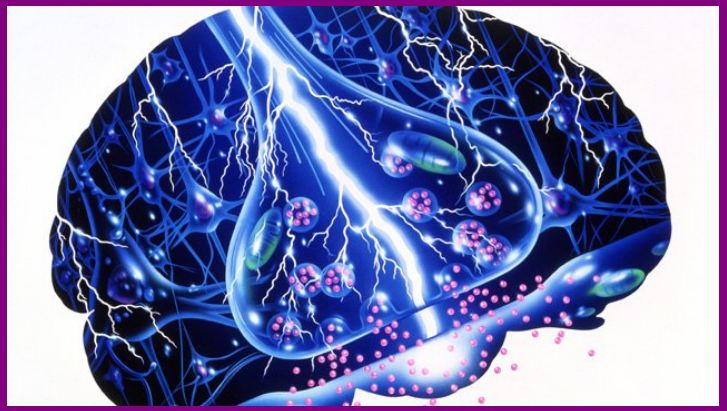
Clinical Experience with Cannabis in Treatment-Resistant Pediatric Epilepsy

Margaret M. Gedde, MD, PhD
Gedde Whole Health, LLC
Marijuana for Medical Professionals Conference
September 9-11, 2014

Treatment-Resistant Epilepsy

- Seizures are episodes of synchronized, excessive electrical activity in the brain.
- Seizures are disabling when they occur, plus they cause direct damage to neural tissues.
- A primary aim of treatment is to completely control seizures.



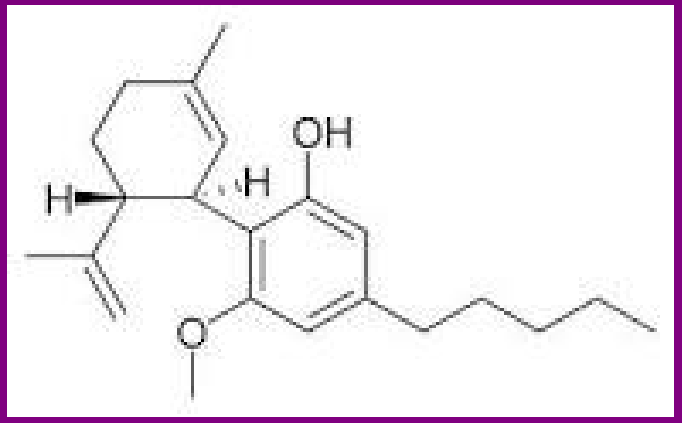
Seizures are not controlled in about 30% of patients, even with the best current therapies.

Best Available Treatments Are Often Damaging While Being Partially Effective

- Anti-epileptic drugs (AEDs) frequently have significant adverse physical, behavioral and cognitive side effects.
- Surgeries can be highly invasive and disabling, with mixed effect on seizures.
- Side effects of treatments add to the short and long term damaging effects of the seizures.
- Patients with treatment-resistant seizures are at risk of sudden unexpected death, termed SUDEP (sudden unexpected death in epilepsy).

What About Cannabis?

- Cannabinoids have been used to control seizures for centuries.
- Both THC & CBD have been reported to reduce seizures (anecdotally, and in laboratory & animal studies).
- Seizures qualify a patient to receive medical marijuana in Colorado.



Cannabidiol (CBD):

- Has a positive record controlling seizures in laboratory and animal studies.
- Has no psychoactive effect.
- May protect neural tissues against damage during seizures.

Doctors & Federal Law: Talk, but Don't Treat

- Physicians have the right to counsel patients – to recommend marijuana – and patients have the right to receive that counsel.

  "The government is permanently enjoined from: (i) revoking any physician class member's DEA registration merely because the doctor makes a recommendation for the use of medical marijuana based on a sincere medical judgment and (ii) from initiating any investigation solely on that ground."

  Conant v Walters, CV-97-00139-WHA, 2002, United States Court of Appeals for the Ninth Circuit.

- Physicians cannot prescribe or dispense marijuana without putting their DEA registration at risk.
  - Physicians can advise, but not treat: we are forbidden to dispense.
  - Physicians do not have control over what marijuana patients use.
  - Physicians do not know what their patients are using without exerting proactive efforts to learn this from them.

But Should Medical Marijuana Be Recommended for Children?

Options for treatment of pediatric treatment-resistant epilepsy:

Treatment Option	Efficacy	Adverse Effects	Beneficial Effects	Risks
No Treatment	Seizures are uncontrolled	Ongoing damage from seizures	None known	Ongoing brain damage, sudden death
Currently Available Medications	Partial to poor control	Sedation, mood and behavior problems, organ damage, suppressed development	None known	Known & unknown toxicity
Cannabinoids	Potential; unknown	Minor	May protect against damage from seizures	Unknown; apparently minor

Ethical Position

- “If a patient and their healthcare professionals feel that the potential benefits of medical marijuana for uncontrolled epilepsy outweigh the risks, then families need to have that option…”
- Epilepsy Foundation, Thursday, February 20, 2014.

