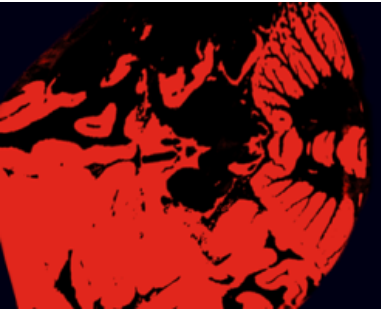
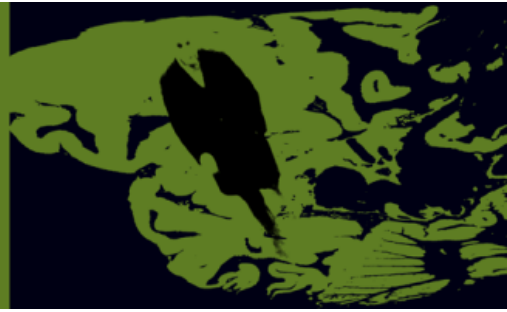


BRAINWEEK™ twenty 21 | Live Virtual Conference | MAY 7–9



Examining Cannabinoids in the Epilepsy Treatment Spectrum

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Kennedy Krieger Institute

Disclosure

- Research grant—Lundbeck (funding to institution only, investigator initiated trial), not currently active
- No speakers bureau or marketing activities

Disclaimer

- Local laws vary widely in terms of tolerance and availability of cannabinoid products
  - As is often the case, society and culture are far ahead of politics and medicine in terms of advancing conventional wisdom
- Evidence is still largely based on anecdote
- Most recommendations made in this talk will not be adherent to specific FDA indications
- Abundant caution is prudent

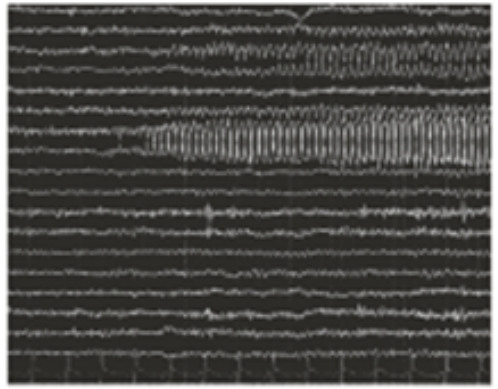
Learning Objectives

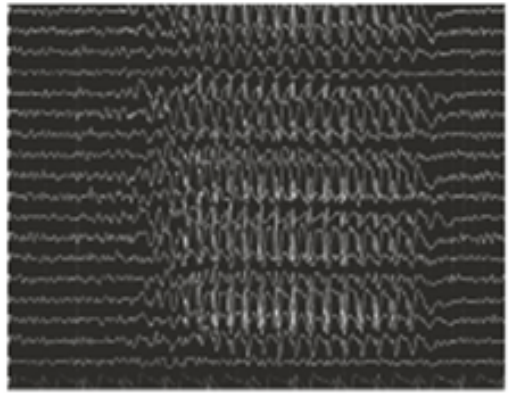
- Gain familiarity with the overlaps of neurologic and psychiatric diagnostic and treatment approaches in epilepsy
- Learn the role and range of influence of the endocannabinoid system
- Learn potential treatment options and practical strategies for using cannabinoid based products for epilepsy

Overlap of Psychiatry and Neurology

- Paradigm shift—neuropsychiatry
- Not neuro or psych
- Instead, neuroscience that is more than the sum of the parts
  - Brain diseases with comorbid psychiatric symptoms?
  - Conditions with neurobehavioral phenotypes
  - Novel approaches to treatment are necessary

Epilepsy





- Hyperexcitable neurons
  - Focal versus generalized
  - Awareness impaired or not
- Prototype neuropsychiatric illness

Psychiatric Problems are Overrepresented in Epilepsy

- Isle of Wight Childhood Epidemiology Study: Psychiatric illness in 29% epilepsy vs 16% chronic medical illness
- Psychiatric comorbidity in epilepsy more than asthma or diabetes

Rutter M, Graham P, Yule W. A Neuropsychiatric Study in Childhood. Clinics in Developmental Medicine, nos. 34/35. Spastics International, Heineman Medical, London 1970.

Hoare P. *Dev Med Child Neurol* 1984;26:3-13.

