

MEDICAL CANNABIS INDICATIONS

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M Health Fairview

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DISCLOSURE

I have no relevant financial relationships with a commercial interest to disclose.

Objectives

- Differentiate the spectrum of medical and non-medical cannabis indications
- Discuss the pharmacologic profiles of tetrahydrocannabinol (THC) and cannabidiol (CBD)
- Demonstrate compliance with federal and state laws for cannabis and hemp derivatives

Why focus on cannabis?

- Federal law does not authorize use of cannabis derivatives including tetrahydrocannabinol (THC) and cannabidiol (CBD)
- Drug Enforcement Agency (DEA) Scheduled 1 drugs are not approved for medical use due to:
 - high potential for abuse
 - no accepted medical treatment in the U.S.
 - lack of safety for use under medical supervision
- Contaminated vaping products containing THC have entered into the public mainstream resulting in severe lung injury and death

Reference: <https://www.deadiversion.usdoj.gov/schedules/>

DEA Classification of Cannabis Derivatives

- Schedule 1: no approved medical use
 - Tetrahydrocannabinol (marijuana, THC)
 - Conundrum: 31 states have approved medical cannabis
- Schedule 2: high potential for abuse
 - Nabilone (Cesamet®, THC) is FDA approved for chemotherapy nausea/vomiting
- Schedule 3: moderate potential for abuse
 - Dronabinol (Marinol®, THC) is FDA approved for appetite stimulation and nausea/vomiting
- Schedule 5: lower potential for abuse
 - Cannabidiol (Epidiolex®, CBD) is FDA-approved for epilepsy
 - Conundrum: all other CBD products for medical use are schedule 1

Cannabis

- Cannabis has been used for medicinal purposes dating back to ancient times
- Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most biologically active phytocannabinoids in cannabis capable of mimicking human endocannabinoids
- Potency of THC and CBD depends on plant species, cultivation, and storage
- Three species of cannabis identified (*C. sativa*, *C. indica*, and *C. ruderalis*)
 - *C. sativa* contains higher THC than CBD (marijuana and hemp)
 - *C. indica* contains higher CBD than THC

Reference: Mayo Clin Proc 2019; 4(9):1840-51

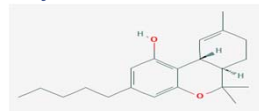
Cannabis Sativa



Leaves predominantly used for CBD and THC content in medical cannabis products and recreational marijuana

Seeds used for industrial hemp products including food and dietary supplements

Phytocannabinoids



Tetrahydrocannabinol (THC)

- Most prevalent component of cannabis
- Psychoactive properties
- Analgesic affect mediated by binding and activation of the cannabinoid receptors (CB1 agonist)



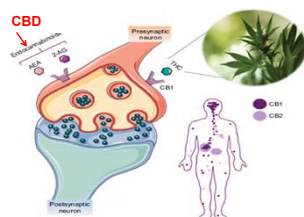
Cannabidiol (CBD)

- Second most prevalent component of cannabis
- No psychoactive properties
- Modulates endocannabinoid system through indirect mechanisms

Reference: <https://pubchem.ncbi.nlm.nih.gov>

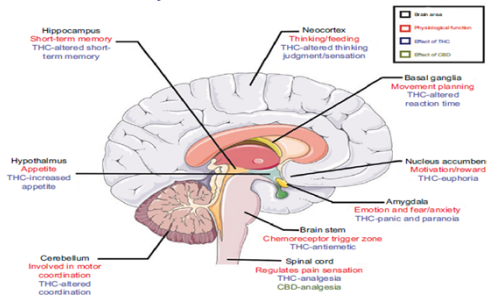
Mechanism of Action

- CB1 is a member of the Gprotein coupled receptor (GPCR) family
- Under normal biological conditions, neurotransmitters interact with the CB1 receptor to produce physiological effects
 - N-arachidonylethanolamide (AEA)
 - 2-arachidonoylglycerol(2-AG)
- In contrast, exogenous THC (marijuana) interacts directly at the CB1 receptor



References: Drug, healthcare and patient safety 2018, 10, 45-66
Adv Pharmacol. 2017 ; 80: 169-206

