CW hemp oil when it became available?

Joel Stanley says, "Many want to try it but are still afraid because the DEA considers hemp illegal. Or their neurologist or the local hospital won't approve. Others may have found another option that worked."

Ray Mirzabegian agrees: "People are afraid to order and use the oil because it's federally illegal." The RoC California waiting list had reached about 1,200 when the Stanleys decided to ship CW hemp oil across state lines in January. Only 25 ordered it immediately. As we go to press in late November, RoC is shipping to 325 Californians, and "several hundred" more are picking up their oil directly from Mirzabegian.

Mirzabegian's original plan had been to open a Realm of Caring Health Center —a bricks-and-mortar dispensary— in Los Angeles. The city attorney nixed the project before it opened. For most of 2015 Mirzabegian consulted with patients' families by appointment at a North Hollywood dispensary, NoHo's Finest. In November he opened the "Center for Complementary and Alternative Treatments" in Burbank.

Bonni Goldstein, MD, says admiringly: "Ray has made himself very available —he gives out his email and phone number— and he takes hundreds of calls a day. He's trying to help those who are non-responders to Charlotte's Web."

With CBD-rich oil available from Colorado, Mirzabegian is growing strains with various amounts of THCA and THC and making concentrates which he distributes under the brand name Canniatric.

"We grow and extract our own THC strains," Mirzabegian says. "Our products are formulated based on parents' and doctors' feedback." In addition to tinctures, Canniatric makes a 10-gram syringe of cannabis extract containing 2500 mg THC and an equal amount of CBD.

As 2015 came to an end, Mirzabegian's daughter Emily was "one pill away from weaning off Topamax," her last AED.

He thinks his most important role now is to educate doctors about cannabis in the treatment of epilepsy. "More doctors are needed," he says, leaving unspoken "who know about the endocannabinoid system."

The 2015 Harvest

In 2015, according to Joel Stanley, the company grew Charlotte's Web plants on 20 acres in Colorado —"more than enough to supply all the Realm patients with hemp oil." At two smaller sites they grew out different strains and testing cultivation methods. Joel estimates that "RoC members will utilize 50-60 percent of the harvest."

The company also grew hemp on 65 acres in Kentucky for an additional CBD supply and "to explore other uses — seed, fiber, ethanol, etc.," Joel said. "Although RoC membership is always growing, many more people are buying CW products to supplement their diet. As more people realize the potential general benefits of CBD, the total percentage of RoC member sales is decreasing," Joel says.

"The specific cultivars for Charlotte's Web Hemp Oil are only grown in Colorado," he adds. Extraction is by alcohol, as per the original process. "Most RoC clients prefer the original formulation. We don't even grow it out from seeds, we keep growing from clones and tissue culture."

The retail price of CW Hemp Oil was 10¢/milligram as of November 2015. RoC members get a code which discounts it by 50%.

CBD-rich plants grown by the Stanley Brothers in Kentucky will go into other CBD products such as topicals, less concentrated tinctures, and vape oils. The company keeps upgrading its technology for bigger batch sizes. Two supercritical CO2 extraction machines were used in 2015, Joel said, and a third —"capable of extracting roughly 620 lbs of pure CBD per week"— is being delivered.

As for relations with the federal government, "The FDA has not contacted us directly," Joel says. "Nor were we included in the FDA warning letters concerning unapproved labeling claims (as we do not make any claims). All of our products are manufactured under strict GMP standards in an FDA registered facility, as all foods and supplements sold interstate are regulated by the FDA."

The Uruguay connection

In 2014 the Stanley Brothers arranged a partnership with the first Uruguyan farmer licensed to grow hemp. Their plants will go into the ground in December 2015 —early summer in the Southern Hemisphere. (The 2014 presidential election in Uruguay was in part a referendum on legal marijuana, which was opposed by the center-right candidate. Left-leaning Tabore Vazquez, a 74-year-old, pro-cannabis oncologist, won with a 53-40 margin.)

Uruguay allows hemp to contain up to 1% THC, which Joel Stanley calls "a significant advance for hemp farmers. You are

continued on page 45

Hemp ready for harvest

CBD-rich plants are examined by Jordan Stanley prior to historic harvest in late September, 2014. Pipe overhead pivots to irrigate circular field. The plants were grown on 17 acres at an elevation of 3,500 feet. Oil extracted from them would supply some 3,000 patients with CW Hemp Oil through the Realm of Caring foundation. Photo by Matt Nager.

Colorado Department of Public Health funding 9 medical marijuana studies

Amendment 64, passed by Colorado voters in November 2012, took effect in January, 2014. It legalized the sale of marijuana to adults over 21 and cultivation of industrial hemp (<0.3% THC). It also mandated that some of the tax money raised from marijuana sales go to research projects to be chosen by the state Department of Public Health. Some 70 studies were proposed, including one by Realm of Caring that would have involved Charlotte's Web in a double-blind, placebo-controlled trial (but didn't make the cut).

In October 2014, nine projects were chosen to receive $9 million worth of funding in the years ahead.

• Do Adolescents and Young Adults with Inflammatory Bowel Disease Benefit from Use of Marijuana? Principal investigator: Edward J. Hoffenberg, University of Colorado School of Medicine.

• A Randomized, Double-blind, Placebo-controlled Crossover Study of Tolerability and Efficacy of Cannabidiol (CBD) on Tremor in Parkinson's Disease —Maureen A. Leehey, Department of Neurology, University of Colorado School of Medicine

• Treating PTSD with Marijuana: Clinical and Functional Outcomes —Marcel O. Bonn-Miller, Dept. of Psychiatry, University of Pennsylvania, and VA National Center for PTSD

• Cannabidiol (CBD) and Pediatric Epilepsy — George Sam Wang, Department of Pediatrics, University of Colorado School of Medicine.

• Medical Marijuana in the Pediatric Brain Tumor Population (palliative care) —Nicholas Foreman, Dept. of Pediatrics, Pediatric Neuro-oncology, Children's Hospital Colorado

• Use of Medicinal Cannabinoids as Adjunctive Treatment for Medically Refractory Epilepsy (pediatric epilepsy) — Kelly Knupp, Dept. of Pediatrics, Children's Hospital Colorado and University of Colorado School of Medicine.

• A Double Blind, Placebo-Controlled Cross Study Comparing the Analgesic Efficacy of Cannabis versus Oxycodone — Emily Lindley, Dept. of Orthopedics, University of Colorado School of Medicine.

• Colorado Cannabis Cohort: Efficacy, Safety, and Usage Patterns of Medical Marijuana for Sleep —Russell Bowler, National Jewish Health.

• Placebo-controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment- Resistant Post Traumatic Stress Disorder (PTSD) —Marcel O. Bonn-Miller, University of Pennsylvania and VA National Center for PTSD.

Although Sue Sisley, MD, is not the principal investigator on the last-named study, it is an expanded version of the one that she and the Multidisciplanary Association for Psychedelic Studies designed back in 2011, and which the University of Arizona would not let her conduct.

Sisley was fired from her U of A faculty position in July. She will be seeing 36 veterans with PTSD at a private office in Phoenix. A NIDA favorite named Ryan Vandrey will see 40 vets with PTSD at Johns Hopkins University in Baltimore. The investigation will take three years and cost $2,156,000 —making it the most expensive of the nine studies Colorado is funding.

The principal investigator, Marcel Bonn-Miller, was a two-time winner. His other state-funded PTSD study will look at people who obtain marijuana through Colorado dispensaries. They need not be veterans, although the Denver VAMC is listed as a source of potential study subjects, along with the University of Colorado and "community." The budget is $1,181,127.

Is there anything to add to the understanding laid out in Tod Mikuriya's paper, "Cannabis Eases Post-Traumatic Stress?"

[Google "Mikuriya PTSD"]

Maybe. Tod didn't live to see CBD-rich cannabis become available to his patients.

Paige Figi wants *you*…

Paige Figi has been lobbying Congress to pass the Charlotte's Web Medical Access Bill of 2015, which was first introduced in 2014 by Rep. Scott Perry of Pennsylvania. This interview was conducted by managing editor Fred Gardner (no relation to the Colorado Senator).

