

# **CBD: The Issue and the Evidence**

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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?

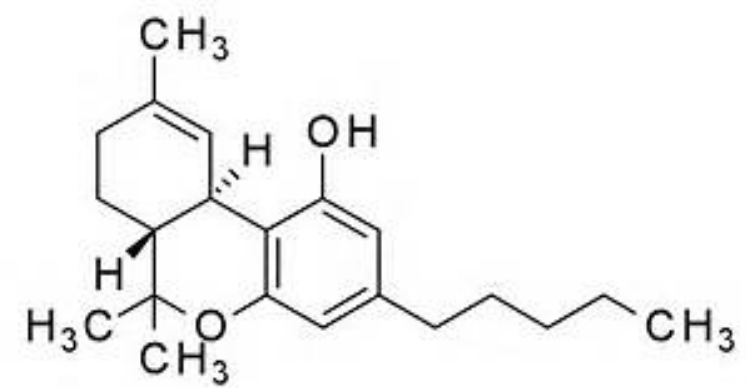
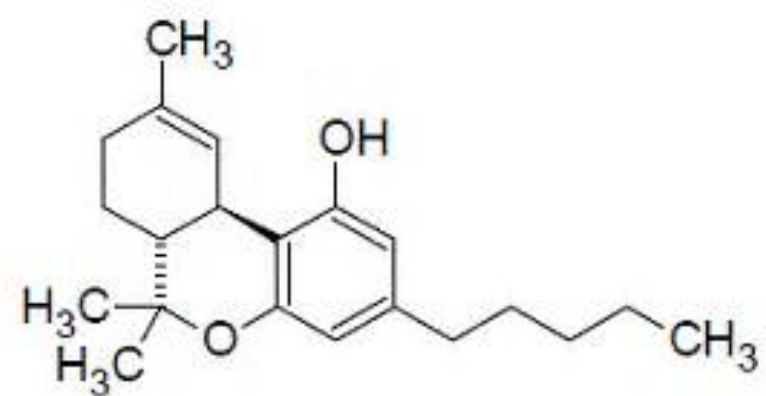
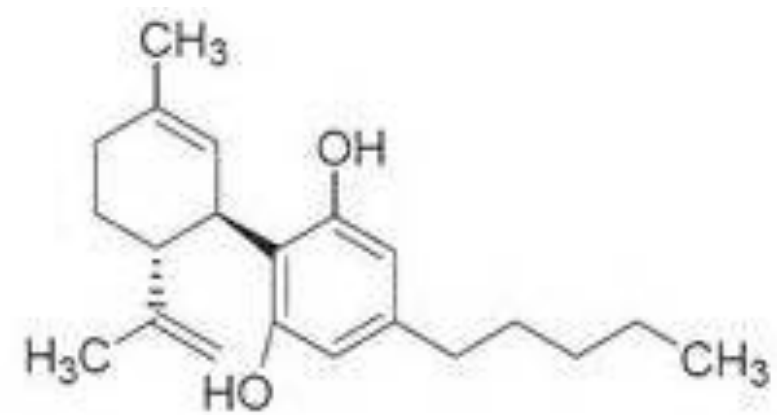
- Does not bind well to CB<sub>1</sub> or CB<sub>2</sub> receptors
- Affinity to adenosine A2A receptor, GPR55
- Signaling events such as stimulating arachidonic acid release and phospholipid hydrolysis, stimulation of cyclooxygenase 2 (COX2), reduction in prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), reduction of nitrous oxide and other free radicals
- Animal models

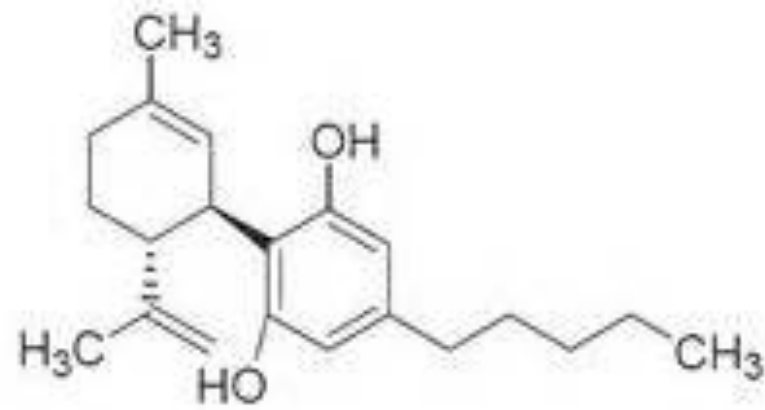
# What is CBD?

