

Cannabidiol, Medical Miracle or Just Another Trend?

Shanice Coriolan, PharmD., RPh
PGY1 Pharmacy Practice Resident
NYU Winthrop Hospital
NYSCHP CE Webinar
June 23rd, 2020

Disclosures

- ❑ The author of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

Overview



Background



Legal and
Regulatory
Considerations



Endocannabinoid
System



Cannabinoid
Pharmacology



Clinical and Potential
Uses

Learning Objectives

1. Discuss the current influence and impact of cannabidiol (CBD) on the market
2. Discuss the taxonomy of the cannabis plant
3. Explain the legal considerations that surround marijuana and hemp plants
4. Discuss the pharmacology of cannabidiol and associated drug interactions and side effects
5. Discuss the current clinical application of CBD
6. Assess the clinical evidence surrounding the support of non-prescription cannabidiol products
7. Identify the role of a clinician in cannabidiol products

Background

6 Product results: "CBD"

Sort by: Relevancy

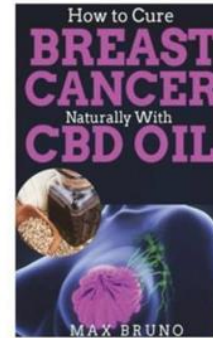


LORD JONES
High CBD Formula Body Lotion
\$60.00
★★★★★

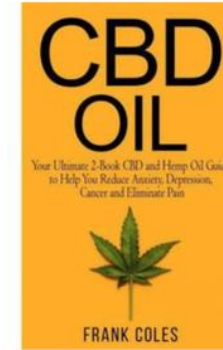
exclusive
HERBIVORE
Emerald CBD + Adaptogen
Deep Moisture Glow Oil
\$58.00
★★★★★

FLORA + BAST
Age Adapting CBD Serum
\$77.00
★★★★★

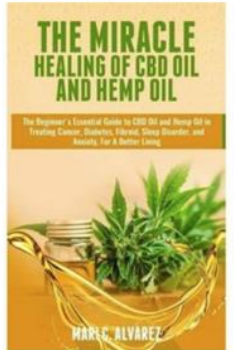
NEW
BRIOGEO
B.Well 100mg CBD + Arnica
Flower Soothing Skin & Scalp
Oil
\$48.00
★★★★★



How to Cure Breast Cancer Naturally with CBD Oil - by Max Bruno (Paperback)
\$8.45
Only ships with \$25 orders
Not in stores
[Add for shipping](#)



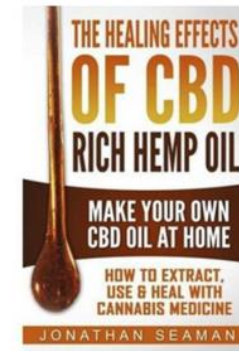
CBD Oil - by Frank Coles (Paperback)
\$6.99
Only ships with \$25 orders
Not in stores
[Add for shipping](#)



The Miracle Healing of CBD Oil and Hemp Oil - by Mari C Alvarez (Paperback)
\$15.95
Not in stores
[Add for shipping](#)



CBD Oil - by Chris Harbin (Paperback)



The Healing Effects of CBD Rich Hemp Oil - Make Your Own CBD



CBD Oil for Pets - by Eric Hilton (Paperback)

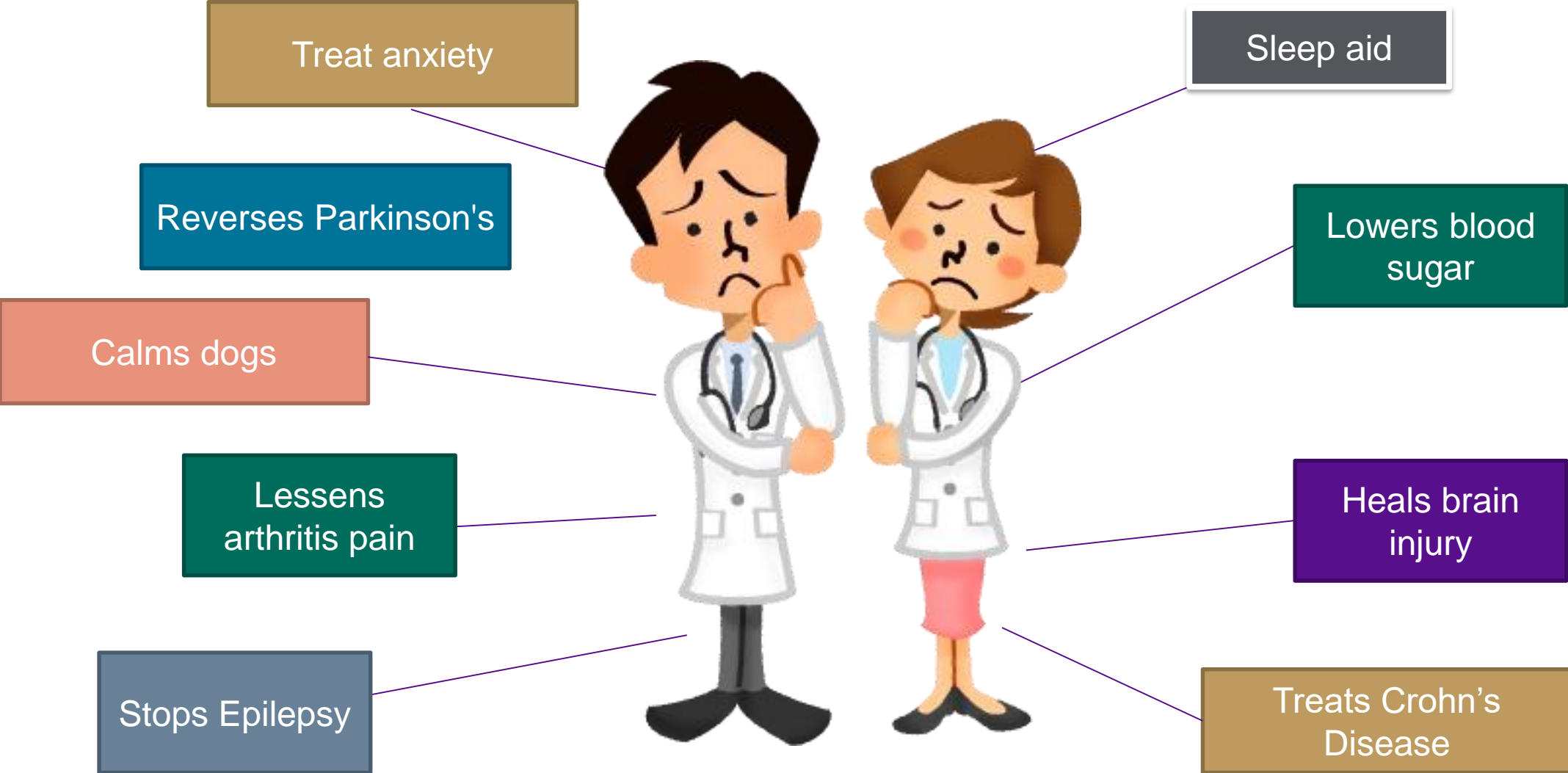
Market Projection

- Exploding market affecting industries such as cosmetics, food & beverage and pharmaceuticals
- CBD sales is expected to exceed \$20 billion in the United States by 2024
- CBD product sales have outgrown overall dispensary sales
- CBD consumers are an average age of 40, have higher education, and are more likely than non-consumers to be employed full time