Our Medical Marijuana Clinics Are in Two Locations

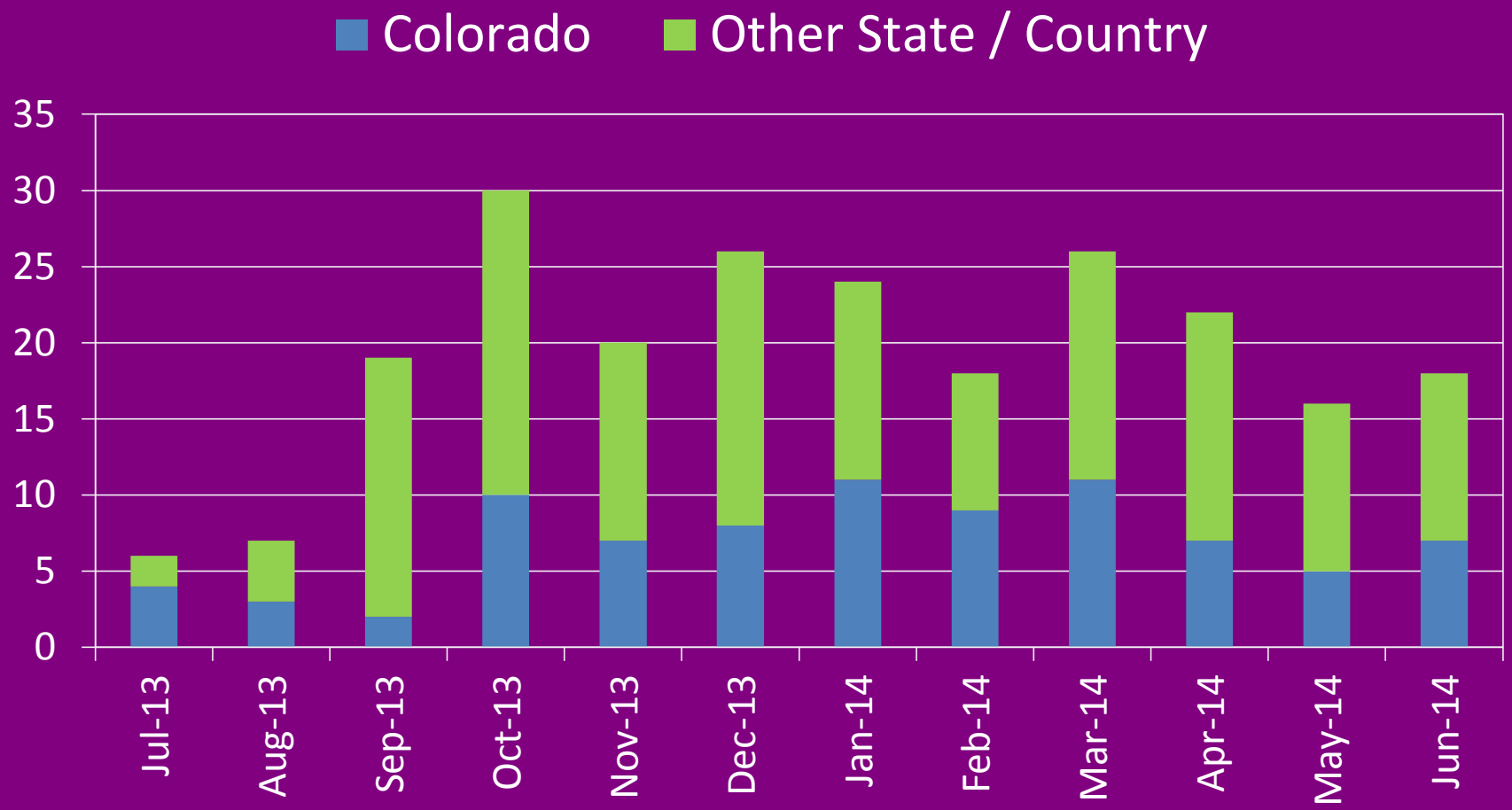
Colorado Springs, CO

and

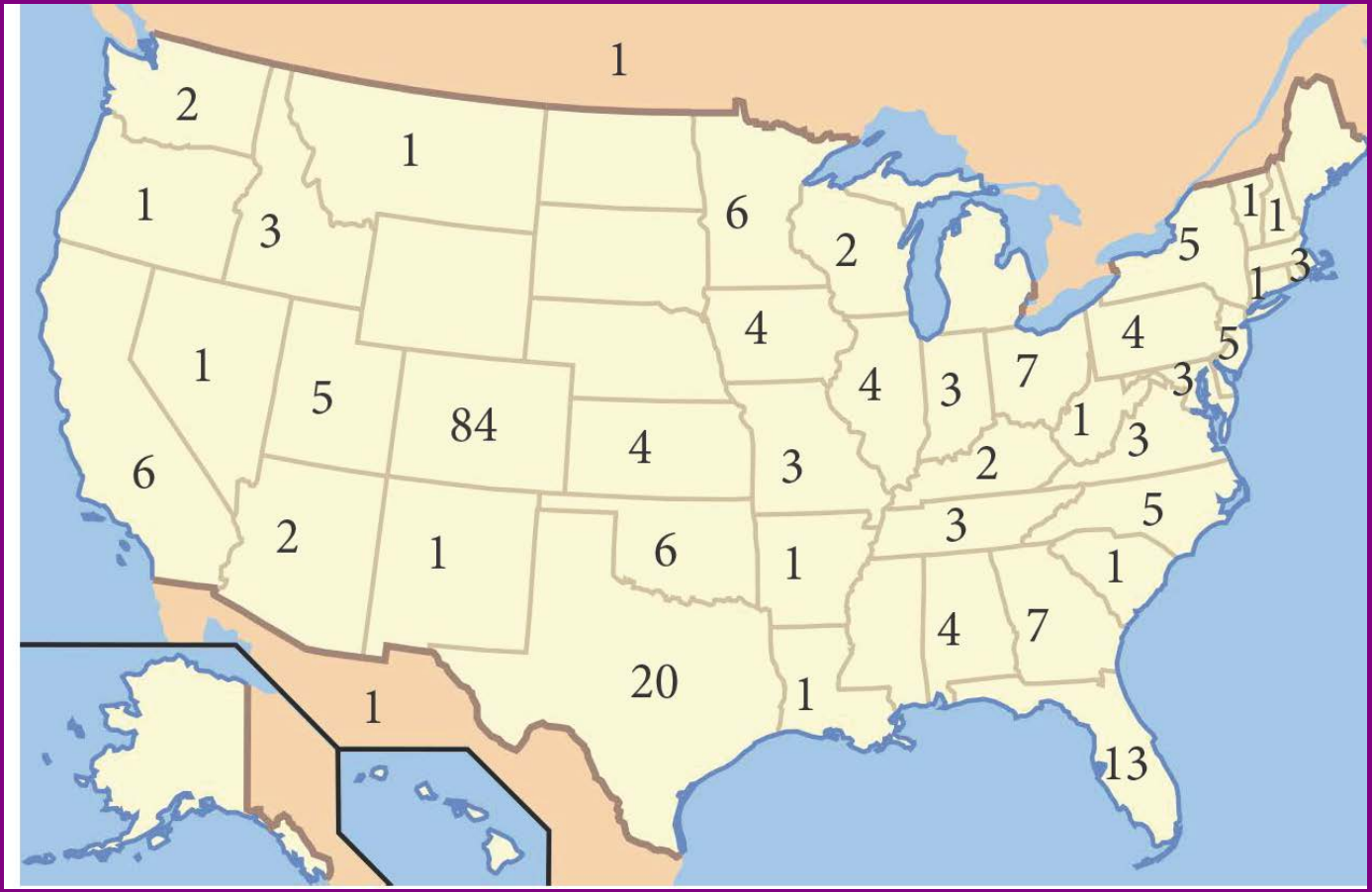
Gedde Whole Health Clinic
Buena Vista, CO

- First pediatric seizure patient seen in February, 2012.
- A high level of interest in high CBD, low THC cannabis oil to treat seizures continues.
- Because high CBD oil has been in short supply, parents have tried several other cannabis-based approaches also.
- We counsel about and provide ongoing follow up on any cannabis therapy parents obtain, to help optimize effectiveness of seizure control.

Pediatric Epilepsy Patients Seen from In & Out of State, by Month



Patients Came from 40 US States & 2 Other Countries



Issues in Clinical Cannabis Practice

- Doctors cannot dispense. Patients & families must locate and acquire appropriate products.
- Doctors don't prescribe. We can recommend, but have no control over what patients use.
- Doctors rely on patient reports to know what and how much they are using.
- Optimal doses are little known or unknown.
- Optimal dosing schedules are unknown.

How the Clinical Process Works

- Baseline data collection, counseling and goal setting are done at the first clinic visit.
- We counsel parents about appropriate cannabis products and known sources.
- Parents independently source cannabis products.
- On follow up, we query parents in detail about the composition & potency of their products.
- Dose and composition are adjusted to maximize benefit for that child.
- Parents continue to consult with their pediatrician and neurologist, especially regarding changes in prescribed anti-epileptic drugs.

Advantages of Working with Pediatric Seizure Populations

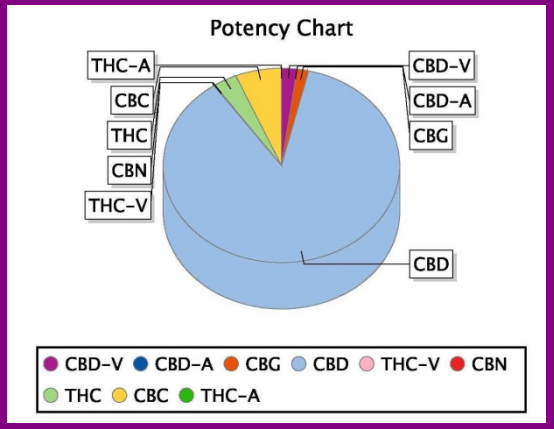
- Parents are highly motivated to improve their children's' prospects.
- Parents often have extensive support via online & other groups, and can bring insights & suggestions to clinical visits.
- Parents may have support in acquiring appropriate cannabis products and getting them lab tested.