Austin JK et al. *Epilepsia* 1992; 33(6):1115-1122.

Austin JK et al. *Pediatrics* 2001;107:115-122.

Psychiatric Comorbidity in Epilepsy

- ADHD
  - 38% prevalence, as measured by rating scales and CBCL
    - Dunn DW, Austin JK, Harzelak J, Ambrosius WT, (2003) *Dev Med Child Neurol* 45(1):50-54.
    - Salpekar JA, Mishra G, *Epilepsy & Behavior* 37 (2014), 310-315.
- Autism spectrum disorder
  - Epilepsy in 10%-30%; commonly focal with awareness change
  - Anomalous connectivity and hyperexcitability
  - Cases of improved social skills and language with AEDs
    - Olssonl. Arch Neurol. 1988;45:666-668. Steffenburg. Arch Neurol. 1996;53:904-912. Plioplys. Arch Pediatr Adolesc Med. 1994;148:220-222.
- Anxiety and depression: 10%-33%
  - Generalized seizures associated with less mood disorder
  - External “locus of control”
  - 20% with suicidal ideation in a controlled study
    - Caplan R, et al. *Epilepsia*. 2005;46:720-730
  - Epilepsy associated with 5-fold increase in SI
    - Hesdorffer DC, et al. *JAMA Psychiatry*. 2016;73(1):80-86
    - Salpekar JA, et al. *Epilepsy & Behavior* 46 (2015) 12-18.

Depression Common with Temporal Lobe Seizure Foci

- Left temporal foci with more depression than those with right or bilateral foci
  - Altshuler LL, Devinsky O, Post RM, Theodore W, (1990). Depression, Anxiety, and Temporal Lobe Epilepsy: Laterality of Focus and Symptoms. *Arch Neurol* 47:284-288.
- Pathologic circuit between the OFPFC, amygdala, and caudate described in adults
  - Drevets WC, Videen TO, Price JL et al. J Neurosci. 1992;(9):3268-3641.

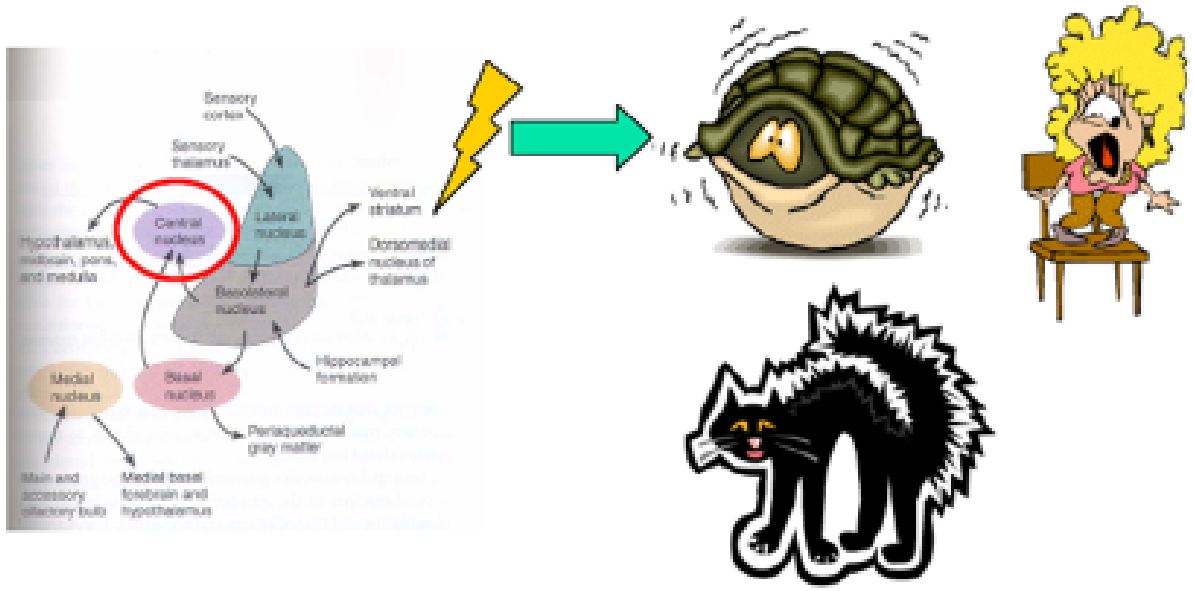
Temporal Lobe Foci Associated with Depressive Symptoms

