Cannabis Confusion

Sorting Out the Differences and Legality of CBD, Marijuana, and Hemp Products

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Dr. Laura Borgelt is an Associate Dean of Administration and Operations at the University of Colorado Skaggs School of Pharmacy and Professor in the Departments of Clinical Pharmacy and Family Medicine at the University of Colorado Anschutz Medical Campus. For the past 10 years, Dr. Borgelt 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 rule-making involving 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 and the Colorado Department of Public Health & Environment.

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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UAN: **0430-0000-20-031-H03-P**
Credits: 1.5 hour (0.15 CEU)
Type of Activity: Application

Learning Objectives

- **Apply** available scientific information to counsel patients about the health benefits, concerns, and unknowns regarding medical marijuana and cannabidiol (CBD)-containing agents, including both over-the-counter (OTC) and United States Food and Drug Administration (FDA)-approved agents
- **Explain** the pharmacologic mechanisms of cannabis-derived substances, including CBD
- **Assess** the content of CBD/tetrahydrocannabinol (THC)-containing agents available in medical dispensaries, including issues relating to purity, consistency, and dose
- **Differentiate** among cannabis substances, including CBD, cannabinoids, oils, and street or home-grown plant-based substances
- **Discuss** current laws relating to the purchase, distribution, and use of cannabis-derived agents and products

Overview

Current Culture of CBD and Medical Marijuana or Cannabis

ARS #1

Which statement is correct regarding the effects of CBD and THC in the brain?

1. CBD produces a euphoric effect in the brain
2. CBD produces a non-euphoric effect in the brain
3. THC produces a euphoric effect in the brain
4. THC produces a non-euphoric effect in the brain

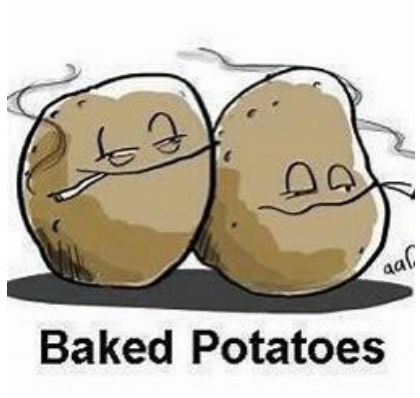
Cannabis

- Contains over 400 compounds
  - Over 100 cannabinoids have been isolated
  - Terpenes are variable, contribute to aroma (limonene, pinene) and serve as a 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
- The first documented date of cannabis use for medicinal purposes was in 400 A.D.
- Cannabis was mentioned in the USP in 1850

USP, United States Pharmacopeia.

Delta-^{9}-tetrahydrocannabinol (THC)

- Major component of cannabis that causes the “high” or “euphoric” feeling
  - 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)*, hyperemesis syndrome, 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

Cannabidiol (CBD)

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

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.

Differences Between Hemp and Marijuana

	Hemp	*Marijuana*
Statutory definition	"the plant *Cannabis sativa* L. and any part of the plant...whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3% 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 • Does not include fiber, oil, or cake from the seed • Does not include sterilized seed incapable of germination
Psychoactive properties	Non-psychotropic	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

1. 2018 Farm Bill. P.L. 115-334, §10113
2. Federal Food, Drug, and Cosmetic Act. 21 U.S.C. §802(16).

DEA, U.S. Drug Enforcement Administration.

Impact of 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".

Photos: https://www.colorado.gov/pacific/agplants/industrial-hemp.

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
- Schedule V
- The first FDA-approved cannabinoid prescription drug
- Used for:
  - Lennox-Gastaut syndrome
  - Dravet syndrome

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; 2016.

Other Products

Cesamet® (Nabilone)

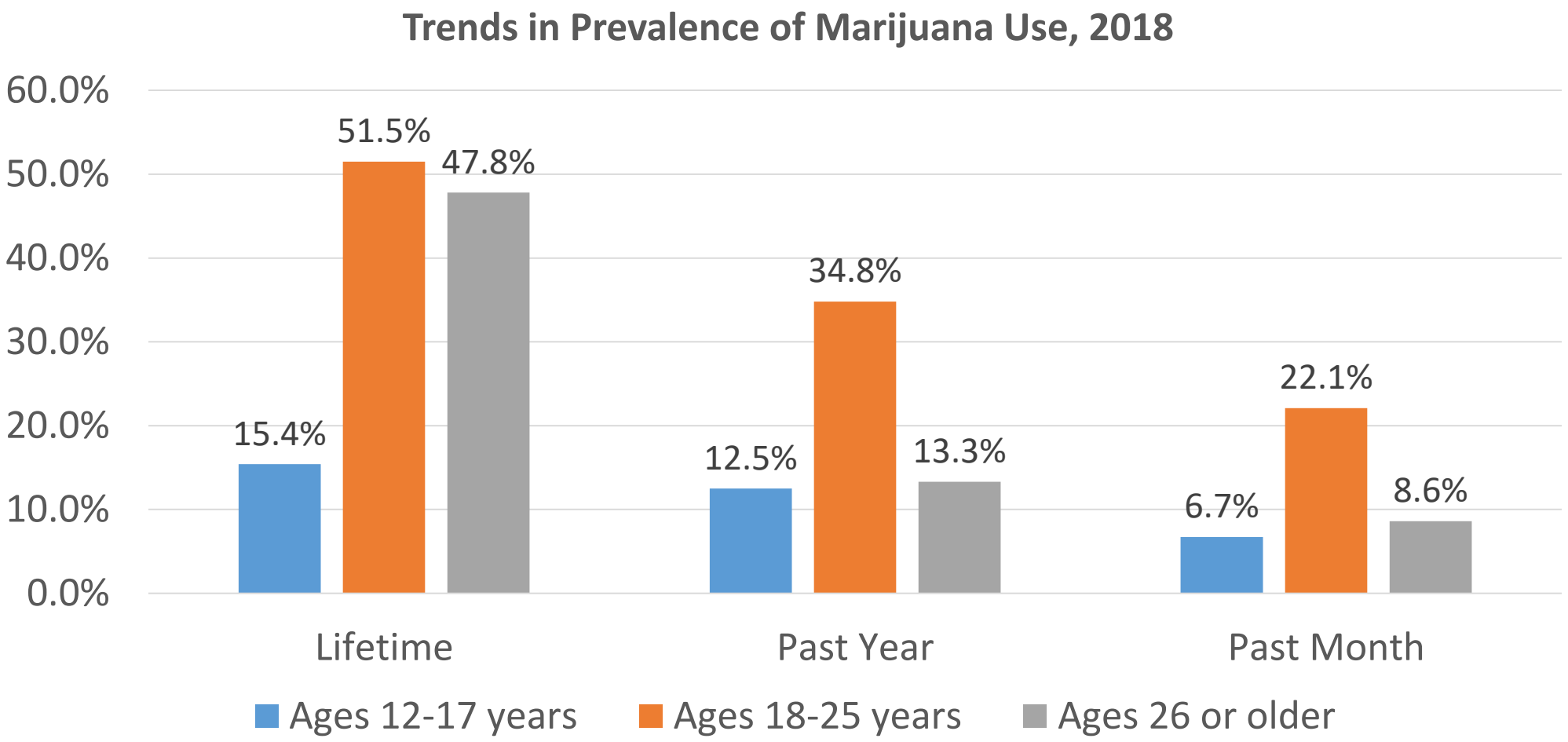
- FDA approved in 2006
- Synthetic cannabinoid
- Schedule II
- Used for:
  - Nausea and vomiting for cancer-related chemothera

Sativex® (THC and CBD)

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

Sativex (THC and CBD) [package insert]. Cambridge, UK: GW Pharmaceuticals; 2016.

