Navigating Cannabidiol Use in Seizure Disorders:

A Roadmap for Managed Care and Specialty Pharmacists

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Dr. 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 and Department of Neurology in the School of Medicine.

Dr. Bainbridge is a member of numerous professional organizations, including the Epilepsy Foundation of Colorado, the American Academy of Neurology, the American Epilepsy Society, the Epilepsy Foundation of America, the American College of Clinical Pharmacy, the American Association of Colleges of Pharmacy, and the American Society of Health-System Pharmacists. 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, and movement disorders.

Faculty

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Disclosures

Dr. Bainbridge has disclosed that she has received grant/research support from GW Pharmaceuticals, Corbus Pharmaceutical, and the Colorado Department of Public Health and Environment.
Dr. Rich has no relevant affiliations or financial relationships with a commercial interest to disclose.
The clinical and legal reviewer, **Gerald Gianutsos, PhD, JD**, has no actual or potential conflict of interest in relation to this program.

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Type of Activity: Application

Learning Objectives

- **Explain** the pharmacologic mechanisms of cannabis-derived substances, including cannabidiol (CBD) oral solution
- **Apply** updated recommendations for the CBD oral solution approved by the United States Food and Drug Administration and understand its place in therapy and necessary patient/family education
- **Identify** current legal, regulatory, distribution, and administration issues relevant to CBD oral solution in seizure disorders and the treatment of other medical conditions
- **Differentiate** among cannabis substances, including cannabinoids, CBD oral solution, CBD oils, and street or home-grown plant-based substances

Why Cannabis for Seizures?

Developing a Cannabis Pharmaceutical

- The story of a mother (Evelyn Nussembaum) desperate to help her son (Sam Vogelstein)
  - Sam's seizures started in 2005, at the age of 4 years old
  - 2 months passed before Sam had another seizure, but, eventually, he was having 100 seizures per day
    - At worst, he was having a seizure every 3 minutes
  - Sam was diagnosed with epilepsy with myoclonic-absences—abrupt unresponsiveness and sudden body jerks
  - He tried numerous medications: some helped briefly, others caused hallucinations, full body rashes, and uncontrolled anger
  - Mom described that life for Sam was like a bad cell phone connection: every few minutes, the signal dropped out

KQED Science. https://www.kqed.org/futureofyou/443383/meet-sam-the-berkeley-kid-who-inspired-first-marijuana-based-drug. Published August 3, 2018.

Joining the Underground

- In 2011, Mom read a study in a British medical journal about a small CBD study in rats
- At the time, CBD was not easy to obtain (DEA Schedule 1)
- Mom joined an underground epilepsy collective that worked with an herbalist to cook up their own CBD
  - Homemade CBD achieved poor results
- Mom learned about a British pharma company (GW Pharmaceuticals) that was using a highly concentrated CBD to treat MS spasticity
- Family flew to London after obtaining approval to try the product
- After 1 day, his seizures were down to 30; after 2 days, down to 10; after 3 days, down to 1.

KQED Science. https://www.kqed.org/futureofyou/443383/meet-sam-the-berkeley-kid-who-inspired-first-marijuana-based-drug. Published August 3, 2018.

DEA, Drug Enforcement Administration; MS, multiple sclerosis.

Back to the United States

- Sam returned to the U.S. and needed to find a way to keep getting the drug
- Dr. Roberta Cilio, a neurologist as UCSF agreed to enroll Sam in a 1-patient trial
- Sam was the first person in the world to receive purified CBD (later named Epidiolex)
- First study (214 patients) was published in 2015
  - Showed efficacy in approximately 37% of patients

KQED Science. https://www.kqed.org/futureofyou/443383/meet-sam-the-berkeley-kid-who-inspired-first-marijuana-based-drug. Published August 3, 2018.


Jacquelyn Bainbridge

Cannabis

Main constituents of cannabis and the endocannabinoid system

ARS Question #1

Which of the following statements is true regarding the side effects of cannabis?

1. THC produces a non-euphoric effect on the brain
2. CBD produces a non-euphoric effect on the brain
3. Hemp produces a euphoric effect on the brain
4. Sativa produces a sedating effect on the brain compared to Indica

Cannabis

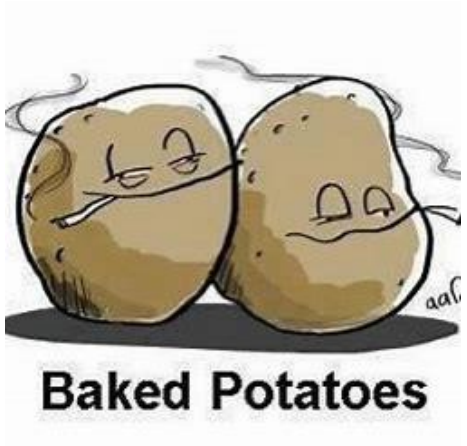
- Naturally growing plant containing over 400 different cannabinoid compounds
  - Over 100 cannabinoids have been isolated
  - Terpenes are variable
    - Contribute to aroma (limonene, pinene)
    - Serve as precursor to cannabinoids
- Cannabinoids & terpenes are found in:
  - Flowering tops > buds > top leaves > lower leaves > stems > stalks
- *Indica* and *sativa* have been cross-bred so there are no generalizable characteristics

Cannabis

- Most prominent cannabinoid compounds:
    1. Delta-9-tetrahydrocannabinol (THC)
        - Euphoric compound → “high”
        - Predominantly used recreationally
    2. Cannabidiol (CBD)
        - Non-euphoric compound
        - Predominantly used medically

Delta-9-tetrahydrocannabinol

- Major component of cannabis that causes the “high”
  - Mechanism of action: partial CB1 agonist
- Beneficial effects
  - Helpful in preventing nausea and vomiting due to cancer chemotherapy
  - Appetite promoter
  - Some medical conditions
- Adverse effects
  - Short term:
    - Memory loss, loss of time, impaired coordination
    - Altered thinking, panic, delusions & hallucinations, paranoia, and psychosis
  - Long term:
    - Addiction (9% overall), altered brain development*, diminished life satisfaction and achievement*, cognitive impairment (lower IQ)*, symptoms of chronic bronchitis, increased risk of chronic psychosis disorders, and poor educational outcome



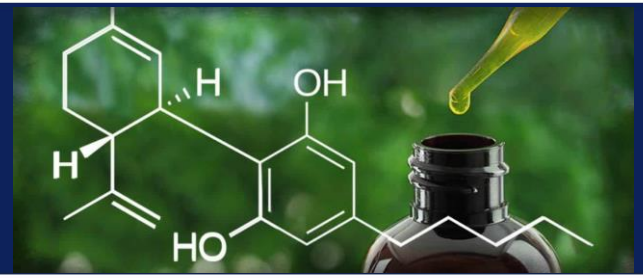
Volkow ND, et al. *N Engl J Med*. 2014;370(23):2219-27.

