CBD: The Issue and the Evidence

Kenneth Finn, MD
Springs Rehabilitation, PC

What is CBD?

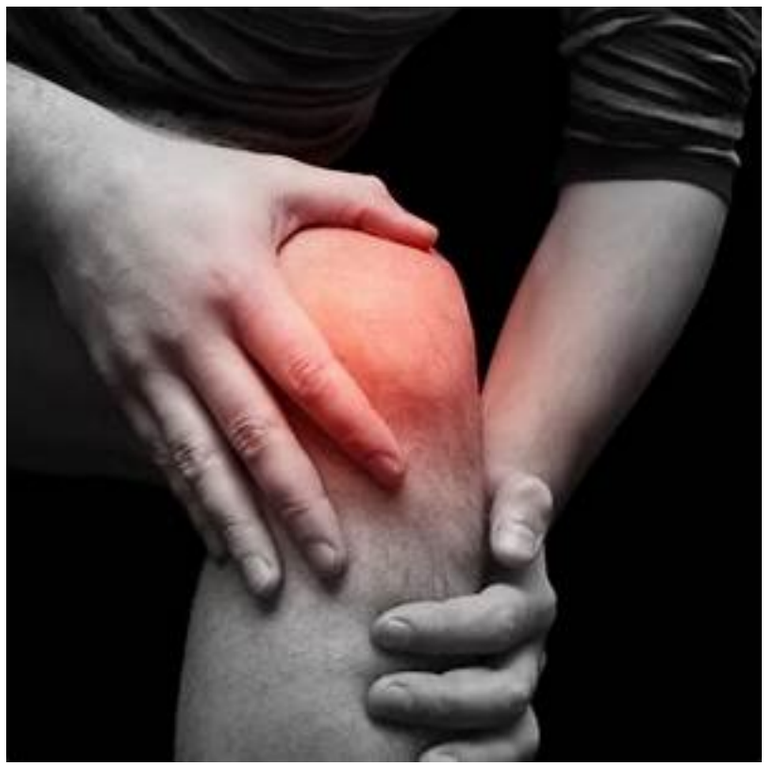
- Cannabidiol (CBD)
- Exogenous cannabinoid which may impact the endocannabinoid system
- Mechanism not completely understood in pain
- Possible anti-inflammatory effect
- Non psychoactive properties

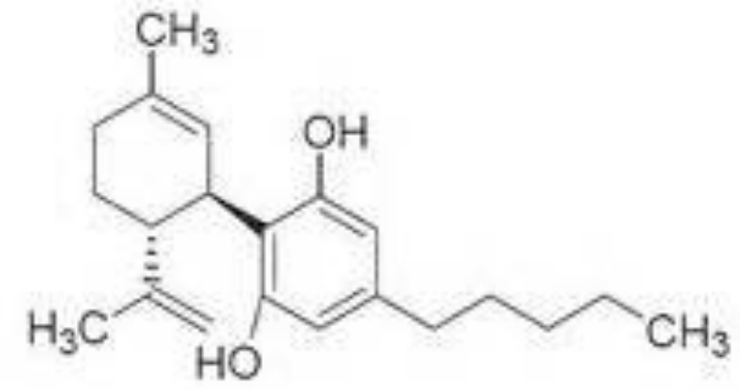
What is CBD?

- Does not bind well to CB_1 or CB_2 receptors
- Affinity to adenosine, A2A, GPR55
- Signaling events such as stimulating arachidonic acid release and phospholipid hydrolysis, stimulation of cyclo-oxygenase 2 (COX2), reduction in prostaglandin E_2 (PGE_2), reduction of nitrous oxide and other free radicals
- Animal models

What is CBD?

- May have an effect on modulating intracellular Ca^{++}
- May impact cytokine production
- Effects in human anti-inflammatory process have not been rigorously evaluated

