Medical Marijuana and Cannabidiol (CBD): Perceptions vs Facts

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Newsweek

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

CBC.ca

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

The New York Times

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

The Washington Post

Opinions

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

As CBD Oils Become More Popular, The FDA Considers Whether To Set New Rules

May 31, 2019 · 12:59 PM ET

USA TODAY

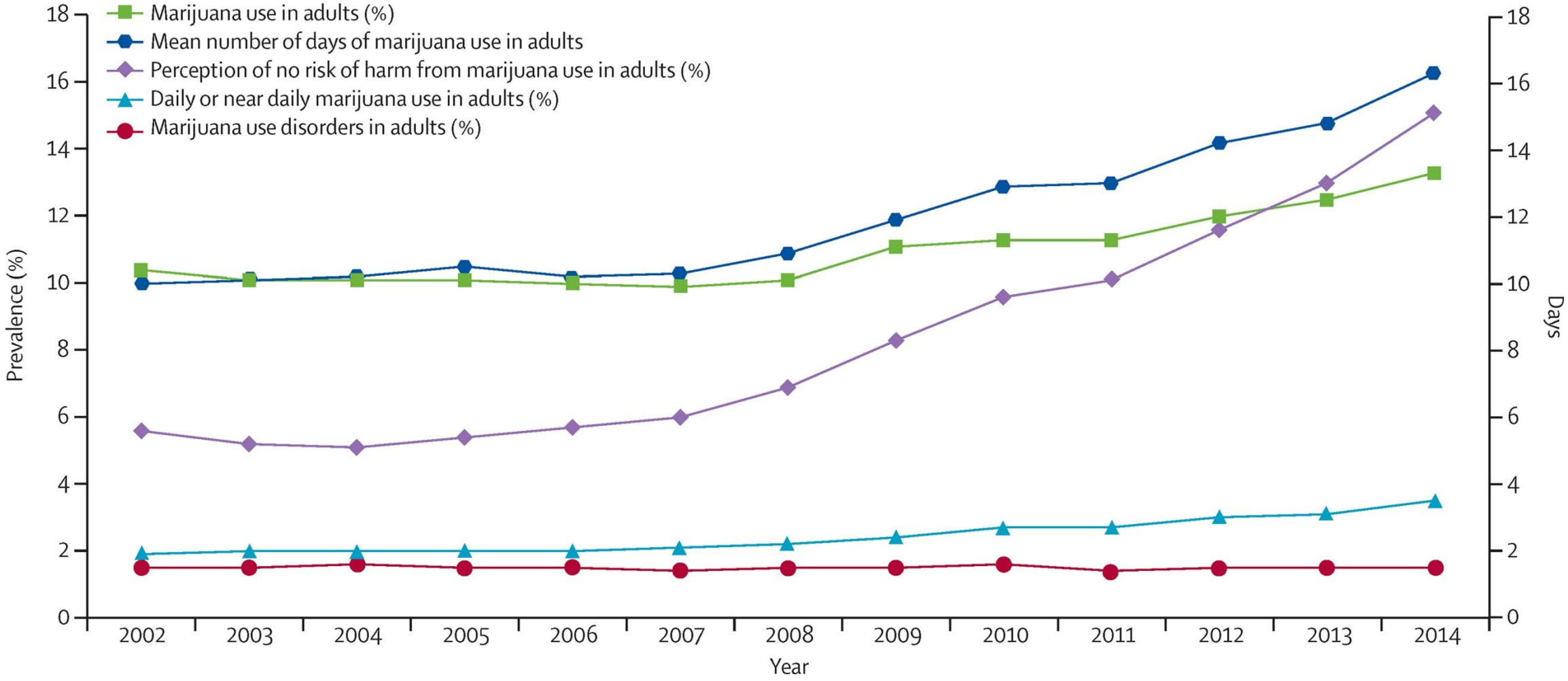
Sketchy THC vape products. Sneaky teens. How patchwork regulations on e-cigarettes led to health crisis

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



Compton, et al. *Lancet*, 2016.

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 cannabidiol 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)