- Presurgical patients (26 male, 14 female; ages 6-17, mean 11.4)
- Baseline psychiatric evaluation, CBCL, VEEG, Engel outcomes
- Initial EEG or clinical change justified grouping temporal vs extra-temporal
  - Diagnosis of MTS = temporal group
- Temporal lobe foci had more depressive symptoms on CBCL
- Temporal lobe foci trended toward significance for depression Dx
- No group differences for social and somatic problem categories
- ADHD and anxiety diagnoses equally present

» Salpekar JA et al. *Epilepsia*, 54(6):1074–1082, 2013

Evidence of the Role of the Amygdala

The Amygdala and Fear: The Central Nucleus



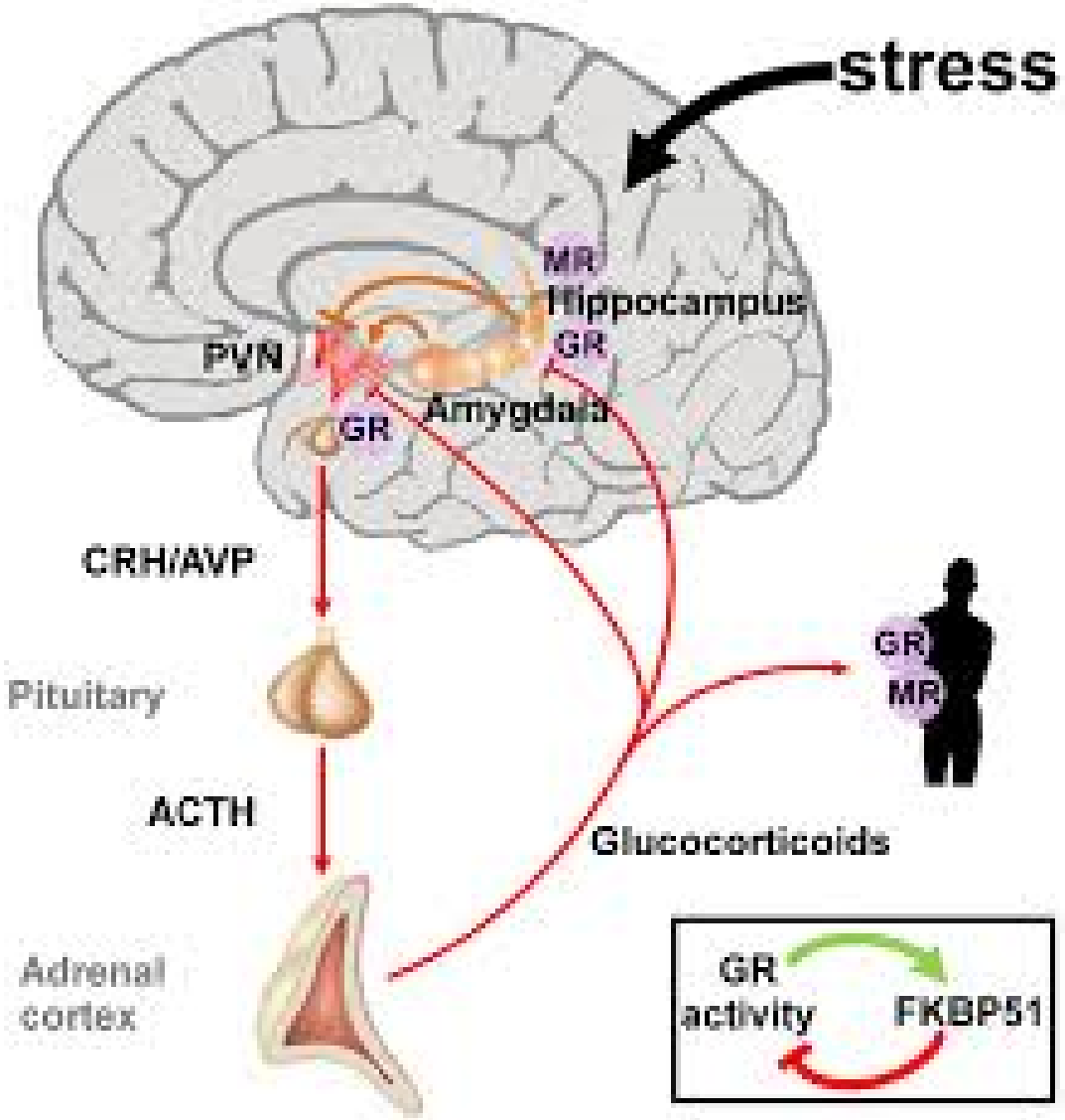
- **Stimulation** of the **Central Nucleus** of the amygdala produces a fear-like response:
freezing and shivering; autonomic nervous system activation (piloerection, **Epi**, **NorEpi** and **cortisol** secretion, increased heart rate, blood pressure etc)