*Effect is strongly associated with initial marijuana use early in adolescence

THC Dosing

- THC dosing is known
  - Dosing is not known for other cannabinoids
- Typical “effective” dosing of inhaled THC
  - Low dose: < 7 mg
  - Medium dose: 7 – 18 mg
  - High dose: > 18 mg
- Known tolerance to THC down-regulation of CB1 receptors and G-protein activation
  - High probability of tolerance with chronic use and low with intermittent use
    - Chronic use = daily for a week
    - Intermittent use = weekly use

Cannabidiol



- Major non-euphoric component of cannabis
  - Precise mechanism of action unknown
    - May be an antagonist
- Beneficial effects
  - No significant adverse neurologic effects
  - No effects on vital signs or mood
  - Enhances the activity of endogenous cannabinoid (anandamide)
- Adverse effects
  - Somnolence, decreased appetite, diarrhea, fatigue
  - 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):270-8.

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

U.S. Department of Agriculture. https://nifa.usda.gov/industrial-hemp.

USDA, United States Department of Agriculture.

Pharmacodynamics of Cannabis

The endogenous cannabinoid system

Cannabis Pharmacodynamics

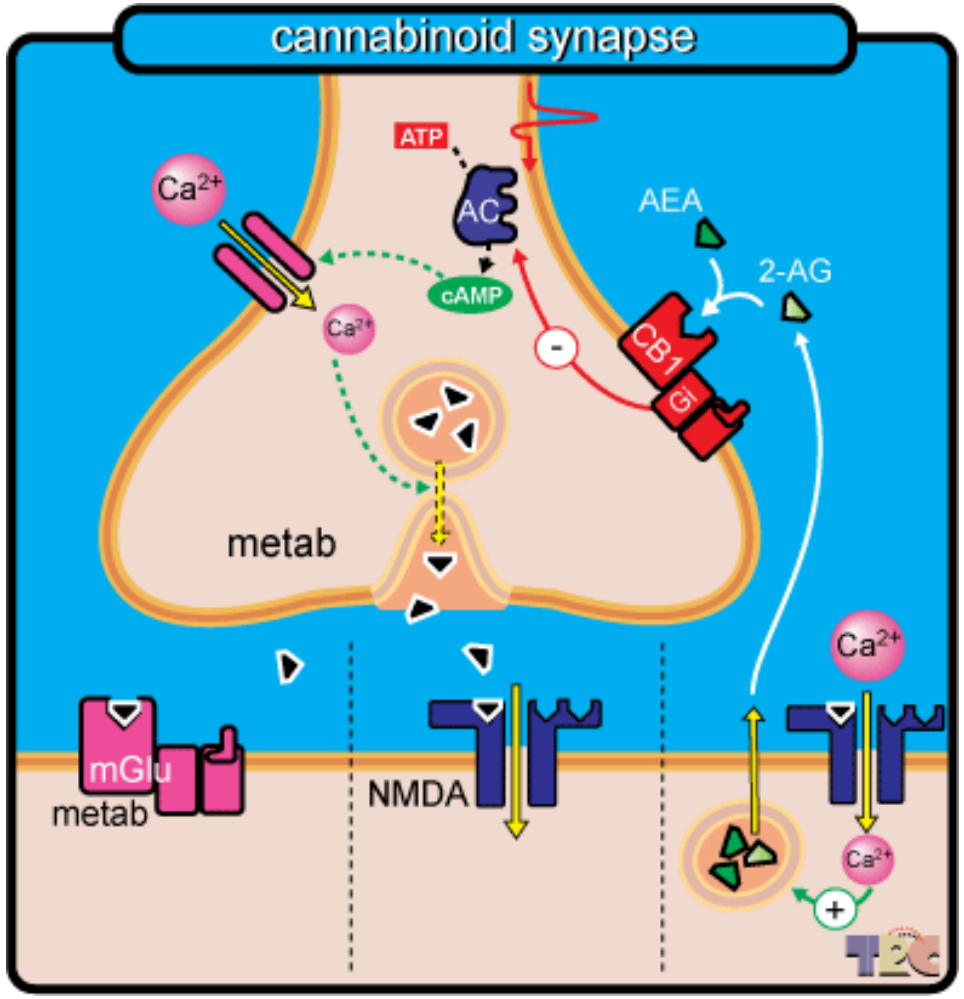
- Our bodies contain an extensive endocannabinoid system
  - Cannabinoid receptors (CB)
- CB1 receptors found in:
  - Central nervous system (CNS)
- CB2 receptors found on:
  - Immune cells & tissues (affect inflammation and immunosuppressive activity)

Cannabis Pharmacodynamics

- THC interacts with CB receptors
  - Induces biologic response (euphoric)
  - Also associated with the most pharmacologic effects
- How CBD exerts its activity is unknown
  - May be an inverse agonist
  - Decreases psychotropic effects of THC
- CBD has no affinity for CB1 or CB2 receptors
  - Research into other receptors (e.g., opioid, G-protein receptors, G-protein-coupled receptors, etc.)

Borgelt LM, et al. *Pharmacotherapy.* 2013;33(2):195-209.;
Grotenhermen F. *Clin Pharmacokinet.* 2003;42(4):327-60.

Regulatory Effect of Cannabinoids at the CB1 Receptor

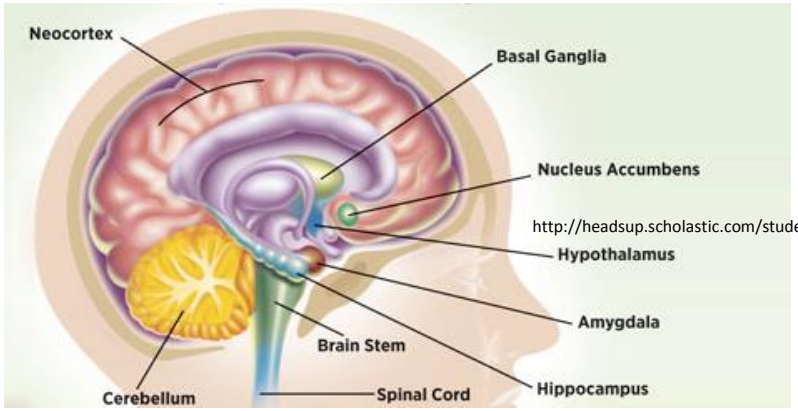


1. Inhibit adenylyl cyclase activity
2. Alter second messenger systems so Ca^{2+} influx is inhibited

Neuromodulation by anandamide is particularly relevant to modulation of GLU (shown), ACh, GABA, DA, and NE

ACh, acetylcholine; DA, dopamine; GABA, gamma amino-butyric acid; GLU, glutamate; NE, norepinephrine.