Some High Ratio CBD:THC Products Used by Pediatric Patients

- Locally Grown Strains
  - Charlotte's Web
  - Haleigh's Hope
  - R4
  - Ballantine
  - Unknown
- Typically, cannabis concentrate extracted by a CO2 or ethanol method was infused into an edible oil base (as reported by the manufacturer).
- Imported Hemp Tincture
  - Bluebird Botanicals
  - Cibdex
  - Dixie Dew Drops
- Typically, imported hemp concentrate was infused into vegetable glycerin (as reported by the manufacturer).
- CBD Transdermal Patches & Gels - Mary's Medicinals
- High Ratio = about 15-35:1 CBD:THC

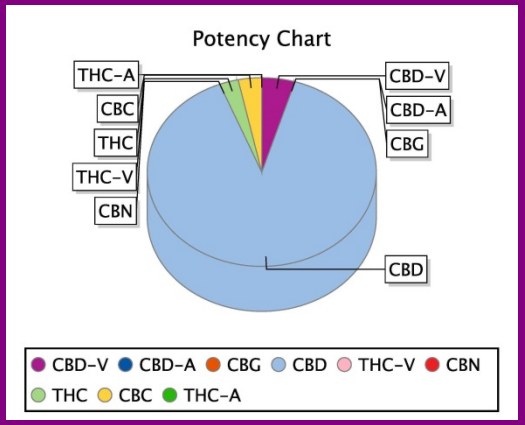
Composition of High Ratio CBD:THC Products

Locally Grown Strain Example 1



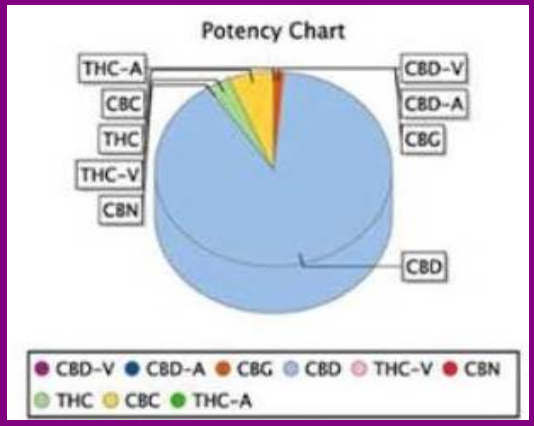
Max CBD: Max THC 27:1

Imported Hemp Example



Max CBD: Max THC 33:1

Locally Grown Strain Example 2

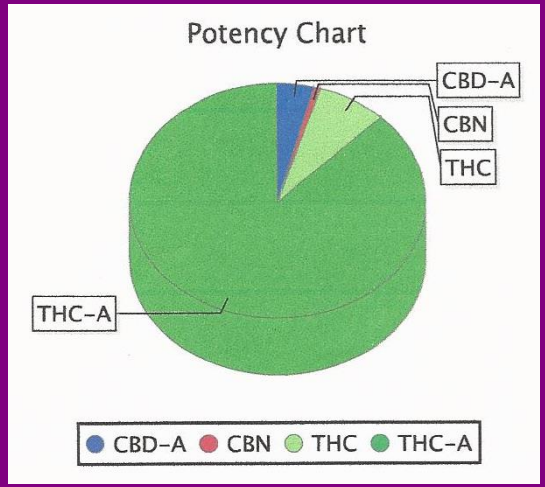


Max CBD: Max THC 29:1

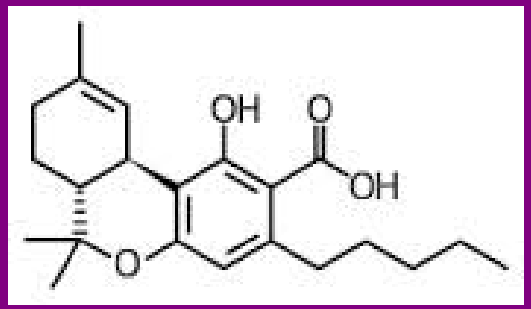
Composition of High Ratio CBD:THC strains varied batch-to-batch for the same strain, and often was similar between products.

THC-A as a CBD Alternative

- THC-A is “raw THC”:
  - Nonpsychoactive
  - Readily available
    - Predominant cannabinoid in fresh, unheated plant material of all THC strains
  - Reported anecdotally to control seizures
  - Is relatively unstable; must be carefully prepared and stored
- Used by patients in my practice since January, 2014.
- Parents report use of ingested oils and transdermal patches.



Example of THC-A oil used clinically

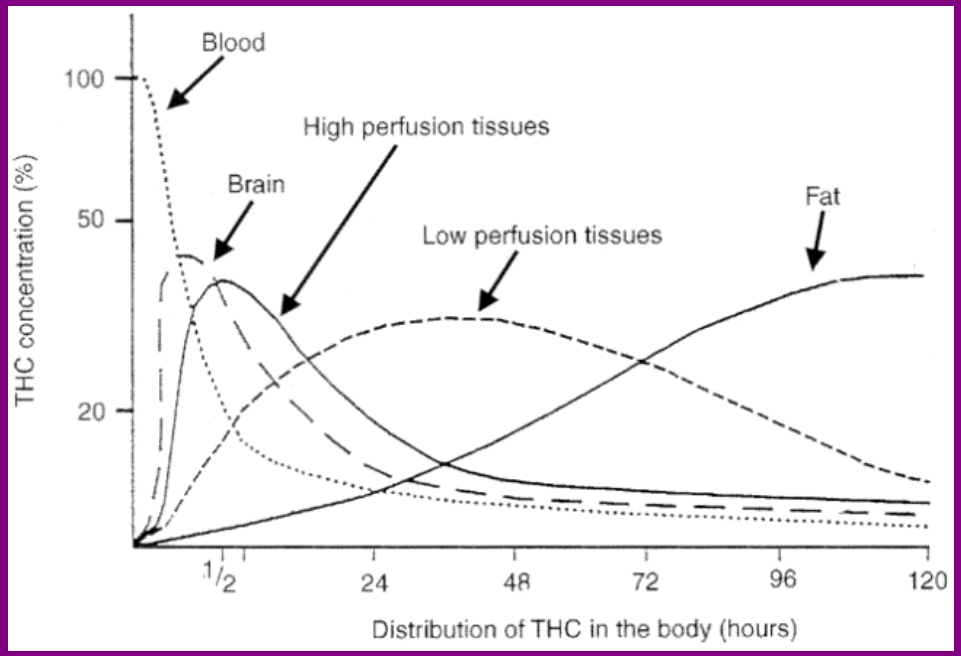


Tetrahydrocannabinolic acid

Cannabinoid Pharmacokinetics: Observed Clinical Patterns

Time to Steady State

- Cannabis distributes into multiple compartments and is slow to be eliminated.
- We advise that patients stay at a given dose level for three weeks and reassess efficacy before increasing the dose.



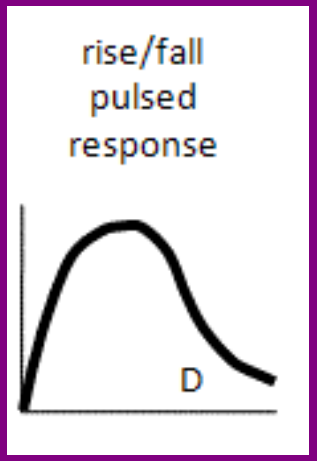
From Ashton CH. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry. 2001 Feb;178:101-6.

