CBD, Hemp, and Pharmacist Implications: What's It All About?

An "Ask the Experts" Forum

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Greenwich Biosciences.

Faculty

Jacquelyn L. Bainbridge, BSPharm, PharmD, FCCP, MSCS, FAES

Professor, Clinical Pharmacy & Department of Neurology
University of Colorado Anschutz Medical Campus
Skaggs School of Pharmacy and
Pharmaceutical Sciences
Aurora, Colorado

Dr. Jacci Bainbridge received her Doctor of Pharmacy degree from the University of Colorado, where she subsequently completed a specialty residency in neurology. She currently serves as a Professor at the University of Colorado Anschutz Medical Campus in the Skaggs School of Pharmacy and Pharmaceutical Sciences and the Department of Clinical Pharmacy, as well as the Department of Neurology in the School of Medicine. Dr. Bainbridge is an Investigator on several federal and state funded clinical research trials in neurology and cannabis. She is a frequent lecturer on topics of neurological and pharmacological interest in the areas of restless legs syndrome, multiple sclerosis, epilepsy, migraine, neuroprotection, chronic pain disorders, cannabis, and movement disorders.

Faculty

Laura Borgelt, PharmD, MBA, FCCP, BCPS

Professor and Associate Vice Chancellor of Strategic Initiatives
Departments of Clinical Pharmacy and Family Medicine
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Dr. Laura Borgelt is an Associate Vice Chancellor of Strategic Initiatives at the University of Colorado Anschutz Medical Campus and a Professor at the Skaggs School of Pharmacy and the Departments of Clinical Pharmacy and Family Medicine. For the past 10 years, she has investigated the potential effectiveness and risks of cannabis in a comprehensive manner and has provided evidence-based presentations to medical, nursing, pharmacy, and patient organizations at the state and national levels. She has served on 8 different working groups regarding rulemaking for consumer safety and social issues in the state of Colorado.

Disclosures

Dr. Bainbridge has disclosed that she has received grant/research support from Greenwich Biosciences.

Dr. Borgelt has disclosed that she has no actual or potential conflicts of interest in relation to this program.

The clinical/legal reviewer, **Gerald Gianutsos, JD, PhD,** has no actual or potential conflicts of interest in relation to this program.

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Type of Activity: Application

Learning Objectives

- **Assess** the most up-to-date data about medical marijuana and cannabidiol (CBD)–containing agents, including both over-the-counter products and agents approved as prescription agents by the US Food and Drug Administration
- **Assess** CBD, tetrahydrocannabinol (THC), and other cannabinoid-containing products including issues relating to purity, consistency, formulation, and dose
- **Describe** the differences among cannabis products in medical or recreational dispensaries compared with street products or home-grown, plant-based substances
- **Discuss** current laws related to cannabis-derived agents and products in the US

Outline for Presentation

- **Overview: CBD and Medical Marijuana or Cannabis**
- **CBD in Neurologic and Psychiatric Disorders**
- **Legal Implications**
- **Conclusions and Additional Q&A**

OVERVIEW:
CBD AND MEDICAL MARIJUANA OR CANNABIS

Cannabis

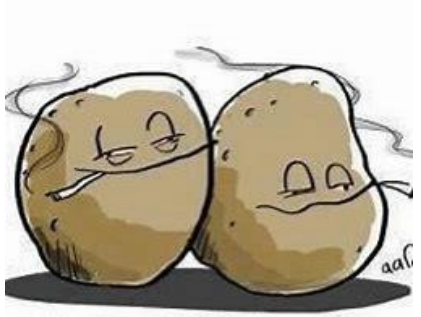
- Contains over 400 compounds
  - Over 100 cannabinoids have been isolated
  - Terpenes are variable, contribute to aroma (limonene, pinene), serve as a precursor to cannabinoids
- Cannabinoids and terpenes are found in:
  flowering tops > buds > top leaves > lower leaves > stems stalks
- *Indica* and *sativa* have been crossbred, so there are no generalizable characteristics
- The first documented date of cannabis use for medicinal purposes was in 400 AD
- Cannabis was mentioned in the USP in 1850

USP, United States Pharmacopeia.

Borgelt LM, et al. *Pharmacotherapy*. 2013;33(2):195-209.

Delta-9-tetrahydrocannabinol (THC)

- Major component of cannabis that causes the “high” or “euphoric” feeling
  - Mechanism of action: partial CB1 agonist
- Beneficial effects
  - Helps prevent nausea/vomiting due to cancer chemotherapy
  - Appetite promoter
  - Some medical conditions



- *Short-term* adverse effects
  - Memory loss, loss of time, impaired coordination, increased heart rate & variability
  - Altered thinking, panic, delusions/hallucinations, paranoia, psychosis
- *Long-term* adverse effects
  - Addiction (9% overall), altered brain development*, diminished life satisfaction and achievement*, cognitive impairment (lower IQ)*, hyperemesis syndrome, symptoms of chronic bronchitis, increased risk of chronic psychosis disorders, poor educational outcome

*Strongly associated with initial marijuana use early in adolescence.

Volkow ND, et al. *N Engl J Med*. 2014;370(23):2219-2227.

Cannabidiol (CBD)

- Major noneuphoric component of cannabis (no high)
- Precise mechanism of action is unknown; may be an antagonist or an inverse agonist
- Indirect effect on the CB1 receptor, via anandamide (2AG) and other endocannabinoids
- Endocannabinoids bind to CB1 and CB2 receptors
  - CB1 receptors are found primarily in the central and peripheral nervous systems and CB2 receptors are found primarily in the immune system and peripheral tissues
- Research into other receptors (eg, opioid, G-protein receptors, G-protein–coupled receptors [GPR55]) is ongoing

Borgelt LM, et al. *Pharmacotherapy*. 2013;33(2):195-209. Devinsky O, et al. *Epilepsia*. 2014;55(6):791-802. Devinsky O, et al. *Lancet Neurol*. 2016;15(3):270-278. Grotenhermen F. *Clin Pharmacokinet.* 2003;42(4):327-360.

Cannabidiol (CBD) *(continued)*

- Beneficial effects
  - No significant neurologic effects
  - No effects on vital signs or mood
  - Can increase sedation
  - Enhances the activity of the endogenous cannabinoid (anandamide)
- Adverse effects
  - Somnolence, decreased appetite, diarrhea, fatigue, increased liver function tests, convulsion
  - May increase risk of infection

Borgelt LM, et al. *Pharmacotherapy*. 2013;33(2):195-209. Devinsky O, et al. *Epilepsia*. 2014;55(6):791-802. Devinsky O, et al. *Lancet Neurol*. 2016;15(3):270-278. Grotenhermen F. *Clin Pharmacokinet.* 2003;42(4):327-360.

Industrialized Hemp

- Federal law defines *industrialized hemp* as “a plant of the genus cannabis and any part of the plant, whether growing or not, containing a delta-9-tetrahydrocannabinol (THC) concentration of no more than 0.3% on a dry weight basis”
- Must be a registered industrial hemp farmer with the USDA
- Marijuana must be grown inside with regulated light, temperature, humidity, CO_2, and O_2 levels
  - Maximize THC concentration
- Hemp must be grown outdoors to maximize size and yield
  - Less attention paid to individual plants

USDA, United States Department of Agriculture. https://nifa.usda.gov/industrial-hemp.

Differences Between Hemp and Marijuana

	Hemp	Marijuana
Statutory definition	"the plant *Cannabis sativa* L. and any part of that plant... whether growing or not, with a delta-9-tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis"[1]	"all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture or preparation of such plant, its seeds or resin."[2] Does not include: • Mature stalks • Fiber, oil, or cake from the seed • Sterilized seed incapable of germination
Psychoactive properties	Nonpsychotropic	Psychotropic
Threshold for psychoactive compounds	No more than 0.3% delta-9-THC on a dry weight basis	No THC threshold specified
Primary federal agencies with regulatory oversight	USDA FDA	DEA FDA

DEA, US Drug Enforcement Administration.

1. 2018 Farm Bill. PL 115-334, §10113. 2. Federal Food, Drug, and Cosmetic Act. 21 USC §802(16).

