

Vaping, Medical Marijuana, CBD

*KCU-CME Update in Medicine
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Objectives

1. Define vaping and discuss the benefits and risks associated with it.
2. Discuss the reasons for increasing health concerns related to vaping.
3. Define medical marijuana and discuss relevant federal and state regulations.
4. Discuss the potential uses/benefits and adverse effects of medical marijuana.
5. Explain why fatty acid amide hydrolase (FAAH) is of interest to pharmaceutical manufacturers.
6. Contrast cannabidiol (CBD) with Δ -9-tetrahydrocannabinol (THC).
7. Discuss the FDA-approved use of CBD, and other uses undergoing investigation.
8. Discuss the legal status of CBD, and the impact this has on CBD sales.

Vaping

How an E-cigarette Works

E-cigarettes create an aerosol by using a battery to heat up liquid that usually contains nicotine, flavorings, and other additives.

- Users inhale this aerosol into their lungs.
- E-cigarettes can also deliver other drugs such as cannabinoids.

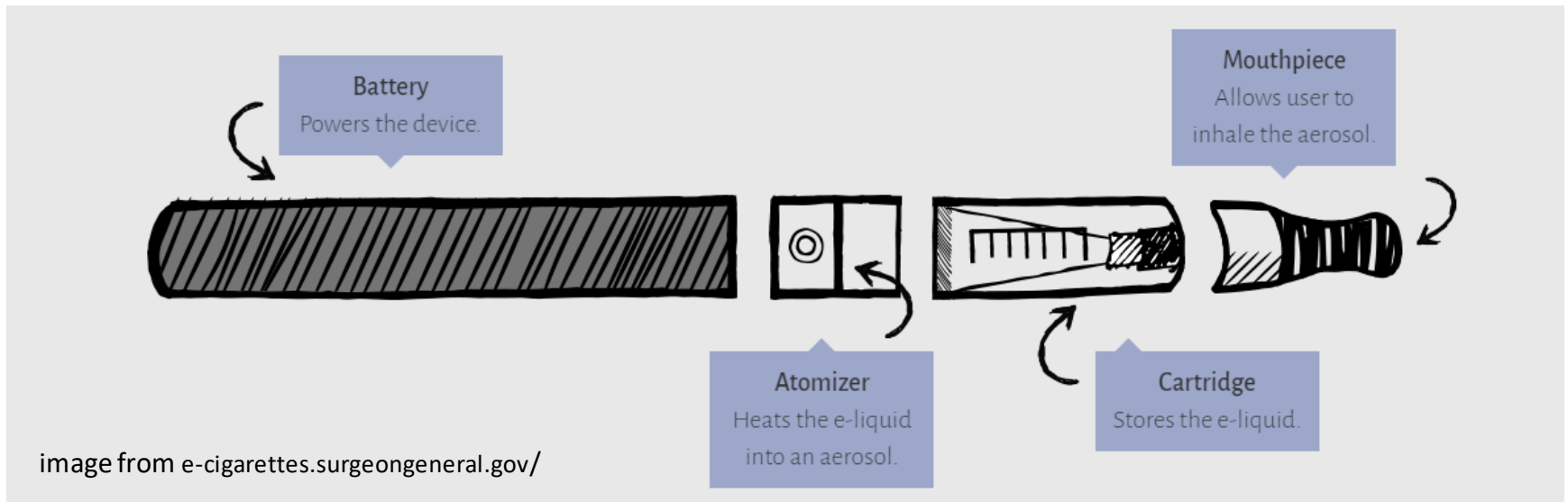


image from wikipedia

E-cigarettes are available in all shapes/sizes...

Juul had 72% of Market Share in Sept. 2018 with \$2 billion of revenue



Juul has multiple flavors other than tobacco...
... all have nicotine, with choice of 3% or 5%



- plus there are multiple sellers of Juul pod clones, usually unlicensed... e.g., from 1/18 – 8/18, Juul:
 - sued 30 Chinese business entities
 - blocked >16,000 listings on eBay and Amazon

but, can also DIY the e-liquid...