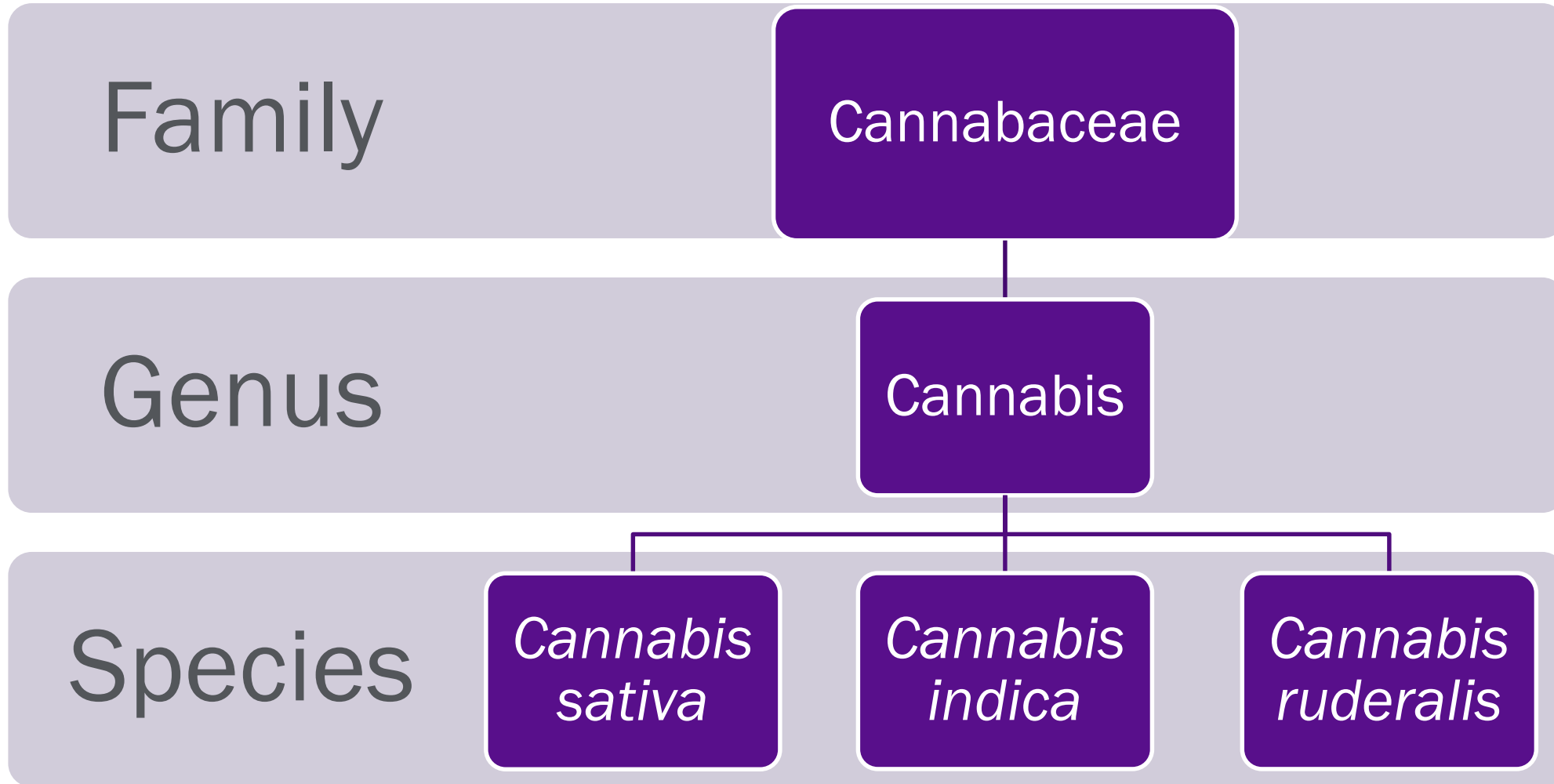


Syosset Pharmacy – CBD Dispensary

Can CBD really do all that?



