Law: Legal, Ethical, and Therapeutic Assessment of CBD

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Objectives:

- At the conclusion of this lecture the successful learner will be able to:
  - Describe the legal status of CBD on the federal level, when isolated or when included with other constituents (cannabinoids, terpines) of the Cannabis Sativa plant
  - Describe the legal status of CBD on the state level, when isolated or when included with other constituents (cannabinoids, terpines) of the Cannabis Sativa plant
  - Describe salient pharmacologic and pharmacokinetic properties that might impact patient care
  - Describe the strength and nature of the human data suggesting benefits and adverse events

Disclosure:

- Dr White has spoken at advisory boards where CBD was discussed but the sponsoring company does not have a CBD product for sale in the United States or one that is under investigation. I will be discussing the use of a prescription CBD product called Epidiolex but also the use of CBD products that would be used off label and secured either through medical marijuana dispensaries or other vendors.

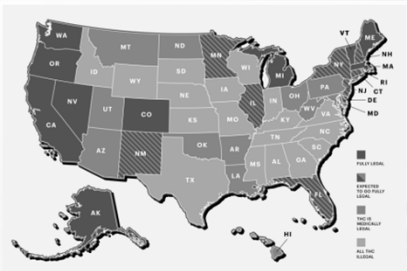
C. sativa

- *C. sativa* contains >60 CBs
  - THC and CBD are the most abundant CBs
- Marijuana is C. sativa with 0.3% THC or greater
- Hemp is *C. sativa* with <0.3% THC
  - CBD is the most abundant CB
- Both forms of *C. sativa* contain bioactive terpines
- Entourage effect

Legality of Marijuana

- The cultivation, distribution, possession, and use of Marijuana is illegal according to federal law
  - **Rohrabacher–Farr amendment** – passed in 2014 and states that the DOJ cannot expend funds to prosecute or impede states allowing medical marijuana usage
    - Needs to be reinserted in each federal appropriations law to remain in effect
    - Cannot distribute or use products across state lines
- States can determine their own processes and policies governing medical marijuana

Current and Anticipated Marijuana Laws By State



https://www.rollingstone.com/culture/culture-features/cannabis-legalization-states-map-831805/

CBD Legality

- 2018 Farm Bill
  - Until this Farm Bill, hemp was considered a controlled substance and few U.S. farmers were granted rights to plant and harvest it
  - The Agriculture Improvement Act of 2018 legalized the growth, sale and transportation of industrial hemp across state lines as well as hemp related products
  - Farmers should monitor their hemp's THC content
    - In the heat of the summer, THC levels typically remain low, but rise with cold and rain.
    - If the harvest runs into the fall or a rainy pattern develops, even THC levels in hemp could exceed acceptable levels and become marijuana
  - It is now legal to create hemp related beauty products, building insulation, cloth, and rope
    - The products have to contain <0.3% THC just like the hemp plant itself
  - Cultivation regulations now under auspices of Dept of Agriculture, not the DEA
  - Is it legal to produce, sell, possess, and use CBD health products?

https://cannabisindustryjournal.com/column/the-2018-farm-bill-legalized-industrial-hemp-bow-what-get-your-answers-here/ 7

Epidiolex: Prescription CBD is Legal

- Epidiolex is isolated, purified CBD and has <0.1% THC
  - Epidiolex was FDA approved for the treatment of 2 forms of drug-resistant epilepsy
    - Lennox-Gastaut and Dravet syndrome
  - In 2018, the DEA made Epidiolex Schedule V (drugs with a relatively low risk of abuse)
    - All other CBD products extracted from *Cannabis sativa* will remain Schedule I (high risk of abuse or harm, limited or no medicinal value, illegal to possess) until they are FDA approved and prove that, like Epidiolex, they contain less than 0.1% THC

White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387. 8

FDA Stance on Non-Epidiolex CBD Products: FDA Website

- **Question. "Can I legally sell CBD?"**
  - Answer. It depends on the intended use of the product and how it is labeled and marketed. Even if a CBD product meets the definition of "hemp" under the 2018 Farm Bill, it still must comply with the FD&C Act.
- **Question. "Can THC or CBD products be sold as dietary supplements?"**
  - Answer. No. FDA has concluded that THC and CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act [21 U.S.C. § 321(ff)(3)(B)]. Under that provision, if a substance (such as THC or CBD) is an active ingredient in a drug product that has been approved under section 505 of the FD&C Act [21 U.S.C. § 355], or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are excluded from the definition of a dietary supplement.
- **Final Statement. FDA is not aware of any evidence that would call into question its current conclusions that CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act**

https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers#legaltosell 9

Is Non-Epidiolex CBD Legal for People to Possess and Use?