Trends in Cannabis Use



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

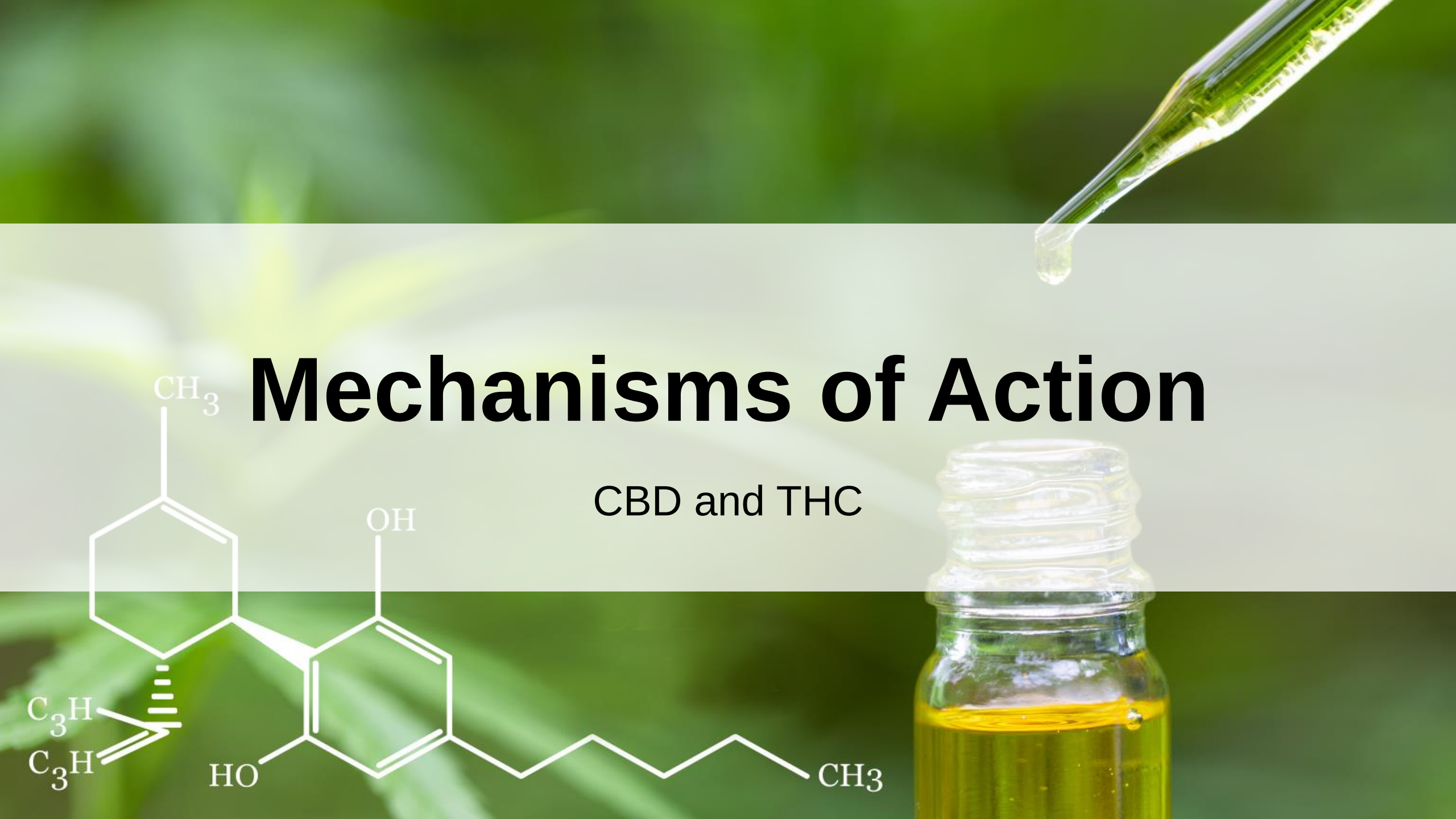
CBD Use in the United States

- 14% of Americans say they use CBD products (2019)
  - 40% for pain
  - 20% for anxiety
  - 11% for sleep

Gallup. https://news.gallup.com/poll/263147/americans-say-cbd-products.aspx.

Mechanisms of Action

CBD and THC



ARS #2

CBD binds to which receptor in the body?

1. CBD binds directly to the CB1 receptor
2. CBD binds directly to the CB2 receptor
3. CBD binds indirectly to the CB1 receptor
4. CBD binds indirectly to the CB2 receptor

Cannabis Pharmacodynamics: Endogenous Cannabinoid System

- There are already different types of cannabinoids in our body that stimulate CB1 and CB2 receptor function
  - Located in different parts of the body (i.e., brain, organs, connective tissue, glands, and immune cells)
    - CB1 – Increased concentration in the CNS (hippocampus, cerebral cortex)
    - CB2 – Found in the immune system (decreased production of pro-inflammatory molecules)
  - Each tissue has different tasks within the system to maintain homeostasis (balance)
  - Examples of effects:
    - Increased appetite
    - Decreased nausea and vomiting

Aso E, Ferrer I. *Front Pharmacol.* 2014;5:37.

CNS, central nervous system.

Cannabis Pharmacodynamics

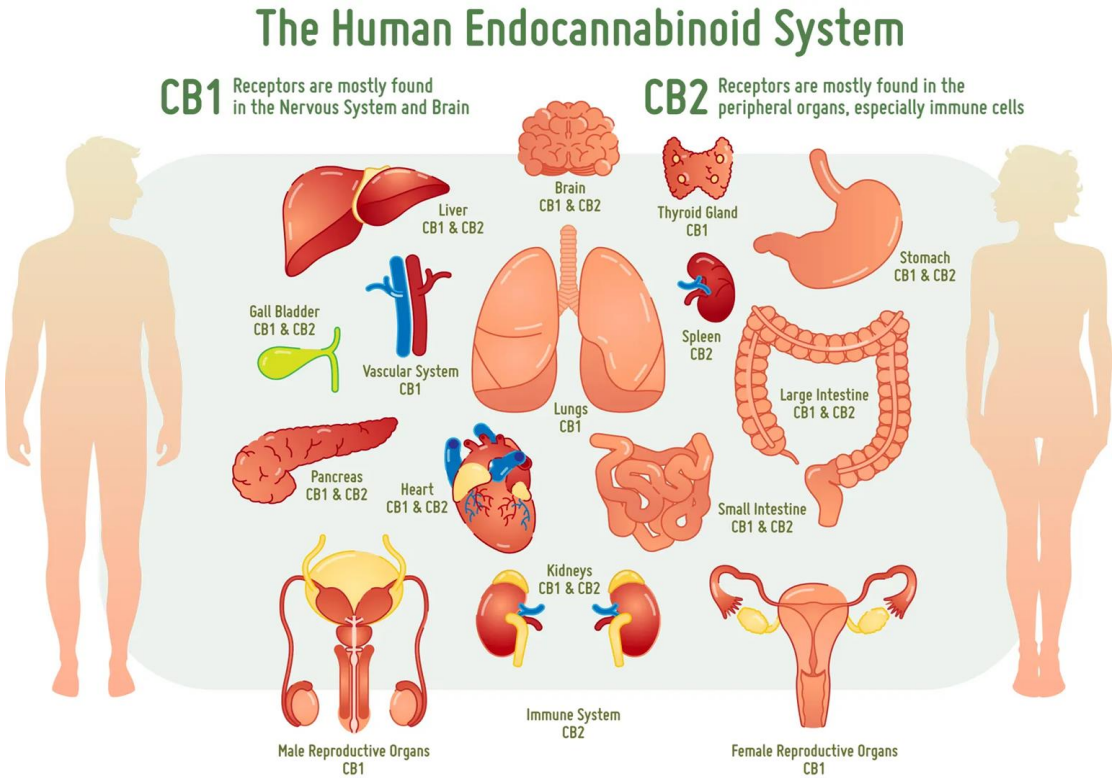
- THC interacts with CB receptors
  - Induces biologic response (euphoric)
  - Also associated with the most pharmacologic effects
- How CBD exerts its activity is unknown
  - May be an inverse agonist
  - Decreases psychotropic effects of THC
- CBD has no direct affinity for CB1 or CB2 receptors
  -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