1

base liquid... generally a mixture of propylene glycol and vegetable glycerin (< \$15 ea / qt)

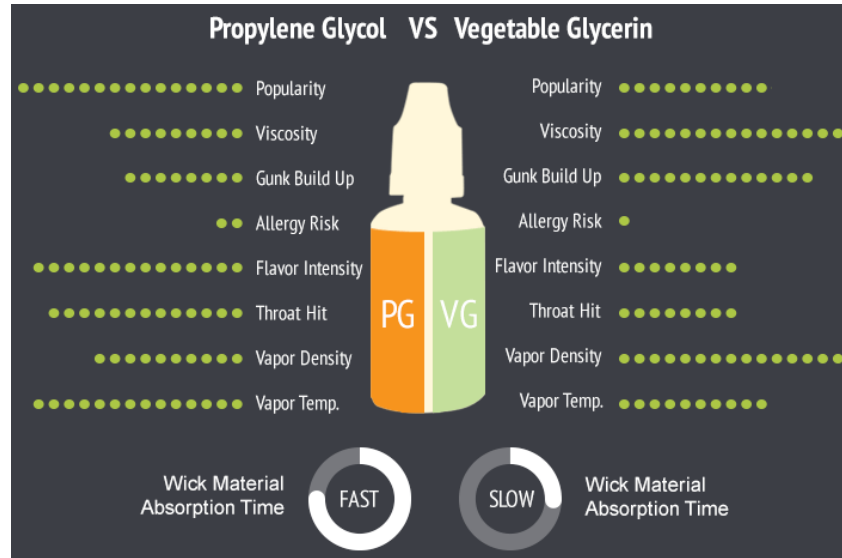
2



water-soluble flavor concentrates... 1000s to choose from, typically few \$/ml

3

e-liquid nicotine, 48 mg/ml (\$33 / L)



+ recipes and/or creativity

Benefits of Juul / Vaping

The American Cancer Society notes that cigarette smoke contains **thousands of chemicals** including **≥ 70 known carcinogens**.

E-cigarette liquids have far fewer chemicals (~ 80 total)

- **Vaping is less expensive** than smoking cigarettes ... 1 pod \cong 1 cigarette pack.
KC average price for Marlboro is \$5.68. Juul 4-pod pack \leq \$16 or \sim \$4 ea.; less for Juul pod clones or homemade
- **Vape tastes better than cigarette smoke**
- **Fingers no longer stink** of cigarette smoke, **stains slowly disappear**
- **Teeth get whiter** as tar build-up wears off
- **Overall looks improves** because skin and hair are not damaged as happens with cigarette smoke
- **Sense of smell and taste improve**
- **Social interactions increase** since vaping lacks the gross/dirty stigma associated with cigarette smoking
- **Don't need to go outside for a smoke break**
- Vaping causes **less damage to the lungs** than cigarette smoke
- Can help people **stop smoking cigarettes**



Learn Amazing Tricks!



Tricks by Austin Lawrence
GQ Magazine's Vape God
<https://www.youtube.com/watch?v=zVXR7xttUeo>



Impress your Friends!



Reasons for Concern (1)

- In 2018, MMWR noted that **19% of girls** and **23% of boys** in middle and high schools used tobacco products
 - common for students to use **both** e-cigarettes and conventional cigarettes
 - use is greater among **older students** and those who are **Non-Hispanic Whites** or **Hispanics**
- **68% of e-cigarette users in high school use flavors**