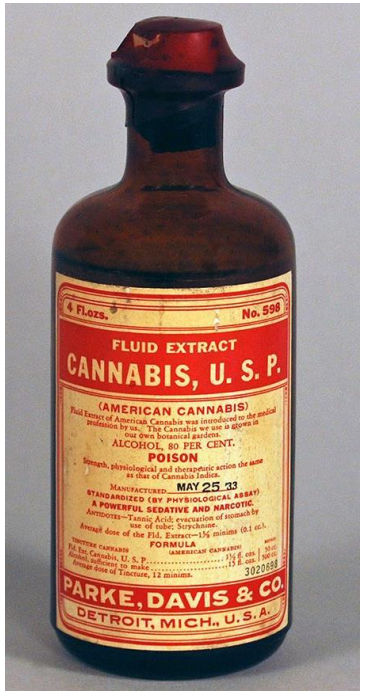


Photo:https://libguides.law.uga.edu/c.php?g=522835&p=3575350

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**

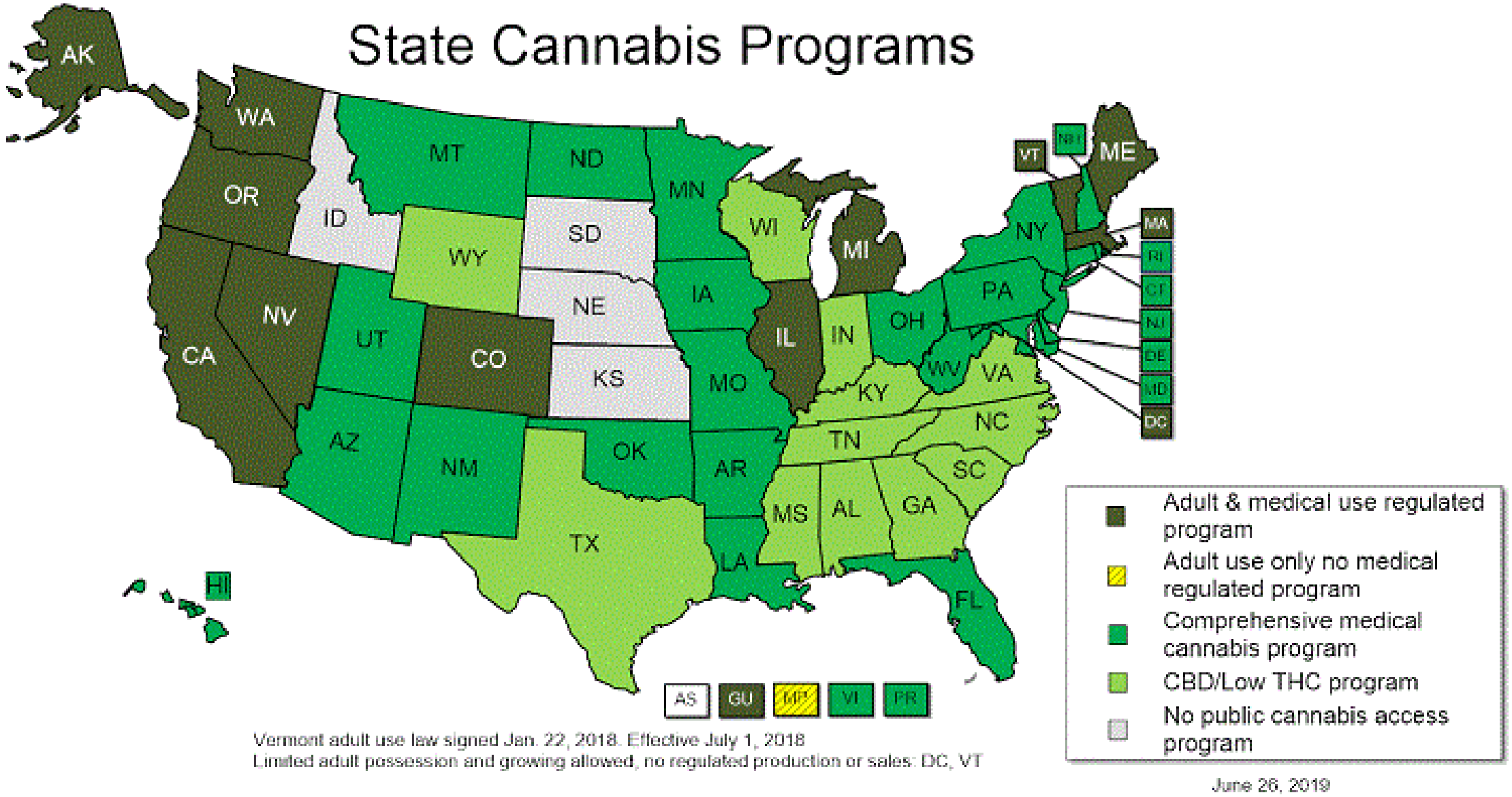
Evolution of Laws & Regulation

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 Colombia
  - 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)



Retrieved from: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

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)

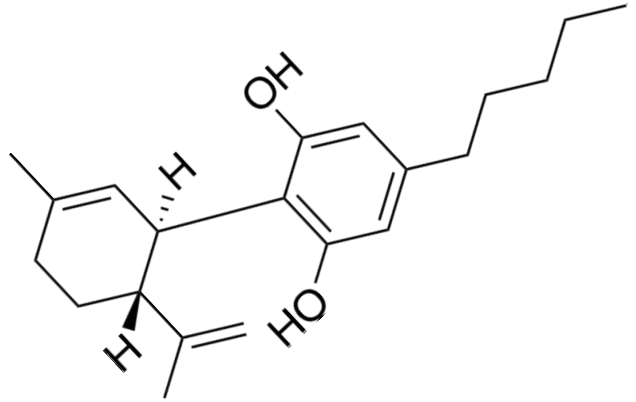
- Held a public hearing for "Products Containing Cannabis or Cannabis-Derived Compounds" on May 31, 2019
  - Gather scientific data and information regarding safety, manufacturing, product quality, marketing, labeling, and sale of products
  - Participants included government officials, researchers,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