O'Shaughnessy's: Where do things stand with the Charlotte's Web bill?

Paige Figi: The Senate version of the Perry bill was introduced by Cory Gardner of Colorado. Slight language differences, but they'll mirror each other when they get through. We have the support of Orrin Hatch of Utah. He wrote the Dietary Supplement Act in '94. This bill puts CBD as a dietary supplement.

O'S: How does the Gardner CBD bill relate to the Rand Paul/Corey Booker/Kristen Gillibrand bill?

My bill is just a CBD and agricultural hemp de-scheduling bill.

Figi: The CARERS Act is a broad, very comprehensive bill … My bill, the Perry bill, is one component of their bill. Theirs has multiple components. One of them is to de-schedule CBD. And my bill is just a CBD and agricultural hemp de-scheduling bill. CBD, that component in the plant, is removed from the Controlled Substances Act entirely. And agricultural hemp is removed from the Controlled Substances Act entirely. Separating those two things out from the umbrella of the whole cannabis plant that is on Schedule I.

O'S: Don't you think supporting the Charlotte's Web bill will give some politicians cover not to vote for the broader bill?

Paige: Our bill was there before there was a CARERS Act. There are politicians who will never, while they're in office, ever vote for a comprehensive medical marijuana bill. They just will never do it. They would have never allowed for a hemp agricultural bill if not for Charlotte's Web —even though it's benign and harmless, they still would never sign onto it and let it pass. But people that opposed all of this before are saying 'you know what, I agree with this now that it's CBD and hemp.' They're coming on board with this bill –people who are absolutely opposed to medical marijuana.

O'S: What do you think the odds are that it will get through?

Paige: 100 percent.

O'S: 100 percent? And what do you think the odds are on the CARERS bill?

Figi: I think there is no chance. It has to go through the Judiciary Committee and Senator Grassley will not give it his blessing.

O'S: Zero chance?

Figi: I wish it would pass. I want it to pass. I'm in support of it. But when I sit down with the leadership, especially the people who have the ability to never let it see the light of day, I've heard from them: 'I'll never let this see the light of day.'

That's what I've heard from leadership, unfortunately.

O'S: Leadership meaning Mitch McConnell?

Figi: Yup. Grassley, McConnell, the other leaders that won't let it happen. I think that if you can pass something now and help maybe five million people... That's not enough, that's not everybody. That's not the CARERS Act. But five million people is a lot of people —people like my child, cancer patients...

I have to focus all my attention on what I know. It's so time consuming, it's extremely difficult.

O'S: How time consuming is it? How much time do you spend away from Colorado?

Paige: You know, it looks like it's more. I'm leaving for DC on Sunday again, for this. But I try and only travel when my husband is not in Afghanistan.

O'S: He's a contractor now?

Paige: He is a contractor for now. So it's only the bare, bare minimum that I travel. If I can get a meeting, I only meet with potential opposition and leadership—really critical meetings. I don't just go chasing down the halls of the Senate and lobby like crazy. I only set up these private meetings where I could be the most effective. I'm very efficient is what I'm saying, and I don't like to be away from my children.

O'S: Who is against your bill?

Paige: There a large, a well-funded lobby against this bill. I shouldn't have said our chances are 100%. Pharmaceutical interests are lobbying against this bill, saying this should not exist as a dietary supplement, wait till it's available from the pharmaceutical industry and paid for by insurance.

To a Senator or Congressman who's afraid for their career might be swayed —'treat it like a pharmaceutical' might seem like a quick, easy out. But it's not a quick, easy out if you've got a two year old.

We say: Treat CBD like Vitamin C —a dietary supplement that shouldn't be owned and patented and pharmaceuticalized. It can be —that process can happen simultaneously, however long it takes— but it doesn't have to be.

There are legislators who have said, "I don't have anyone in my district that has epilepsy."

The legislators need to hear from people. There are legislators who have said, "I don't have anyone in my district that has epilepsy." And I'm like "You have one percent of your district just with epilepsy alone!"

They're just not hearing from anybody. We could put a dagger through the heart of the pharmaceutical lobby, because we have numbers and we've got an army.

O'S: Let me ask you a few questions about Colorado. Has the influx of patients slowed down now that you're able to ship to so many other states?

Paige: There are still a lot of refugees who come here for THC and THCA. And they come here for CBD —even Charlotte's Web— because even though they can get it shipped, they can't go to the hospital in Texas or Idaho and tell them they're using a Schedule 1 substance. They can't tell them at school. They worry about local law enforcement because it's still illegal in their state. So there's still refugees coming here.

We've lost a lot of advocacy for the coalition because people are like 'It's shipped to my door now. I don't need to work this hard to change the laws.' I'm hoping they realize this isn't done until we federally amend the scheduling.

O'S: How did you finally decide to ship across state lines?

Figi: The Stanley Brothers decided to that. Because the state of Colorado Department of Agriculture governs the crop and tests it, inspects it and it meets the definition of hemp under the federal farm bill, they believe they're in their legal rights to ship it. People are dying, this is ridiculous! The brothers decided to ship it to support parents. It's the parents who have to face local law enforcement and make that decision for themselves.

I want to push that we have this really powerful army of voices. And everyone is kind of scattered on so many different bills happening. And if we could all align and push them all, we could be a very, very scary force. I know there's a lot of dissension, but there's a majority now. If you poll the country, there's over 50 percent in support of medical cannabis. We don't have funds, money on our side, but we have the numbers.

O'S: Do you have any dealings with the reform groups like Americans for Safe Access or NORML?

Figi: I am in touch with them. I've heard two different statements —they're not in support of CBD and then they are in support of some of the CBD states. I've heard different back-and-forth on that.

The hemp industry is fully in support of these bills. They've never been able to get Orrin Hatch or Lamar Alexander on board for anything [without us] and they've been trying for 15 years.

O'S: What were the changes that Perry made in his bill between 2014 and 2015?

Figi: They added a sunset provision into the bill. They made it a little more conservative so that if the sky falls because you legalized CBD and agricultural hemp, it will sunset after three years. And then they changed the name, in the Senate bill to "The Therapeutic Hemp Medical Access Act—S.1333."

O'S: It's odd to see "cannabidiol-rich" defined in terms of THC content. "Therapeutic hemp" seems more accurate —although the Hemp Industry Association thinks it creates confusion.

Figi: This bill has a big chance of passing. They just need to hear from people.

O'S: Some observers say that having a CBD-only law in Florida hurt the chances of the broader bill, Amendment 2.

Figi: The CBD bill in Florida —the Charlotte's Web bill, they nicknamed it—existed before Amendment 2. And I don't feel that it did hurt, because people were made aware [of the medical benefits of marijuana] through the media around the Charlotte's Web bill. I think they actually help each other.

O'S: What happens next to the federal Charlotte's Web bill?

Figi: The bills have to pass out of the Senate and House Judiciary Commitees. If you're in a district of anyone on those two committees, we should be reaching out to them. Just educating them and asking 'Please co-sponsor this bill. … When they're in Washington, I can explain 'This is what you're signing onto exactly' and put them in touch with doctors and law enforcement to answer questions. But first they need to hear from their constituents.

Also, we need the Democrats who are for the CARERS bill. If they would see the importance of this one piece of their bill, they can help five million people right now. Once they're on board, all the Democrats will see this as something they can support. Now they see it as a Republican bill, even though the co-sponsors are bipartisan.

Hemp should be an industry in this country. Why import it?

O'S: Do you have any allies?

Figi: The Coalition for Accesss, a 501(c)4, is a platform for all the voices backing this bill. Everyone told me it takes money to pass a bill and I didn't believe it because everybody knows that CBD helps these kids —it's not controversial. I'm sad to say that it does take money. There are very few people who don't want this to pass, but they're heavily funded. We have public opinion but no funding.

I have a leader in each state that collects advocates. If it's a large state like Texas and California, two or three. And they help all the advocates that contact us either to do media, go to DC, or when their legislator is on recess, ask them to co-sponsor it.