Cannabis Taxonomy

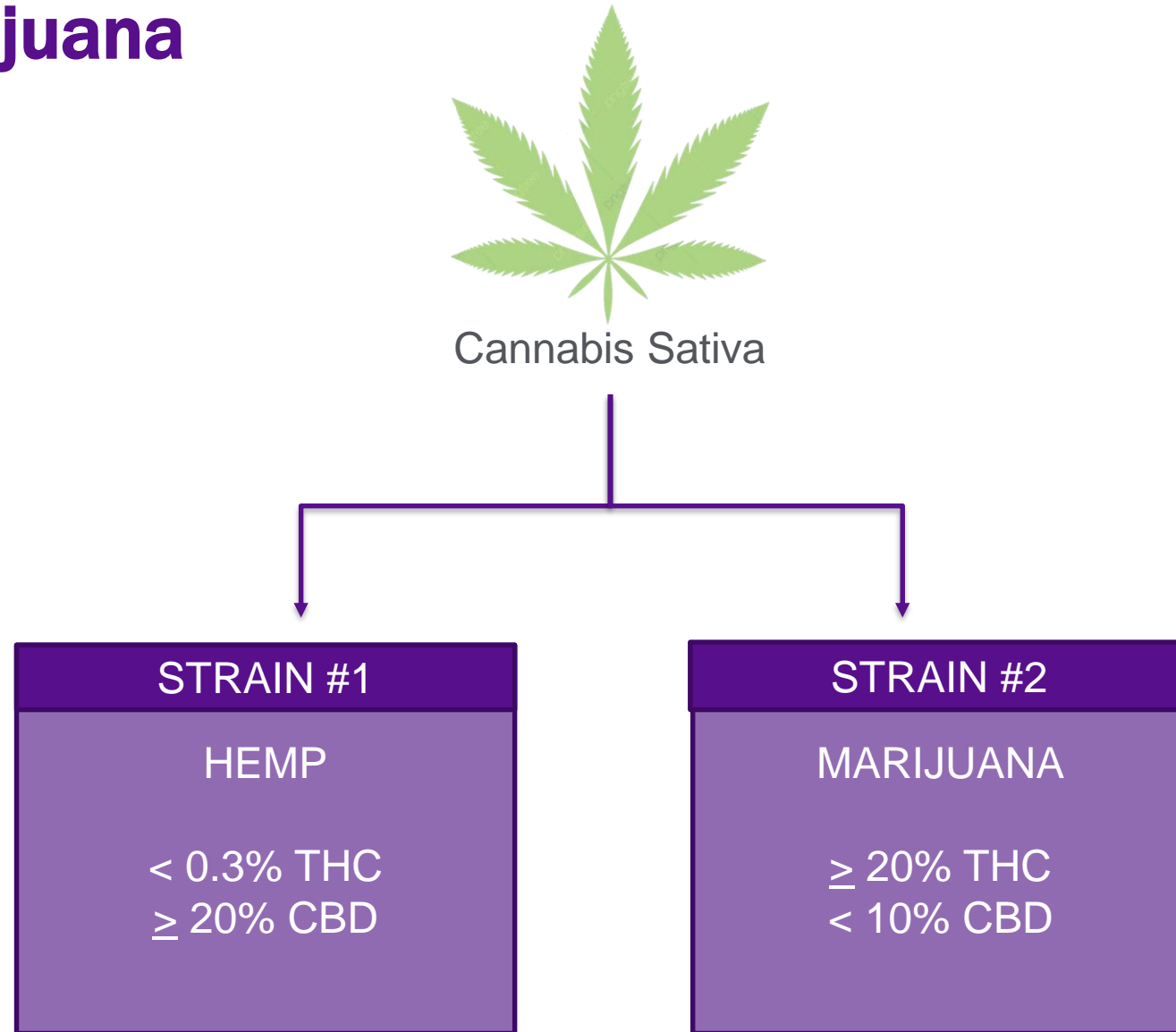




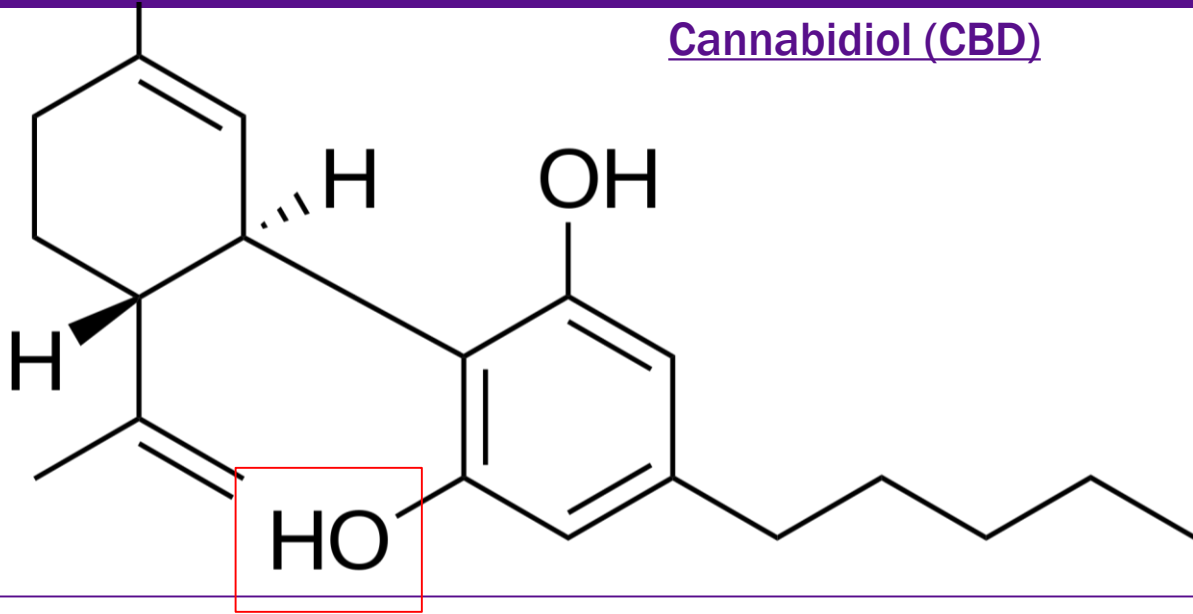
Cannabis Sativa

- The use of *Cannabis Sativa* by eastern Asians can be documented as far back as 4,000 years ago
 - Cultivated and used for industrial fiber, seed oil, food, recreation, religious purposes and medicine
- Hemp and marijuana are both plants in the *C. sativa* family however they differ in structure and active ingredients

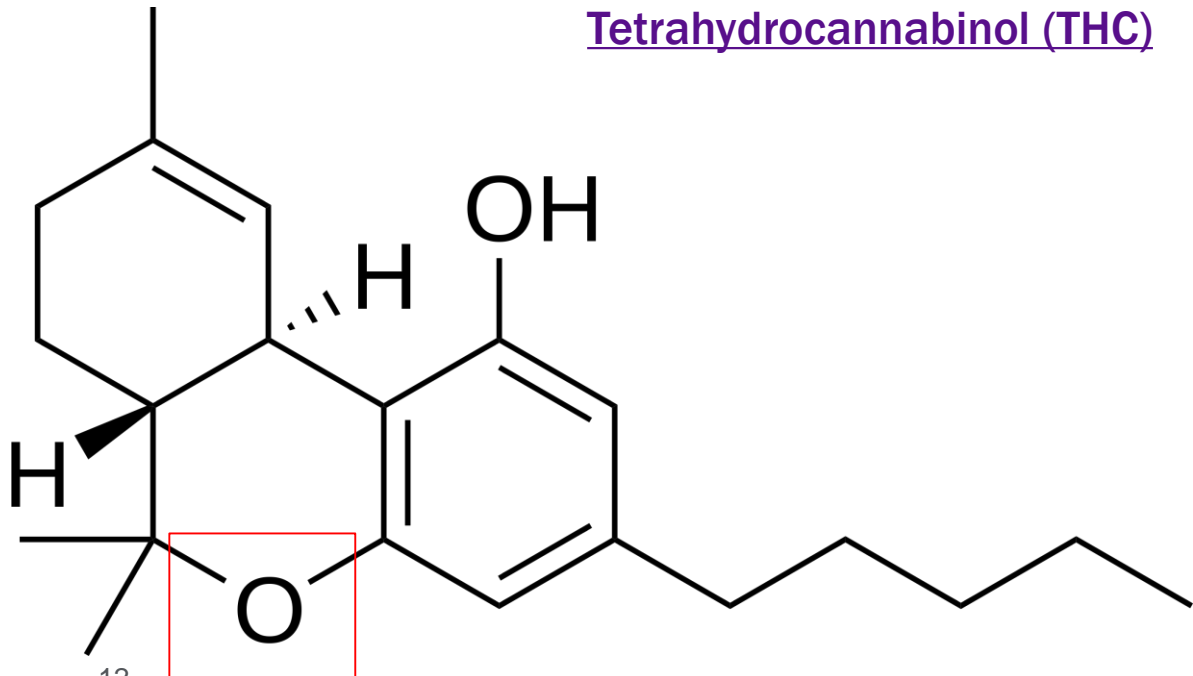
Hemp vs. Marijuana



Cannabidiol (CBD)



Tetrahydrocannabinol (THC)



$C_{21}H_{30}O_2$
Mostly Identical

Legal and Regulatory Considerations



The Farm Bill

- Previous legislation failed to make any distinction between the marijuana and hemp plants
 - Hemp is banned and classified as a Schedule 1 drug alongside cannabis
- 2014 Farm Bill allowed the creation of small state-level pilot programs
- US congress voted to pass the Agriculture Improvement Act of 2018
- Bill confirmed the legalization of hemp and provisions for its cultivation, transport and sale
- Today, hemp is allowed much more broadly



Learning Question

What is the legal limit of THC content allowed in CBD products?