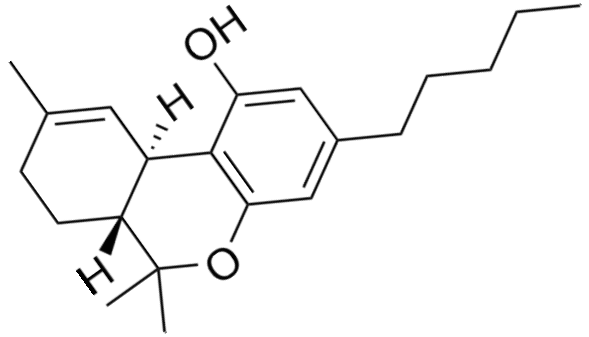
Cannabis

- *Cannabis sativa* (hemp) vs *Cannabis indica*
  - Contain >100 cannabinoids
    - Most common cannabinoids are:
      - cannabidiol (CBD)
      - delta-9-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)

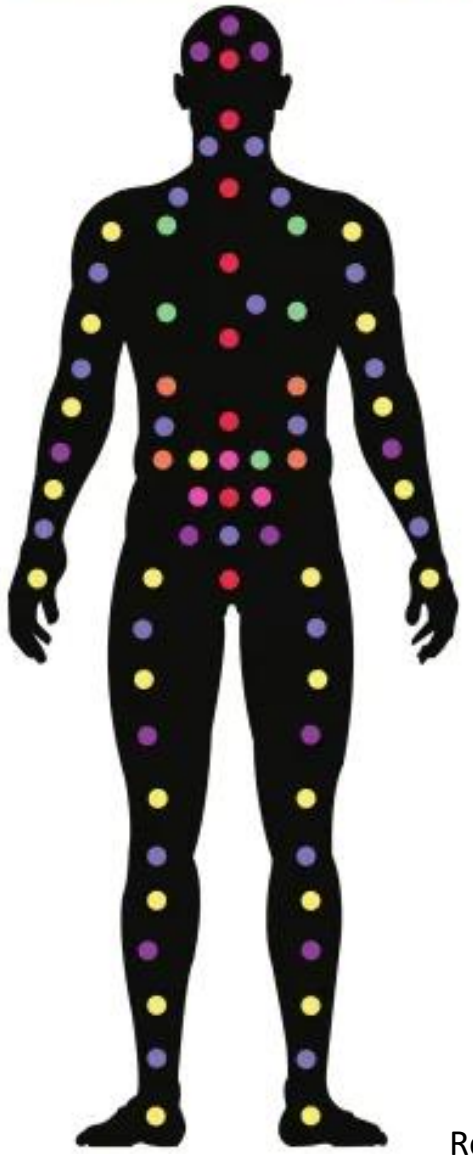
HUMAN CANNABINOID RECEPTORS

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.

TRVP1
Receptors are concentrated in the blood, bone, marrow, tongue, kidney, liver, stomach & overies.