So these parents go push our narrow message —they show pictures of their children wearing helmets— and reach out and help drive up that advocacy number, drive up the co-sponsorship number.

O'S: Many small reforms get sold to progressives as "a first step" towards bigger reforms. And then they turn out to be all we get —the last step, not the first. So there's reason to fear that a CBD-only bill could take the wind out of the sails of the medical marijuana movement, like some people say Obamacare took took the wind out of the sails of Single Payer Healthcare.

But this situation could be different because so many people are educated about cannabis and know that THC is beneficial and in many cases necessary. And especially if you, Paige Figi, are committed to keep pushing for the CARERS Act.

Figi: Absolutely. And why make the farmers wait? The farmers don't care about THC. They want this crop. Hemp should be an industry in this country. Why import it? And the kids need CBD. Why is it ethical to make them wait?

114TH CONGRESS
1ST SESSION

H. R. 1635

To amend the Controlled Substances Act to exclude cannabidiol and cannabidiol-rich plants from the definition of marihuana, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

MARCH 25, 2015

Mr. PERRY (for himself, Mr. AUSTIN SCOTT of Georgia, Mr. MASSIE, Mr. HONDA, Mr. GRAYSON, Ms. NORTON, Mr. LOWENTHAL, Mr. BLUMENAUER, Mr. MCCLINTOCK, Mr. JONES, Mr. BARR, Mr. DOLD, Mr. COHEN, Mr. YARMUTH, Mr. COOPER, Mr. DAVID SCOTT of Georgia, Mr. WOODALL, Ms. HANNA, and Mr. VAN HOLLEN) introduced the following bill; which was referred to the Committee on Energy and Commerce, and in addition to the Committee on the Judiciary, for a period to be subsequently determined by the Speaker, in each case for consideration of such provisions as fall within the jurisdiction of the committee concerned

A BILL

To amend the Controlled Substances Act to exclude cannabidiol and cannabidiol-rich plants from the definition of marihuana, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Charlotte's Web Medical Access Act of 2015".

SEC. 2. EXCLUSION OF CANNABIDIOL AND CANNABIDIOL-RICH PLANTS FROM DEFINITION OF MARIHUANA.

THE CHARLOTTE'S WEB MEDICAL ACCESS ACT OF 2015 would "amend the Controlled Substances Act to exclude cannabidiol-rich plants from the definition of marijuana, and for other purposes." It states that "The Federal Food, Drug and Cosmetic Act shall not apply to cannabidiol or cannabidiol-rich plants as those terms are defined in section 102 of the Controlled Substances Act as amended by this Act." Also, "Nothing in this Act shall prohibit or otherwise restrict any activities related to the use, production, or distribution of marijuana in a State in which such activities are legal under State law."

Introduced by Senators Paul, Gillibrand and Booker

ASA pushing the CARERS Act

Steph Sherer, Executive Director of Americans for Safe Access, helped educate Kirsten Gillibrand of New York and Cory Booker of New Jersey on the need for changes in federal law to make marijuana available as a medicine to all who need it. It's understandable why Sherer strongly supports the CARERS Act —she had a hand in writing it.

Some backers of the CARERS Act fear that bills legalizing CBD will enable politicians to mollify constituents who want access to medical marijuana. These skeptics point to the 2014 vote in Florida, in which a ballot initiative to legalize medical marijuana (the whole plant, starring delta-9-tetrahydrocannabinol) fell less than 2% shy of the 60% needed for passage.

Governor Rick Scott had stated that he would never allow any kind of medical marijuana bill to be enacted in the Sunshine State. But during the campaign, strategists convinced him that signing SB-1030 (dubbed "Charlotte's Web" by the media), would make his opposition to medical marijuana seem less inhumane. With a stroke of the pen, Scott transformed his image from arch foe of medical marijuana to pro-CBD centrist. (*See cartoon below by Andy Marlette of the* Penascola News-Journal.)

In signing. Scott said, "As a father and grandfather, you never want to see kids suffer" —as if aunts and uncles just might. "Charlotte's Web will ensure that children in Florida who suffer from seizures and other debilitating illnesses will have the medication needed to improve their quality of life."

A very skeptical, previously reliable source in Washington source says, "Feinstein and Grassley don't want Charlotte's Web, they don't want farmers here growing crops to produce CBD, they want this thing locked up for the pharmaceutical industry."

Steph Sherer, Executive Director of Americans for Safe Access, speaking at ASA's "Unity Conference" in Washington, DC, March 28. Sherer launched the group in 2002, with support from dispensary operators. Only four dispensaries had representatives at the 2015 conference. "Now we have trade associations," one of them explained.

What it would do

By Mike Liszewski

On March 15, 2015, U.S. Senators Cory Booker (D-NJ), Rand Paul (R-KY), and Kirsten Gillibrand (D-NY) introduced the Compassionate Access, Research Expansion, and Respect States (CARERS) Act —the first comprehensive piece of medical marijuana legislation to be introduced in the U.S. Senate. Americans for Safe Access was honored to have played a role in shaping direction of the bill, and many of the patient-focused issues we brought up were addressed in the final legislation.

The bill's introduction comes just a few months after passage of the Rohrabacher-Farr Amendment, which was guided through the conference committee by the leadership of Senator Mikulski (D-MD). The Rohrabacher-Farr Amendment arguably should have defunded the prosecution of the Kettle Falls Five by the US Attorney for Eastern Washington, but the denial of their motion to dismiss shows that there is some legal dispute as to whether Rohrabacher-Farr Amendment will end federal prosecutions. There is no question that such prosecutions would end under the CARERS Act, which states:

"Notwithstanding any other provision of law, the provisions of this title relating to marihuana shall not apply to any person acting in compliance with State law relating to the production, possession, distribution, dispensation, administration, laboratory testing, or delivery of medical marihuana."

Prior to introduction of the CARERS Act, many Senators have avoided taking an official position on medical marijuana because there was no legislation in the Senate on the issue. Now Senators must confront it.

Patient advocates and other stakeholders have an opportunity to discuss each of the bill's issues in a substantive way. Rather than decry any perceived shortcomings, patient advocates can make strategic use of their time lending support to help get the bill heard before the Senate Health, Education, Labor, and Pensions Committee and offering suggested amendments to improve the bill.

To help better understand the bill, below is some section-by-section analysis (skipping Section 1, which is simply the title of the bill):

2. Federalism in Drug Policy

This is the section quoted above. It allows all state-legal medical marijuana conduct to continue to exist without any federal interference. Unlike the Department of Justice's August 2013 Cole Memo or even the Rohrabacher-Farr Amendment to the DOJ budget, this protection is both binding and permanent. ASA was successful in making certain that testing labs were included along with producers and dispensers. The exemption from the Controlled Substances Act does two additional things:

1) It will provide 280e tax relief to medical marijuana businesses (which should result in lower prices for patients) and

2) It will allow state programs to go on unimpeded, regardless of where marijuana is placed in the CSA, because the CSA will no longer apply in those states where medical marijuana is legal under state law.

Section exempts state programs from the Controlled Substances Act, so they could continue to operate regardless of any potential implications of Schedule II status.

This section creates binding and unequivocal legal protections from federal interference for anyone abiding by their state's medical marijuana law.

It is unclear whether or not dual-licensed medical/adult-use businesses would be covered, but it appears they would for the medical portion of their business.

114TH CONGRESS
1ST SESSION

S. 683

IN THE SENATE OF THE UNITED STATES

March 10, 2015

Mr. Booker (for himself, Mrs. Gillibrand, and Mr. Paul) introduced the following bill; which was read twice and referred to the Committee on the Judiciary

A BILL

To extend the principle of federalism to State drug policy, provide access to medical marijuana, and enable research into the medicinal properties of marijuana.

Section 1. Short title

This Act may be cited as the "Compassionate Access, Research Expansion, and Respect States Act of 2015" or the "CARERS Act of 2015".

