Reflections on Adding Oil to the Fire
Medical Marijuana Use for Seizures in Pediatric Epilepsy Patients

Charuta Joshi MBBS
Clinical Professor
Pediatric Neurology
Director of Pediatric Epilepsy
Objectives

At the end of this talk the audience will:

1. Know the history behind the recent “Marijuana Revolution”
2. Review published literature on effectiveness of CBD
3. Review trials of CBD in Iowa

I shall be discussing a NON FDA approved and ILLEGAL substance

I have NO CONFLICTS OF INTEREST
My initial “exposure” to the substance

- Charas
- Hashish
- Bhang
- Ganja
History of Cannabis Use
History of Cannabis use

- China

- India - Atharva Veda

- Egypt

  Hemp fibre use for rope, clothing, bowstrings, paper, livestock, feed, medicine, construction material, seeds, seed oils etc
Medicinal uses

- **China** - menstrual disorders, gout, rheumatism, malaria, constipation, absent mindedness

- **Islamic countries** - nausea, vomiting, epilepsy, inflammation, pain, fever

- **Western medicine** - inflammation and pain (before aspirin); W. Gowers - epilepsy

- **Recent uses** - glaucoma, spasticity, nausea, insomnia, anxiety, epilepsy - Bill passed in Colorado 2008
Where it all began...recently...
August 2013- Dr Sanjay Gupta

Why I changed my mind on weed

By Dr. Sanjay Gupta, CNN Chief Medical Correspondent
Updated 8:44 PM ET, Thu August 8, 2013

Dr. Sanjay Gupta: I've tried marijuana 03:27

Story highlights
Over the last year, I have been working on a new documentary called "Weed." The title "Weed" may sound

The Marijuana Debate
Washington's pot shops ready to open
Adam Markus has bet nearly everything he has on a pot shop.

Pot smokers fight stereotypes
Lighting up a freshly packed pipe is just the kind of afternoon delight iReporter Robert20 has after dealing with a stressful day at work as an insurance agent.

Gupta: 'I am doubling down' on medical marijuana
I feel very badly that people have suffered for too long, unable to obtain the legitimate medicine that may have helped them, Sanjay Gupta writes.
Charlotte Figi - Dravet syndrome
Seizures 300/wk ..to 2-3/ month
Dravet syndrome - Charlotte Dravet

Charlotte Dravet

- Initially normal children
- Febrile status epilepticus
- Normal till about age 2
- Regression thereafter
- Increased risk for SUDEP (sudden unexplained death in an epilepsy patient)
Terms used

• **Marijuana** = preparation of the cannabis plant - used as a psychoactive drug and medicine. Per DEA this is a schedule 1 substance.

• **Cannabinoids**: active compounds repress neurotransmitter release in the brain.

• **Cannabinoids in the cannabis plant** = THC and CBD
Cannabinoid pharmacology

- Dr Raphael Mechoulam

- **1940** - CBD isolated
- **1964** - Delta 9 THC = psychoactive - (Isolated and characterized)
- **1990s** - THC binds to CB1 and CB2 receptors through endogenous ligands called anandamide (in brain) and 2 arachidonic glycerol (periphery)
Terms used- Cannabinoids

• Classification of cannabinoids:
  1. **Endocannabinoids** (anandamide)
  2. **Phytocannabinoids**: THC, CBD etc
  3. **Synthetic cannabinoids**:
     • **Dronabinol** (marinol) appetite stimulant, antiemetic, analgesic
     • **Nabilone** (Cesamet) same as marinol
     • **Sativex** (Nabiximols) - antispasticity
Neuroactive Phytocannabinoids

- TetraHydroCannabinol
- Cannabis sativa
- (higher THC:CBD ratio)
- More stimulating

- Cannabidiol: CBD
- Cannabis indica
- (higher CBD:THC ratio)
- More sedating

**THC activates endocannabinoid system** - a system of G protein coupled cannabinoid receptors, synthetic and degradative enzymes and transporters

Modulate eating, pain, anxiety, learning, memory, growth and development through synaptic mechanisms
CB1 and CB2 receptors

CB1 receptors

CB2 receptors
Periphery

• Immune system
• Hematopoietic cells
Charlotte Figi - Dravet syndrome
Seizures 300/wk..to 2-3/month
Cannabinoid concentration

- Varies per plant Genus, Moisture, Temperature
- **Charlottes Web** = High CBD- Low THC cannabis extract
- Developed by Stanley brothers- cross breeding cannabis and hemp
- “Hippies disappointment”