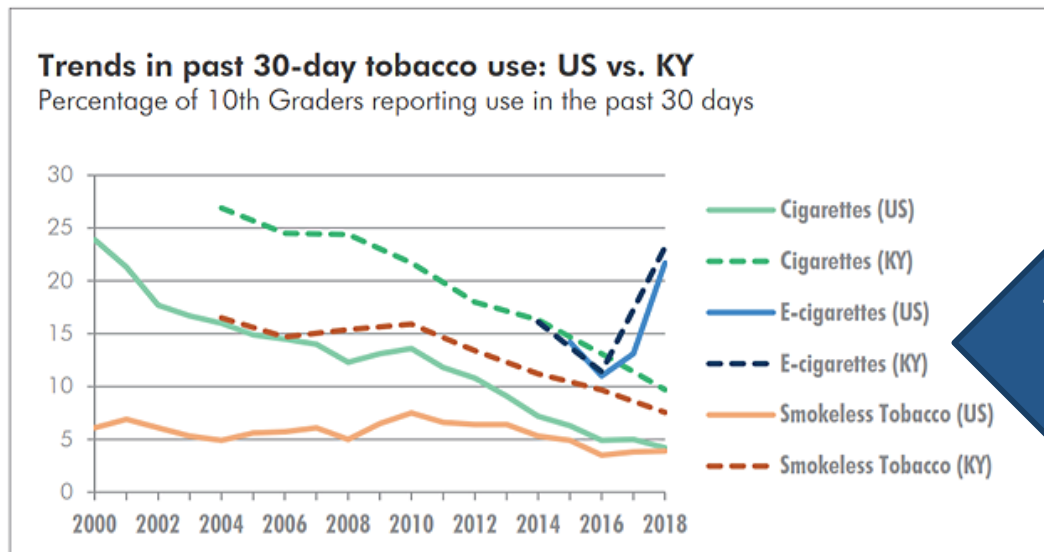


image from Univ of Kentucky

?! ... abrupt upward trend
grabs one's attention

content from <https://e-cigarettes.surgeongeneral.gov>

Reasons for Concern (2)

- **reasons for vaping include:**
 - use by friend/family member
 - taste, variety of flavors
 - belief that less harmful than other tobacco products... 10% believe e-cigarettes cause no harm and 62% that they cause little to some harm
 - curiosity... packaging, sexual content/themes, etc., are aimed at youth and young adults
- **students become addicted to nicotine...**
 - nicotine can harm the developing brain, which continues to develop until ~ age 25
 - leads them to burned tobacco products
 - former smokers become re-addicted to nicotine

Commercial Vaping Products are Contaminated

Endotoxin and (1→3)- β -D-Glucan Contamination in Electronic Cigarette Products Sold in the United States. MS Lee , JG Allen and DC Christiani, Environmental Health Perspectives Vol. 127, No. 4, **April 2019**

- authors selected 37 cartridges and 38 e-liquid products with the highest nicotine content from the ten top-selling U.S. brands
- **23% had detectable bacterial endotoxin (17 of 75) and 81% had detectable fungal glucan (61 of 75)**
 - higher in cartridges than e-liquids
 - higher in tobacco-flavored products than fruit-flavored products
- this lab previously detected various other toxins in e-cigarettes and/or common flavorings including:
 - **formaldehyde**
 - **diacetal** causes bronchiolitis obliterans, i.e., “popcorn lung” as seen in popcorn factory workers
 - **but not seen thus far from vaping**



image from advances-in-medicine.net

Lung Illness Outbreak Linked to Vaping

- **298 cases in 23 states** so far this summer
- thus far, vaping is only common link...
 - unknown if due to street concoction, contaminant, defective device, etc.
 - biopsies from various patients are not the same
 - some have injuries consistent with chemical injury
 - young woman interviewed in NV had eosinophilic pneumonia
 - 7 interviewed from 20 in MN acknowledged vaping THC
- thus far, **1 death of adult**
 - age range of patients is 16 – 72
 - most seriously ill patients have **extensive lung damage** requiring oxygen and days on ventilator; some will have **permanent** lung damage

Other Adverse Consequences of Vaping



Injuries due to e-cigarette explosion



Young patient who used e-cigarettes for 5 years... also drank high-sugar energy drinks in part because vaping made his mouth dry

Vaping... bottom line

- definitely safer than burned tobacco products, but vape still contains harmful chemicals
- most vaping products contain nicotine, which is addictive
- vaping now appears to be more common in military than smoking regular cigarettes... 10 – 11% overall vape daily, but ~20% of junior enlisted ranks
- overall impact on health still has not been determined, e.g.:
 - compounds that are safe to ingest may not be safe to inhale
 - source(s) of summer lung injuries remain unknown



image from news.stlpublicradio.org

Medical Marijuana



image from leafly.com

What is Medical Marijuana?