- a) More than 0.3% THC
- b) Less than 0.3% THC
- c) More than 0.4% THC
- d) Less than 0.4% THC



What is Hemp?

U.S. Law:

“The plant *Cannabis sativa* and any part of that plant, including the seeds thereof and all derivatives, extract cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9-tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis”

-Section 297A of the Agricultural Marketing Act of 1946

2018 FARM BILL EFFECT

Under the 2018 Farm Bill, hemp has been removed from the Controlled Substances Act (CSA) and is now considered an agricultural product.



HEMP-DERIVED
CBD IS LEGAL



HEMP FARMERS
CAN APPLY FOR
CROP INSURANCE



MORE BANKS WILL BE
WILLING TO WORK WITH
HEMP COMPANIES



“BIG AG” WILL BEGIN
MOVING INTO THE
HEMP INDUSTRY

HEMP-DERIVED CBD PRODUCT SALES



HEMP INDUSTRY GROWTH



\$2.5
BILLION
BY 2022



The Farm Bill also allows individual states to create their own regulations and programs for industrial hemp productions



State plans must include

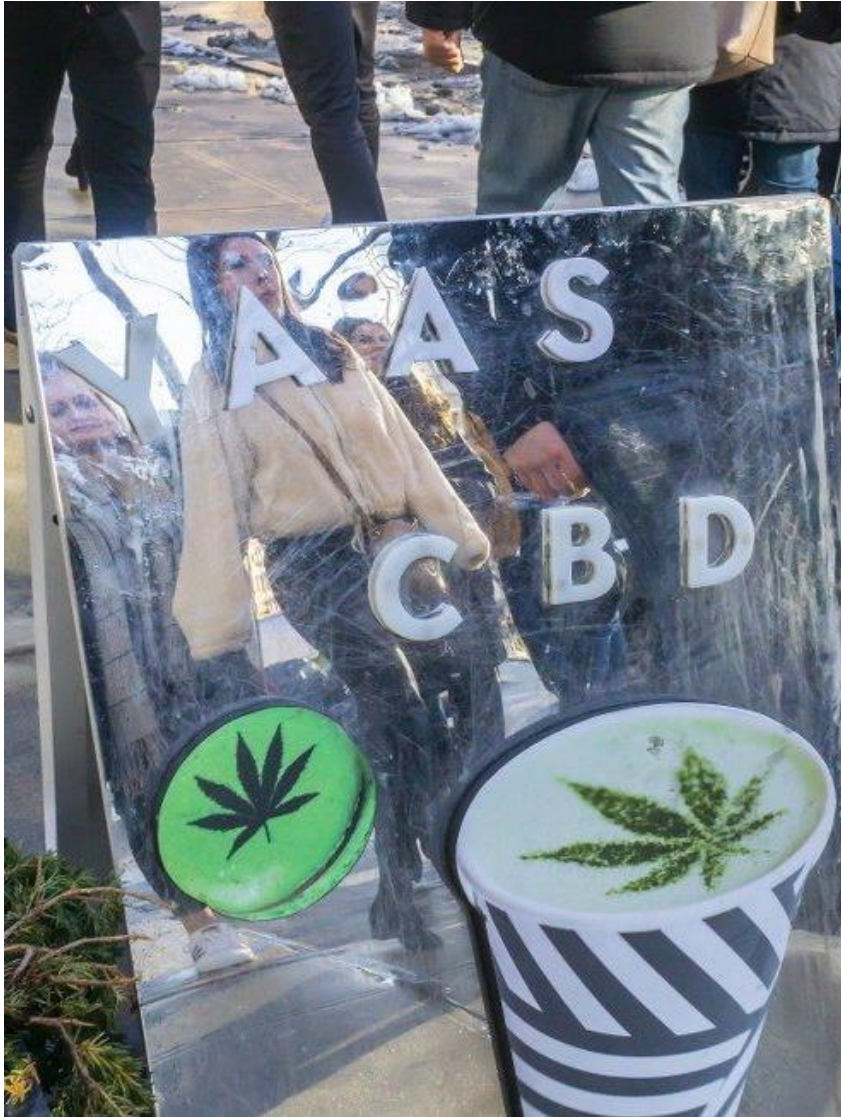
A practice to record and describe land on which hemp is grown	A procedure for testing THC concentration	A procedure for non-compliant product disposal	A procedure for enforcing regulations
---	---	--	---------------------------------------



Allows transfer of hemp-derived products across states lines for commercial purposes



No clear regulations for CBD products at the federal level



A cafe on the Lower East Side in New York advertises the availability of CBD infused beverages on its menu.

Legal Status in NY

- CBD derived hemp can be legally sold in stores around the state
- In February 2019, the NYC department of health and mental hygiene ordered restaurants under its jurisdiction to not sell food products that contained CBD
 - CBD was not deemed as a safe food additive
- The health department said they would start docking points from non-compliant food and drink establishments
- This ban went into affect July 1st, 2019

The Endocannabinoid System

Endocannabinoid system



Biological system containing endogenous cannabinoids, cannabinoid receptors and the synthetic and degrading enzymes responsible for synthesis and degradation of endocannabinoids



Endocannabinoids are endogenous lipid-based neurotransmitters that bind to cannabinoid receptor proteins



May be involved in regulating physiological and cognitive processes including appetite, pain, mood and memory



The body has its own endogenous cannabinoids

Anandamide
2-arachidonylglycerol

Cannabinoid Receptors

CB1 Receptor

- Effects
 - Appetite stimulant
 - Increased palatability
 - Cognition
 - Pain
 - Thermoregulation
 - Intraocular pressure
- Found on central and peripheral neurons