Functional Effects of Anandamide at CB1 Receptors in the CNS

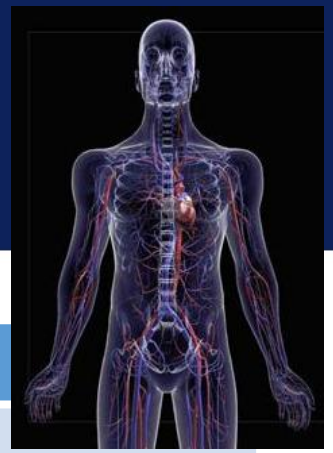


http://headsup.scholastic.com/students/endocannabinoid

Structure	Anandamide regulation	Resultant effect
Basal ganglia	Modulate DA & GABA, motor activity	Slowed reaction time
Hypothalamus	Appetite (2-AG) Stimulate DA & inhibit NE	Increased appetite Inhibition of prolactin, enhances ACTH
Amygdala	Emotions, fear, anxiety	Anxiety stimulation, reduction, & sedation
Nucleus accumbens	Motivation (2-AG)	Engages reward pathway
Hippocampus	Inhibit release of ACh, short-term memory Inhibit release of GLU, long-term memory	Impaired short-term (working) memory Impaired long-term memory consolidation
Cerebellum	Inhibit GLU, motor coordination	Impaired coordination, balance
Brain stem	Modulates info transfer between brain & spinal cord	Anti-nausea effects
Hippocampus, temporal lobe, forebrain	Inhibit GLU & neuronal excitability	Increased seizure threshold

2-AG, 2-arachidonoylglycerol;
ACTH, adrenocorticotropin hormone.

Functional Effects of Anandamide CB1 & CB2 Receptors



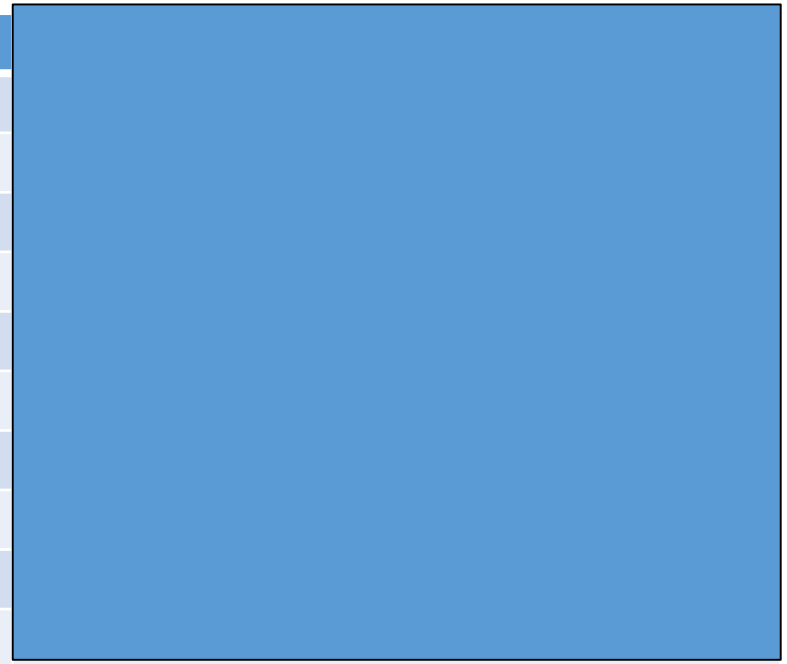
Structure	Anandamide regulation	Resultant effect
Spinal cord	Inhibit GLU & info transfer between body & brain	Decreased pain sensitivity
Parasympathetic nervous system	Inhibit ACh release, HR regulation, urination regulation	HR stimulation, sometimes inhibits urination
Sympathetic nervous system	Inhibit NE release, HR regulation, blood vessel constriction	Delayed reduction in HR and blood pressure
Neuronal cells	Inhibition of GLU-induced excitotoxicity	Neuroprotective effect to prevent cell injury
Adipose tissue	Stimulates lipogenesis	Increased adiposity, insulin resistance
Reproductive tissue	Reduces testosterone, luteinizing hormone	Reduced fertility, altered menstrual cycle
Skin	Reduces histamine	Anti-pruritic effect
General	Role in relaxing, eating, sleeping, forgetting, protecting	Provides relief from stress, reduction of injury
General	Inhibits immune B lymphocytes, natural killer cells	Anti-inflammatory activity

HR, heart rate.

Scholastic. http://headsup.scholastic.com/students/more-facts-about-how-drug-abuse-puts-your-whole-body-at-risk. Published 2007.

Cannabis Activity at CB1 Receptors

Structure	THC effect	
Neocortex	Altered thinking, judgement	
Basal ganglia	Slowed reaction time	
Hypothalamus	Increased 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



TRVP, transient receptor potential vanilloid.