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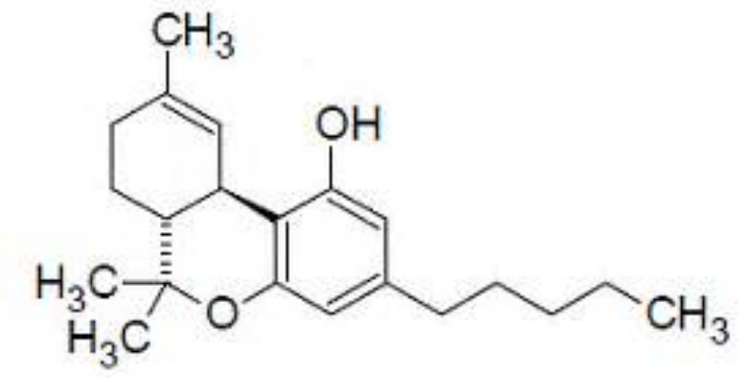
CH3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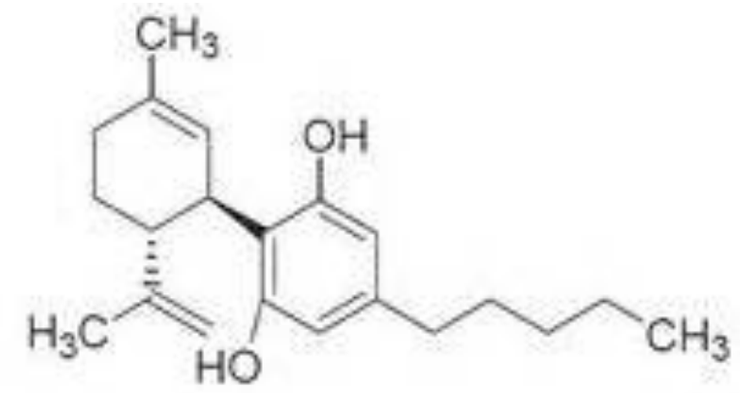
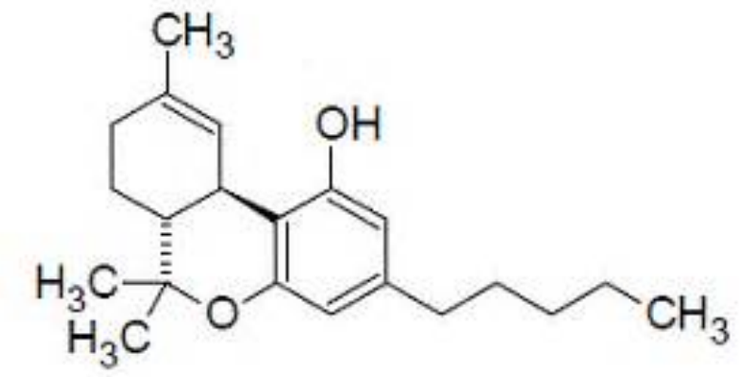
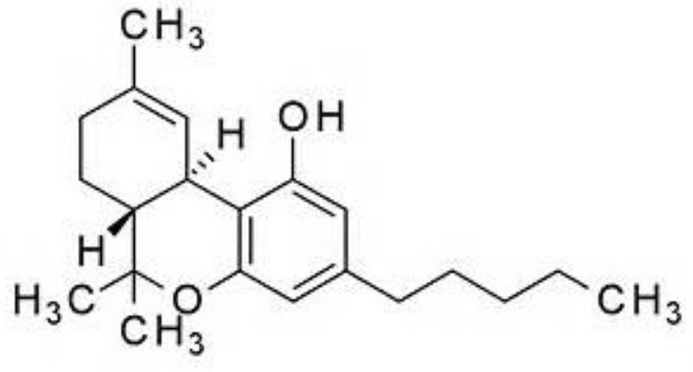


CBD



Dronabinol



THC


sparoom
PERFECT BLENDS FOR BETTER LIVING
CBD OIL
MULTI-PURPOSE
DIFFUSE
ROLL-ON
EVERYDAY WELLNESS
BALANCE IN MIND & BODY
RELIEVE STRESS
ENHANCE RELAXATION
DERIVED FROM INDUSTRIAL HEMP PLANT
NO THC
CALM STATE OF MIND
PROVEN QUALITY ASSURANCE
Shop Online @
Closet &
39.99
29.99
DOG WHISPERER
CBD OIL
250 MG ORIGINAL BLEND
HEALTHY DOGS BOND BETTER


Decaf CBD Blend
Original CBD Blend
ROASTED with SOLAR POWER
ETHIOPIA
GUATEMALA
MEDIUM ROAST
DECAF

Edible CBD

- Conversion of cannabidiol to Δ9-tetrahydrocannabinol and related cannabinoids in artificial gastric juice, and their pharmacological effects in mice
  - Forensic Toxicol (2007) 25:16–21
- Identification of Psychoactive Degradants of Cannabidiol in Simulated Gastric and Physiological Fluid
  - Cannabis and Cannabinoid Research Volume 1.1, 2016

Product Integrity

- Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products

- San Francisco, Los Angeles, Seattle
  - Regarding THC
    - 17% accurately labeled
  - Regarding CBD
    - 59% had detectable levels of CBD