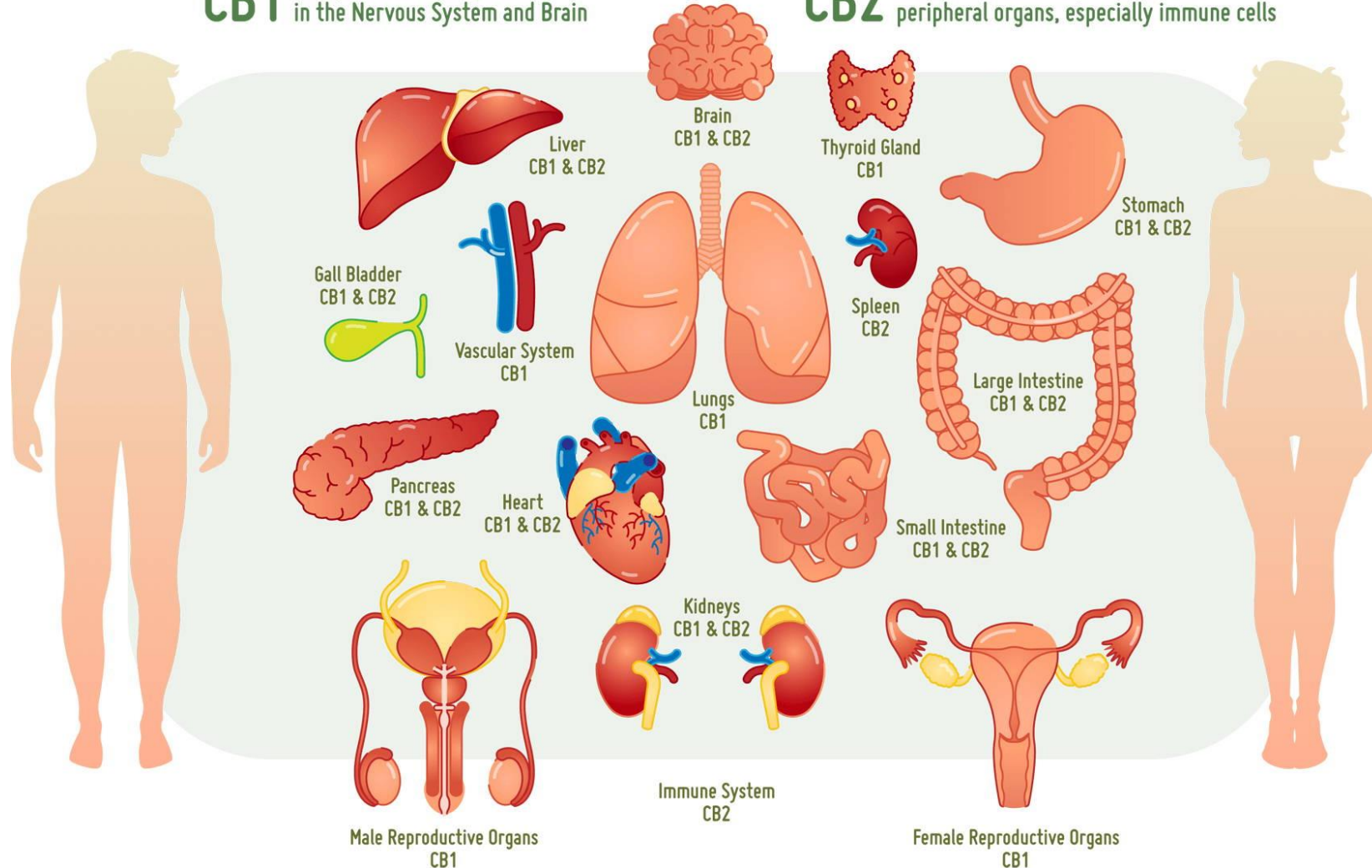
CB2 Receptor

- Effects
 - Pain
 - Inflammation
 - Immune function
- Found in immune cells (leukocytes, spleen, tonsils)

The Human Endocannabinoid System

CB1 Receptors are mostly found in the Nervous System and Brain

CB2 Receptors are mostly found in the peripheral organs, especially immune cells



Example Types of Cannabinoids

Cannabinoid Types	Potency towards cannabinoid receptors
Endocannabinoids	
2-arachidonoylglycerol	Both CB1 and CB2
Anandamide	Preferentially CB1 Some activity on TRPV-1
Phytocannabinoids	
Delta-9-tetrahydrocannabinol (THC)	Both CB1 and CB2
Cannabidiol (CBD)	Preferentially CB2
Synthetic Cannabinoids	
Dronabinol	Both CB1 and CB2
Nabilone	Both CB1 and CB2

Phytocannabinoids



Plant derived cannabinoids have been researched as potential therapeutic options because of their modulation of the endocannabinoid system



The most notable and well understood phytocannabinoids are **THC** and **CBD**



Tetrahydrocannabinol (THC) has been noted to work mostly through the CB1 receptor as an agonist



Cannabidiol has been found to work through a variety of more complex pharmacological actions including

Inhibition of endocannabinoid reuptake
Increasing serotonin 5-HT1A



Learning Question

Which of the following is an endogenous cannabinoid?

- a) CBD
- b) THC
- c) Terpenes
- d) Anandamide

Cannabidiol Pharmacology

Mechanism of Action



CBD has a low affinity for CB1 receptors

Acts as a negative allosteric modulator of the CB1 receptor



Targets several receptors outside of the EC system including 5-HT1a receptors, affecting a range of biological and neurological processes

Anti-anxiety affects
Appetite
Sleep
Nausea and vomiting



Interacts with a receptor called TRPV1 (transient receptor potential cation channel subfamily V1)

Involved with the mediation of pain perception, inflammation, and body temperature

Pharmacokinetics/Pharmacodynamics

Absorption

- Lipophilic and rapidly distributed in highly perfused tissues
- Absorption and onset of action are variable and depend upon the route of administration
- High fat and high calorie meals increase the extent of absorption

Metabolism

- Primarily metabolized by
 - CYP2C19 and CYP3A4
 - UGT1A7, UGT1A9, and UGT2B7

Excretion

- Primarily in feces, with some in urine

Cannabidiol Drug Interactions

Interacting Medications	Potential Outcomes/ Management
CYP2C19 inhibitors CYP3A4 inhibitors	<ul style="list-style-type: none"> Increased CBD levels ; not clinically significant at normal doses of CBD
CYP2C19 inducers CYP3A4 inducers	<ul style="list-style-type: none"> Decreased CBD levels; significant if strong enzyme inducers are used with high CBD doses
CBD may inhibit CYP2C19 CBD may inhibit CYP2D6 CBD may inhibit CYP3A4	<ul style="list-style-type: none"> Possible increase in levels of substrates; monitor for increased effects/toxicity Consider reducing the dose of substrate With antidepressant, monitor for serotonin syndrome and cognitive changes
Other <ul style="list-style-type: none"> CBD may increase sensitivity to valproate – monitor for increased effects, especially an increase in LFTS CBD can cause a 3-fold increase in the active metabolite of clobazam – this may cause excessive fatigue, lethargy, and somnolence CBD may potentiate the effects of antihistamines, macrolides, and sildenafil 	

Common Adverse Reactions

Drowsiness

Fatigue

Decreased
appetite

Diarrhea

Nausea/Vomiting

Infection

Increased serum
alanine
aminotransferase
($>3x$ ULN)

Cannabidiol Clinical Application

Clinical Trials



	Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.	Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome.
Study Design	Multicenter, double-blind, placebo-controlled trial	Multicenter, double-blind, placebo-controlled trial
Population	Children and young adults 2 to 18 years of age with the Dravet syndrome whose seizures were not controlled by their current antiepileptic-drug regimen	Patients with the Lennox-Gastaut syndrome (age range, 2 to 55 years) who had two or more drop seizures per week
Intervention	120 children and young adults with DS were randomly assigned to receive oral cannabidiol solution (20 mg/kg/day) or placebo, in addition to standard antiseizure drug treatment	A total of 225 patients were enrolled; 76 patients were assigned to the 20-mg cannabidiol group, 73 to the 10-mg cannabidiol group, and 76 to the placebo group.
Outcomes	From baseline to 14 weeks, the median convulsive seizure frequency decreased from 12.4 to 5.9 per month in the cannabidiol group and from 14.9 to 14.1 in the placebo group (adjusted median difference in relative seizure reduction 23 percent, 95% CI 5-41).	During the 28-day baseline period, the median percent reduction from baseline in drop-seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group , and 17.2% in the placebo group (P=0.005 for the 20-mg cannabidiol group vs. placebo group, and P=0.002 for the 10-mg cannabidiol group vs. placebo group).