FDA-Approved Products

Marinol®/Syndros® (dronabinol)

- FDA approved in 1985
- Synthetic THC
- Schedule III
- Used for:
  - Anorexia in patients with AIDS
  - Nausea and vomiting associated with cancer chemotherapy

Epidiolex® (cannabidiol)

- FDA approved in June 2018
- Plant-derived CBD
- The first FDA-approved cannabinoid prescription drug
- Used for:
  - Lennox-Gastaut syndrome
  - Dravet syndrome
  - Tuberous sclerosis complex

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc; 2018.
Marinol (dronabinol) [package insert]. North Chicago, IL: AbbVie Inc; 2017.
Syndros (dronabinol) [package insert]. Chandler, AZ: Insys Therapeutics, Inc; 2016.

Other Products

Cesamet® (Nabilone)

- FDA approved in 2006
- Synthetic cannabinoid
- Schedule II
- Used for:
  - Nausea and vomiting for cancer-related chemotherapy

Sativex® (THC and CBD)

- Licensed for use in the United Kingdom
- Not FDA approved
- Used for:
  - Multiple sclerosis–related spasticity

Cesamet (nabilone) [package insert]. Costa Mesa, CA: Valeant Phamaceuticals; 2006.
Sativex (THC and CBD) [package insert]. Cambridge, UK: GW Pharmaceuticals; 2016.

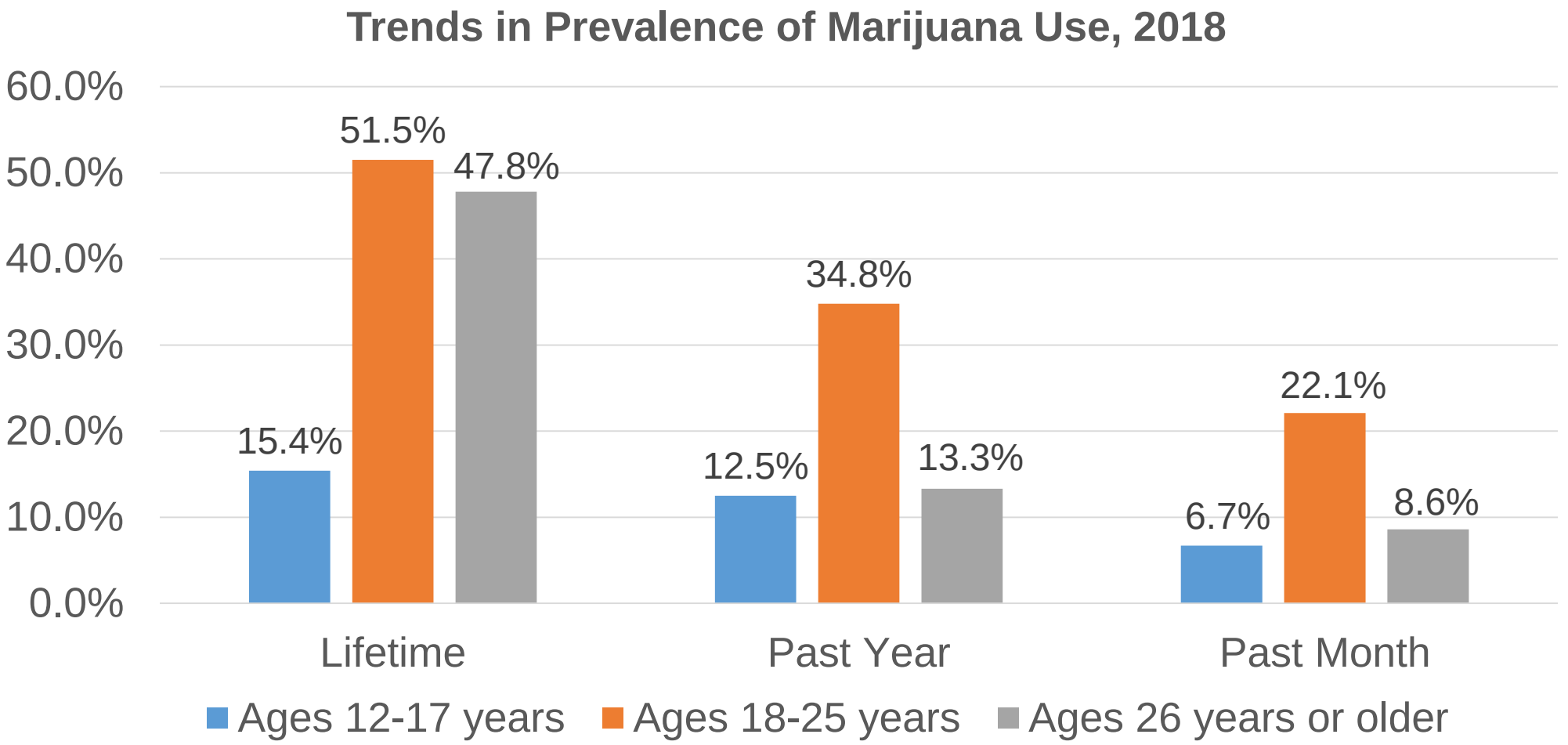
Cannabis Activity at CB1 Receptors

Structure	THC effect	
Neocortex	Altered thinking, judgement	
Basal ganglia	Slowed reaction time	
Hypothalamus	↑ appetite	1992
Amygdala	Panic, paranoia	
Nucleus accumbens	Euphoria	
Hippocampus	Impaired memory	
Cerebellum	Impaired coordination	
Brain stem	Anti-nausea effects	1985
Hippocampus, forebrain	Anti-epileptic effects?	
Spinal cord	Altered pain sensitivity	1996

Dose-response effects of CBD not established

- Low dose <300 mg → inconsistent effects
- Typical response can be seen at 600 mg

Trends in Cannabis Use



National Survey on Drug Use and Health. https://www.drugabuse.gov/drugs-abuse/marijuana.

Cannabis Use in the United States

- Medical cannabis use (Mahabir 2020)
  - Average age 45.5 years
  - 54.8% were male and the majority were Caucasian (87.5%)
  - 67% of patients reported cannabis experience prior to seeking medical certification
  - Primary medical conditions: chronic pain, anxiety, and PTSD
  - Average number of comorbid conditions reported was 2.7
- 14% of Americans say they use CBD products (2019)
  - 40% for pain
  - 20% for anxiety
  - 11% for sleep

PTSD, posttraumatic stress disorder.

Gallup. https://news.gallup.com/poll/263147/americans-say-cbd-products.aspx.
Mahabir VK, et al. *J Cannabis Res*. 2020;2(1):32.

Summary

- Cannabis is a complex plant with over 100 cannabinoids; THC and CBD remain the most well-known
- The importance of understanding the differences between cannabis-based products is important for patient care
- Rigorous research needs to be conducted to truly decide which medical conditions can best be treated with cannabis