3. Rescheduling of Marijuana

The rescheduling portion of the bill is probably the section that will get the most criticism from patient advocates and others. While placement in Schedule II does not appear to be appropriate based on its widespread medical acceptance and lower abuse potential than other Schedule II substances like cocaine and methamphetamine, it would show that the U.S. government has finally accepted that there *is* medical use for marijuana.

Placement on Schedule II could also potentially open up health insurance coverage to medical marijuana therapy, but that would not happen automatically. There are some who have expressed concerns that if marijuana were placed in Schedule II that it would mean pharmacies would have to take over distribution and that pharmaceutical companies would take over production.

However, Section 2 of the bill, completely exempts state programs from the CSA, so they could continue to operate regardless of any potential implications of Schedule II status.

4. Exclusion of Cannabidiol from Definition of Marijuana

The concept of this section of the bill similar to Rep. Scott Perry's HR 5226 from the 113th Congress, but has been slightly modified. This language would completely remove derivatives of marijuana with less than 0.3% THC content from the CSA, which would help enable transportation of high-CBD extracts across state lines.

States that have not already passed full medical marijuana laws or CBD-only laws would still need to pass such laws for protections to be complete in those states. It is a fairly safe assumption that most, if not all remaining states without CBD protections would adopt such laws in the wake of federal passage.

5. CBD Determination by States

This section was inspired by a similar provision in the S. 134, Industrial Hemp Farming Act of 2015, which had a safety valve provision for states that allow more than 0.3% THC in their CBD laws. ASA provided the Senate offices with language that will protect the patients in states that allow 0.5% to 5% THC in their CBD laws, such as Alabama, Florida, Iowa, Missouri, South Carolina, Tennessee, and Virginia.

6. Banking

The banking section of the bill used Rep. Perlmutter's HR 2652, the Marijuana Access to Banking Act of 2013, as its basis. The provision would allow anyone acting in conformity with their state marijuana laws to be able to access banking services. This section would exempt banks from filing suspicious activity reports on marijuana businesses. It would explicitly forbid the federal government from penalizing marijuana businesses or incentivizing banks to discriminate against legal marijuana businesses.

7. Research

ASA urged the Senate sponsors to make sure that the two biggest barriers to medical marijuana research in the US were addressed, the Public Health Service Review Process and the NIDA monopoly on the supply of available research marijuana. The Obama Administration has already removed the Public Health Service review. The CARERS Act would end the single source monopoly for federal marijuana made available for FDA-approved research. This will help ensure that a greater variety of marijuana is available to help foster meaningful research in the U.S.

8. Veterans

ASA also urged the bill sponsors to include a section that would allow VA doctors to fill out state medical marijuana recommendation forms.

Mike Lisziewski is government affairs director for Americans for Safe Access.

Senate Drug Caucus investigates the political potential of cannabidiol

By O'S News Service

The Senate Caucus on International Narcotics Control was created in 1985 (the height of the Ronald Reagan era) and given special powers to issue subpoenas and call hearings. Chairman Chuck Grassley (Republican, Iowa), arranged for a hearing June 24, 2015 on "Barriers to Cannabidiol Research and Potential Medical Benefits."

After opening statements by Grassley and his Democratic counterpart, Dianne Feinstein of California, three Senators who have introduced CBD-related bills —Orrin Hatch, Kirsten Gillibrand, and Cory Booker laid out their views. Then came testimony by Joe Rannazzasi of the DEA, Dr. Douglas Throckmorton a deputy director at FDA, and Dr. Nora Volkow, the director of NIDA. Booker and Gillibrand joined Grassley and Feinstein in questioning the agency officials.

Grassley recounted the basic story —kids with epilepsy getting seizure relief from "a substance called cannabidiol, or CBD... a compound derived from the marijuana plant that can be administered in the form of an oil. It's not smoked, and it can't be used to get high."

Desperate parents are "buying CBD products that haven't undergone the usual testing for safety and efficacy associated with new medicines, and in many cases haven't been evaluated for concentration or purity. Sometimes these products may be helping children, but sometimes they have no effect, or may even cause harm."

Grassley described GW Pharmaceuticals' Epidiolex, which is "undergoing FDA-approved clinical trials to treat two rare forms of pediatric epilepsy. I'm glad that one of the sites at which it's being tested is the University of Iowa."

Earlier in the year Grassley and Feinstein had urged the Department of Justice and the Department of Health and Human Services Department to get rid of impediments to CBD research. Grassley took credit for HHS dropping its requirement that the Public Health Service approve all studies involving cannabinoids. PHS approval had not been required "for any other Schedule I substance," Grassley noted. (Indeed, the requirement had been imposed by HHS under Donna Shalala in the Bill Clinton era.)

Dianne Feinstein

Even the staunchest Drug Warriors in Congress have constituents whose epileptic children have been helped by CBD. Dianne Feinstein said she did, too. But "I've heard from other constituents, like Catherine Jacobson, who, after researching cannabidiol as a treatment, went to a medical marijuana dispensary to obtain it for her six-year-old son who has epilepsy. Instead she was given plant material, not cannabidiol in any form that her son could ingest.

Sen. Orrin Hatch (Rep.-Utah), introduced the "Therapeutic Hemp" Act, which would remove CBD from the Controlled Substances Act. In 1994 Hatch wrote the Act in which Congress defined "dietary supplement" and advised the Food and Drug Administration that dietary supplements were to be regulated as the former. The dietary supplement industry has been booming ever since. In Utah it's a $7 billion bnsiness.

Hatch told the Senate Drug Caucus that he wants to see the medicine that reduced Charlotte Figi's seizures —cannabidiol— available as a dietary supplement.

Senators Chuck Grassley (Republican, Iowa) and Dianne Feinstein (Democrat, California) at the Senate Caucus on International Narcotic Control's June 24 hearing on "Barriers to Cannabidiol Research and Potential Medical Benefits."

"Ms. Jacobson is still trying to find a safe and reliable form of cannabidiol to treat her son, but is worried about a lack of data, the high variability in oils, dosing, and cannabidiol's potential interaction with other medications. All of this points toward the need for research and regulation."

Orrin Hatch

The Senator from Utah began his testimony with the story of Charlotte Figi, and his words echoed her mom: "I understand the desire for caution. We're Congress. We act slowly. But we must remember that these are people whose lives we're dealing with... for whom a five- or 10-year delay is not an inconvenience but a potential death sentence.

My home state of Utah —certainly no redoubt of hippie liberalism— was the very first state to legalize CBD.

"Given that CBD produces no psychoactive effect, I frankly see no reason why it should remain illegal under federal law... Parents who wish to obtain CBD to treat their suffering children risk federal prosecution for the sole reason that CBD is derived from the cannabis plant. Never mind that it produces no high, never mind that it actually counteracts the effects of THC. Under current law, because it is derived from the cannabis plant it is unlawful.

"To remedy this situation I've recently co-sponsored bipartisan legislation with Senators Gardner, Wyden, Alexander, and others, to exempt CBD from the definition of marijuana under federal law. Our bill, 13-33, will allow parents to obtain this life-changing therapy without threat of federal prosecution. It will enable parents, if they choose, to use a therapy that has shown great success in reducing seizures in children for whom all other treatments have failed.

"Now I want to reiterate that CBD cannot be used to get high. That point is critical. It's what differentiates CBD from all these other attempts to legalize marijuana, whether for medical purposes or otherwise. CBD is not a camel's nose under the tent for advocates of full marijuana legalization. Fifteen states have now legalized CBD. These include some of the most rock-ribbed conservative states in the country such as Alabama, Oklahoma, and Texas. In fact, my home state of Utah —certainly no redoubt of hippie liberalism— was the very first state to legalize CBD.

"And I continue to oppose marijuana and efforts to legalize its use. I remain unconvinced by claims that it is safe and that the side effects it causes are no big deal..."

23 and DC

Sen. Kirsten Gillibrand of New York, had also met with parents of children suffering seizure disorders, and said she had come to understand that cannabis (not just CBD) could be beneficial in treating a wide range of disorders (not just epilepsy). Gillibrand said that 23 states and Washington, DC, had passed medical marijuana laws that could not be fully implemented "until we change our outdated federal laws."