http://mentor.lscf.ucsb.edu/course/summer/psyc003/

Bidirectionality

- ASD and epilepsy
  - Children with epilepsy, diagnosed at a young age, had increased hazard ratios for a later diagnosis of autism
  - Increased prevalence of autism and epilepsy among siblings in Swedish and Danish population registries
    - Su CC et al. Eur Child Adolesc Psychiatry 2016; 25:979.
    - Sundelin et al. Neurol 2016; 87:192.
    - Christensen J et al. Epilepsia 2016; 57:2011.
- ADHD is a risk for development of epilepsy (Iceland population study)
    - Hesdorffer DC et al. Arch Gen Psychiatry. 2004;61(7):731-736
- Stress and epilepsy

Hypothalamopituitary Adrenal Axis



HPA Axis

- Upregulated in epilepsy
- Acute versus chronic effects
- HPA axis hyperactivity is a hallmark of mood disorders and also implicated in anxiety states.
- Shared pathological features of HPA axis hyperactivity may contribute to the comorbid appearance of affective states in epilepsy
    - Maguire & Salpekar, 2013.

Anticonvulsants are Neuropsychiatric Medicines

- Most AEDs are effective for a wide variety of seizure types
- Targets include impulsivity, rage outbursts, mood lability, anxiety
- As with treatment of epilepsy, low doses of adjunctive AEDs may improve behavior
- Seizure control and behavior control may go hand in hand
- **Some anticonvulsants may have a dual role.**
  - CGI-I ratings for psychiatric symptoms were better with carbamazepine, divalproex sodium, lamotrigine, or oxcarbazepine monotherapy than for other anticonvulsants
    - Salpekar JA et al. *Epilepsy and Behavior* 2006

Epilepsy & Behavior 70 (2017) 277

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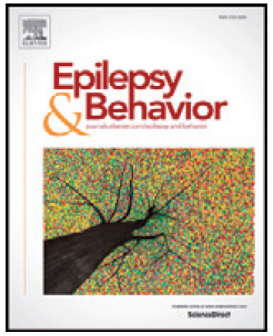
journal homepage: www.elsevier.com/locate/yebeh



Cannabinoids and epilepsy — Introduction☆

Jerzy P. Szaflarski, MD, PhD [a,*], Orrin Devinsky [b]

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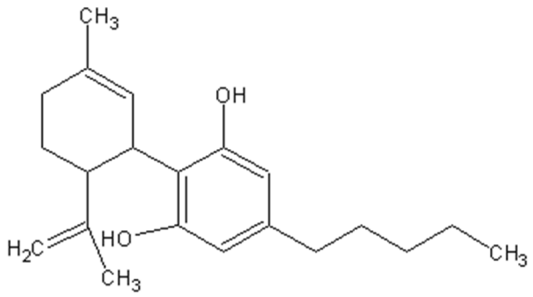
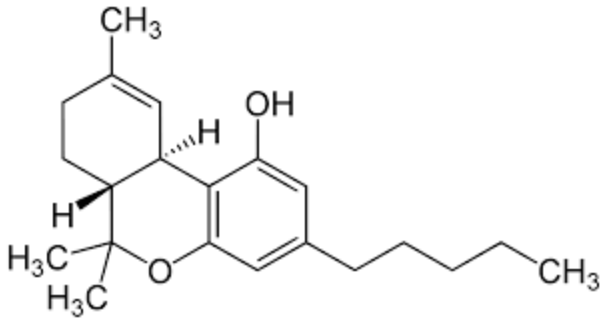
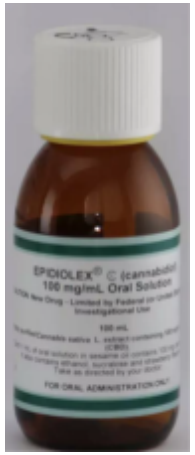
Cannabinoid Science

