Neuroscience Education Institute

DOOBIE DO OR DOOBIE DON'T? WHERE THE EVIDENCE LIES REGARDING *CANNABIS* USE

Learning Objectives

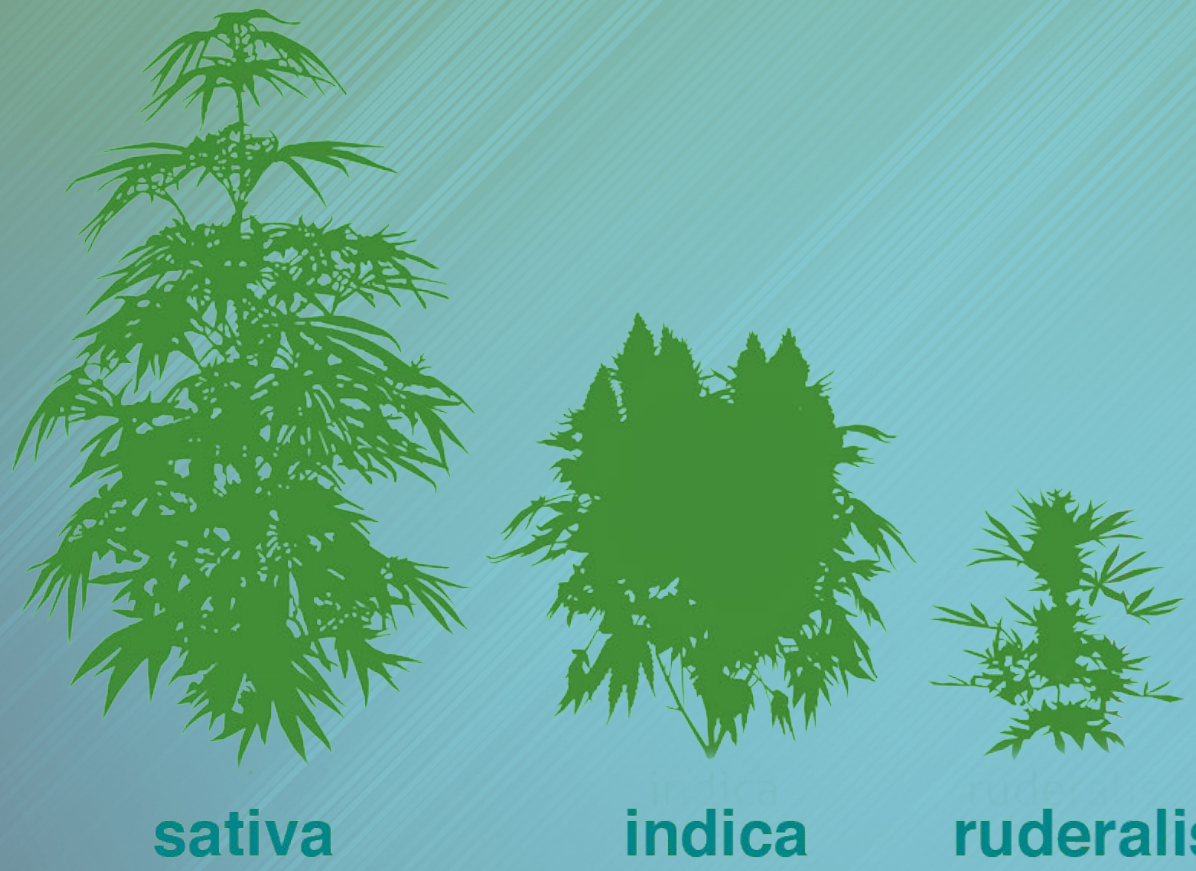
- Discuss the purported mechanisms of various components of *Cannabis*
- Interpret clinical studies discussing the efficacy of *Cannabis* for treating various syndromes
- Describe doses patients could use based on the differences in how quickly, how long, and how reliably various *Cannabis* formulations get into the body

What component do you talk to your patients about?

