Medical Marijuana and Cannabidiol (CBD): Perceptions vs Facts

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UW Health
Newsweek
Pop Culture Says CBD Cures Everything—Here's What Scientists Say

The New York Times
Ads Pitching CBD as a Cure-All Are Everywhere. Oversight Hasn't Kept Up.

CBC.ca
CBD oil is seen as a magic elixir — but the jury is still out on its medical effectiveness

The Washington Post
Opinions
The CBD craze is getting out of hand. The FDA needs to act.

USA TODAY
Sketchy THC vape products. Sneaky teens. How patchwork regulations on e-cigarettes led to health crisis

Forbes
AARP Takes Medical Marijuana Mainstream
Learning Objectives

• Summarize the prescription and commercial cannabis and cannabidiol products available
• Analyze literature on effectiveness of cannabis and cannabidiol products for various indications
• Discuss common drug interactions with cannabis and cannabidiol products
• Describe common adverse effects of cannabis and cannabidiol products
History of Medicinal Cannabis Use

• Cannabis plants originated in Central and South Asia
• 2700 BC - Initial medicinal use (China)
• 390 - Inhaled cannabis for pain during childbirth (Jerusalem)
• 800 - Liquid cannabinol for wound dressing (Western Europe)
• 1839 - Cannabis extracts for cholera, infantile convulsions, tetanus (Ireland)
• 1850 - Described in the United States Pharmacopoeia (removed in 1942)
• 1863 - Cannabis with opium prescribed for dysentery and diarrhea (US)
Evolution of Laws & Regulation

- **1920s** - International treaty controls trade of cannabis and Narcotic Drugs Import and Export Act passed in US
- **1937** - Marijuana Tax Act passed resulting in federal restriction on use and sale of cannabis
- **1951** - Boggs Act passed setting mandatory sentences for drug convictions (criminalization)
- **1970** - Controlled Substances Act (CSA) outlawed growing and selling of both hemp and marijuana
Evolution of Laws & Regulation

1996 Proposition 215 - California passes state law allowing use of medical marijuana

- Similar laws passed in additional states
  - 1990s - Oregon, Washington, Alaska, Maine and District of Columbia
  - 2000s - Nevada, Montana, Colorado, New Mexico, Hawaii, Vermont, Rhode Island, Maryland, Michigan, New Jersey

Types of state cannabis programs

- Adult recreational use – allows possession & use of small amount of marijuana (14 states)
- Comprehensive medical use - protection from criminal penalties; allows dispensaries, variety of strains/products, smoking/vaping, NOT a limited trial program (33 states)
- CBD/Low THC - limits THC content, may limit source of products and medical conditions (13 states)
State Cannabis Programs

Limited adult possession and growing allowed, no regulated production or sales. DC, VT

Evolution of Laws & Regulation

• 2018 Agriculture Improvement Act ("Farm Bill") changed authority for production and marketing of hemp
  • “Cannabis plants and derivatives that contain no more than 0.3% THC on a dry weight basis,” are no longer considered controlled substances
• However, FDA still has authority to regulate products containing cannabis or cannabis-derived compounds
  • Regulation per Federal Food, Drug, and Cosmetic (FD&C) Act and section 351 of the Public Health Service (PHS) Act
US Food & Drug Administration (FDA)

• Held a public hearing for “Products Containing Cannabis or Cannabis-Derived Compounds” on May 31, 2019
  • Gather scientific data and information regarding safety, manufacturing, product quality, marketing, labeling, and sale of products
  • Participants included government officials, researchers, physicians, pharmacists, consumers, manufacturers, retailers
  • Docket open for public comments through July 16, 2019
Cannabis

• *Cannabis sativa* (hemp) vs *Cannabis indica*
  • Contain >100 cannabinoids
    • Most common cannabinoids are:
      • cannabinol (CBD)
      • delta-9-\text{tetrahydrocannabinol} (THC)
    • THC and CBD have different receptor affinity and activity in the body
  • Terpenes vary by strain
CBD vs THC

• **Cannabidiol (CBD)** - a non-psychoactive phytocannabinoid

• **Delta-9-tetrahydrocannabinol (THC)** - a psychoactive phytocannabinoid

• Medical marijuana - contains both CBD and THC, recommended by a physician for certain conditions
Mechanism of Action

CBD receptor activity
- Equilibrative nucleoside transporter (ENT), G-protein-coupled receptor (GPR55), and transient receptor potential melastatin type 8 (TRPM8) blockers (antagonists)
- Serotonin (5-HT1A), adenosine A2A (ADORA2A), transient receptor potential ankyrin type 1 (TRPA1), and alpha 1 & 3 glycine (GLRA1, GLRA3) activity
- Transient receptor potential vanilloid type 1 (TRPV1) and type 2 (TRPV2), and peroxisome proliferator-activated receptor gamma (PPARγ) activity

THC receptor activity
- Partial agonist cannabinoid type 1 (CB1) and type 2 (CB2)
HUMAN CANNABINOID RECEPTORS

**CB1**
Receptors are concentrated in the brain & the central nervous system but are also present in some nerves and organs.