Without referring to the CARERS Act, Gillibrand said, "Let's pass a new, modern law on medical marijuana that respects state laws and respects modern scientific research."

Nor did Cory Booker of New Jersey use the occasion to pitch the more comprehensive bill. He described constituents whose children had been helped by CBD and found themselves forced to choose between breaking the law or seeing their children go without the best anti-seizure medicine. "There is a moral urgency here," he said.

"Although this hearing is limited to CBD," Booker added, "I do not want to lose sight of the government's overall policy on medical marijuana. Other Americans are dealing with other conditions. We need to consider the issue as a whole."

Throckmorton of the FDA

Douglas Throckmorton, MD, is deputy director for regulatory programs in the Center for Drug Evaluation and Research at the FDA. He testified:

"FDA is the agency that is responsible for the assessment and regulation of new drugs in the United States, including drugs derived from plants like marijuana. The Food, Drug and Cosmetics Act requires that those drugs be shown to be safe and effective for their intended use before being marketed.

"In addition, drugs must be shown to be manufactured consistently, lot-to-lot, with high quality. Because many factors influence the make-up of plant materials, such as temperature, time of year, location grown, this essential part of drug development presents special challenges when the drug is derived from a botanical source like marijuana.

"To address these challenges, FDA has published guidance to investigators to give recommendations about the types of studies to be conducted when developing drugs from plants... In addition to working directly with investigators to support their studies, FDA has several [expediting] mechanisms... such as 'fast track designation,' 'accelerated approval,' 'priority review,' and 'breakthrough' designation.

"Wherever possible we are applying these tools to the development of the products derived from marijuana and cannabidiol. For example, fast-track designation was granted to an investigation of cannabidiol, Epidiolex, being developed for a rare form of childhood epilepsy."

Throckmorton said that, according to the manufacturers, "20 Epidiolex intermediate-sized expanded access programs have been authorized to treat approximately 420 children."

He saw it as a win-win: "Importantly, these children are getting access to an investigational product under close medical supervision, and the data obtained from their use of the investigational agent is being collected to help support drug development."

Exposing Scammers

Throckmorton said, "We are also mindful of protecting consumers. In February of 2015, FDA took action against marketed, unapproved drug products that were making egregious health claims, including products that allegedly contained cannabidiol and other compounds from marijuana. For example, products containing cannabidiol were advertised nationally making unsubstantiated claims as being effective in the treatment of conditions such as breast cancer, rheumatoid arthritis, and ebola infection.

"We analyzed the products and found that many did not even contain the ingredients listed on their labels. For example, when we tested products that allegedly contained cannabidiol, around one-third of those products, in fact, contained no cannabidiol...

"These products and their marketing can create false hope in those seeking relief from serious medical conditions for themselves or their loved one. Moreover, it can divert patients from products with demonstrated safety and effectiveness.

Cannabinoids 101

Dr. Nora Volkow, the head of NIDA, gave the Senators a fast introduction to the endocannabinoid system. "Cannabidiol has a very low affinity for these receptors," she said reassuringly, "and is devoid of rewiring or pleasurable effects...

"Pre-clinical research has indeed suggested that CBD may have a range of therapeutic effects, most notable of which are anti-seizure, neuroprotective, anti-inflammatory, analgesic, anti-tumor, anti-psychotic, and anti-anxiety relieving properties. Most of the recent public interest has focused on the potential value of CBD in the treatment of seizure disorders. And indeed, multiple studies using animal models have shown that CBD reduces the severity of seizures. And ongoing studies are in-

text continues on next page

Douglas Throckmorton, MD, Deputy Director for the Center for Drug Evaluation and Research, Food and Drug Administration

Senate Drug Caucus *continued from previous page*

vestigating its mechanism of action. In the meantime, clinical case studies and reports from patients have provided suggestive evidence that CBD may be effective in treating children with drug resistant epilepsy...

"The evidence is insufficient to arrive at a firm conclusion. This is likely to change in the near future," Volkow said, citing the "ongoing clinical trials being conducted by GW Pharmaceuticals to test the efficacy of Epidiolex in pediatric epilepsy."

"NIH identifies CBD as an interesting target for therapeutic studies that go beyond its value as an anti-seizure medication."

Volkow seemed relieved to be talking, for a change about possible benefits. "NIH [National Institutes of Health] identifies CBD as an interesting target for therapeutic studies that go beyond its value as an anti-seizure medication... NIH institutes are funding work on the therapeutic value of cannabinoids, including CBD, in the treatment of neurologic, psychiatric, immunological, metabolic, and oncological disorders."

Volkow concluded: "It appears that CBD is a safe drug with no addictive effects. The preliminary data suggests that CBD may have therapeutic value for a number of medical conditions. Addressing barriers that slow clinical research with CBD would accelerate progress."

Questions and Answers

Grassley said that each Senator could ask seven minutes' worth of questions. He started with one for Volkow. "NIDA," he said, "is the agency responsible for providing researchers with marijuana to support CBD research. NIDA does so by contracting with the University of Mississippi to grow multiple strains of marijuana and recently NIDA, in consultation with the Drug Enforcement Administration. dramatically increased the supply of research marijuana grown at the university.

"However, there is still a question about whether the arrangement as it currently exists will continue to meet the needs for research-grade marijuana. Do you believe that it would be beneficial to allow NIDA ,in coordination with the DEA, to grant more than one contract to approved entities to grow marijuana for research?"

Volkow was unequivocal: "The answer is yes. I think it would be beneficial."

In the 1980s, Grassley recalled, there was a program under which the drug Marinol [synthetic THC] was used experimentally by some 20,000 cancer patients prior to approval by FDA. Could large numbers of patients use Epidiolex, too?

"Absolutely," said Throckmorton. "That program was a precursor to the current expanded access program through which 400 children are getting access to Epidiolex now. It's a program set up by the manufacturer to work with an individual physician or medical center to allow access to an investigational product."

Joseph Rannazzisi, Deputy Assistant Administrator of Drug Diversion with the Drug Enforcement Agency.

Dr. Nora Volkow, Director, National Institute on Drug Abuse.

Grassley asked, "Is there any reason that more children couldn't be enrolled in that program?

Throckmorton explained: "The manufacturer has to make the decision to set up an expanded access program. In this case, GW Phamaceuticals has made that decision and so they're making the product available.

"The product is available under medical supervision, so it requires that the patient be under care of a physician to watch for side effects, to monitor for adverse effects and efficacy... and report back to us.

"It also requires that institutional review boards be aware of and approve the administration of this investigational drug to the patient.

"The fourth thing for a controlled substance like this is that the manufacturer would need to work with the DEA and make certain that there was authorization to manufacture enough of that controlled substance. I know that the DEA has made that step possible in this case, so that's not an issue here today. But, so as long as those four conditions are met, and so long as other reporting requirement are met by the manufacturer, FDA has approved 99 percent of these expanded access programs since 2010. We don't get in the way. And they are being used broadly.

Grassley made reference to the CARERS Act without naming it. "There are legislative proposals before Congress to change marijuana from Schedule I to Schedule II," he said. " Some believe that these proposals will make CBD products being sold on the black market immediately available under federal law." He directed his question to Throckmorton: "Would moving marijuana to Schedule II change the legal requirements that CBD-based medicines, like all medicines, have to be approved by the DEA and the FDA before being prescribed by doctors? And if not, could you describe the federal regulations that would govern the approval process for a medicine developed from a Schedule II substance.

Throckmorton said that a scheduling change "would not affect the drug development and approval process... The major impact would be on the controls that would be in place over research."

DiFi Heart GWP

Feinstein asked again if a scheduling change would have an impact on research. Throckmorton tried to kick it to the DEA man: "Well, there are additional controls. I think as Mr. Rannazzisi said, there –

Feinstein: "Answer that, yes or no."

Throckmorton: "There are additional steps, so to the extent that those additional steps exist they are additional things that need to happen."

Feinstein: "Okay, now this company GW that the 400 children are utilizing the cannabidiol, are the doses standardized? Are they by prescription? How does it work?

