#### Medical Cannabis & Mito Disease

Historical Perspectives, Mechanism of Action and Other Need to Knows



#### Fran D. Kendall, M.D.

Clinical Biochemical Genetics Metabolic, Mitochondrial & Inherited Disorders

VMP Genetics - Founder, Managing Director University of Georgia - Adjunct Assistant Professor

#### Disclaimer

Dr Kendall and VMP Genetics have no financial interest in any laboratory.

Dr Kendall is a paid consultant to Stealth BioTherapeutics,Inc.



# WARNING

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 this information, or for proper medical treatment or legal advice, rests with you.

# Historical Perspectives of Marijuana

- Antiquity references dating to Chinese in 1500 BC, Greeks and Egyptians
- Brought to North American via Jamestown settlement in early 1600's
- Addition to US Pharmacopoeia in 1854 with subsequent removal in 1942
- Cannabis was widely prescribed by physicians from the mid-1800's until 1937, when medical cannabis use was burdened with severe taxation by the Federal Marijuana Tax Act of 1937.
- The first medical conference on cannabis was held in 1860 by the Ohio State Medical Society. By 1900, more than 100 scientific articles had been published in the US and Europe.



# Historical Perspectives of Marijuana

- Criminalization with Boggs Act in 1952 (first offense conviction carried a minimum sentence of 2-10 yrs and a fine up to \$20,000).
- Narcotics Control Act of 1956
- Controlled Substance Act of 1970 formalized the criminalization of marijuana possession or use, regardless of quantity or context and classified it, along with heroin, as a Schedule I substance, deeming it highly addictive and devoid of medical value or safety.
- Identification of psycho-active ingredient of Cannabis, Delta-9 tetrahydrocannabinoid or THC in mid 1960's
- Legalization of medical marijuana in California in 1996
- Colorado legalizes both medical and recreational use of marijuana in 2012
- Legalization of medical marijuana in Georgia on April 16, 2015 for use in 8 diseases, including *mitochondrial disease*.

# **General Legalities**

- Cannabis is still a schedule I substance
- 10 states where cannabis is legal for recreational use- AK, CA, CO, MA, ME, MI, NV, OR, VT, WA, & Washington DC
- 4 states have no state cannabis program; cannabis remains banned- ID, KS, NE, SD
- Remaining 36 states where cannabis is legal for medical use only, some limited to CBD oil\* -AK, AL\*, AR, AZ, CT, DE, FL, GA\*, HI, IA, IL, IN\*,KY\*, LA, MD, MN, MO, MS\*,MT, NC\*, ND, NH, NJ, NM, NY, OH, OK, PA, RI, SC\*,TN\*,TX\*, UT, VA\*, WV, WI\*, WY\*
- In states with restricted programs, patients can only acquire their cannabis out of state or risk prosecution under federal law.

# CARERS Act of 2019

- There is no unifying Federal law regarding the medicinal or recreational use of marijuana.
- The CARERS (Compassionate Access Research Expansion and Respect States) Act of 2019 was introduced into the House of Representatives on February 19, 2019 (H.R. Bill 127). Two previous versions, submitted in 2015 and 2017 languished in Congress.
- The bill removes restrictions on, and creates new protections for, conduct and activities related to medical cannabis that are authorized by state law

# CARERS Act of 2019

- Eliminates regulatory controls and administrative, civil, and criminal penalties under the Controlled Substance Acto for producing, possessing, distributing, dispensing, administering, testing, recommending or delivery medical cannabis in compliance with state law.
- Establishes a new, separate registration process to facilitate medical cannabis research
- Authorizes health care providers employed by the Department of Veterans Affairs to make recommendations to veterans regarding participation in state marijuana programs

# GA's Medical Cannabis Laws HB1

- HB1 Haleigh's Hope Act, consisting of three components, was signed into law on April 16, 2015
- Allowed for possession of up to 20 ounces of cannabis oil *ONLY* with no more than 5% THC with at least the same amount of CBD for patients with one of eight qualifying conditions, including mitochondrial disease.
- It did *NOT* establish a cannabis cultivation and distribution program.

# **HB1 Qualifying Conditions**

- Cancer (end stage)
- ALS (severe or end stage)
- Seizure disorders
- Multiple sclerosis (severe or end stage)
- Crohn's disease
- Mitochondrial disease
- Parkinson's disease (severe or end stage)
- Sickle cell disease (severe or end stage)

#### Expanding Haleigh's Hope Act Part II

- SB16 passed GA legislature during 2017 session and was signed into law by Gov. Deal on May 9, 2017.
- Seven additional conditions were added to include ASD under 18, AIDS, Peripheral neuropathy, severe Tourette's syndrome, Alzheimer's disease, Epidermolysis Bullosa and hospice patients.
- Allowed reciprocity for card holders from other states with GA mandated qualifying conditions for up to 45 days.
- Eliminated the original 1 year residency requirement to register in the program.