**CB2**
Receptors are mostly in peripheral organs, especially cells associated with the immune system.

**TRPV1**
Receptors are concentrated in the blood, bone, marrow, tongue, kidney, liver, stomach & ovaries.

**TRPV2**
Receptors are concentrated in the skin, muscle, kidney, stomach & lungs.

**GPR 18**
Receptors can be found primarily in bone marrow, the spleen and lymph nodes, and to a lesser extend the testes.

**GPR 55**
Receptors are found in the bones, the brain, particularly the cerebellum, and the jejunum and ileum.

**GPR 119**
Receptors are found predominantly in the Pancreas and the intestinal tract, in small amounts.
The Endocannabinoid System (ECS)

- Involved in regulating homeostasis
- Chronic inflammation, immune system
- Endogenous cannabinoids
  - Anandamide
  - 2-arachidonylglycerol (2-AG)

Pharmacokinetics of CBD

**Absorption**
- Bioavailability 31% (inhalation), 6% (oral)
- Onset up to 4 h (Tmax)

**Distribution**
- Volume of distribution 32 L/kg
- Protein binding >94%

**Metabolism**
- Hepatic and gut CYP enzymes

**Excretion**
- Half-life- 1.4-10.9 hours (oromucosal spray), 2-5 days (oral), 24 hours (IV), 31 hours (inhalation)
Pharmacokinetics of THC

**Absorption**
- Bioavailability 10-35% (inhalation)
- Onset up to 4-6 h (Tmax)

**Distribution**
- Volume of distribution 1-10 L/kg
- Protein binding 95-99%

**Metabolism**
- Hepatic and gut CYP enzymes

**Excretion**
- Half-life- 25 hours (oral), 20-36 hours (IV)
Objective #1

• Summarize the prescription and commercial cannabis and cannabidiol products available
Dronabinol

• synthetic delta-9-tetrahydrocannabinol (THC)
• FDA approval in 1985
• Schedule III (capsule) and schedule II (oral solution) controlled substance

• Indications
  • appetite stimulant for HIV/AIDS, chemotherapy-induced nausea & vomiting (CINV)

• Duration of action
  • 4-6 hours (psychoactive effects), ~24 hours (appetite stimulation)
Dronabinol

• Dosage forms
  • 2.5 mg, 5 mg, and 10 mg capsules
  • 5 mg/mL oral solution*

• Dosing
  • Capsules
    • 2.5 mg twice daily before meals, max dose 20 mg/day (appetite)
    • 5 mg 1-3 hours before chemo and every 2-4 hours after chemo, max dose 15 mg/dose (CINV)
  • Oral solution
    • 2.1 mg twice daily before meals, max dose 16.8 mg/day (appetite)
    • 4.2 mg 1-3 hours before chemo and every 2-4 hours after chemo, max dose 12.6 mg/dose (CINV)
  • No renal or hepatic dose adjustments

• Administration
  • High fat/high calorie meals increase absorption
Nabilone

• FDA approval in 2006
• Synthetic cannabinoid (similar to THC)
• Schedule II controlled substance
• Indication
  • Refractory nausea and vomiting associated with chemotherapy (CINV)
Nabilone

• Dosage form
  • 1 mg capsule

• Dosing
  • 1-2 mg twice daily (max dose 6 mg/day)
  • No renal or hepatic dose adjustments

• Administration
  • Give 1-3 hours prior to chemotherapy
Cannabidiol

• FDA approval in 2018
• Schedule V controlled substance
• Indication
  • treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients ≥2 years old
Cannabidiol

• Dosage form
  • 100 mg/mL oral solution
  • Strawberry flavor

• Administration
  • Take consistently with or without food
  • Discard after 12 weeks of opening bottle
Cannabidiol

• Dosing
  • 2.5 mg/kg twice daily; may increase after 1 week to 5 mg/kg twice daily (max dose 10 mg/kg twice daily)
  • Hepatic impairment
    • Moderate (Child-Pugh class B)- 1.25 mg/kg twice daily; may increase after 1 week to 2.5 mg/kg twice daily (max dose 5 mg/kg twice daily)
    • Severe (Child-Pugh class C)- 0.5 mg/kg twice daily; may increase after 1 week to 1 mg/kg twice daily (max dose 2 mg/kg twice daily)
  • No renal dose adjustments
Nabiximols

• Investigational drug in US (not FDA approved)
• Available in 25 countries (including Canada and UK)
• CDSA-II controlled substance
• Nonsynthetic 1:1 THC and CBD preparation
Nabiximols

• Indication
  • Spasticity or neuropathic pain associated with multiple sclerosis (MS), cancer pain

• Dosage form
  • THC 27 mg/CBD 25 mg/mL buccal liquid
Nabiximols

• **Dosing**
  - Initial: 1 spray twice daily on first day
  - Titration: Increase by 1 spray daily as needed/tolerated
  - 4 to 8 sprays daily (max dose 12 sprays/day)*
  - No renal or hepatic dose adjustments (has not been studied)

• **Administration**
  - Shake well
  - Prime for initial use
  - 15 minutes between sprays
Commercial CBD & THC Products

Commercial CBD Products

• Are commercial CBD products FDA-approved?
  • No

• Per the FD&C Act, “if a product is intended to have a therapeutic or medical use, it is a drug”