Endocannabinoid System



Reference: Drug, healthcare and patient safety 2018, 10, 45-66

Community Cannabis Preference

- Study of on-line posts on preferred products used by consumers for recreational or medical use
- Data from 2.26 million posts in a cannabis-specific forum on the Reddit social media platform posted from January 2010-December 2016
- Smoking was the most common method of use due to the subjective high(17.7%)
- Vaping has the highest adverse effects with "cough" term common (5%)
- Edibles viewed as "safer" than other uses but onset of high delayed due to oral absorption

Reference: Drug Alcohol Depend. 2018 July 01; 188: 364-369

Oral THC Pharmacokinetics

- Mainly metabolized in liver by the cytochrome P450 enzymes
- Peak plasma concentration 1-2 hours after oral ingestion
- Potency of oral edibles greater than inhalation due to the active 11-hydroxy Δ^9 -Tetra hydrocannabinol (11-OH-THC) metabolite
- Safe edible dose for an adult estimated at 10mg THC
- Highly lipid soluble
- Distributes into highly perfused organs with highest concentration in cardiac and fatty tissues
- Insufficient data on drug interactions

Reference: Drug, healthcare and patient safety 2018, 10, 45-66

Vaping

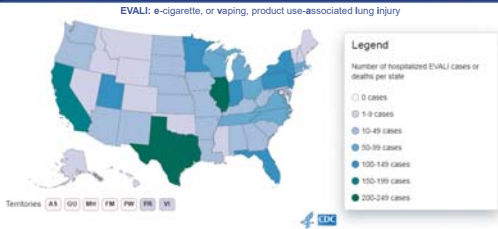
- “Vaping” (i.e., heating) is the practice of inhaling an aerosol created by heating liquid or wax containing substances containing nicotine and/or cannabinoids (THC and CBD) combined with additives and flavorings
- Vaping product use associated lung injury is an acute or subacute respiratory illness with damage to the alveoli that can be severe and life-threatening
- Vitamin E acetate is an oily chemical commonly added to THC vaping liquids to dilute or thicken them – may interfere with the surfactant in the lung leading to severe inflammation

Vaping Products

- FDA: as of January 29, 2020, 820 (76%) of the 1,070 samples connected to patients with vaping respiratory illnesses have undergone some level of testing
 - 508 of these samples have been found to contain THC
 - 51% of the THC products have been found to contain vitamin E acetate as a diluent
 - 26% of the THC products have been found to contain another diluent such as medium chain triglycerides

FDA Press Release 1/29/2020: <https://www.fda.gov/news-events/public-health-focus/lung-illnesses-associated-use-vaping-products>

Number of Hospitalized EVALI Cases or Deaths Reported to CDC as of January 21, 2020



- Over 2,600 cases of lung injury or death report related to vaping and e-cigarettes
- Sixty deaths reported in 27 states including 3 from Minnesota

https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information

Gateway Conundrum: Cannabis for Opioid Use Disorder

- Several state medical cannabis programs now approve use for opioid use disorder (OUD)
- Indicated for opioid withdrawal symptoms while the patient is transitioning to medication assisted treatment with buprenorphine or methadone



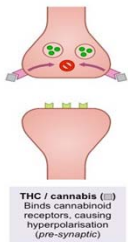
Dopamine Reward Pathway

- The prominent function of CB1 receptors in the ventral tegmental area (VTA) is to disinhibit dopamine neurons in reward-related behavior
- Exposure to CB1 agonists generate dopamine cell bursting and phasic dopamine release within the nucleus accumbens (NAc) which drives reward seeking
- CB1 receptors shape synaptic activity in the mesolimbic dopamine system to promote cue-directed reward seeking
- CB1 is the primary target for THC psychoactive and reinforcing properties

Reference: Brain Res. 2015 December 2; 1628(0 0): 233–243. doi:10.1016

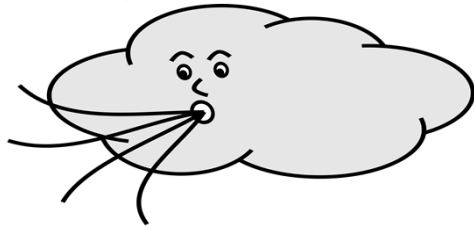
Recreational THC Impact

- Potent THC synthetic analogs are now being incorporated into edible and inhalation products
- Repeated heavy use of cannabis depletes presynaptic dopamine release in the ventral striatum
- Reduced dopamine is directly associated with negative emotion levels (increased stress and irritability) and addiction severity
- Endpoint is impaired cognition and working memory which negatively impacts education and occupational performance in critical decision-making