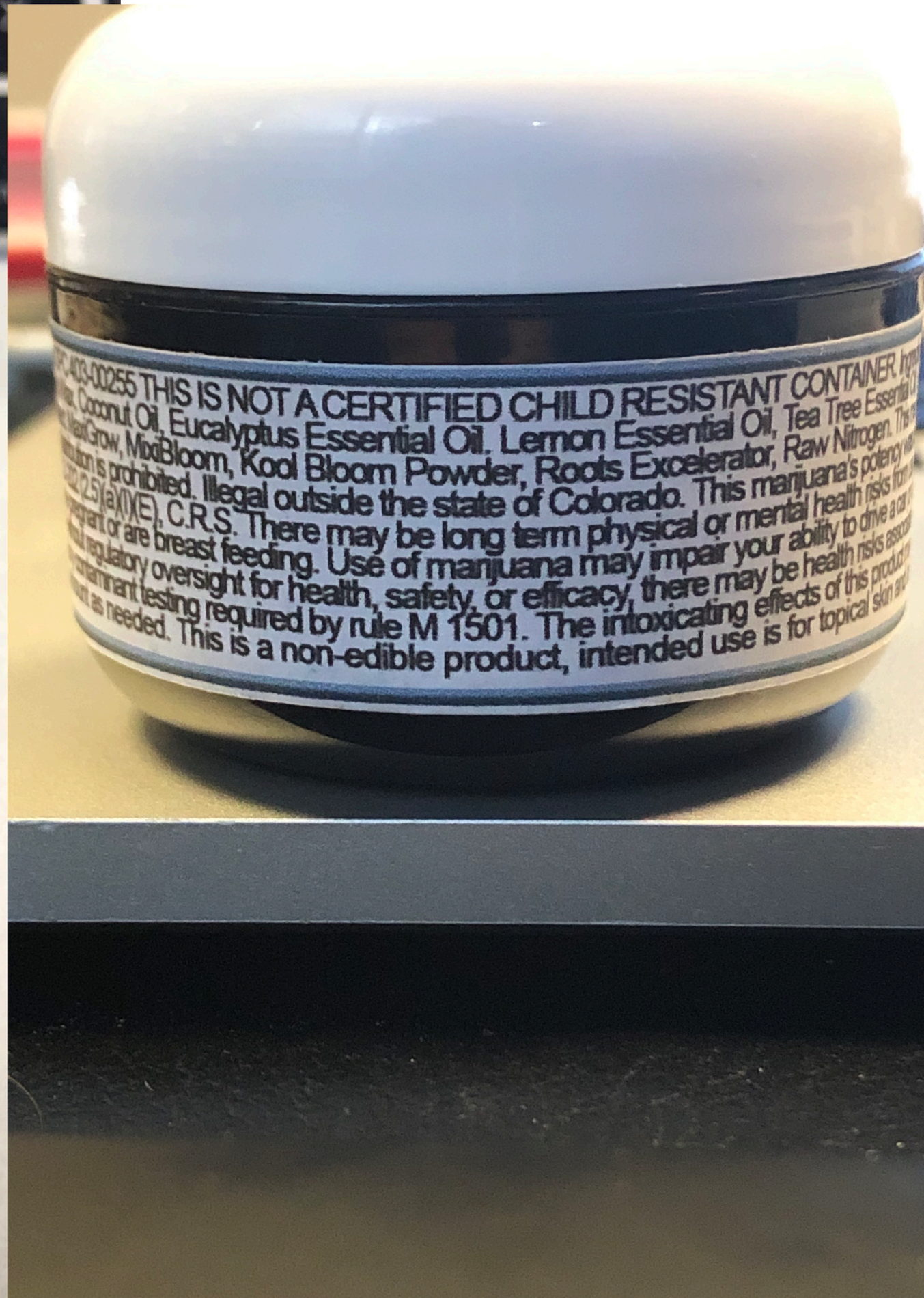
JAMA, June 23/30, 2015, Volume 313, Number 24, p. 2491

Product Integrity

- Labeling Accuracy of Cannabidiol Extracts Sold Online
- Wide range of CBD concentrations
    - 0.10 mg/ml to 655.27 mg/ml
    - Regarding CBD
        - 31% were accurately labeled
        - THC was detected in 21.4%

JAMA, November 7, 2017, Volume 318, Number 17


NEW! NOW WITH
CBD
WHITE BUFFALO
THC
Contains Marijuana. Keep
out of reach of children.