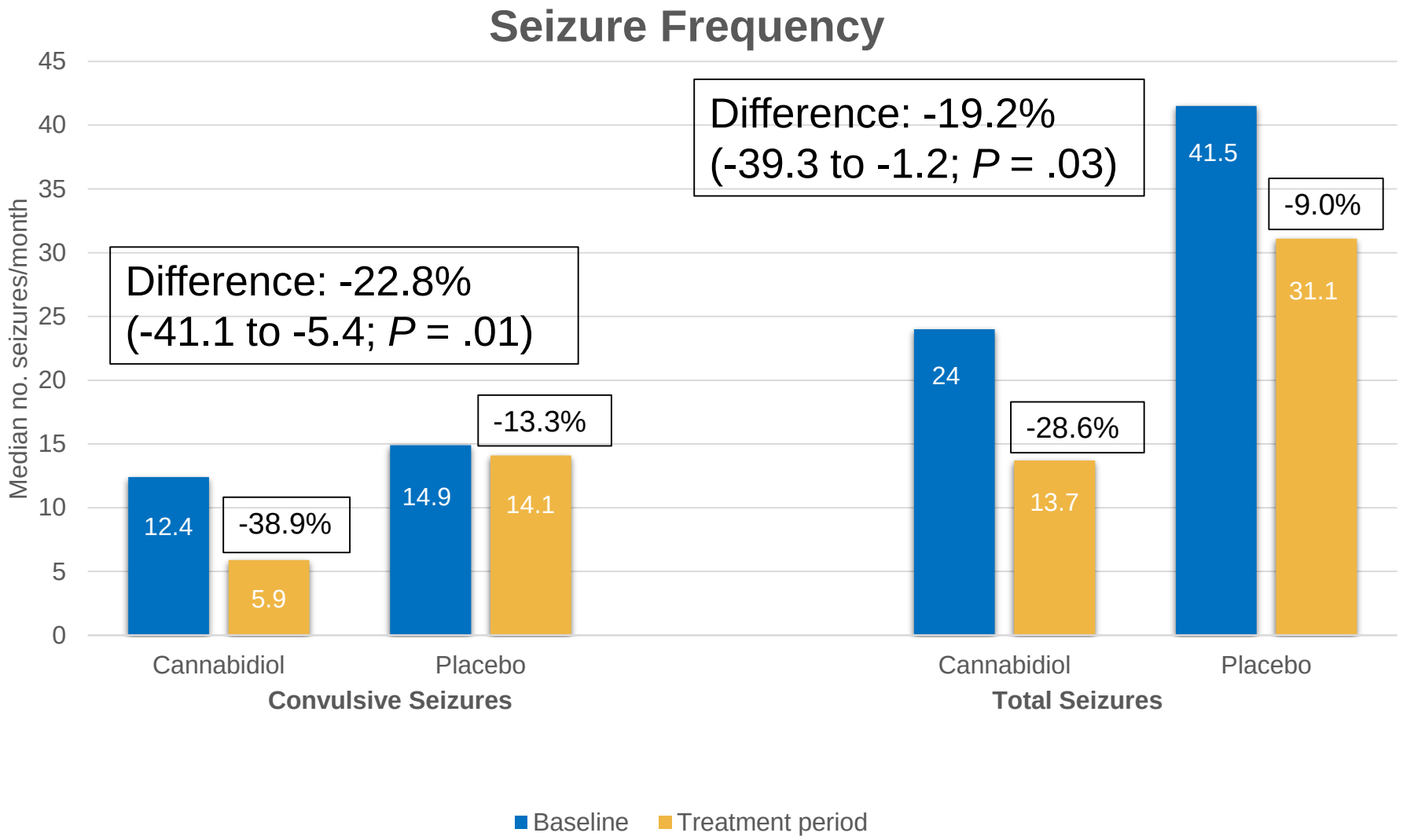
Questions & Answers

Medical Benefits of CBD

- **Epidiolex**
  - Lennox-Gastaut syndrome
  - Dravet syndrome
  - Tuberous sclerosis complex

- **Other CBD products**
  - No FDA-approved indications
  - Growing number of studies for other conditions

Cannabidiol (Epidiolex): Dravet Syndrome



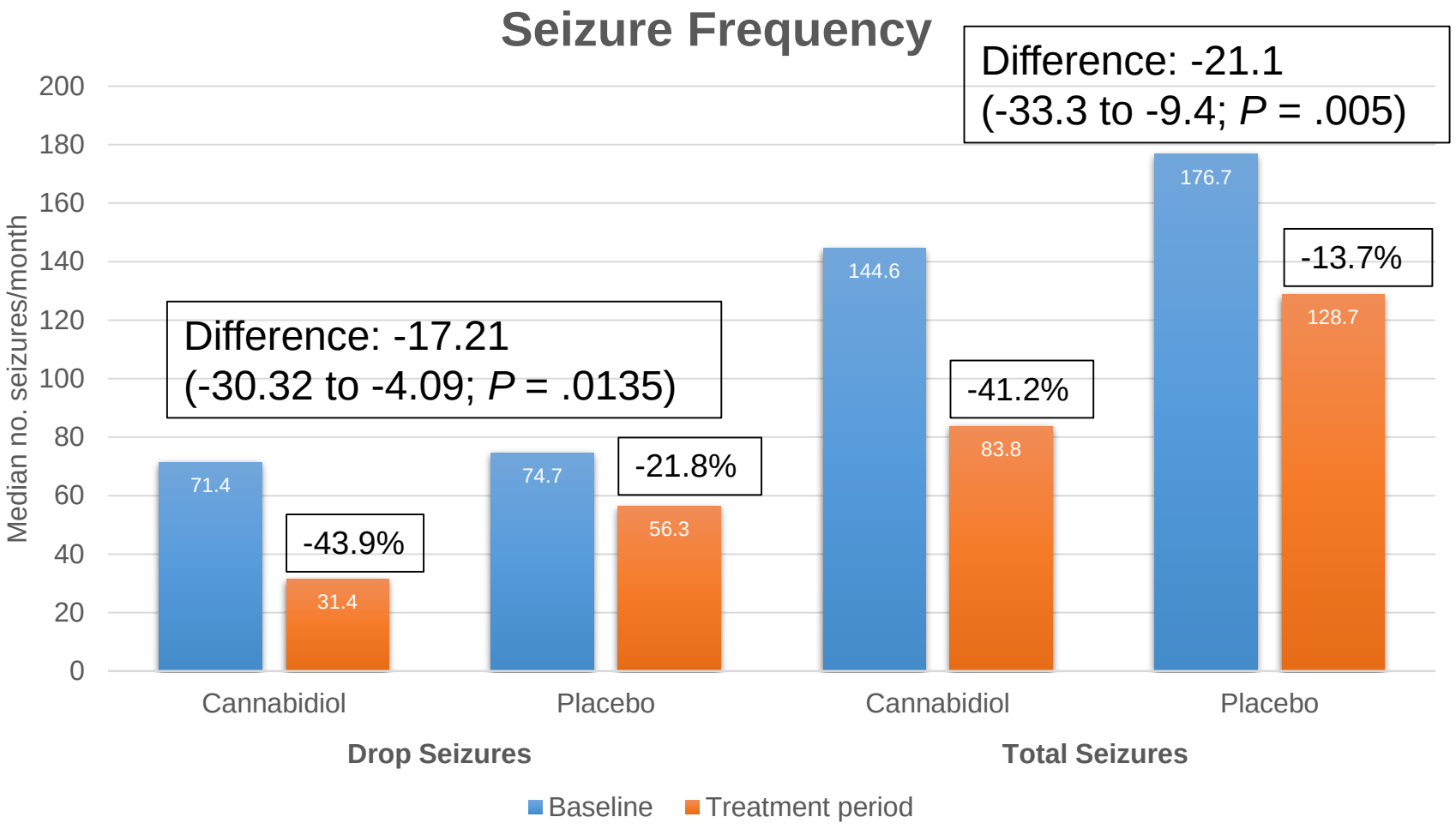
Adverse Effects
- 93% of cannabidiol
- 75% of placebo

Cannabidiol:
- 84% mild/moderate
- Vomiting, fatigue, pyrexia, upper respiratory tract infection, ↓ appetite, convulsion, lethargy, **somnolence**, and diarrhea
- 8 withdrew from trial

Placebo:
- 95% mild/moderate
- 1 withdrew from trial

Devinsky O. *N Engl J Med*. 2017;376(21):2011-2020.

Cannabidiol (Epidiolex): Lennox-Gastaut



Adverse effects
- 86% of cannabidiol
- 69% of placebo

Cannabidiol:
- 78% mild/moderate
- Diarrhea, somnolence, pyrexia, ↓ appetite, vomiting
- 14 withdrew

Placebo:
- 97% mild/moderate
- 1 withdrew

Devinsky O. *N Engl J Med*. 2017;376(21):2011-2020.

Other Conditions: Evidence With CBD

Condition	Types of Evidence
• Breast cancer • Anxiety • Depression • Osteoarthritis	• Meta-analysis • Systematic review • Randomized controlled trial (RCT) • Prospective observational study • Retrospective observational study • Case-control study • Case series • Case report • Preclinical or animal studies

CBD and Breast Cancer

***Mol Cancer Ther*. 2011;10(7):1161-1172.**

"Our study revealed an intricate interplay between apoptosis and autophagy in CBD-treated breast cancer cells and highlighted the value of continued investigation into the potential use of CBD as an antineoplastic agent."

***Breast*. 2018;41:34-41.**

"The results suggest that CBD treatment induces an interplay among PPARγ, mTOR and cyclin D1 in favor of apoptosis induction in both ER-positive and triple negative breast cancer cells, proposing CBD as a useful treatment for different breast cancer subtypes."