<table>
<thead>
<tr>
<th>Type of substance</th>
<th>THC content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industrial hemp</td>
<td>&lt;0.3%</td>
</tr>
<tr>
<td>Hashish (1960s)</td>
<td>5%</td>
</tr>
<tr>
<td>Marijuana (1960s)</td>
<td>2-3%</td>
</tr>
<tr>
<td>Marijuana (current)</td>
<td>25%</td>
</tr>
<tr>
<td>Charlottes web</td>
<td>&lt; 0.3%THC</td>
</tr>
<tr>
<td>GW pharmaceuticals- Epidiolex</td>
<td>99% CBD</td>
</tr>
</tbody>
</table>
Charlotte’s web

Charlotte's web (cannabis)

From Wikipedia, the free encyclopedia

For other uses, see Charlotte's Web (disambiguation).

Charlotte's Web is a high cannabidiol (CBD), low tetrahydrocannabinol (THC) Cannabis extract marketed as a dietary supplement under federal law and medical cannabis under state laws. It is produced by the Realm of Caring Foundation (RoC) in Colorado. It does not induce the psychoactive "high" typically associated with recreational marijuana strains that are high in THC. September 2014, RoC announced that they would ensure that the product consistently contained less than 0.3% THC.
DEA classification

• **Controlled Substance Act- 1970**

• **Schedule 1 drugs**
  1. no accepted medical use
  2. lack of accepted safety for use under medical supervision
  3. high potential for abuse

• **Others**: Heroin, LSD, Quaalude (methaqualone), MDMA/Ecstasy
Mechanism of action of CBD in epilepsy (animal models)

- **DOES NOT ACTIVATE CB1 or CB2 receptors**

- Acts through TRPV, adenosine receptors, glycine receptors, 5HT

- **CBD interacts with other non endocannabinoid systems**

- **Multi target effect**
Potential mechanisms of CBD in animal models-Low-sub micromolar levels

- Blocks
- Equilibrative nucleoside transporter (transports adenosine into the cell)
- Orphan G protein coupled receptor GPR55; and
- Transient Receptor Potential of melastatin (M ion channels for transport of calcium).

- Activates
- Activates 5HT-1a receptor, alpha1 (serotonin pathway) and alpha 3 glycine receptors, transient receptor potential of ankyrin type 1 (TRPA1-chemosensor) channel, has bidirectional effect on intracellular calcium.
Potential mechanisms of CBD in animal models - High macromolar levels

**Blocks**

- Reduces psycho activity of THC and enhances therapeutic window of THC
- Reverse agonist at CB1 receptor

**Activates**

- Activates nuclear peroxisome proliferator activated receptor Gamma, activates transient receptor potential of vanilloid type 1 and 2 (TRPV1 and 2; these are selective Ca and Mg ion channels); inhibits cellular uptake and degradation of anandamide
CBD pharmacology humans
Sativex studies..GW

• **Multiple potential routes**
  
  **Inhaled** - peak plasma concentration - 10 minutes with 31% bioavailability

  **Oil based capsule-PO-Bio** availability = 6% (high first pass through liver)

  **Oral/ mucosal route** Less variability

  **Transdermal** - less well understood – lipophilic - likely to accumulate in skin

• **Highly lipophilic** so - transdermal route may lead to accumulation in skin
Distribution and elimination

- **Highly lipid soluble** - Vd=32L/kg - highly distributed to brain, adipose tissue

- **Metabolized extensively through liver**
  - Hydroxylated to 7-OH- CBD by cytochrome P450 enzymes (CYP3A/CYP2C)

- **Most excretion through feces**

- **Terminal T1/2** = 18-32 hrs
How does one get CBD in Iowa?

- GW pharma is one option
September 2013 - Dravet patient
My first encounter with GW

GW pharmaceuticals
Obtaining a non FDA approved drug

• Emergency IND – applied - December 2013 - approved January 2014
• DEA 1 license
• IRB application
FIRE S- Applied for CBD in December 2013
Patient discharged March 2014- started CBD April 2014

At baseline had 6 partial complex seizures at night with apnea / desaturation
Parents reported no seizures for the next several months
Published data about CBD in (pediatric) epilepsy
CBD in Epilepsy - Cochrane May 2012 and March 2014

Cannabinoids for epilepsy (Review)