403-00255 THIS IS NOT A CERTIFIED CHILD RESISTANT CONTAINER. Ingr
Coconut Oil, Eucalyptus Essential Oil, Lemon Essential Oil, Tea Tree Essential O
MaxiGrow, MaxiBloom, Kool Bloom Powder, Roots Excelerator, Raw Nitrogen. This m
ution is prohibited. Illegal outside the state of Colorado. This marijuana's potency
2)(2.5)(a)(I)(E), C.R.S. There may be long term physical or mental health risks from
regnant or are breast feeding. Use of marijuana may impair your ability to drive a car
ral regulatory oversight for health, safety, or efficacy, there may be health risks assoc
contaminant testing required by rule M 1501. The intoxicating effects of this product
ount as needed. This is a non-edible product, intended use is for topical skin

Eucalyptus Lemon Salve

THC: 258* CBD: 80.9*
THCa: 5.42* CBG: 9.0*

Batch: 071219ELSALVE Package: 00748

...product. The medical marijuana contained within
...more hours. Instructions for use: apply dime size
...(oz) Extracted with ethanol. MMR_____ Date_____ 1 OZ

CONSISTENT RESULTS - REPORTED MEDICATION DETECTED (PARENT DRUG AND/OR METABOLITE)

REPORTED MEDICATION	ANTICIPATED POSITIVE(S)	TEST OUTCOME	TEST RESULT (ng/mL)	DETECTION WINDOW[1]	COMMENTS
FENTANYL	Fentanyl	**POSITIVE**	1	24-48 hrs (IV); Detection window not established for other dosage forms. Drug half-life for transdermal formulation suggests fentanyl can be detected for up to 4-6 days.	The sample tested positive for Fentanyl, Norfentanyl which is consistent with patient having taken FENTANYL
	Norfentanyl	**POSITIVE**	9	72-96 hrs (IV); Detection window not established for other dosage forms. Drug half-life for transdermal formulation suggests fentanyl can be detected for up to 4-6 days.	

INCONSISTENT RESULTS - REPORTED MEDICATION NOT DETECTED (NEITHER PARENT DRUG NOR METABOLITE)

REPORTED MEDICATION	ANTICIPATED POSITIVE(S)	TEST OUTCOME	DETECTION WINDOW[1]	COMMENTS
NORCO	Hydrocodone	Negative	1-2 days	The sample tested negative for Hydrocodone, Hydromorphone, Norhydrocodone which suggests the patient is not currently taking NORCO (within the detection window)
	Norhydrocodone	Negative	1-2 days	
	Hydromorphone	Negative	1-2 days	

INCONSISTENT RESULTS[2] - ANALYTE DETECTED BUT NO CORRESPONDING MEDICATION REPORTED

DETECTED ANALYTE	TEST OUTCOME	TEST RESULT (ng/mL)	DETECTION WINDOW[1]	COMMENTS
Meperidine	**POSITIVE**	144	0.5-2 days	Meperidine was detected, but could not be matched to any of the reported prescriptions. Sources of Meperidine include Demerol. Meperidine is also known as Pethidine.
Normeperidine	**POSITIVE**	1,115	Detection window not established. Drug half-life suggests normeperidine can be detected for 3-4 days.	Normeperidine is a metabolite of Meperidine(Demerol), and is not available as a prescription. The presence of normeperidine indicates meperidine use; however no prescription for such was reported.
Duloxetine	**POSITIVE**	34	Detection window not established. Drug half-life suggests duloxetine can be detected 2-4 days.	Duloxetine was detected, but could not be matched to any of the reported prescriptions. Sources of Duloxetine include Cymbalta & Yentreve.
Gabapentin	**POSITIVE**	> 100,000	1-2 days	Gabapentin was detected, but could not be matched to any of the reported prescriptions
cTHC (Marijuana metabolite)	**POSITIVE**	> 1,000	Single use: 2-3 days; Moderate use (4 times/wk): 5-7 days; Heavy use: 10-15 days; Chronic use: 19-40 days; Oral ingestion: 1-5 days	cTHC was detected and is found in marijuana. Marijuana is a DEA Schedule I controlled substance with very limited pharmaceutical application. Historical cTHC creatinine-corrected levels may be useful when monitoring for abstinence from marijuana. Consider contacting a toxicologist for assistance with interpretation of historical levels.
cis-3-methylfentanyl	PENDING	PENDING	Detection window not established	Results Pending. Final results will generally be available the next business day.

Drug Interactions

- 9 major and 498 moderate drug interactions
  - Metabolized by CYP3A4 and CYP2C19.

  - Co-administration with a moderate or strong inhibitor of CYP3A4 or CYP2C19 will increase cannabidiol plasma concentrations, which may result in a greater risk of adverse reactions

https://www.drugs.com/drug-interactions/cannabidiol-index.html

Drug Interactions

- Acetominophen, celecoxib, diclofenac (oral and topical)
- Baclofen, carisoprodol, tizanidine
- Buprenophine (major), tramadol, tapentadol
- Zolpidem
- Some SSRI, SNRI

Drug Interactions

- Antibiotics
- Organ transplant medications
  - cyclosporin, tacrolimus
- Antiseizure medications
- Benzodiazapine (diazepam)
- Coumadin


EPIDIOLEX®
(cannabidiol) 100 mg/mL
Oral Solution
100
mg/mL
2 x 100mL Bottles
EPIDIOLEX®
(cannabidiol) 100 mg/mL
Oral Solution
CAUTION: New Drug – Limited by Federal
(or United States) Law to
Investigational Use
GW Pharma Ltd
EPIDIOLEX® (cannabidiol)
100 mg/mL Oral Solution
100 mL
Investigational Use
Take as directed by your doctor
FOR ORAL ADMINISTRATION ONLY.