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

GPR55
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

MCANZ
/MCANewZealand/
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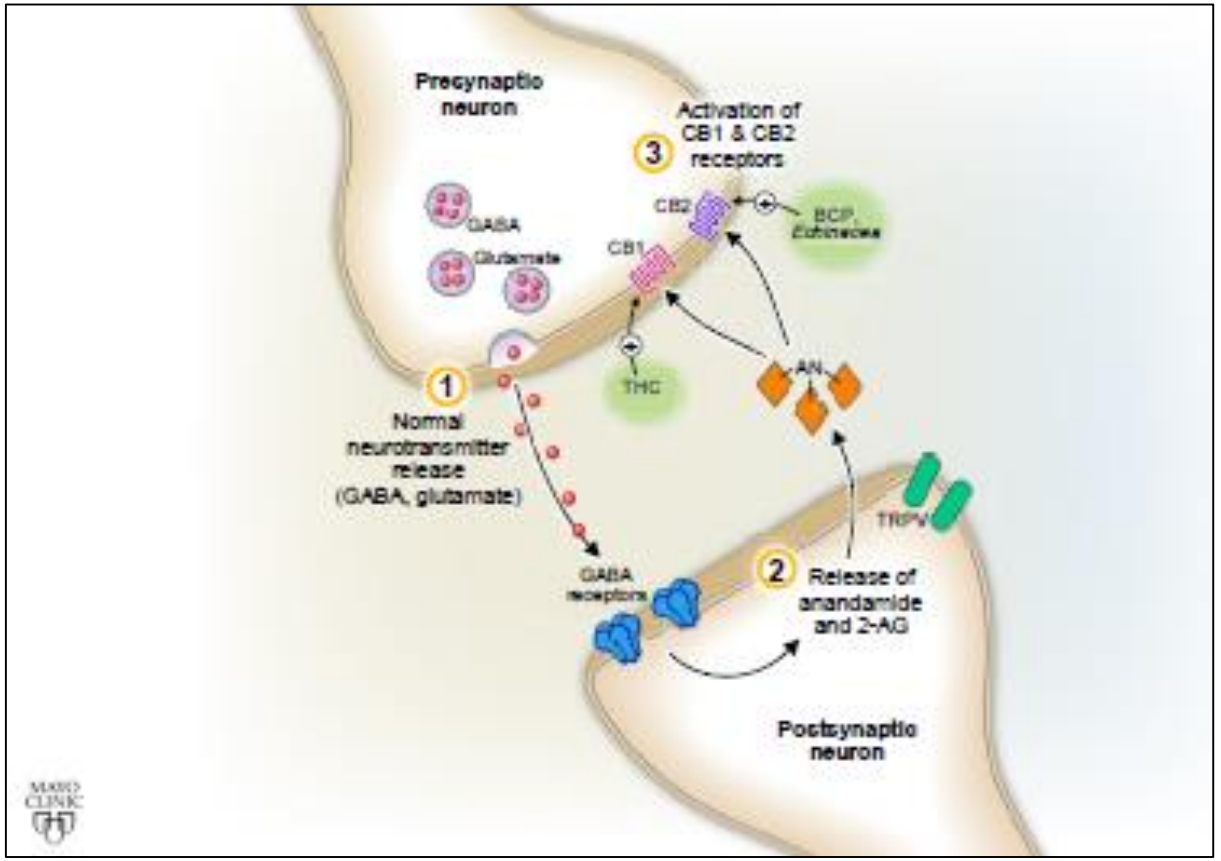
mcawarenessnz.org/

Retrieved from: https://mcanz.org.nz/the-endocannabinoid-system/

The Endocannabinoid System (ECS)

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



VanDolah HJ, et al. *Mayo Clin Proc,* 2019.

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

Retrieved from: https://www.webmd.com/a-to-z-guides/news/20171215/world-health-group-pots-cbd-has-health-benefits