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

The Endocannabinoid System

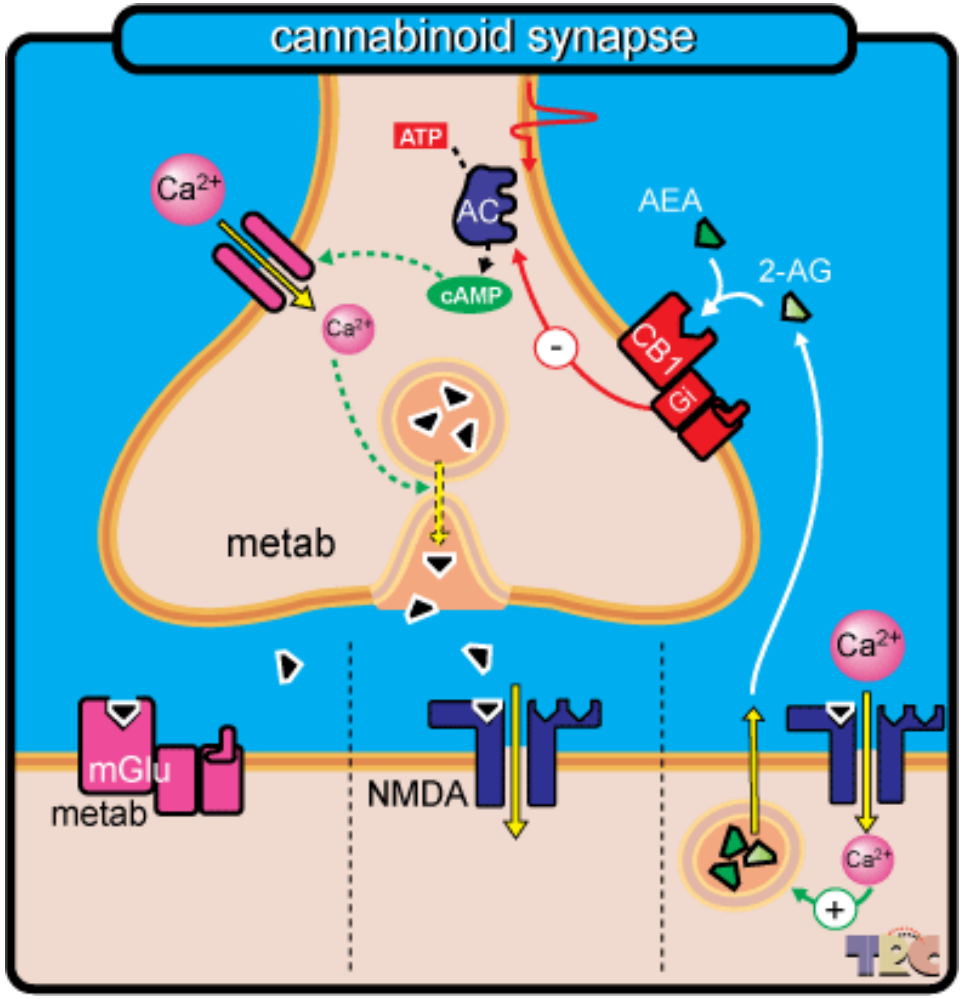
- The human body naturally produces endocannabinoids, which are responsible for maintaining homeostasis (balance)
  - Anandamide (2-AG) → natural cannabinoid found in the body

- Endocannabinoids bind to CB1 and CB2 receptors
  - CB1 receptors are found primarily in the central and peripheral nervous systems
  - CB2 receptors are found primarily in the immune system and peripheral tissues



Aso E, Ferrer I. *Front Pharmacol.* 2014;5:37.;
SatiMedUSA. https://satimedusa.com/pages/what-is-the-endocannabinoid-system.

Regulatory Effect of Cannabinoids at the CB1 Receptor



1. Inhibits adenylyl cyclase activity
2. Alters second messenger systems so Ca++ influx is inhibited

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

Pertwee RG. *Br J Pharmacology*. 2008;153(2):199-215.

ACh, acetylcholine; DA, dopamine; GABA, gamma aminobutyric acid; Glu, glutamate; NE, norepinephrine.

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

Dosing Is Known for THC, But Not 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 involves down-regulation of CB1 receptors and G-protein activation
  - High probability of tolerance with chronic use; low probability with intermittent use
    - *(chronic = daily for a week, intermittent = weekly)*

Zuurman L, et al. *Br J Clinical Pharmacology*. 2009;67(1):5-21.

How is Cannabis Consumed?

MARIJUANA CONSUMPTION

SMOKING

burning the herb
or other forms of cannabis such as hash or concentrates

Starts at 800°C 1470°F

Creates smoke

Effects after ~10 minutes

Last 2-3 hours

VAPORIZING

heating the herb before it burns
or other forms of cannabis such as hash or concentrates using a specific vaporizer (like the GPen for concentrates)

Starts at 157°C 315°F

Creates vapor
(if right temperature)

Effects after ~10 minutes

Last 2-3 hours

EATING

swallowing the herb
as it is or extracted with fat or alcohol, after decarboxylation