Less May Work Better than More

Dose-Response Curve

Clinical experience suggests cannabinoids have an bell shaped dose response curve with respect to seizure control.

1/3 of patients experienced better seizure control after reducing cannabinoid dose.



Receptor Pharmacology

- Cannabidiol binds to multiple receptors:
  - Equilibrative nucleoside transporter
  - G-protein-coupled receptor GPR55
  - Transient receptor potential vallinoidtype-I channel
  - 5-HT 1a serotonin receptor
  - Alpha-3 and alpha-1 glycine receptors
- Activation of high affinity sites at low doses, then of low affinity sites at higher doses, could underlie the clinically-observed “less is more” dynamic.

To Answer the Question "What Are You Seeing": A Retrospective Cohort Study

- Cohort consists of all patients with pediatric onset treatment-resistant epilepsy seen in clinic from February, 2012 through March, 2014.
- Of the cohort of 187 patients, 6 have been reported on previously.

- Efficacy endpoint is percent seizure reduction during treatment relative to baseline.
- Seizure reduction was assessed from the clinical chart for a time within 16 weeks of start of treatment, and for the most recent interaction.
- Concomitant medications, adverse effects, and beneficial side effects were also assessed.

- The study was investigator-funded. In particular, I have no financial relationship with any provider of cannabis.

Observational Study: Limitations & Advantages

Limitations

- No standard data collection; data based on parent report; quality of reported data highly variable
- **Relies on assessments done by one investigator & staff**
- Wide range of diagnoses included
- **Wide range of products used**
- Uncertainty about doses, product composition, quality
- **Concomitant surgeries, illnesses, medication changes**
- Some incomplete assessments or patients lost to follow up
- **Unavoidable bias on part of physician, patients/families**
- Evolving clinical approach to treatment during study period

Advantages

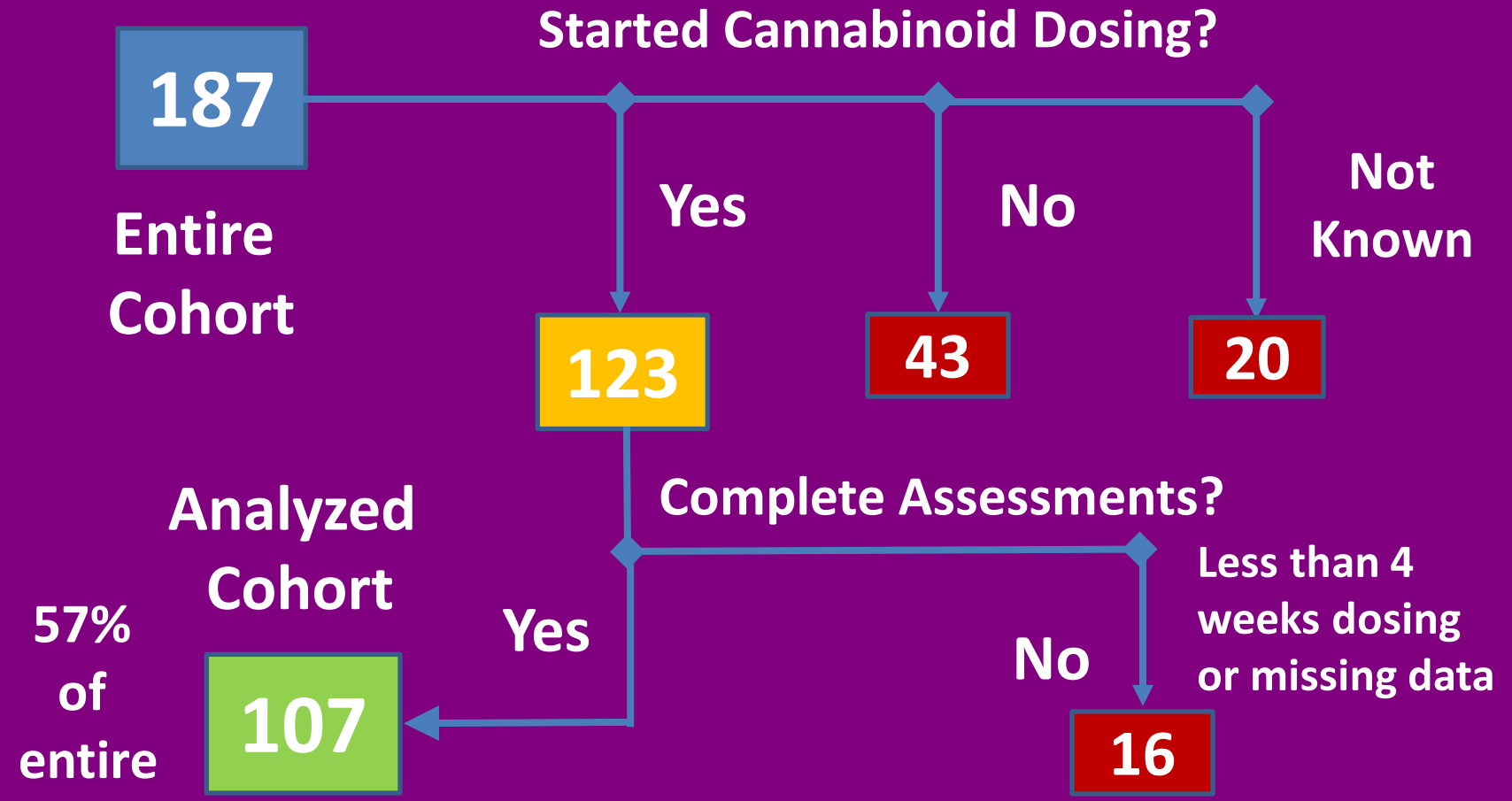
- Simple to conduct; all data originates in clinical record
- **Captures real clinical experience**
- Evolving, customized treatment plans maximize patient response
- **Shows application to broad range of diagnoses & conditions**
- Gives insight on unanticipated product combinations
- **May reveal unexpected insights**

Reports on Cannabidiol-Enriched Cannabis Use in Children with Treatment-Resistant Epilepsy

- "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy" – 2013. Parents were self-selected from among members of a Facebook pediatric cannabis therapy group. Of 19 children with treatment-resistant epilepsy using cannabidiol-enriched cannabis, parents reported:
  - 84% had some seizure reduction.
  - 74% had at least 25% reduction.
  - 42% saw > 80% reduction.
  - 11% saw 100% reduction.
- **Porter BE, Jacobson C. Epilepsy Behav. 2013 Dec;29(3):574-7.**

- "Whole cannabis extract of high concentration cannabidiol may calm seizures in highly refractory pediatric populations" – 2013. Patients who had used a high CBD ratio cannabis extract for intractable seizures were selected by the provider of the extract.
  Of 11 parents who then completed interviews with the investigator:
  - 100% had at least 20% seizure reduction.
  - 82% had at least 75% reduction.
  - 73% had at least 98% reduction.
  - 45% had 100% reduction.
- **Gedde MM, Maa E. 2013 Annual Meeting of the American Epilepsy Society.**

Cohort: Patients with Pediatric Onset Treatment-Resistant Epilepsy



Ages 6 mo. to 45 yr.; average 9.9 yr.