Throckmorton: "Absolutely, and I should have made that clearer. Thank you for that question. Absolutely, and it's one of the really important things about the expanded access program is it takes place in the context of a drug development program. GW Pharmaceuticals has developed a formulation of cannabidiol with dosing and manufacturing information – all of the things that we'd expect for a drug that you take every day or are given in a hospital or something like that. And then, they're using that exact same product, the same product that they would hopefully be able to market once they've provided the clinical trials to us, that's the product being given to the children under the expanded access program."

Senator Kirsten Gillibrand, (Democrat, New York).

Feinstein *(impressed)*: "Can that program be expanded now?"

Throckmorton: "The limitations on it are the ones that I mentioned before, which is the manufacturers control this. So the FDA can't force a manufacturer to do this or not do this. This is something that they have chosen to do. There needs to be a physician that's able to supervise the patient to make certain that the adverse events are identified."

Feinstein: "Well, that's very good news, I think. And my sense is the Senate would certainly support that."

Throckmorton: "We've had a very good relationship working very closely with this manufacturer. I have an expanded access crew that is trying to do anything we can to help them.

Feinstein: "Right. Well, I think that's very good to hear... I understand that our country has a patent on cannabinoids, including CBD, which states that 'non-psychoactive cannabinoids such as CBD are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids.' How, if in any way, will that patent factor into the scientific and medical evaluation?

Volkow explained that the federal patent on CBD is specifically for its use as an anti-oxidant for neuroprotection, and has nothing to do with its potential as an anti-seizure medication. [O'Shaughnessy's broke the story of the federal patent. Hey, dude, where's our Pulitzer?[

Feinstein repeated her admiration for GW Pharmaceuticals' approach. Throckmorton reiterated that the company "has enrolled fully two trials of children for severe seizure disorders... Those clinical trials are important because they're going to form the data that the FDA is going to to use to [assess] the efficacy and safety of the product while we make it available under the expanded access program."

He ran it by her one more time: The investigational new drug is being given to patients under the expanded access program by doctors conducting placebo-controlled trials.

Feinstein: "Well, for whatever it's worth, I'm really pleased that FDA is taking that position and allowing expansion."

Gillibrand Skeptical

Senator Gillibrand didn't open with any niceties. "How many patients nationwide need access to CBD?" she asked Throckmorton. He said "I don't have that information."

"Estimate," she demanded. "Is it tens of thousands? Is it hundreds of thousands? Is it hundreds? I just need to know because 400 patients [a reference to the Epidiolex patients, down from 420 when first mentioned] is not even meeting the need for New York state. So how many patients need access to medicine?

Throckmorton: "The challenge is that we have many medicines approved for the treatment of seizure disorders. We recognize they have side effects. We recognize that not all of them work in all patients. So to identify the subgroup of individuals that have tried all of those – and they're not working for them – I wouldn't have an estimate. It's many patients. Rather than trying to decide what that number is, I really – my job is –"

"So what I hear from you is that having this one drug company who's got 400 patients –we're solving the problem? That's outrageous!

Gillibrand *(with increasing anger):* I don't want to limit the access to CBD to one drug company. It is absurd that we're saying that that's going to solve the problem. So what I hear from you is that having this one drug company who's got 400 patients – we're solving the problem?! That's outrageous. That's an outrageous impression to leave on this committee, because you have thousands of patients in my state alone who need access to this medicine and they don't all get accepted by the drug trials.

"And when you talk to a parent they tell you, 'The other medicines that are approved for my kid are barbituates that knock him out and put him in a coma-like state, that's not a quality of life I want for any child.'

"So, let's be clear. We need to change the laws to remove impediments so we have research being conducted across the country as is being done in other countries like Canada and Israel. We cannot have only one place where this plant can be grown. It needs to be distributed more widely so that people can get access to the materials they need to do the research.

"We have to change the Schedule, you said Schedule 1 to Schedule 2 releases impediments. What are those impediments? Explain to us what is the difference between Schedule 1, Schedule 2 in terms of a researcher's ability to research this drug and a drug company's ability to produce a medicine that has the protections that Sen. Feinstein needs for her constituents?"

Throckmorton: "Be happy to talk about the one particular role that Schedule 1 has in terms of the FDA, and then I'd ask Mr. Rannazzisi to talk about the DEA's role.

When a Schedule 1 product is being studied they have to report to us any changes in their protocol. So if they've got a clinical trial and they are enrolling a number of patients and they're following it for six weeks, and they decide that they need to change the conditions of that study so that instead of three weeks it's going to be followed for four weeks –something like that. Typically those changes come into us but the trial is allowed to continue to go forward. For controlled substances, for Schedule 1 substances, there's a review that's required. The DEA sends that protocol change to us. We are on a 30-day clock to look at that and get an answer back to the DEA. And then the DEA goes back to that investigator and says yes the trial can go forward.

Gillibrand: Is it fair to say the process is very cumbersome?

Throckmorton: It is not a straight – there is that additional step. This additional exchange that has to happen that doesn't occur for products that are in different schedules, less controlled schedules.

Throckmorton explained that Schedule II products have a high risk of abuse but

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Senate Drug Caucus *from previous page*

an accepted medical use. For example opioids, approved by the FDA for treatment of pain in cancer, etc.

Rannazzisi: "The Schedule 1 researcher has to apply for separate research registration. He submits protocols. The protocols basically outline who he is, what his background is, then what his research is going to be and under what authority he's doing that research. For instance, is he doing it with an institution? Is he doing it pursuant to an IND? We get that protocol. We submit it to FDA for approval. And once it's approved it comes back to us. We ensure that he's got a secure container to keep his drugs in, and we explain the paperwork to him for procurement, and he gets his registration."

Gillibrand confronted Volkow: "Given that NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, what specific steps is NIDA taking to advance research into the medical *benefits* of marijuana? To put it another way, how can NIDA control the research supply in medical marijuana studies that seek to find benefits when the mission is solely focused on the negative consequences of marijuana use? And is there an agency better suited to handle the research supply of marijuana?

Volkow: "I want to answer that question... One of the things that NIDA does is study the effects of drugs in the human brain. But the research is not just focused per se on the negative effects of marijuana, and in fact as I very explicitly stated, we're very interested on doing research that relates to the potential benefits that cannabidiol may have on the treatment of drug addiction.

"Being the only source of research material for marijuana, that's not something that NIDA chose to do."

"We're also interested in understanding how cannabidiol or other cannabinoids may be utilized for the better management of pain, as well as for the potential management of patients suffering from HIV.

"Being the only source of research material for marijuana, that's not something that NIDA chose to do. There is a law that requires that we be that agency, and we comply with the law.

Gillibrand asked, "Given that marijuana is a multi-compound botanical substance? Is it reasonable to expect that marijuana could ever make it through the FDA approval process? If not, would it make sense to develop a new approval protocol for multi-compound botanical substances such as marijuana in the FDA?

Throckmorton: "It's absolutely reasonable to expect that marijuana would be able to be developed as a drug. We've done it before. We've approved other plant-derived drugs. We have guidance that we put out. I have in place a team whose job it is to help developers who want to develop drugs from plants– to give them any advice and help that they can. So, yes, there is a pathway laid out. Yes, it's been done."

Gillibrand: "What's the timing for that pathway currently?"

Throckmorton: "What we need is an interested investigator working with us and doing the studies that we need to have to be certain that we have a product that's well characterized, that's studied appropriately in a patient population, that we can identify, so I can give a prescription, I can tell a prescriber that they can prescribe that medicine to those patients."

Gillibrand: "So the current 400-person study, is that sufficient for you to begin the process?"

Throckmorton: "This process begins with conversations about the drug itself. So in the case of a plant-derived product like a marijuana product, it would start with a discussion how they want to develop it, what patients they want to study it in, what kinds of treatments they want to measure, what outcomes they –"

Senator Cory Booker (Democrat, New Jersey) asked why the DEA was ignoring an Act of Congress ordering an end to raids on medical marijuana providers operating legally under state law.

Gillibrand: "Is that happening with this company that you talked about?"