• Commercial drug products
  • Premarket approval through the New Drug Application (NDA)
  • Conform to a "monograph" for a particular drug category through Over-the-Counter (OTC) Drug Review
    • CBD was NOT considered under the OTC drug review
  • Unapproved new drug cannot be distributed or sold in interstate commerce
CBD Product Marketing

• CBD can NOT be marketed for therapeutic or medical uses
  • Violation of law
  • Risk to patients
    • Products have not been proven safe or effective by FDA
    • Patients may be influenced to use CBD over prescription medications that have been proven safe and effective

Forbes
Survey: Nearly Half Of People Who Use Cannabidiol Products Stop Taking Traditional Medicines
CBD Products vs Dietary Supplements

• Can CBD be sold as dietary supplements?
  • No, excluded from definition

• Dietary supplements
  • Regulated by FDA under DSHEA
  • Botanical dietary supplements
    • Content often varies from label claim (e.g. supplements marketed for weight loss or performance enhancement)
    • USP certification ensures quality
Commercial CBD & THC Product Labeling

- State laws require medical cannabis is assayed and labeled
  - Lack of labeling consistency
    - Ratios
      - THC:CBD or CBD:THC
    - Percent concentrations
      - X% THC, X% CBD
      - Difficult to calculate amount of mg, missing volumes
  - Label contents
  - Safe practice recommendations
    - Specify THC & CBD concentration in metric units
      - mg, g, mg/mL
    - Consistent ratios

Roussel, ISMP, 2019.
Commercial CBD & THC Product Labeling

• Label accuracy of online CBD products
  • 84 products purchased & analyzed
    • CBD
      • 42.85% (95% CI, 32.82-53.53%) underlabeled (product contained more)
      • 26.19% (95% CI, 17.98-36.48%) overlabeled (product contained less)
    • Trends
      • Vaporization liquid most frequently mislabeled
      • Oil most frequently labeled accurately
  • THC
    • 21.43% (95% CI, 14.01-31.35%) up to 6.43 mg/mL
Commercial CBD & THC Product Labeling

• Survey of CBD-containing products by National Center for Natural Products Research at the University of Mississippi
  • 25 products purchased & analyzed
    • CBD dose accuracy
      • 8 No dose indicated
      • 4 underlabeled
      • 12 overlabeled
      • 1 labeled appropriately
    • THC content >0.3%
      • 3 products
  • Contained synthetic cannabinoids
    • 4 products
FDA Warning Letters

• FDA issues letters to firms for unapproved marketing and inaccurate labeling of cannabidiol-related products
  • Since 2015, over 40 letters
Patient Case- CBD for Osteoarthritis

• CC: 50 yo healthy female presents with altered mental status

• HPI:
  • She had been taking CBD from “reputable source” made in USA for the past two years for joint pain. She scraped the bottom of her CBD bottle to get the last couple drops.
  • Around 2 hours later she developed difficulty focusing, weakness in hands and feet, felt anxious, “heavy” and unable to speak. EMS was called as she reported feeling weak and trouble keeping her eyes open. She was instructed to go to ED for further workup.
Patient Case- CBD for Osteoarthritis

• Summary of hospital admission:
  • BP 80/50 mmHg, HR 92 bpm, Temp 98F, RR 19 (on arrival)
  • Wt 66 kg, Ht 5’8”
  • ROS
    • Constitutional: diaphoresis (+), chills, fever (-)
    • HENT, respiratory, cardiovascular, genitourinary: (-)
    • Gastrointestinal: nausea (+), abdominal pain, diarrhea, vomiting (-)
    • Neurological: tingling (+), sensory change and weakness (+), seizures, headaches (-)
Patient Case - CBD for Osteoarthritis

• Summary of hospital admission:
  • Work-up
    • ECG (normal)
    • head CT (normal)
    • brain MRI (normal)
  • Labs
    • CBC, CMP, Mg, troponin, CRP (WNL)
    • Urine drug screen, marijuana (+)
  • Given IV fluids (vitals normalized), held overnight for observation
Patient Case - CBD for Osteoarthritis

• Assessment
  • Patient denies recreational drug or marijuana use
  • Only positive finding, urine drug screen positive for marijuana
    • likely THC concentrate in CBD oil

• Plan
  • Patient instructed to stop CBD oil
  • Return for follow-up with PCP
Commercial CBD Product Quality

• Mayo Clinic checklist for selecting higher-quality product
  ✓ Does it meet the following quality standards?
    • Current Good Manufacturing Practices (CGMP) certification from FDA
    • European Union (EU), Australian (AUS), or Canadian (CFIA) organic certification
    • National Science Foundation (NSF) International certification
  ✓ Does the company have an independent adverse event reporting program?
  ✓ Is the product certified organic or eco-farmed?
  ✓ Have their products been laboratory tested by batch to confirm THC levels <0.3% and no pesticides or heavy metals?
Objective #2

• Analyze literature on effectiveness of cannabis and cannabidiol products for various indications
Cannabis Research Barriers

- Cannabis supply availability
- Regulatory pathway
- Funding
- Drug delivery
- Blinding
Effectiveness of Cannabis and CBD

• Utilized “The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research,” published in 2017 by National Academies of Sciences, Engineering, and Medicine