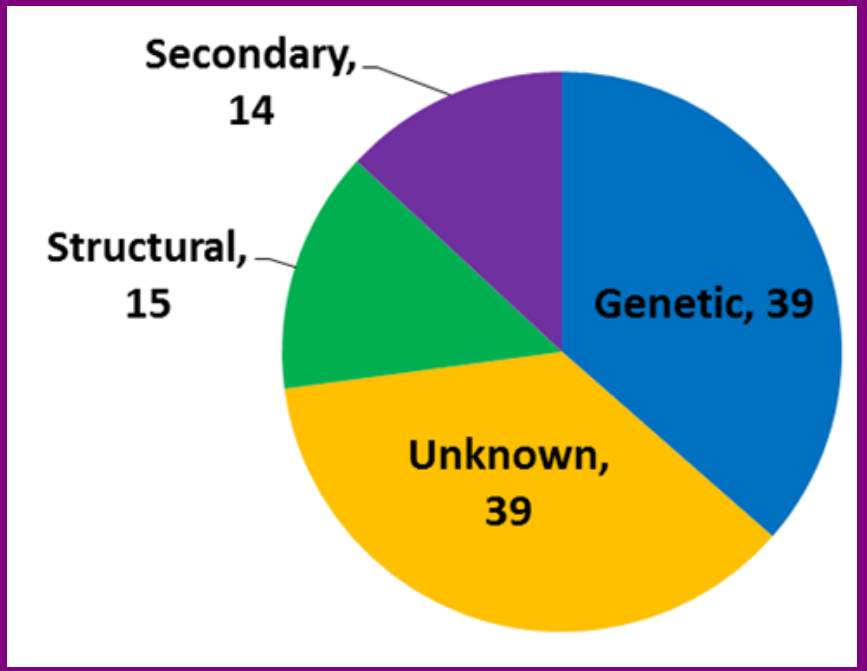
Data Collected from the Clinical Record

- Baseline / Initial Visit
  - Sex; Age at First Visit
  - Diagnosis; Etiology if known
  - Seizure Types at Baseline
  - Seizure Frequencies at Baseline (per dy, wk, mo)
  - Concomitant treatments /medications & doses
  - Issues in other areas: eating, sleeping, behavior, pain
- Follow Up Assessments
  - Cannabinoid product used & route since last visit
  - Date cannabinoid dose started or changed
  - Milligram dose per day (calculated from product information)
  - Patient weight (lb.)
  - Seizure types
  - Seizure rates since last visit
  - Changes in other treatments
  - Adverse side effects
  - Beneficial side effects

Etiologies of Epilepsy in the Analyzed Cohort

Major etiologies are represented:

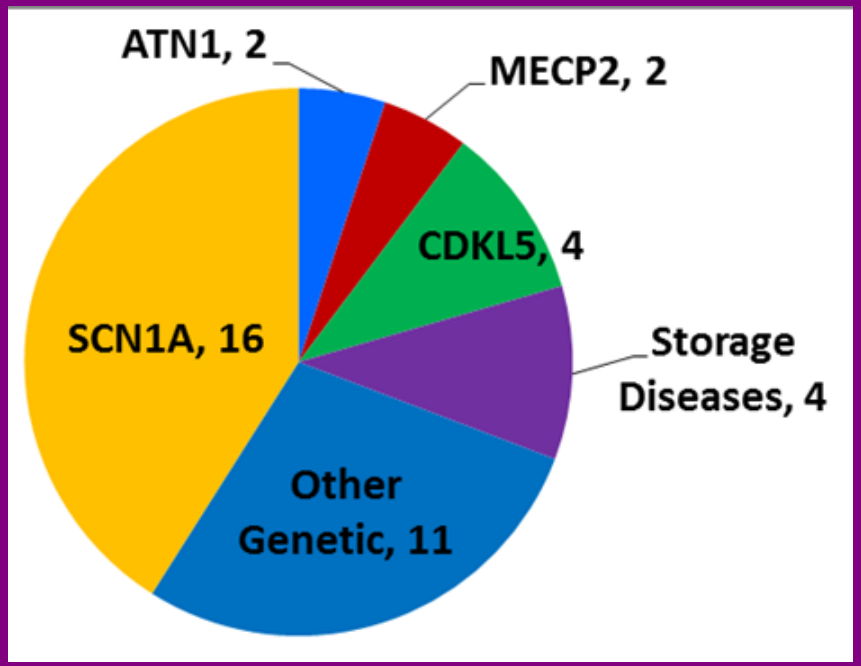
- Genetic 36%
- Structural 14%
- Secondary 13%
- Unknown 36%



Terminology follows “The Organization of the Epilepsies”, ILAE Commission for Classification and Terminology, 2010.

Genetic Etiologies in the Analyzed Cohort

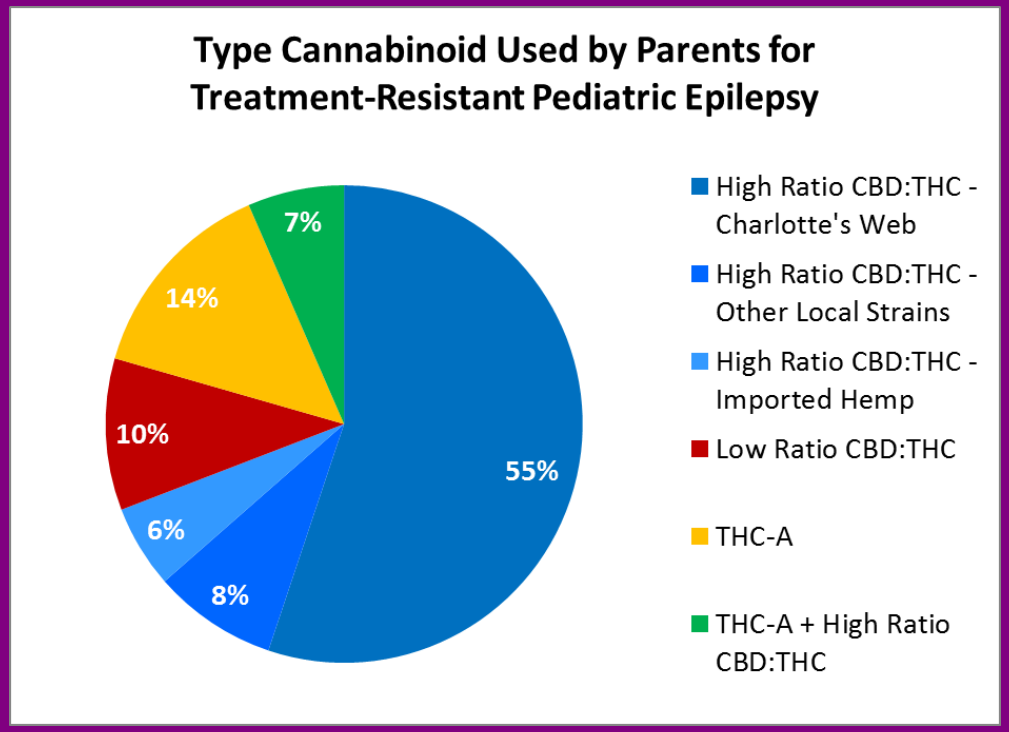
- Genes & Syndromes
  - SCN1A – Dravet Syndrome
  - CDKL5 – Atypical Rett & other syndromes
  - MECP2 – Rett Syndrome
  - ATN1 – Dentatorubral-pallidoluysian atrophy (DRPLA)



Diagnoses Represented in the Structural and Secondary Etiology Groups

- Structural Causes of Epilepsy in Cohort
  - Cortical dysplasia
  - Cortical band heterotopia
  - Microcephaly
  - Macrocephaly
  - Schizencephaly
  - Hemimegalencephaly
  - Bilateral perisylvian polymicrogyria
- Secondary Causes of Epilepsy in Cohort
  - Hypoxia
  - Trauma
  - Infection
  - Stroke
  - Toxic exposure

Several Cannabinoid Combinations Were Used by This Cohort



2/3 of patients used High Ratio CBD:THC

1/3 of patients used THC-A, Low Ratio CBD:THC, or a combination

Outcome: Efficacy Endpoint Is % Change in Seizure Frequency

- Seizure frequencies based on parental reports were extracted from the clinical record.
- Seizure number per 4 weeks was recorded for 3 points: at baseline, within 16 weeks of dosing start and at the most recent assessment.
- % change in seizure frequency was calculated for two time points relative to baseline for each patient.
- Limitation: This measure looks at seizure count only, not at length or severity of seizures.