Gloss D, Vickrey B

THE COCHRANE COLLABORATION®

- Cannabinoids for epilepsy (Review)
- Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>author</th>
<th>N (CBD)</th>
<th>Dose of CBD mg</th>
<th>Patient characteristics</th>
<th>ADRs</th>
<th>f/u period</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulam 1978</td>
<td>9 (4)</td>
<td>200</td>
<td>?</td>
<td>none</td>
<td>3 month</td>
<td>2/4= sz free</td>
</tr>
<tr>
<td>Cunha 1980</td>
<td>15 (8)</td>
<td>200-300</td>
<td>TLE</td>
<td>none</td>
<td>4/12 month</td>
<td>4/8 nearly sz free</td>
</tr>
<tr>
<td>Ames 1985</td>
<td>12 (?)</td>
<td>300-200</td>
<td>MR</td>
<td>drowsiness</td>
<td>1 month</td>
<td>No details</td>
</tr>
<tr>
<td>Trembly 1990</td>
<td>12 (10)</td>
<td>200</td>
<td>TLE</td>
<td>none</td>
<td>?12 m</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Brief Communication

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter, Catherine Jacobson *

* Department of Neurology, Stanford University, USA
Results of the parent survey

Overall 13/19 patients reported > or equal to 50% seizure reduction (68.4%)

13 patients had Dravet syndrome:
  • 2 reported 25% change / decrease in seizures
  • 2 reported NO change
  • 2 reported > 50% seizure reduction
  • 5/12 reported > 80% seizure reduction
  • For Dravet: 7/12 (58%) reported > 50% reduction

4 patients had Doose syndrome
  • 3 reported > 80% seizure reduction
What about addiction?

Published in final edited form as:

Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin-seeking and normalizes discrete mesolimbic neuronal disturbances

Yanhua Ren¹, John Whittard¹, Alejandro Higuera-Matas², Claudia V. Morris¹, and Yasmin L Hurd¹
¹Departments of Psychiatry and Pharmacology & Systems Therapeutics, Mount Sinai School of Medicine, USA
²Psychobiology Department, School of Psychology, Univ. Nacional de Educacion a Distancia, Madrid, Spain
14 studies: 9 animal; 5 human
Animal studies involved opioids, cocaine
Human studies- THC

Results:
CBD may have therapeutic effects on opioid, cocaine, psychostimulant addiction
May have beneficial effect in THC and tobacco addiction in humans
The Pulse survey- 2014
Epilepsy currents Sept/ October 2014

CBD and marijuana: Q-PULSE Survey

Do you have patients who currently use cannabis (in any form) for seizure control?

- Yes, 60, 64%
- No, 24, 26%
- Don't Know, 9, 10%

n=93

The Pulse Survey - If legal would you support/“prescribe”

If you were in a state (such as Colorado) where medical marijuana was legal, would you:

- Write a prescription for medical marijuana, 3, 4%
- Support its use, but recommend they seek another physician for a prescription, 12, 13%
- I don’t feel that I know enough to make a recommendation, 25, 27%
- I understand the issues and information, but would not support the use of medical marijuana at this time, 26, 28%

n=92
The Pulse Survey - why not?

What factor(s) influence your decision to not provide a prescription for marijuana for seizures? Please check all that apply.

- I am concerned about medico-legal liability (mine or my hospital's)
- I have inadequate knowledge of potential interactions with other medications
- I have inadequate knowledge of proper dosing
- I have inadequate knowledge of potential side effects
- I do not believe the available options allow for monitoring or stable levels
- I do not believe it is safe
- I do not believe it will be effective

n=36/38
The Survey - what is needed to be recommend CBD?

What do you feel the next step should be in exploring cannabis treatment for epilepsy? Please check all that apply.

- Controlled manufacturing process
- Trials of safety, dosing and PK information
- Improve/change DEA scheduling
- States should continue to pass legislation allowing physicians to legally prescribe CBD oil
- Open-label trial restricted to a few sites with careful follow-up of patients
- Randomized controlled clinical trial with placebo control and a classical design

n=92
The case for assessing cannabidiol in epilepsy

*Maria Roberta Cilio, †Elizabeth A. Thiele, and ‡Orrin Devinsky

doi: 10.1111/epi.12635
Survey

May - September 2014...

Table 1. Comparison of type of medical personal and patients with geographic region in answering Epilepsia's survey on the use of medical marijuana and CBD in treating patients with epilepsy

<table>
<thead>
<tr>
<th>Category</th>
<th>Africa</th>
<th>Asia Oceania</th>
<th>Eastern Med</th>
<th>Europe</th>
<th>Latin America</th>
<th>North America</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Epileptologist</td>
<td>3</td>
<td>11</td>
<td>2</td>
<td>39</td>
<td>12</td>
<td>73</td>
<td>140</td>
</tr>
<tr>
<td>General neurologist</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>12</td>
<td>31</td>
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<tr>
<td>General physician</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Basic researcher</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>26</td>
<td>36</td>
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<tr>
<td>Nurse/allied health</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Patients/public</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td>33</td>
<td>4</td>
<td>305</td>
<td>353</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>27</td>
<td>2</td>
<td>101</td>
<td>24</td>
<td>449</td>
<td>609</td>
</tr>
</tbody>
</table>

Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: Result of Epilepsia’s survey

*Gary W. Mathern, †Laurie Beninsig, and ‡Astrid Nehlig

Epilepsia, 56(1):1–6, 2015
doi: 10.1111/epi.12843
There are sufficient **Safety** data to...