"Great-grandmother with CBD oil arrested at Disney World" in May 2019

"Still illegal: Texas law on CBD oil lands grandmother in jail after DFW airport search" in May 2019

- **Drug sniffing dogs picked up Cannabis scent, patients arrested, product confiscated and tested**
  - **No one prosecuted but if the product has >0.3% THC, the manufacturer and possessor could be at risk**
- **Remember, legal to possess and use doesn't mean you cannot be drug tested and then lose your job or not be hired**

https://www.foxnews.com/travel/grandmother-cbd-arrested-disney-world https://www.star-telegram.com/news/local/article230704704.html 10

Self Assessment Question #1:

- What is the amendment that prevents federal dollars from being used to prosecute people in states working under state created medical marijuana dispensaries called?
  a) Orville-Redenbacher amendment
  b) Rohrabacher–Farr amendment
  c) Farfale-Tartufo amendment

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Legality of CBD From CT Dispensary

- CBD products are legal in CT as long as a patient is registered by a physician in the state medical marijuana program for an accepted and specified medical condition and you receive the product from a licensed medical marijuana dispensary in CT
  - Doesn't need to have low THC content
  - CT law cannot protect you across state lines
  - You cannot receive products from medical marijuana dispensaries in other states

White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387. 12

Legality of CBD in CT

- CBD laws in CT are very liberal
- CBD derived from hemp is not a controlled substance and may be manufactured and sold in CT
- Manufacturing
  - Purchasing of the raw hemp plant and cooking it into a food product (fried hemp chips or CBD granola bars) or extracting the CBD requires a license
  - The manufacturer is responsible for costs of disposal of CBD/hemp products with >0.3% THC or may seek permission from DCP to combine such product with a different batch of hemp to achieve a THC concentration of less than 0.3% in the aggregate
- Selling
  - Legally obtained hemp and CBD products may be obtained from outside of CT
    - If a person is converting hemp into a consumable in CT, they are required to hold a manufacturer of hemp consumables license, regardless of where the hemp was grown
  - Legally obtained hemp and CBD products may be sold at retail without a license
- There is nothing preventing the Federal Government from arresting or intervening even if it is not technically illegal in CT

https://portal.ct.gov/-/media/DCP/Hemp/CBD-HempFAQs_DCP.pdf?la=en

CBD Quality Control

- Epidiolex provides the concentration of CBD specified on the label with little variation over time
- In 2016, investigators purchased 84 non–FDA-approved CBD products from 31 different companies over the Internet and tested them using HPLC in a commercial laboratory
  - Triplicate test results were averaged and reported by product weight
- If average detected concentration was 90% to 110% of the labeled value, accurately labeled
  - For CBD, only 31% (95% confidence interval [CI], 22%–41%) were labeled correctly, with 43% (95%CI, 33%–54%) of products underlabeled and 26% (95%CI, 18%–36%) overlabeled
- The frequency of accurate labeling for CBD vaporization liquids, tinctures, and oils was 12.5%, 25%, and 45%
- Products contained unlabeled delta-9-THC at a mean concentration of 0.45 mg/mL (range, 0–6.4) in 21% of samples
  - Inhaled doses of 2 to 3 mg and ingested doses of 5 to 20 mg of delta-9-THC can provoke adverse effects and the "high"