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

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**

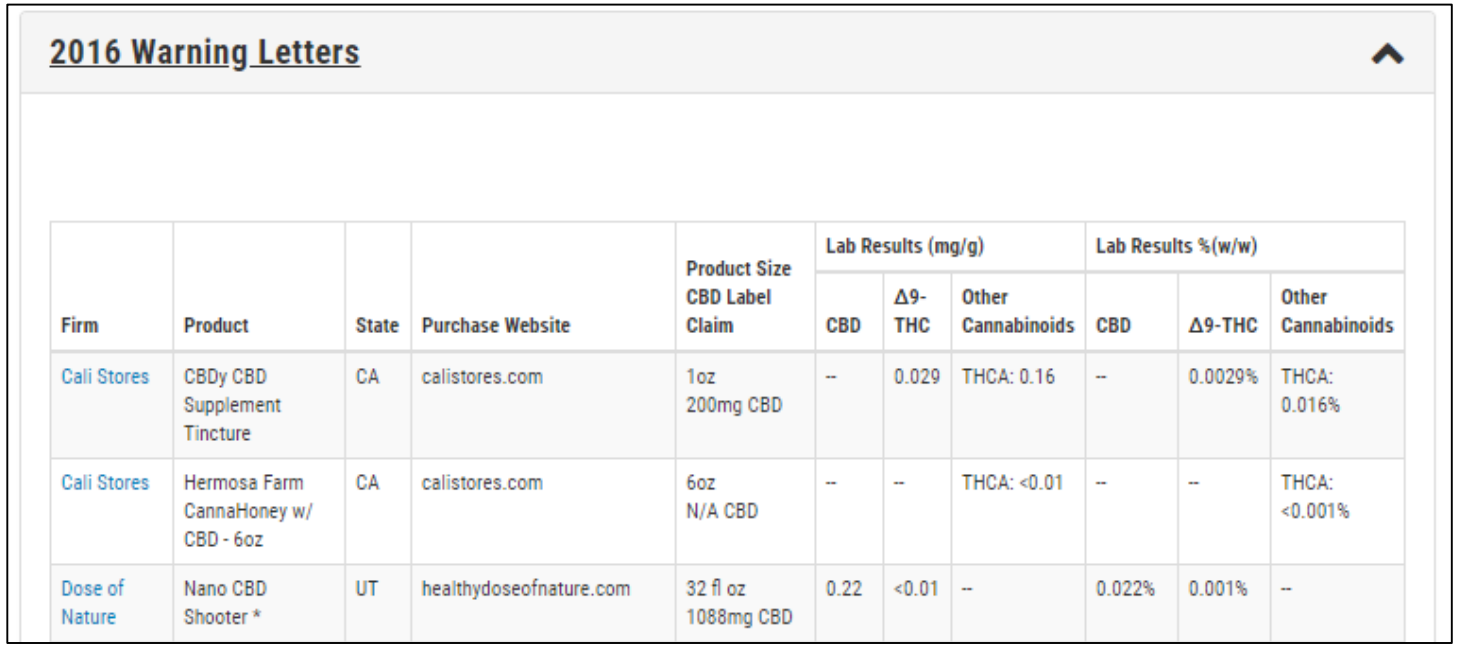
Retrieved from: Flickr

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



2016 Warning Letters

Firm	Product	State	Purchase Website	Product Size CBD Label Claim	Lab Results (mg/g)			Lab Results %(w/w)		
					CBD	Δ9-THC	Other Cannabinoids	CBD	Δ9-THC	Other Cannabinoids
Cali Stores	CBDy CBD Supplement Tincture	CA	calistores.com	1oz 200mg CBD	--	0.029	THCA: 0.16	--	0.0029%	THCA: 0.016%
Cali Stores	Hermosa Farm CannaHoney w/ CBD - 6oz	CA	calistores.com	6oz N/A CBD	--	--	THCA: <0.01	--	--	THCA: <0.001%
Dose of Nature	Nano CBD Shooter *	UT	healthydoseofnature.com	32 fl oz 1088mg CBD	0.22	<0.01	--	0.022%	0.001%	--

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)

	Trial characteristics
Type of cannabis/ cannabinoid	13 nabiximols, 4 smoked cannabis, 5 nabilone, 3 THC oromucosal spray, 2 dronabinol, 1 vaporized cannabis, 1 capsules, 1 oral THC
Comparison	27 placebo controlled, 1 compared nabilone vs amitriptyline
Type of chronic pain	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

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)

	Trial characteristics
Type of cannabis/ cannabinoid	14 nabilone, 3 dronabinol, 1 nabiximols, 4 levonantradol, 6 THC
Comparison	20 active comparator (antiemetic), 2 combination therapy (cannabinoid + antiemetic), 8 placebo controlled

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)

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

Epilepsy (Lennox-Gastaut)

Study Design	Randomized, double blind, placebo-controlled		
Patient Population	Lennox-Gastaut and drug-resistant drop seizures		
	Cannabidiol 20 mg/kg (n=76) Mean age: 16 yrs	Cannabidiol 10 mg/kg (n=73) Mean age: 15.4 yrs	Placebo (n=76) Mean age: 15.3 yrs
Inclusion Criteria	2 - 55 years old, established diagnosis, ≥2 types of generalized seizures, including drop seizures at baseline, 1-4 antiepileptics, ≥2 drop seizures/week		
Primary Endpoint	percentage change from baseline in the frequency of drop seizures (average per 28 days)		
Results	Cannabidiol 20 mg/kg median percent reduction 41.9% P-value = 0.005	Cannabidiol 10 mg/kg median percent reduction 37.2% P-value = 0.002	Placebo median percent reduction 17.2%
Conclusions	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		

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

	Trial characteristics
Type of cannabinoid	6 nabiximols, 3 dronabinol, 1 nabilone, 1 THC/CBD
Comparison	11 placebo controlled

- 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

	Trial characteristics
Type of cannabinoid	4 dronabinol
Comparison	3 placebo controlled, 1 megastrol