Throckmorton: "That's already happened with this company. It happened. And any additional conversations they need, we're having. Any investigator that's interested in coming in and talking to us about developing a drug for marijuana we have a process to put them into involving a discussion with the right review division, specifically to lay out what kinds of trial designs they'd need to use."

Booker of New Jersey

Booker decried "NIDA's monopoly" on marijuana for research and cited an instance of egregious delaying.

Volow said she had already expressed her view: "If there were alternative sources of cannabidiol, would I support that? The answer is yes. It should make the research much more efficient. So some of these delays –

Booker: I only have five minutes, so I just want to get my answers –

Feinstein *(sourly correcting him)*: You have seven minutes.

Booker *(to Feinstein):* I have five left. *(Gillibrand taps him under the table as if to say "Stay cool." Booker returns his attention to Volkow.)* In other words efficiency, effectiveness, availability for research would be better if it was not a monopoly.

Volkow: Correct.

Booker: And so, does that monopoly exist for other Schedule 1 drugs?

Volkow: Not to my knowledge.

Booker observed that researchers could obtain heroin from more than one supplier. "Why would you treat heroin differently than you're treating pot?" he asked. "Why would that be? Is there any scientific reason whatsoever?

Volkow: There is no scientific reason. No.

Booker asked Throckmorton if he acknowledged the "chokehold on the ability for us to conduct research... as a problem?"

Throckmorton said, "I think there are advantages to broad availability of a variety of different kinds of marijuana.... Expanding the numbers of growers is one potential solution."

Booker asked if moving marijuana to Schedule II would expedite research.

Throckmorton said yes, not just logistically but politically. Rescheduling might kindle "the perception that it is now easier, it is now something that an investigator could be interested in doing, could make a career of, a sort of sense of the possible. It sends a message that it's important to do this and it's possible to do it.

Booker said, "I'm going to take that as a 'yes,' and turned to Rannazzissi (whose name he mangled. "One year ago Senator-Paul and I offered an amendment to a federal spending bill that would prohibit the Department of Justice and the DEA from using taxpayer money to undermine state medical marijuana laws. The amendment was ultimately inserted into the House and Senate omnibus Appropriations Act, which subsequently passed and was signed into law. I'm concerned now, though, that the DEA is failing to implement this amendment and continuing to erect barriers to prevent states from making CBD and other medicines available without federal interference.

"What steps is the DEA taking to implement this policy? What assurances can you give that state medical marijuana programs are not being undermined by federal laws? Because I see people moving out of my state to go to states so that they can get access to this medicine, I'm concerned that they still have the threat of the DEA enforcement.

Rannazzasi said, "I'm not aware of any effort to undermine that particular provision within the law. And I'll go back to the department and bring this up."

Booker pressed on: "In April, a spokesperson for the Justice Department told the *Los Angeles Times* that the bipartisan Medical Marijuana Amendment does not prevent it from prosecuting people for medical marijuana and seizing their property, including CBD...If you can find out for me why does the department ignore the clear intent of Congress for the amendment to protect marijuana including CBD patients and providers from prosecution and forfeiture."

Rannazzasi said he would look into it.

Booker's concern would be addressed in October when US District Judge Charles Breyer ruled that the DEA was prevented by wording in the 2015 Appropriations Act from interfering with medical marijuana production and distribution when it is allowed under state law.

Fairfax dispensary can reopen

Breyer to DOJ: Acts of Congress Matter

"This court has a lengthy history with this defendant on these issues," wrote US District Judge Charles Breyer in an order filed October 19 allowing the Marin Alliance for Medical Marijuana to reopen because Congress has changed its spending priorities.

MAMM proprietor Lynette Shaw first appeared before Breyer in 1998, when the US Attorney for the Northern District of California sought an injunction to close hers and five other dispensaries (including the San Francisco and Oakland Cannabis Buyers' Clubs).

Back then Breyer granted a preliminary injunction on the grounds that the federal Controlled Substances Act took precedence over the medical marijuana law enacted by California voters.

Some of the dispensaries remained open, however, arguing that they were serving patients whose cannabis use was a matter of necessity. This argument was rejected by Breyer, then accepted by the Ninth District Court of Appeal, then rejected by the US Supreme Court. Breyer issued a permanent injunction in 2002, but Shaw stayed open for business in the small Marin County city of Fairfax. MAMM had thousands of members and a business license from the city.

It wasn't until 2011 that US Attorney Melina Haag closed the dispensary by threatening to seize the property from the landlord. Slammed with a $3 million claim from the IRS, Shaw retreated to Los Angeles. In 2014, when she returned to the Bay Area to auction off MAMM memorabilia, she was at loose ends. Now she plans to reopen the dispensary at another location in Fairfax if she can get financial backing.

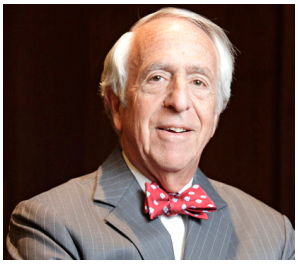
Greg Anton of Sebastopol is the lawyer who sought to get the injunction against MAMM "dissolved" on the grounds that it violates Section 538 of the Appropriations Act of 2015, also known as the Rohrabacher-Farr Amendment after the Santa Ana Republican and Santa Cruz Democrat who introduced it. The Amendment forbids the Department of Justice (DOJ) to spend funds to prevent California and 32 other states "from implementing their own State laws that authorize the use, distribution, possession or cultivation of medical marijuana."

Although Breyer left the injunction against MAMM in place, "The plain reading of the text of Section 538," he wrote, "forbids the Department of Justice from enforcing this injunction against MAMM to the extent that MAMM operates in compliance with California law."

Breyer's order was sharply critical of the US Attorney. "Where to start?" he asked after summarizing the DOJ arguments. He was appalled by the notion that closing down an occasional dispensary "may be presumed to have such a minimal effect on California's medical marijuana regime that it does not 'prevent' California from 'implementing' its State law.

"This 'drop-in-the-bucket' argument is at odds with fundamental notions of the rule of law. It has never been a legal principle that an otherwise impermissible goventment intrusion can be countnanced because any one defendant is a small piece of the legal landscape.

"To the extent the Government cites a few cases addressing Section 538, none are analogous or even particularly favorable to the Government's position," Breyer observed scornfully. The cases cited by DOJ all involved individuals or organizations that violated state law. But DOJ never alleged that MAMM had violated state law. Lynette Shaw treasured her license from the city and ran a legal operation, according to former Fairfax mayor Larry Bragman, whose letters of support Breyer cited in his order.



US District Judge Charles Breyer ruled that Congressional action superceded the injunction closing the Marin Alliance for Medical Marijuana. Breyer originally issued the injunction 2002. The DEA, acting on orders from US Attorney Melinda Haag, finally enforced in 2011.

photo by Hillary Jones-Maxon, The Recorder

Lynette Shaw may get the last laugh in her long struggle to operate a medical cannabis dispensary in Fairfax, California.

photo from the Marin I-J.

Hemp closer to *indica*

Sativa / Indica Genetics Gap Quantified

It has long been assumed that the difference between plants considered by cultivators to be *Cannabis sativa* and plants considered *C. indica* was the result of differences in the genes determining cannabinoid content. But the differences are spread throughout the genome, according to a new study by Canadian plant geneticists.

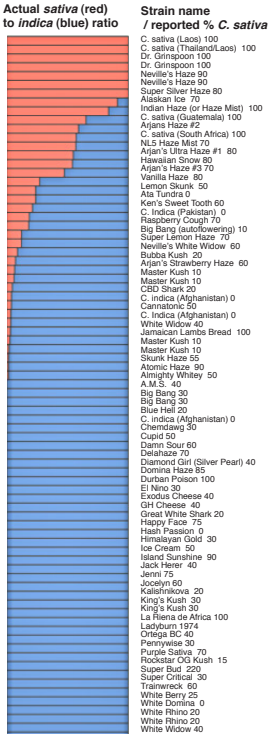
The researchers analyzed 81 marijuana and 43 hemp samples and found that "marijuana and hemp are significantly differentiated at a genome-wide level, demonstrating that the distinction between these populations is not limited to genes underlying THC production."

