



# Medical Marijuana and Epilepsy

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# Objectives

- Why is understanding medical marijuana important for an epileptologist/neurologist?
- What is the science behind medical marijuana and its effects in epilepsy?
- What is the future of cannabidiol in epilepsy?

# Denver Health: An Integrated Safety Net Health Care Delivery System

- Acute care, Level I Trauma Center, Paramedic Division, Family Health Clinics, School Based Clinics, Specialty Care Clinics, Public Health Department, Poison Control Center, 24 hour Nurseline, Alcohol Detoxification Facility
- Provides health care for 1:3 adults and 2:5 children in Denver County (pop. 650K)
- Provides health care for special populations: *poor, uninsured, undocumented*, mentally ill, *incarcerated*, persons addicted to alcohol and other substances, homeless, and patients with HIV/AIDs.



# A County Hospital Comprehensive Epilepsy Program (2007 to present)

- 1000 unique adult epilepsy patient visits annually
- 4 bed Epilepsy Monitoring Unit
- 1 Adult Epileptologist, 1 Pediatric Epileptologist
- 5 EEG Technologists
- 80-120 adult EMU evaluations annually
- 40-50 pediatric EMU evaluations annually
- 15+ VNS implants annually
- 10 epilepsy surgeries annually
- Clinical trial pathway
- Treatment for Non-Epileptic Seizures
- Epilepsy Patient Support Group
- +1 Adult Epileptologist in August 2014!!!

# Why is understanding medical marijuana important?





## Colorado Department of Public Health and Environment

Center for Health and Environmental  
Information and Statistics



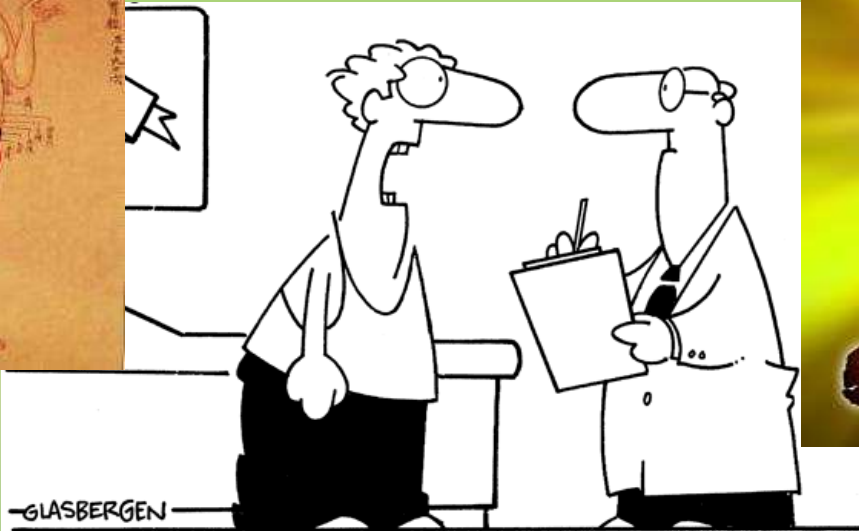
In the November 2000 general election, Coloradans passed Amendment 20, and the Colorado Department of Public Health and Environment (CDPHE) was tasked with implementing and administering the Medical Marijuana Registry program. In March of 2001, the State of Colorado Board of Health approved the Rules and Regulations pertaining to the administration of the program, and **on June 1, 2001, the Registry began accepting and processing applications for registry identification cards.**

Statistics of the registry include:

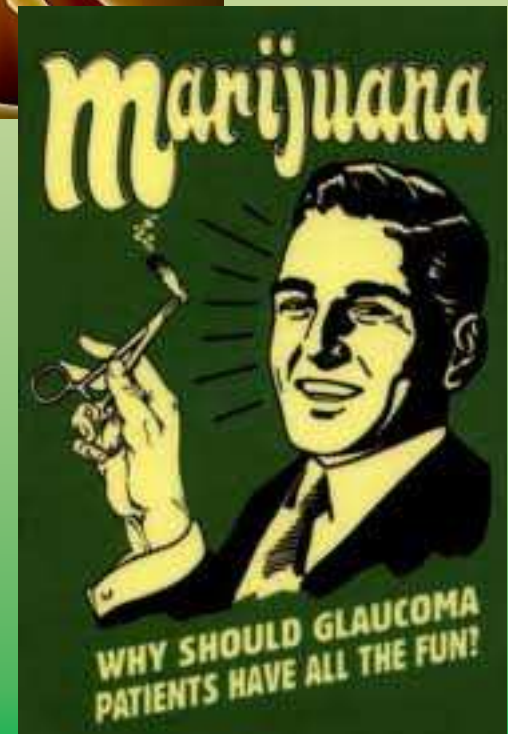
- **247,905** new patient applications have been received to date since the registry began operating in June 2001.
- Sixty-seven percent of approved applicants are male.
- The average age of all patients is 41. Currently **215 patients are minors** (under the age of 18).
- Patients on the registry represent all the debilitating conditions covered under Amendment 20. Severe pain accounts for 94 percent of all reported conditions; muscle spasms account for the second-most reported condition at 13 percent. Note that percentages do not add up to 100 percent because some patients have more than one condition.
- More than 800 different physicians have signed for current patients in Colorado.



# Complementary/Alternative Medicine



**"I'm learning how to relax, doctor —  
but I want to relax better and faster!  
I want to be on the cutting edge of relaxation!"**





# Survey

## Complementary and Alternative Medicine (CAM) for the Treatment of Seizures and Epilepsy Questionnaire

1) Age \_\_\_\_\_

2) Male/Female

3) Single/Married-Civil Union/Separated/Divorced/OTHER: \_\_\_\_\_

4) Ethnic Background

Caucasian	African American
Hispanic	Asian/Pacific Islander
Native American	Other

5) Education

Some high school or less	High school degree or equivalent
Trade school	Some College
College Degree	Professional Degree

6) Employment

Employed	Unemployed	Disabled	Retired	Other
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7) Income

<\$15,000
\$15,000 to \$30,000
\$30,000 to \$50,000
\$50,000 to \$75,000
\$75,000 to \$100,000
>\$100,000

8) Seizure Diagnoses if Known (check all that apply)

Complex Partial Seizures	Generalized Tonic Clonic Seizures
Primary Generalized Epilepsies (Absence, JME, PGTC, etc...)	Non Epileptic Seizures
Unknown	

9) Seizure Frequency per Month

Seizure Free	< 1
1 to 5	6 to 10
11 to 15	>16

10) Number of AEDs Currently Taking (VNS counts as 1 medication)

None	1
2	3
4	>4

1) CAM Use (please check impact on sz frequency and write in side effects for all that apply)

CAM	Reduces Sz Frequency	Unsure	No Benefit in Sz Reduction	Side effects
Acupuncture				
Aromatherapy				
Black Cohosh				
Chiropractic				
Cranberry				
Diet (Atkins, Ketogenic, Southbeach, etc...)				
Diet Pills				
Echinacea				
Evening Primrose				
Garlic				
Ginkgo biloba				
Ginseng				
Grapeseed				
Magnet Therapy				
Marijuana (Medical, etc.)	V			
Massage Therapy				
Meditation				
Melatonin				
Prayer/Spiritual Healing				
Soy				
St. John's Wort				
Stress Management				
Therapeutic Touch				
Valerian Root				
Vitamins (Mega, etc...)				
Yoga				
OTHER:				
OTHER:				

2) How Frequently Do You Use CAM?

Less than Daily	Daily	Twice Daily	Three Times Daily	When Available	As Needed
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OTHER? Please Describe:

3) How Did You Learn About the CAM?

Your Doctor	Friend/Family	Internet/Media	OTHER:
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4) Where Do You Obtain the CAM?

Practitioner/Office	Health Food/Supply Store	Dispensary	Online	OTHER:
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5) How Much Do You Spend Per Month on the CAM?