- 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

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

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

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

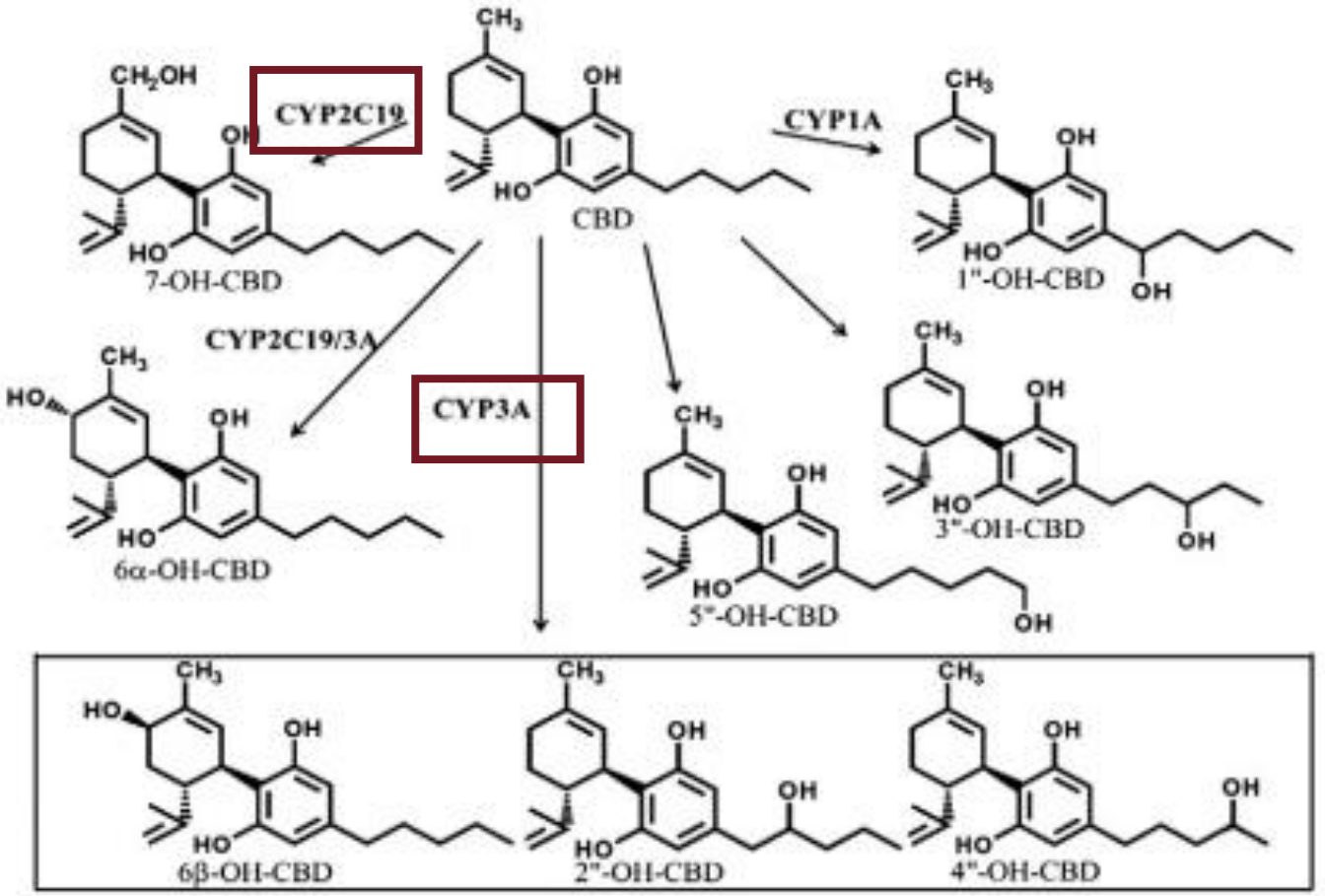
- **Insufficient evidence** that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia.

Trial design	Type of cannabinoid	Results
double-blind crossover study, 19 patients	CBD extract 1.25 or 2.5 mg capsules (avg dose 0.146 mg/kg/day)	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)
randomized, double-blind, placebo-controlled, 21 patients	CBD at 75 mg/day or 300 mg/day	No statistically significant differences were seen in the UPDRS between the three study arms
open-label observational study, 22 patients	smoked 0.5 g of cannabis	Motor symptoms score on the UPDRS improved from 33.1 (± 13.8) to 23.2 (± 10.5) (p <0.001)