• Conclusion categories
  • Conclusive or substantial, moderate, limited, OR no or insufficient evidence that cannabis or cannabinoids are effective
  • Limited evidence of a statistical association between cannabinoids and better outcomes
Chronic Pain

• **Substantial evidence** that cannabis is an effective treatment for chronic pain in adults

• Systematic review (28 RCTs, 2,454 patients)
  • Reduction in pain of ≥30% (8 RCTs)
  • Pooled OR 1.41 favors cannabinoids vs placebo (95% CI, 0.99-2.00)

<table>
<thead>
<tr>
<th>Trial characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of cannabis/ cannabinoid</td>
<td>13 nabiximols, 4 smoked cannabis, 5 nabilone, 3 THC oromucosal spray, 2 dronabinol, 1 vaporized cannabis, 1 capsules, 1 oral THC</td>
</tr>
<tr>
<td>Comparison</td>
<td>27 placebo controlled, 1 compared nabilone vs amitriptyline</td>
</tr>
<tr>
<td>Type of chronic pain</td>
<td>12 neuropathic pain (central or peripheral), 3 cancer pain, 3 diabetic peripheral neuropathy, 2 fibromyalgia, 2 HIV-associated neuropathy, 1 refractory pain from MS, 1 rheumatoid arthritis, 1 non-cancer pain, 1 central pain, 1 musculoskeletal pain, 1 chemotherapy-induced pain</td>
</tr>
</tbody>
</table>

Whiting, et al 2015
Chemotherapy-induced Nausea and Vomiting (CINV)

• **Conclusive evidence** that oral cannabinoids are effective antiemetics in the treatment of CINV

• Systematic review (28 RCTs, 1,772 patients)
  • Greater benefit of cannabinoids vs comparator or placebo
    • Not all reached statistical significance (3 RCTs)
    • OR 3.28 favors dronabinol or nabiximols vs placebo (95% CI, 1.55-9.42)

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<tr>
<td>Type of cannabis/cannabinoid</td>
<td>14 nabilone, 3 dronabinol, 1 nabiximols, 4 levonantradol, 6 THC</td>
</tr>
<tr>
<td>Comparison</td>
<td>20 active comparator (antiemetic), 2 combination therapy (cannabinoid + antiemetic), 8 placebo controlled</td>
</tr>
</tbody>
</table>

Whiting, et al 2015
Chemotherapy-induced Nausea and Vomiting (CINV)

- Cochrane review
  - Conclusion: No evidence to support the use of cannabinoids over current first-line antiemetic therapies
  - **Cannabinoids are useful adjunctive treatment** for patients receiving moderate or highly emetogenic chemotherapy when alternatives have been trialed
# Epilepsy (Dravet Syndrome)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, double blind, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Population</strong></td>
<td>Dravet syndrome and drug-resistant seizures</td>
</tr>
<tr>
<td>Cannabidiol (n=61)</td>
<td>Mean age: 9.7 yrs</td>
</tr>
<tr>
<td># of antiepileptics: 4.6</td>
<td>Placebo (n=59)</td>
</tr>
<tr>
<td>Mean age: 9.8 yrs</td>
<td># of antiepileptics: 4.6</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Established diagnosis, ≥1 antiepileptic, ≥4 convulsive seizures at baseline</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Change in convulsive-seizure frequency over a 14-week treatment period</td>
</tr>
<tr>
<td>Results</td>
<td>Cannabidiol 12.4 to 5.9 seizures/month</td>
</tr>
<tr>
<td></td>
<td>Placebo 14.9 to 14.1 seizures/month</td>
</tr>
<tr>
<td></td>
<td>Adjusted median difference −22.8 percentage points (95% CI, −41.1 to −5.4)</td>
</tr>
<tr>
<td></td>
<td>p-value = 0.01</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo</td>
</tr>
</tbody>
</table>
## Epilepsy (Lennox-Gastaut)

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<tbody>
<tr>
<td><strong>Patient Population</strong></td>
<td></td>
</tr>
<tr>
<td>Lennox-Gastaut and drug-resistant drop seizures</td>
<td>Cannabidiol 20 mg/kg (n=76) Mean age: 16 yrs</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>2 - 55 years old, established diagnosis, ≥2 types of generalized seizures, including drop seizures at baseline, 1-4 antiepileptics, ≥2 drop seizures/week</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>percentage change from baseline in the frequency of drop seizures (average per 28 days)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
</tr>
<tr>
<td>Cannabidiol 20 mg/kg</td>
<td>median percent reduction 41.9% P-value = 0.005</td>
</tr>
<tr>
<td>Cannabidiol 10 mg/kg</td>
<td>median percent reduction 37.2% P-value = 0.002</td>
</tr>
<tr>
<td>Placebo</td>
<td>median percent reduction 17.2%</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>Addition of cannabidiol at a dose of 10 mg or 20 mg/kg/day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo</td>
</tr>
</tbody>
</table>
Patient Case- Cannabidiol & Clobazam

• CC: 39 year old male seen in neurology clinic for Lennox-gestaut syndrome and is having daytime sedation
• HPI: Since starting cannabidiol six months ago, staff at group home rarely observe seizure activity
• Medications: Cannabidiol 150 mg twice daily, valproic acid 500 mg twice daily, clobazam 20 mg daily
• Labs
  • AST 57 U/L (up from 40)
  • ALT 50 U/L
  • Tbili 0.3 mg/dL
Patient Case- Cannabidiol & Clobazam

• Assessment
  • Cannabidiol can increase N-desmethylclobazam by 2-3 fold and cause sedation.
  • Valproic acid along with cannabidiol can result increased risk of liver enzyme elevations.