CBD Quality Control

- The FDA has issued warning letters to numerous manufacturers for false claims but also tested those products for CBD content
  - The FDA found that many of the products contain little to no CBD, in marked contrast to their labeled amounts
- In the Netherlands, 8 CBD products were assessed
  - 4 were labeled correctly (<10% variability), 2 had 18% or 35% higher concentrations, and 2 had 74% or 98% lower CBD concentrations than the label stated
  - THC concentration was <0.03% for all CBD products
- ConsumerLabs has assessed a variety of CBD products for CBD content
  - The labeled CBD dosages bear little resemblance to what was contained in the products and that the cost per 10 mg of CBD ranged from $0.80 to $4.50.
- No CBD products have been verified by the United States Pharmacopeia
- **It is impossible to know the exact dose of CBD a patient is taking if they buy products that are not FDA approved or independently tested by outside laboratories**

CBD Quality Control: Adulteration and Contamination

- Five patients in Utah experienced symptoms such as seizures, confusion, unconsciousness, and hallucinations in 2017 due to CBD
- An in-depth investigation found that a CBD product included a synthetic cannabinoid
- From that time to May 2018, a total of 52 people were harmed due to this adulterant
- International Cannabis and Cannabinoid Institute in the Czech Republic assessed 29 CBD products and found that 69% of them exceeded recommended levels of polycyclic
- aromatic hydrocarbons
  - Class IIa carcinogens and genotoxic mutagens according to the International Agency for Research on Cancer.
- Possibility of pesticide or heavy metal contamination in unregulated CBD products

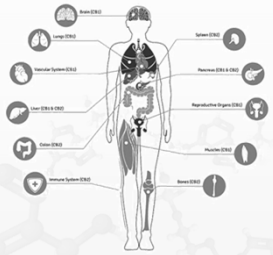
Self Assessment Question #2:

- A patient is enrolled in the state medical marijuana program and purchases a high concentration CBD product with 0.7% THC, are they at risk of arrest for marijuana possession?
  a) Not if the product is maintained in the State of Connecticut
  b) Yes, the THC concentrations of all CBD products must remain under 0.3%
  c) High concentration CBD products cannot be sold in marijuana dispensaries

CBD Pharmacology, Kinetics, and Adverse Events

Endocannabinoid System

- Complex homeostasis-protecting system
- Anandamide and 2-arachidonylglycerol
  - Endogenous cannabinoids
- Exert effects via CB_1 and CB_2 receptors
- Stimulation of CB_1 and CB_2 receptors can yield opposing, modified, or complimentary effects



White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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CBD Pharmacology - In Vitro and Animal Effects

Receptor Effects
CB_1 antagonist - Attenuation of impaired learning,memory, hypothermic, and psychosis effects induced by delta-9-THC
CB_2 inverse agonist - Binds but induces a pharmacological response opposite of agonist - Anti-inflammatory effects
$TRPV_1$ agonist - Anti-inflammatory, pain relieving, and sebum producing effects
Adenosine enhancer - Anti-inflammatory effects
GPR55 antagonist – Anti-proliferative effects

CB_1, CB_2, cannabinoid receptors; CBD, cannabidiol; GPR55, G-coupled protein receptor 55; $TRPV_1$, transient receptor potential vanilloid receptor 1.
White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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CBD Pharmacokinetics

- CBD demonstrates a less-than-dose–proportional increase in concentration
- T_{max} is 2.5 to 5 hours
- Volume of distribution is ~30,000 liters
- Elimination half-life is 56 to 61 hours
- High fat/high calorie meals dramatically increase C_{max} and AUC 5- and 4-fold, respectively
- CBD vaporization thought to increase T_{max}, but pharmacokinetic data are lacking
- Transdermal CBD pharmacokinetics not available, but modest molecular size may enhance penetration and bioavailability while high lipophilicity might impede it

AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; T_{max}, time to C_{max}.
Epidiolex® (cannabidiol) prescribing information. Carlsbad, CA: Greenwich Biosciences; 2018.

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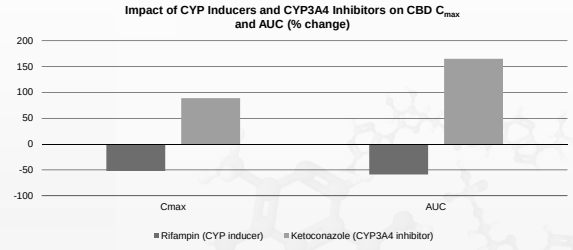
CBD Drug Interactions



Stott C. *Springerplus*. 2013;2:236.