Reference: Nature. 2016 November 17; 539(7629): 369–377
Figure: <http://ib.bioninja.com.au/options/option-a-neurobiology-and/a5-neuropharmacology/psychoactive-drugs.html>

Winds of Change



Minnesota Medical Cannabis



NEW for 2020: 9 more locations

2020 UPDATE: MDH approved two new delivery methods to give patients more options. The new methods being added are water-soluble cannabinoid multi-particulates (for example, granules, powders and sprinkles) and orally dissolvable products such as lozenges, gums, mints, buccal tablets and sublingual tablets.

Photo Credit: Minnesota Department of Health

QUALIFYING MEDICAL CONDITIONS

- By law, only certain conditions currently qualify for treatment with medical cannabis in Minnesota:
- Cancer associated with severe/chronic pain, nausea or severe vomiting, or cachexia or severe wasting
 - Glaucoma
 - HIV/AIDS
 - Tourette syndrome
 - Amyotrophic Lateral Sclerosis (ALS)
 - Seizures, including those characteristic of epilepsy
 - Severe and persistent muscle spasms, including those characteristic of multiple sclerosis
 - Crohn's disease
 - Terminal illness, with a life expectancy of less than one year, if the illness or treatment produces severe/chronic pain, nausea or severe vomiting, cachexia or severe wasting
 - Intractable pain (defined in [Minnesota Statute 62A.02](#))
 - Post traumatic stress disorder
 - Autism
 - Obstructive sleep apnea
 - Alzheimer's

NEW Qualifying Conditions- Coming August 1, 2020

- Chronic pain
- Age-related macular degeneration

Photo Credit: Minnesota Department of Health

Minnesota Statistics: Vaping-Related Lung Injury

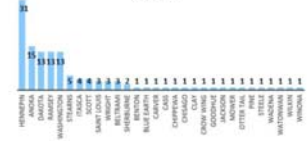
UPDATE: On Wednesday, October 16, 2019 MDH issued the following press release: [health officials confirm two more deaths from severe lung injuries associated with vaping](#)

UPDATE: On Friday, October 4, 2019, The FDA strengthened its warning to consumers to stop using Tetrahydrocannabinol (THC)-containing vaping products and any vaping products obtained off the street. To see the full statement, please visit the FDA website.

The Minnesota Department of Health has been working with federal and local public health, and health care providers to investigate the reports of vaping-related severe lung injuries. If you believe you might be experiencing lung injury related to vaping, please seek medical attention immediately. Patients experiencing symptoms, such as difficulty breathing, should avoid further use of vape products.

Vaping is one of several delivery methods allowed under Minnesota's medical cannabis program. While the evidence to date connects the lung injuries with use of illegal THC products and not medical cannabis, MDH cannot give complete assurance of the safety of any specific vaping product until investigators determine a cause of the lung injuries. Patients in the medical cannabis program who have concerns about vaping should talk to their provider or pharmacist at Minnesota's patient cannabis centers about alternatives that may be right for them.

Confirmed and Probable Cases by County



Reference: <https://www.health.state.mn.us/diseases/lunginjuries/countydata.html>

Hemp-Derived Products **ARE NOT** Medical Cannabis

- The federal Agriculture Improvement Act of 2018, Pub. L. 115-334, (the 2018 Farm Bill) was signed into law on Dec. 20, 2018.
- This new law changed production and marketing of hemp, defined as "the plant Cannabis sativa L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis."
- These changes include removing hemp from the CSA, which means that cannabis plants and derivatives that contain no more than 0.3 percent THC on a dry weight basis are no longer controlled substances under federal law.
- The 2018 Farm Bill, however, explicitly preserved FDA's authority to regulate products containing cannabis or cannabis-derived compounds under the FD&C Act and section 351 of the Public Health Service Act (PHS Act).