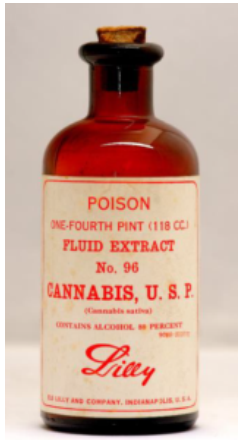


Cannabidiol

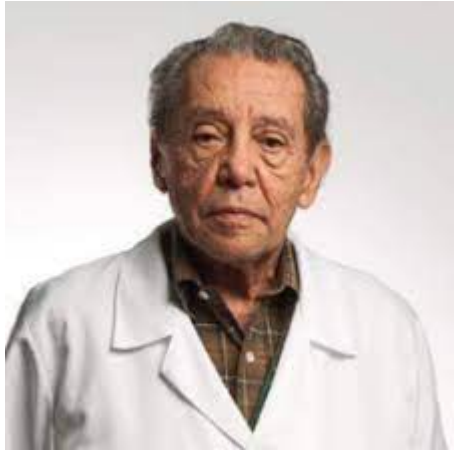


Δ-9 Tetrahydrocannabinol





Prof. Raphael Mechoulam



Prof. Elisaldo Carlini

Endocannabinoid System

- CB1 receptors: brain, GI tract, many on GABA interneurons
- CB2 receptors: little in brain, but may increase with microglial activation, otherwise mostly in immune cells
- Receptors may dimerize or multimerize with other receptors, commonly:
  - Dopamine
  - Alpha-2
- G protein mediated, usually inhibitory G proteins
- Most common endogenous endocannabinoids:
  - 2-AG: (2-arachadionoyl glycerol)
  - AEA: anandamide (N-arachidonoyl ethanolamine)
    - Lu HC & Mackie K, 2020

Endocannabinoid System

- Direct effects on post-synaptic cation channels, also for 5HT3 and glycine
- May also serve as retrograde messengers—acting on the presynaptic nerve terminal
- CB1 present in development in utero
  - Cortex, hippocampus, cerebellum, C/P by week 14
  - Intense expression on CA1 and CA2 of the hippocampus and the basal nuclear group of the amygdala by week 20
    - Mato S, 2003, Wang 2003, Lu HC & Mackie K, 2020

Endocannabinoid System

- THC weakly binds CB1 receptors on presynaptic nerve terminals, and may reduce neurotransmitter release
- Synthetic cannabinoids (eg, Spice, K2), strongly binds receptors
- eCB system modulates neuronal transmission
- May be neuroprotective in the context of cerebrovascular injury
- In contrast, pathways may also relate to development of schizophrenia

The Universe of Cannabinoids in Clinical Treatment

- There is very little, if any, real class I data
- Often CBD findings overlap with approaches for medical cannabis
  - Sagar, KA & Gruber, S (2018). International Review of Psychiatry. 1-17.
- There is also limited data
  - The more THC involved, the more information is anecdotal or based on recreational users as opposed to a clinical population
- Synthetic THC that is FDA approved
  - Nabilone, dronabinol, (historically for glaucoma, spasticity)
- Hemp extracted cannabinoid
  - Nabiximol (1:1 THC:CBD product; MS, analgesic in cancer)

Cannabidiol (CBD)

- Small study in 1980: 7/8 improved with CBD in epilepsy compared to 1/8 placebo (Cunha et al. 1980)
- Very little progress over the next 3 decades
- Charlotte's Web: ultimate result of lay public effort to use CBD in the treatment of refractory seizures
- Cannabidiol—"pharma grade," Epidiolex®
  - Approved for treatment of seizures associated with Lennox-Gastaut Syndrome and Dravet's Syndrome, recently tuberous sclerosis added
  - Abu-Sawwa R, Stehling C, J Pediatr Pharmacol Ther. 2020 Jan-Feb; 25(1): 75–77

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY®

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Barbara S. Koppel, MD, FAAN
John C.M. Brust, MD, FAAN
Terry Fife, MD, FAAN
Jeff Bronstein, MD, PhD
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Gary Gronseth, MD, FAAN
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ABSTRACT

Objective: To determine the efficacy of medical marijuana in several neurologic conditions.