The study, published August 26 on PLOS1, developed "evidence that hemp is genetically more similar to *C. indica* type marijuana than to *C. sativa* strains."

The authors concluded that there is a "moderate correlation between the genetic structure of marijuana strains and their reported *C. sativa* and *C. indica* ancestry." They also found that "marijuana strain names often do not reflect a meaningful genetic identity" —confirming what Dr. Jeffrey Raber and other chemists have concluded.

The reported ancestry of the 124 plants analyzed was determined via online database searches, seed companies and licensed cultivators. Co-author Darryl Hudson (DOC Solutions in Ontario) estimated the identity of 26 strains for which no online information was available. Only three strains were found to actually be 100% Sativa: Dr. Grinspoon, Neville's Haze, and Super Silver Haze.

The graphic at right lists the strains tested and the ratio of Sativa (left hand part of each horizontal bar, in red) to Indica genetics (right hand part, blue). How inaccurate the commonly used names can be is illustrated by the total absence of Sativa genetics in Durban Poison, Jamaican Lambs Bread and La Riena de Africa —all reputed to be 100% Sativas.



Lead author Jason Sawler is with Anandia Labs in Vancouver and Dalhousie University's Agriculture Faculty. The study was planned by Sean Myles, also of Dalhousie, and Jonathan Page of Anandia Labs and the University of British Columbia Botany Department.

2015 harvest

Thousands of acres of hemp grown in Kentucky, Colorado and Tennessee

In 2015 the Tennessee Department of Agriculture licensed 47 farmers to plant hemp on 1,595 acres, and allowed importation of 38,180 pounds of seed for them (almost all from Canada). But, as reported by Clay Duda in the *Knoxville Mercury,* "One shipment that arrived in Memphis was sent back to Canada after the carrier, FedEx, discovered the package contained hemp seed, which the company considered a narcotic... Other delays were attributed to the DEA slow-walking necessary paperwork to import the seeds."

So instead of planting in April and May —when fast-growing hemp would have shaded out weeds— Tennessee farmers were planting in June and July and their *Cannabis* had to compete with weeds. (The University of Tennessee had a one-acre hemp plot on which 15 herbicides and pesticides were tested.)

FedEx —but not the DEA— was also responsible for blocking hemp seed deliveries from Canada to Kentucky farmers. The Kentucky Agriculture Department licensed some 1,700 acres but only about 800 were planted, according to Eric Steenstra of the Hemp Industry Association. Heavy sprintime rains also impeded planting.

In Colorado 166 farmers were licensed to plant 3,657 acres of hemp in 2015. Some 2,300 acres were planted, availability of seeds being the main limiting factor. Colorado's Agriculture Department also licensed 571,000 square feet of space for indoor hemp cultivation.

Most of the crops are going towards CBD production. "Colorado tested 52% of the acres this year and only 8% were above 0.3% THC," Steenstra says. Plants in only one field were found to contain more than 1% THC. "Given the lack of certified seed, that level of compliance is really quite good," Steenstra observes

Bill Polyniak is a Kentucky farmer who considers the hemp program "an absolute success." Originally involved because he has a son with epilepsy, Polyniak now sees hemp as a way to "revitalize" individuals' lives and the overall economy.

In 2015, Polyniak grew hemp in three Bluegrass Country locations —two dedicated to CBD oil production, one to seeds for planting in the future. "I'm thinking about 2025," he says. "These children are going to need oil all their lives."

After a CO2 extraction process in Kentucky, a portion of Polyniak's CBD-rich oil is trucked to South Carolina, where it is further refined, bottled and sold by a company called Palmetto Harmony —"created after a collection of parents with special children ran out of options using modern medicine," the website says. Palmetto Harmony CBD products are sold at healthfood stores in South Carolina.

Polyniak and his wife have developed their own brand of CBD-rich oil, "Genesis Blend," available through their Kentucky Cannabis Company & Bluegrass Hemp Oil websites. The 2014 harvest enabled Polyniak to get the price per milligram of CBD below a dime. The 30 ml bottle holds 300 milligrams of CBD oil and provides 10 milligrams per full dropper. (The dropper holds 30 milliliters.)A stronger extract of 1500 mg per bottle provides 50 mg of CBD per dropper-full. Both strengths are available in larger 4 ounce bottles.

Polyniak has applied for licenses to cultivate 20 acres of hemp in 2016. The goal of the breeding program is to maximize CBD content, seed production and fiber quality and quantity.

When Hemp Reigned in Kentucky

In 1900, Macmillan published "The Reign of Law: a tale of the Kentucky Hemp Fields," *by James Lane Allen. If published nowadays it would probably be shelved among the romance novels. The heroine, Gabriella, comes from a wealthy family (even though they've lost their slaves). She is a devout young woman, takes the Bible literally. The hero, David, is the son of a devout hemp farmer. David goes off to college and learns about evolution. He comes home, gets expelled from the church founded by his great grandfather, and feels the wrath of his father and the disappointment of Gabriella. He gets pneumonia and is near death. He pulls through. He decides to go back to college and study the physical sciences. Gabriella, though her faith in Christianity is unwavering, will go with him.*

The first chapter, "Hemp," is a florid paean to its subject. Some excerpts follow:

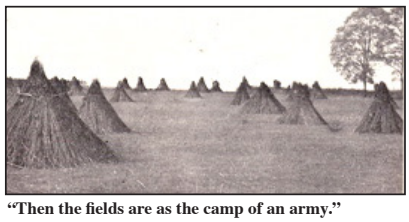
The Anglo-Saxon farmers had scarce conquered foothold, stronghold, freehold in the Western wilderness before they became sowers of hemp—with remembrance of Virginia, with remembrance of dear ancestral Britain...

Hemp in Kentucky in 1782—early landmark in the history of the soil, of the people. Cultivated first for the needs of cabin and clearing solely; for twine and rope, towel and table, sheet and shirt. By and by not for cabin and clearing only; not for tow-homespun, fur-clad Kentucky alone. To the north had begun the building of ships, American ships for American commerce, for American arms, for a nation which Nature had herself created and had distinguished as a sea-faring race. To the south had begun the raising of cotton. As the great period of shipbuilding went on—greatest during the twenty years or more ending in 1860; as the great period of cotton-raising and cotton-baling went on—never so great before as that in that same year—the two parts of the nation looked equally to the one border plateau lying between them, to several counties of Kentucky, for most of the nation's hemp.

It was in those days of the North that the CONSTITUTION was rigged with Russian hemp on one side, with American hemp on the other, for a patriotic test of the superiority of home-grown, home-prepared fibre; and thanks to the latter, before those days ended with the outbreak of the Civil War, the country had become second to Great Britain alone in her ocean craft, and but little behind that mistress of the seas. So that in response to this double demand for hemp on the American ship and hemp on the southern plantation, at the close of that period of national history on land and sea, from those few counties of Kentucky, in the year 1859, were taken well-nigh forty thousand tons of the well-cleaned bast.

"Let these men be the strongest."

What history it wrought in those years, directly for the republic, indirectly for the world! What ineffaceable marks it left on Kentucky itself, land, land-owners! To make way for it, a forest the like of which no human eye will ever see again was felled; and with the forest went its pastures, its waters. The roads of Kentucky, those long limestone turnpikes connecting the towns and villages with the farms—they were early made necessary by the hauling of the hemp. For the sake of it slaves were perpetually being trained, hired, bartered; lands perpetually rented and sold; fortunes made or lost. The advancing price of farms, the westward movement of poor families and consequent dispersion of the Kentuckians over cheaper territory, whither they carried the same passion for the cultivation of the same plant,—thus making Missouri the second hemp-producing state in the Union,—the regulation of the hours in the Kentucky cabin, in the house, at the rope-walk, in the factory,—what phase of life went unaffected by the pursuit and fascination of it. Thought, care, hope of the farmer oftentimes throughout the entire year!



"Then the fields are as the camp of an army."