Reference: <https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>

Food, Drug and Cosmetics Act

- The United States Federal Food, Drug, and Cosmetic Act (FD&C), is a set of laws passed by Congress in 1938 giving authority to the U.S. Food and Drug Administration (FDA) to oversee the safety of food, drugs, medical devices, and cosmetics
- FD&C act can supersede Farm Bill when public safety is a concern allowing FDA intervention
- FDA currently does not classify THC and CBD as dietary supplements so cannot be marketed in this manner (**only hemp seed components can be incorporated into food and supplements**)
- FDA has not approved cannabis compounds derived from hemp for medical use so cannot be marketed
- Cosmetic products are excluded from premarket approval by the FDA so currently not regulated

Reference: <https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>

CBD Imposters

- Over the past several years, FDA has issued warning letters to firms that market unapproved new drugs that allegedly contain cannabidiol (CBD)
- As part of these actions, FDA has tested the chemical content of cannabinoid compounds and many were found to not contain the levels of CBD they claimed

Reference: <https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products>

Firm	State	Product Website
Bar CBD LLC	CA	barcbd.com
Flax Collections Inc.	CA	flaxcollections.com
Leaf SF LLC	TX	leafsf.com
Nature's Path LLC	OR	naturespath.com
Whole Leaf Organics LLC	CA	wholeleaforganics.com
Indica Probot Company LLC	CO	indicaprobot.com
Aqua Hemp SF LLC	OR	aquahemp.com
King Plant Labs	NY	kingplantlabs.com
Leafly Inc.	FL	leafly.org
Healthy Hemp Organics LLC (aka Hemp Company)	CA	hempco.com
Protein Plant LLC	NC	proteinplant.com
Planta Botanica Inc. (aka Plant Botanica)	CA	plantabotanica.com
Leaf of Wisdom Inc.	AZ	leafofwisdom.com
Leafy Wellness Co.	CA	leafywellness.com
Leafly Leaf LLC (aka Leafly Leaf Hemp Co.)	NY	leaflyleaf.com
Harvest Apothecary LLC	FL	harvestapothecary.com
Nature's Path Academy Inc.	AR	naturespathacademy.com
Alternative Labors Inc.	FL	alternativelabors.com
Greenleaf Inc.	MA	greenleafinc.com
Advanced Green and Plant LLC (aka Green Leaf)	NJ	advancedgreen.com
Leafy Plant LLC	MA	leafyplant.com
Flaxseed Hemp Inc.	FL	flaxseedhemp.com

Minnesota Department of Agriculture Hemp Program

- Effective January 1, 2020**, products containing CBD derived from hemp can be legally sold under Minnesota state law only if all the conditions outlined in M.S. 151.72 are met.
- Individuals and business in Minnesota must get licensed in the MDA Hemp Program to grow and process hemp. The MDA's Pilot Program will continue to be in effect until the USDA has approved the state plan.
- Minnesota statutes and the Food and Drug Administration (FDA) contend that CBD cannot be added to foods and cannot be sold as a dietary supplement. The 2018 Farm Bill did not change the Federal Food, Drug, and Cosmetic Act. The MDA Hemp Program does not have authority to make any determinations for the legality of food, beverage, cosmetic, drug, or animal feed products.
- Application deadline for hemp pilot program March 1, 2020

Reference: <https://www.mda.state.mn.us/plants/hemp/industrialhempquestions>

Healthcare Professional Role

- Assess patient risk for illicit use and addiction prior to medical cannabis authorization
- Educate patient on safe and responsible use
 - Consider risks for employment in jobs involving public safety
 - Discuss potential for positive urine drug tests which may be prohibited for federal jobs, sports, schools, and treatment programs
- Advocate use of medical cannabis and CBD according to state law

Helpful Resources Through Creative Commons

Medical Cannabis Primer
Mouhamed, Y., Vishnyakov, A., Qorri, B., Sami, M., Frank, S. S., Nowierski, C., Lamba, A., Bhatti, U., Szewczuk, M. R. (2018). Therapeutic potential of medicinal marijuana: an educational primer for health care professionals. *Drug, healthcare and patient safety*, 10, 45-66. doi:10.2147/DHPS.S158592

Cannabis and Hemp
VanDolah HJ, Bauer BA, Mauck KF. Clinician's guide to cannabidiol and hemp oils. *Mayo Clin Proc* 2019; 4(9):1840-51

Chemical Structures and Pharmacology
Pub Chem Website. <https://pubchem.ncbi.nlm.nih.gov/>

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