Starts at 80°C 176°F

More 11-OH-THC

11OH

Stronger than regular THC

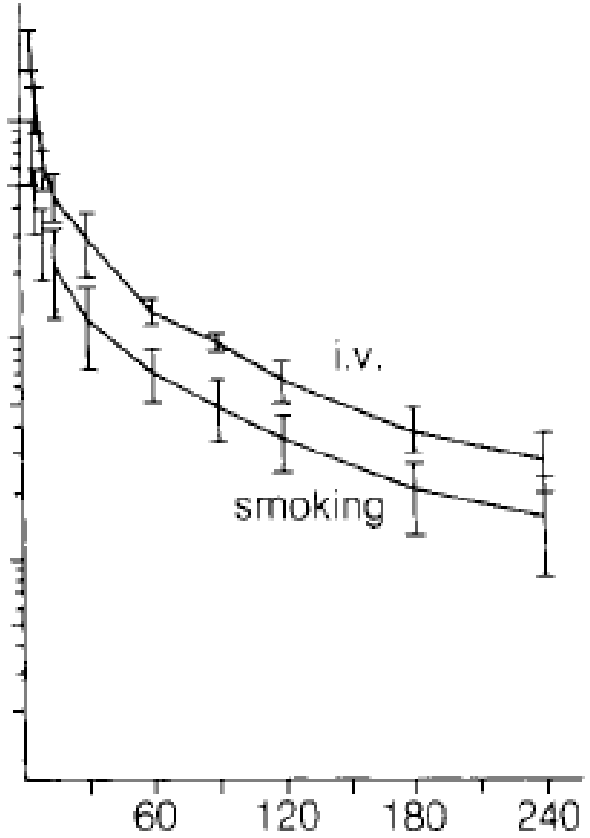
Effects after ~60 minutes

Last 4-8 hours

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

Pharmacokinetics of Smoked THC

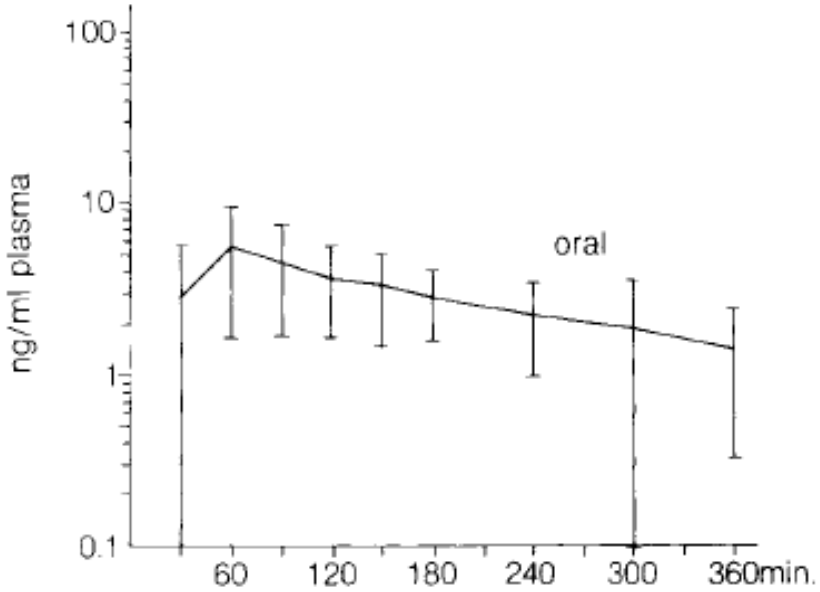
- Smoking cannabis turns ~50% of the THC content into smoke
- Up to 50% of inhaled smoke is exhaled again and some undergoes localized metabolism in the lung
- Bioavailability of an inhaled dose of THC is 10% to 25%
- Effects are perceptible within seconds and fully apparent within a few minutes
- Effects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



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

Pharmacokinetics of Oral THC

- Bioavailability of THC after oral ingestion ranges from 5% to 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.

Pharmacokinetics 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

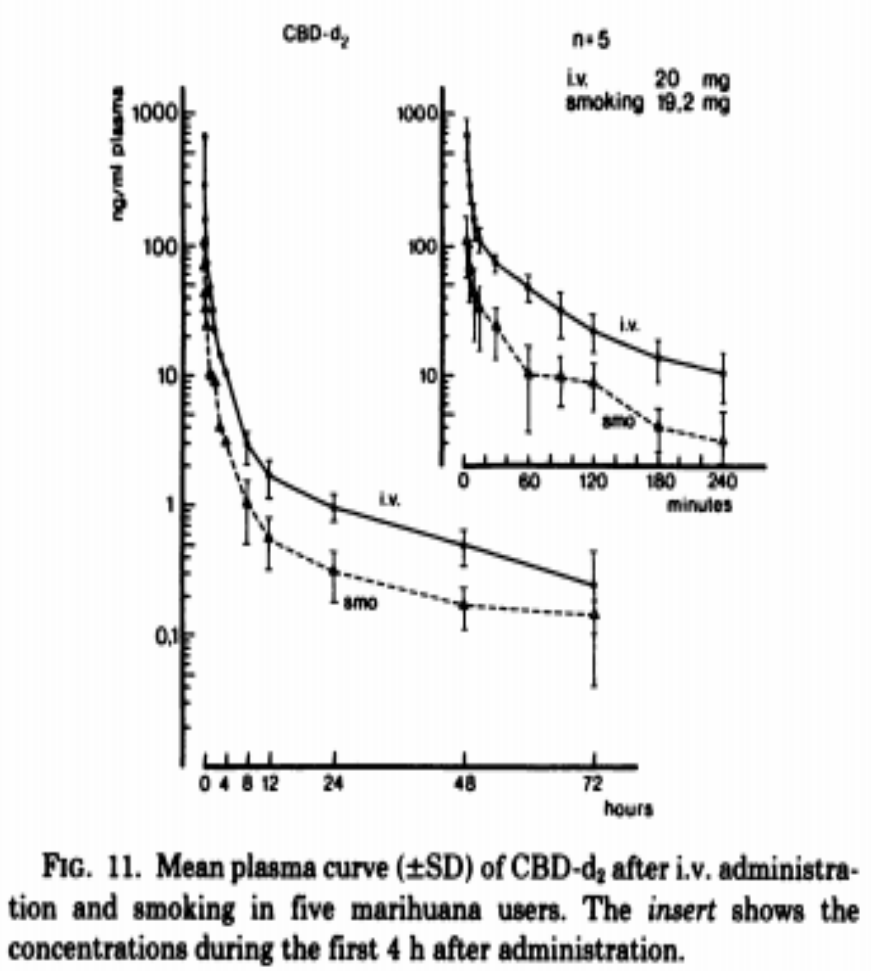
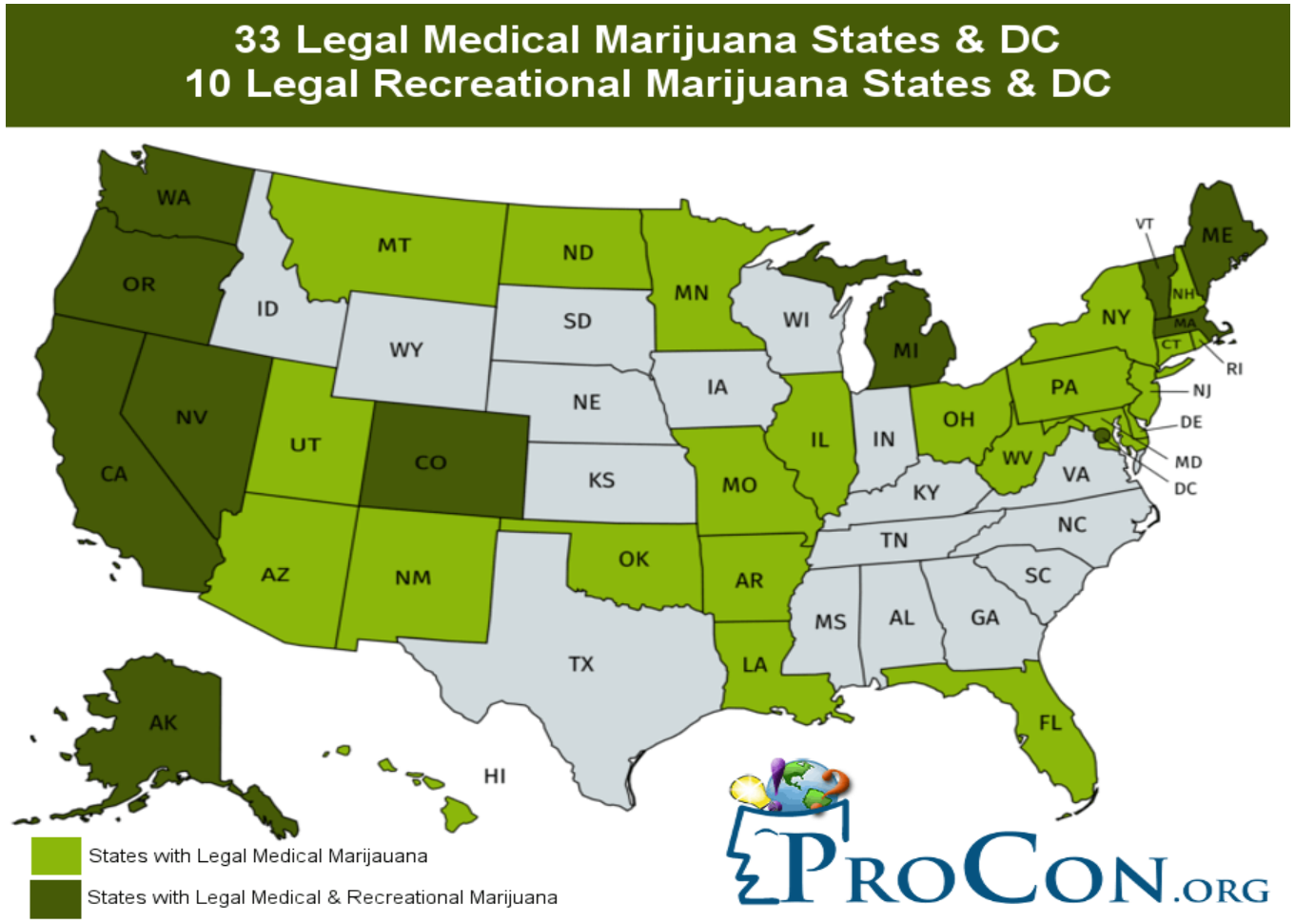