Preclinical evidence or animal studies

CBD and Anxiety: Systematic Review

- 8 articles: 6 small RCTs, 1 case series, and 1 case report
- Role of CBD in the anxiety response of healthy volunteers
  - Generalized anxiety disorder, social anxiety disorder, anxiety component of PTSD
- CBD administration
  - Orally as capsule or sublingual spray and as either monotherapy or adjunctive therapy
  - Doses varied widely with fixed doses of 6 mg to 400 mg per dose
- Results
  - CBD demonstrated improved clinical outcomes among anxiety assessment scales
  - CBD was well-tolerated and associated with minimal adverse effects, with the most commonly noted adverse effects being fatigue and sedation

Mixed evidence, small sample sizes, variety of dosing and administration, lack standardized assessment tool

Skelley JW, et al. *J Am Pharm Assoc*. 2020;60(1):253-261.

CBD and Depression

CNS Neurol Disord Drug Targets.

2014;13(6):953-960.

"Studies involving animal models, performing a variety of experiments…suggest that CBD exhibited an anti-anxiety and antidepressant effects…Most of the studies demonstrated a good interaction between CBD and the 5-HT1A neuro-receptor."

***Mol Neurobiol*.**

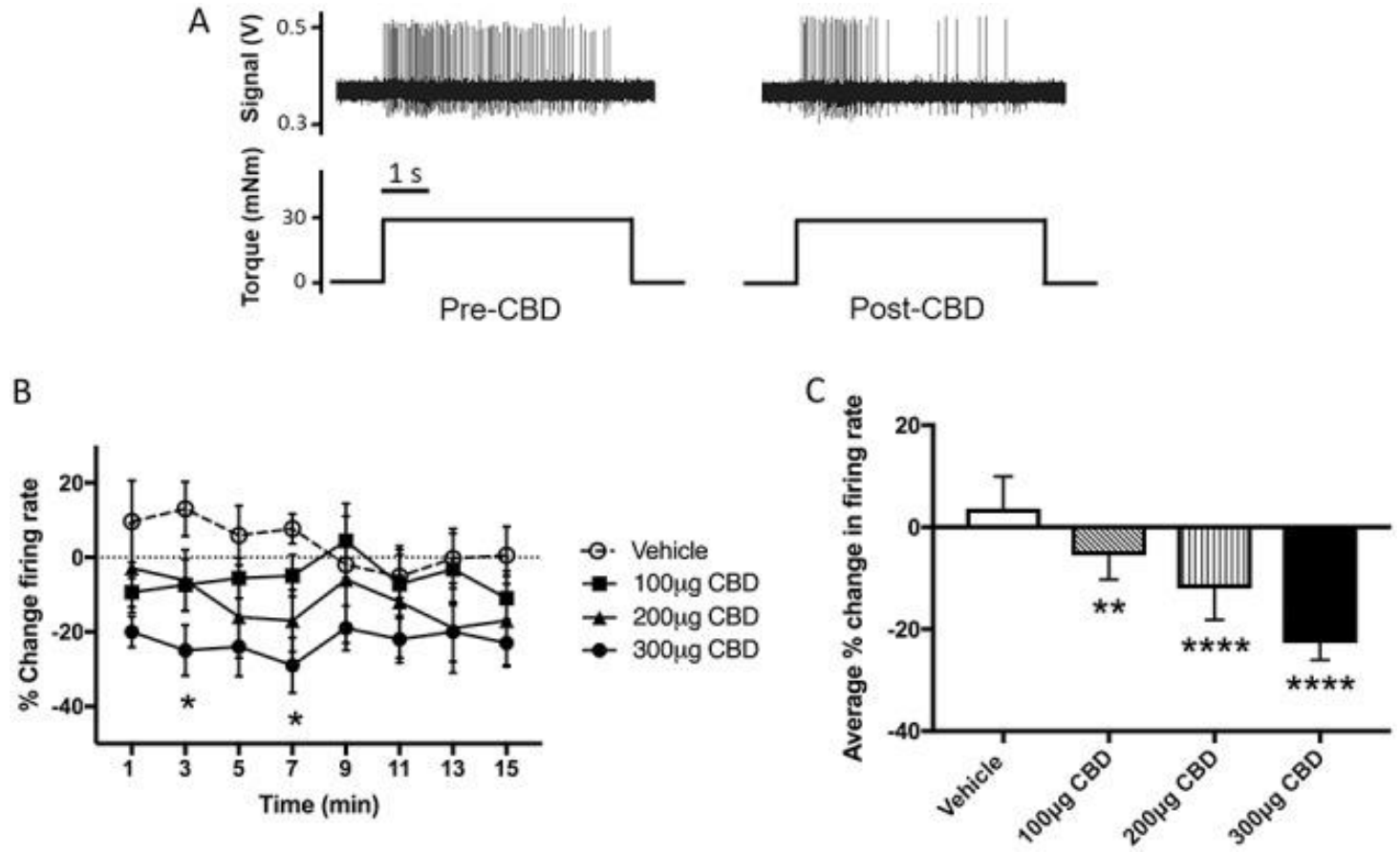
2019;56(2):1070-1081.

"These results indicate that CBD induces fast and sustained antidepressant-like effect in distinct animal models relevant for depression…The data support a promising therapeutic profile for CBD as a new fast-acting antidepressant drug."

Preclinical evidence or animal studies

CBD and Osteoarthritis

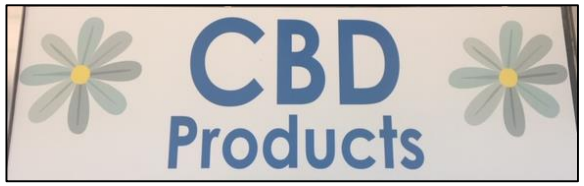
- Male Wistar rats with knee osteoarthritis
- CBD 100-300 mcg applied topically or vehicle



Preclinical evidence or animal studies

Philpott HT, et al. *Pain*. 2017;158(12):2442-2451. Mlost J. *Int J Mol Sci*. 2020;21(22):8870.

Purity and Potency of CBD Products



FDA

"FDA is aware that some companies are marketing products containing cannabis and cannabis-derived compounds in ways that violate the Federal Food, Drug and Cosmetic Act (FD&C Act) and that may put the health and safety of consumers at risk.
The agency is committed to protecting the public health while also taking steps to improve the efficiency of regulatory pathways for the lawful marketing of appropriate cannabis and cannabis-derived products."

https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd.

Inaccurate Labeling of CBD Products

84 CBD PRODUCTS TESTED FOR LABEL ACCURACY		
UNDERLABELED (CBD content exceeded label value)	**OVERLABELED** (CBD content below labeled value)	**ACCURATE** (CBD content within 10% of labeled value)
36 (42.9%)	22 (26.2%)	26 (31.0%)

THC was detected in 18 of the 84 samples tested

Bonn-Miller MO, et al. *JAMA*. 2017;318(17):1708-1709.
https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis.

Potential for Contamination

- FDA and EPA have not provided guidance on how to regulate contaminants or on cannabis-related exposures that can be considered safe
  - States have had to determine this on their own
- Chemical solvents
- Microbial contamination
- Pesticides and insecticides
- Metal contamination
  - Cannabis is known to be a “hyperaccumulator”

https://ehp.niehs.nih.gov/doi/full/10.1289/EHP5785.

Ensuring Quality of CBD Products

- **Third-party testing (certificate of analysis)**
  - Potency; how much CBD? THC? Total?
  - Contaminants, solvents, pesticides, microbiological tests
  - CO_2-extracted products
- **GMP-certified**
- **Certified organic**
- **Choosing brands**
  - Following best practices
  - Reliable source of hemp
  - Sustainable business
  - Support team to answer questions
- **Note: Hemp seed oil is not CBD**
- **Avoid products with health claims**

Third-Party Testing

CoA Prepared: 17-Aug-19

Said Zeinab
Senior Manager, Quality Control

Potency		wt %	mg/g
Total THC equivalents	(Δ9-THC + Δ9-THCA x 0.877)	20.98%	209.82
Total CBD equivalents	(CBD + CBDA x 0.877)	BLQ	BLQ

Most abundant minor cannabinoids

	wt %		wt %
CBGA	0.23%	THCVA	0.09%
CBCA	0.19%	CBG	0.07%

Terpenes

Most abundant of the 39 terpenes quantified

	wt %		wt %
alpha-Pinene	0.509	Guaiol	0.050
beta-Myrcene	0.310	alpha-Bisabolol	0.047
beta-Pinene	0.161	Linalool	0.041
Limonene	0.133	trans-Nerolidol	0.039
trans-Caryophyllene	0.087	alpha-Humulene	0.034

