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See, Be, Deceived…or Relieved?
Evaluating CBD for Pain Management

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Disclosure

Honoraria: Quest Diagnostics

The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs, as well as employers, employee affiliates and/or pharmaceutical companies mentioned or specific drugs discussed.

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Learning Objectives

- Compare the mechanism of action (MOA) and effects on the nervous system between marijuana (THC) and cannabidiol (CBD)
- Summarize the available published evidence on the use of CBD in pain management, including studied dosage forms and pain indications
- Review the potential implications of prescribing or recommending CBD for pain management

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What are cannabinoids?[1]

- Endocannabinoids (brain-derived) vs. Phytocannabinoids (plant-derived) vs. Synthetic cannabinoids (laboratory-derived)
- Endogenous endocannabinoids include anandamide and 2-arachidonylglycerol
- Most well-known phytocannabinoids include *cannabidiol (CBD)* and *tetrahydrocannabinol (THC)* – typically derived from flowers and leaves
- The endocannabinoid system (ECS) is involved in the body's process for maintaining homeostasis and connecting the various organs and systems

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CBD Mechanism of Action (MOA)[1-4]

- Nonintoxicating
- Negative allosteric modulator of CB_1
- CB_2 receptor antagonist
- Agonist activity at 5HT-receptor
- Stimulation of vanilloid receptor type 1 (TRPV1)
- Protective against inflammatory tissue injury via attenuation of reactive oxygen species generation
- US sales of CBD are projected to reach >$20 million by 2024
- 6/22/21 search of ClinicalTrials.gov found 20+ studies looking at cannabidiol or combination CBD products for chronic pain management in various stages of completion

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Boyaji et al's Comparison of THC with CBD[5]

Property/Function	THC	CBD
CB1 receptor	Partial agonist, with high binding affinity	Noncompetitive negative allosteric modulator
CB2 receptor	Partial agonist	Receptor modulator
TRPV1, TRPA1 receptors	---	Receptor modulator
Metabolism	Hepatic cytochrome 450 (CYP450) isoenzymes, especially 2C9 and 3A4	Hepatic cytochrome 450 (CYP450) isoenzymes
Psychoactive	Yes	No
Analgesic properties	Yes	Yes
Anxiolytic	---	Yes
Anticonvulsant	---	Yes
Anti-inflammatory	Yes	Yes

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CBD and THC: A History[6]

- Likely started growing in Asia around 500 BC as herbal medicine
- From Asia, the hemp plant was introduced around the world
- Hemp fiber was used to make clothing, paper, sails, and rope and the seeds were used as food
- After ~800 AD: Hashish used in the Middle East and parts of Asia
- 1830s: Sir William Brooke O'Shaughnessy, an Irish doctor studying in India, found that cannabis extracts could help those with cholera
- Late 1800s: cannabis extracts sold in pharmacies and doctors' offices to treat various ailments
- Early 1900s: Recreational marijuana use introduced in the US
- By 1931 (Prohibition era): 29 states outlawed cannabis
- Marijuana Tax Act of 1937: first federal U.S. law to criminalize marijuana nationwide

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CBD and THC: A History[6]

- Signed by President Richard Nixon
- Repealed the Marijuana Tax Act and listed marijuana as a Schedule I drug

Controlled Substances Act of 1970

1972 "Marijuana: A Signal of Misunderstanding"

- Report from the National Commission on Marijuana and Drug Abuse

- CA is the first state to legalize marijuana for medicinal use by people with severe or chronic illnesses

Compassionate Use Act of 1966

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CBD and THC: A History[7]

As of May 18, 2021: 36 states and 4 territories allow for the medical use of cannabis products.

As of June 22 2021: 18 states, two territories and the District of Columbia have enacted legislation to regulate cannabis for adult use.

Approved measures in 11 states allow use of "low THC, high cannabidiol (CBD)" products for medical reasons in limited situations or as a legal defense.

At the federal level, marijuana remains classified as a Schedule I substance under the Controlled Substances Act

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CBD: Legal or Illegal?[8-9]

- Cannabis plants with higher levels (>0.3%) of THC are considered 'marijuana' and are federally illegal in the U.S
- Low THC (<0.3%) cannabis plants (hemp) and its extracts were recently deemed federally legal in the U.S. via pilot programs in Section 7606 of the 2014 Farm Bill - made permanent via the 2018 Farm Bill
- Interim Final DEA Rule from August 2020: Implementation of the Agriculture Improvement Act of 2018:
  - Definition of "Tetrahydrocannabinols" does not include "any material, compound, mixture, or preparation that falls within the definition of hemp set forth in 7 U.S.C. 1639o."
  - Removes from control in schedule V under 21 CFR 1308.15(f) a "drug product in finished dosage formulation that has been approved by the U.S. Food and Drug Administration that contains cannabidiol (2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol) derived from cannabis and no more than 0.1% (w/w) residual tetrahydrocannabinols."
  - Modifies 21 CFR 1308.11(d)(58) by stating that the definition of "Marihuana Extract" is limited to extracts "containing greater than 0.3 percent delta-9-tetrahydrocannabinol on a dry weight basis."