<\$50	\$50-100	\$100-300	>\$300
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6) Have You Recommended CAM to Other Patients? Yes/No

7) Have You Notified Your Physician About Your Use of CAM? Yes/No

8) If Not:

Doesn't Come Up	Embarrassed	Afraid MD Will Not Approve	None of Their Business	OTHER:
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9) Would You Be More Likely to Use CAM if it Were Covered By Insurance? Yes/No

10) Would You Be More Likely to Use CAM if it Were Thoroughly Studied By Clinical Trials? Yes/No

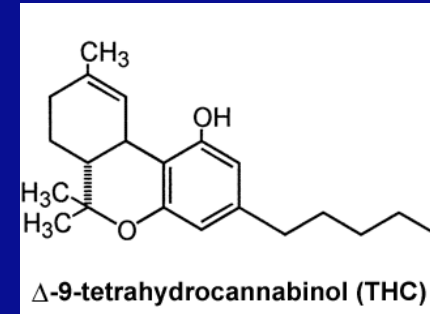
# Results of CAM Survey

- 120 of 178 unique patients responded to the survey (between 9/2011-12/2011)
- 56% men, mean age of 39.4
- 44% women, mean age of 38.7
- **CAM use was reported by 70% of our patients**
  - 1) **Marijuana-33%**
  - 2) Prayer-31%
  - 3) Meditation-19%
  - 4) Vitamins-19%
  - 5) Stress Management- 16%
- **Most Helpful for Seizure Reduction**
  - 1) Stress Management- N=19; 74%
  - 2) **Marijuana- N=39; 54%**
  - 3) Prayer-N=37; 49%
  - 4) Yoga-N=12; 42%
  - 5) Massage Therapy-N=16; 38%

# Why is understanding medical marijuana important?

- Because given enough time and availability, your patients will use it whether you ask about it or not!
- There are significant implications to concomitant medications that you must be aware in order to avoid iatrogenic complications.

# Marijuana



- *Cannabis sativa* has 489 known constituents, only 70 of which are cannabinoids with the remainder including potentially neuroactive substances such as terpenes, hydrocarbons, ketones, aldehydes, and other small hydrophobic compounds capable of crossing the blood brain barrier. (Elsohly 2005)
- $\Delta^9$ THC is the most common phytocannabinoid and is psychoactive
- CBD is the best studied of the non-psychoactive phytocannabinoids (Izzo 2009).

# Review of Sz Models

- Simple partial, acute
  - PCN, bicuculline, picrotoxin, strychnine (GABAR inh)
- Simple partial, chronic
  - Cobalt, zinc, magnesium, aluminum, iron (Na/K pump blockers), cryogenic lesions
- Complex partial
  - Kainic acid, kindling, tetanus toxin
- Generalized Tonic Clonic
  - Audiogenic, MES (Na<sup>+</sup> channel), hypoxia, O<sub>2</sub>/CO<sub>2</sub>, fever, hypoglycemia, PTZ/picro/bicuc
- Status Epilepticus
  - Pilocarpine, cobalt, recurrent shock

# What's the preclinical evidence for THC?

- Whole cannabis extract (17% THC) was anticonvulsant in MES rodents (Ghosh & Bhattacharya 1978)
- Smoked cannabis (6 mg THC) was anticonvulsant against penicillin in tracheostomized dogs (Labrecque et al. 1978)
- $\Delta^9$ THC was anticonvulsant against audiogenic seizures in mice (Boggan et al. 1973)
- $\Delta^9$ THC & CBD were anticonvulsant against MES and 6Hz electroshock, similar to PHT and PB. Ineffective against 60 Hz similar to PHT. (Karler and Turkanis 1980)
- $\Delta^9$ THC was ineffective against strychnine, nicotine, or PTZ seizures, but confirmed effective against MES (Sofia et al. 1974)



# What's the preclinical evidence for THC?

- Low dose  $\Delta^9$ THC was proconvulsant in rabbits, but coadministered with CBD, seizures stopped (Martin & Consroe 1976)
- $\Delta^9$ THC was anticonvulsant in amygdala kindled cats (Wada et al. 1975) and baboon in a follow up study later that year.
- $\Delta^9$ THC reduced photic stimulated seizures in epileptic chickens, but was ineffective against PTZ (Johnson et al. 1975).