Loss on Drying 7.3%

Contaminant Analysis

Microbial Quality

Total aerobic microbial counts	pass
Total yeast and mold counts	pass
Bile-tolerant gram-negative bacteria	pass
E coli	absent
Salmonella spp	absent

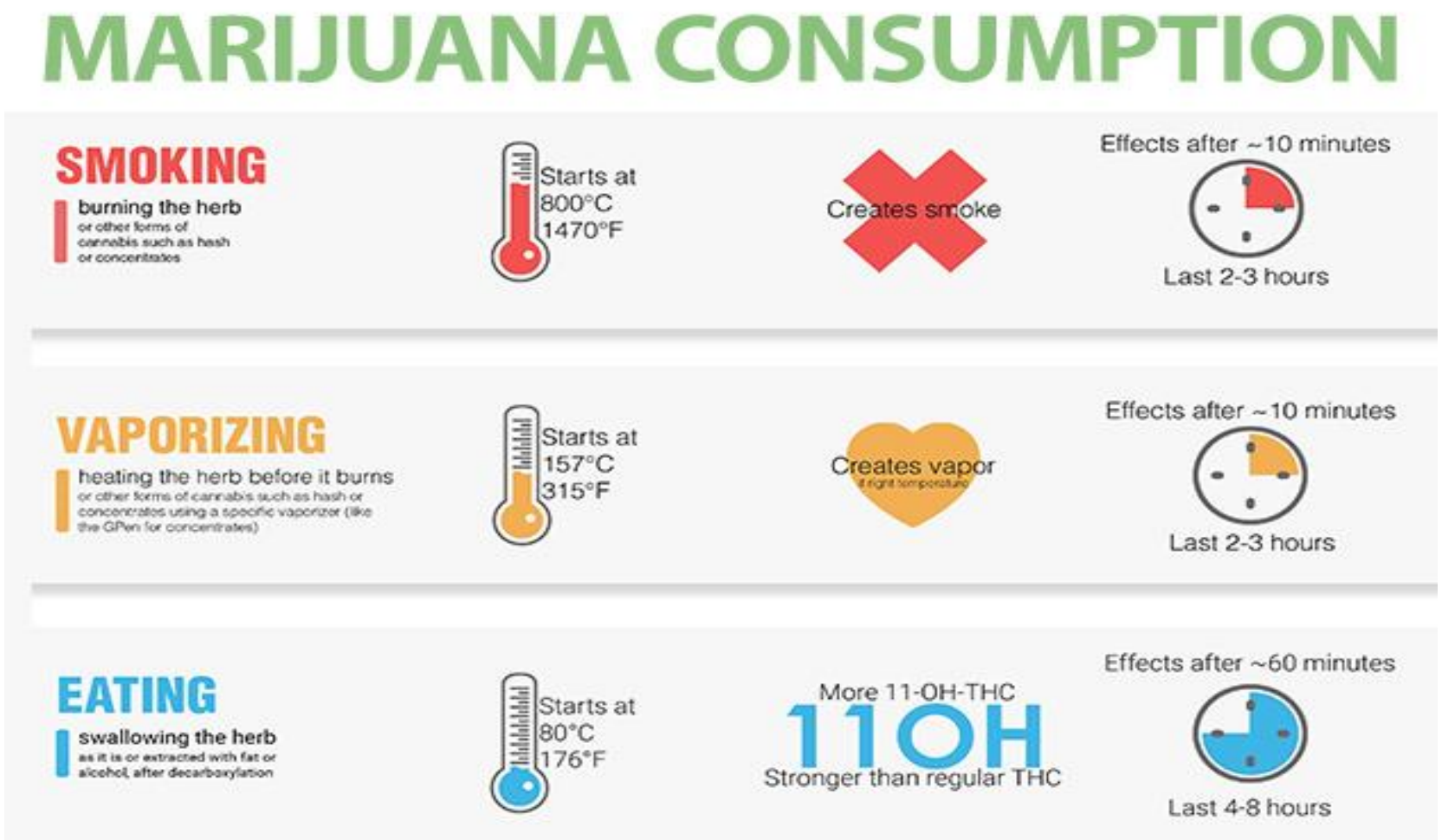
Aflatoxins	Aflatoxin B1, B2, G1, G2	pass
Heavy Metals	Arsenic, Cadmium, Lead, Mercury	pass
Pesticides		None detected

FDA Warnings: CBD Products (Dec 2020)

- FDA issued 5 warning letters to companies for selling products containing CBD in ways that violate the FD&C Act
- All 5 warning letters address the illegal marketing of unapproved CBD products claiming to treat medical conditions
- CBD products that are concerning from a public health perspective due to route of administration, including nasal, ophthalmic, and inhalation
- Address violations relating to the addition of CBD to food, and the impermissible marketing of CBD products as dietary supplements
- Two of the letters also address CBD products illegally marketed for pets, including a product for use in the eye

https://www.fda.gov/news-events/press-announcements/fda-warns-companies-illegally-selling-cbd-products.

Formulations



http://azmarijuana.com/dans-stash/marijuana-consumption-styles/.

Dosing: Cannabidiol (Epidiolex)

- Cannabidiol (Epidiolex): oral solution 100 mg/mL
- Lennox-Gastaut and Dravet syndromes
  - Starting dose is 2.5 mg/kg by mouth twice daily (5 mg/kg/day)
  - After 1 week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily
- Tuberous sclerosis
  - Starting dose is 2.5 mg/kg by mouth twice daily (5 mg/kg/day)
  - Increase dosage weekly by 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day)

McCallum CA, et al. *Eur J Intern Med*. 2018;49:14-19.
Millar SA. *Br J Clin Pharmacol*. 2019;85(9):1888-1900.
Zuurman L. *Br J Clin Pharmacol*. 2009;67(1):5-21.

Dosing: Other Medical Cannabis Products

- Doses vary in form and usage
- Cannot confirm safe, beneficial dosages outside approved dosages
- Systematic review of CBD dosing
  - 35 studies of CBD dosing in 13 medical contexts
  - Dosing range <1 to <50 mg/kg/day
- Typical “effective” dosing of inhaled THC
  - Low dose <7 mg
  - Medium dose = 7–18 mg
  - High dose >18 mg
- **“Start low, go slow, and stay low”**

McCallum CA, et al. *Eur J Intern Med*. 2018;49:14-19.
Millar SA. *Br J Clin Pharmacol*. 2019;85(9):1888-1900.
Zuurman L. *Br J Clin Pharmacol*. 2009;67(1):5-21.

Summary

Prescription Cannabis-Based Products	OTC Cannabis-Based Products
• Rigorous regulatory process • Rigorous clinical trials • Evidence they work for therapeutic indications • Ingredients are known and consistent • Standardized dose and formulation	• No clinical trials • No specific indications and companies should not include any health claims on the label • Ingredients may be known and may be consistent (or may not be) • Variable dosing and many different formulations

Questions & Answers

CBD IN NEUROLOGIC AND PSYCHIATRIC DISORDERS

CBD Effects on Seizure Activity

- Studies have demonstrated endogenous cannabinoid systems are altered in a variety of models of seizures and epilepsy
  - External modulation can prevent/modulate seizure activity
- CBD antiseizure activity considered to be mediated by mechanisms other than CB1/2 agonism
  - 10 proposed targets
- THC antiseizure activity mediated by partial agonism of CB1 receptor
  - Inconsistent activity demonstrated
  - Psychotropic effects make it undesirable for treatment in epilepsy

Perucca E. *J Epilepsy Res*. 2017;7(2):61-76.

Dravet Syndrome (DS)

- Rare genetic infantile epileptic encephalopathy
  - Frequent and prolonged seizures → status epilepticus
  - Poor motor, interpersonal, and language skills; hyperactivity
  - Autonomic dysfunction, sleep problems
- Due to SCN1A mutation (in the sodium channel) or other mutations
  - Present in 85% of children with DS[1-4]
  - Not inherited from the parents
  - A blood test may confirm diagnosis
- Incidence in US is approximately 1 in 20,000[5-8] to 1 in 40,000[9]
- Treatment includes valproate, clobazam, stiripentol, fenfluramine, ketogenic diet, vagus nerve stimulation (VNS), **cannabidiol (Epidiolex)**

1. Escayg A, et al. *Epilepsia*. 2010;51(9):1650-1658. 2. Fukuma G, et al. *Epilepsia*. 2004;45(2):140-148. 3. Wang JW, et al. *Epilepsia*. 2008;49(9):1528-1534. 4. Zuberi SM, et al. *Neurology*. 2011;76(7):594-560. 5. Wu YW, et al. *Pediatrics*. 2015;136(5):e1310-e1315. 6. Brunklaus A, et al. *Epilepsia*. 2011;52(8):1476-1482. 7. Rogona F, et al. *Brain Dev*. 2010;32(1):71-77. 8. Ragona F, et al. *Epilepsia*. 2011;52(2):386-392. 9. Knupp KG, et al. *CNS Drugs*. 2018;32(4):335-350.