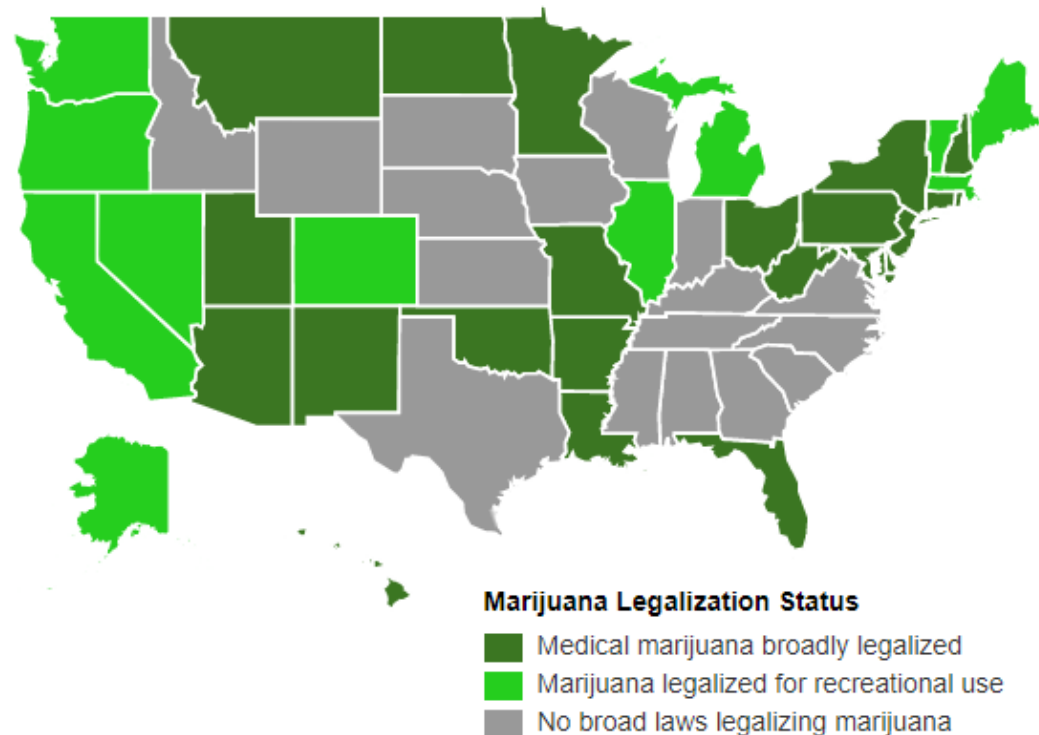
- use of marijuana plant or chemicals from it to treat medical conditions rather than for recreational use
- marijuana plants have > 100 chemicals referred to as cannabinoids, with the main two being:
 - Δ -9-tetrahydrocannabinol (THC), responsible for “high”
 - cannabidiol (CBD)



image from wvtf.org

Regulations

- still Schedule I at the federal level, which makes research more difficult due to need for special permits
- nonetheless, medical marijuana is legal in 33 states and DC
- getting it as a patient requires:
 - written recommendation from a licensed doctor
 - a qualifying condition
 - ± a medical card



Missouri Medical Marijuana Regulations

- **must obtain ID card, costs \$25**
- **qualifying conditions include:**
 - cancer
 - epilepsy
 - glaucoma
 - intractable migraines
 - chronic condition that causes severe persistent pain or muscle spasms... includes multiple sclerosis, Parkinson disease, Tourette syndrome
 - debilitating psychiatric disorders such as post-traumatic stress disorder
 - HIV/AIDS
 - others....



With approval of Amendment 2 in 2018, MO will award 348 licenses from 2163 applications

- **192 for dispensaries**
- 60 for cultivation facilities
- 86 for manufacturing facilities
- 10 for testing labs
- applications “blind-scored” by 11/30/19
- dispensaries to open late spring 2020

Home grown...

- can be indoors or outdoors, but must be locked
- limited to ≤ 6 flower plants, ≤ 6 in “vegetative state and ≤ 6 seedlings

Routes of Administration

- smoke it
- vape it
- eat it – brownie, lollipop, etc.
- apply to skin in lotion spray, oil or cream
- place drops sublingually

Potential Benefits of Cannabinoids

- **stimulate appetite** in people with cancer and AIDS
- **control nausea and vomiting** caused by cancer chemotherapy
- **reduce anxiety**
- **reduce inflammation / pain**
- **reducing spasticity** and spasticity-related pain in multiple sclerosis
- **slowing cancer cell growth...** evidence is lacking

Adverse Effects

- **affects judgement and coordination** thereby increasing risk for accidents
- **bloodshot eyes, depression, dizziness, tachycardia, hypotension, hallucinations**
- concern of **adverse effects on intelligence and mental function in younger people** with still-developing brains
- National Institute of Drug Abuse considers marijuana to be **addictive** and a **“gateway” drug**

Dronabinol

- orally administered **synthetic Δ -9-THC**, peak effects in 2-4 hrs
- has \cong affinity for CB₁ and CB₂ receptors, but less efficacy at CB₂ receptors...
 - so, **analgesia, appetite enhancement, muscle relaxation** and **hormonal actions** are mediated by **CB₁ receptors**
 - **psychological effects** lasting 4-6 hrs are divided into:
 - **affective** (euphoria, easy laughter)
 - **sensory** (increased perception of external stimuli, own body)
 - **somatic** (feeling of body floating or sinking in bed)
 - **cognitive** (altered time perception, memory lapses, etc.)
- labeled indications: **anorexia** in AIDS patients, **chemotherapy-induced nausea and vomiting**
- off-label use: moderate to severe **obstructive sleep apnea**

Other cannabinoid-related things of interest...