Epidiolex

- The **ONLY** FDA-approved, purified CBD
- Prescription medicine that is used to treat seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.
- EPIDIOLEX may cause liver problems

IMPORTANT SAFETY INFORMATION & INDICATIONS

CONTRAINDICATION: HYPERSENSITIVITY

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.

WARNINGS & PRECAUTIONS

Hepatocellular Injury:

EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Transaminase and bilirubin levels should be obtained prior to starting treatment, at one, three, and six months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury.

Somnolence and Sedation:

EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Suicidal Behavior and Ideation:

Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.

EPIDIOLEX® (cannabidiol) oral solution, CV
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older (1)

DOSAGE AND ADMINISTRATION

- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- EPIDIOLEX is to be administered orally. (2.2)
- The recommended starting dosage is 2.5 mg/kg taken twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). (2.2)
- Based on individual clinical response and tolerability, EPIDIOLEX can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day). See Full Prescribing Information for titration. (2.2)
- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment. (2.5, 8.6)

Hematologic Abnormalities

EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In controlled trials of patients with LGS or DS, the mean decrease in hemoglobin from baseline to end of treatment was -0.42 g/dL in EPIDIOLEX-treated patients and -0.03 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.5% in EPIDIOLEX-treated patients, and -0.4% in patients on placebo. There was no effect on red blood cell indices. Thirty percent (30%) of EPIDIOLEX-treated patients developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point), versus 13% of patients on placebo.

Increases in Creatinine

EPIDIOLEX can cause elevations in serum creatinine. The mechanism has not been determined. In controlled studies in healthy adults and in patients with LGS and DS, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting EPIDIOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS and DS.

American Epilepsy Society March 2016

- “Unlike the product used in the GW Pharmaceutical study, the families and children moving to Colorado are receiving unregulated, highly variable **artisanal preparations** of cannabis oil prescribed, in most cases, by physicians with no training in pediatrics, neurology or epilepsy.”

- “As a result, the epilepsy specialists in Colorado have been at the bedside of children having severe dystonic reactions and other movement disorders, developmental regression, intractable vomiting and **worsening seizures** that can be so severe they have to put the child into a **coma** to get the seizures to stop.”

Michael D. Privitera, MD, President, American Epilepsy Society, 2016
Director, Epilepsy Center, University of Cincinnati Neuroscience Institute

American Epilepsy Society July 2019

- "**Pharmaceutical grade** CBD demonstrates moderate efficacy in specific types of seizures"

- "CBD does have important **adverse effect**s and several important **drug interactions**"

- "Artisanal products are produced and sold with **little or no regulatory control**"

- "Advise patients and caregivers to **avoid** purchasing and using the **artisanal products** of CBD"

https://journals.sagepub.com/doi/pdf/10.1177/1535759719878716

Cannabis

(Genus)

Marijuana Strain

(5-25% THC)

Industrial Hemp Strain

(0.3% THC)

Hemp, CBD, THC

How is THC or CBD Content Calculated?

- The Agricultural Act de-schedules cannabis products derived from hemp, previously defined as ≤0.3% THC in the plant
  - The act seems to expand the definition from the plant to finished product, thus making finished product legal if it contains less than 0.3% THC

- Dry goods (g/g or mg/mg): Weight of the final product (mg) x claimed THC content (%) = mg of THC
  - **Or mg THC / mg of dry product = % THC**

- Liquid goods (g/mL): THC and CBD are not water soluble, so you need to know the weight of the carrier oil
  - Ex. Most nutritional oils weigh ~920mg per mL
    - **0.3% THC in sesame oil = 0.003 x 920 = 2.7 mg/mL**

GREENWICH™ BIOSCIENCES

How Much is 0.3% THC?

A 30 milliliter bottle of CBD oil– a common retail unit– could contain **81 mg of THC** and still fall below 0.3% THC

State recreational marijuana laws (OR)-- **5 mg THC**/ serving; **50 mg THC**/product

A single 4-gram CBD gummy can have 12mg Of THC

The starting dose for prescription THC (synthetic) is **2.5 mg of THC; 81 mg=32 doses**

- The 0.3% limit on hemp derived products in solution legally supports the sale of **2.7 mg THC** per milliliter.