Lennox-Gastaut Syndrome (LGS)

- The causes of LGS can be divided into 2 categories
  - **Symptomatic:** brain injury, generally diffuse injuries (encephalitis, meningitis, tuberous sclerosis complex, brain malformations, hypoxia at birth, trauma) to the frontal lobes of brain
    - Identifiable cause; 75% have this type
  - **Cryptogenic:** no clear cause; may be associated with mutations or changes on parts of the genes that could contribute to the development of LGS
- Most seizures associated with LGS typically occur at age 3 years (between 1 and 7 years); 5 times more common in boys[1-4]
- Incidence is approximately 2.8 per 100,000 live births[5]
- Represents 4% to 10% of all childhood epilepsies[4-7]

1. Epilepsy Foundation. https://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs/lennox-gastaut-syndrome-overview. 2. Gastaut H, et al. *Epilepsia*. 1966;7(2):139-179. 3. Arzimanoglou A, et al. *Epileptic Disord*. 2011;13(suppl 1):S3-S13. 4. Panayiotopoulos CP. ILAE classification and practice parameter guidelines; 2010. 5. Rantala H, et al. *Epilepsia*. 1999;40(3):286-289. 6. Gastaut H, et al. *Epilepsia*. 1975;16(3):457-461. 7. Trevathan E, et al. *Epilepsia*. 1997;38(12):1283-1288.

Treatment of LGS

- Ketogenic diet—may be helpful
- Vagus nerve stimulation (VNS)—may be helpful
- Responsive neurostimulation—may be helpful
- Corpus callosum surgery—may decrease the number of seizures
- **Cannabidiol, CBD (Epidiolex)—approved June 2018**
- Clobazam (Onfi)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Felbamate (Felbatol)
- Rufinamide (Banzel)

Epilepsy Foundation . https://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs/lennox-gastaut-syndrome-overview.

Tuberous Sclerosis Complex (TSC)

- Autosomal dominant (1 mutated gene) genetic condition that can involve multiple organ systems, including the heart, brain, kidneys, lungs, eyes, and skin (ash-leaf spots)
  - Mutations in 1 of 2 genes (TSC1 and TSC2) in 70% of cases
  - 1/3 of cases are inherited from parents, while 2/3 occur spontaneously
- Occurs in 1 out of 6000 people
- Diagnosis based on specific clinical criteria and/or genetic testing
- Epilepsy present in >90% of TSC patients and may become intractable to autism spectrum disorders (ASDs)
- Autism develops in 25% to 50% of patients with TSC
- Seizures—infantile spasms, focal, tonic, clonic, atonic, absence
- Treatment—infantile spasms (vigabatrin), other ASDs, ketogenic diet, VNS, surgery, sirolimus, everolimus (giant cell astrocytomas)

Cannabidiol (Epidiolex)

- First FDA-approved cannabinoid prescription drug from plant material that is different from other CBD products
- **Indication:** Treatment of LGS, DS, and TSC
- **DEA schedule:** Now descheduled (was schedule V)
- **Dosage form:** Oral solution (100 mg/mL)
- **Contains:** <0.1% THC in the API powder and <0.01% THC in the finished oral solution
- **Side effects (10%):**
  - Somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, asthenia, rash, insomnia, sleep disorder, poor quality sleep, infections

API, Active Pharmaceutical Ingredient.

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.
Gaston TE, et al. *Epilepsia.* 2017;58(9):1586-1592.

Epidiolex: Mechanism of Action

- The precise mechanisms by which Epidiolex exerts its anticonvulsant effect in humans are **unknown**
  - Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors
- Cannabidiol potentially:
  - Blocks GPR55 receptors
  - Desensitizes TRPV1 channels
  - Inhibits adenosine reuptake pumps
- Decreasing calcium and increasing extracellular adenosine
- Decreasing neuroexcitability

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA; Greenwich Biosciences, Inc.; 2020.

Epidiolex: Pharmacokinetics

Absorption	Tmax 2.5-5 h High-fat/high-calorie meal ↑ Cmax 5-fold, ↑ AUC 4-fold
Distribution	Protein bound >94%
Metabolism	$t_{1/2}$ 56-61 h Liver (CYP2C19, CYP3A4, UGT1A7, UGT1A9, UGT2B7) 7-OH-CBD metabolite is active
Excretion	Feces, minor renal clearance

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA; Greenwich Biosciences, Inc.; 2020.

Epidiolex: Dosing Strategies for LGS and DS

RECOMMENDED DOSAGE[1]

WEEK 1	WEEK 2	IF TOLERATED AND REQUIRED	
Starting **5 mg/kg/day** (2.5 mg/kg twice daily)	**Maintenance** **10 mg/kg/day** (5 mg/kg twice daily)	**Next titration** **15 mg/kg/day** (7.5 mg/kg twice daily)	**Maximum** **20 mg/kg/day** (10 mg/kg twice daily)

**NOTE: Total dosage should be split and administered twice daily. See additional dosing considerations for more information.*

- When discontinuing, dose decreased gradually to minimize risk of increased seizure frequency or status epilepticus

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA; Greenwich Biosciences, Inc.; 2020.

Epidiolex: Dosing Strategies for TSC

- Starting dose is 2.5 mg/kg twice daily (5 mg/kg/day)
- Increase the dose in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day)
- Recommended maintenance dosage of 12.5 mg twice daily (25 mg/kg/day)
- For patients in whom a more rapid titration to 25 mg/kg/day is needed, the dosage may be increased no more frequently than every other day

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA; Greenwich Biosciences, Inc.; 2020.

Epidiolex: Warnings

- Epidiolex causes dose-related elevations of ALT and AST
  - In 2/3 of cases, discontinuation or reduction of Epidiolex resolved transaminase elevations
  - In 1/3 of cases, elevations resolved without dose reduction of Epidiolex
- Dose adjustment recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
  - Slower dose titration may be necessary
- Increased incidence of liver enzyme elevations with valproate administration
- *Epidiolex meets highest standards for safety and quality, unlike other medical marijuana products*

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.
Gaston TE, et al. *Epilepsia.* 2017;58(9):1586-1592.

Epidiolex: Drug-Drug Interactions

- Epidiolex metabolized by CYP3A4 and CYP2C19
- Coadministration with moderate to strong inhibitors will increase Epidiolex concentration
  - 3A4 inhibitors—diltiazem, verapamil, ketoconazole, itraconazole, erythromycin
  - 2C19 inhibitors—fluvoxamine, isoniazid, ritonavir
- Coadministration with strong inducers will decrease Epidiolex concentration
  - 3A4 inducers—carbamazepine, St. John's wort, phenobarbital, phenytoin, rifampin
  - 2C19 inducers—carbamazepine, phenytoin, rifampin

CYP, cytochrome P450.

Drug-Drug Interactions *(continued)*

- Epidiolex* + clobazam
  - Produces 3-fold increase in plasma concentrations of active metabolite of clobazam (substrate of CYP2C19)
- Epidiolex + valproate
  - Concomitant use increases the incidence of liver enzyme elevation
- Epidiolex* + rufinamide or topiramate or eslicarbazepine
  - Increased serum concentration of rufinamide or topiramate or eslicarbazepine

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.
*Gaston TE, et al. *Epilepsia.* 2017;58(9):1586-1592.

Epidiolex: Counseling and Monitoring

- Monitor liver function tests (LFTs) at baseline and at 1, 3, and 6 months after initiation and periodically thereafter, as clinically indicated
- Can cause weight loss, a decrease in hematocrit and hemoglobin, and elevations in serum creatinine
- Screen for drug interactions and contraindications
- Store at room temperature and discard after 12 weeks of opening
- Pregnancy precaution
- Do not discontinue abruptly
- Causes sedation (use caution when operating hazardous machinery)
- May cause a positive drug screen for cannabis since it contains <0.1% THC in the API powder and <0.01% in the finished product

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.
Gaston TE, et al. *Epilepsia.* 2017;58(9):1586-1592.

