

To CBD or Not to CBD? That is the Question : The Neuroscience of CBD Oils

Merrill Norton Pharm.D.,D.Ph, CMAAC
CEO
Chemical Health Associates, Inc.
mernort@gmail.com



1

Learning Objectives:

- **Learning Objectives:**
- **Participants will:**
- **Evaluate medical cannabinoid products and their beneficial potential and adverse effects;**
- **Formulate the profile of adverse drug effects of CBD oils and Delta 8 THC;**
- **Develop an understanding of the effects of CBD and Delta 8 THC on the developing adolescent brain and body.**
- **This presentation is a medication safety review of CBD and Delta 8 THC products. The author is NOT advocating any use of the products that maybe discuss in this talk.**

2

Buyer Beware!!!!

The Confusing World of CBD Products



6/10/22

Dr. Merrill Norton Pharm.D., D.Ph., CMAC

3

3



CBD
Cannabidiol

CC1=C(C=C(C=C1)O)C2=CC(=C(C=C2)O)C(C)C

6/10/22

Dr. Merrill Norton Pharm.D., D.Ph., CMAC

4

4

Latest News on Cannabis Sales and Marketing

- 2021 Cannabis sales were over \$25 Billion;
- BDSA forecasts US cannabis sales will reach \$48 billion in 2026;
- The Feds Are Coming For Delta-8 THC;
- Wholesale prices for both THC and CBD have slumped by 50%;
- In 2021-2022, the average price for an ounce of high-quality dispensary ganja is about \$450. The same amount sells on the street for an average of \$220. For any cannabis user out there, the gigantic difference between street prices vs. dispensary prices certainly makes illegal weed offerings a very tempting option.

5



6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

6

6



7



8



9

What's In A Name? The Different and Confusing Names of CBD Products

CBD	Cannabidiol—it is a phytocannabinoid, a major component of <i>Cannabis sativa</i> , that lacks significant psychotropic effects
CBD Oil	Oil derived from hemp or any cannabidiol rich strain of cannabis. It can be made from the entirety of the plant (flowers and leaves), not just the seeds.
Full Spectrum CBD Oil	Cannabidiol oil extracted from <i>Cannabis sativa</i> , along with other components such as terpenes, essential oils, and other cannabinoids along with THC (tetrahydrocannabinol)
Broad Spectrum CBD Oil	Cannabidiol oil extracted from <i>Cannabis sativa</i> , along with other components such as terpenes, essential oils, and other cannabinoids <i>without</i> THC.
Whole Plant CBD	Similar to full spectrum, whole plant CBD contains a variety of cannabinoids. However, in addition, it will contain fats, waxes, and other fibrous materials.
CBD Oil Isolate	Ideally, this product is the purest, filtered form of CBD and CBD only.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D

10

10

What's In A Name? The Different and Confusing Names of CBD Products

6/10/22

Food Grade Hemp Seed Oil	Hemp Oil created from hemp plant that is considered nontoxic and safe for human consumption.
Hemp Seed	Seed of the hemp plant <i>C. sativa</i> . These seeds typically contain over 30% oil and about 25% protein, with considerable amounts of dietary fiber, vitamins and minerals.
THC Oil	An oil created from marijuana <i>C. sativa</i> that contains a high concentration of THC.
Cannabis oil	Same as THC Oil
Hash Oil	Concentrated form of cannabis oil and contain a higher concentration of THC

Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D

11

11

What's In A Name? The Different and Confusing Names of CBD Products

6/10/22

CBD Hemp Oil	CBD oil extracted from hemp plant source that contains Omega-6 and omega-3 fatty acids, γ-linolenic acid, and nutritious antioxidants.
Hemp Extract	Unlike hemp oil, which is made from the seeds of a hemp plant, extract can come from the plants seeds, stalks, and flower. It is often high in minerals such as potassium, magnesium, and calcium and contains fatty acids. May contain CBD depending on hemp source.
CBD Hemp Extracts	Made from non-psychoactive industrial hemp plants and can be used to make a variety of hemp derived products that contain CBD.
Hemp Oil	Oil created by pressing the seeds of the hemp plant. The cannabinoid CBD is not found in the seeds of this plant and therefore should not be present in hemp oil as well.
Hemp Oil Extract	Same as Hemp Oil
Hemp Seed Extract	Same as Hemp Oil

Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D

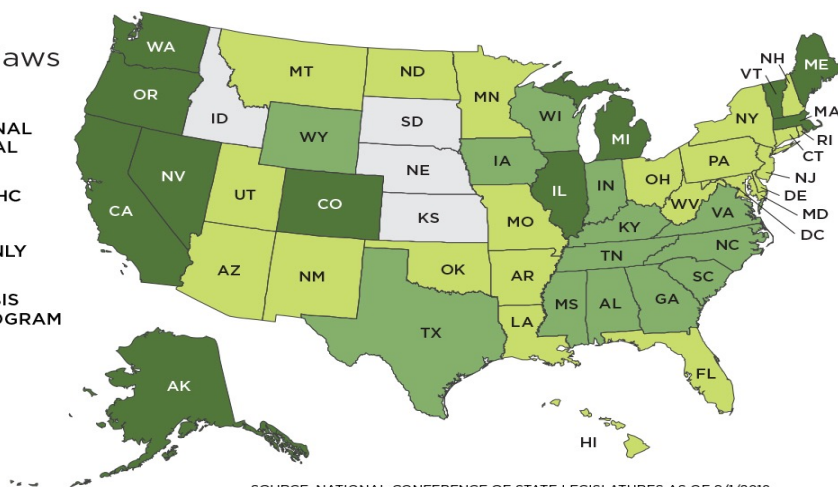
12

12

Medical Cannabis States 12/2021

Current marijuana laws by state

- RECREATIONAL AND MEDICAL
- CBD/LOW THC
- MEDICAL ONLY
- NO CANNABIS ACCESS PROGRAM



6/10/22

SOURCE: NATIONAL CONFERENCE OF STATE LEGISLATURES AS OF 8/1/2019
Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

13

13

IS DELTA 8 LEGAL IN MY STATE?

✓ YES ✗ NO




6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

14

14



Federal Law Definitions

6/10/22

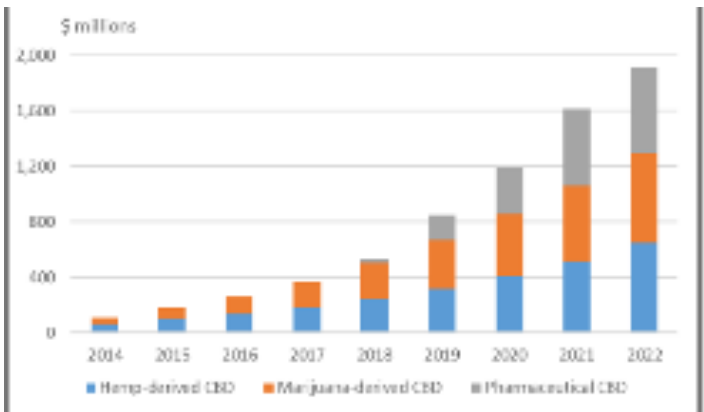
- **Cannabinoid:** Cannabinoids are the naturally-occurring, biologically active, chemical constituents in hemp and marijuana, both of which are varieties of cannabis. Examples include CBD, THC, and cannabitol.
- **CBD:** cannabidiol (“CBD”) is a cannabinoid that is chemically similar to THC, but does not have the same psychoactive effects. One CBD-based medication has federal approval for seizure treatment. Researchers continue to investigate whether CBD may also help individuals manage anxiety, insomnia, and chronic pain.
- **THC:** delta-9-tetrahydrocannabinol (“THC”) is a cannabinoid that is responsible for producing psychoactive effects.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC
15

15

Total US Sales of CBD

6/10/22



Year	Hemp-derived CBD	Marijuana-derived CBD	Pharmaceutical CBD	Total
2014	~50	~50	0	~100
2015	~100	~100	0	~200
2016	~150	~150	0	~300
2017	~200	~200	0	~400
2018	~300	~300	0	~600
2019	~400	~400	~100	~900
2020	~500	~500	~200	~1,200
2021	~600	~500	~300	~1,400
2022	~700	~500	~400	~1,600

- **Source:** Hemp Business Journal, *The CBD Report: 2018 Industry Outlook, 2019 (New Frontier Data)*. All pharmaceutical channel sales are represented by the drug Epidiolex®.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC
16

16

CBD Market in the United States

- From an industry perspective, there are three markets for CBD: hemp-derived CBD, marijuana-derived CBD (currently a Schedule I controlled substance), and pharmaceutical CBD (currently only Epidiolex®). In 2018, CBD sales in the United States from all three markets were estimated at \$534 million, according to the *Hemp Business Journal*.
- More than 1,000 companies produced and marketed CBD for the U.S. market. Compared to 2014, when total CBD sales were a reported \$108 million, U.S. sales of CBD have risen fivefold.
- The *Hemp Business Journal* projects U.S. sales of CBD will exceed \$1 billion in 2020 and reach nearly \$2 billion in 2022, divided about evenly among the three markets.
- At the retail level, CBD is marketed in a range of foods and beverages, dietary supplements, and cosmetic and personal care products, some of which are now being sold by large retailers such as CVS Pharmacy and Walgreens.