Dose-response effects of CBD not established

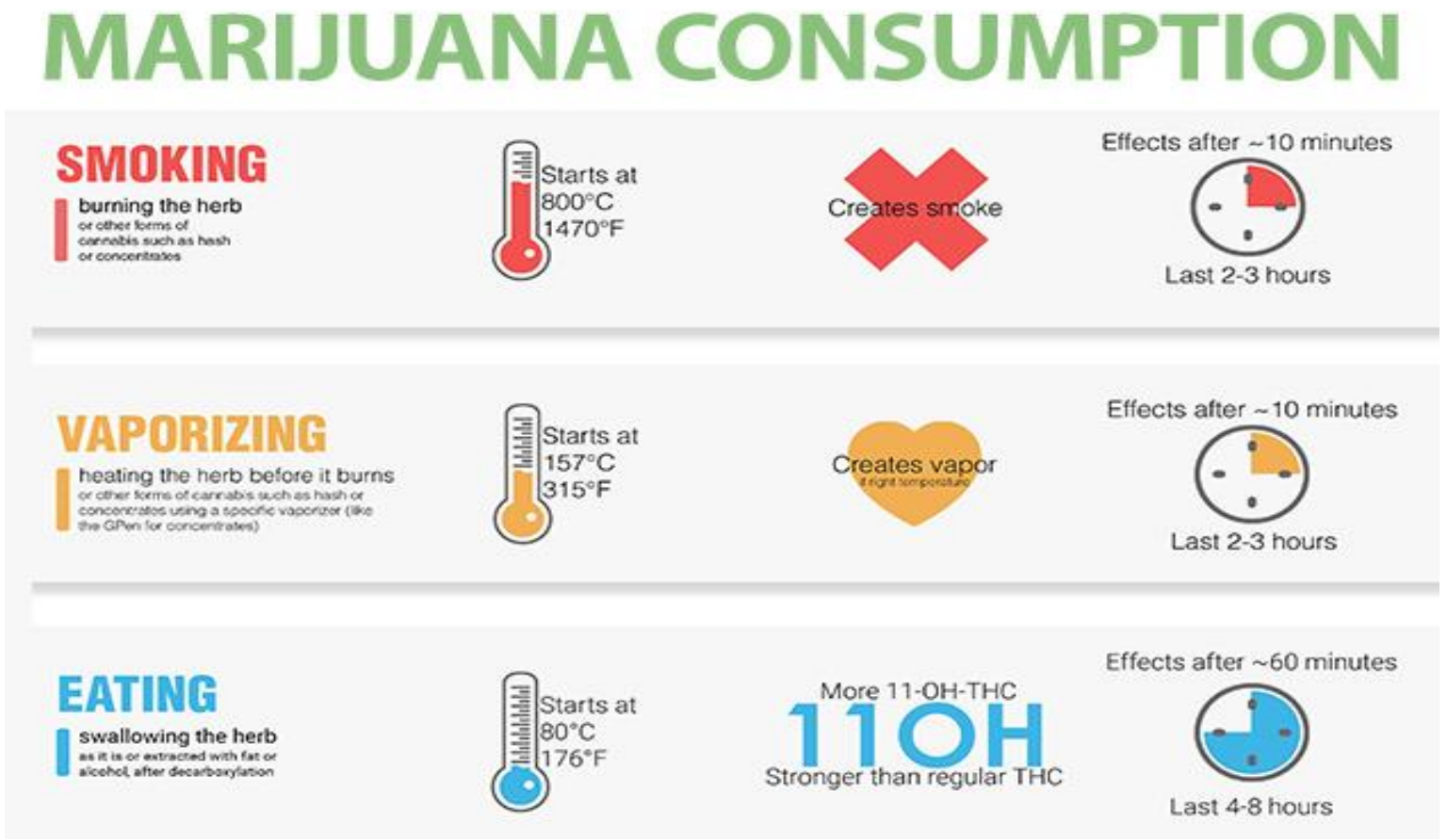
- Low dose (< 300 mg) → inconsistent effects
- Typical response can be seen at 600 mg

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

Pharmacokinetics of Cannabis

Inhaled Cannabis vs. Edibles

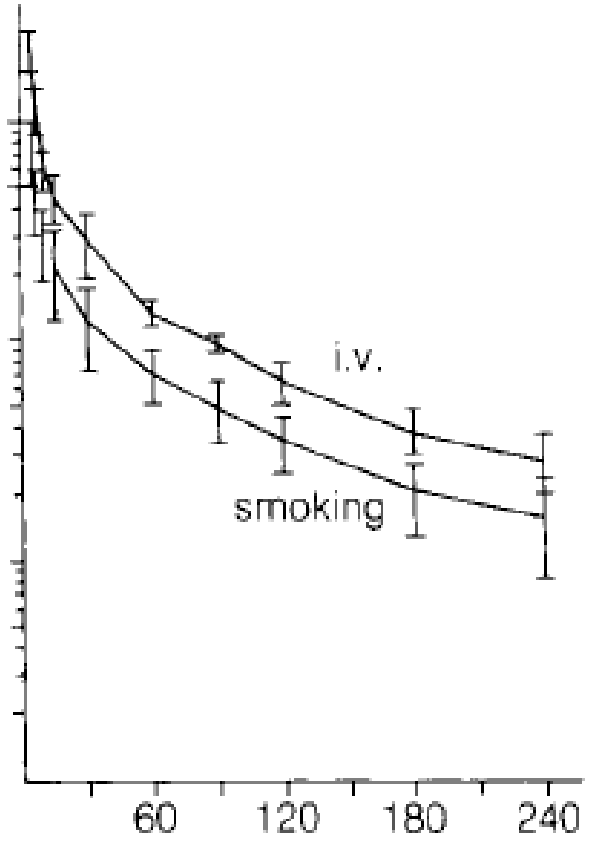
How is Cannabis Consumed?



Kingston D. http://azmarijuana.com/dans-stash/marijuana-consumption-styles/. Published May 13, 2015.

Pharmacokinetics of THC

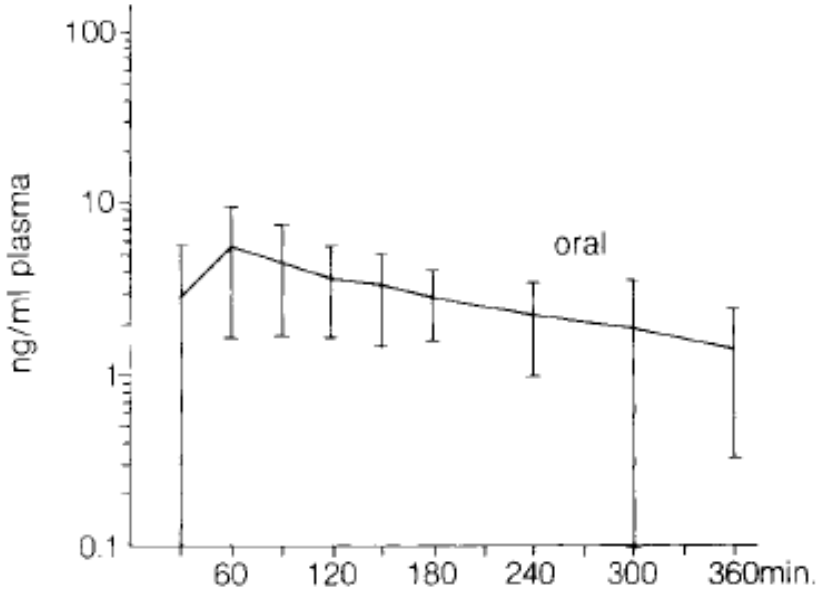
- Smoking cannabis turns ~50% of the THC content into smoke
- Up to 50% of inhaled smoke is exhaled again, and some undergoes localized metabolism in the lung
- Bioavailability of a inhaled dose of THC is between 10%-25%
- Effects are perceptible within seconds and fully apparent within a few minutes
- Effects last about 3 hours



Strougo A, et al. *J Psychopharmacology*. 2008;22(7):717-26.