What Is the Future?

- Additional cannabis-based formulations in clinical trials and approved in other countries (Sativex)
- Use of Epidiolex for treatment-resistant epilepsy (currently off-label use)
- Quality of OTC products is needed prior to making appropriate dosing recommendations and medical claims
- Clinical trials and additional research

The Contribution of Various Cannabis Use to Variation in the Incidence of Psychotic Disorder Across Europe (EU-GEI): A Multicentre Case–Control Study

- Daily cannabis use was associated with increased odds of psychotic disorder compared with never having used it
  - Results largely unchanged when considering age of first use, money spent, and type of cannabis used
- Use of high-potency cannabis (THC of at least 10%) modestly increased the odds of a psychotic disorder compared with never use; daily use increased risk 4-fold
  - Using high-potency cannabis by age 15 showed a doubling of risk
  - Locations with high rates of high-potency cannabis use associated with large increases in risk: Paris (4x greater), London (5x greater), Amsterdam (>9x greater)
- **Conclusion:** These findings are consistent with previous evidence of the harmful effect on mental health of daily use of cannabis, especially high-potency cannabis
- ***Emphasizes the importance of public health to recognize the need to address the potential adverse effects associated with daily cannabis use***

Di Forti M, et al. *Lancet Psychiatry*. 2019;6(5):427-436.

Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

[a]Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, [b]Department of Psychology and Neuroscience, and [c]Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; [d]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; [e]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and [f]Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

- A prospective longitudinal study investigating the correlation between persistent cannabis use over 20 years in a birth cohort of 1037 individuals
- Also observed the effect of cannabis cessation and the restoration of neuropsychological function for adolescents who were former persistent cannabis users

Meier MH, et al. *Proc Natl Acad Sci U S A*. 2012;109(40):E2657-E2664.

Effect on Neuropsychological Functioning

- Persistent cannabis users show neuropsychological decline from childhood to midlife
- Prospective study of 1037 individuals followed from birth (1972/1973) to 38 years of age
- Within-person IQs:
  - Never used: 100.64
  - Used, never regularly: 101.24
  - Used regularly: 90.77
- Led to impairment of learning, memory, and executive functions
- Cessation of cannabis did not restore the loss of neuropsychological functioning
  - This may suggest neurotoxic effects of marijuana in adolescents

Meier MH, et al. *Proc Natl Acad Sci U S A*. 2012;109(40):E2657-E2664.

Natural and Synthetic Cannabinoids for Agitation and Aggression in Alzheimer's Disease: A Meta-Analysis

- Agitation is one of the most common and difficult-to-treat neuropsychiatric symptoms in Alzheimer's disease (AD) patients
  - Occurs in 20% to 50% of patients with moderate-to-severe AD
- Meta-analysis of 6 primary publications (251 patients) through August 2018
- Formulations of cannabis used in each study: THC, dronabinol, nabilone
- Agitation is associated with more rapid AD progression, increased fall risk, weight loss, and mortality—*important to treat*
- No great treatment currently without morbidity and mortality
- Why study cannabis in AD?
  - CB1 receptor agonist (memory and learning)
  - CB2 may remove beta amyloid plaques
- **Preliminary findings:** THC in some patient populations (multiple sclerosis, schizophrenia) helps anxiety and depression, is an analgesic, and causes increased sedation

Ruthirakuhan M, et al. *J Clin Psychiatry.* 2019;80(2):18r12617.

Results

- Researchers found no significant difference in cannabinoids and placebo on agitation in AD patients
- Subgroup analysis revealed a signal for improvement in agitation for those treated with synthetic cannabinoids compared to placebo or THC
- A meta-regression using MMSE scores revealed a significant reduction in agitation with drug compared to placebo in those with a lower baseline MMSE
- No change in BMI; however, a significant difference seen in patients with a lower BMI
- Sedation was significantly greater in THC group
- **Conclusion:** Efficacy of cannabinoids on agitation and aggression in patients with AD remains inconclusive; however, there is a signal for potential benefit with synthetic cannabinoids

BMI, body mass index; MMSE, Mini-Mental State Examination.

Ruthirakuhan M, et al. *J Clin Psychiatry.* 2019;80(2):18r12617.

Anti-Anxiety Effects

Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Neuropsychopharmacology (2011) 36, 1219–1226

www.neuropsychopharmacology.org

Mateus M Bergamaschi[1,2,3], Regina Helena Costa Queiroz[2,3], Marcos Hortes Nisihara Chagas[1,3], Danielle Chaves Gomes de Oliveira[1,3], Bruno Spinosa De Martinis[3,4], Flávio Kapczinski[3,5], João Quevedo[3,6], Rafael Roesler[3,7], Nadja Schröder[3,8], Antonio E Nardi[3,9], Rocio Martín-Santos[3,10], Jaime Eduardo Cecílio Hallak[1,3], Antonio Waldo Zuardi[1,3] and José Alexandre S Crippa*[1,3]

Population	Allocation	Intervention	Outcome Measures
Treatment-naïve adults with social anxiety disorder (SAD)	• N = 12 subjects w/SAD receiving 600 mg CBD • N = 12 subjects w/SAD receiving placebo • N = 12 healthy controls w/o SAD (no capsule given)	Receive capsule (placebo or CBD) 90 minutes prior to simulated public speaking test	Visual analogue mood scale, negative self-statement scale, physiological markers

Conclusion: CBD intervention significantly lowered symptoms and negative self-assessment of subjects with SAD to levels near the healthy control group

Bergamaschi MM, et al. *Neuropsychopharmacology*. 2011;36(6):1219-1226.

Anti-Anxiety Effects *(continued)*

ORIGINAL RESEARCH & CONTRIBUTIONS

Cannabidiol in Anxiety and Sleep: A Large Case Series

Scott Shannon, MD[1]; Nicole Lewis, ND[2]; Heather Lee, PA-C[3]; Shannon Hughes, PhD[4]

Perm J 2019;23:18-041

Population	Allocation	Intervention	Outcome Measures
Adult psychiatric patients with a diagnosis of anxiety or sleep disorder	72 total patients Anxiety disorder: N=47 Sleep disorder: N=25	CBD 25-75 mg/d capsule Anxiety: 1 capsule po qAM Sleep: 1 capsule po qhs **CBD adjunctive to current psychiatric medications and routine patient care*	Anxiety: Hamilton Anxiety Rating Scale Sleep: Pittsburgh Sleep Quality Index **Tracked at monthly visits*

Results: Sleep scores showed no sustained improvement; anxiety scores decreased modestly during the 1st month and were sustained during trial period; CBD well tolerated

Conclusion: CBD *may* hold benefit for anxiety-related disorders; prospective randomized clinical studies are needed

Shannon S, et al. *Perm J*. 2019;23:18-041.

Summary

- Currently, Epidiolex is the only FDA-approved cannabis product on the market to treat severe types of epilepsy
- Additional cannabis-based formulations are in clinical trials and approved in other countries (Sativex)
- Use of Epidiolex for treatment-resistant epilepsy (currently off-label use)
- Cannabis appears to be harmful to the developing brain
- There is no evidence that AD is helped by cannabis
- There may be a mild effect of CBD in anxiety and sleep
  - More research needs to be completed
- Clinical trials and additional research

Questions & Answers

LEGAL IMPLICATIONS

Legal Status of Cannabis Across the US

Cannabis is federally illegal with an exception for hemp and FDA-approved products