6/10/22

17

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

17

Legality of CBD

- In 2018, the United States Congress elucidated on the current governing definition of hemp with an amendment to the 2014 Farm Bill.
- The new bill, stated in section 297A of the Agricultural Marketing Act of 1946, *defines "hemp" as a derivative of the Cannabis sativa plant that contains no more than 0.3% concentration on a dry weight basis of delta-9-tetrahydrocannabinol, or THC.*
- As a result, *"marijuana" is defined as anything above that specified threshold (>0.3%) with no definite limit to the amount of THC.*
- This expansion, in efforts to decrease restriction on research, allowed the governing bodies to draw a distinction between marijuana and hemp.

6/10/22

18

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

18

The FDA Has Provided Approved Medical Cannabinoid Medications for Prescribers

6/10/22

- **CBD Products**
- ***Epidiolex- CBD Oil***
- **THC Products**
- ***Cesamet (Nabilone) Capsules***
- ***Marinol (Dronabinol) Tablets, Capsules***
- ***Syndros (Dronabinol) Oil Extract***
- ***Combination CBD/THC Products***
- ***Sativex (Awaiting FDA approval) Buccal Spray***

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

19

19

Checklist for Finding a High Quality CBD and Hemp Oil Product

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

- **1.) Does it meet the following quality standards?**
- **Current Good Manufacturing Practices Certification(CGMP) from FDA;**
- **EU, AUS, or CAN organic certification;**
- **National Science Foundation International certification.**
- **2.) Does the company have an independent review adverse event reporting program?**
- **3.) Is the product certified organic or ecofarmed?**
- **4.) Have the company's products been lab tested to confirm THC levels(<0.3% and no pesticides or heavy metals).**

6/13/22 20

20

The Impact of CBD and Delta 8 THC on the Adolescent Brain

- Neuroimaging studies have shown that **acute CBD induces significant alterations in brain activity and connectivity patterns during resting state and performance of cognitive tasks** in both healthy volunteers and patients with a psychiatric disorder.
 - Research studies on both animals and humans have shown that **CBD may help lower feelings of isolation, relieve autism symptoms, and reduce the effects of post-traumatic stress disorder (PTSD)**.
 - The most consistent data suggests that **cannabis causes exacerbation of psychosis and worsens it** which raises the possibility of a vulnerable group. It has been found that acute effects of cannabis were modified by the subject's level of vulnerability for psychosis.
- *Batalla, A., Bos, J., Postma, A., & Bossong, M. G. (2021). The Impact of Cannabidiol on Human Brain Function: A Systematic Review. Frontiers in pharmacology, 11, 618184. <https://doi.org/10.3389/fphar.2020.618184>*

21

The Impact of CBD and Delta 8 THC on the Adolescent Brain

- CBD use also carries some risks. Though it's often well-tolerated, CBD can cause side effects, such as dry mouth, diarrhea, reduced appetite, drowsiness and fatigue.
- CBD can also interact with other medications you're taking, such as blood thinners.
- Another cause for concern is the unreliability of the purity and dosage of CBD in products.
- A recent study of 84 CBD products bought online showed that more than a quarter of the products contained less CBD than labeled.
- In addition, THC was found in 18 products.

22

The Impact of CBD and Delta 8 THC on the Adolescent Brain

- Delta 8 THC is a powerful cannabinoid that has the ability to bind with CB1 receptors in your brain which can cause everything from **anxiety and paranoia, bloodshot eyes, dry mouth, and a slowed reaction time.**
- 66% described adverse events after ingestion of delta-8 THC-containing food products (e.g., brownies, gummies).
- Adverse events included, but were not limited to: **hallucinations, vomiting, tremor, anxiety, dizziness, confusion, and loss of consciousness.**
- **Research is minimal when it comes to the long-term risks associated with delta 8 THC.** It possesses similar side effects to delta 9 THC, as both cannabinoids are classified as tetrahydrocannabinol.
- Like delta 9, young people could be at a higher risk of developing behavioral addiction.

23

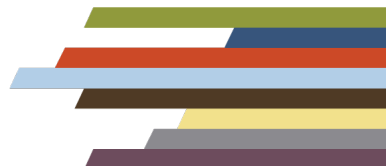


PTTC Prevention Technology Transfer Center Network
Funded by Substance Abuse and Mental Health Services Administration

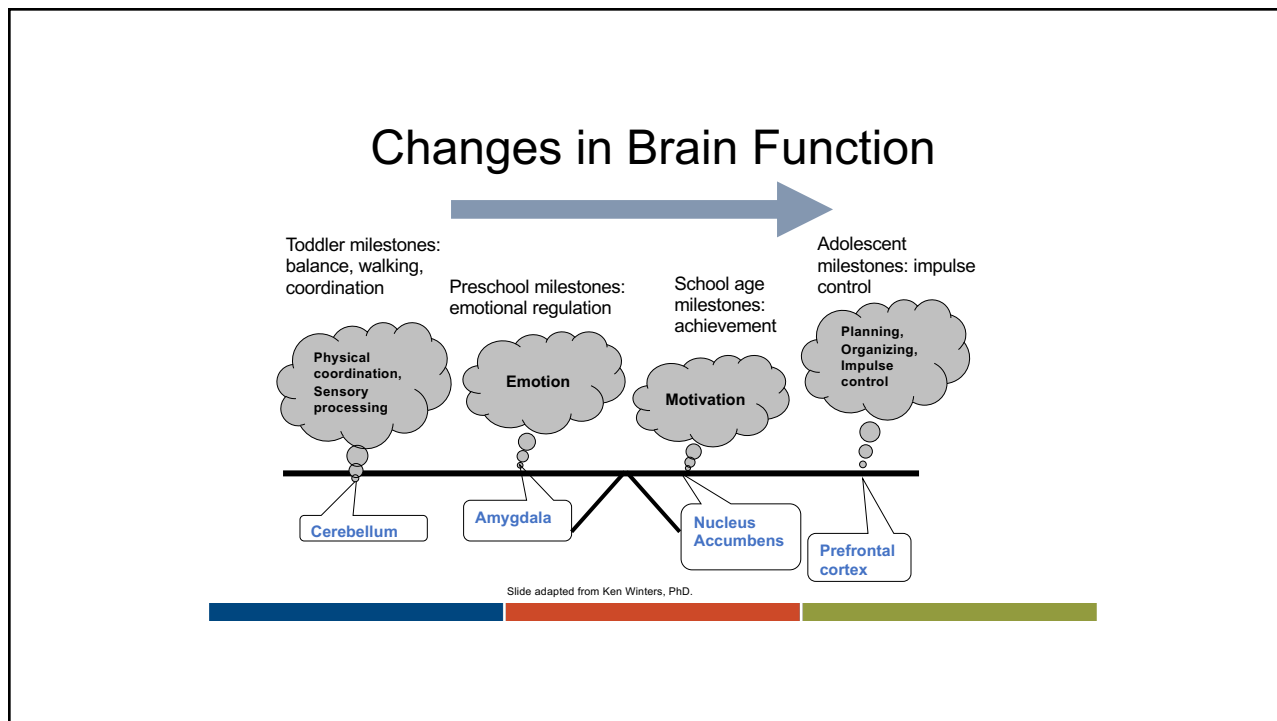
Cannabis and the Adolescent Brain

Key Information for Prevention Practitioners to Share with Key Stakeholders and Communities

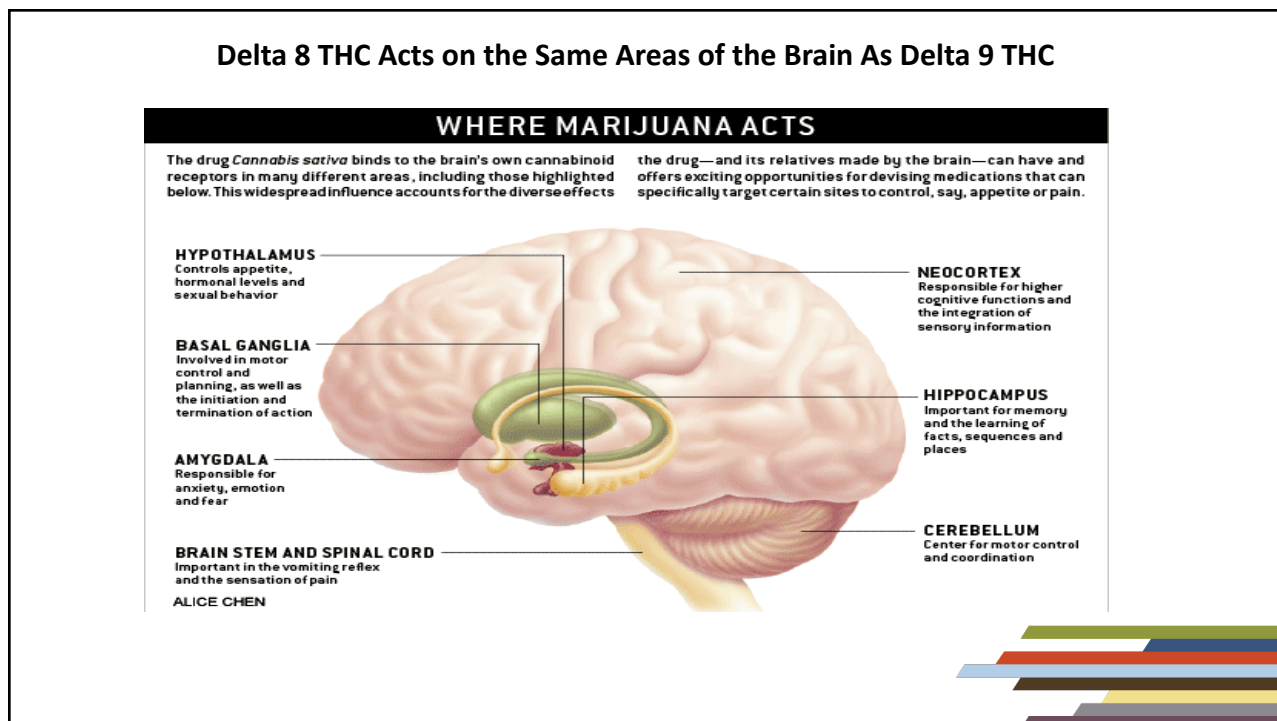
SAMHSA
Substance Abuse and Mental Health
Services Administration



