

Summary - Medical Cannabis and Mitochondrial Disease

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Metabolic, Mitochondrial and Inherited Disorders

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“The following information is not meant to be recommendations or a substitute for professional advice and services rendered by qualified doctors, lawyers, allied medical personnel, and other professional services. The responsibility for any use of the information, or for proper medical treatment or legal advice, rests with the you.” (quoted from slide 3).

Sebastien Cotte is both a parent and avid patient advocate, working with Dr. Kendall on this topic. Mr. Cotte and Dr. Kendall have co-authored several blogs about cannabis, both posted on Facebook and on Dr. Kendall's website. Cotte has been instrumental in getting the medical cannabis laws passed in Georgia and recommends the following Facebook groups for ongoing information about laws and regulations regarding

Cannabis as well as additional support:

- [Pediatric Cannabis Therapy](#)
- [CBD 4 Children with Epilepsy](#) (also open to adults)

Historical Perspective (slide 4)

- Historical references to marijuana date back to the Chinese in 1500 BC. Ancient references indicate that the substance was also widely used by the Egyptians and Greeks during antiquity.
- Documents dating to the early 1600's provide evidence that marijuana was brought to North America by the Jamestown settlers.
- The continued use of cannabis led to the addition of marijuana to the US pharmacopeia in 1850 and the passage of a marijuana tax act in 1937.
- Subsequent legislation including both the Boggs Act of 1952 and Narcotics Control Act of 1956 lead to the criminalization of marijuana possession due to concerns about the psychoactive component of marijuana, thus removing it from the US pharmacopeia.
- Identification of this psychoactive component, specifically: Delta-9 tetrahydrocannabinoid, or THC, occurred in the mid 1960s. Twenty-five years later, receptors (CB1 and CB2) that bind with THC were discovered, reopening the door for marijuana to be used for medicinal therapy.
- California became the first state to legalize medicinal marijuana (1996).
- Colorado became the first state to legalize its recreational and medical use (2012).

- Haleigh's Hope Act was signed into law by Governor Nathan Deal in the state of Georgia, legalizing medical marijuana for use in eight diseases, including mitochondrial disease (April, 2015).

Mechanism of Action (slide 5)

- Human bodies contain two forms of receptors for cannabinoids, CB1 and CB2. Cannabinoid refers to the over 80 phytocannabinoids, found inside the cannabis plant that have certain actions within the human body. THC is the best known and more psychoactive cannabinoid. CB1 receptors are predominantly found in the central nervous system, connective tissue, gonads, glands and organs. CB2 receptors are primarily located in the immune system and its associated structures.
- Endocannabinoids are the substances our bodies make naturally to stimulate these receptors. The two most well understood of these molecules are called anandamide and 2-arachidonoylglycerol.
- **THC, THCa and CBD** are the most widely used cannabinoids for medicinal purposes.
 - THC - used medicinally as a muscle relaxant, pain reliever, appetite stimulant, and anti-emetic (reduces nausea), despite having psychoactive components.
 - THCa - A derivative of THC, Tetrahydrocannabinolic Acid, or THCa, is a non psychoactive form of THC utilized for its anti-inflammatory, antiproliferative, and antispasmodic effects.
 - CBC - (Cannabidiol) - used for seizure control, having no psychoactive properties. CBD has been linked to improved seizure control without associated psychoactive effects and has been the focus of increased efforts by the medical and patient communities to improve epilepsy management, particularly those poorly controlled by typical anticonvulsant therapy. CBC is also used for mitochondrial disorder.

CBD and Seizure Management (slide 6)

- Evaluation of the efficacy of cannabis therapy in 213 children and adults with 12 different forms of severe epilepsy, including Dravet syndrome and Lennox-Gastaut (both associated with intellectual disability and lifelong seizures), treated with a liquid form of CBD daily for 12 weeks was presented to the American Academy of Neurology (AAN).
- Among the 137 patients who completed the study, the number of seizures fell by an average of 54%. Convulsive seizures fell by 53% in the 23 participating patients with Dravet syndrome and 11 patients with Lennox-Gastaut syndrome had a 55% decline in "atonic" seizures which cause a sudden loss of muscle tone.
- Due to intolerance issues, 12 patients discontinued the cannabis citing drowsiness (21 percent), diarrhea (17 percent), fatigue (17 percent), and decreased appetite (16 percent) as the primary causes.
- Dr. Kendall shared her personal experience with management of a patient with seizures, Leigh's Disease, and progressive encephalopathy. This child had 12-15 seizures per day, despite multiple conventional seizure medications and life style modifications. This child then used a cannabis oil that contained CBD, and also THC and THCa for other purposes, including pain. His seizure activity subsequently decreased to 1-4 daily, most often with 3-4 seizures per day, a marked decrease! Other quality of life improvements were noted, such as a 60-70% reduction