For comparison, if calculated as final product:

- FDA approved (CII) prescription THC has a recommended starting dose of **2.5 mg of THC**
- For comparison…within Epidiolex (CV) – the only FDA approved botanically-derived CBD medication – the THC content is **0.01%, or 0.09mg/ml**

GREENWICH™ BIOSCIENCES

…And how much THC does it take to get high?

- GW2015-1: 5mg THC: CNS side effects in 2/6 subjects

According to a recent study from Johns Hopkins University, marijuana-infused brownies containing **10 mg of THC** result in a psychoactive effect in adults[1]

The average marijuana joint in Colorado contains **63 mg of THC but only about 17 mg enters the body from smoking the whole joint.**

GREENWICH™ BIOSCIENCES

Vandrey R et al, *J Analytical Tox*, 2017: 1-17

What Is the Impact of Unknowingly Ingesting THC?

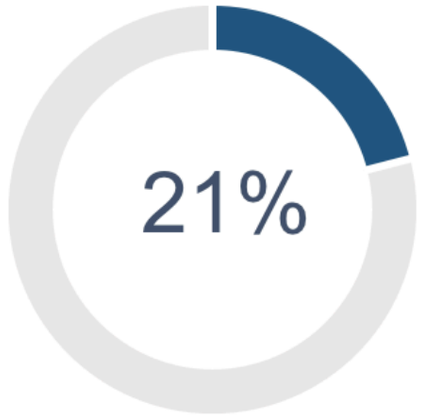
- Side effects of THC:
  - Exacerbation of mania, depression, schizophrenia (*significant after 28mg in avg adult)
  - Cognitive impairment
  - Impaired abilities including driving
  - Hemodynamic instability (heart rate, blood pressure, etc)
  - Seizures
  - Substance abuse
  - Nausea, vomiting, abdominal pain

Employment: Many believe CBD products contain so little THC that they will not “test positive” on a drug screen

FDA Package Insert. Marinol (dronabinol) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf.

AE Data on Non-GW CBD

A recent open label publication using a 50:1 CBD:THC (Tilray) showed



of the patients experienced **seizure worsening**

- Authors attributed the worsening to THC

- 42% laboratory abnormalities,

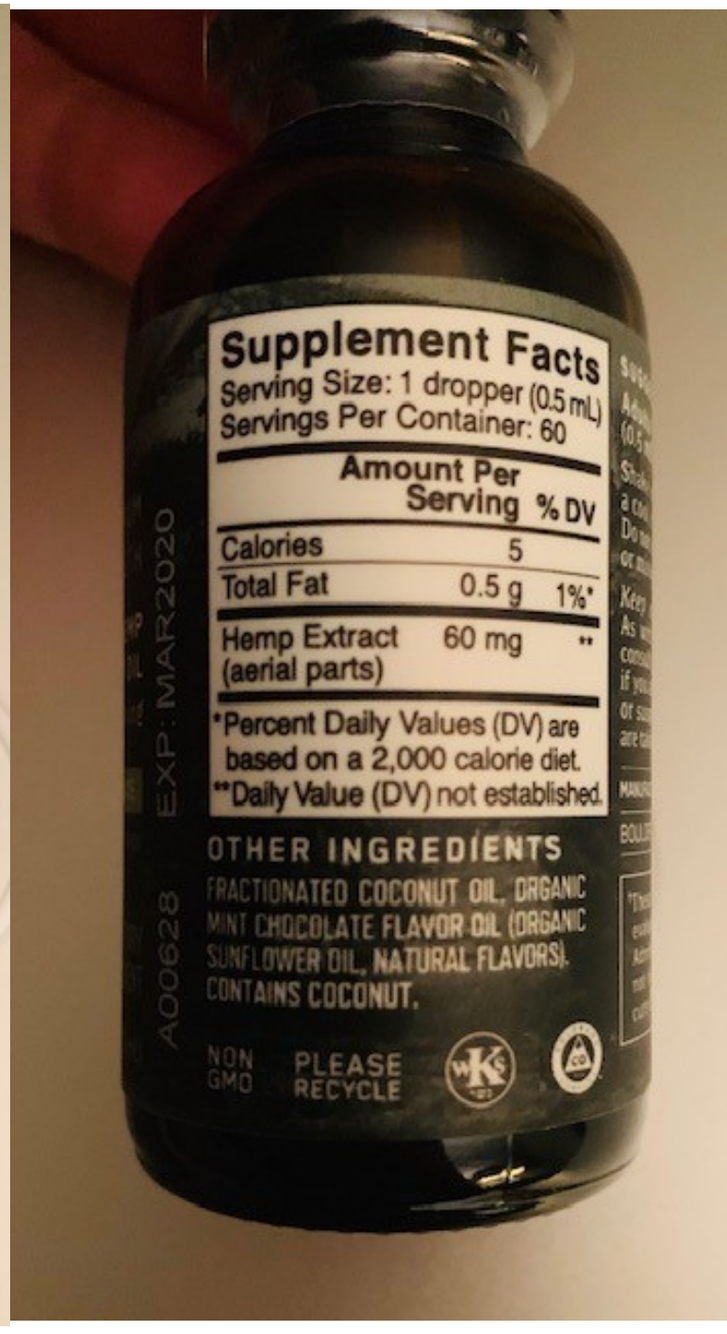
other adverse events >10% included somnolence, GI side effects, balance issues, sleep and mood disturbances, infections, anorexia, increased appetite