24



25



26

Cannabis and the Adolescent Brain

- Regular cannabis use early in life can result in impairments such as:

- Poor academic performance
- Deficits in attention, information processing, and memory



(Batalla, A, et.al., 2013;
Bossong, M., et.al., 2012)

27

Cannabis Use and Misuse

How Does Cannabis Interact with the Teen Brain?

Chronic or frequent use

- Impaired executive function
- Impaired higher-level control of attention
- Impaired working memory
- Decreased cortical thickness
- Possible decreased myelination

28

Brain Differences in Adolescent who Use Cannabis: Structural

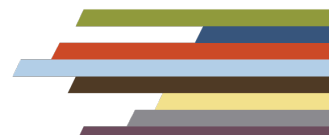
- Structural differences are apparent in brain images of adolescents who have used cannabis compared to those who have not. These differences include:
 - Size (both increases and decreases)
 - Connectivity
 - Quality of various brain structures
- The earlier that individuals started regular use, the more impaired the nerve connections were in the brain. Those who began using cannabis at a later age did not experience the same negative effects (Schacht, J., et al., 2013).



29

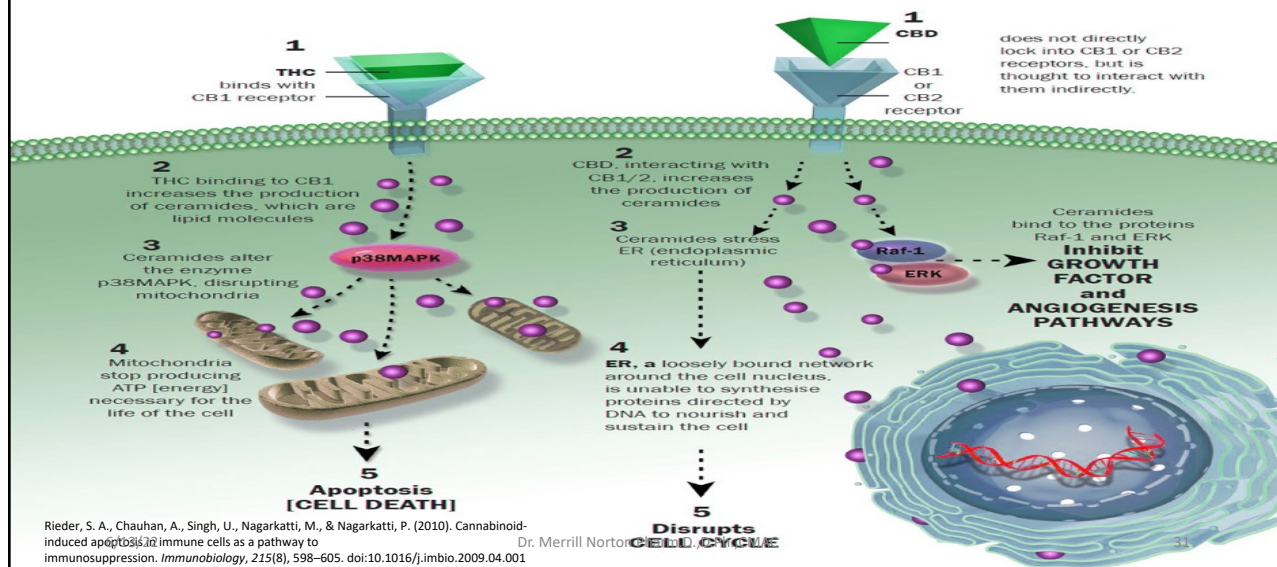
Brain Differences in Adolescent who Use Cannabis: Functional

- Functional differences are also found in brain images of adolescents who use cannabis compared to those who don't use, particularly greater activity while completing tasks:
 - This increased activity indicates the brain was working harder to perform a task
 - These differences were observed in brain regions critical for executive functioning (e.g., planning and decision making, establishing and completing goals) (Smith, A., et al., 2010; Smith, A., et al., 2011; Hatchard, T., et al., 2014).



30

Cell Destruction Occurs with both THC and CBD: The Result is Suppressed Immune Function



Rieder, S. A., Chauhan, A., Singh, U., Nagarkatti, M., & Nagarkatti, P. (2010). Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. *Immunobiology*, 215(8), 598–605. doi:10.1016/j.imbio.2009.04.001

31

CBD Products for 2022



Dr. Merrill Norton Pharm.D., D.Ph., CMAc

32

32

Three Types of CBD

The three categories of CBD are distinctly different in several ways.

Industrial hemp-derived CBD is just one of many different types of products that are derived from the industrial hemp plant. Other products produced from the plant are food items, building materials, and fiber products for paper, jewelry, and rope.

Marijuana-derived CBD differs from industrial hemp-derived CBD primarily by the amount of THC in the product and how each state regulates the medical use of the product.

Pharmaceutical-derived CBD is an approved drug by FDA and is available nationally.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

33

33

Industrial Hemp-Derived CBD

Typically, “1 acre of hemp can yield an average of 700 pounds of grain, which in turn can be pressed into about 22 gallons of oil and 530 pounds of meal.

The same acre will also produce an average of 5,300 pounds of straw, which can be transformed into approximately 1,300 pounds of fiber.

Industrial hemp’s CBD oil is derived from the stalk, stems, leaves, and flowers of the hemp plant.

The only part of the hemp plant that does not contain CBD oil is the seed.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

34

34

Industrial Hemp-Derived CBD

In 2019, 48 states and Puerto Rico considered more than 200 bills related to industrial hemp-derived CBD production and regulation.

Industrial hemp is considered a low-maintenance crop. This means once planted, hemp plants require little attention to produce significant yields.

On average, a cultivated industrial hemp plant, consisting of spindly stalk and leaves, can grow to be 10 feet or higher in height. As for time, it can take anywhere between 70 to 140 days for the plants to be harvested.

The number of days can depend on a variety of factors, such as the intended purpose of the crop, the location, and the climate in which it is grown.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 35

35

Industrial Hemp-Derived CBD

CBD oil can be found in a variety of products such as body lotions, tinctures, and capsules.

The market for these products is expanding, with the CBD industry expected to grow to \$22 billion by 2022, a drastic increase from \$327 million in 2017.

This type of growth is making many producers eager to join the industry and develop new products.

However, this rapid growth comes with the need for increased scrutiny of these products.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 36

36

Industrial Hemp-Derived CBD

It is crucial to ensure that companies selling CBD products are using industrial hemp extract along with carrier oils that have been grown and processed in ways that are healthy for consumers and the environment.

Companies should be transparent about their production practices in the labeling and advertising of these products.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

37

37

Marijuana-Derived CBD

The main difference between CBD oil from industrial hemp versus marijuana is the ratio between THC and CBD.

Industrial hemp-derived CBD oil usually contains high concentrations of CBD, while its THC content does not exceed the legal 0.3% limit.

Marijuana-derived CBD oil is sourced from selectively bred high-CBD strains, but it also comes with significant amounts of THC (ranging between 5% and 30%).

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

38

38

Marijuana-Derived CBD

Marijuana-derived CBD oil is extracted from marijuana plants that have thick, lush foliage and flowers that are generally grown and consumed for their intoxicating properties.

While most marijuana plants contain THC as the predominant cannabinoid, there are several strains of marijuana that are rich in CBD oil.

A critical difference between industrial hemp-derived CBD oil and marijuana-derived CBD oil is the resin content of each plant.

Cannabis resin is found within the trichomes of buds and, to a lesser extent, on the leaves.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

39

39

Marijuana-Derived CBD

Marijuana plants usually contain copious amounts of resin, while industrial hemp plants contain significantly less.