Pharmacokinetic Profile of Oral THC

- Bioavailability of THC after oral ingestion ranges from 5%-20% in the controlled environment of clinical studies
- Onset of effect is delayed: 1-3 hours due to slow absorption from the gut
- Weight, metabolism, gender, and eating habits also play a role in absorption
- Effects last about 6-12 hours



Agurell S, et al. *Pharmacol Rev*. 1986;38(1):21-43.

Oral Formulations (Edibles) Increase Risk of Toxicity

- The slow onset, extended duration, and variable absorption lead to toxicity
  - Users can't wait for effect
- People rely on others' descriptions of potency
- JAMA study: too much product variability
  - 23% under-labeled, 60% over-labeled

Baca R. http://www.thecannabist.co/2014/03/09/tests-show-thc-content-marijuana-edibles-inconsistent/6421/. Published March 9, 2014.;
Erowid E, Erowid F. https://erowid.org/general/newsletter/erowid_newsletter21.pdf. Published November 2011.; Vandrey R, et al. *JAMA*. 2015;313(24):2491-3.

Pharmacokinetic Profile of CBD

- CBD administration
  - IV 20 mg
  - Smoking 18.8-19.4 mg
- Similar curve profiles of CBD concentration
  - IV resulted in slightly higher CBD plasma concentrations overall

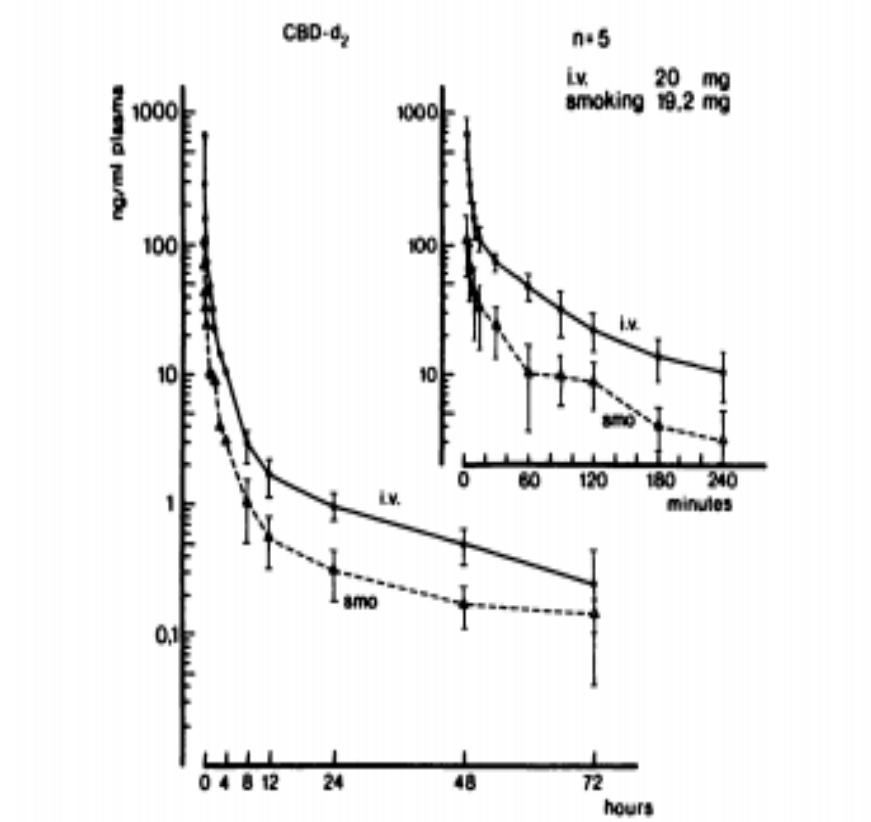


FIG. 11. Mean plasma curve (±SD) of CBD-d_2 after i.v. administration and smoking in five marihuana users. The *insert* shows the concentrations during the first 4 h after administration.

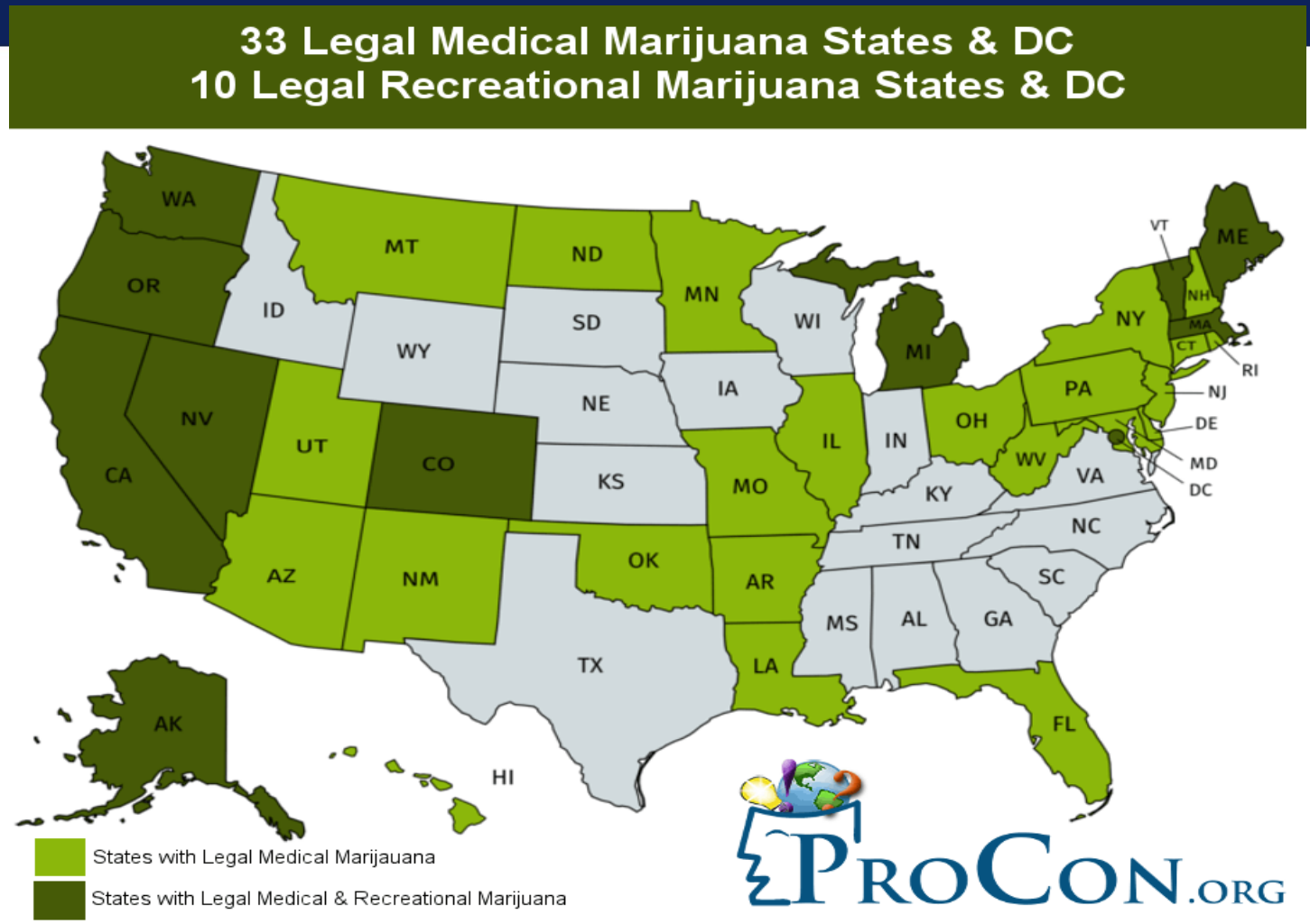
Agurell S, et al. *Pharmacol Rev*. 1986;38(1):21-43.