The outcome measure was divided into 6 categories:

Worse – 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

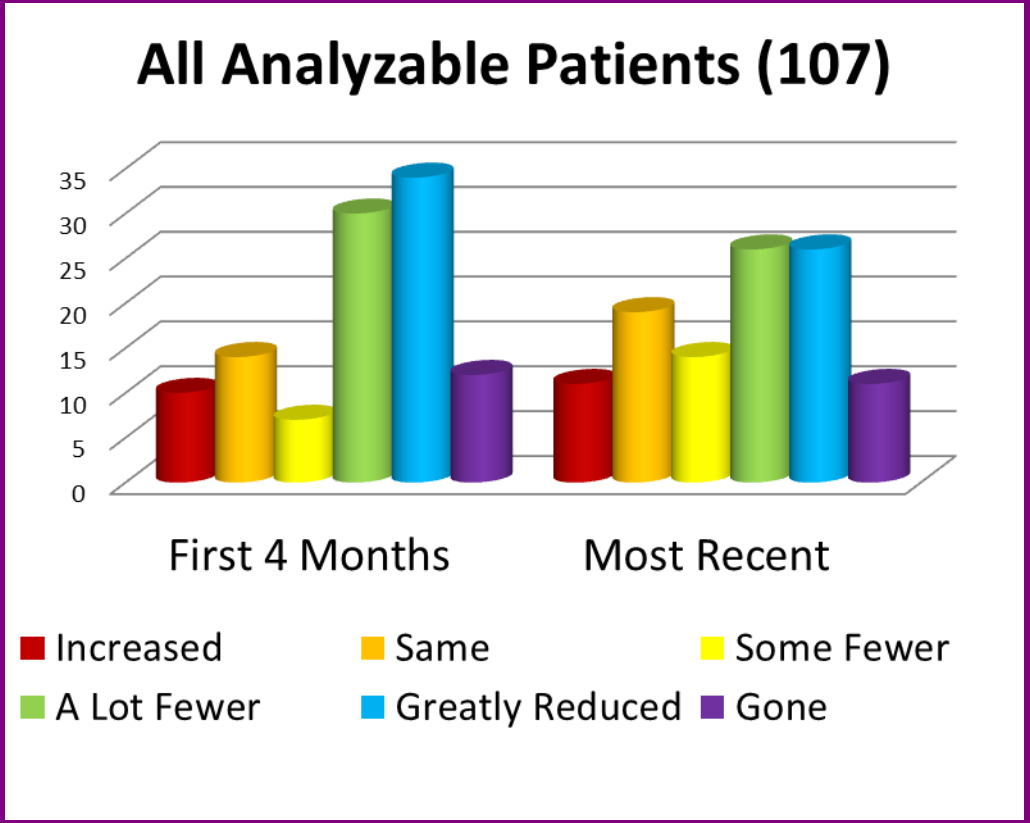
A Lot Fewer – At least 50%, up to 80% reduction in seizures

Greatly Reduced – At least 80%, up to 100% reduction in seizures

Gone – 100% reduction; patient was seizure free for at least 4 weeks.

Outcome: Change in Seizure Frequency in Entire Analyzed Cohort

Outcome at Last Assessment	%
No Improvement, or Worsened	28
Some Improvement	37
80% or Greater Seizure Reduction	35



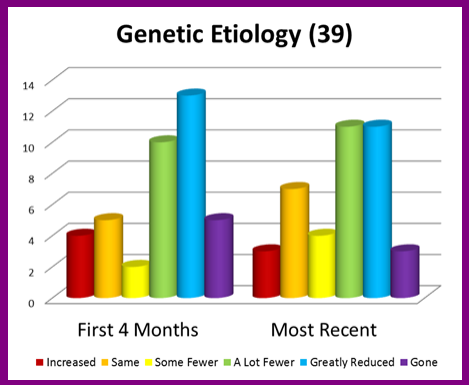
Average Change in # AED = - 0.47

No significant difference in outcome between the two assessments, by chi-square test.

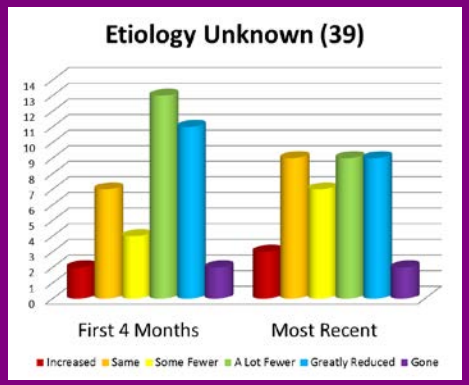
First Assessment: avg 13 wks. (min 4, max 16)

Last Assessment at avg of 27 wks. (min 4, max 118)

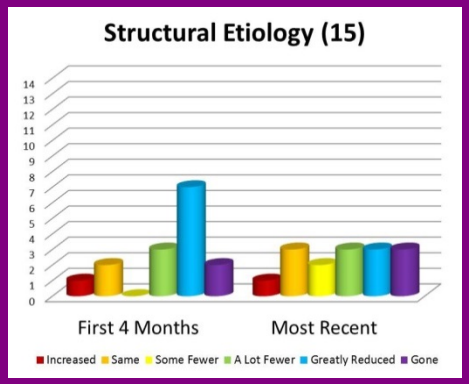
Outcome: Change in Seizure Frequency By Etiology