# Georgia's Hope Act

- HB 324 passed GA legislation during the 2019 session and was signed into law by Gov Kemp on April 17, 2017.
- Set framework for instate cultivation and distribution, to include establishing 2 Class 1 licenses (100,000 sq ft cultivation space) and 4 Class 2 licenses (50,000 sq ft cultivation space) and distribution licenses to pharmacy and retail locations.
- Creates a 7 member commission to draft rules, regulations and award licenses.
- Allows the commission to purchase low THC oil from other states.
- Requires all products to have third party lab testing.

# Georgia's Low THC Oil Registry

- Overseen by the GA Department of Public Health
- Patient must have one of the 15 qualifying conditions and an existing relations with the doctor treating the condition
- Physician signature and form submission required to obtain registry card
- Detailed instructions can be found at: https://dph.Georgia.gov/low-thc-oil-faq-general-public

# Low THC Oil Registration & Maintenance Process

- Download, complete and notarize the patient form found on the DPH website
- Physician electronic submission of completed and notarized document required
- Within approximately 2 weeks the DPH will contact the patient/family and provide option of picking up the card at one of 18 state wide offices
- A picture ID and \$25.00 fee are required to obtain the card upon pick-up.
- The card expires in 2 years.
- State mandated biannual follow-up forms to be completed by the patient/family and submitted on behalf of the card holder by the signing physician

# The Georgia Experience

Haleigh's Hope Act Statistics

- 12,800 patients were registered by June 2019
- Based on review of the 2018 data the most registered conditions are:
  - Seizures
  - Cancer
  - Multiple Sclerosis
  - Crohn's disease

# Mechanism of Action of Marijuana

part 1

- Cannabinoids are the chemicals found in the cannabis plant.
- The human body contains two forms of receptors for cannabinoids: CB1, most abundant receptors in the brain, and CB2, expressed in immune cells where they play a role in regulating immune function and inflammation.
- Humans have several naturally occurring cannabinoids known as endocannibinoids to include anandamide, that stimulate these receptors.
- Over 80 cannabinoids, known as phytocannabinoids, are found in the cannabis plant, including the best known and most psychoactive, THC.

# Mechanism of Action of Marijuana

- THC, THCa and CBD are the most widely used cannabinoids for medicinal purposes.
- THC has been used medicinally as a muscle relaxant, pain reliever, appetite stimulant and anti-emetic.
- THCa is a non-pyschoactive form of THC and is used for anti inflammatory, antiproliferative and antispasmodic effects.
- CBD, or cannabidiol, is used for seizure control. It has no psychoactive properties. CBD, or cannabidiol, is used for seizure control.



### **Available Cannabis Products**

- OTC products classified as Hemp with less than 0.3% THC
- Medical Cannabis multiple products and distributors with varying percentages of any number of cannabinoids to include CBD and THC.
- FDA Approved Cannabis products
- Legal recreational or illegal "street" marijuana varies but on average the amount of THC in recreational marijuana is 20%+ with some strains having up to 34% THC. By comparison, similar products in the 1960's and 70's generally had no more than 3% to 4% THC.

#### **Medical Cannabis Products**

There are multiple distributors of medical cannabis products and examples include:

- Haleigh's Hope
- Copper Mountain

### FDA Approved Cannabinoid Meds

Dronabinol Nabilone Cannabidiol

#### Dronabinol - brand name Marinol

- An isomer (compounds with the same formula but with a different arrangement of the atoms in the molecule and different properties) of THC shown to be chemically identical to plant-derived THC
- Approved by the FDA in 1985 for the treatment of chemotherapy-induced nausea and vomiting in patients lacking adequate response to existing antiemetics
- Approved by the FDA in 1992 for anorexia and cachexia in AIDS patients
- Classified as a Schedule II substance
- It is administered in 2.5-10 mg oral capsules and 5 mg/ml oral solution.

#### Nabilone - brand name Cesamet

- THC analog that is chemically similar but not identical to THC
- Approved by the FDA in 1985 for the treatment of chemotherapy-induced refractory nausea and vomiting and used off-label for analgesia
- It is considered more potent than synthetic THC (Dronabinol)
- Classified as a Schedule II substance
- It is available in 1 mg capsules and is administered in doses of 1-2 mg BID for adults and 0.5-1 mg BID for pediatric patients

#### **Cannabidiol** - brand name Epidiolex

- Highly purified form of cannabidiol (CBD) from plant extract
- Approved by the FDA in 2018 for patients over 2 years of age with Dravet or Lennox Gastaut syndrome
- Classified as a Schedule V substance
- It is available in an oral solution of 100 mg/ml with a maximum dosing of 10 mg/kg twice daily or 20 mg/kg/day.
- There is reported dose related transaminase elevations.