- FAAH (fatty acid amide hydrolase) inhibitors, breaks down endocannabinoids anandamide and 2-arachidonylglycerol (2-AG)
- FAAH KO mice have an analgesic phenotype
- Scottish woman with FAAH mutation experiences little anxiety or fear and is insensitive to pain, and heals quickly
- multiple drugs FAAH inhibitors were developed, but no successful clinical trials so far
 - various trials put on hold when BIA 10-2474 caused severe adverse effects in 5 patients and death of 6th
 - BIA 10-2474 now recently shown to have numerous off-target effects



image from bioquicknews.com

Cannabidiol (CBD)

second-most abundant cannabinoid

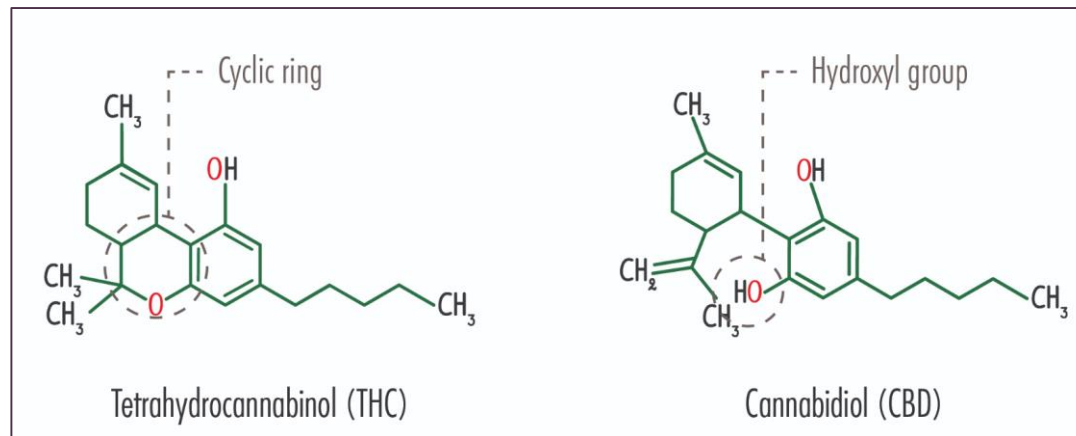


image from analyticalcannabis.com

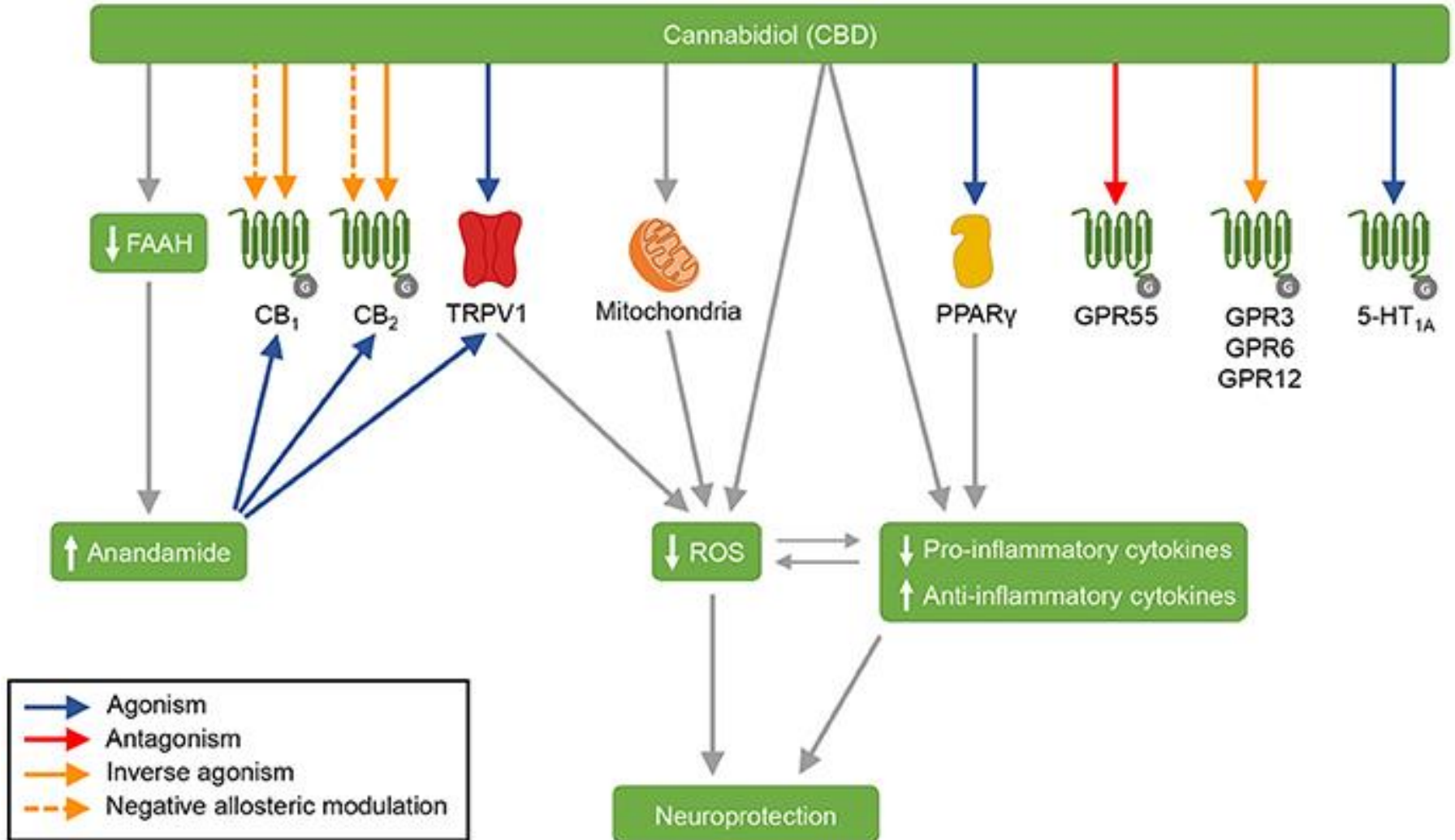
CBD exists in a legal gray zone

- under US federal law, illegal to sell as a food, dietary supplement or animal feed
- CBD derived from hemp (with 0.3% THC or lower) was delisted as a federally scheduled substance by the 2018 Farm Bill.
 - hemp CBD is legal to sell as a cosmetics ingredient
 - FDA regulations still apply

CBD Pharmacokinetics

- refers to the **naturally occurring (-)-CBD enantiomer**
 - (+)-CBD has been synthesized but is less studied
- CBD is **generally administered orally** as either a capsule, or dissolved in sesame or olive oil solution at doses ranging from 100 – 800 mg/day
 - **poor aqueous solubility** → to **erratic absorption** from the GI tract
 - **oral bioavailability ~6%** due to **significant first-pass metabolism**
- aerosolized inhaled CBD has higher bioavailability and gives peak plasma concentrations in 5–10 minutes; also can be administered through sublingual or intranasal routes