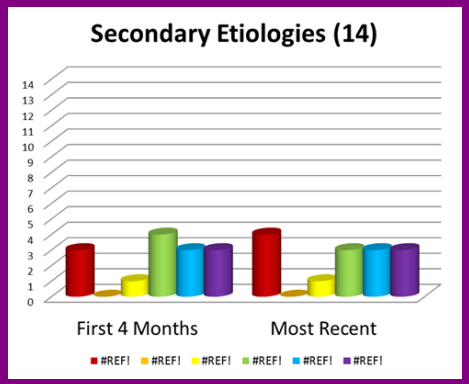
Avg Change # AED = - 0.41



Avg Change # AED = - 0.64



Avg Change # AED = - 0.40

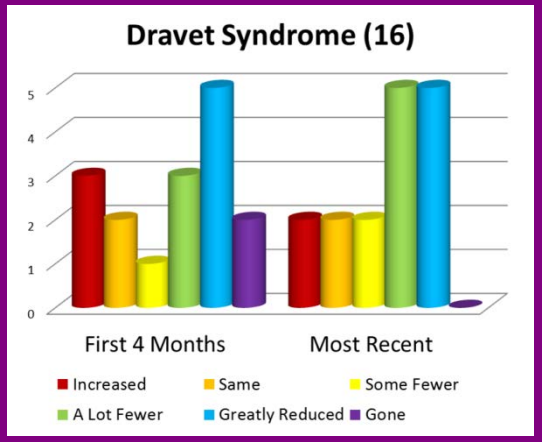


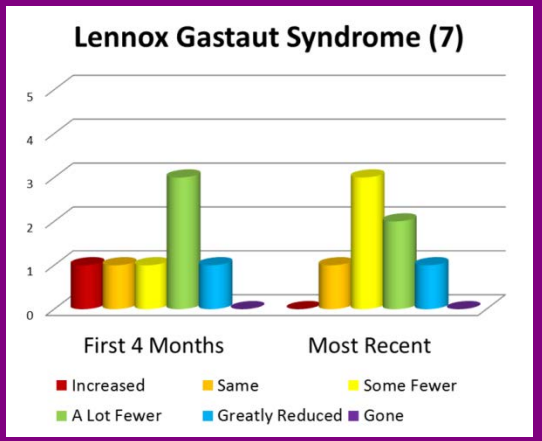
Avg Change # AED = - 0.21

AED = anti-epileptic drug

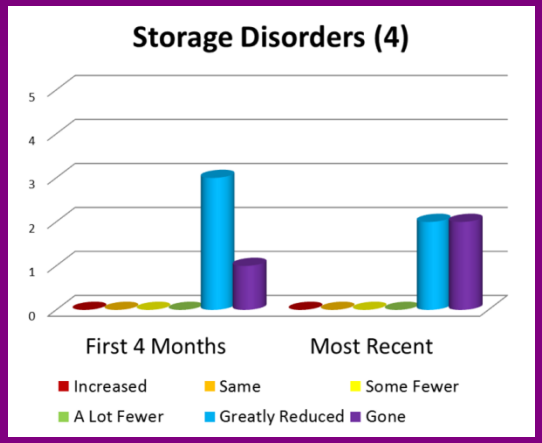
- No difference in outcome among etiologies by chi-square analysis of responders vs non-responders (responders defined as having 50% or greater seizure reduction).
- All groups had a net reduction of other AEDs during the study.

Focus on Outcomes for Orphan Disorders



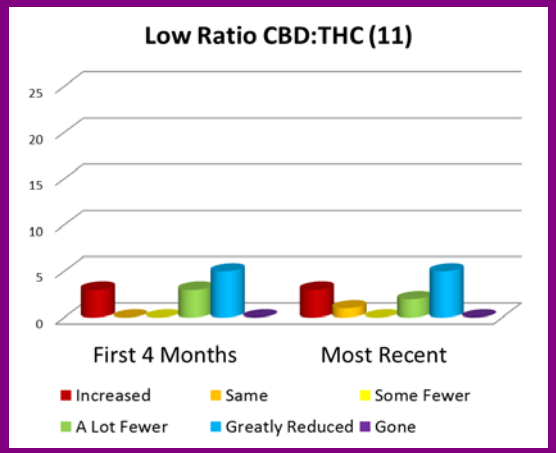


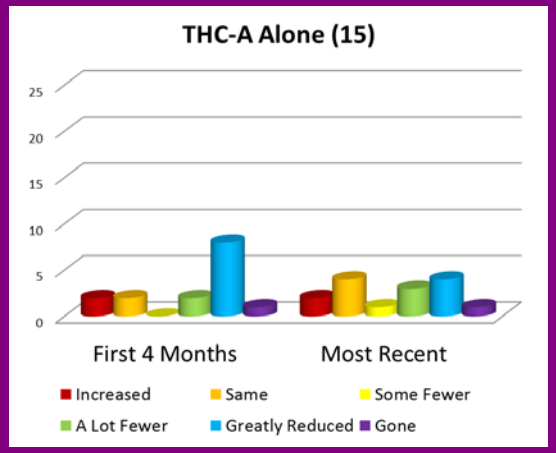
Dravet Syndrome and Lennox Gastaut Syndrome are "orphan disorders" – they have no effective approved therapy, and are of particular interest to the FDA.

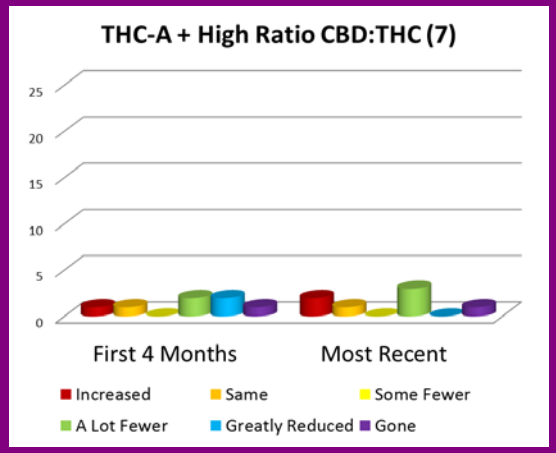


- Storage disorders are usually fatal during childhood.
- Diagnoses: Infantile neuroaxonal dystrophy; Metachromatic leukodystrophy; Neuronal ceroid lipofuscinosis (2).
- Seizures in patients with storage diseases responded especially well to cannabinoids

Outcome: Change in Seizure Frequency by Cannabinoid Type - Others







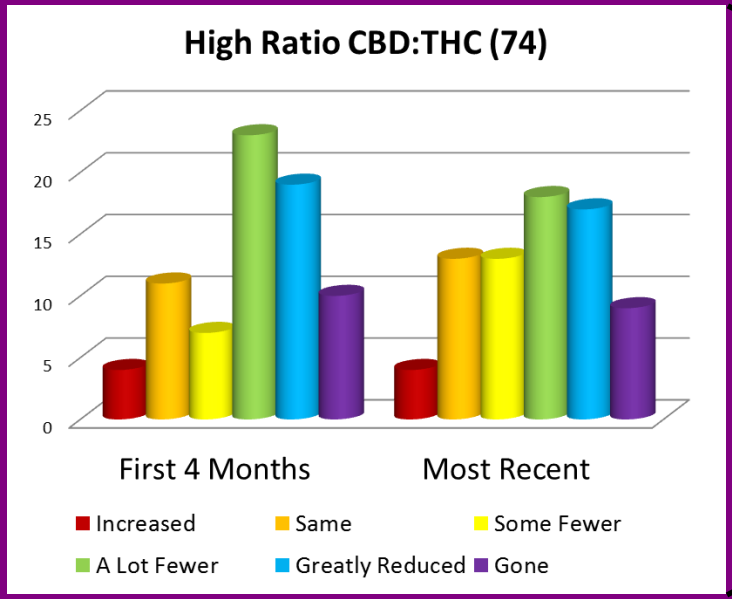
Low Ratio CBD:THC

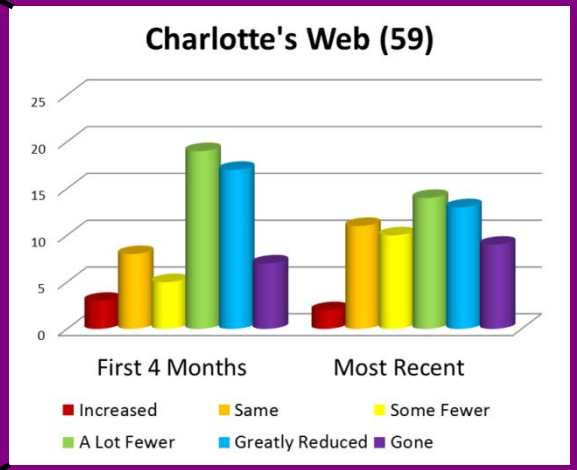
THC-A Alone

THC-A + High Ratio CBD:THC

Positive outcomes (seizure reduction of 50% or greater) occurred with treatment with each of the observed types of cannabinoid products.