• Plan
  • Decrease clobazam from 20 to 10 mg daily
  • Contact patient caregiver via phone in 4 weeks to assess adverse effects
  • Recheck AST, ALT, Tbili in 3 months
Spasticity with Multiple Sclerosis (MS)

- **Substantial evidence** that oral cannabinoids are an effective treatment for improving patient-reported MS spasticity symptoms

- **Systematic reviews**
  - 11 studies, 2,138 patients
    - Not all reached statistical significance
    - Patient-reported improvement favored nabiximols over placebo
    - Pooled OR 1.44 (95% CI, 1.07–1.94)
  - 17 studies
    - Conclusion: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective for patient-reported improvement
Appetite Stimulant in HIV/AIDS

- **Limited evidence** that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS

- **Systematic review**
  - 4 RCTS, 255 patients
  - High risk of bias
  - Not statistically significant

- **Cochrane review**
  - 7 RCTs, changes in appetite (secondary outcome)
  - Conclusion: Evidence for the efficacy and safety of cannabis and cannabinoids for AIDS-associated anorexia is lacking

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<tbody>
<tr>
<td>Type of cannabinoid</td>
<td>4 dronabinol</td>
</tr>
<tr>
<td>Comparison</td>
<td>3 placebo controlled, 1 megastrol</td>
</tr>
</tbody>
</table>
Sleep disorders

• **Moderate evidence** that cannabinoids are an effective treatment to improve short-term sleep outcomes (associated with obstructive sleep apnea (OSA), fibromyalgia, chronic pain, and MS)

• Systematic reviews
  • 2 studies, 54 patients
  • 19 studies
    • Chronic pain and MS
      • Reported sleep outcomes
      • Nabixmols showed greater improvement in sleep quality and disturbance

<table>
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<tr>
<th>Trial design</th>
<th>Type of cannabinoid</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>parallel-group, placebo</td>
<td>Dronabinol</td>
<td>OSA index mean difference from baseline, −19.64; p value = .02 Limitation: high risk of bias</td>
</tr>
<tr>
<td>controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossover, amitriptyline</td>
<td>Nabilone</td>
<td>Insomnia in patients with fibromyalgia mean difference from baseline, −3.25 (95% CI, −5.26 to −1.24)</td>
</tr>
</tbody>
</table>
Anxiety

• **Limited evidence** that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders
  
  • Systematic review
    
    • 1 study, 24 patients, high risk of bias
      • Greater improvement on the anxiety factor of a visual analogue mood scale (mean difference from baseline, $-16.52$; $p$ value = .01)
    
    • 4 RCTs, 232 patients, high risk of bias
      
      • Placebo-controlled
      • Dronabinol 10–20 mg daily; nabilone maximum dose of 2 mg daily; and nabiximols, maximum dose of 4–48 sprays/day
      
      • short-term benefit with cannabinoids on self-reported anxiety symptoms
Post-traumatic stress disorder (PTSD)

- There is **limited evidence** that nabilone is effective for improving symptoms of post-traumatic stress disorder
  - double-blind, randomized crossover trial
  - Canadian male military personnel with trauma-related nightmares despite standard treatments for PTSD
  - 10 patients
  - nabilone 0.5 mg titrated to maximum of 3.0 mg/day

- **Results**
  - Nightmares, global clinical state, and general well-being were improved more with nabilone (p <0.05)
  - No effect on sleep quality and quantity
  - Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment period
Parkinson’s Disease

• **Insufficient evidence** that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson’s disease or the levodopa-induced dyskinesia.

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<tr>
<th>Trial design</th>
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<th>Results</th>
</tr>
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<tbody>
<tr>
<td>double-blind crossover study, 19 patients</td>
<td>CBD extract 1.25 or 2.5 mg capsules (avg dose 0.146 mg/kg/day)</td>
<td>Primary outcome: score on Part IV (dyskinesia section, items 32–34) of the Unified Parkinson’s Disease Rating Scale (UPDRS) Overall treatment effect was 10.52, which indicated a worsening but was non-significant (p = 0.09)</td>
</tr>
<tr>
<td>randomized, double-blind, placebo-controlled, 21 patients</td>
<td>CBD at 75 mg/day or 300 mg/day</td>
<td>No statistically significant differences were seen in the UPDRS between the three study arms</td>
</tr>
<tr>
<td>open-label observational study, 22 patients</td>
<td>smoked 0.5 g of cannabis</td>
<td>Motor symptoms score on the UPDRS improved from 33.1 (± 13.8) to 23.2 (± 10.5) (p &lt;0.001)</td>
</tr>
</tbody>
</table>
Objective #3

• Discuss common drug-drug interactions (DDI) with cannabis and cannabidiol products
CBD Metabolism

Jiang, 2011.
THC Metabolism

Huestis, 2016.
Clinically Significant Pathways

Figure 1. Cytochrome P-450 (CYP-450) metabolic pathways for cannabinoids and investigated metabolites based on in vitro data. Supporting data (Bland et al., 2005; Bornheim et al., 1992; Chimalakonda et al., 2012; Jiang et al., 2011; Matsunaga et al., 2000; Richardson et al., 1995; Watanabe et al., 1995, 2002, 2007).