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CBD Impact on Other Drug Kinetics

- CBD seems to be an inducer of some enzymes and an inhibitor of others
- Upregulation of CYP3A4, CYP2C, and CYP2B10 mRNA has occurred in mice, and induction of CYP1A1 has occurred in vivo
- CBD seems to be an inhibitor of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 metabolism
- Impact of CBD on clobazam and its N-desmethylclobazam metabolite assessed in 13 patients
  - Clobazam and N-desmethylclobazam levels increased by 60% and 500% after 4 weeks of concomitant therapy

Epidiolex® (cannabidiol) prescribing information. Carlsbad, CA: Greenwich Biosciences; 2018.
Geffrey AL. *Epilepsia*. 2015;56:1246-51. https://doi.org/10.1111/epi.13060

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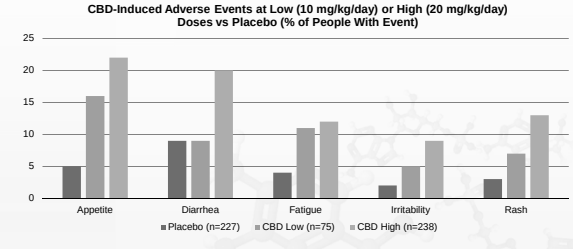
Common Adverse Events: 700-1,400mg in 70kg Person



Epidiolex® (cannabidiol) prescribing information. Carlsbad, CA: Greenwich Biosciences; 2018.

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Adverse Events: Hepatotoxicity

- The risk of raising liver function tests is related to the CBD dose administered and to other drugs the patient was receiving
- ALT elevations greater than 3 times the ULN were reported in 17% of patients taking CBD 20 mg/kg/day compared with 1% of patients taking CBD 10 mg/kg/day
- The majority of ALT elevations occurred in patients taking valproate (a known hepatotoxic drug)
  - The incidence of ALT elevations greater than 3 times the ULN was 21% to 30% in patients taking valproate + CBD ± clobazam and 3% in patients taking CBD without valproate or clobazam

ALT, alanine transaminase; ULN, upper limit of normal.

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Zygel® (STAR 1 Trial): ADE Breakdown

Adverse Event	Zygel 195mg/day	Zygel 390mg/day	Placebo
Nausea (%)	3	7	3
Fatigue (%)	6	5	2
Application Site Dryness (%)	2	7	0
Application Site Itchiness (%)	0	5	0
Headache (%)	6	5	3

Bonn-Miller M. American Epilepsy Society Annual Meeting. Houston, TX. December 2-6, 2016.

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Oral CBD Potential Efficacy

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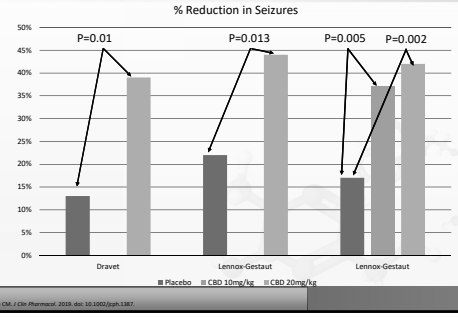
Self Assessment Question #3:

- What can best be said about CBD adverse events?
  - CBD does not cause adverse events
  - CBD's adverse events can include common things like nausea and rare but serious things like hepatotoxicity and the risk is unrelated to the dose used
  - CBD's adverse events can include common things like nausea and rare but serious things like hepatotoxicity but the risk is dose related

Epidiolex CBD in Epilepsy Syndromes



White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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CBD in Stress and Relaxation

- Acute effects of single-dose CBD on stress and relaxation have been studied
  - Oral doses are predominantly 300–600 mg given ~1–2 hours before stressful situations
- In public speaking-induced stress, pre-medicating with CBD was effective at reducing stress and enhancing relaxation in most studies
- In non-public speaking-induced stress, impact of CBD on stress or relaxation was variable
- Specifics on studies are given in back-up slides

White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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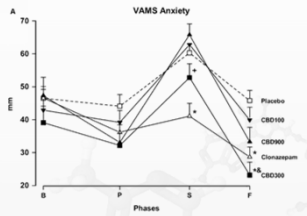
Focus on Public Speaking Stress and Relaxation