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

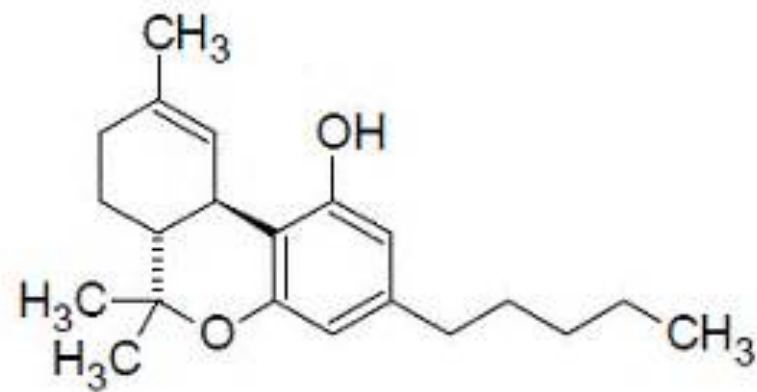








CBD



Dronabinol



THC

# False Medical Claims

**Trending News:** Clinically  
Validated CBD For Chronic  
Pain Available Legally Now..



# False Medical Claims

- April 2, 2019
- Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance agency's continued evaluation of potential **regulatory pathways** for cannabis-containing and cannabis-derived products
- A **public hearing** on May 31, as well as a broader opportunity for written public comment, for stakeholders to share their experiences and challenges with these products, including information and views related to **product safety**



# False Medical Claims

- October 22, 2019
- FDA, FTC warn company marketing unapproved cannabidiol products with unsubstantiated claims to treat teething and ear pain in infants, autism, ADHD, Parkinson's and Alzheimer's disease
- This is especially concerning when companies are peddling unproven CBD products for use in vulnerable populations like infants and children," said Acting FDA Commissioner Ned Sharpless, M.D.









# Edible CBD

- Conversion of cannabidiol to  $\Delta$ 9-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

# 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%







Eucalyptus Lemon Salve

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

Batch: 071219ELSALVE Package: 00748

For use of  
plus or  
additional  
product  
The medical marijuana contained within  
Instructions for use: apply dime size  
Extracted with ethanol. MMR \_\_\_\_\_ Date \_\_\_\_\_ 1 OZ

MIPS 404-111  
Extracted Marijuana  
CBD Isolate  
Medical Marijuana  
minus 15%  
risks for women  
contains marijuana  
this package  
portion to



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

REPORTED MEDICATION	ANTICIPATED POSITIVE(S)	TEST OUTCOME	TEST RESULT (ng/mL)	DETECTION WINDOW <sup>1</sup>	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 <sup>1</sup>	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<sup>2</sup> - ANALYTE DETECTED BUT NO CORRESPONDING MEDICATION REPORTED

DETECTED ANALYTE	TEST OUTCOME	TEST RESULT (ng/mL)	DETECTION WINDOW <sup>1</sup>	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

# Drug Interactions

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

# Drug Interactions

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



**EPIDIOLEX<sup>®</sup>**  
(cannabidiol) 100 mg/mL  
Oral Solution

**100**  
mg/mL

**EPIDIOLEX<sup>®</sup>**  
(cannabidiol) 100 mg/mL <sup>Ⓒ</sup>  
Oral Solution

**CAUTION: New Drug – Limited by Federal  
(or United States) Law to  
Investigational Use**

GW Pharma Ltd

2 x 100mL Bottles



**EPIDIOLEX<sup>®</sup> <sup>Ⓒ</sup> (cannabidiol)**  
**100 mg/mL Oral Solution**

**CAUTION: New Drug – Limited by Federal (or United States) Law to  
Investigational Use**

100 mL

Purified Cannabis sativa L. extract containing 100 mg/mL  
(CBD).

Each 1 mL of oral solution in sesame oil contains 100 mg of  
cannabidiol (CBD). It also contains ethanol, sucralose and strawberry flavor.  
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<sup>®</sup> safely and effectively. See full prescribing information for EPIDIOLEX.**

**EPIDIOLEX<sup>®</sup> (cannabidiol) oral solution, CV**

**Initial U.S. Approval: 2018**

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### **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)

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### **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 effects** 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”



# 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  $\leq 0.3\%$  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  $\text{mg THC} / \text{mg of dry product} = \% \text{ THC}$
- 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  $\sim 920\text{mg}$  per mL
  - **$0.3\% \text{ THC in sesame oil} = 0.003 \times 920 = 2.7 \text{ mg/mL}$**



# 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**



## ...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<sup>1</sup>



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



# What Is the Impact of Unknowingly Ingesting THC?

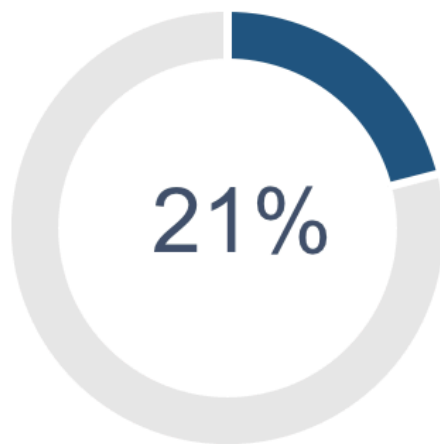
- Side effects of THC:
  - Exacerbation of mania, depression, schizophrenia (\*significant after 28mg in avg adult)
  - Cognitive impairment
  - Impaired abilities including driving
  - Hemodynamic instability (heart rate, blood pressure, etc)
  - Seizures
  - Substance abuse
  - Nausea, vomiting, abdominal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