Objective #3

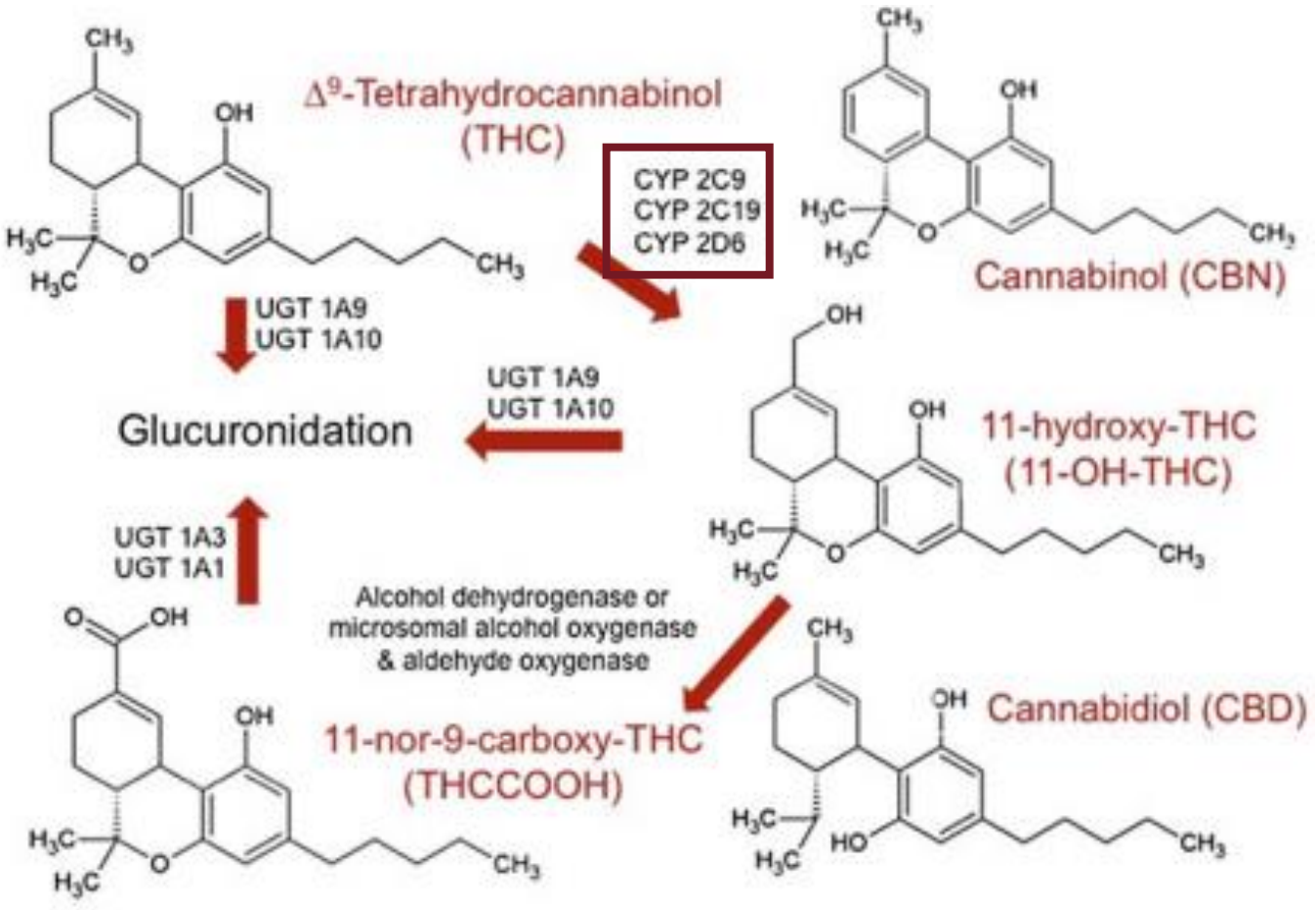
- Discuss common drug-drug interactions (DDI) with cannabis and cannabidiol products

CBD Metabolism



Jiang, 2011.

THC Metabolism



Huestis, 2016.

Clinically Significant Pathways

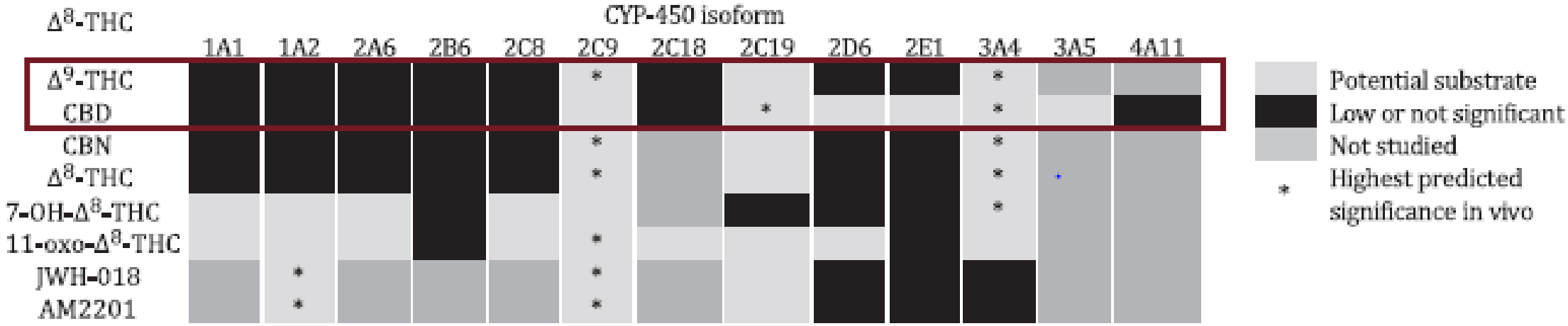


Figure 1. Cytochrome P-450 (CYP-450) metabolic pathways for cannabinoids and investigated metabolites based on *in vitro* data. Supporting data (Bland et al., 2005; Bornheim et al., 1992; Chimalakonda et al., 2012; Jiang et al., 2011; Matsunaga et al., 2000; Richardson et al., 1995; Watanabe et al.,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

Stout, 2019.