GREENWICH™ BIOSCIENCES

Insidious Products


MAXIMUM
STRENGTH
HEMP
EXTRACT OIL
60 mg/serving
MINT CHOCOLATE
Flavor
DIETARY
SUPPLEMENT
1 fl oz (30 mL)
A00628 | EXP: MAR2020


SUGGESTED USE:
Adults take one full dropper (0.5 mL) 2-3 times per day.
Shake well before using. Store in a cool, dry place away from light. Do not use if safety seal is broken or missing.
Keep out of reach of children. As with any dietary supplement, consult your physician, before use, if you are pregnant, nursing, have or suspect a medical condition or are taking any medications.
MANUFACTURED BY: dba CHARLOTTE'S WEB
BOULDER, CO 80301 | 1.855.790.8169
†These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
600.069.061801


Supplement Facts
Serving Size: 1 dropper (0.5 mL)
Servings Per Container: 60
Amount Per Serving
% DV
Calories 5
Total Fat 0.5 g 1%*
Hemp Extract (aerial parts) 60 mg **
*Percent Daily Values (DV) are based on a 2,000 calorie diet.
**Daily Value (DV) not established.
OTHER INGREDIENTS
FRACTIONATED COCONUT OIL, ORGANIC MINT CHOCOLATE FLAVOR OIL (ORGANIC SUNFLOWER OIL, NATURAL FLAVORS).
CONTAINS COCONUT.
NON GMO
PLEASE RECYCLE
A00628 EXP: MAR2020

CHARLOTTE'S WEB™
STANLEY BROTHERS Boulder, CO 80301 • 719-419-8169

CERTIFICATE OF ANALYSIS

Product Name: Charlotte's Web Hemp Extract Oil Maximum Strength Mint Chocolate 30mL

Product Batch: A00700

Product Code: 910.069

Best By: July 2020

Parameter	Result
Cannabinoids *Testing performed by Eurofins Food Chemistry Testing – Boulder, CO*	
THC	2.8 mg/mL
THC-A	0.033 mg/mL
THC-V	None Detected
CBD	64.3 mg/mL
CBD-A	0.44 mg/mL
CBD-V	0.31 mg/mL
CBG	0.32 mg/mL
CBG-A	None Detected
CBN	0.23 mg/mL
CBC	2.3 mg/mL
Total THC per Bottle	84 mg
Total THC per Serving	1.4 mg

Manufactured By: Charlotte's Web Inc.

Manufacture Date: 16JAN19, 18JAN19 - 20JAN19

Batch Size: 297,540 mL

Units Manufactured: 9,773

Assistant principal nearly loses job after testing positive for THC

- A Clayton County educator says he is grateful that he will be allowed to keep his job with the district after he tested positive for low levels of THC.

- He said the CBD caused him to fail the drug test. “As a result of that, the hearing tribunal found me guilty and recommended termination,” Blackwood said.

https://www.wsbtv.com/news/local/clayton-county/assistant-principal-nearly-loses-job-after-testing-positive-for-thc/994840209


PUBLIC SAFETY
PUBLIC SAFETY
PUBLIC SAFETY
PUBLIC SAFETY
PUBLIC SAFETY
PUBLIC SAFETY

Spiked vapes and emergency room visits reveal dark side of CBD craze
September 2019

Jay Jenkins said he hesitated when a buddy suggested they **vape CBD**

What he vaped **didn't have any CBD.** Instead, the oil was spiked with a powerful street drug

AP commissioned lab testing found that 10 of the 30 products tested contained types of **synthetic marijuana** while others had **no CBD** at all.

https://www.usatoday.com/story/news/health/2019/09/16/vaping-lung-illness-cbd-cheap-synthetic-marijuana-used-sub/2339545001/

Investigation Finds Some Texas CBD Samples Spiked With Synthetic Marijuana

September 2019

The Houston Forensic Science Center detected synthetic marijuana in about two dozen CBD vape samples, according to the AP report

Lab tests compiled by the AP showed synthetic marijuana ended up in vapes or edible products sold as CBD in 13 states

https://www.sacurrent.com/sanantonio/investigation-finds-some-texas-cbd-samples-spiked-with-synthetic-marijuana/Content?oid=21995204

Houston Officials Find Spiked CBD Being Sold in Stores September 2019

Products promoting the cannabis extract CBD are for sale all over Texas, but they don't always contain what they promise. Houston officials have found **spiked CBD vapes** sold in stores

The Associated Press gathered the results for an investigation into how some operators are capitalizing on the CBD boom by substituting the cheap street drug for real CBD.