# What's the preclinical evidence for CBD?

- CBD was anticonvulsant in MES rodent (Izquierdo et al. 1973)
- CBD was anticonvulsant in MES and amygdala kindled rats (Turkanis et al. 1979)
- CBD was ineffective against cobalt seizures (Colsanti et al, 1982)
- CBD was anticonvulsant against MES, 3-mercaptopropionic acid, picrotoxin, isonicotinic acid hydrazine, bicuculline, PTZ, but ineffective against strychnine (Consroe et al. 1982)
- CBD was anticonvulsant against PTZ, pilocarpine, and penicillin in Wistar-Kyoto rats (Jones et al. 2012).

# What is the clinical evidence?

- Mechoulam 1978
  - Randomized 9 subjects with medication resistant temporal lobe epilepsy into 2 groups
  - 4 subjects treated with CBD, 5 subjects with PBO
  - Treatment group received CBD 200 mg daily for 3 months, both groups continued AEDs
  - At 3 months, 2/4 treated subjects were sz free, 1/4 showed partial improvement, 1/4 no change
  - 0/5 PBO subjects improved
  - No side effects were observed
  - Problems: baseline sz freq was not reported, groups were not compared, no definition of improvement was provided

# What is the clinical evidence?

- Cunha 1980
  - Randomized 15 subjects with EEG documented epilepsy with baseline freq of 1 GTC per week into 2 groups
  - 7 subjects CBD, 8 subjects PBO (1 control crossed over to treatment)
  - Baseline freq established for 2 weeks
  - Treatment group received 200-300 mg CBD daily for 3-18 weeks
  - 4/8 treatment patients were sz free, at end of study
  - 1/7 PBO was sz free, at end of study
  - Problems: baseline characteristics were not compared, investigators were not blinded, escalation of dose from 200 to 300 mg may have unblinded subjects

# What is the clinical evidence?

- Ames 1985
  - 12 Non-randomized, developmentally delayed subjects were divided into 2 groups, and separated into different treatment wards
  - Treatment group received 300 mg CBD daily for week 1, then 200 mg daily for next 3 weeks; vs. PBO
  - No differences were observed; no immediate side effects except mild drowsiness was reported
  - Problems: this was a letter to the editor

# What is the clinical evidence?

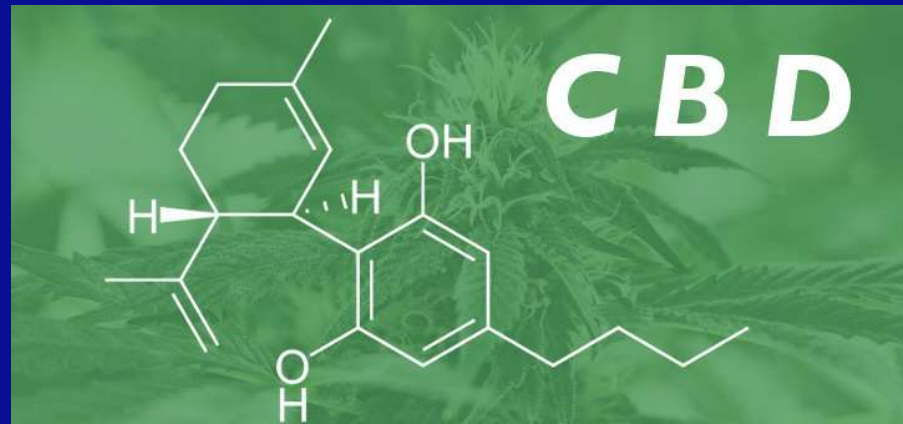
- Trembly 1990
  - 10 or 12 patients in a randomized crossover trial
  - 3 month baseline, 6 months of PBO, followed by randomization to PBO vs CBD 100 mg tid for another 6 months, then crossover for another 6 months, followed by 3 month washout.
  - “no discernable effect” but no analysis was provided

# Pharmacology of CBD

- Routes of Administration:
  - Inhaled (31% bioavailability)
  - Oral (6% bioavailable, not water soluble/erratic)
  - Sublingual (6% bioavailable, less variability than oral)
- Distribution:
  - Highly lipophilic
  - Highly protein bound (10% bound to RBC)