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What is Δ-8?[10-11]

US sales in 2021 increased by 144% compared to last year

Variable dosage forms: vapes, gummies, tinctures and flower

Legality limbo

Recipes to "home cook" from CBD

More relaxing, "THC-light" high

Naturally occurring compound found in marijuana plants

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Epidiolex® [12]

- Cannabidiol oral solution (100mg/mL)
- Approved in the US in 2018
- **FDA-approved indication:** treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome [maintenance dose: 5 mg/kg twice daily (10 mg/kg/day)], or tuberous sclerosis complex [maintenance dose: 12.5 mg/kg twice daily (25 mg/kg/day)] in patients 1 year of age and older
  - Dose adjustment recommended in moderate to severe hepatic impairment
- Prior to starting therapy, obtain AST/ALT and total bilirubin levels
  - Recheck at 1 month, 3 months, and 6 months after initiation of treatment and periodically thereafter or as clinically indicated
- **Warnings/precautions:** hepatocellular injury, somnolence/sedation, and suicidal behavior/ideation

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Epidiolex® [12]

- **Drug interactions:**
  - Strong CYP3A4 or CYP2C19 Inducers
    - Ex: rifampin
  - UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 Substrates
    - UGT1A9 such as propofol and fenofibrate
    - UGT2B7 such as lamotrigine, morphine or lorazepam
    - CYP1A2 such as caffeine and tizanidine – may see increased exposure to applicable substrates
    - CYP2B6 such as bupropion – consider dose adjustment
    - CYP2C9 such as phenytoin
    - CYP2C19 such as diazepam – consider dose ↓ in substrates
  - Consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced

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Epidiolex® [12]

Adverse Reactions

- In Lennox-Gaustat syndrome and Dravet syndrome: somnolence, ↓appetite, diarrhea, ↑transaminases, fatigue, malaise, asthenia, rash, insomnia, sleep disorder, poor quality sleep, and infection
- In tuberous sclerosis complex: diarrhea, ↑transaminases, ↓appetite, somnolence, pyrexia, and vomiting

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Epidiolex® approval vs. General CBD[3]

- Epidiolex® was approved for 2 disorders associated with substantial morbidity and mortality
  - These disorders are generally resistant to previously approved anticonvulsant medications
- Risk:benefit profile for approving CBD for pain is not the same

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Other commercially available cannabinoid products[4,13-14]

Nabiximols

- Not currently approved by the FDA for use in the United States
- Approved in 29 countries total
- Oromucosal spray
- 27mg THC and 25mg CBD per mL
- 2.7mg THC and 2.5mg per single spray/actuation
- "indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy"

Dronabinol

- FDA approved for:
  - Anorexia associated with weight loss in patients with AIDS
  - Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
- Capsules (2.5mg, 5mg and 10mg)
- Synthetic THC

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CBD and Chronic Pain: Literature Review

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Wade et al.[15-16]

- Double-blind, randomized placebo-controlled crossover study
- **Study size:** 24 patients with known neurological diagnosis unresponsive to standard pain treatments
- 20 patients completed → 14 multiple sclerosis (MS), 4 spinal cord injuries (SCI), 1 brachial plexus lesion with neuropathy, 1 phantom limb pain s/p amputation
- **Intervention:** Whole-plant cannabis medicinal extracts (CME) of 2.5mg/spray THC, 2.5mg/spray CBD, 1:1 CBD:THC, or matched placebo (sublingual spray)
  - 2 week open-label THC:CBD use, then 8 week double-blind phase with four 2-week stages using one of the CMEs
- **Outcomes:** CBD significantly improved pain; THC significantly improved pain, muscle spasm, spasticity and appetitie; THC:CBD significantly improved muscle spasm and sleep

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Notcutt et al.[15,17]