FIG. 11. Mean plasma curve (±SD) of CBD-d_2 after i.v. administration and smoking in five marihuana users. The *insert* shows the concentrations during the first 4 h after administration.

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

IV, intravenous.

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

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. doi: 10.17226/24625.

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

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. doi: 10.17226/24625.

Approved Medical Conditions

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

Summary

- The importance of understanding cannabis pharmacokinetics and pharmacodynamics cannot be understated
- The method by which consumers are ingesting cannabis gives rise to potential adverse effects
- Rigorous research needs to be conducted to truly decide which medical conditions can best be treated with cannabis

Research on CBD

Neurologic and Psychiatric Conditions

ARS #3

Which of the following correctly describes the formulation of Epidiolex®?

1. Purified CBD plant product
2. Synthetic CBD product
3. Purified from hemp
4. CBD that contains no THC component
5. Unsure

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
  - MRI and EEG tests usually normal at first

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

EEG, electroencephalogram;
MRI, magnetic resonance imaging.

Pathophysiology of Lennox-Gastaut Syndrome (LGS)

- The cause of LGS can be divided into 2 categories
  - Symptomatic group – brain injury, generally diffuse injuries to the frontal lobes of brain (encephalitis, meningitis, tuberous sclerosis complex, brain malformations, hypoxia at birth, trauma)
    - 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 Foundation 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 and 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.

Cannabidiol (Epidiolex®)

- First FDA-approved cannabinoid prescription drug from plant material that is different from other CBD products
- **Indication:** Treatment of LGS and DS
- **DEA schedule: now de-scheduled was schedule V**
- **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
- **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

Epidiolex [package insert]. Carlsbad, CA: GW 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 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(8):1586-92.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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.

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 times
  - Those who started 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: 4x greater in Paris, 5x greater in London, and > 9x greater in Amsterdam
- 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):427-36.

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 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
- Sub-group 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 patients 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

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

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

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):E2657-64.

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

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

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

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 patients total 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: Pittsburg 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
- 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

Acknowledgements

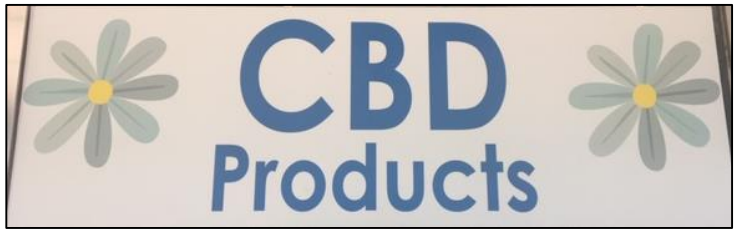
Purity and Potency of CBD and Medical Marijuana

ARS #4

Which of the following contaminants may be present with cannabis formulations that are not FDA approved?

1. Chemical solvents
2. Microbes
3. Heavy metals
4. All of the above

CBD Products



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.

Food and Drug Administration. https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd. Accessed March 30, 2020.

Labeling Accuracy with CBD Products

84 CBD PRODUCTS TESTED FOR LABEL ACCURACY		
UNDERLABELED (CBD content exceeded label value by >10%)	**OVERLABELED** (CBD content tested >10% below labeled value)	**ACCURATE** (CBD content tested 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):1708-9.;
https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis.

Labeling Accuracy with Edible Cannabis Products

75 PRODUCTS TESTED FOR LABEL ACCURACY		
UNDERLABELED (THC content exceeded label value by >10%)	**OVERLABELED** (THC content tested >10% below labeled value)	**ACCURATE** (THC content tested within 10% of labeled value)
17 (23%)	45 (60%)	13 (17%)

- 44 products (59%) had detectable levels of CBD
- Only 13 had CBD content labeled

Vandrey R, et al. *JAMA*. 2015;313(24):2491-3.

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 on their own

- Chemical solvents
  - Many states borrowed from U.S. Pharmacopeia
  - 59 solvents categorized into those that should be avoided, limited, or regarded as safer than others
    - Concentration limits recommended by USP
  - **Do not include butane and propane**

EPA, environmental protection agency.

https://ehp.niehs.nih.gov/doi/full/10.1289/EHP5785. Accessed March 31, 2020.