- like THC, CBD **rapidly distributes**, has **high volume of distribution** (~32L/kg), **accumulates in adipose tissue** due to high lipophilicity
- CBD is **extensively metabolized in the liver by 7 CYPs**, primarily by CYP3A4 and CYP2C19...

CBD Pharmacodynamics



- CBD effects are very different from THC, often opposing effects

CBD Adverse Reactions in Humans

- CBD it is **generally well tolerated**, with no cardiovascular effects and a good safety profile
 - have seen increased drowsiness, fatigue, decreased appetite, diarrhea, anemia, infections, etc., with Epidiolex
- CBD **does not produce the psychoactive effects** that are typically seen with cannabinoids such as THC
- CBD has **not been shown** to have a **potential for abuse**
- human studies of CBD **tolerance** and **withdrawal** have **not been reported**

CBD Toxicology

- has **no effect** on **embryonic development** (limited research)
- has **no effect** on a **wide range of physiological and biochemical parameters** or significant effects on animal behavior unless extremely high doses are administered
- **no evidence of abuse potential or dependence** from animal studies
- **effects on the immune system are unclear**; there is evidence of immune suppression at higher conc., but lower conc. may stimulate
- **some potential for CBD to be associated with drug interactions** through inhibition of some cytochrome P450 enzymes, but relevance at clinical conc. is not yet clear
- with recently FDA-approved Epidiolex[®], there is:
 - recommendation to look for evidence of liver toxicity
 - recommendation to look for suicidal ideation (rare)