- Double-blind, randomized placebo-controlled crossover study
- **Study size:** 34 patients with chronic uncontrolled neuropathic pain [ex: MS, variety of back pain, complex regional pain syndrome (CRPS)]
  - Required patients to abstain from driving during the study
  - 2 patients withdrew from the study
- **Intervention:** sublingual spray and each actuation delivered 2.5 mg of THC, 2.5 mg CBD, or 2.5 mg THC + 2.5 mg CBD (THC:CBD) or matching placebo in 0.1 ml
  - Each patient received each Cannabis Based Medicinal Extracts (CBME) and placebo for two separate 1-week periods
  - Non-cannabinoid medication for BTP was allowed and documented
- **Outcomes:** THC and THC:CBD did better than placebo in terms of addressing the main symptom ($p < 0.01$ and $p < 0.05$, respectively) and secondary symptom ($p < 0.001$ and $p < 0.054$, respectively)
  - Of the 28 who benefitted from CBME, 11 preferred THC:CBD; 14 found THC and THC:CBD equally satisfactory; 2 preferred THC; and 2 found THC and CBD equally satisfactory

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Capano et al.[8,15]

- Prospective, single-arm cohort study, 8 weeks long
- **Study size:** 97 patients completed the study; moderate to severe chronic pain for ≥3 years with stable opioid regimen for at least 1 year (MEDD required to be ≥50)
- **Intervention:** each soft gel contained 15.7 mg CBD, 0.5 mg THC, 0.3 mg cannabidivarin (CBDV), 0.9 mg cannabidiolic acid (CBDA), 0.8 mg cannabichrome (CBC), and >1% botanical terpene blend (94 of 97 patients)
- **Outcomes:** Over half of chronic pain patients (53%) reduced or eliminated their opioids within 8 weeks after adding to their regimens. Almost all CBD users (94%) reported quality of life improvements. The results indicated a significant relationship between CBD and PSQI ($p = 0.003$), and PEG ($p = 0.006$). There was a trend toward improvement but no significant relationship between CBD use and PHQ and PDI.

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Cunetti et al.[15,18]

- Open-label study evaluating kidney transplant patients with chronic pain who requested to trial CBD for pain
- **Study size:** 7 patients over 3 weeks
- **Intervention:** CBD initial dose at 100mg/day with titration up to 300mg/day
  - CBD dose reduction to 50mg/day in 1 patient due to side effects
- **Outcomes:** 2 patients had total pain improvement, 4 had a partial response in the first 15 days, and in 1 there was no change
  - 3 patients had change in tacrolimus level at some time during the study; 1 patient's level normalized without dose adjustment in tacrolimus and 2 patients' levels required dose adjustment of tacrolimus
    - Adverse effects reported were nausea, dry mouth, dizziness, drowsiness, and episodes of intermittent heat

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van de Donk et al.[1-2,15]

- Single center, double-blind, randomized placebo-controlled 4-way crossover trial
- **Study size:** 20 female chronic pain patients with fibromyalgia completed the study
- **Intervention:** 4 different cannabis varieties administered as a vapor - Bedrocan (22.4mg THC, <1mg CBD), Bediol (13.4mg THC, 17.8mg CBD), Bedrolite (18.4mg CBD, <1mg THC), and placebo variety
  - Excluded patients on "strong opioids or other painkillers except paracetamol and/or ibuprofen"
  - Product met 2 of the Mayo Clinic's Checklist items
- **Outcomes:** pain rating on 11-point visual analogue scale (VAS), pressure pain test, and electrical pain test plus 2 questionnaires to assess the effect of drug treatment on mental and psychoactive cannabis effects
  - None of the treatments had an effect greater than placebo on spontaneous pain scores or electrical pain responses; both Bedrocan and Bediol caused a significant increase in tolerance to the pressure pain test
  - CBD inhalation increased THC plasma concentrations but diminished THC-induced analgesic effects

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CBD Considerations

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Mayo Clinic's Checklist for Finding High Quality CBD and Hemp Oil Product[1]

1. Does it meet the following quality standards? a) Current Good Manufacturing Practices (CGMP) certification from the US Food and Drug Administration b) European Union (EU), Australian (AUS), or Canadian (CFIA) organic certification c) National Science Foundation (NSF) International certification
2. Does the company have an independent adverse event reporting program?
3. Is the product certified organic or ecofarmed?
4. Have their products been lab tested by batch to confirm tetrahydrocannabinol levels <0.3% and no pesticides or heavy metals?

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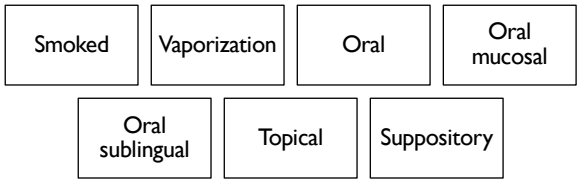
CBD Routes of Administration[4,15]



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Pharmacokinetic Considerations[4]

- Absorption is affected by product lipophilicity, bioavailability, and inherent organ tissue differences (such as alveolar (lung), dermal, or gastric)
  - Also affected by recent meal consumption, depth of inhalation, duration of breath holding, and temperature of vaporizer
- Absorption can vary by 20-30% orally vs. 10-60% via inhalation