IV, intravenous.

Medical Uses of Cannabis

Evidence from National Academies: Health Effects of Cannabis

Legal Status of Cannabis in the U.S.



ProCon.org. https://marijuana.procon.org/legal-recreational-marijuana-states-and-dc/. Accessed September 11, 2019.

Number of States with Various Approved Medical Conditions

Alzheimer's disease (14)	Epilepsy/seizures (28)	Nausea (21)
ALS (15)	Glaucoma (30)	Pain (32)
Arthritis (7)	Hepatitis C (14)	Parkinson's disease (13)
Cachexia (28)	HIV/AIDS (27)	PTSD (32)
Cancer (31)	Multiple sclerosis (30)	Neuropathy (10)
Crohn's/GI disorders (24)	Muscle spasticity (22)	Autism (10)
Huntington's disease (4)	Tourette's syndrome (8)	Migraine (5)

ALS, amyotrophic lateral sclerosis; GI, gastrointestinal; PTSD, post-traumatic stress disorder.

ProCon.org. https://marijuana.procon.org/legal-recreational-marijuana-states-and-dc/. Accessed September 11, 2019.

Approved Medical Conditions

Indication	# of States Approved	Clinical Evidence	Indication Appropriate?	Why?
Cancer	25	One pilot with 2 patients, preclinical	No	Not enough evidence showing antitumor effects
Seizures	24	Weak; small RCTs, case report/surveys	Possibly	Not enough evidence, not 1st line
HIV/AIDS	24	None	No	Improved appetite and sleep quality, but does not treat HIV/AIDS
Muscle spasticity	22	Moderate; large RCTs	Yes	Improved mobility, perceptions of spasticity/pain
Glaucoma	21	Moderate, but effect only lasts 3 hours	No	AGS does not recommend
Cachexia	21	Mixed; large RCTs, cancer & HIV-related	Possibly	Lack consistent results, not 1st line
Pain	20	Moderate; large RCTs, neuropathic & cancer-related ONLY	Yes	UC Center for Medicinal Cannabis Research showed superiority to duloxetine and gabapentin in neuropathic pain
Nausea	19	Moderate; large RCTs	Yes	Efficacy similar to prochlorperazine, ASCO doesn't recommend 1st line

ASCO, American Society of Clinical Oncology; AGS, American Glaucoma Society; RCT, randomized controlled trial.

The National Academies Press. https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state. Published 2017.

Approved Medical Conditions

Indication	# of States Approved	Clinical Evidence	Indication Appropriate?	Why?
Crohn's/ IBD	16	Surveys, case reports	No	Improved cramping/diarrhea, but does not treat disease. Possible worsening of disease, more surgery.
Hepatitis C	10	Surveys, case reports	No	Improved nausea, reduced weight loss, but does not treat HCV. Possible worsening of disease, more fibrosis.
ALS	9	Small RCT, case reports	No	Improved appetite, depression, pain, spasms, drooling, but doesn't treat ALS
Alzheimer's	7	Preclinical, case reports	No	Reduced nighttime agitation, increased appetite, but does not treat Alzheimer's
PTSD	6	Weak, small RCTs, surveys, cohorts	Possibly	Reduced nightmare occurrences/severity, flashbacks, night sweats.
Parkinson's	5	Surveys, open-label trial	No	Improved tremor, rigidity, & bradykinesia, but does not treat Parkinson's
Huntington's	2	Surveys, pilot study	No	Mixed results on improvement of chorea, but does not treat Huntington's

HCV, hepatitis C virus; IBD, inflammatory bowel disease.

The National Academies Press. https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state. Published 2017.

Approved Medical Conditions

- Current legislation is misleading
- Cannabis may alleviate symptoms but not actually treat the disease
  - MS, cancer, HIV/AIDS, hepatitis C, Crohn’s disease, and Alzheimer’s disease
- Do our patients/consumers know the difference?

Lennox-Gastaut Syndrome & Dravet Syndrome

Overview and Treatment

ARS Question #2

True or False?
The treatment of Lennox-Gastaut and Dravet syndromes generally require only 1 anti-seizure drug for treatment.

1. True
2. False

Pathophysiology of Dravet Syndrome (DS)

- Rare genetic infantile epileptic encephalopathy
- Due to an 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 U.S. is approximately 1 in 20,000[5-8] to 1 in 40,000[9]

1. Escayg A, Goldin AL. *Epilepsia*. 2010;51(9):1650-8.; 2. Fukuma G, et al. *Epilepsia*. 2004;45(2):140-8.; 3. Wang JW, et al. *Epilepsia*. 2008;49(9):1528-34.; 4. Zuberi SM, et al. *Neurology*. 2011;76(7):594-60.; 5. Wu YW, et al. *Pediatrics*. 2015;136(5):e1310-5.; 6. Brunklaus A, et al. *Epilepsia*. 2011;52(8):1476-82.; 7. Rogona F, et al. *Brain Dev*. 2010;32(1):71-7.; 8. Ragona F, et al. *Epilepsia*. 2011;52(2):386-92.; 9. Knupp KG, Wirrell EC. *CNS Drugs*. 2018;32(4):335-50.

Pathophysiology of DS - *continued*

- Characterized by an onset before 12 months of age with normal development before seizure onset
- Age 2 to 3 years: patients will have frequent and prolonged seizures
  - Refractory hemiclonic, myoclonic, generalized tonic-clonic, and febrile seizures
- Commonly misdiagnosed
  - Magnetic resonance imaging and EEG tests usually normal at first

Knupp K, Wirrell E. *CNS Drugs*. 2018;32(4):335-50.

EEG, electroencephalogram.