Methods: We performed a systematic review of medical marijuana (1948–November 2013) to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders. We graded the studies according to the American Academy of Neurology classification scheme for therapeutic articles.

Results: Thirty-four studies met inclusion criteria; 8 were rated as Class I.

Conclusions: The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non–chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications. ***Neurology*® 2014;82:1556–1563**

The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda

Board on Population Health and Public Health Practice

Health and Medicine Division

A Report of

The National Academies of

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Printed in the United States of America

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Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Evidence for Cannabidiol Treatment

- Thiele E et al:
  - DBRCT for LGS, 20mg/kg/day
  - Drop in seizures: 44% CBD to 22% placebo
  - Lancet 2018;391:1085-96.
- Devinsky O et al:
  - DBRCT for LGS, 10 or 20mg/kg/day
  - Drop in seizures: CBD-20 mg: 42%; CBD-10 mg: 37%; placebo: 17.2%
  - N Engl J Med 2018;378:1888-97.

Pharmaceutical Grade Cannabidiol

- Note that FDA indication is not specific for seizure types
- Seizures associated with these conditions include primary and secondarily generalized tonic clonic seizures as well as atypical absence and focal onset events

Pharma Grade Cannabidiol as a Clinical Treatment

- Dosing
  - Initial: 5 mg/kg/day
  - Maintenance: 10-20 mg/kg/day
  - Usually divide doses, BID
- Absorption: C_{max} and AUC affected by food, T_{max} 2-5 hours
- Distribution: >94% protein bound, distributes into lipid
- Metabolism: CYP2C19, CYP3A4, UGT to active (7-OH CBD) and inactive metabolites
- – Elimination: fecal, half-life 56-61 hours

- Wirrell EC. Can J Neurol Sci. 2016;43(suppl 3):S13-S18; Piña-Garza JE, Boyce D, Tworek DM, et al. Epilepsy Behav. 2019;90:148-153; Song J. Swallow E. Said Q, et al. J Neurol Sci. 2018;391:104-108.
- Epidiolex package insert (https://www.epidiolex.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_(cannabidiol)_USPI.pdf)

Pharma Grade Cannabidiol as a Clinical Treatment

- Interactions – inhibits CYP2C8, 2C9, 2C19, and UGT
  - Clobazam – 3-fold increase in active N-desmethylclobazam metabolite, increased C_{max} of active 7-OH CBD metabolite
  - Levetiracetam
  - Liver enzyme checks (BL and 1-6 months)
- Adverse effects
  - Common: somnolence, decreased appetite, diarrhea,
  - Less common: transaminase elevations, fatigue, malaise, asthenia, rash, insomnia
- Dosage forms
  - 100 mg/mL oral solution (sesame seed oil, dehydrated alcohol, sucralose, strawberry flavor)

- Wirrell EC. Can J Neurol Sci. 2016;43(suppl 3):S13-S18; Piña-Garza JE, Boyce D, Tworek DM, et al. Epilepsy Behav. 2019;90:148-153; Song J. Swallow E. Said Q, et al. J Neurol Sci. 2018;391:104-108.
- Epidiolex package insert (https://www.epidiolex.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_(cannabidiol)_USPI.pdf)

Cannabinoid Varieties

- THC-delta-9-tetrahydrocannabinol, binds partially to CB1 and CB2
- CBD: cannabidiol, also binds moderately to CB1 and CB2
- THCa: in raw form is carboxylated—then may be effective for nausea. If heated or exposed to light, then decarboxylates, and becomes regular THC
- CBDa: carboxyl form of CBD

Cannabinoid Varieties

- CBGa: cannabigerolic acid, carboxylic precursor of both THCa and CBDa
- CBC: cannabichromene, blocks nitric oxide, which may block release of substance P, possibly a mechanism for anti-inflammation
  - Romano B et al, 2013
- CBN: cannabinol, “aged” oxidative byproduct of THC, may be sedative, may be more often found in ruderalis species
  - DePetrocellis et al, 2011

Cannabinoid Varieties

- Pentyl vs propyl cannabinoids
- Propyl forms include:
  - CBDVA: cannabidivarin, precursor to pharma grade CBD
  - THCVA: may be less psychoactive
- Some cultivation efforts combine both pentyl and propyl cannabinoids to make CBD