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MacCallum et al's Administration Factors in Cannabis Delivery Methods[4]

Issue	Smoking/vaporization	Oral	Oromucosal	Topical
Onset (min)	5-10	60-180	15-45	Variable
Duration (h)	2-4	6-8	6-8	Variable
Pro	Rapid action, advantage for acute or episodic symptoms (nausea/pain)	Less odor, convenient and discrete, advantage for chronic disease/symptoms	Pharmaceutical form (nabiximols) available, with documented efficacy and safety	Less systemic effect, good for localized symptoms
Con	Dexterity required, vaporizers may be expensive, and not all are portable	Titration challenges due to delayed onset	Expensive, spotty availability	Only local effects

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General Risks with CBD[1,4,19-20]

- Liver toxicity
- Extreme sleepiness/somnolence
- Diarrhea
- Dizziness
- Dry mouth
- Decreased appetite
- Irritability
- Agitation
- Anxiety
- Nausea
- Cough, phlegm, bronchitis (smoking route only)
- Drug interactions
  - CNS depressants
- Product contamination
- Combining THC with CBD can minimize potential adverse effects

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CBD Product Quality[3,21]

- Bonn-Miller et al examined the content of 84 CBD products sold online
  - 42% under-labeled the content of CBD in the product
  - 26% over-labeled the CBD content
  - The CBD concentrations of the extracts analyzed varied more than 1000-fold (0.1 mg/mL to 655 mg/mL)
  - Substantial levels of THC were detected in 22% of the products

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Patient Case with CBD and UDS[22]

- A 63-year-old male with CRPS and CLBP presents to his pain management physician's office and reports using a CBD oil product for pain and sleep for the last month or so. Routine urine drug screen in clinic reveals a positive result for THC (as well as oxycodone, negative for all other substances tested). The patient adamantly denies using marijuana. Prescribed medications include omeprazole for GERD, lisinopril for HTN, atorvastatin for hyperlipidemia, and oxycodone/acetaminophen 5 mg/325 mg Q6H PRN pain.
- How would you address/interpret the UDS result?

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CBD in Pregnancy and Breastfeeding[19-20]

- No comprehensive research
- In pregnant test animals, high doses of CBD were found to cause issues with the reproductive system of developing male fetuses
  - Changes seen include: ↓ in testicular size, inhibition of sperm growth and development, ↓ circulating testosterone
- Likely that some amount of CBD will be transferred to babies via breast milk
- CBD product contamination can present risks to the fetus or breastfed baby
  - Contaminants such as pesticides, heavy metals, bacteria and fungus
- "FDA strongly advises that during pregnancy and while breastfeeding, you avoid using CBD, THC, or marijuana in any form."

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Cannabis Contraindications[4]

- Pregnancy
- Lactation
- Psychosis (except CBD-predominant formulations)
- Use with caution in unstable cardiac conditions
- Controversial: use in children and teens
- Controversial: use in addiction and dependency
- Avoid smoking in COPD and asthma

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Conclusion

- CBD and other variants or strains of marijuana have gained popularity with consumers
- Further studies are needed to better understand and characterize the mechanism of CBD and its role in chronic pain management
- Further studies are needed to better understand the implications of long-term CBD or cannabis use
- The route of administration and the formulation of CBD itself can impact its absorption and overall efficacy
- If prescribing a patient a CNS depressant(s) and they express interest in using a CBD or cannabis product, have a thorough discussion on the risks vs. benefits on the combination of medications
- CBD and cannabis use is NOT recommended in pregnant or lactating women

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Assessment Question #1

- Which of the following is NOT part of Mayo Clinic's Checklist for Finding High Quality CBD and Hemp Oil Product?

a) The product is certified organic or ecofarmed
b) Batch tested product to confirm THC levels <0.3%
c) The product is endorsed by Amazon and advertised on TV
d) The product has a Current Good Manufacturing Practices (CGMP) certification from the US Food and Drug Administration

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Assessment Question #2

- Patient tested positive for THC. He then reports use of CBD. You are asked to interpret the results. Which of the following is correct?

a) CBD products never cause a positive THC result
b) CBD products may cause positive result because they may contain THC
c) CBD products are highly regulated by the FDA to ensure less than 0.3% of THC
d) CBD products will always lead to THC positive result

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Assessment Question #3

- Which of the following is an important counseling point when discussing CBD use with a chronic pain patient?

a) CBD products are not regulated and therefore can contain contaminants, some of which could be dangerous, or may not contain the ingredients as listed/advertised
b) CBD can interact with other medications (prescription or OTC)
c) The route of administration of CBD is variable depending on the study and can affect the onset of action, potential for adverse effects, and bioavailability
d) All of the above

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QUESTIONS?

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