# Pharmacology of CBD

- Metabolism
  - Hydroxylation in liver by CYP3A2/4, CYP2C8/9/19
  - Excreted in feces
  - $T_{1/2}$  18-32 hours
  - Clearance 960-1560 ml/min





# Pharmacology of CBD

- Safety Data
  - No psychoactive properties
  - Few adverse effects in oral doses up to 1500 mg/day and up to 30 mg IV
  - No effects on BP/pulse/RR
  - No negative mood effects
  - No psychomotor slowing
  - *No long term use or teratogenicity data*
  - *Possible immunosuppression (inhibits IL8 & IL10 in vitro)*

Bergamaschi et al. 2011

# Pharmacology of CBD

- Drug-Drug Interactions:
  - Other CYP3A4 metabolized drugs: warfarin, chemotherapy, benzodiazepines, CCB, SSRIs
  - Induction of CYP2B family: valproate, clobazam
  - Inhibition of P-glycoprotein (affects other drug absorption and BBB penetration by AEDs)
  - Drugs affecting CBD metabolism:
    - CYP3A4 inducers (CBZ, PHT)
    - CYP3A4 inhibitors (ketoconazole)

# Charlotte's Web

“Charlotte Figi’s Story Brings Families to Colorado for Her Medical Marijuana Strain”



“Marijuana stops child’s severe seizures”



“How pot helped Charlotte Figi, 5, with her seizures and inspired ‘Charlotte’s Web’”

# Case Report: Charlotte Figi

- Sz onset at 3 m/o, presenting in SE
- Continued having febrile and afebrile SE
- Sz types: tonic, GTC, myoclonic
- Sz freq: 30-50 GTC/day; myoclonic sz uncountable
- Failed meds: LEV, OXC, TPM, ZNM, VPA, CBL, CZP/DZP
- Failed ketogenic diet x2
- Dravet Syndrome confirmed: SCN1A gene mutation
  - DNA variant I: transition C>T
  - nucleotide position 2791
  - codon 931
  - amino acid change: Arginine>Cysteine
  - variant type: disease associated mutation
- Losing milestones: motor delay -> non-ambulatory, feeding tube, verbal regression, full assist with ADLs

# Case Report: Charlotte Figi

- Started “Hippie’s Disappointment” (CBD:THC > 20:1) at 0.5 mg/lb/day
- First week 0 sz noted (first time since 3 m/o)
- Escalated every 2 weeks by 0.5 mg/lb/day
- By end of first month, had weaned CBL off and had only had 3 GTC the entire month.
- Reached a steady state of 4 mg CBD/lb/day
- Have tried weans 3 times, but each time CBD tapered to 2 mg/lb/day, her seizures return
- Currently: having 2-3 nocturnal GTC per month, feeding and drinking independently, improved autistic behaviors and improved communication