Outcome: Change in Seizure Frequency by Cannabinoid Type – High Ratio CBD:THC





Outcomes in patients using high ratio CBD:THC oil mirror those in the entire analyzed cohort.

Adverse Effects of Cannabinoids Used by Cohort

- CBD = cannabidiol
  - At therapeutic doses: sleepiness, increased drooling that resolve
  - Above optimal doses: excessive sleepiness, increased seizures or new seizure types
- THC-A = delta-9-tetrahydrocannabinolic acid
  - At therapeutic doses: none
  - Above optimal doses: excessive sleepiness, increased seizures or new seizure types

Beneficial Side Effects

CBD = cannabidiol

- Improved cognition & interactions
- Better sleep and appetite
- Better gut function – relief of chronic constipation
- Improved immune resistance
- Better muscle tone – improvements in both hypertonia & hypotonia
- Better fine and gross motor control
- Relief of anxiety
- Faster recovery after seizures; shorter, less severe seizures

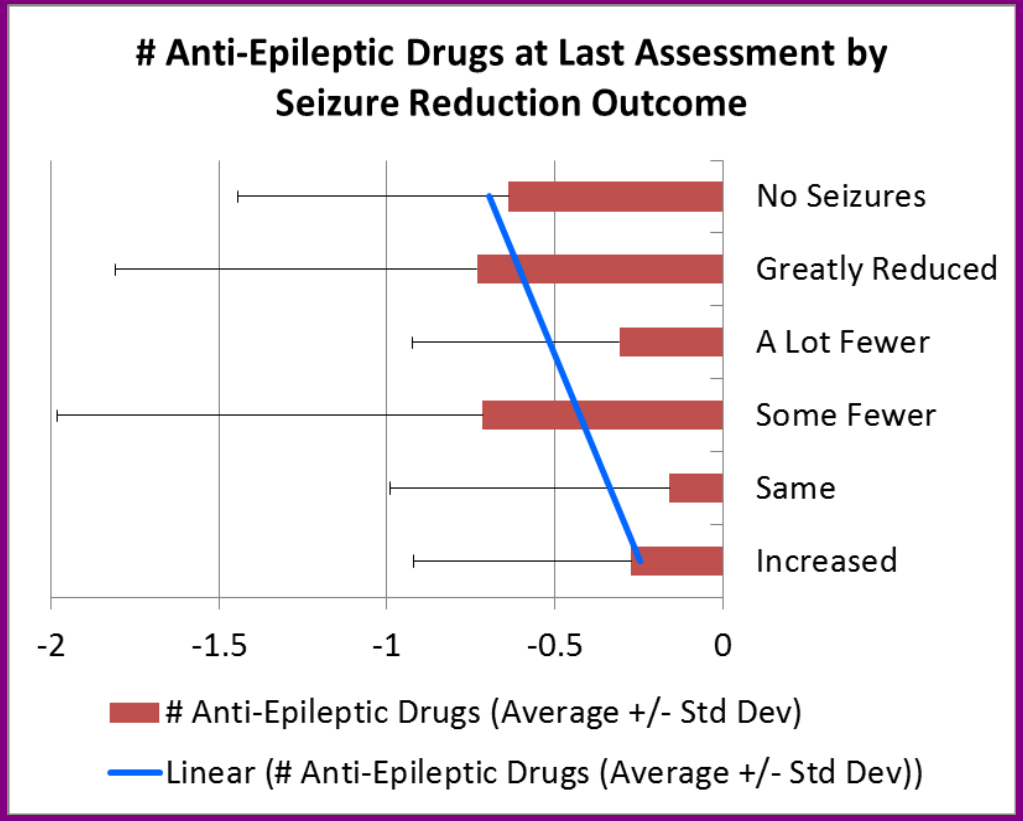
THC-A = delta-9-tetrahydrocannabinolic acid

- Improved alertness
- Improved cognition
- Improved language
- Better sleep

* Ability to reduce or eliminate other AEDs and their adverse effects & toxicities

On Average, Each Group Reduced Other Anti-Epileptic Drugs while on Cannabinoid Therapy

- Change in # AEDs: Ranged from +2 to -4, with Median of 0 and Average of -0.47.
- # Patients taking no AEDs increased from 7 to 14.
- Drugs that patients stopped the most were: clobazam, clonazepam, levetiracetam, valproic acid, zonisamide.



Cannabinoid Doses at First Assessment

Cannabinoid Type	mg per day (avg +/- stdev)	mg/lb per day (avg +/- stdev)
High Ratio CBD:THC	132 +/- 117	2.2 +/- 1.6
Low Ratio CBD:THC	94 +/- 83	1.8 +/- 2.2
THC-A alone	17 +/- 6	0.2 +/- 01
THC-A + High Ratio CBD:THC	39 +/- 30	1.3 +/- 1.4

avg = average; stdev = standard deviation

Summary of Seizure Reduction Efficacy – Entire Analyzable Cohort

Seizure Reduction	Percent of Patients	# of Patients
At least 50%	71%	66 / 107
At least 80%	43%	36 / 107
100%	11%	12 / 107

Retrospective cohort study; data extracted from clinical records; outcomes are based on assessments within the first 16 weeks dosing.

Conclusions and Take Aways

- By last assessment, some patients had responded well and others had not, with about 10% doing worse and 10% seizure free.
- All groups reduced other anti-epileptic drugs on average, yet largely maintained seizure control.
- For many patients, lower doses gave better seizure control than did higher doses, plus fewer side effects.
- All four cannabinoid combinations were associated with reduction of seizures in this cohort.

What Are Other Providers Seeing?

- Patients having difficulty using cannabis products may be more likely to present to emergency departments than those who are doing well.
- Case-control studies comparing patients using cannabis to control patients matched on key parameters could be done without conflict.

GW Pharma Epidiolex Open Label Study

- Epidiolex = purified cannabidiol (CBD)
  - This was a physician-led expanded access treatment program.
  - Efficacy Endpoint = Average of 4-week seizure frequencies through 12 week treatment period relative to 4-week baseline expressed as percent reduction.
  - Reported on 27 patients with treatment-resistant epilepsy.

% Reduction in Seizure Frequency Compared to Baseline Seizure Frequency	% of All Patients
At least 50%	48%
At least 70%	41%
At least 90%	22%
100% (seizure free)	15%

Data from GW Pharmaceuticals press release of June 17, 2014.

Study to Be Proposed

- Prospective observational design
  - Consent and enrollment at clinic visit
  - Standardized instructions & assessments
- Community-acquired cannabis products
  - Products to be acquired by parents as usual under medical marijuana program
  - Study to fund independent testing of products acquired by parents
  - Study to support patient purchases of cannabis?

Clinical Cannabis in the Future

When Doctors Can Prescribe & Cannabis Preparations Are Standardized:

- 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.

Final Summary

- A retrospective cohort study allowed us to capture outcomes from a dynamic clinical process where doses, cannabinoid types, and concomitant medications all changed in order to optimize response for each patient.
- Cannabinoid therapy was generally effective across diagnostic & etiologic categories.
- Multiple cannabinoid combinations appear effective and well tolerated.
- Cannabinoid therapy yielded positive side effects plus reduced negative effects from reduced AEDs.

Acknowledgements & Call for Collaboration

- Thanks to:
  - Jessica Hogan –
    Owner, Vibrant Health Clinic
  - Kirk Anderson, MD –
    Staff Physician, Vibrant Health Clinic
  - Kathy Cihlar, RN –
    Staff Nurse, Gedde Whole Health
  - Karla Costanza –
    Clinics Administration, Gedde Whole Health

- To physicians & other collaborators who would like to participate in this work: Call Us.