Pathophysiology of DS and associated issues

- Children will often have poor motor skills, poor language skills, hyperactivity, and poor interpersonal skills
- Other comorbid conditions
  - Autonomic dysfunction
  - Sleep problems
- Status epilepticus (SE) is a recurring issue, especially in early childhood
  - Mortality reaches 10% in the first 10 years of life and continues to escalate with age
- Adult patients are rarely able to live independently

Knupp K, Wirrell E. *CNS Drugs*. 2018;32(4):335-50.

Treatment of DS

- Ketogenic diet – may be helpful
- Vagus nerve stimulation – may be helpful
- Cannabidiol, CBD (Epidiolex) – approved in June 2018
- Stiripentol (Diacomit)

Pathophysiology of Lennox-Gastaut Syndrome (LGS)

- The cause of LGS can be divided into 2 categories
  - Symptomatic group – brain injury, generally diffuse (encephalitis, meningitis, tuberous sclerosis complex, brain malformations, hypoxia at birth, trauma) injuries to the frontal lobes of brain
    - Identifiable cause
    - 75% have this type
  - Cryptogenic group – no clear cause, may be associated with mutations or changes on parts of the genes that could contribute to the development of LGS
- West syndrome
  - Occurs in infants in the 1st year of life
    - Infantile spasms (IS)
  - EEG pattern is distinctive – hypsarrhythmia
  - Not a specific cause of LGS, but up to 30% of children who develop LGS have a history of IS or West syndrome
  - Patients with LGS and an early history of IS or West syndrome usually have a poor outlook for seizure control and cognition

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

Pathophysiology of LGS - *continued*

- Most seizures associated with LGS typically occur at age 3 years (between 1 and 7 years)
  - It is 5 times more common in boys[1-4]
- The incidence is approximately 2.8 per 100,000 live births[5]
- Represents 4% to 10% of all childhood epilepsies[4-7]
- Most LGS patients have daily seizures[1]
- It may be hard to tell what type of seizure these patients are having
  - Video-EEG monitoring may be helpful to classify each seizure type[1]
- It is important to classify the seizures so that you can better select treatment[1]

1. Epilepsy Foundation of America. 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):139-79.; 3. Arzimanoglou A, Resnick T. *Epileptic Disord*. 2011;13 Suppl 1:S3-13.; 4. Panayiotopoulos CP. ILAE classifications an practice parameter guidelines. 2nd ed. London: Springer; 2010.; 5. Rantala H, Putkonen T. *Epilepsia*. 1999;40(3):286-9.; 6. Gastaut H, et al. *Epilepsia*. 1975;16(3):457-61.; 7. Trevathan E, et al. *Epilepsia*. 1997;38(12):1283-8.

Pathophysiology of LGS - *continued*

- LGS includes many different seizure types
  - Tonic
    - Associated with a poor prognosis for development
    - Can lead to SE
  - Atonic
    - Occurs in > 50% of LGS patients
  - Atypical absence
    - Involve more than just staring facial expression and eye blinking
  - Focal seizures (with and without awareness)
  - Tonic-clonic
    - Can lead to SE
  - Clonic

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

Pathophysiology of LGS - *continued*

- Classic pattern on sleep EEG: background slowing and spike-wave bursts at frequencies less than 2.5 per second[1]
- The cause of this disorder is unknown in 1 out of 4 children[1]
- Generally, these seizures are hard to control and will require life-long treatment[1]
  - Multiple ASDs are required generally
- LGS can often lead to SE
  - Seizure emergency plan needs to be addressed[1]
- SUDEP is a concern for patients with LGS[2-4]

ASD, anti-seizure drug; SUDEP, sudden unexplained death in epilepsy.

1. Epilepsy Foundation of America. https://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs/lennox-gastaut-syndrome-overview.; 2. Knupp K, Wirrell E. *CNS Drugs*. 2018;32(4):335-50.; 3. Genton P, et al. *Epilepsia*. 2011;52 Suppl 2:44-9.; 4. Harden C, et al. *Neurology*. 2017;88(17):1674-80.

Treatment of LGS

- Ketogenic diet – may be helpful
- Vagus nerve stimulation – 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 of America. https://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs/lennox-gastaut-syndrome-overview.

Cannabidiol (Epidiolex)

- First FDA-approved cannabinoid prescription drug from plant material
- Indication: treatment of LGS and DS
- Dosage form: oral solution
  - 100 mg/mL
  - Starting dosage: 2.5 mg/kg twice daily
  - After 1 week, increase to 5 mg/kg twice daily
    - Maximum: 10 mg/kg twice daily
- Side effects (≥ 10%):
  - Somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, asthenia, rash, insomnia, sleep disorder, poor quality sleep, infections

Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.
Gaston TE, et al. *Epilepsia* 2017;58(9):1586-92.

Cannabidiol (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 the incidence of liver enzyme elevations with valproate administration
- *Epidiolex meets highest standards for safety and quality, unlike other medical marijuana products*

Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.; Gaston TE, et al. *Epilepsia.* 2017;58(9):1586-92.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Cannabidiol (Epidiolex): Counseling and Monitoring

- Monitor LFTs at baseline and at 1 month, 3 months, and 6 months after initiation and periodically thereafter, as clinically indicated
- Can cause weight loss
- Can cause a decrease in hematocrit and hemoglobin
- Can cause 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 or motor vehicles
- May cause a positive drug screen since it contains 0.1% THC

LFTs, liver function tests.

Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.; Gaston TE, et al. *Epilepsia*. 2017;58(9):1586-92.

CBD Drug-Drug Interactions

Cannabidiol (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.

Cannabidiol (Epidiolex): Drug-Drug Interactions

- 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 [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.; *Gaston TE, et al. *Epilepsia.* 2017;58(9):1586-92.


Sheldon Rich

ARS Question #3

Epidiolex is a controlled substance in which DEA schedule?

1. CI
2. CII
3. CIII
4. CIV
5. CV
6. It is not a controlled substance

DEA Scheduling

- No approved medical use - CI
  - Marijuana
  - CBD
- FDA-approved synthetic THC analogs
  - Cesamet (nabilone) - CII
    - For chemo-related nausea/vomiting
  - Marinol and Syndros (dronabinol) - CIII
    - For anorexia/weight loss (AIDS-associated)
    - For chemo-related nausea/vomiting
- Epidiolex (cannabidiol) – CV
  - Treatment of LGS or DS

FDA Considerations

- FDA has yet to offer a clear regulatory framework for CBD other than Epidiolex
  - Other CBD products likely differ in composition and have not been properly studied as medicines
- Attempts to market the products as dietary supplements, which do not require prior FDA approval, are running afoul of the agency
  - FDA warns: “FDA has concluded based on available evidence that CBD products are excluded from the dietary supplement definition”
- The FDA is working quickly to establish potential pathways for marketing CBD
  - Consumers must beware of products with unsubstantiated claims
  - FDA has sent a series of warning letters to CBD producers in the past few years
- *“There are many unanswered questions about the science, safety, effectiveness and quality of unapproved products containing CBD”*

BioPharmDive. https://www.biopharmadive.com/news/fda-warns-cannabis-company-for-illegal-marketing-of-cbd-products/559442/. Published July 24, 2019.