# **CBD** and Seizure Management

April 2015

- Evaluation of 213 children and adults with 12 different forms of severe epilepsy including Dravel syndrome and Lennox-Gastaut treated for 12 weeks with daily CBD.
- 137 completed the study with a 54% reduction in seizure activity.
- Convulsive seizures fell by 53% in the 23 patients with Dravet syndrome.
- Atonic seizures were diminished by 55% in the 11 patients with Lennox-Gastaut.
- 12 patients discontinued the cannabis due to intolerance citing drowsiness (21%), diarrhea (17%), fatigue (17%) and decreased appetite (16%) as the primary causes.

#### **Mito Function and Cannabis**

- **FASEB Journal** article published in April 2017 determined that the bioenergetics of brain mitochondrial are impaired by THC.
- In research published in Oncotarget in July 2017, the authors suggest that THC may inhibit the progression of Parkinson's disease by promoting mitochondrial biogenesis.



#### Our Experience with Cannabis Products in Mitochondrial Disease

- 50 cards for high CBD/low THC oil are active as of March 2020.
- 100+ patients are using Hemp oil (<0.3% THC) product only



#### General Clinical Improvements with Cannabis in the Mito Population

- Marked improvement in seizure control\*
- Considerable reduction in anxiety
- Increase in focusing and mental clarity leading to improved functionality in adults and skill attainment in children
- Improvement in gut dysmotility, particularly leading to reduction in constipation
- Improvement in pain management, including symptoms of peripheral neuropathy\*\*

\* In patients on multiple anticonvulsants, THC component appears critical to allow for weaning off of the epilepsy medications.

\*\* Pain resolution is limited with Hemp products and often requires 5% or more of THC.

#### **Individual Patient Experience**

- Patient #1 with autosomal recessive POLG disease and regression, ataxia and intractable seizures weaned from 4/5 anticonvulsants with 80% reduction in seizure activity within several weeks.
- Patient #2 with ASD, seizures and language regression noted improved seizure control and "recovery" of language.
- Patient #3 with Leigh disease and seizures has shown a marked improvement in seizure control, pain relief and increased GI functionality.
- Patient #4 an adult with myopathy has shown improvement in muscle and nerve pain

#### Individual Patient Experience cont.

- Patient #5 with ASD and seizures has been seizure free since introduction of cannabis
- Patient #6 with global delays began speaking
- Patient #7 with ASD has shown a decrease in stimming behaviors
- Patient #8 with DD, hyptonia has shown a marked improvement in debilitating anxiety
- Patient #9 with ASD, seizures and hypotonia has shown marked reduction in behavioral outbursts and increased socialization.

#### Relationship of Opioid Analgesic Overdose to Use of Medical Cannabis

JAMA Internal Medicine 2014;174(10):1668-1673 1999-2010

- Three states had medical cannabis laws effective prior to 1999 (CA, OR, WA) and 10 states (AK, CO, HI, ME, MI, MT, NV, NM RI and VT) enacted medical cannabis laws between 1999 and 2010.
- Study premise Opioid analgesic overdose mortality in the US is rising, driven by increases in the use of these medications for chronic pain. The use of medical cannabis for chronic pain may change overdose mortality related to opioid analgesic overdose mortality.
- Findings Analyzing death certificate data compiled by the CDC, states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared to states without similar laws. In addition, the data shows that the reduction in mortality per state increases every year after passage of the medical cannabis law typically reaching 34% after 5 years of legalization.

### **Dosing and Safety Information**

- Dosing of cannabis is based on patient weight and type of cannabinoid to be used.
- Cannabinoids are typically administered several times per day.
- Drowsiness, fatigue, agitation and diarrhea are the most common side effects although 10% of patients on high dose THC can experience seizures.
- Cannabinoids can be administered by smoking or using edibles, oils, tinctures and topicals in the form of a patch, gel or salve/cream.

#### **Procuring a Safe Cannabis Product**

- Find a legitimate vendor
- Know the lab that is testing the cannabis product
- Know which laboratory tests are needed to ensure a safe product



# **Product Testing**

- Potency testing how concentrated is the product?
- Microbial testing is there fungus, mold, bacteria or yeast in your product?
- Residual solvent testing does any ethanol, butane or hexane remain in your cannabis?
- Heavy metal testing if grown outdoors does your cannabis product have residual arsenic, mercury or lead in it?

#### Thank You!



Fran D. Kendall, M.D. www.vmpgenetics.com info@vmpgenetics.com

404.793.7800 voice | 866.744.5665 fax