Potential for Contamination - *continued*

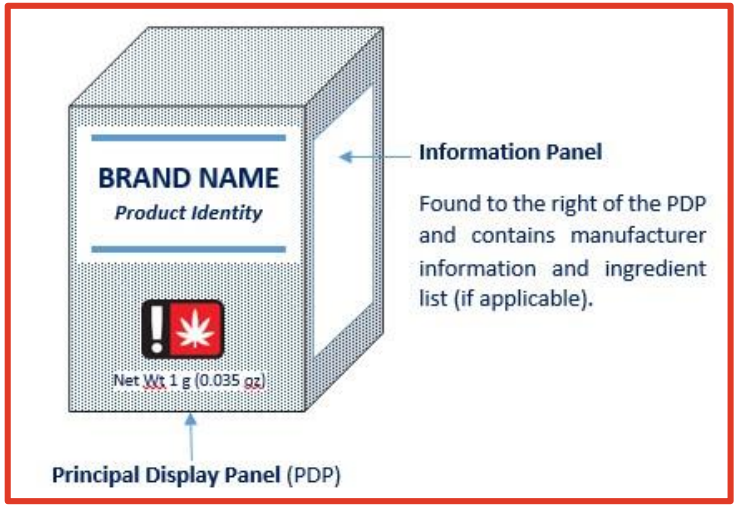
- Microbial contamination
  - Cannabis plants can pick up molds, bacteria, and fungi while growing or during handling processes (e.g., aspergillus, pseudomonas)
    - Concern for immunocompromised patients
  - Fungicides and insecticides can be harmful to human health if not removed from the plant matter

- Metals
  - Cannabis = “hyperaccumulator” because it takes up unusually high levels of metals from the soil or growing medium through its roots and potentially into its flowers
  - Pesticides may contain lead, mercury, cadmium, and other toxic metals
  - Vape pens and cartridges could also potentially release metals

https://ehp.niehs.nih.gov/doi/full/10.1289/EHP5785. Accessed March 31, 2020.

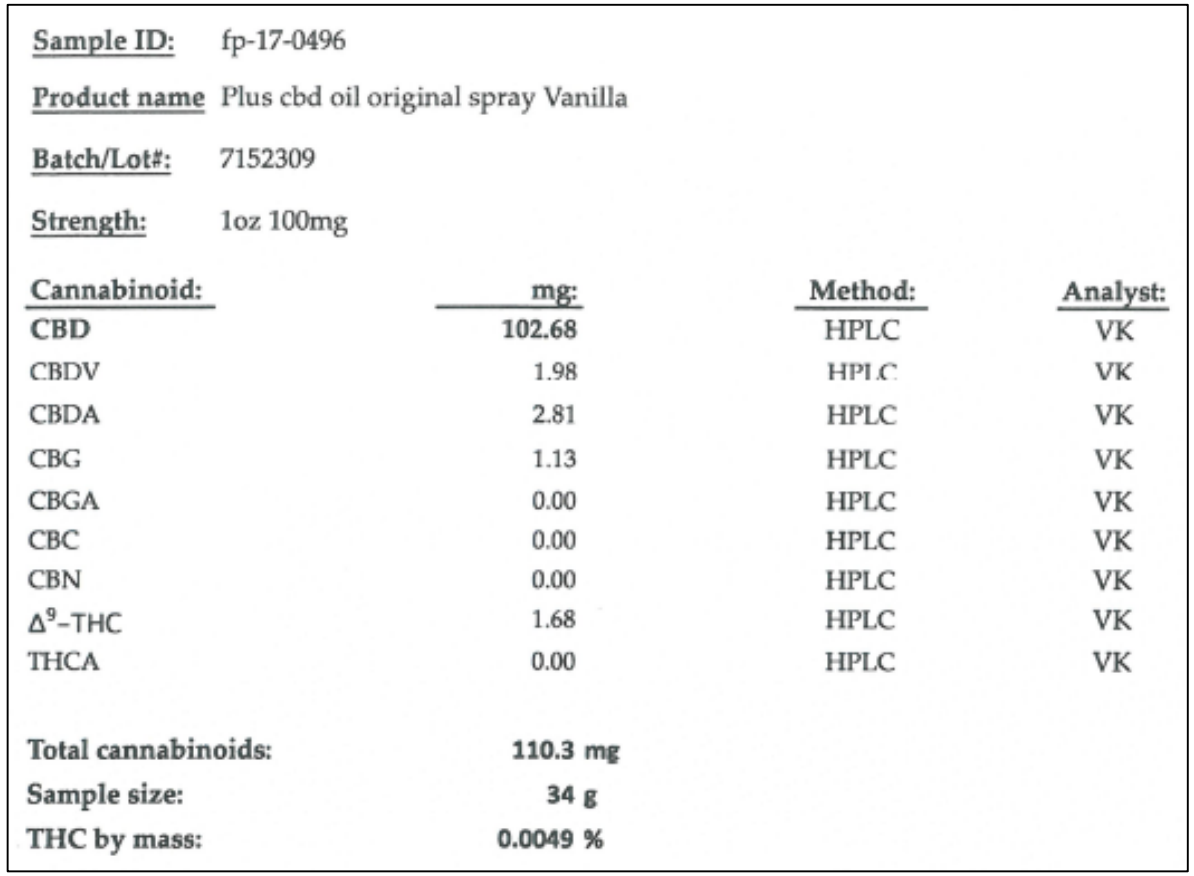
Patient Safety Issues

- Unintentional exposure
- Consistency (or lack thereof)
- Quality and purity
- Packaging
- Labeling
- Testing – content and contaminants
- Accuracy of education provided
- Drug interactions
- Duplication of therapy
- Assessment of adverse reactions



What Can Pharmacists Do to Ensure CBD Product Quality?

- **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**



Sample ID: fp-17-0496

Product name Plus cbd oil original spray Vanilla

Batch/Lot#: 7152309

Strength: 1oz 100mg

Cannabinoid:	mg:	Method:	Analyst:
CBD	**102.68**	HPLC	VK
CBDV	1.98	HPLC	VK
CBDA	2.81	HPLC	VK
CBG	1.13	HPLC	VK
CBGA	0.00	HPLC	VK
CBC	0.00	HPLC	VK
CBN	0.00	HPLC	VK
Δ^9-THC	1.68	HPLC	VK
THCA	0.00	HPLC	VK

Total cannabinoids: **110.3 mg**

Sample size: **34 g**

THC by mass: **0.0049 %**

Photo: https://cvsciences.com/wp-content/uploads/2018/05/7152309-Released.pdf.