Guideline Use

Based on this data, the US Food and Drug administration approved cannabidiol for the treatment of seizures associated with Dravet Syndrome and Lennox-Gastaut syndrome in June 2018

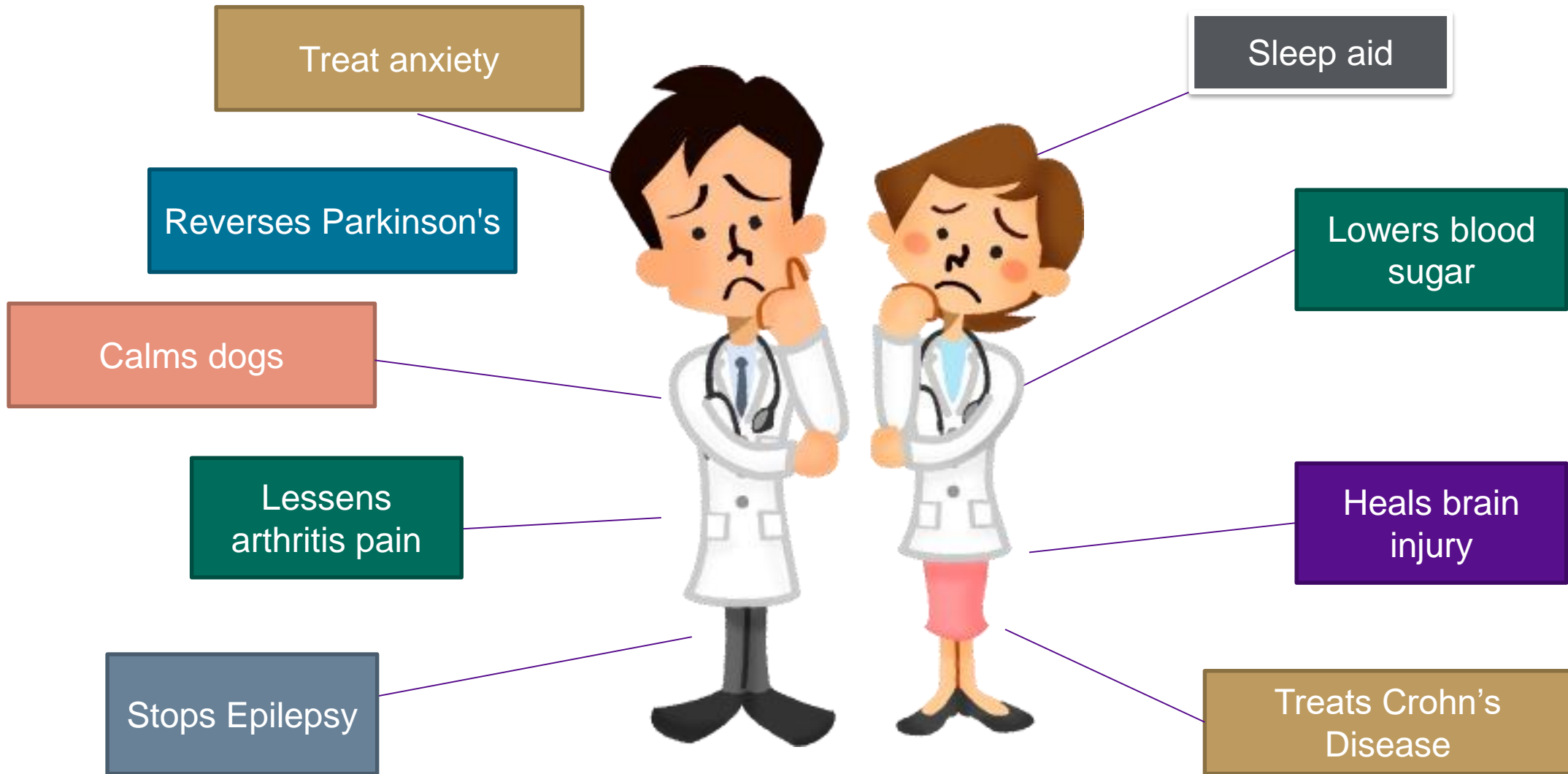
Currently, there is no evidence to support the use of cannabidiol as a first-line agent or as a monotherapy for this indication

Prescription Cannabidiol Products

Product (Brand)	Indication	Usual Dosing Regimens	Side Effects/ Precautions
<p>Cannabidiol (Epidiolex) Oral Solution; 100 mg/mL</p> 	<p>FDA Indication: Intractable seizures; Dravet's syndrome; Lennox-Gestaut Syndrome</p>	<p>Initial Dose; 2.5 mg/kg twice daily; titrate every week in increments of 2.5mg/kg based on clinical response and as tolerated Max: 10 mg/kg twice daily</p>	<ul style="list-style-type: none"> Common side effects (>10%): diarrhea, fatigue, malaise, asthenia, rash, infections, decreased appetite, increase LFTs
<p>Not approved in US: Nabiximols (Sativex) Oromucosal (buccal) spray 27 mg/mL THC; 25 mg/mL CBD</p> 	<p>Multiple Sclerosis spasticity and pain in adults; cancer pain in adults that is refractory to high dose opioids</p>	<p>For buccal use only. Initial dose: 1 spray in the morning and in afternoon or evening (max 2 sprays on day 1) May increase by 1 spray daily as needed/tolerated. Usual dose: 4-8 sprays per day</p>	<ul style="list-style-type: none"> Dizziness and fatigue Caution in elderly Caution with use of other CNS depressant Contains 50% ethanol

Promising Future Indications

Can CBD really do all that?



Anxiety Case Series

Study	N	Dose of CBD	Findings
Bergamaschi et al.	12	600 mg 90 minutes before public speaking	Pretreatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech
Shannon et al.	72	25 mg daily after breakfast	Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration
Linares et al.	57	150 mg (n=15), 300 mg (n=15), 600 mg (n=12) or placebo (n=15)	Compared to placebo, pretreatment with 300 mg of CBD significantly reduced anxiety during the speech.