So how/when is CBD useful? Epilepsy

- Epidiolex® is an oral CBD solution recently approved by the FDA as a Schedule V drug for treatment of rare child-hood epilepsies in people 2 years of age and older
 - Lennox-Gastaut syndrome and Dravet syndrome
 - unknown if safe/effective in children younger than 2
- this use of CBD dates back to studies in the 1970s in animals, small trials showing benefit resulted in larger clinical trials
- in controlled trial for **Dravet syndrome** with 120 children,
 - CBD decreased convulsive seizures from 12.5 to 5.9 in CBD group with no change in placebo
 - 5% of CBD treated patients were seizure-free
- In a 14-wk study of CBD in 171 patients ages 2-55 with **Lennox-Gastaut syndrome** in US, Netherlands and Poland, there was a 43.9% decrease in drop seizures in treatment group vs 21.8% in placebo group.
 - 44% percent reduced drop frequency > 50% vs 24% for placebo
 - 3 of 86 CBD patients were seizure-free during treatment period
- there is evidence that some adverse effects of cannabidiol observed in the clinical studies may relate to interactions with other antiepileptic drugs, e.g., clobazam

Dravet Syndrome

- rare disorder affecting affects < 1:40000 births
- ~80% have non-inherited mutations in SCN1A (gives dysfunctional Na⁺-channels in brain)
 - main presentation is epileptic seizures
 - most children also have some developmental disability
- **myoclonic seizures** develop between ages 1 to 5 in 85% of these children, can be general or on one side
- found in 3 – 8% of children with a seizure before age 1
- **seizures lasting > 10 min**, occurring on **one side** and **triggered by warm baths** are considered risk factors
- **responds poorly to conventional antiepileptic therapies, high mortality**



Chase 16 month old myoclonic seizure

gif from <https://www.youtube.com/watch?v=VC6HJPzr1VU>

Lennox–Gastaut syndrome

- **complex, rare severe childhood-onset epilepsy** typically presenting **ages 3-5** and **persisting into adulthood**
- **seizures** often occur **daily**, generally **tonic seizures** lasting a few seconds that occur during **non-REM sleep**...
 - characteristic **consistently slow spike wave on awake EEG**
 - many also have **nonconvulsive status epilepticus** which can lead to falls and injury
- associated with variety of **gene mutations** (e.g., tuberous sclerosis), **perinatal insults**, **congenital infections**, **brain malformations** or **tumors**
- **responds poorly to conventional antiepileptic therapies**, **high mortality**



Epilepsy in schools: how to deal with a tonic seizure
629,194 views



gif made from Epilepsy Action movie



<https://www.youtube.com/watch?v=pjmDY3tR6ak>

CBD Therapeutic Applications... other

- **Alzheimer disease**... animal studies suggesting potential for benefit due in part to anti-inflammatory actions
- **nausea and vomiting**... unlike CB₁ agonist THC, CBD may exert similar beneficial effects by indirect activation of somatodendritic 5-HT_{1A} receptors in the dorsal raphe nucleus
- **pain**... evidence thus far for cannabinoids altogether in humans is not impressive
- **fragile X syndrome**... patent was recently granted based on clinical evidence that a CBD product was an effective treatment for many of its behavioral and emotional symptoms
- **skin diseases**... CBD is reported to normalize unwanted skin growth, reduce excessive production of oils and reduce inflammation and infection
- **cancer**... in vitro evidence of benefit but animal/human studies remain inconclusive
- **CBD tampons**... yes, these are in development to relieve menstrual pain; cannabinoid receptors are abundant in vagina
- **ADHD**... little scientific evidence supporting this
- **anxiety/depression**... some evidence of benefit from animal studies, but limited clinical data
- **schizophrenia**... only clinical trial to date failed

CBD is legal for sale in “cosmetics”



Short list of benefits may include relief of issues resulting from hemp*:

- pain, inflammation, headaches/migraines, arthritis, anxiety, depression or other mental illness, digestion, smoking, drug withdrawals, sleep/insomnia, diabetes, acne, Alzheimer disease, glaucoma