Patients (N=60) randomized to placebo, clonazepam, or CBD (100, 300, or 900 mg)

Readings taken at baseline (B, t=0 m), pre-speech (P, t=80 m), speech (S, t=153 m), and final (F, t=216 m)

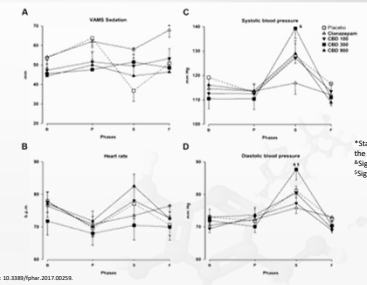


*Statistically significant differences compared with placebo.
†Significant difference compared with CBD 900 mg.
‡Significant difference compared with CBD 100 mg.

VAMS, visual analog mood scale.
Zuardi AW. *Front Pharmacol*. 2017. doi: 10.3389/fphar.2017.00259.

31

CBD on Sedation and Hemodynamics During Stress



*Statistically significant differences compared with the other groups.
‡Significant difference compared with clonazepam.
†Significant difference compared with CBD 100 mg.

Zuardi AW. *Front Pharmacol*. 2017. doi: 10.3389/fphar.2017.00259.

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CBD Impact on Public Speaking Stress/Relaxation

Public Speaking Stress Studies		
Bergamaschi 2011 (N=24)	Patients with untreated social anxiety disorder; randomized, double-blind, placebo-controlled, single-dose; CBD or placebo was also included for comparative purposes **Evaluations**: Baseline, 80 min after ingestion (pre-test), immediately before speech (anticipatory), during speech, and 15 and 35 minutes post speech	CBD 600 mg (STI Pharmaceuticals and THC Pharmaceuticals) or placebo; oral
Results: CBD 600 mg significantly reduced VAMS-anxiety, VAMS-discomfort, and VAMS-cognitive impairment during the speech vs placebo. No significant benefits on VAMS occurred vs placebo during pre-test, anticipatory phase, and 15 and 35 min post-speech. CBD 600 mg significantly reduced SSPS-N scores vs placebo both in the anticipatory phase and during the speech but not at other time periods. **Conclusion**: Pre-medicating with CBD 600 mg reduced anxiety.		
Zuardi 2017 (N=60)	Normal volunteers, randomized, double-blind, placebo-controlled, AC, single-dose **Evaluations**: Baseline, 80 min after ingestion (pre-test), during speech, and 60 min post-speech	CBD 100, 300, 900 mg (BSPG-Pharm), placebo or clonazepam 1 mg; oral
Results: VAMS-anxiety significantly reduced with clonazepam during and 1 hour after the speech, and it was reduced with CBD 300 mg 1 hour post-speech vs placebo. CBD 300 mg patients had higher SBP and DBP during public speaking than clonazepam patients. No other differences observed between groups at other times. **Conclusion**: Pre-medicating with CBD 300 mg reduced anxiety after public speaking.		
Linares 2018 (N=57)	Normal volunteers, randomized, double-blind, placebo-controlled, single-dose **Evaluations**: Baseline, 90 min after ingestion (pre-test), immediately before speech (anticipatory), during speech, immediately after speech, and 30 min post speech	CBD 150, 300, 600 mg or placebo; oral
Results: VAMS-anxiety significantly reduced with CBD 300 mg during the speech vs placebo but not with the other 2 doses of CBD. No other VAMS-anxiety differences observed between groups at other times, although all of the CBD groups were qualitatively lower than the placebo group at all evaluable time points. **Conclusion**: Pre-medicating with CBD 300 mg reduced anxiety during public speaking.		