That practice has sent dozens of people nationwide to **emergency rooms**. Unlike CBD, synthetic marijuana gives an intense high.

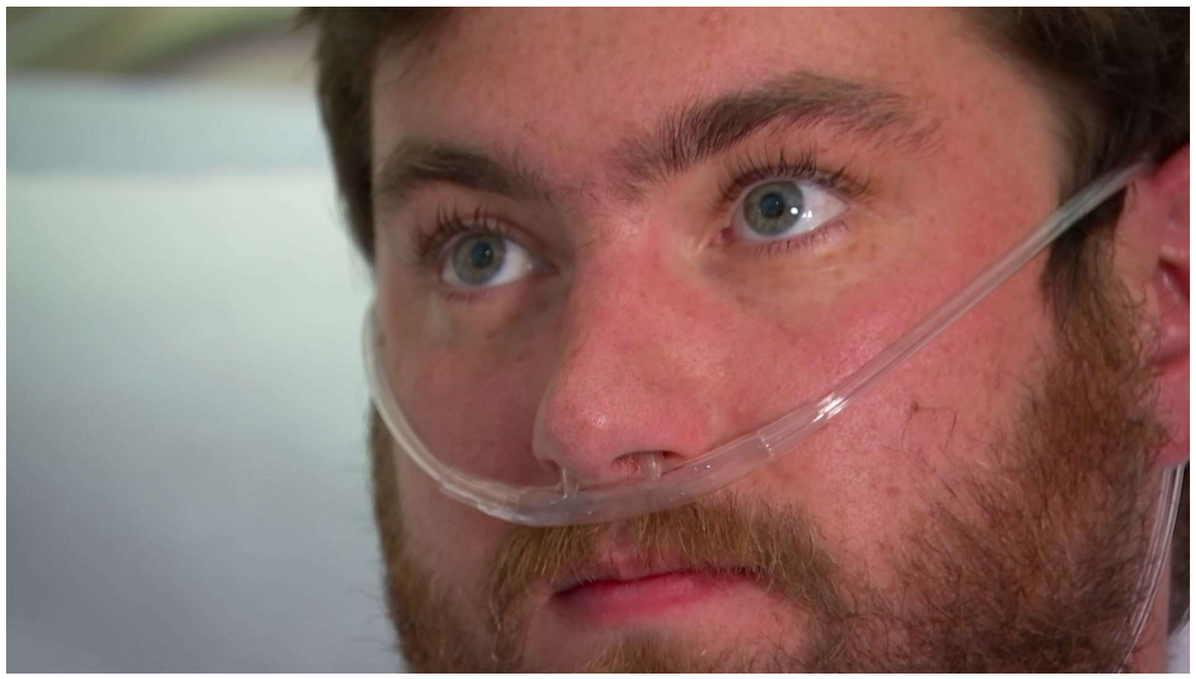
https://www.usnews.com/news/best-states/texas/articles/2019-09-16/houston-officials-find-spiked-cbd-being-sold-in-stores

NTX Man Says Vaping E-Liquid Caused Critical Lung Damage September 2019

A North Texas man says **THC vaping** nearly killed him, but he says he's one of the lucky ones as he shares his warning with others

He said he regularly used medical marijuana to manage life with Crohn's disease while he lived in Colorado. He said he thought a **THC vape pen** would have the same effect, so he said, he bought one off the streets

The outbreak has affected people who use both THC and nicotine-containing products, but it is **more prevalent** among **THC vapers** than people who self-report using only nicotine products



https://www.msn.com/en-us/health/medical/ntx-man-says-vaping-e-liquid-caused-critical-lung-damage/ar-AAHuL2k

Summary

- CBD is not psychoactive
- There is only **ONE** purified FDA-approved CBD
- All other products have potential for contamination
- CBD has potential serious liver effects, some significant drug interactions, and other negative physiologic effects
- Zero evidence of medical benefit for pain in regulated and non-regulated markets (QoL, function, pain reduction)

Summary

- Physicians, patients, legislators, and public need education
- Support FDA drug-development protocols
- Support adequate safety studies to protect consumers
- Support mechanisms to ensure public safety from contaminated products
- Develop position statement

Thank you