Entourage Effect

- Do other compounds in less purified CBD have an effect?
  - ie, is the “dirtier” drug better?
- Less purified CBD may contain additional compounds
  - Phytocannabinoids
  - Combination of various forms of THC plus CBD
  - THCV, CBDV

- Pamplona FA, Da Silva LR, Coan AC. Potential clinical benefits of CBD-rich cannabis extracts over purified CBD in treatment-resistant epilepsy: observational data meta-analysis. Front Neurol. (2018) 9:759. doi: 10.3389/fneur.2018.00759
- Bitencourt RM, Takahashi RN and Carlini EA (2021) From an Alternative Medicine to a New Treatment for Refractory Epilepsies: Can Cannabidiol Follow the Same Path to Treat Neuropsychiatric Disorders? Front. Psychiatry 12:638032. doi: 10.3389/fpsyt.2021.638032

Anxiety and Depression

- Blockade of the eCB system leads to depressive symptoms
- Anxiety control may depend upon CBD components of the specific product
- Some evidence that energizing strains of cannabis may worsen anxiety by exacerbating adrenergic symptoms (eg, tachycardia)

- National Academies of Sciences, Engineering, and Medicine 2017. *The Health. Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

Chronic pain

- Paradoxically, cannabis may interfere with addiction in opiate mediated reward systems

Autism spectrum disorder

- Reduction of inflammation may play a role, to the degree that ASD is considered a disorder of hyperexcitability or excessive inflammation

- National Academies of Sciences, Engineering, and Medicine 2017. *The Health. Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

Pharma Grade CBD vs Artisanal CBD

- Extraction methods differ—ethanol versus CO_2
  - Suspicion that pH of the solution for extraction and quality of “flower” makes a difference regarding the terpene profile
- Ratio of CBD:THC may matter
  - Pharma grade CBD is about 50:1, Charlotte’s web is about 28:1
  - Varying opinions about what is ideal for seizure control and what is better for associated conditions such as anxiety or mood
- Strain/chemovar may matter, if it can even be identified
- Quality control

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate[a]	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under[b]	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over[c]	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)	26.15 (12.50-39.74)	36.86 (16.21-57.51)
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)	18.33 (2.00-160.00)	15.00 (1.33-800.00)
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	11.52 (8.10-14.94) [1098.70]	9.16 (4.96-13.36) [380.26]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

[a] Cannabidiol content tested within 10% of labeled value.

[b] Cannabidiol content exceeded labeled value by more than 10%.

[c] Cannabidiol content tested more than 10% below labeled value.

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R.
Labeling Accuracy of Cannabidiol Extracts Sold Online.
JAMA. 2017;318(17):1708–1709. doi:10.1001/jama.2017.11909

The Universe of Cannabidiol as a Clinical Treatment

- **<u>The evidence on this topic is evolving</u>**
- Cross-tolerance with benzodiazepines
- Liver monitoring
- Tolerance may be enhanced with THC components
- Activation may occur with certain chemovars
- Modulating effects may come from other plant components
  - Terpenoids

Terpenes

A-Pinene

Anti-inflammatory
Bronchodilator
Anti-bacterial
Aids Memory

Pine Needles

Linalool

Anesthetic
Anti-convulsant
Analgesic
Anti-Anxiety

Lavender

Beta Caryophylene

Anti-inflammatory
Analgesic
Help digestive tract

Black Pepper

Myrcene

Sleep Aid
Muscle Relaxant

Hops

Limonene

Anti-Anxiety
Antidepressant
Treats Acid Reflux

Citrus

Summary

- Neuropsychiatric conditions such as epilepsy require a paradigm shift in terms of conceptualizing phenomenology and treatment strategies
- Some treatments may improve psychiatric and neurologic symptoms simultaneously
- Study of the endocannabinoid system represents an advance in the understanding of neuronal function

Summary (continued)

- CBD and THC represent two distinct aspects of cannabinoid function, though synergy of the two compounds cannot be ruled out
- Data quality and quality control of products vary widely and challenge understanding of treatment strategies
- However, class I evidence exists confirming efficacy of high ratio CBD for seizure control
- Less evidence exists that confirms the utility of “full-spectrum” products or specific components such as terpenoids