in his muscle pain as documented by complete elimination of his morphine therapy for severe episodic pain. Of note, his parents do use a THC topical cream in addition to the oil for any signs of breakthrough episodic pain. This patient also experienced increased awareness, improved demeanor and eye tracking, and increased vocalizations.

Mito and Medical Cannabis (slide 7)

- Most current data on the use of cannabis in mitochondrial patients is primarily anecdotal, but cannabis appears to provide symptomatic relief with improved seizure control and pain relief in treated individuals. Some patients also report relief of gastrointestinal symptoms as well.
- In a recent German study, researchers showed that exposure to cannabis can improve mitochondrial function in rodent models. This study suggests that marijuana (or the activation of the brain's cannabinoid system) triggers the release of antioxidants, which act as a cleansing mechanism, a process known to remove damaged cells and improve the efficiency of mitochondria. This animal based study is preliminary, and results may or may not translate into humans.
- These discoveries shed new insight on how natural marijuana cannabinoids hold the capacity to literally halt brain inflammation responsible for causing cognitive decline, neural failure, and brain degeneration, offering new hope to patients with Alzheimer's disease, Parkinson's disease, Huntington's disease, premature brain aging, and more. Certainly, mitochondrial disease, particularly the subset associated with neurodegenerative symptoms, likely would benefit as well.

Dosing and Safety Information (slide 8)

- *Dosing* of cannabis is based on a given patient's weight and type of cannabinoid used and is typically administered at least several times a day. The cannabinoids most therapeutic in mitochondrial disease patients would be CBD, THC and THCa.
- *Side effects*, as reported by parental feedback, include drowsiness and fatigue, agitation and diarrhea, with similar findings reported in the study presented at the AAN. Dosing must be monitored carefully because 10% of patients on high dose THC can experience seizures.
- Cannabinoids can be administered via a number of delivery systems, depending on the product and purpose of the medication for the individual patient. Administration methods include smoking, edibles (in food), oils (olive, MCT/coconut, safflower), tinctures (alcohol and vegetable glycerin), and topicals in the form of a patch, gel, salve/cream.

General Legalities (slide 9)

- Cannabis is still a schedule 1 substance and is illegal under federal law. State specific legalities regarding marijuana are complex and varied. However, the current administration has provided amnesty from legal prosecution for patients in states with laws allowing legal medical marijuana provided the states have enacted strict regulatory measures for overseeing their programs and provided safeguards to protect children.
- Nationwide, 23 states have comprehensive medical marijuana programs.

- 13 states, including Georgia, have limited programs, which restrict the amount of THC allowed in available products and limit the mechanism of delivery to oil only. In these 13 states, patients can only acquire their medical cannabis out of state or risk prosecution under federal law.
- Although several companies are now shipping cannabis out of state, these distributors are subject to prosecution through the Drug Enforcement Agency (DEA) should the DEA elect to enforce federal law. This method of receiving cannabis may not be available long term because the DEA's position remains firm: they do not differentiate between CBD and THC and all products containing any cannabinoids are classified as schedule 1 under the Controlled Substance Act (CSA), rendering cannabis use illegal.
- The legal system surrounding the use of medicinal cannabis is very complex. Gaining understanding of both the federal and state laws from a legal professional will protect those who decide to utilize medical marijuana.