Stout, 2019.
## Drug interactions (CYP2C9)

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Cannabinoid</th>
<th>Research</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9 inhibition</td>
<td>THC (CBD)</td>
<td>In vitro, animal, human*</td>
<td>Substrates: Topiramate*, phenobarbital, phenytoin, diclofenac, ibuprofen, meloxicam, piroxicam, celecoxib, amitriptyline, imipramine, warfarin*, glipizide, losartan, irbesartan, valsartan, carvedilol, torsemide, diazepam, diphenhydramine, doxepin, febuxostat, fluoxetine, fluvastatin, pitavastatin, sulfonyleureas, methadone, montelukast, zafirlukast, zileuton, omeprazole, sildenafil, vardenafil, tamoxifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibitors: amiodarone, clopidogrel, fenofibrate, fluconazole, gemfibrozil, leflunomide, metronidazole, sertraline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inducers: carbamazepine, phenobarbital, phenytoin, primidone, rifampin, St. John’s wort</td>
</tr>
</tbody>
</table>
Patient Case- CBD & Warfarin

• CC: 40 year old male with a history of multiple DVTs and PE was seen in anticoagulation clinic and INR elevated.

• Patient findings:
  • Recently started taking CBD oil
  • No missed/extra warfarin doses, no major bleeding, no change in diet or activity

• Medication: warfarin 25 mg daily
Patient Case - CBD & Warfarin

• Labs
  • Hgb 15.5 (13.6-17.2 g/dL), Hct 44 (40-52 %), Plt 202 (160-370 K/uL), Creatinine 1.07 (0.73-1.18 mg/dL), INR 4.4

• Assessment
  • INR increased to 4.4. INR was 2.8 one week ago. Patient recently started CBD oil for depression and chronic pain. No signs/symptoms of bleeding. Would benefit from dose decrease of 20%.

• Plan
  • **Decrease warfarin** to 10 mg today, then 20 mg MWF, 25 mg 4x week
  • Recheck INR in 1 week
Drug interactions (CYP2C19)

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Cannabinoid</th>
<th>Research</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
</table>
| CYP2C19 inhibition | CBD (THC) | In vitro, animal, human* | **Substrates:** Clobazam*, PPIs, diazepam, carisoprodol, nelfinavir, amitriptyline, desipramine, cilostazol, citalopram, escitalopram, sertraline, vilazadone, clomipramine, clopidogrel, diazepam, diphenhydramine, doxepin, indomethacin, methadone, primidone, progesterone, propranolol, voriconazole, warfarin  
**Inhibitors:** cimetidine, esomeprazole, felbamate, fenofibrate, fluconazole, fluoxetine, fluvoxamine, isoniazid, ketoconazole, modafinil, oxcarbazepine, topiramate, vilazodone  
**Inducers:** carbamazepine, phenobarbital, phenytoin, rifampin, St. John’s wort |
# Drug interactions (CYP3A4)

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Cannabinoid</th>
<th>Research</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inhibition</td>
<td>CBD &amp; THC</td>
<td>In vitro</td>
<td>Substrates: alfuzosin, alprazolam, amitriptyline, <strong>amiodarone</strong>, <strong>apixaban</strong>, aripiprazole, <strong>atorvastatin</strong>, budesonide, buprenorphine, buspirone, canaglifozin, carbamazepine, chloroquine, cilostazol, ciclesonide, citalopram, clarithromycin, <strong>clopidogrel</strong>, clozapine, colchicine, darifenacin, dexamethasone, PPIs, benzodiazepines, <strong>diltiazem</strong>, <strong>dronedarone</strong>, eplerenone, ergotamine, PPIs, estrogens, felodipine, <strong>fentanyl</strong>, fluticasone, guanfacine, haloperidol, <strong>hydrocodone</strong>, -azoles, levonorgestrel, lidocaine, -gliptins, <strong>lovastatin</strong>, lurasidone, <strong>methadone</strong>, midazolam, nimodipine, oral contraceptives, paroxetine, pioglitazone, quetiapine, risperidone, <strong>rivaroxaban</strong>, sertraline, <strong>PDE-5s</strong>, <strong>tacrolimus</strong>, <strong>ticagrelor</strong>, tolterodine, trazodone, triazolam, <strong>warfarin</strong></td>
</tr>
</tbody>
</table>
# Drug interactions (CYP3A4)

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Cannabinoid</th>
<th>Research</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inhibition</td>
<td>CBD &amp; THC</td>
<td>In vitro</td>
<td><strong>Inhibitors:</strong> amiodarone, amlodipine, cimetidine, ciprofloxacin, clarithromycin, cyclosporine, diltiazem, dronedarone, erythromycin, -azoles, fluoxetine, fluvoxamine, isoniazid, mifepristone, nefazodone, nifedipine, ticagrelor, verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Inducers:</strong> carbamazepine, clobazam, garlic, modafinil, oxcarbazepine, phenobarbital, phenytoin, primidone, rifampin, St. Johns wort</td>
</tr>
</tbody>
</table>
# Drug interactions (CYP3A5)