DBP, diastolic blood pressure; SBP, systolic blood pressure.
White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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CBD Impact on Non-public Speaking Stress/Relaxation

Crippa 2004 (N=10)	Randomized, double-blind, placebo-controlled, CO; single-dose **Evaluations:** VAMS 30 min before drug ingestion, at the time of drug ingestion, at 60 min (at the time of stressor (cannula insertion) and at 75 min afterwards	CBD 400 mg (THC Pharmaceuticals) or placebo; oral
Results: CBD 400 mg significantly reduced VAMS-anxiety scores and increased VAMS-mental sedation scores significantly at both 60 and 75 minutes after ingestion vs placebo. **Conclusion**: CBD has anxiolytic and sedative properties.		
Bhattacharyya 2010 (N=15)	Randomized, double-blind, AC, single-dose; drugs taken 1 hour before fMRI scanning (scanning lasted for 1 hour; assessments made at baseline (drug admin), 1 hour (begin scan), 2 hours (end scan), and 3 hours (post scan); viewing fearful faces and visual and auditory stimulation tasks were given.	CBD 600 mg (THC Pharmaceuticals), placebo, THC 10 mg, or THC 10 mg + CBD 600 mg; oral
Results: CBD alone did not impact the PANNS, STAI, or VAMS scores vs placebo at any time point, but THC alone did. In a second phase, pre-treatment with CBD attenuated THC-induced PANNS score increases significantly at 30 minutes. **Conclusion:** CBD alone did not provide anti-anxiety or -psychotic effects but did attenuate the psychotic effects of THC.		
Das 2013 (N=48)	Randomized, double-blind, placebo-controlled, single-dose. Patients were shocked according to a room-specific pattern, and then the pattern was repeated but no shocks were given, both on the same day. CBD was given either before the second pattern occurred or after. Patients then came back another day to repeat the procedure. The MRS scale was determined before and after the procedures on both days.	CBD 32 mg (STI Pharmaceuticals) or placebo; inhaled (vaporized)
Results: CBD and placebo both reduced the MRS-anxiety score ; no significant differences occurred between them. **Conclusion**: CBD did not provide anti-anxiety effects.		
Arndt 2017 (N=38)	Randomized, double-blind, placebo-controlled, crossover, single-dose. Drug administered 2.5 hours before testing began. Mood evaluations conducted over 4.75 h.	CBD 300, 600, 900 mg (Insys Therapeutics) or placebo; oral
Results: POMS, IAPS, DEIT, ABT, CB, ES scales showed no differences between groups. **Conclusion**: CBD did not provide anti-anxiety effects after emotional, anxiety-producing stimuli.		
Hundal 2018 (N=32)	Randomized, double-blind, placebo-controlled, single-dose. 3D virtual reality (VR) provided the stressor. Evaluations conducted 130 min after taking CBD or placebo. Mood evaluations conducted at baseline and immediately after leaving the VR scenario. Cortisol, SBP, DBP, heart rate taken periodically throughout.	CBD 600 mg (GW Pharmaceuticals) or placebo; oral
Results: Anxiety outcomes (BAI, UMACL) and persecutory ideation outcomes (SPSS, CAPE) showed no significant differences between groups after the stressor. CBD showed trend toward increased anxiety via the BAI post-stressor (P=.09). No differences in cortisol, SBP, DBP, or heart rate between groups. **Conclusion**: CBD provided no anti-anxiety or persecutory ideation effects.		

STAI, State-Trait Anxiety Inventory.
White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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CBD Impact on Cannabis User Stress/Relaxation

Cannabis User Stress-Induced Anxiety Models		
Hindocha 2015 (N=48)	Randomized, double-blind, placebo-controlled, crossover, single-dose. Assessments: patients completed an emotional facial affecter cognition task including fearful, angry, happy, sad, surprised, and disgusted varying in intensity from 20% to 100%. Baseline evaluations conducted followed by drug inhalation, and re-testing began 10 minutes thereafter.	CBD 16 mg (STI Pharmaceuticals), THC 8 mg or placebo, inhaled (Vaporized)
Results: CBD and THC had no effect on VAS-anxiety scores. CBD enhanced correct facial recognition for facial images at 60% intensity but not the others, while THC reduced facial recognition at 40% intensity. **Conclusion**: CBD did not provide beneficial anti-anxiety effects.		
Studies in Patients Diagnosed With Social Anxiety Disorder		
Crippa 2011 (N=10)	Randomized, double-blind, placebo-controlled, crossover, single-dose. Evaluations of the VAMS were made 30 min before drug ingestion, at the time of drug ingestion, and at 60 min (cannula insertion), 75 min (stress period), and 140 min (post stress).	CBD 400 mg or placebo; oral
Results: Patients had severe baseline anxiety via SPIN and BSPS scores of >52 and >54, respectively. CBD group had lower VAMS-anxiety scores at 60, 75, and 140 minutes post dosing vs placebo, but there were no differences between groups for VAMS-mental or VAMS-physical sedation scores vs placebo. **Conclusion**: CBD therapy reduces anxiety during a stressful event.		