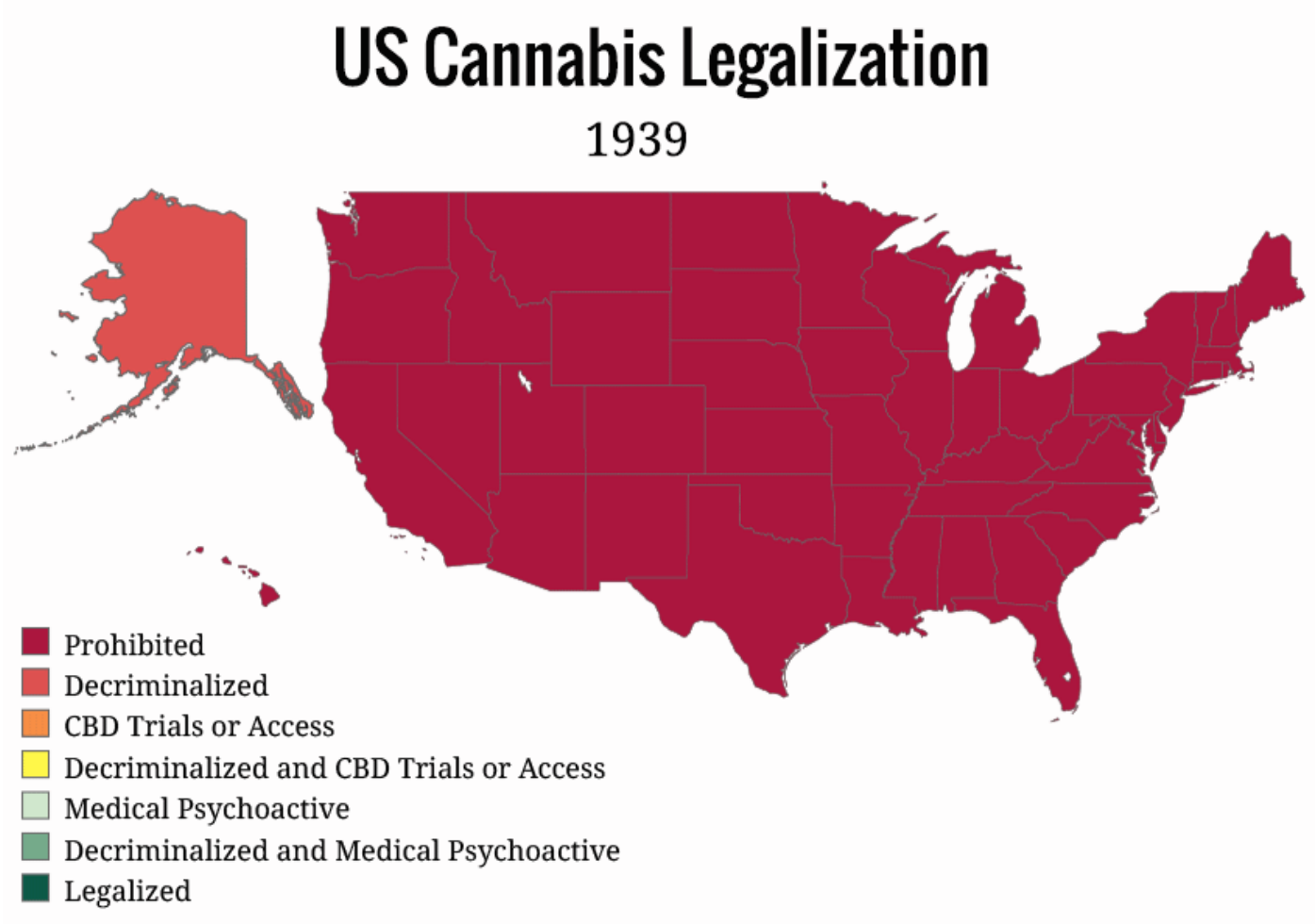
GMP, good manufacturing practices.

Summary

- Providers should be aware of the patient safety concerns that can impact patients and friends/families of patients
- Unsubstantiated claims of effectiveness and content pose significant risks and may delay time to seek appropriate medical care

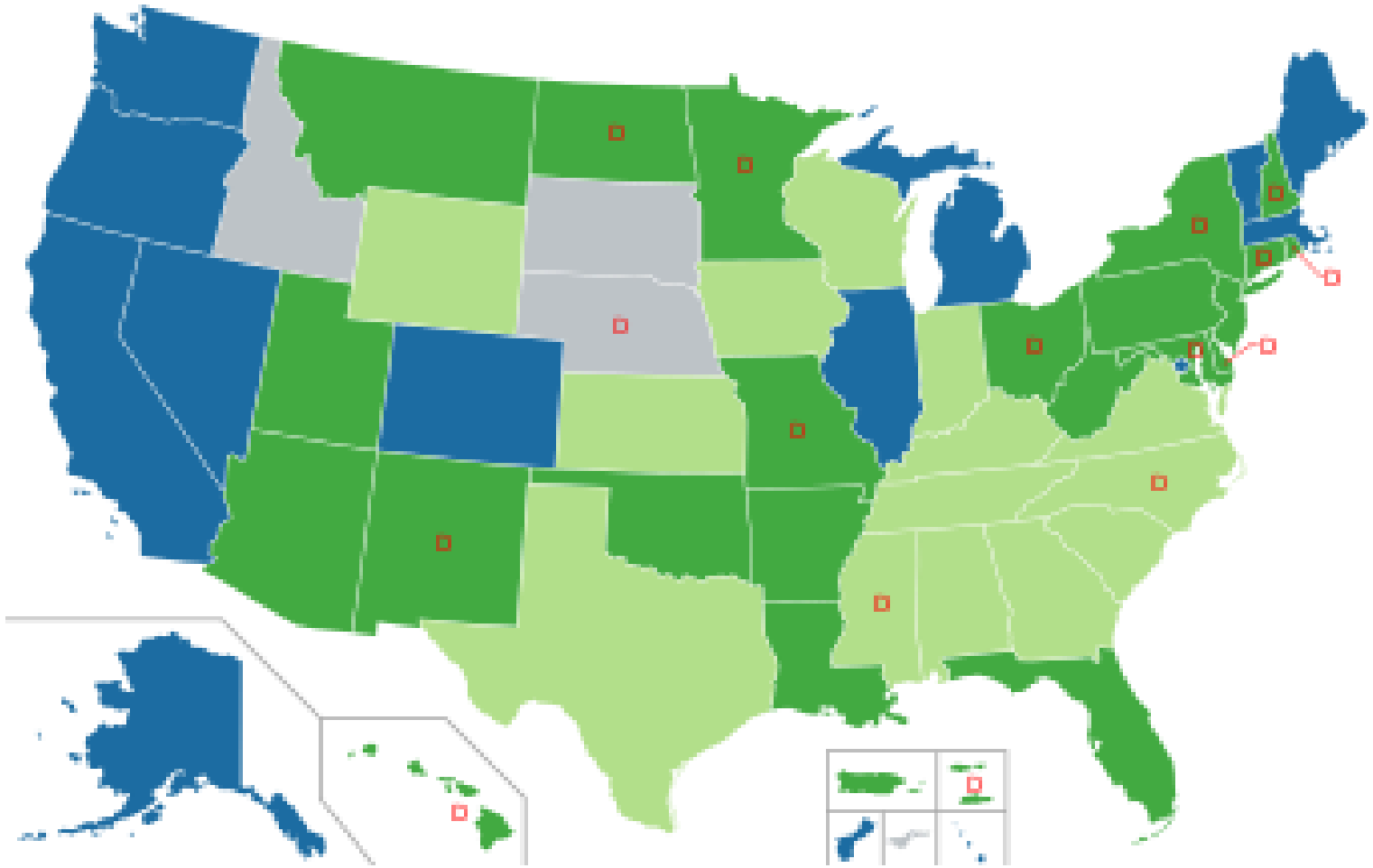
Legal Issues

Evolving Status of Cannabis in the U.S.: 1939-today



Putina V. https://thereliefleaf.com/where-is-cannabis-legal-in-the-u-s .; https://commons.wikimedia.org/w/index.php?curid=57784069; https://en.wikipedia.org/wiki/Timeline_of_cannabis_laws_in_the_United_States#/media/File:For-wiki-gif.gif.