Marijuana offers a more abundant source of CBD oil than hemp, thus the extraction of CBD oil from industrial hemp plants requires a larger quantity.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

40

40

Marijuana-Derived CBD

States license a finite number of pharmaceutical processors to cultivate and distribute marijuana-derived CBD oil.

The number of pharmaceutical processors that can be licensed varies from state to state.

In states without legalized recreational marijuana, pharmaceutical processors are permitted to distribute marijuana-derived CBD oil to patients who have obtained a valid written certification from a state registered physician with the state medical, pharmacy, or health boards.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 41

41

Marijuana-Derived CBD


The law provides an affirmative defense for these patients if they are criminally charged with possession of the substance.

An affirmative defense in this circumstance would require the defendant to produce evidence that they have a written certification from an approved practitioner.

All products classified as marijuana remain illegal under federal law.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 42

42



**Marijuana-Derived
CBD**

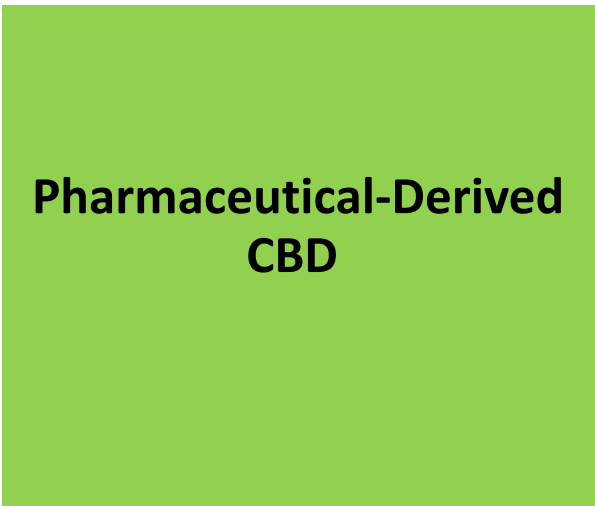
Registered physicians may issue certifications to patients if they determine the patient will medically benefit from marijuana-derived CBD oil.

In some states, registered physician assistants and nurse practitioners may also issue certifications.

State regulations also allow for the legal possession of marijuana-derived CBD oil for individuals with valid written certifications.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 43

43



**Pharmaceutical-Derived
CBD**

Since 1985, FDA has licensed four drugs based on cannabinoids.

First is dronabinol, the generic name for *synthetic Delta 9-THC*, which is marketed under the trade name of Marinol.

It is clinically indicated to counteract the nausea and vomiting associated with chemotherapy and to stimulate appetite in patients with AIDS affected by cachexia, or wasting syndrome.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 44

44

**Pharmaceutical-Derived
THC**

Nabilone (Cesamet), which is a *synthetic analog of Delta 9-THC*, is another drug that is prescribed for similar indications

Both dronabinol and nabilone are given orally and have a slow onset of action.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 45

45

**Pharmaceutical-Derived
THC**

Syndros was approved in 2016.

It is a liquid formulation of dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies.

This agent is also indicated for treating anorexia associated with weight loss in patients with AIDS.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 46

46

Pharmaceutical-Derived THC

Two additional cannabinoid-based medications have been examined by FDA.

Nabiximols (Sativex) is an *ethanol cannabis extract composed of delta 9 THC and CBD in a one-to-one ratio.*

Sativex is administered as an oral-mucosal spray and is indicated in the symptomatic relief of multiple sclerosis and as an adjunctive analgesic treatment in cancer patients.

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 47

47

Pharmaceutical-Derived CBD

Epidiolex was FDA approved on June 25, 2018, and on September 28, 2018, DEA rescheduled FDA-approved drugs containing CBD derived from cannabis with no more than 0.1% THC in Schedule V.

25 June 2018

2024

Consensus estimates expect sales of \$1.7 billion in 2024, which would make it the largest cannabis-related, FDA-approved drug in history (it is also the first plant-based cannabinoid to gain approval).

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC 48

48

Pharmaceutical-Derived CBD

The most common side effects that occurred in Epidiolex-	treated patients in the clinical trials were	sleepiness,	sedation,	and lethargy;
elevated liver enzymes;	decreased appetite;	diarrhea;	rash;	fatigue,
malaise and weakness;	insomnia,	sleep disorder,	poor quality sleep;	infections.

6/10/22
Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC
49

49

Pharmaceutical-Derived CBD

Epidiolex must be dispensed to the patient with a medication guide that describes important information about the drug's uses and risks.






As is true for all drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression, and panic attacks.

Epidiolex is also shown to cause liver injury, generally mild, but raising the possibility of rare, but more severe, injury. Severe liver injury can cause nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, and/or dark urine.

6/10/22
Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC
50

50

Hemp-Derived Products

Product	Risk of THC?	Processing Required	Ability to Reduce THC?	Applications	Benefits
Hemp Flower		Minimal	Genetics	Smoking	Alternate combustible with lower risk of getting "high"
Full-Spectrum Extract		Moderate	Genetics	Oils, tinctures, topicals, balms, capsules	"Entourage Effect" Contains terpenes and other cannabinoids
Broad-Spectrum Extract		Moderate-Significant	Genetics Refinement Distillation	Oils, tinctures, topicals, balms, capsules	Better efficacy Contains some terpenes and cannabinoids
THC-Free CBD Distillate		Significant	Refinement, Processing, Distillation, Reformulation	Oils, tinctures, topicals, balms, capsules, vape	Low chance of THC, Contains terpenes and cannabinoids, unique formulations
CBD Isolate		Significant	Refinement, Processing, Distillation	Oils, tinctures, topicals, balms, capsules, drinks, vape	Minimal chance of THC, CBD only

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

51

51

Industrial Hemp vs. Marijuana

Type	Is it Cannabis?	Chemical Makeup	Psychoactive?	Cultivation	Applications
Hemp	Yes	Less than 0.3% THC	No	<ul style="list-style-type: none"> Minimal care Adaptable to most climates 	<ul style="list-style-type: none"> Textiles Health and Beauty Clothing Construction Topicals
Marijuana	Yes	High THC	Yes	Grown in controlled atmospheres	Medical and recreational use

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

52

52

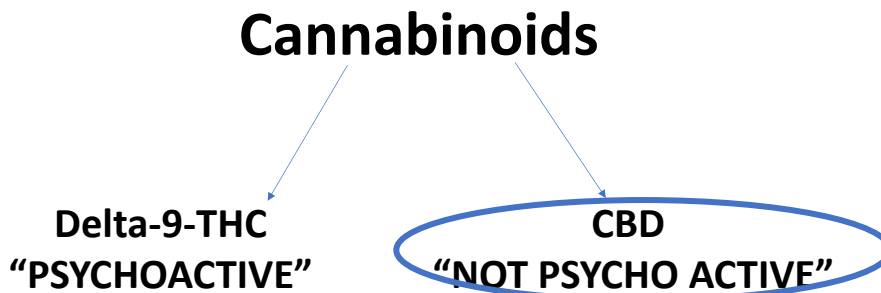
51 Medical Conditions For Which Marijuana Is Approved by a State

- | | |
|---|--|
| 1. Alzheimer's Disease | 26. Lupus |
| 2. Anorexia | 27. Migraines |
| 3. Arnold-Chiari malformation | 28. Multiple Sclerosis |
| 4. Arthritis | 29. Muscle spasms |
| 5. Ataxia | 30. Muscular dystrophy |
| 6. Cachexia | 31. Myasthenia gravis |
| 7. Cancer | 32. Myoclonus |
| 8. Cardiopulmonary respiratory syndrome | 33. Nail-patella syndrome |
| 9. Causalgia | 34. Nausea or vomiting |
| 10. Cervical dystonia | 35. Neurofibromatosis |
| 11. Crohn's disease | 36. Neuropathy |
| 12. Decompensated cirrhosis | 37. Pain |
| 13. Dystonia | 38. Pancreatitis |
| 14. Epilepsy | 39. Parkinson's disease |
| 15. Fibromyalgia | 40. Peripheral neuropathy |
| 16. Glaucoma | 41. Post-traumatic stress disorder (PTSD) |
| 17. Hepatitis C | 42. Reflex sympathetic dystrophy |
| 18. HIV/AIDS | 43. Residual limb pain from amputation |
| 19. Huntington's disease | 44. Seizure disorders |
| 20. Hydrocephalus | 45. Sjogren's syndrome |
| 21. Inflammatory autoimmune-mediated arthritis | 46. Spasticity |
| 22. Inflammatory bowel disease (IBS) | 47. Spinal cord damage with intractable spasticity |
| 23. Inflammatory demyelinating polyneuropathy | 48. Syringomyelia |
| 24. Interstitial cystitis | 49. Terminal illness |
| 25. Lou Gehrig's disease (amyotrophic lateral sclerosis, ALS) | 50. Tourette's syndrome |
| | 51. Traumatic brain injury |

Sources: Marijuana Policy Project, 2014. Key Aspects of State and D.C. Medical Marijuana Laws, from National Conference of State Legislatures, "State Medical Marijuana Laws," www.ncsl.org; 22
 Dr. Merrill Norton Pharm.D., D.Ph., CMCAC
 Rahn, B., 2014. Qualifying Conditions for Medical Marijuana by State, www.leafly.com 53

53

Psychoactive (Personal) vs Non-Psychoactive(Medical)



6/10/22

54

54

Charlotte

- Charlotte is a little girl from Colorado with Dravet syndrome
- Frequent bouts of febrile and afebrile status epilepticus
- Failed multiple medications:
 - Levetiracetam, oxcarbazepine, topiramate, zonisamide, valproate, clobazam, clonazepam, and diazepam
- At 5 years of age, had significant cognitive and motor delays, required a feeding tube, and needed full assistance with activities of daily living
- 50 generalized tonic-clonic seizures per day



<http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/>

55

Charlotte's Web

- A high concentration CBD/THC strain of cannabis produced by a medical marijuana group in Colorado
- Charlotte's Web, supplied by Realm of Caring, is based out of Colorado and parents and families are moving there to attempt treatment



Parents began giving Charlotte low doses of plant extract and slowly increased the dose over time

Month 3: >90% reduction in generalized tonic-clonic seizures and weaned from other AEDs

Month 20: 2-3 nocturnal generalized tonic-clonic seizures per month, feeds and drinks by mouth by herself and autistic behaviors have improvement, walking and talking

<http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/>

56

CBD: Pharmacodynamics Drug to Body

Lacks detectable psychoactivity and does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations.