BSPS, Brief Social Phobia Scale; SPIN, Social Phobia Inventory.
Hindocha C. *Eur Neuropsychopharmacol*. 2015;25:325–34.
Crippa A. *Neuropsychopharmacology*. 2004;29:417–26.
White CM. *J Clin Pharmacol*. 2019. doi: 10.1002/jcph.1387.

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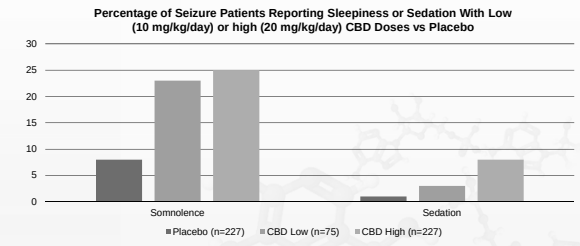
Chronic CBD Impact on Sleepiness and Relaxation



Epidiolex® (cannabidiol) prescribing information. Carlsbad, CA: Greenwich Biosciences; 2018.

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CBD Impact on Sleep Quality

- Four patients with Parkinson's disease-associated REM sleep behavior disorder assessed
  - Disorder is characterized by parasomnia characterized by the nightmares and loss of muscle atonia during REM sleep
  - One patient received 75 mg/day CBD, and 3 patients received 300 mg/day CBD
- At baseline, patients had between 2 and 4 episodes per week, but over 6 weeks, three of the patients had no events and the remaining patient (receiving 300 mg/day CBD) had a reduction to 1 episode per week

REM, rapid eye movement.
Chagas MH. *J Clin Pharm Ther.* 2014. doi: 10.1111/jcpt.12179.

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CBD Impact on Pain or Inflammation

- Only one controlled pain trial available
- Randomized, double-blind, multigroup crossover trial assessing pain and spasticity
  - Patients (N=24) with multiple pain and spasticity disorders were enrolled
    - Only 12 patients, 16 patients, and 8 patients completing the pain, spasm, and spasticity assessments, respectively
  - CBD group (titrated from 2.5 to 120 mg/24 hours) had significantly better but modest pain control (54.8 ± 22.6 vs 44.5 ± 22.7, P<.05)
  - No significant improvements in spasm (54.6 ± 19.1 vs 47.3 ± 22.6), spasticity (47.8 ± 18.5 vs 42.3 ± 18.1), bladder function (60.5 ± 28.4 vs 54.9 ± 28.8), or coordination (38.3 ± 22.9 vs 40.6 ± 21.1) compared with placebo

Wade DT. *Clin Rehabil.* 2003;17:21–9.

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Self Assessment Question #4:

- Orally administered CBD has adequate data to say that it controls which disease/disorder?
  a) Anxiety
  b) Parkinson's disease
  c) Seizures

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Topical Effects of CBD Products

Local Administration, Local Action

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Topical Delivery of CBD

- Hammell 2016
  - Four days of administration (CBD gel) to rats
  - Treatment with high doses of CBD (6.2 and 62 mg/day) reduced immunoreactivity to the levels in naïve animals
  - CFA + low dose CBD = 272 ± 46, p > 0.05 vs. CFA + VEH
  - CFA + high-dose CBD = 144 ± 28, p < 0.05 vs. CFA + VEH

Hammell DC. Eur J Pain. 2016;20(6):936–948.

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Topical CBD for Acne

- Study 1: Researchers administered CBD to cultured human sebocytes and human skin organ culture, which inhibited the lipogenic actions of various compounds (arachidonic acid, linoleic acid, and testosterone) and suppressed sebocyte proliferation and lipogenesis
- Study 2: Male volunteers applied a cannabis seed extract (3%) in a vehicle to one cheek or a vehicle alone to the other cheek for 12 weeks
  - Researchers found a significant reduction in sebum production with cannabis extract (P<.05)
  - The contribution of CBD to these effects vs other cannabinoids and terpines is unknown

CB, cannabinoid.
Olah A. *J Clin Invest*. 2014;124:3713–24.
Ali A. *Pak J Pharm Sci*. 2015;28:1389–95.