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



# 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

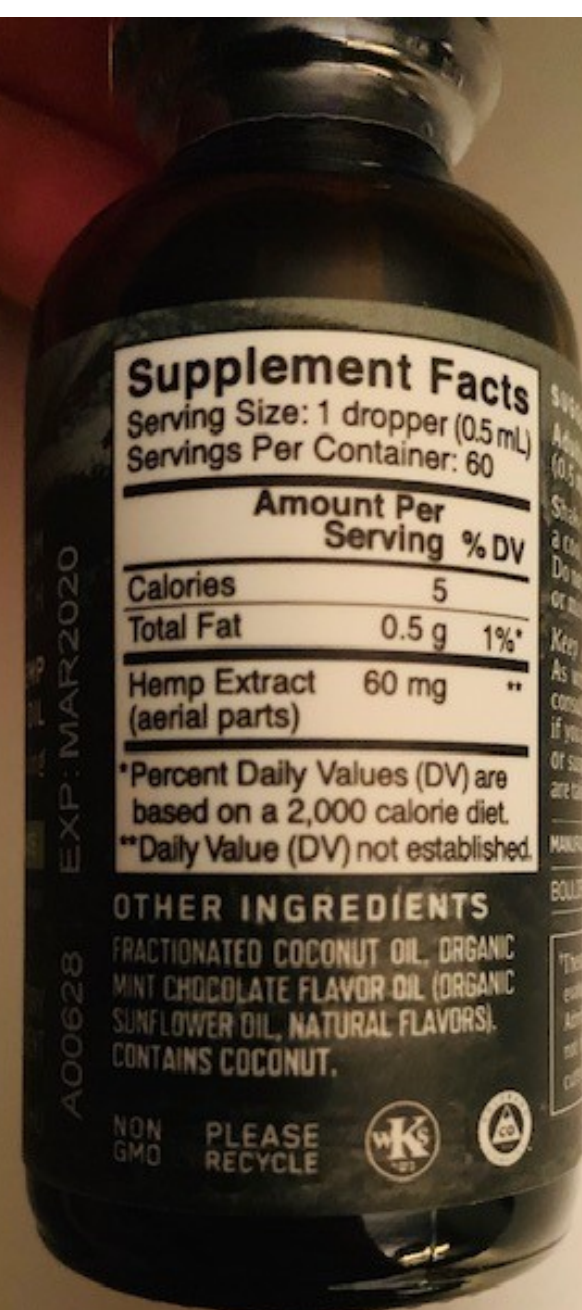
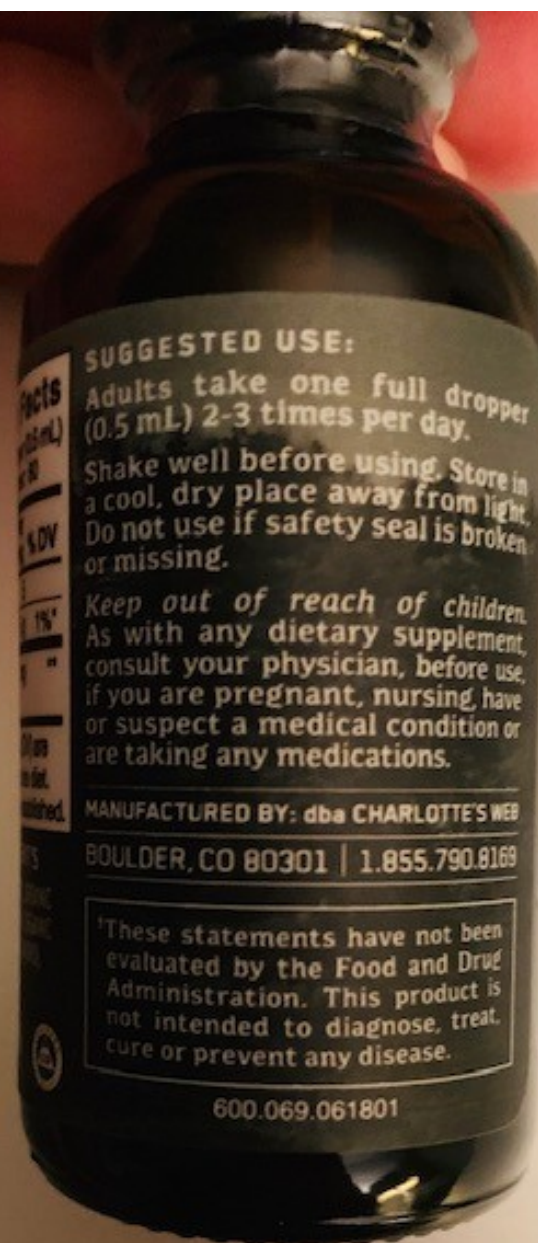
- **42%** laboratory abnormalities, other adverse events >10% included somnolence, GI side effects, balance issues, sleep and mood disturbances, infections, anorexia, increased appetite



# Insidious Products









# 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
<b>Cannabinoids</b>	
<i>Testing performed by Eurofins Food Chemistry Testing – Boulder, CO</i>	
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.









# 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