Affects the activity of a significant number of other targets including ion channels, receptors, and enzymes.

May have anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects.

57

CBD: Pharmacokinetics Body To Drug

Absorption

Oral Bioavailability: 13 – 19% due to marked first pass effect

IV preferable

Distribution

Like THC, it is highly lipophilic – rapidly distributed and easily passes the blood brain barrier (BBB)

58

CBD: Pharmacokinetics

Metabolism

undergoes multiple hydroxylations, oxidations to carboxylic acids, beta-oxidation, conjugation, and epoxidation

Excretion / Elimination

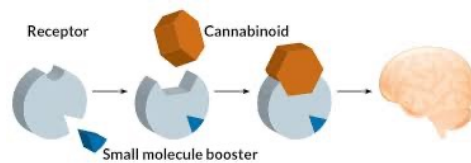
prolonged due to lipophilicity (stays in system longer)

excreted from urine, both in free state and as its glucuronide

****Half life = 9 hours

59

- **Dopamine**
 - Emotion
 - Movement
 - Sensations of pleasure and pain
- **Serotonin**
 - Mood & happiness
- **Opioid**
 - Pain



CBD ALSO HAS AN AFFINITY FOR OTHER RECEPTORS:

60

60

CBD ADMINISTRATION

- Inhalation (vape)**
 - quickest onset
 - may have a greater bioavailability
- Topical application**
 - lotions/creams
- Oral CBD**
 - oil based capsules
 - oils/tinctures (sublingual or added to food/beverages)
- Edibles**
 - gummy bears
- Transdermal skin patch**

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D 61

61

Different Routes of Administration and the Effect on Plasma Concentrations

- Intravenous Route**
- Oral Route**
- Vaporization/ Inhalation**
- Dabbing**

62

Why Are People Using Medical CBD?

- % of participants reporting reason for CBD-Type use
- Seizures. 3%
- Cancer. 5%
- Insomnia. 10%
- Depression. 12%
- Anxiety. 15%
- Chronic pain. 18%
- Well-being. 39%

63

What Is the Evidence ??

- **Seizure disorders: Pharma CBD**
- 225 pts (2-55 years) with Lennox-Gastaut CBD 10 & 20mg/kg
- 17% PBO vs 37% 10mg/kg vs 42% 20mg/kg CBD median decrease in seizure frequency
- 366 patients open-label extension of above for mean 826 days, mean CBD 24mg/kg/day
- 33% withdrew from treatment, 48% median decrease in seizure frequency
- 120 children (2-18 years) with Dravet's syndrome CBD 20mg/kg/day
- 9% placebo (PBO) vs 29% CBD median decrease in seizure frequency
- 224 patients (>1 year) with tuberous sclerosis complex associated seizures CBD 25mg/kg/day
- 20% PBO vs 43% CBD median decrease in seizure frequency

64

What Is the Evidence ??

- **Pain disorders (CBD-type Cannabis)**
- *4-way crossover in 20 female pts with fibromyalgia*
- Compared hybrid, THC type, CBD type
- Hybrid ↓ pain symptoms; hybrid & THC type ↓ evoked pain; **CBD type no effect**
- *Controlled trial 29 older adults peripheral neuropathy*
- Compared topical CBD to placebo for 4 weeks
- ↓ **intense pain, sharp pain, cold, and itchy sensation**
- Controlled trial 100 pts acute, non-traumatic low back pain
- **CBD 400mg or PBO** with standard analgesic medication
- After 2 hours, **no difference in pain, median length of stay or oxycodone use**
- *Open label trial 97 pts with pain treated with opioids*
- Provided broad spectrum cannabis of CBD 30mg x 8 weeks
- 53% reported ↓ opioid use, **no change in Pain Disability Index, 4-item Patient Health Quest.**

65

What Is the Evidence ??

- **Anxiety disorders (CBD-type & THC-type Cannabis)**
- *12 pts with social anxiety disorder & 12 controls simulated public speaking test: CBD 600mg vs. placebo vs. control subject response*
- After CBD, pts had ↓ **in anxiety, cognitive impairment**
- *72 adults with anxiety & sleep complaints CBD 25mg titrated to 50-75mg/day x 3 months*
- 79% had ↓ **HAM-A month 1, 78% had ↓ HAM-A month 2;**
- 15% had ↑ **HAM-A months 1, 20% had ↑ HAM-A month 2**
- *11 PTSD pts used variable doses CBD capsule or spray*
- After 8 weeks mean CBD dose 49mg (range 2-100) : 8 pts **28% ↓ in PCL-5**
- *14 OCD pts used 7%THC vs. 10% CBD vs. placebo in lab*
- CBD & THC ↓ **STAI-S, no change in YBOCCS, OCD-VAS**
- *Bergamaschi MM, et al.*

66

What Is the Evidence ??

- **Wellbeing (CBD-type *Cannabis*)**
- 13 untrained males CBD 150mg x 3 days post muscle damaging exercise
- **No beneficial effects on either muscle function or perceived soreness**
- 11 pts in split-face study of 3% Cannabis seeds extract
- Twice daily ↓ skin sebum and erythema content
- 517 UK Rugby players surveyed about CBD
- 472 aware of CBD -113 of these used or had used CBD 10-500mg
- 67% benefited, 41% sleep, 14% improving recovery, 6% mood, 3% anxiety

67

What Is the Evidence ??

- **Sleep (CBD type *Cannabis*)**
- CBD: low dose stimulating; high-dose sedating
- 17 insomniacs received CBD 40, 80 or 160mg vs placebo
- 160mg but **not 40 or 80mg slept** more than placebo, **less dream recall**
- 72 adults with anxiety & sleep complaints CBD 25mg titrated to 50 or 75mg/day x 3 months
- 67% ↓ Pittsburgh Sleep Quality Index (PSQI) month 1, 56% ↓ PSQI month 2;
- 25% ↑ PSQI month 1, 27% ↑ PSQI month 2

68

What Is the Evidence ??

- **Depression (CBD-type)**
- 118 health care providers unblinded CBD 300mg vs standard care x 4 weeks
- % CBD pts PHQ-9 score >10 46%-21%, GAD-7 score >10 45%-18%
- Naturalist study of depression, anxiety, and stress symptoms from THC & CBD
- After 20 minutes, 89% had 50% ↓ depression; 94% had 58% ↓ in anxiety
- CBD type was associated with the largest changes in depression ratings
- **But! Baseline symptoms of depression exacerbated across time**
- Meta-analysis of 11 longitudinal and prospective studies
- The OR of adolescent *Cannabis* use risk compared to non-users:
 - 3.46 (95% CI, 1.53-7.84, I2 = 61.3%) suicidal attempt
 - 1.37 (95% CI, 1.16-1.62; I2 = 0%) developing depression
- Meta-analysis of pts with depression found 12% had CUD

69

What Is the Evidence ??

- **Depression (Pharma CBD & CB1 receptor antagonist)**
- Pharma CBD trials of usually 12 weeks > 27,000 pts
- AED group compared with the placebo group
- Incidence of suicidal behavior or ideation (**CBD 0.43%** vs. PBO 0.24%)
- **4 CBD** : 0 PBO patients committed suicide in the trials
- CRESCENDO trial of the weight-loss drug rimonabant (inhibits eCBsystem) >18,000 pts evaluated for cardiovascular outcomes
- Rimonabant group compared with the placebo group
- Serious psychiatric side effects (**rimonabant 2.5%** vs. PBO 1.3%)
- **4 CBD**: 1 PBO patients committed suicide during the study
- **EMA pulled rimonabant from market**

70



CBD- Is It Safe to Take????