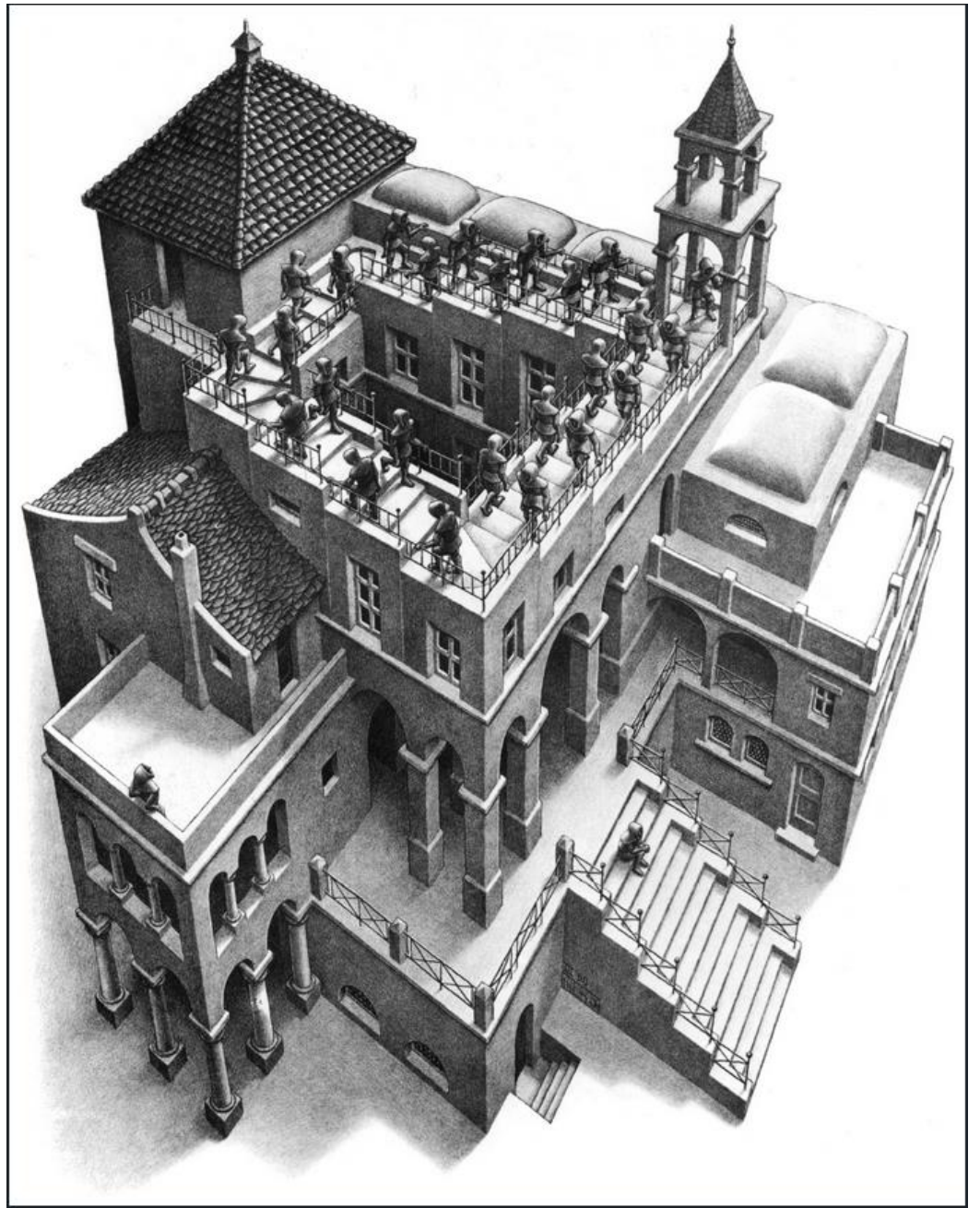
* with the obligatory, “This statement has not been evaluated by the Food and Drug Administration.”

... the FDA has clamped down on some larger sellers for similar statements

CBD Summary

- CBD is a naturally occurring cannabinoids found in cannabis plants
- In both humans and experimental models, CBD exhibits no effects suggestive of abuse or dependence
 - it is not a substitute for tetrahydrocannabinol in animal models of drug discrimination
 - there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD
- CBD was an effective treatment of epilepsy in several clinical trials
- CBD may be a useful treatment for a number of other medical conditions
- There is unsanctioned medical use of CBD based products with oils, supplements, gums, and high concentration extracts available online for the treatment of many ailments
- CBD is generally well tolerated with a good safety profile
 - reported adverse effects may be as a result of drug-drug interactions between CBD and patients' existing medications
- several countries have modified their national controls to accommodate CBD as a medicinal product

-- end --



MC Escher's "Ascending and Descending", 1960