Psychosis and Schizophrenia

Study	N	Dose of CBD	Findings
Zuardi et al.	6	Up to 600 mg/d for 4 weeks	Improvement of symptoms, no adverse effects
Leweke et al.	42	Up to 800 mg/d for 4 weeks in 3-4 divided doses	CBD was as effective as amisulpride for improvement of symptoms; CBD had superior adverse effect profile
McGuire et al.	88	1000 mg/d in 2 divided doses for 6 weeks	CBD group had lower levels of positive psychotic symptoms and subjects were more likely to have been rated as improvements and as not severely unwell by their clinician

Zuardi AW, et al. *J Psychopharmacol.* 2009;23:979-983.

Leweke FM, et al. *Transl Psychiatry.* 2012;2:e94.

McGuire P, et al. *Am J Psychiatry.* 2018;175:223-231

Pain Case Series

Study	N	Dose of CBD	Findings
Good et al.	22	2.5%, 5%, 7.5% topical cream	A consistent and noticeable decrease of 32% reduction of pain was reported in the 2.5% and 5% group. The 7.5% group noted a 35% decrease in pain
Wade et al.	24	20 mg vs placebo	The CBD group had significantly better but modest pain control compared with placebo

Other Clinical Applications

- **PTSD**
 - The Department of Veteran Affairs is currently conducting its first study on CBD, pairing it with psychotherapy
 - The trial is a phase 2 clinical randomized control trial at the VA San Diego Medical Center to evaluate the efficacy of using CBD as an adjunct to Prolonged Exposure therapy (PE)
- **Skin Related disorders**
 - Cannabidiol could theoretically impact inflammatory skin conditions however, currently there is no human data that suggests CBD's impact on rosacea, eczema, or psoriasis
 - There is no available evidence that suggests CBD-enhanced moisturizers improve outcomes as compared with un-enhanced moisturizers

Other Clinical Applications

- **Crohn's Disease**

- Twenty patients with refractory Crohn's disease were randomized to receive CBD 10mg twice daily or placebo
- After 8 weeks of treatment, no differences in IBD signs and symptoms occurred
- CBD is an anti-inflammatory cannabinoid that has been shown to be beneficial in an animal model of inflammatory bowel disease (IBD)
 - It is possible that refractory patients were not amenable to benefits or the dose was too low

- **Addiction**

- A recent study found that acute CBD administration of (400 or 800mg of CBD for 3 consecutive days) significantly reduced both craving and anxiety in drug-abstinent individuals with heroin-use disorder

Patient Case

Patient JM asks you about starting CBD for chronic generalized anxiety disorder. What should you tell him?

- a) CBD has been shown to alleviate acute but not chronic anxiety
- b) CBD has been proven to alleviate chronic but not acute anxiety
- c) CBD has not been proven to impact either acute or chronic forms of anxiety
- d) CBD is best consumed when baked into cookies and put into beer



A Pharmacist's Role

Counseling Points

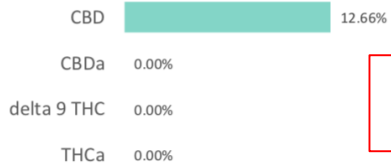
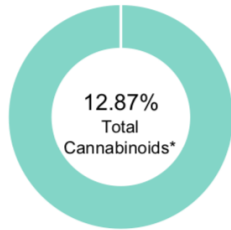
- Patients interested in oral CBD for non-FDA approved indications should be cautioned that there is not currently enough data to support other uses
 - Preliminary data is promising, but should not replace FDA-approved therapies
- Patients should disclose CBD use to all of their healthcare providers so they can assess the impact, DDI and potential adverse effects
- Patients should be reminded to buy CBD products with independent laboratory certification
 - Consumers can request CBD products certificate of analysis (CoA), which provides information about testing for contaminants and THC and CBD levels
 - Consumers can also look to see if the CoA states that the lab complied with the standards set by one of three organizations
 - The Association of Official Agricultural Chemists (AOAC)
 - The American Herbal Pharmacopoeia (AHP)
 - The U.S. Pharmacopeia (USP)

CERTIFICATE OF ANALYSIS

Broad Spectrum Master Batch

Batch ID:	0028	Test ID:	5994352.009
Reported:	16-Jul-2019	Method:	TM14
Type:	Concentrate		
Test:	Potency		

CANNABINOID PROFILE



Compound	LOQ (%)	Result (%)	Result (mg/g)
Delta 9-Tetrahydrocannabinolic acid (THCA-A)	0.07	0.00	0.0
Delta 9-Tetrahydrocannabinol (Delta 9THC)	0.03	0.00	0.0
Cannabidiolic acid (CBDA)	0.08	0.00	0.0
Cannabidiol (CBD)	0.04	12.66	126.6
Delta 8-Tetrahydrocannabinol (Delta 8THC)	0.04	0.00	0.0
Cannabinolic Acid (CBNA)	0.09	0.00	0.0
Cannabinol (CRN)	0.04	0.00	0.0
Cannabigerolic acid (CBGA)	0.06	0.00	0.0
Cannabigerol (CBG)	0.03	0.00	0.0
Tetrahydrocannabivarinic Acid (THCVA)	0.06	0.00	0.0
Tetrahydrocannabivarin (THCV)	0.03	0.00	0.0
Cannabidivarinic Acid (CBDVA)	0.07	0.00	0.0
Cannabidivarin (CBDV)	0.04	0.21	2.1
Cannabichromenic Acid (CBCA)	0.05	0.00	0.0
Cannabichromene (CBC)	0.06	0.00	0.0

Total Cannabinoids	12.87	128.70
Total Potential THC**	0.00	0.00
Total Potential CBD**	12.66	126.60

NOTES:
N/A

% = % (w/w) = Percent (Weight of Analyte / Weight of Product)
 * Total Cannabinoids result reflects the absolute sum of all cannabinoids detected.
 ** Total Potential THC/CBD is calculated using the following formulas to take into account the loss of a carboxyl group during decarboxylation step.
 Total THC = THC + (THCa *(0.877)) and Total CBD = CBD + (CBDA *(0.877))

FINAL APPROVAL

Daniel Weidensaul
 Daniel Weidensaul
 16-Jul-2019
 4:11 PM

PREPARED BY / DATE

David Green
 David Green
 16-Jul-2019
 5:20 PM

APPROVED BY / DATE

Testing results are based solely upon the sample submitted to Botanacor Laboratories, LLC, in the condition it was received. Botanacor Laboratories, LLC warrants that all analytical work is conducted professionally in accordance with all applicable standard laboratory practices using validated methods. Data was generated using an unbroken chain of comparison to NIST traceable Reference Standards and Certified Reference Materials. This report may not be reproduced, except in full, without the written approval of Botanacor Laboratories, LLC. ISO/IEC 17025:2005 Accredited A2LA Certificate Number 4329.02



Certificate of Analysis



Dosing Strategies

TITRATION!

- Currently there is not enough evidence out there to support specific dosages for specific indication other than for Epidiolex.
- CBD is generally considered safe to consume, however its best to use a precautionary practice in making recommendations to patients to lower the risk of overdose, overwhelming the patient, or an over-reaction.
- Titration is the best practice to introduce CBD to the body.