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D

71

71

Short and Long-Term Adverse Effects of CBD

- | | |
|---|--|
| <ul style="list-style-type: none"> • Short Term • Sleepiness or Insomnia • Decreased appetite • Diarrhea, abdominal pain • Irritability, anxiousness • Orthostatic hypotension • Headache • Gait disturbances • Transaminase elevations (doses > 600mg) | <ul style="list-style-type: none"> • Long-term • Weight loss • Anhedonia • Suicidal thoughts or behaviors (RR 1.8-3.5) |
|---|--|

72

BUYER BEWARE!!!!!!

BTW a 2OZ bottle of pure CBD oil will cost more than the \$24.95. It is an expensive extraction process!!!!



6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D 73

73

CBD OVERDOSE STATS

None reported

- No apparent tolerance issues
- Not addicting
- No (or minimal) CB2 receptors on the brainstem so no respiratory depression

6/10/22 Dr. Merrill Norton Pharm.D.,D.Ph.,JCCDP-D 74

74

Concerns about CBD Safe Products

- High dose side effects:
- Tiredness
- Decreased appetite
- Gastrointestinal problems
- Altered liver enzymes (see following section for more on liver enzymes)
- Other issues include:
- Pesticides and heavy metals from bad farming practices
- High levels of THC (more than desired)
- Synthetic cannabinoids
- Any kind of contaminants (mold, bacteria, rancidity, etc)

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

75

75

Colorado Marijuana Analysis – March 2015

Denver lab analyzed more than 600 samples of bud provided by certified growers and sellers

average THC level was 18.7%, and some retail pot contained 30% THC or more

Little or no cannabidiol (CBD) — the average CBD amount: 0.1%

- Recall: CBD lacks detectable psychoactivity and instead has anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects – the “medical” in medical marijuana.

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

76

76

Mapping Cannabis Potency in Medical and Recreational Programs in the United States: 2020

- Evaluation of the advertised THC and CBD content of cannabis products offered online in dispensaries in the United States to determine products' suitability to medicinal use and compare the strength of products offered in legal medical and recreational programs.
- A total of 8,505 cannabis products across 653 dispensaries were sampled.
- THC concentration advertised online in medicinal programs was similar ($19.2\% \pm 6.2$) to recreational programs ($21.5\% \pm 6.0$) when compared between states with different programs;
- Lower CBD concentrations accompanied higher THC products.
- *Cash MC, Cunnane K, Fan C, Romero- Sandoval EA (2020) Mapping cannabis potency in medical and recreational programs in the United States. PLoS ONE 15(3): e0230167. <https://doi.org/10.1371/journal.pone.0230167>*

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

77

77




“Low” THC Oil

per Georgia law “low” THC oil can contain up to
5% THC.

78

Vape Shop Products



guaranteed!

- . One-hit wonder
- . ANML
- . Boosted
- . Dragon
- . CutWood
- . Space Jam
- . Ruthless
- . Bomb Sauce
- . Beard Company
- . **Carry over 50 Brands of Premium E-liquids**

79

Dosing Concerns

5% THC oil contains about 5g of THC in 100ml of oil.

So 1ml of oil would contain 50mg of THC.

Consider that in Colorado the maximum recommended dosage of THC per serving in an edible THC product is 10mg.

But Georgia is allowing 5 times that amount in 1ml of oil, and referring to it as “low THC” oil.

Therefore, 1ml of “low THC oil” would contain enough THC to cause intoxication in 5 adult men.

Statements that somebody cannot get intoxicated on 5% THC oil are simply not accurate and are dangerously misleading.

80

CBD – Pharmacological Actions

Well Documented:

- Anti-seizure effects

Suggested:

- Analgesic (acute and chronic pain)
- Antipsychotic
- Anxiolytic
- Anti-cancer
- Anti-inflammatory

6/10/22

81

81

CBD DOSAGES

- Not established for OTC products
 - Bioavailability dependent on mode of administration
- Epidiolex (100 mg purified CBD/ml)
 - FDA approved in June 2018
 - Only approved for rare genetic seizure disorder
 - Maximum recommended dose 20 mg/kg/day
 - Recommended starting dose is much lower
 - Adjusted rates for hepatic impairment
 - Recommended monitoring of liver enzymes & bilirubin



6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

82

82

WHO SHOULD NOT TAKE CBD?

The American College of Obstetricians and Gynecologists

- Pregnant women (or women considering pregnancy) and breast-feeding mothers should avoid marijuana and CBD products.
- THC crosses the placenta and passes into milk
- THC may cause low birth weight, pre-term delivery, still birth and affect fetal brain development
- Scant studies on CBD



6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

83

83

- Sedation/lethargy
- Decreased appetite
- Diarrhea
- Rash
- Sleep disorder
- Psychiatric (suicidal ideation, depression, anxiety)
- Liver toxicity
 - Long-term consequences??



6/10/22

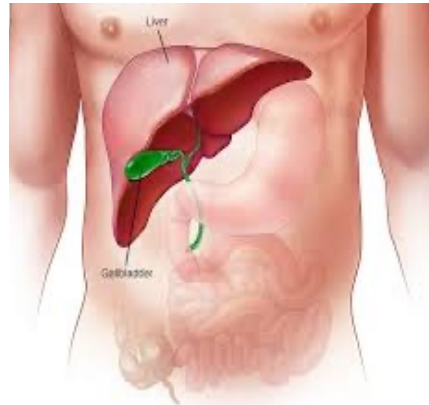
Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

84

84

CBD DRUG INTERACTIONS

- CBD is metabolized by the liver by the Cytochrome (CYP) enzyme system
- Many drugs either “ramp up” or “ramp down” the CYP metabolic pathway which can affect CBD concentration in the blood
- CBD competes as a substrate for some of the same CYP enzymes that metabolize coumadin; coumadin blood levels elevate resulting in an increased risk of bleeding



6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

85

85

The FDA Safety Warnings

- **CBD has the potential to harm you, and harm can happen even before you become aware of it.**
 - CBD can cause liver injury.
 - CBD can affect the metabolism of other drugs, causing serious side effects.
 - Use of CBD with alcohol or other Central Nervous System depressants increases the risk of sedation and drowsiness, which can lead to injuries.
- **CBD can cause side effects that you might notice. These side effects should improve when CBD is stopped or when the amount ingested is reduced.**
 - Changes in alertness, most commonly experienced as somnolence (drowsiness or sleepiness).
 - Gastrointestinal distress, most commonly experienced as diarrhea and/or decreased appetite.
 - Changes in mood, most commonly experienced as irritability and agitation.
- **There are many important aspects about CBD that we just don't know, such as:**
 - What happens if you take CBD daily for sustained periods of time?
 - What is the effect of CBD on the developing brain (such as children who take CBD)?
 - What are the effects of CBD on the developing fetus or breastfed newborn?
 - How does CBD interact with herbs and botanicals?
 - Does CBD cause male reproductive toxicity in humans, as has been reported in studies of animals?
- **It will take time to discover these answers and others that will arise-so buyer be aware!!!**
- **<https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>**

6/10/22

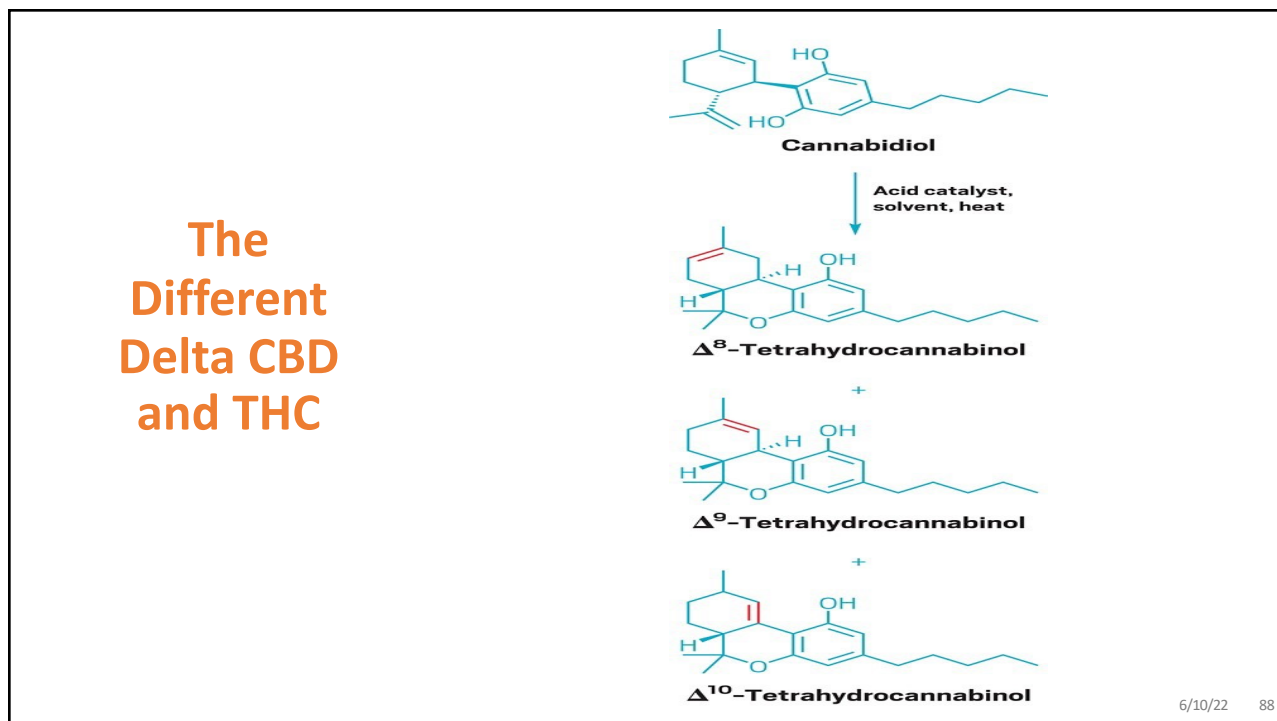
Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