Recent FDA Actions

- FDA warns cannabis company for illegal marketing of CBD products
  - Sent a warning letter on July 22, 2019 to Curaleaf telling the company that it is illegally marketing CBD products as medicines
  - Criticized Curaleaf for a range of statements on its website and social media accounts, including:
    - *CBD has also been shown to be effective in treating Parkinson's disease*
    - *CBD has been linked to the effective treatment of Alzheimer's disease*
    - *CBD is being adopted more and more as a natural alternative to pharmaceutical-grade treatments for depression and anxiety*
    - *CBD can also be used in conjunction with opioid medications, and a number of studies have demonstrated that CBD can in fact reduce the severity of opioid-related withdrawal and lessen the buildup of tolerance*
    - *CBD has been demonstrated to have properties that counteract the growth and spread of cancer*
    - *CBD was effective in killing human breast cancer cells*
    - *Heart disease is one of the leading causes of death in the United States each year, and CBD does a number of things to deter it. The two most important of these are the ability to lower blood pressure and the ability to promote good cholesterol and lower bad cholesterol.*
  - The company was given 15 days to respond

BioPharmDive. https://www.biopharmadive.com/news/fda-warns-cannabis-company-for-illegal-marketing-of-cbd-products/559442/. Published July 24, 2019.

Additional Federal and State Considerations

- Currently, 33 states and Washington, DC have legalized medical marijuana in restricted quantities
  - Some also have CBD-specific regulations
- The 2018 Farm Bill legalized the industrial cultivation of hemp that contains less than 0.3% THC
  - State-federal regulatory process
  - States submit licensing and regulation plans to the USDA for approval
  - The Farm Bill removes a hemp-derived product like CBD from its CI status if it is produced under state and federal laws related to hemp
  - USDA received oversight authority of hemp cultivation but FDA explicitly maintains control over marijuana and CBD

Marcoux R, et al. *P T*. 2019;44(5):290-3.

Formulary Management and Benefit Design

- Medical marijuana and CBD oil products are typically not covered
  - Must not cover them if health plan is participating in a federal government program (e.g., Medicare or Medicaid)
- Epidiolex usually covered with some prior authorization (PA) or step-therapy approach
  - Due to relative high cost
  - Prevents off-label use
  - Assures other therapies utilized first
- Hospital formularies need to address patients bringing in own product for use
  - Usually medical marijuana that is smoked is not allowed
  - Federal funding could be put at risk due to CI status

O'Donnell J, et al. *P T*. 2019:44(7):410-33.

ARS Question #4

True or False?

Any retail pharmacy may dispense Epidiolex with a valid prescription.

1. True
2. False

Distribution

- Epidiolex is available only from a network of specialty pharmacies including:
  - AcariaHealth
  - Accredo
  - AllianceRx Walgreens Prime
  - Amber Pharmacy
  - CVS Specialty
- And some select hospital outpatient pharmacies

Provider/Patient Education

- Advise patients who are prescribed Epidiolex to use the adapter and oral dosing syringes provided
- Instruct patients to discard any unused Epidiolex oral solution after 12 weeks of first opening the bottle
- Inform patients about the potential for elevations of liver enzymes
  - Advise patients of the clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) and to contact a healthcare provider promptly if these signs or symptoms occur

Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.

Provider/Patient Education: Warnings

- Somnolence and sedation
  - Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Epidiolex does not affect them adversely
- Suicidal thinking and behavior
  - Counsel patients, their caregivers, and their families that AEDs, including Epidiolex, may increase the risk of suicidal thoughts and behavior
  - Advise them to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm

Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.

AED, anti-epileptic drug.

Provider/Patient Education: Precautions

- Withdrawal of AEDs
  - Advise patients not to discontinue use of Epidiolex without consulting with their healthcare provider
  - Normally, Epidiolex should be gradually withdrawn to reduce the potential for increased seizure frequency and SE
- Pregnancy registry
  - Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during Epidiolex therapy
  - Encourage women who are taking Epidiolex to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant
- Drug testing
  - Advise patients of the potential for positive cannabis drug screens

Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018.

Epidiolex Market Update

- More than 7600 patients have received Epidiolex prescriptions since launch
- More than 1900 physicians have generated dispensed prescriptions since launch
- Pharmacy distribution network now includes over 145 distribution points
- Approximately 75% of 900 patients in expanded-access program and open-label extension now transitioned to commercial product
  - Remaining patients expected to transition by end of Q2
- Over 90% of all U.S. lives now covered
  - 65% have either PA to indication or less restrictive
- New commercial coverage determination recently announced by United HealthCare, OptumRx, and Prime Therapeutics
- 99% of state fee-for-service Medicaid lives now have a coverage determination
  - 67% of covered lives have either PA to indication or less restrictive
  - 7 states cover Epidiolex without restrictions
- Approximately 90% of managed Medicaid lives have a coverage determination
  - 40% have a PA to indication or less restrictive
- Targeting 5000 healthcare professionals, including all Level 3 and 4 epilepsy centers

FirstWord Pharma. http://www.firstwordpharma.com/node/1639053#axzz5uPimcgJw. Published May 6, 2019.

Epidiolex Market Update - *continued*

- CHMP opinion supporting coverage (July 2019)
  - Initial decision was not to cover
- Launches expected in major 5 European markets by end of 2019
- Positive results in phase 3 trial in Tuberous Sclerosis Complex
  - Primary efficacy measure achieved with both Epidiolex doses compared to placebo
  - sNDA submission expected in Q4 2019
- IND open for pivotal phase 3 trial in Rett Syndrome with expected start in Q2 2019
- Several new formulations of CBD in development, including modified oral solution, capsule, and intravenous formulation
  - PK data expected in 2019
- 7 years of orphan exclusivity confirmed by FDA, plus 6-month pediatric extension expected
  - 10 years of orphan exclusivity in Europe plus 2-year pediatric extension

FirstWord Pharma. http://www.firstwordpharma.com/node/1639053#axzz5uPimcgJw. Published May 6, 2019.

CHMP, Committee for Medicinal Products for Human Use; IND, investigational new drug; PK, pharmacokinetic; sNDA, supplemental New Drug Application.

Question & Answer


Thank You!