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Cannabinoid</th>
<th>Research</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A5 inhibition</td>
<td>CBD</td>
<td>In vitro, animal</td>
<td>Substrates: testosterone, progesterone, nifedipine, cyclosporine</td>
</tr>
</tbody>
</table>
# Drug interactions (CYP2D6)

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Cannabinoid</th>
<th>Research</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
</table>
| CYP2D6 inhibition | CBD | In vitro | **Substrates:** amphetamine, aripiprazole, atomoxetine, bisoprolol, **carvedilol**, chloroquine, ciclesonide, cinacalcet, TCAs, clozapine, codeine, cyclobenzaprine, dextromethorphan, donepezil, flecainide, **fluoxetine**, fluvoxamine, formoterol, **hydrocodone**, lidocaine, **metoprolol**, mirtazapine, nebivolol, olanzapine, **ondansetron**, **oxycodone**, paroxetine, propranolol, risperidone, ritonavir, tamoxifen, timolol, tolterodine, **tramadol**, **trazodone**, **venlafaxine**  
**Inhibitors:** amiodarone, bupropion, celecoxib, cimetidine, citalopram, clobazam, darifenacin, diphenhydramine, doxepin, d**uloxetine, escitalopram, fluoxetine, haloperidol, hydroxychloroquine, iloperidone, methadone, mirabegron, paroxetine, propranolol, ranitidine, ritonavir, sertraline, terbinafine, vilazodone |
Potential Drug Interactions

• In vitro research for CBD & THC, theorized as low significance, more studies needed

<table>
<thead>
<tr>
<th>CYP450 enzyme</th>
<th>Medications metabolized by this pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1 inhibition</td>
<td>theophylline</td>
</tr>
<tr>
<td>CYP1A2 inhibition</td>
<td>Acetaminophen, amitriptyline, clopidogrel, cyclobenzaprine, diazepam, doxepin, duloxetine, estradiol, lidocaine, melatonin, methadone, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, propranolol, ropinirole, tizanidine, verapamil, warfarin, zolmitriptan</td>
</tr>
<tr>
<td>CYP1B1 inhibition</td>
<td>theophylline, omeprazole, clozapine, progesterone, lansoprazole</td>
</tr>
<tr>
<td>CYP2A6 inhibition</td>
<td>nicotine, warfarin, valproic acid, disulfiram</td>
</tr>
<tr>
<td>CYP2B6 inhibition</td>
<td>ketamine, phenobarbital, dexamethasone</td>
</tr>
<tr>
<td>CYP2C8 inhibition</td>
<td>Amiodarone, carbamazepine, chloroquine, diclofenac, repaglinide</td>
</tr>
</tbody>
</table>
# Package Labeling DDI

<table>
<thead>
<tr>
<th>Prescription Drug</th>
<th>Additional drug-drug interaction details</th>
</tr>
</thead>
</table>
| Dronabinol        | - Protein-binding- warfarin, amphotericin B, cyclosporine  
                     - Metronidazole & disulfram should be avoided within 14 days of oral solution (contains alcohol)  
                     - Can increase drowsiness/dizziness with additional CNS depressants |
| Cannabidiol       | - Cilostazol (max dose 100 mg/day)  
                     - Citalopram (max dose 20 mg/day)  
                     - Clobazam  
                     - Valproate (liver toxicity, thrombocytopenia)  
                     - Eslicarbamazepine  
                     - Rufinamide |
Patient Case- CBD for pain & mood

• CC: 61 yo female seen in internal medicine and would like to start **CBD patches for knee pain and mood.**

• PMH: hx of PE, venous stasis, hyperlipidemia, hypothyroidism, sleep apnea, GERD, migraines, schizoaffective disorder, anxiety, depression

• **Medications:** aripiprazole, bupropion, diclofenac gel, ezetimibe, fenofibrate, ferrous sulfate, fluoxetine, furosemide, levothyroxine, omeprazole, quetiapine, sumatriptan, valacyclovir, vitamin D, rivaroxaban
Patient Case- CBD for pain & mood

• Assessment
  • Drug interactions:

<table>
<thead>
<tr>
<th>Medications</th>
<th>Potential adverse effects (due to increased drug concentrations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole, fluoxetine, bupropion XL, quetiapine, topiramate</td>
<td>Drowsiness, dizziness</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Bleeding</td>
</tr>
</tbody>
</table>

• Plan
  • Do NOT recommend taking CBD products as it can increase concentration of several medications noted above and increase risk of drowsiness/sedation and bleeding.
Objective #4

• Describe common adverse effects (AEs) of cannabis and cannabidiol products
# Dronabinol (THC) Adverse Effects