86

86

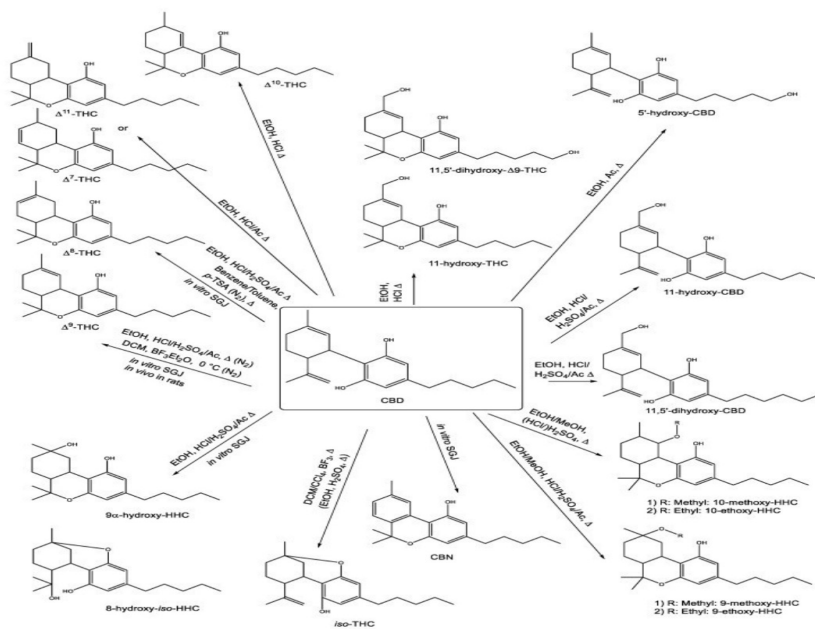


87



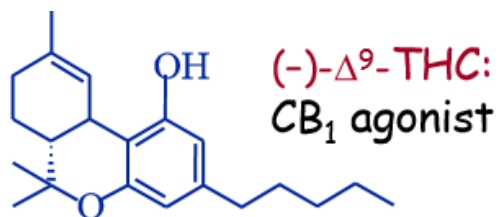
88

Overview of various chemical conversions of cannabidiol (CBD) to different conversion products and the respective conditions, which are reported in the literature.



89

THC - Structure

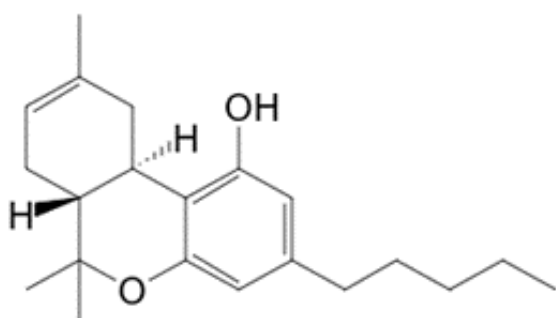


- Converted from THCa by drying, heating.

90

Delta 8 Cannabinoids

Delta 8 THC



The image shows the chemical structure of Delta 8 THC. It consists of a cyclohexene ring fused to a benzene ring. The cyclohexene ring has a methyl group at the 1-position and a hydrogen atom at the 2-position shown with a wedge bond. The benzene ring has a hydroxyl group (-OH) at the 1-position, a methyl group at the 2-position, and a pentyl group (-CH2CH2CH2CH2CH3) at the 3-position. An oxygen atom is attached to the 4-position of the benzene ring, which is part of a ring system.

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

6/10/22

91

91

What Is Delta 8 THC?

Unlike CBD, delta-8-THC produces euphoric effects that are similar to but milder than those of delta-9-THC, the well-known psychoactive compound in cannabis.

Delta-8-THC is an isomer of delta-9-THC. The only difference between the two molecules is the location of a double bond between two carbons.

The delta-8-THC craze began when an oversupply of CBD extracted from US-grown hemp caused the price of CBD to plummet.

Producers began looking for ways to turn the glut of CBD into something profitable. Using simple chemistry reported in the 1960s, the industry got creative and started experimenting with ways to convert CBD into delta-8-THC.

The resulting products target consumers who are looking to relieve stress and anxiety, especially those who don't want to use traditional cannabis products or those who live in places where cannabis products are not legally available.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

92

92

What Is Delta 8 THC?

But with no regulatory oversight and limited laboratory testing, most products sold as delta-8-THC are not actually pure delta-8-THC.

Such products typically contain a high percentage of delta-8-THC and small amounts of other cannabinoids, including delta-9-THC, and reaction by-products.

Some of the cannabinoids are not naturally found in cannabis. In most cases, nothing is known about the health effects of these impurities.

Several states are starting to crack down on sales of delta-8-THC products.

But as long as they are derived from hemp and contain no more than 0.3% of delta-9-THC on a dry-weight basis—the limit under federal law—many lawyers and hemp industry officials consider them legal.

Regardless of whether delta-8-THC is legal, chemists are sounding the alarm after finding several unidentified compounds in products labeled as delta-8-THC.

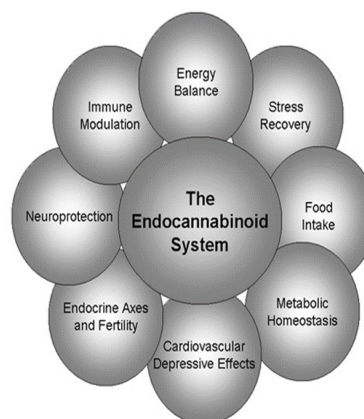
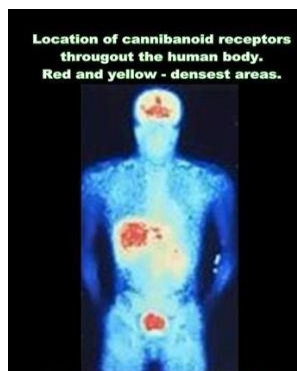
6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

93

93

Made in the Brain: Endogenous Endocannabinoids



94



95



96



97

Why Is Delta 8 THC Legal In Some States?

- Hemp-derived cannabis products, including those that can produce a high similar to traditional marijuana, are legal under federal law, thanks in large part to a 2018 Farm Bill broadly legalizing hemp production.
- According to **The Center for Advancing Health (CFAH)**. [CFAH.org](https://www.cfa-h.org), delta-8-THC is federally legal as long as it is extracted naturally from hemp.
- The DEA includes delta 8 THC on its list of controlled substances (updated August 2020) under "tetrahydrocannabinol."
- However, section 12619(b) of the 2018 Farm Bill — it's very last provision — carved out "tetrahydrocannabinol in hemp."
- This includes any type of THC from hemp plants that contain 0.3% of THC or less. Hemp-derived products (including those containing delta 8 THC) are legal on a federal level, while marijuana remains illegal. (**"The Loophole"**)
- Delta 9 THC is only legal in states that have legalized recreational marijuana.

98

Factors that Determine the Legal Status of Delta 8 THC

- All cannabinoids start from CBGA (cannabigerolic acid). The enzymes in the cannabis plant use CBGA to synthesize CBD, THC, CBC, CBDV, and more.
- There are no enzymes that could allow cannabis to directly convert CBG into delta 8 THC.
- The extraction process is very complicated and expensive.
- Extracting delta 8 THC using a conversion process from CBD requires the use of solvents, reagents, and acids.
- Therefore it calls for knowledgeable lab technicians and high-tech equipment to ensure the bases are properly purged of any toxic chemicals.
- Otherwise, the final product can be dangerous for your health.

99

Special Precautions and Warnings

- Regular use might also cause cannabinoid hyperemesis syndrome (CHS). CHS leads to severe nausea and vomiting that doesn't respond to typical anti-nausea drugs.
- **Children:** Taking delta-8 THC by [mouth](#) is possibly unsafe. Delta-8 THC gummies and candies have been eaten by children by mistake, leading to hospitalization. Side effects might include extreme tiredness, [low blood pressure](#), and slowed [heart rate](#).