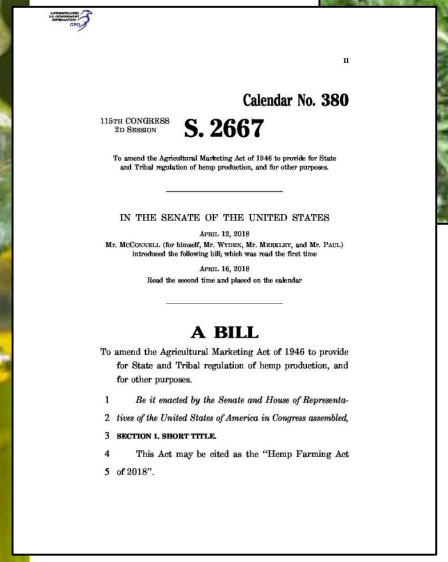
Legal Status of Cannabis in the U.S.



Legal
Legal for medical use
Legal for medical use - limited THC
Prohibited for any use
D Decriminalized

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

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 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. Accessed March 30, 2020.;
https://www.fda.gov/news-events/press-announcements/fda-advances-work-related-cannabidiol-products-focus-protecting-public-health-providing-market. Accessed March 30, 2020.

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

Implications of FDA Approval of Purified CBD

- DEA scheduling information: Schedule I to Schedule V
  - Schedule I: Marijuana
  - Schedule II:
  - Schedule III:
  - Schedule IV:
  - Schedule V:

Where will OTC CBD fit in this schema, if at all?

Answering Patient Questions about Legal Aspects of OTC or Rx CBD

- Performing medication reconciliation
  - Screening for drug interactions
  - Evaluating for duplication of therapy
  - Determining what monitoring may be needed

- Discussing differences of OTC and Rx CBD products with patients
  - Rigorous testing and clinical trials
  - Dose
  - Potential for impurities

Summary

- Cannabis and CBD remain DEA Schedule I by Federal Law
- CBD remains a drug for legal purposes
- There are associated drug interactions that are significant and need to be assessed prior to CBD exposure
- Epidiolex® is not the same as CBD from the internet or dispenseries
- The only purified plant CBD product that is FDA approved is Epidiolex®, which is de-scheduled by the DEA

Educating Patients and Healthcare Providers about Cannabis

Cannabidiol (Epidiolex®): Counseling and Monitoring

- Monitor LFTs at baseline and at 1, 3, 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 for cannabis since it contains < 0.1% THC in the API powder and < 0.01% in the finished product

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

LFTs, liver function tests.

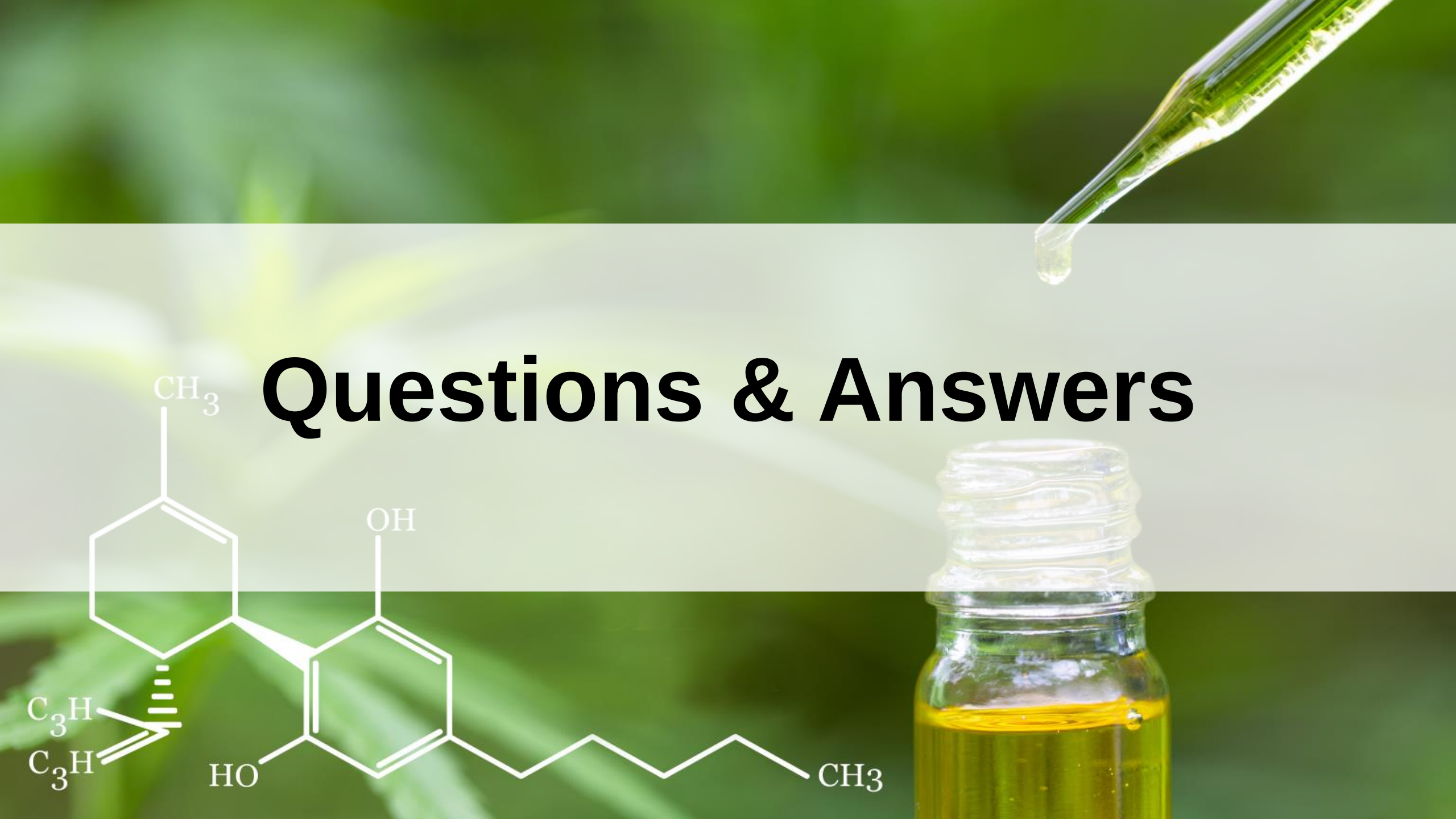
What is the Future?

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

Conclusions

- Medical cannabis and CBD are therapies that have potential medical benefits in certain conditions, but adverse effects and patient safety concerns need to be considered
- Cannabis-derived substances have multiple mechanisms of action that target the endocannabinoid system and indirectly effect the CB1 receptor
- Over-the-counter products differ in purity, content, and dosing from FDA-approved cannabis formulations
- Cannabis-derived products have contained different cannabinoids and are available in many different forms with variable pharmacokinetic and pharmacodynamic profiles
- Current laws may or may not support the purchase, distribution, and use of cannabis-derived agents and products

Questions & Answers



Thank you!