Drug interactions (CYP2C9)

CYP450 enzyme	Cannabinoid	Research	Medications metabolized by this pathway
CYP2C9 inhibition	THC (CBD)	In vitro, animal, human*	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, sulfonylureas, methadone, montelukast, zafirlukast, zileuton, omeprazole, sildenafil, vardenafil, tamoxifen Inhibitors: amiodarone, clopidogrel, fenofibrate, fluconazole, gemfibrozil, leflunomide, metronidazole, sertraline Inducers: carbamazepine, phenobarbital, phenytoin, primidone, rifampin, St. John's wort

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)

CYP450 enzyme	Cannabinoid	Research	Medications metabolized by this pathway
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)

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

Drug interactions (CYP3A4)

CYP450 enzyme	Cannabinoid	Research	Medications metabolized by this pathway
CYP3A4 inhibition	CBD & THC	In vitro	Inhibitors: amiodarone, amlodipine, cimetidine, ciprofloxacin, clarithromycin, cyclosporine, diltiazem, dronedarone, erythromycin, -azoles, fluoxetine, fluvoxamine, isoniazid, mifepristone, nefazodone, nifedipine, ticagrelor, verapamil Inducers: **carbamazepine, clobazam**, garlic, modafinil, **oxcarbazepine, phenobarbital, phenytoin, primidone,** rifampin, St. Johns wort

Drug interactions (CYP3A5)

CYP450 enzyme	Cannabinoid	Research	Medications metabolized by this pathway
CYP3A5 inhibition	CBD	In vitro, animal	Substrates: testosterone, progesterone, nifedipine, cyclosporine

Drug interactions (CYP2D6)

CYP450 enzyme	Cannabinoid	Research	Medications metabolized by this pathway
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, **duloxetine,** 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

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

Package Labeling DDI

Prescription Drug	Additional drug-drug interaction details
Dronabinol	- Protein-binding- warfarin, amphotercin 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:

Medications	Potential adverse effects (due to increased drug concentrations)
Aripiprazole, fluoxetine, bupropion XL, quetiapine, topiramate	Drowsiness, dizziness
Rivaroxaban	Bleeding

- 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

ROS	Adverse effects
Central nervous system	**Euphoria** (antiemetic: 24%; appetite stimulant: 8%), Abnormality in thinking, **paranoia, dizziness, drowsiness** (3% to 10%), amnesia (>1%), anxiety (>1%), ataxia (>1%), confusion (>1%), depersonalization (>1%), hallucination (>1%), nervousness (>1%)
Cardiovascular	Facial flushing, palpitations, tachycardia, vasodilation (>1%)
Gastrointestinal	**Abdominal pain, nausea, vomiting** (3% to 10%)

Nabilone (THC) Adverse Effects

ROS	Adverse effects
Cardiovascular	**Hypotension (8%)**
Central nervous system	**Drowsiness** (52% to 66%), **dizziness** (59%), vertigo (52% to 59%), **euphoria** (11% to 38%), ataxia (13% to 14%), **depression** (14%), **lack of concentration** (12%), **sleep disorder** (11%), dysphoria (9%), headache (6% to 7%), sedation (3%), depersonalization, disorientation (2%)
Gastrointestinal	**Xerostomia** (22% to 36%), anorexia (8%), nausea (4%), increased appetite (2%)
Ophthalmic	**Visual disturbance** (13%)
Neuromuscular & skeletal	Weakness (8%)

Cannabidiol (CBD) Adverse Effects

ROS	Adverse effects
Central nervous system	**Drowsiness**, 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%)
Dermatologic	Skin rash (7% to 13%)
Endocrine & metabolic	**Weight loss** (3% to 18%)
Gastrointestinal	**Decreased appetite** (16% to 22%), **diarrhea** (9% to 20%), gastroenteritis (4%), sialorrhea (≤4%), abdominal distress (≤3%), abdominal pain (≤3%)

Cannabidiol (CBD) Adverse Effects

ROS	Adverse effects
Hematologic & oncologic	**Anemia (30%)**
Hepatic	**Increased serum alanine aminotransferase (>3x ULN: 13% to 17%), increased serum transaminases (8% to 16%)**
Infection	**Infection** (25% to 41%), viral infection (7% to 11%), fungal infection (1% to 3%)
Neuromuscular & skeletal	Asthenia (≤12%)
Respiratory	Pneumonia (5% to 8%), hypoxia (≤3%), respiratory failure (≤3%)

Nabiximols Adverse Effects

ROS	Adverse effects
Cardiovascular	**Hypotension (5%),** palpitations (1%), syncope (1%), tachycardia (1%)
Central nervous system	**Dizziness (12% to 25%)**, drowsiness (8% to 15%), **fatigue (13%),** 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%)

Nabiximols Adverse Effects

ROS	Adverse effects
Gastrointestinal	**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%)
Genitourinary	Urinary retention (5%), hematuria (3%)
Hepatic	**Abnormal hepatic function tests (5%)**
Neuromuscular & skeletal	Weakness (5% to 6%)
Ophthalmic	Blurred vision (2%)
Respiratory	Throat irritation (1%)

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/#

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