100

Delta 8 THC and Pregnancy

- **How Cannabinoids Affect Obstetrical Outcomes:**
- Implantation, the attachment of the fertilized egg to the uterine wall, is dependent upon a number of tightly regulated processes. Evidence suggests that there are five ways in which cannabinoids can affect implantation:
- **Impairment of Fallopian Motility:** Cannabinoid signaling controls muscle contraction and relaxation in the fallopian tube responsible for the movement of a fertilized egg through the fallopian tube and into the uterus.
- **Ectopic Pregnancy:** [Previous studies](#) have shown that the blood collected from women who have had ectopic pregnancies contains significantly higher levels of the naturally occurring cannabinoid, anandamide, compared to normal pregnant controls. Consistency between human and animal data adds confidence that the observed findings in animal models of altered cannabinoid signaling may play a role in ectopic pregnancy.
- **Non-Hatched or Non-Viable Embryo:** In mice models known to have altered cannabinoid signaling, an increased mortality of offspring was observed in association with implantation of slowly developing embryos (6).
- **Decreased Uterine Receptivity:** It is theorized that the binding of exogenous cannabinoids to CB1 receptors in the uterus has embryotoxic effects on the uterine environment. Modeling of this scenario has halted the development of blastocysts *in vivo* and *in vitro* (7).
- **Miscarriage (Spontaneous Abortion):** Folic acid (Vitamin B9) is essential for embryo development and cannot be synthesized by the body which is why women are encouraged to take folic acid supplements during pregnancy. THC significantly decreases fetal folic acid uptake. Low levels of folic acid during pregnancy are associated with higher rates of miscarriages, as well as neural tube defects and low birth weight.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

101

101

Delta 8 THC and Pregnancy

- **How Cannabinoids Affect Embryo Development:**
- THC crosses the placenta, enters fetal blood circulation, passes through the blood brain barrier, and is found at the highest levels in fetal fat tissue. The brain is 60% fat and therefore stores THC following maternal ingestion. The brain is also densely populated with CB1 receptors which mediate THC's psychoactive properties.
- **Folic Acid Uptake:** As stated above, THC interferes with fetal folic acid uptake. Low levels of folic acid during pregnancy are known to be associated with neural tube defects and low birth weight.
- **Cellular Growth:** Exogenous cannabinoids may interfere with critical pathways for cellular growth and angiogenesis (formation of new blood vessels).
- **Neural Development:** Cannabinoids acting upon the CB1 receptor have the ability to influence the differentiation of neural cells from stem cells in the brain. This has tremendous potential to negatively affect learning and memory as well as developmental processes such as limb development.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

102

102

Delta 8 THC and Pregnancy

- **What are the effects of exposure to cannabis in the nursing infant?**
- The bioavailability of cannabis and its metabolites ingested by neonates in the breast milk has not been well-characterized. There are conflicting data regarding the outcomes of infants exposed to cannabis during breastfeeding and very few studies assessing outcomes in this population. These studies are not easy to conduct. First of all, recreational use of cannabis continues to be illegal in many states. Furthermore, it is difficult to disentangle the direct effects of cannabis delivered in the breast milk from the indirect effects of cannabis on the quality of childcare and parenting, especially in heavy, chronic users or when cannabis is combined with other substances.
- In one study, 136 breastfeeding infants were assessed at one year of age. In the 68 infants exposed to cannabis during the first month of life, there was evidence of decreased motor development at one year, when compared with matched infants who were not exposed to cannabis. Specifically, there was a 1465-point decrease in the Bayley index of infant motor development. However, the authors of this study cannot conclude that these findings were entirely due to exposure via breastfeeding, as many of the women also used marijuana during pregnancy.
- In another study, 27 breastfed infants exposed to cannabis were compared to 35 unexposed breastfed infants. At one year, no differences were noted for motor and mental development using the Bayley Scales of Infant Development. However, the small size of this study limited statistical analysis.
- So the jury is still out regarding the effects of cannabis on the nursing infant.
- Both the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics recommend that women refrain from using cannabis during pregnancy and while breastfeeding. Because of the persistence of cannabis and its byproducts in the breast milk for days to weeks, using cannabis and waiting for it to clear out of the breast milk is not a viable option. For women who use cannabis for medical indications, alternative therapies with more safety data during breastfeeding should be considered.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

103

103

CBD Product Testing

- <https://www.labcorp.com/assets/17241>
- <https://cptclabs.com/analytical-services/cbd-product-testing/>
- <https://www.badgerlabs.com/hemp-testing-packages-analysis/>
- <https://www.cbd-boxes.com/blog/guideline-for-cbd-product-testing-requirements/>
- <https://acslabcannabis.com/services/cbd-testing/>

104

Updated Marijuana Information Resources

- <https://themarijuanareport.org>
- <https://www.cdc.gov/marijuana/index.htm>
- <https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know>
- <https://www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx>
- <https://www.health.harvard.edu/blog/medical-marijuana-2018011513085>
- <https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process>

105

Bibliography

- Johnson R. Defining Hemp: A Fact Sheet. Congressional Research Service. 2019:1–4.
- Hudak J. The Farm Bill, hemp legalization and the status of CBD: An explainer. Brookings. <https://www.brookings.edu/blog/fixgov/2018/12/14/the-farm-bill-hemp-and-cbd-explainer/>. Published December 13, 2018. Accessed April 18, 2020.
- Johnson R. 2018 Farm Bill Primer: Hemp Cultivation and Processing. Congressional Research Service. Published 2019.
- Drug Enforcement Administration Pharmacist's Manual an Informational Outline of the Controlled Substances Act. United States Department of Justice Office of Diversion Control. 2010.
- DEPARTMENT OF JUSTICE Drug Enforcement Administration 21 CFR Chapter II [Docket No. DEA-427] Denial of Petition to Initiate Proceedings to Reschedule Marijuana Federal Register. 2016;81(156).
- Flint DL, Shelton DM. Cannabis-Derived Botanical Drugs: A Viable regulatory pathway for marketing medical edibles? 2019:118–224.
- Jeliazekov VD, et al. What Is Industrial Hemp? Oregon State University Extension Service. EM 9240. 2019.
- National Conferences of State Legislatures. The NCSL Podcast. April 16, 2020. Federal Register.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

106

106

Bibliography

- Callaway JC. Hempseed as a nutritional resource: an overview. *Euphytica*. 2004;140(1-2):65–72.
- Hall W. A summary of reviews of evidence on efficacy and safety of medical use of cannabis and cannabinoids. University of Queensland. Published December 2018.
- Carlton J. The Legality and Availability of CBD Oil in Virginia, Issue Brief. Virginia Division of Legislative Services. 2019.
- FDA Newsletter. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Published June 25, 2018.
- Barrus DG, Capogrossi KL, Cates SC, et al. Tasty THC: Promises and Challenges of Cannabis Edibles. *Methods Rep RTI Press*. 2016;2016:10.3768/rtipress.2016.op.0035.1611. doi:10.3768/rtipress.2016.op.0035.1611.
- 7 Things You Need to Know about Edible Cannabis. Canadian Centre on Substance Use and Addiction. 2019:1–3.
- Wang GS. Cannabis (marijuana): Acute intoxication. In: *UpToDate*. Waltham, MA: UpToDate; 2019.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

107

107

Bibliography

- Klein RFX. Analysis of “Marijuana Edibles”—Food Products Containing Marijuana or Marijuana Extracts—An Overview, Review, and Literature Survey. *Microgram Journal*. 2017;14:9–19.
- Koppel B, Brust J, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:1556–1563. doi:10.1212/WNL.0000000000000363.
- Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry Res*. 2018;89:741–53. doi:10.1136/jnnp-2017-317168.
- Epidiolex FDA Approved Package Insert. Greenwich Biosciences, Inc. June 2018.
- Morano A, Fanella M, Albini M, et al. Cannabinoids in the Treatment of Epilepsy: Current Status and Future Prospects. *Neuropsychiatr Dis Treat*. 2020;16:381–396. Published February 7, 2020. doi:10.2147/NDT.S203782.
- Elsaid S, Kloiber S, Le Foll B. Effects of cannabidiol (CBD) in neuropsychiatric disorders: a review of pre-clinical and clinical findings. *Prog Mol Biol Transl Sci*. 2019;167:25–75. doi:10.1016/bs.pmbs.2019.06.005.
- Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015;313(24):2456–73.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

108

108

Bibliography

- The CBD Report: 2018 Industry Outlook. Executive Summary. Hemp Business Journal. 2018:2-5
- State Medical Marijuana Laws. Key Aspects of State and D.C. Medical Marijuana Laws, from National Conference of State Legislatures. www.ncsl.org. Updated March 10, 2020.
- State Medical Marijuana Laws. National Conference of State Legislatures. <https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>. Published March 10, 2020. Accessed June 2, 2020.
- Gill, LL. "CBD Goes Mainstream." Consumer Reports. www.consumerreports.org/cbd/cbd-goes-mainstream/. Published April 11, 2019.
- National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017. doi:10.17226/24625.
- Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *Int J Mol Sci*. 2018;19(3):833. Published March 13, 2018. doi:10.3390/ijms19030833. Accessed April 18, 2020.
- Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6):791-802. doi:10.1111/epi.12631. Accessed April 18, 2020.
- Xiong W, Cui T, Cheng K, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting $\alpha 3$ glycine receptors. *J Exp Med*. 2012;209(6):1121-1134. doi:10.1084/jem.20120242. Accessed April 19, 2020.
- Brown JD, Winterstein
- AG. Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use. *J Clin Med*. 2019;8(7):989. Published July 8, 2019. doi:10.3390/jcm8070989.

6/10/22

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D

109

109

Questions



110