February 1, 2021

WATCH LIVE: Day four of former President Trump's second impeachment trial

CNBC MARKETS BUSINESS INVESTING TECH POLITICS CNBC TV WATCHLIST

POLITICS

Democratic senators will push to pass pot reform bill this year

PUBLISHED MON, FEB 1 2021•5:02 PM EST | UPDATED MON, FEB 1 2021•6:58 PM EST

Christian Nunley
@CNUNLEY7

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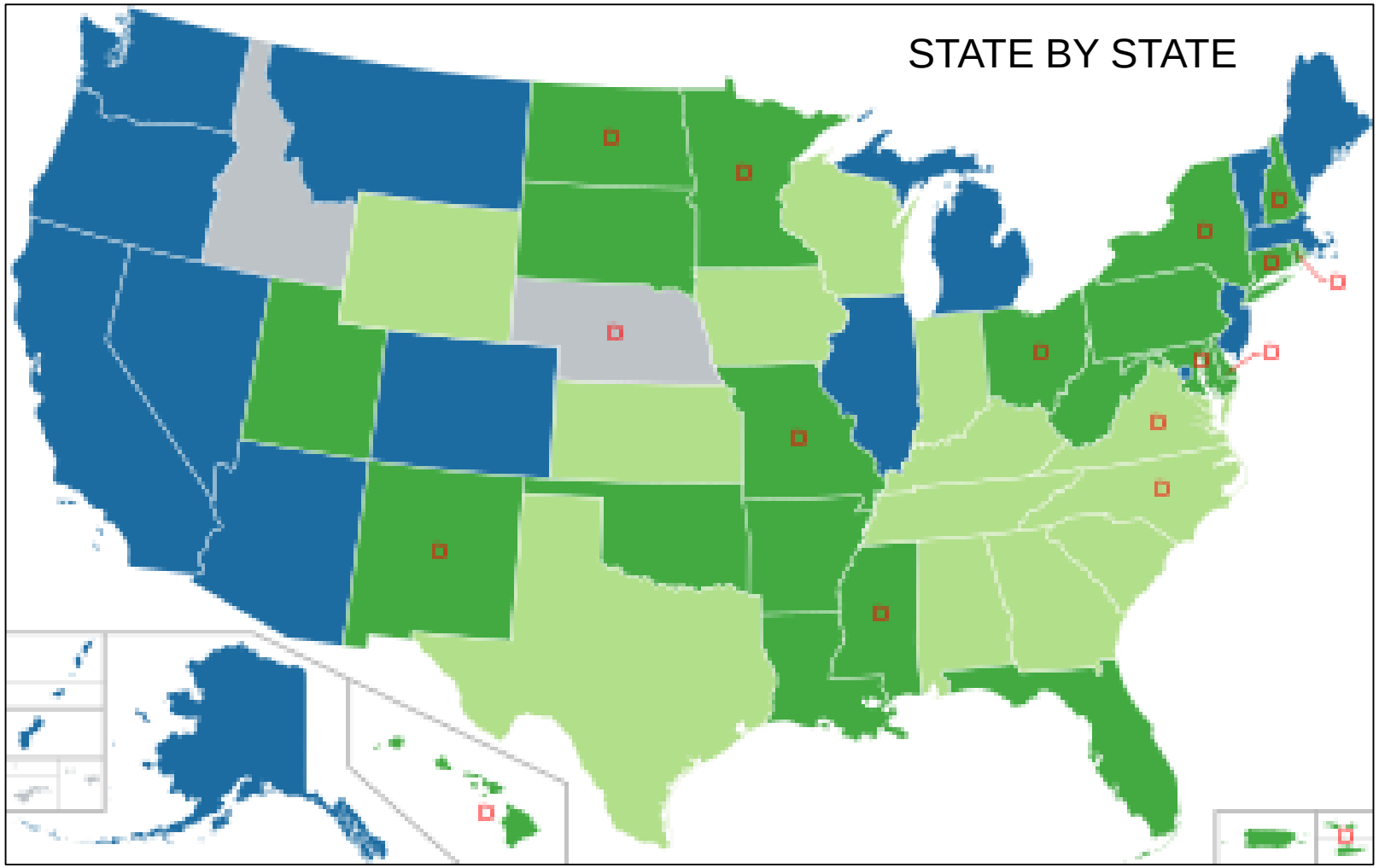
KEY POINTS

- Senate Majority Leader Chuck Schumer and two other Democratic senators said that they will push to pass this year sweeping legislation that would end the federal prohibition on marijuana.
- Pot has been legalized to some degree by many states. "The War on Drugs has been a war on people — particularly people of color," said a statement issued by Schumer, of New York, and Sens. Cory Booker, of New Jersey, and Ron Wyden, of Oregon.

Cannabis ETF
POTX
PROSPEC

Legal Status of Cannabis Across the US



https://en.wikipedia.org/wiki/Legality_of_cannabis_by_U.S._jurisdiction. Attribution: Lokal_Profil.

Cannabis Across State Lines?

- Cannabis is federally illegal
- State-licensed cannabis businesses must cultivate, produce, and sell their products all within the confines of the state in which they are licensed
- If cannabis companies want to expand, they need to procure an entirely new license in each new state
- Hemp-based CBD is federally legal and may be shipped or brought across state lines

The Farm Bill 2018

II

Calendar No. 380

115TH CONGRESS
2D SESSION

S. 2667

To amend the Agricultural Marketing Act of 1946 to provide for State and Tribal regulation of hemp production, and for other purposes.

IN THE SENATE OF THE UNITED STATES

APRIL 12, 2018

Mr. MCCONNELL (for himself, Mr. WYDEN, Mr. MERKLEY, and Mr. PAUL) introduced the following bill; which was read the first time

APRIL 16, 2018

Read the second time and placed on the calendar

A BILL

To amend the Agricultural Marketing Act of 1946 to provide for State and Tribal regulation of hemp production, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Hemp Farming Act of 2018".

- Removed hemp from a Schedule I classification—agricultural commodity
- Hemp: plant containing ≤0.3% THC
- Hemp must be produced in a manner consistent with the Farm Bill, associated federal regulations, associated state regulations, and by a licensed grower
- While more CBD products are available, this does not mean that all CBD products are legal

https://nifa.usda.gov/industrial-hemp.
https://www.natlawreview.com/article/2018-farm-bill-legalizes-hemp-obstacles-to-sale-cbd-products-remain.

FDA Stance on CBD

- If marketed as a drug (intended to have a therapeutic effect), then cannot be sold without FDA approval
- Dietary supplements are regulated differently, although goal remains to protect consumers
  - Currently illegal to put into interstate commerce a food to which CBD has been added or to market CBD as a dietary supplement
  - Agency has issued several warning letters to firms that were marketing unapproved new drugs claiming to contain CBD
  - Continuing to explore viable pathways for CBD products outside the drug context

https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fda-committed-sound-science-based-policy-cbd.
https://www.fda.gov/news-events/press-announcements/fda-advances-work-related-cannabidiol-products-focus-protecting-public-health-providing-market.

FDA Resources

https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis.

DEA Stance on Research

December 22, 2020

On Heels of Senate's Adoption of Cannabis Research Bill, DEA Issues Rule to License More Research Cannabis Growers

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SAUL EWING ARNSTEIN & LEHR LLP

On December 18, 2020, just three days after the U.S. Senate adopted the Cannabidiol and Marihuana Research Expansion Act (CMREA or the Act) (more on this below), the U.S. Drug Enforcement Administration (DEA or the Administration) published in the Federal Register a final rule, "Controls To Enhance the Cultivation of Marihuana for Research in the United States" (Rule), which finally paves the way for DEA to issue nses to grow "marihuana" (i.e., cannabis) for research

/profile/Saul_Ewing_docs/

WRITTEN BY:

Saul Ewing Arnstein Lehr LLP

Contact + Follow

Lauren Farruggia

Jonathan Havens

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Cannabidiol (CBD) oil

THE WALL STREET JOURNAL.

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DEA Widens Path for Medical Marijuana Research

New ruling resolves treaty issue cited by officials to curtail authorization of growing operations for research purposes

Guidance for Pharmacists

- Federal level
  - Farm Bill 2018 removed cannabis and cannabis derivatives that are very low in THC from the definition of marijuana in the Controlled Substances Act
  - Preserved FDA responsibility over CBD products
- State level
  - Some have eliminated certain prohibitions on cannabis or cannabis-derived compounds
- Priority on patient safety
  - Independent testing to confirm potency and purity
  - Patient counseling

Questions & Answers

Conclusions

- It is important for consumers and health care providers to understand the landscape of CBD products and medical marijuana as OTC products and as prescription products approved by the FDA
- Safety concerns exist for CBD and medical marijuana products related to purity, consistency, formulation, and dose
- There are differences among CBD and medical marijuana products with regards to therapeutic effectiveness and availability of products
- The legal framework of CBD and medical marijuana at the national and state level is evolving and will continue to be informed by research and regulatory involvement

Thank you!