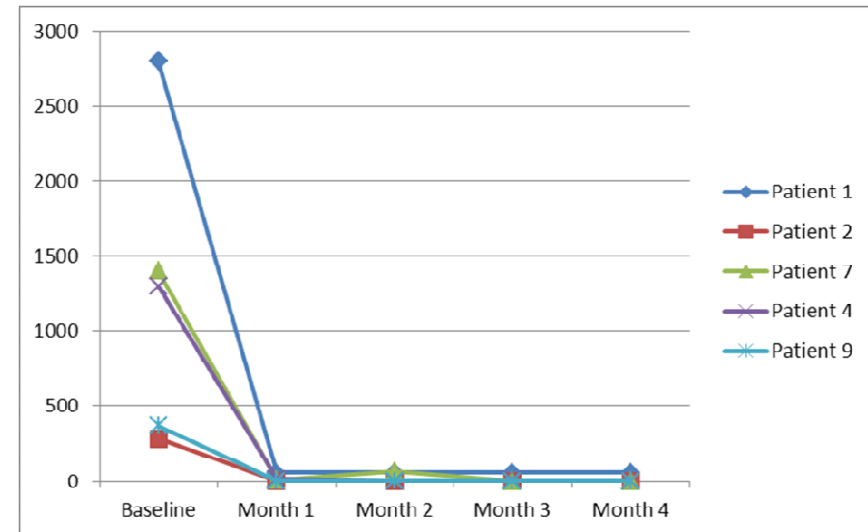
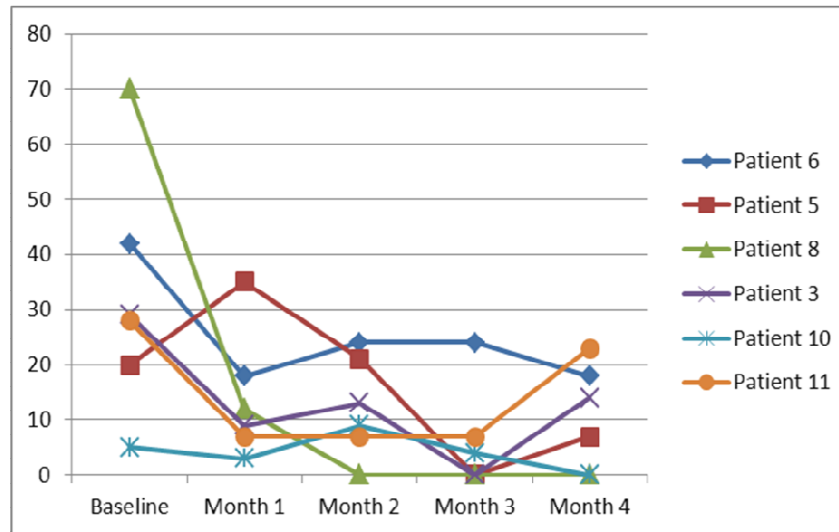
## Whole Cannabis Extract of High Concentration Cannabidiol May Calm Seizures in Highly Refractory Pediatric Epilepsies

- A botanical extract from a strain of cannabis known as Charlotte's Web (CW Realm Oil) is newly available in Colorado for medical use
- Parents who had at least 3 months of experience treating their child's epilepsy with CW were invited to participate in reporting the effects of Realm Oil
- In October 2013, there were 40 children receiving Realm Oil for epilepsy, but only 13 had 3 months or more of experience. 11 of the 13 responded to this survey
- The following results can be considered a ***treatment responder cohort***.



# Combined Seizure Type Frequency per Month of Treatment

(GTC, Myoclonic, Clonic, Tonic, Astatic)



Age	Sex	Epilepsy Diagnosis	Current AEDs	# AED Tried	KD	VNS	Surgery	Baseline Seizure Frequency/Wk	Rescue Meds in prior month	ED visits in prior month
3	F	idiopathic	Clobazam	14	Y	N	N	2800	30	0
22	M	LGS	PB, LEV, TPM	13	Y	N	N	280	30	0
8	M	Doose	LEV, FBM	12	Y	N	N	29	12	1
5	F	Dravet	Clobazam	12	Y	N	N	1300	1	2
13	M	Dravet	PB, VPA, CLB, STP	11	Y	N	Y	20	47	1
3	F	CMD	VPA, VGB	7	Y	N	N	42	0	0
9	M	Doose	ESX, LZP	17	Y	N	N	1400	0	0
3	M	idiopathic	CZP	9	Y	N	N	70	0	0
12	M	MCL	LEV	1	Y	N	N	368	0	0
8	M	Doose	VPA, LTG, FBM	6	Y	Y	N	5	28	0
8	M	Doose	VPA, CLB	12	Y	Y	N	28	0	1





# Epidiolex

- GW Pharma, pharmaceutical grade CBD extract
- Received Orphan Drug status in Dravet and LGS, November 2013
- INDs treating 125 children (NYU, UCSF, MGH, Northwestern, CHoP), currently enrolling
- Expanded INDs are available for case-by-case review: Dr. Eltayb  
([medicaldirector@gwpharm.com](mailto:medicaldirector@gwpharm.com))

# The Future of CBD

- CW versus GW
- EFA versus DEA (remain Schedule 1????)
- Observational studies:
  - EEG pre/post data collection
  - Genetic analysis of CBD responders vs non-responders
  - Epidemiologic studies

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