- Allow open non prescription use
- There is sufficient data to allow “prescription use”
- There is insufficient data on efficacy
Sufficient efficacy data to:

- Allow open non prescription use
- There is sufficient data to allow “prescription use”
- There is insufficient data on efficacy
Would you advise patient with catastrophic epilepsy—who have failed standard treatment to try CBD? N=611
Retrospective chart review
- 75 patients
- 43/75 = 53% reported SOME improvement
- 25/75 (33 %) improvement > 50% -- response-
- 34 patients had moved to Colorado
- Responder rate was (16/34) 47% if family moved to Colorado versus 22% (9/41) if they were from Colorado
- Responder rate to meds in RCT - 10-69%
- Responder rate to placebo in FDA approved drug trials =0-39%

- 8 EEGs available for review - none improved
- Class 3 evidence for tolerability.....
First reported drug interactions in children

- Expanded Access Investigational New Drug trial
- 25 patients
- 13/25 received clobazam as adjuvant treatment for epilepsy
- Clobazam metabolized to desmethylclobazam (norclobazam through CYP450)
- Clobazam levels up by 60+/−80% at 4 weeks (NS)- CI(0.98-1.91)
- Nor Clobazam levels up by 500+/−300% at 4 weeks (CI1.9.7.1)
- Eventually clobazam dose reduced in 10/13
- N Clobazam levels continued to remain elevated at wk 8 despite dose reduction

---

Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy
1Alexandra L. Geffrey, 1Sarah F. Pollack, Patricia L. Bruno, and Elizabeth A. Thiele
Epilepsia, 56(8):1246–1251, 2015
doi: 10.1111/epi.13060
Data extrapolated from open label studies

- **213 patients**
- Average age 10.8 years
- 3 AEDs on average
- 12 week analysis- (137 patients)
- 54% median reduction from baseline in total seizures

**Adverse effects:**
- Somnolence, diarrhea, fatigue, decreased appetite
Open label data

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Primary outcome = Safety and Efficacy

Secondary outcome = median reduction in mean monthly seizure count = 36.5%
Open label study

Hepatotoxicity, hyperammonemia, thrombocytopenia - all associated with concomitant VPA use

Sedation – associated with Clobazam use

Status epilepticus unrelated to concomitant medication reduction

<table>
<thead>
<tr>
<th>Adverse events (reported in &gt;5% of patients)</th>
<th>Safety analysis group (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>41 (25%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>31 (19%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>31 (19%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (13%)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Status epileptic</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Drug concentration increased</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-emergent serious adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status epileptic</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Weight decreased</td>
</tr>
<tr>
<td>Convulsion</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Drug concentration increased</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Hyperammonia</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Unspecified pneumonia</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

Data are n (%). One patient might have had more than one serious adverse event. *Reported by the investigator to be possibly related to cannabidiol use.

Table 3: Adverse events and treatment-emergent serious adverse events
January 2015 - December 2015

- Decriminalization bill passed in IOWA and registration cards available by spring 2015
- At least 30 of my patients have applied
- 6 patients in Expanded access program through GW
- 19 patients enrolled in the GW drug trials
Overall results of the CBD users

- 3 Emergency IND- 1/3 stopped seizing – unless provoked (fever)
- 2/3- had already stopped seizing- FIRES
- Intermediate IND- has 2 patients SPATA5 and NKH- no effect on seizures

- Using the registration cards:
  - 21 patients have received the card
  - 3 in the study- so did not use
  - 7 applied- -want it available for later
  - 10 are on the hemp oil- none better
  - 3 have stopped due to no effect
Overall anecdotal impression

- Many patients getting Charlotte’s web are still seizing...
- They are asked to try CW for 6 months..

- Frequently... what starts as a great cause is at risk of becoming a business and eventually turning into a racket...
Final notes

- Sensationalized media anecdotes tend not to provide a rational denominator and do not report failures

- Media anecdotes should not be the basis of our decisions...

- The real story is yet to be told...
THANK YOU
Bibliography

3. Cannabidiol as a potential treatment for psychosis European NeuropsychopharmacologyVolume 24, Issue 1, January 2014, Pages 51–64