The New Georgia Law (slide 10)

- Haleigh's Hope Act (2015) consists of three parts:
 1. The law dictates participation in ongoing clinical trials utilizing Epidolex, a highly purified CBD extract in liquid formulation created by GW Pharmaceuticals, in the treatment of seizures and possibly other conditions.
 2. Allows possession of no more than 20 ounces of cannabis oil with no more than 5% THC and with at least the same amount of CBD for patients with one of 8 qualifying disorders, including cancer, amyotrophic lateral sclerosis (ALS), seizure disorders, multiple sclerosis (MS), Crohn's disease, mitochondrial disease, Parkinson's disease, and sickle cell anemia. Patients with one of these conditions can legally possess cannabis oil if they register with the Georgia Department of Public Health and carry the registration card with the cannabinoid product. In order to register, a doctor must support and sign documents attesting to the presumed benefit of cannabis use in a given patient. Cannabis oil is a schedule 1 substance which cannot be *prescribed* by a MD, but rather *merely recommended* by a treating physician who has an existing relationship with the patient. Although "existing relationship" is poorly defined in the legislation, the verbiage is meant to prevent inappropriate cannabis distribution from non-treating physicians to patients. The oil must be in a pharmaceutical container and labeled with the percentages of THC and CBD in the compounded mixture.
 3. The last component of the law legislates the creation of an in depth plan by the final day of 2015 for the development of Georgia's instate cannabis cultivation and distribution program.

CARERS Act of 2015 (slide 11)

- Clearly, the laws surrounding cannabis use are complex and vary from state to state. No unifying Federal law exists regarding medical nor recreational marijuana.
- The CARERS (Compassionate Access Research Expansion and Respect States) Act of 2015, was recently introduced in the House of Representatives (H.R. Bill 1538) in Washington DC by Rep. Steve Cohen of Tennessee.
- The bill's goals are to:
 - allow states to legalize marijuana for medical use without federal interference,

- permit interstate commerce in cannabidiol (CBD) oils,
- reschedule marijuana to schedule II which indicates that it has medicinal purposes,
- allow banks to provide checking accounts and other financial services to marijuana dispensaries,
- allow VA physicians to recommend medical marijuana to veterans, and
- eliminate barriers to medical research.
- For patients this law would allow them to legally travel with prescribed medical cannabis without fear of prosecution or imprisonment. Overall, the bill passage would ease federal and interstate regulations currently interfering with access of many patients to a potentially helpful substance.
- Patients and families in support of easier access to medical cannabis should contact their congressmen in support of **HR Bill 1538** to allow for a unifying federal law.

Procuring a Safe Cannabis Product (slide 12)

- With medical marijuana primed to be the next billion dollar business in America, this “green rush” has attracted more than its share of unscrupulous companies/people who are driven by financial gains and not by the best interest of consumers. Patients/parents/caregivers, therefore, must do their due diligence and ask questions before using any cannabis product.
1. Obtaining a legitimate vendor — know your supplier. (See Facebook blog.)
 2. Know the lab that is testing the cannabis product.
 3. Know which laboratory tests are needed to ensure a safe product. In addition, consumers need to become educated on the interpretation of those testing results.
- Potency Testing - how concentrated is the product?
 - Microbial Testing - crucial for patients with weak immune systems. The tests will show if any fungus, mold, bacteria, yeast are present in the cannabis product.
 - Residual Solvent Testing - do any residual solvents (Ethanol, Butane, Hexane, and other compounds) remain present in the product?
 - Heavy Metal Testing - if grown outdoors, does the product have residual arsenic, mercury or lead? Because of its phytoremediation properties (process whereby plants remove toxic agents from the environment), Hemp absorbs everything from the soil, including any heavy metals such as arsenic, mercury, or lead. However, if your grower uses organic soil and only grows indoors or in a greenhouse, this test is not needed.

Summary

Cannabis and various cannabinoids have medicinal effects for a broad range of clinical symptoms and disorders, including mitochondrial disease, as supported by both anecdotal reports and recent studies. The laws surrounding cannabis use are complex and vary from state to state. Ultimately, passage and implementation of federal laws regulating the production and distribution of cannabis products is needed to eliminate these issues. Since this process is in its infancy, patients and parents will need to exercise due diligence in obtaining medical cannabis.

Additional Reading

[Dr. Kendall's webpage and blog](#)

Facebook pages:

[Pediatric Cannabis Therapy](#)

[CBD 4 Children with Epilepsy \(also open to adults\)](#)

[GW Pharma clinical use of CBD for treatment of Pediatric Epilepsy](#)

[Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. Hussain S, Zhou R.](#)