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Topical Penetration of CBD

- Epidermolysis bullosa
  - Group of rare skin disorders characterized by thickened but frail skin and painful blisters
- 3 cases of self-initiated topical CBD in patients with epidermolysis bullosa
  - All 3 reported faster wound healing, less blistering, and amelioration of pain

Chellia MP. Pediatr Dermatol. 2018;35(4):e224-e227.

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Transdermal Effects of CBD Products

Local Administration, Systemic Action

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Transdermal Delivery of CBD

- CBD with ethosomal penetration enhancement
  - In vivo abdominal application of ethosomal CBD 100mg (in a patch) to CDI nude mice for 24 hours before intra-right paw injection of carrageenan (joint damaging substance)
  - Swelling for 4 hours after injection assessed

Lodzki M. J Control Release. 2003;93(3):377-87.

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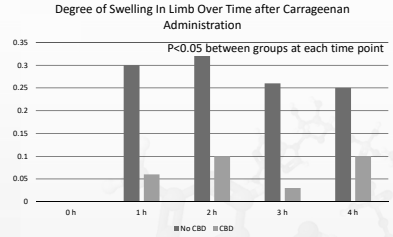
Transdermal Delivery of CBD



Lodzki M. J Control Release. 2003;93(3):377-87.

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Zygel® in Patients with Seizures (STAR 1 Trial)

- In a larger study of patients with epilepsy (called the STAR 1 trial)
- Zygel® 195mg/day (given as 97.5mg twice daily) or 390mg/day (given as 195mg twice daily) was used for 12 weeks
- Zygel® 195mg/day and 390mg/day nonsignificantly reduced seizure frequency from baseline by 18.4% and 14.0% versus an 8.7% reduction for placebo (p=0.89 and p=0.32)

Bonn-Miller M. American Epilepsy Society Annual Meeting. Houston, TX. December 2-6, 2016.

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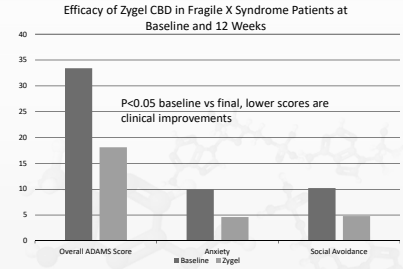
Zygel® in Patients with Fragile X Syndrome

- In a small clinical trial of patients with Fragile X syndrome, therapy was initiated with Zygel® 50mg/day and then maintained or titrated up (if needed) to a maximum dose of 200mg/day



Bonn-Miller M. Military Health System Research Symposium. Orlando, FL. August 15-18, 2016.; 19.; Heussler H. International Fragile X Conference. Cincinnati, OH. July 12, 2018.

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Self Assessment Question #5

- Which of the following things can be said about topical or transdermal CBD?
  - CBD cannot get absorbed in the blood stream through the skin regardless of formulation
  - CBD in the right formulation can enter the blood stream
  - CBD has been proven to treat topical pain and inflammation as well as acne

Conclusions

- CBD is one of many components of *Cannabis sativa*
  - You cannot assume all the benefits of *C.* will be seen with CBD alone
- CBD is promising as a calming agent before acute stressors, and while it can cause sedation it is less sedating than benzodiazepines
  - CBD needs higher-quality and longer-term data
- CBD can cause somnolence, and in Parkinson's disease REM disorder, may provide benefits
  - CBD can also rarely cause irritability
- CBD may have modest pain relieving effects, but this requires further study
- CBD may be an effective additive for topical administration based on pharmacology but needs studies showing benefits
- CBD has adverse events that are dose related and has drug interaction potential with CYP3A4 inhibitors, CYP inducers, and other CYP substrates
- CBD has rarely been shown to raise liver function tests, but this is dose related and occurs mostly with concomitant liver-damaging drugs