<table>
<thead>
<tr>
<th>ROS</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td><strong>Euphoria</strong> (antiemetic: 24%; appetite stimulant: 8%), Abnormality in thinking, <strong>paranoia, dizziness, drowsiness</strong> (3% to 10%), amnesia (&gt;1%), anxiety (&gt;1%), ataxia (&gt;1%), confusion (&gt;1%), depersonalization (&gt;1%), hallucination (&gt;1%), nervousness (&gt;1%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Facial flushing, palpitations, tachycardia, vasodilation (&gt;1%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td><strong>Abdominal pain, nausea, vomiting</strong> (3% to 10%)</td>
</tr>
</tbody>
</table>
# Nabilone (THC) Adverse Effects

<table>
<thead>
<tr>
<th>ROS</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hypotension (8%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td><strong>Drowsiness</strong> (52% to 66%), <strong>dizziness</strong> (59%), vertigo (52% to 59%), <strong>euphoria</strong> (11% to 38%), ataxia (13% to 14%), <strong>depression</strong> (14%), <strong>lack of concentration</strong> (12%), <strong>sleep disorder</strong> (11%), dysphoria (9%), headache (6% to 7%), sedation (3%), depersonalization, disorientation (2%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td><strong>Xerostomia</strong> (22% to 36%), anorexia (8%), nausea (4%), increased appetite (2%)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td><strong>Visual disturbance</strong> (13%)</td>
</tr>
<tr>
<td>Neuromuscular &amp; skeletal</td>
<td>Weakness (8%)</td>
</tr>
</tbody>
</table>
# Cannabidiol (CBD) Adverse Effects

<table>
<thead>
<tr>
<th>ROS</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td><strong>Drowsiness</strong>, lethargy, sedation (≤32%), fatigue (≤12%), malaise (≤12%), insomnia (≤11%), sleep disorder (≤11%), sleep disturbance (≤11%), agitation (≤9%), irritability (≤9%), aggressive behavior (≤5%), outbursts of anger (≤5%), drooling (≤4%), abnormal gait (2% to 3%)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Skin rash (7% to 13%)</td>
</tr>
<tr>
<td>Endocrine &amp; metabolic</td>
<td><strong>Weight loss</strong> (3% to 18%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td><strong>Decreased appetite</strong> (16% to 22%), <strong>diarrhea</strong> (9% to 20%), gastroenteritis (4%), sialorrhea (≤4%), abdominal distress (≤3%), abdominal pain (≤3%)</td>
</tr>
</tbody>
</table>
## Cannabidiol (CBD) Adverse Effects

<table>
<thead>
<tr>
<th>ROS</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic &amp; oncologic</td>
<td>Anemia (30%)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Increased serum alanine aminotransferase (&gt;3x ULN: 13% to 17%), increased serum transaminases (8% to 16%)</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection (25% to 41%), viral infection (7% to 11%), fungal infection (1% to 3%)</td>
</tr>
<tr>
<td>Neuromuscular &amp; skeletal</td>
<td>Asthenia (≤12%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pneumonia (5% to 8%), hypoxia (≤3%), respiratory failure (≤3%)</td>
</tr>
</tbody>
</table>
# Nabiximols Adverse Effects

<table>
<thead>
<tr>
<th>ROS</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td><strong>Hypotension (5%)</strong>, palpitations (1%), syncope (1%), tachycardia (1%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td><strong>Dizziness (12% to 25%)</strong>, drowsiness (8% to 15%), <strong>fatigue (13%)</strong>, confusion (7%), vertigo (5% to 7%), disorientation (4%), disturbance in attention (3% to 4%), depression (3%), equilibrium disturbance (3%), headache (3%), insomnia (3%), intoxicated feeling (3%), panic attack (3%), euphoria (2% to 3%), hallucination (≤3%), depersonalization (2%), dysarthria (2%), falling (2%), feeling abnormal (2%), lethargy (2%), amnesia (1%), malaise (1%), memory impairment (1%), paranoia (1%), suicidal ideation (1%)</td>
</tr>
</tbody>
</table>
# Nabiximols Adverse Effects

<table>
<thead>
<tr>
<th>ROS</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Nausea (10% to 12%), vomiting (4% to 8%), diarrhea (6% to 7%), xerostomia (6%), dysgeusia (3%), glossalgia, oral candidiasis (3%), anorexia, constipation, dental discoloration, oral mucosa changes, oral mucosa ulcer (2%), abdominal pain, increased appetite, stomatitis (1%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Urinary retention (5%), hematuria (3%)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Abnormal hepatic function tests (5%)</td>
</tr>
<tr>
<td>Neuromuscular &amp; skeletal</td>
<td>Weakness (5% to 6%)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Blurred vision (2%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Throat irritation (1%)</td>
</tr>
</tbody>
</table>
Key Points

• Non-FDA approved commercial CBD & THC products are not regulated and dose often varies from labeling

• More research is needed to guide dosing for various dosage forms and indications

• There are numerous drug-drug interactions and ongoing studies are needed to determine clinical significance

• Potential adverse effects that require lab monitoring include liver toxicity and anemia
Resources

• FDA Consumer Updates on CBD
  https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis

• Natural Medicine Database (drug-drug interactions)
  https://naturalmedicines.therapeuticresearch.com/#
References


References

- Gurley BJ. Content vs. Label Claim: A Survey of CBD Content in Commercially Available Products. Oral presentation at: FDA Public Hearing; May, 2019; Silver Spring, MD.
References


References


• Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem*. 2015 Apr 1;23(7):1377-85.