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, terpenes) of the Cannabis Sativa plant.
  - Describe the legal status of CBD on the state level, when isolated or when included with other constituents (cannabinoids, terpenes) 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 terpenes
- 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-831885/
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?

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.

- **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.

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.

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.

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) Crinkle-Redden amendment
  b) Rohrabacher-Farr amendment
  c) Farralle-Tartullo amendment

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.
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

CBD Quality Control

- Epi10 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
- 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: 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
Endocannabinoid System

- Complex homeostasis-protecting system
- Anandamide and 2-arachidonylglycerol
  - Endogenous cannabinoids
- Exert effects via CB1 and CB2 receptors
- Stimulation of CB1 and CB2 receptors can yield opposing, modified, or complimentary effects

CBD Pharmacology - In Vitro and Animal Effects

Receptor Effects

- CB1 antagonist - Attenuation of impaired learning, memory, hypothermic, and psychosis effects induced by delta-9-THC
- CB2 inverse agonist - Binds but induces a pharmacological response opposite of agonist - Anti-inflammatory effects
- TRPV1 agonist - Anti-inflammatory, pain relieving, and sebum producing effects
- Adenosine enhancer - Anti-inflammatory effects
- GPR55 antagonist – Anti-proliferative effects

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
- Transdermal CBD pharmacokinetics not available, but modest molecular size may enhance penetration and bioavailability while high lipophilicity might impede it

CBD Drug Interactions

Impact of CYP Inducers and CYP3A4 Inhibitors on CBD C_{max} and AUC (% change)

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 clonazepam and its N-desmethylclonazepam metabolite assessed in 13 patients
  - Clonazepam and N-desmethylclonazepam levels increased by 60% and 500% after 4 weeks of concomitant therapy

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

CBD-Induced Adverse Events at Low (10 mg/kg/day) or High (20 mg/kg/day) Doses vs Placebo (% of People With Event)
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.

Zygel® (STAR 1 Trial): ADE Breakdown

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zygel 15mg/day</th>
<th>Zygel 30mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (%)</td>
<td>3</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Application Site Dryness (%)</td>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Application Site Itchiness (%)</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Headache (%)</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

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 but the risk is dose related

Epidiolex CBD in Epilepsy Syndromes

<table>
<thead>
<tr>
<th>% Reduction in Seizures</th>
<th>Placebo</th>
<th>CBD 10mg/kg</th>
<th>CBD 20mg/kg</th>
<th>CBD 30mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet</td>
<td>0.013</td>
<td>0.007</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Lennox–Gestaut</td>
<td>0.013</td>
<td>0.007</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

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.
CBD Impact on Public Speaking Stress/Relaxation

Patients (N=60) randomized to placebo, clonazepam, or CBD (100, 300, or 600 mg)

Readings taken at baseline (B, t=0 min), post-speech (P, t=80 min), during speech, and 75 min after ingestion (pre-test), immediately before speech (pre-speech, t=153 min), and after the stressor (cannula insertion) and at 35 min afterwards.

CBD Impact on Cannabis User Stress/Relaxation

Patients (N=227) randomized to placebo, clonazepam, or CBD (100, 300, or 600 mg)

Readings taken at baseline (B, t=0 min), post-speech (P, t=80 min), during speech, and 75 min after ingestion (pre-test), immediately before speech (pre-speech, t=153 min), and after the stressor (cannula insertion) and at 35 min afterwards.

CBD Impact on Non-public Speaking Stress/Relaxation

Patients (N=10) randomized to placebo, clonazepam, or CBD (100, 300, or 600 mg)

Readings taken at baseline (B, t=0 min), post-speech (P, t=80 min), during speech, and 75 min after ingestion (pre-test), immediately before speech (pre-speech, t=153 min), and after the stressor (cannula insertion) and at 35 min afterwards.

CBD Impact on Cannabis User Stress/Relaxation

Patients (N=227) randomized to placebo, clonazepam, or CBD (100, 300, or 600 mg)

Readings taken at baseline (B, t=0 min), post-speech (P, t=80 min), during speech, and 75 min after ingestion (pre-test), immediately before speech (pre-speech, t=153 min), and after the stressor (cannula insertion) and at 35 min afterwards.
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

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 ± 22.6 vs 40.6 ± 21.1) compared with placebo

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

Topical Effects of CBD Products

Local Administration, Local Action

Topical Delivery of CBD

- Hammell 2016
  - Four days of administration (CBD gel) to rats
  - Treatment with high doses of CBD (62 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

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 and 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 terpenes is unknown
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


Transdermal Effects of CBD Products
Local Administration, Systemic Action

Transdermal Delivery of CBD

- CBD with ethosomal penetration enhancement
  - In vivo abdominal application of ethosomal CBD 100mg (in a patch) to C57Bl/6J nude mice for 24 hours before intra-right paw injection of carrageenan (joint damaging substance)
  - Swelling for 4 hours after injection assessed


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 2016.

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

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 high-quality and long-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