Patient Case

Patient BO approaches you and says he wanted to buy CBD pills to help with insomnia, but recently read an article that said he should try to find more information about CBD products because they can be contaminated with all kinds of toxins. He asks you how he can find more information about the safety of CBD products. You advise him:

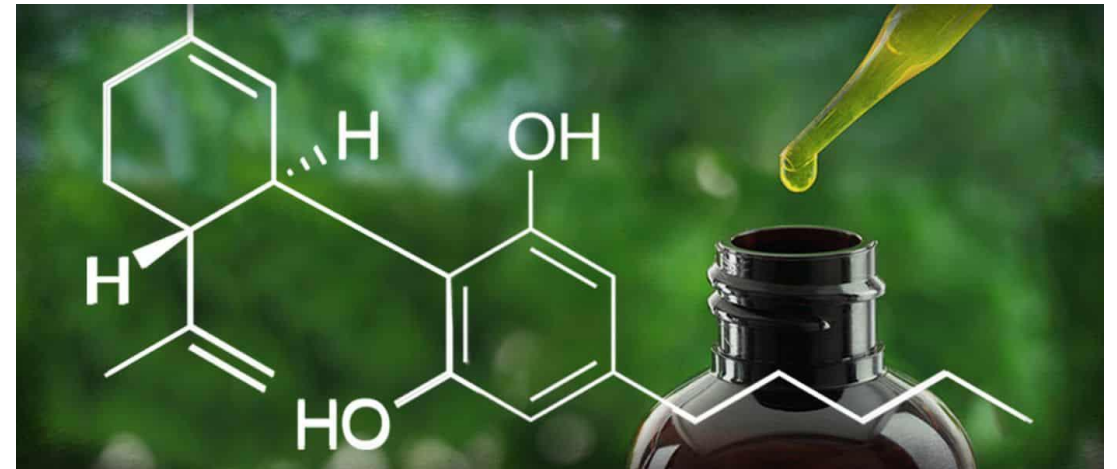
- a) Not to trust or take any CBD products on the market because they're not approved by the U.S. Food and Drug Administration (FDA).
- b) To read the product's label and to search the Internet for any terms or statements she doesn't understand.
- c) To ask for the Certificate of Analysis, which provides information about testing for contaminants and THC and CBD levels.
- d) To purchase CBD and then heat it to 88 degrees Fahrenheit to kill microbial contamination.



Conclusion

Summary

- Cannabidiol is potentially useful for many conditions, is not psychoactive, and is not considered harmful
- CBD can be dispensed as a prescription product Epidiolex or Sativex, or sold over the counter
- Under federal law, CBD derived from marijuana is not considered to have medical use and is illegal
- Selection of CBD products for medical purposes should be made with caution and be based on the reputation and good manufacturing practices of the manufacturer
- Healthcare professionals can counsel patients on the appropriate use of CBD including potential drug-drug interactions



Cannabidiol, Medical Miracle or Just Another Trend?

Shanice Coriolan, PharmD., RPh
PGY1 Pharmacy Practice Resident
NYU Winthrop Hospital

contact: shanice.coriolan@nyulangone.org

Questions?

Thank you!



References

1. <https://bdsanalytics.com/u-s-cbd-market-anticipated-to-reach-20-billion-in-sales-by-2024/>
2. <http://patft.uspto.gov/netacgi/>
3. Mary-Lou E. Florian; Dale Paul Kronkright; Ruth E. Norton (21 March 1991). The Conservation of Artifacts Made from Plant Materials. Getty Publications. pp. 49–.
4. <https://cbdorigin.com/hemp-vs-marijuana/>
5. National Center for Biotechnology Information. PubChem Database. Cannabidiol, CID=644019, <https://pubchem.ncbi.nlm.nih.gov/compound/Cannabidiol> (accessed on Oct. 24, 2019)
6. National Center for Biotechnology Information. PubChem Database. delta9-Tetrahydrocannabinol, CID=2978, <https://pubchem.ncbi.nlm.nih.gov/compound/delta9-Tetrahydrocannabinol> (accessed on Oct. 24, 2019)
7. <https://www.farmers.gov/manage/farmbill>
8. <https://www.nytimes.com/2019/02/05/nyregion/cbd-food-nyc-restaurants.html>
9. <https://www1.nyc.gov/site/doh/business/food-operators.page>
10. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. In Mayo Clinic Proceedings 2019 Aug 22. Elsevier.
11. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ^9 -tetrahydrocannabinol, cannabidiol and Δ^9 -tetrahydrocannabivarin. *British Journal of Pharmacology*. 2008;153(2):199-215.
12. Chu R, Bettinger J. Analgesics of the Future: The Potential of the Endocannabinoid System. *Practical Pain Management*. 2019;19(3)
13. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. In Mayo Clinic Proceedings 2019 Aug 22. Elsevier.
14. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The Pharmacologic and Clinical Effects of Medical Cannabis. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2013 Feb;33(2):195-209.
15. Cannabidiol. In: Lexi-drugs online [database on the Internet].
16. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *European journal of internal medicine*. 2018 Mar 1;49:12-9.

References

17. Pisanti S, Malfitano AM, Ciaglia E, Lamberti A, Ranieri R, Cuomo G, Abate M, Faggiana G, Proto MC, Fiore D, Laezza C. Cannabidiol: State of the art and new challenges for therapeutic applications. *Pharmacology & therapeutics*. 2017 Jul 1;175:133-50.
18. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *New England Journal of Medicine*. 2017 May 25;376(21):2011-20.
19. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *New England Journal of Medicine*. 2018 May 17;378(20):1888-97.
20. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219–1226.
21. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J*. 2019;23:18–041.
22. Linares IM, Zuardi AW, Pereira LC, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Brazilian Journal of Psychiatry*. 2019 Mar;41(1):9-14.
23. Zuardi AW, Cripp JA, Hallak JE, et al. Cannabidiol for the treatment of psychosis in Parkinson disease. *J Psychopharmacol*. 2009;23:979-983.
24. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry*. 2012;2:e94.
25. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *Am J Psychiatry*. 2018;175;223-231.
26. Good L, Bensch D, Ferguson M. Topical CBD for the Management of Acute and Chronic Pain: A Brief Review and Report of an Open-Label Dose-Ranging Clinical Trial. *Chem Pharm Res*. 2019; 1(2): 1-8.
27. Wade DT, Robson P, House H, et al. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clinical rehabilitation*. 2003 Feb;17(1):21-9.
28. <https://clinicaltrials.gov/ct2/show/NCT03518801>
29. Naftali T, Mechulam R, Marii A, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn’s disease, a randomized controlled trial. *Digestive diseases and sciences*. 2017 Jun 1;62(6):1615-20.
30. Hurd YL, Spriggs S, Alishayev J, et al. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *American Journal of Psychiatry*. 2019 May 21;appi-jp.