- Both hemp and marijuana come from *Cannabis* plant
- *Cannabis* contains over 400 compounds
  - Over 100 cannabinoids have been isolated, Δ-9-tetrahydrocannabinol (THC), and cannabidiol (CBD) are the most known
  - Over 200 terpenes have been isolated, contribute to aroma (limonene, pinene, myrcene)

Borgelt LM, Franson KL, Nussbaum AM, Wang GS. Pharmacotherapy 2013.

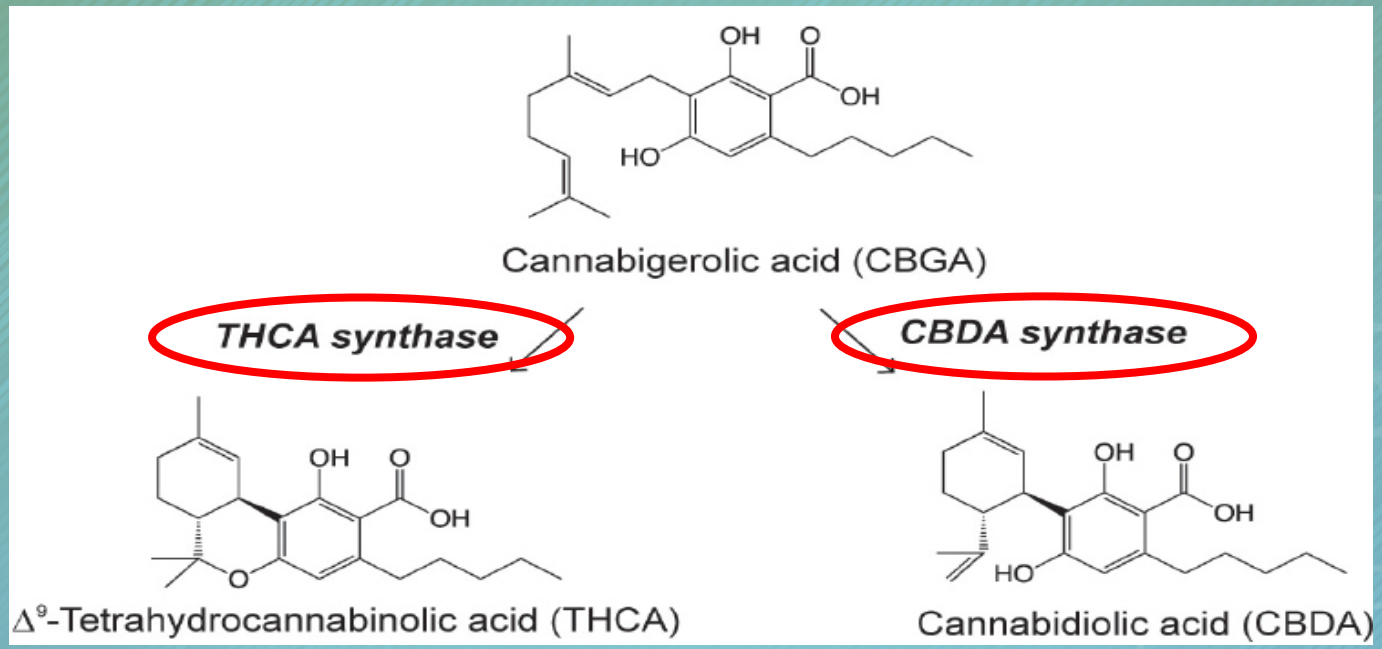
Different *Cannabis* species



C. indica and *C. sativa* have been cross-bred so can't rely on generalizable characteristics

Adapted from Creative Commons: The_Three_Cultivars_of_the_Cannabis_Plant.png

Chemistry of THC vs. CBD



The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. Washington (DC): National Academies Press (US); 2017.

Variation in *Cannabis* phenotypes ("strains")

Chemotype	Typical THC	Typical CBD	Now available
THC-type	0.5-15%	<0.16%	>35%
Hybrid	0.5-5%	0.9-7.3%	
CBD-type	<0.7%	1.0-13.6%	>20%
Industrial hemp	<0.3%		

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. Washington (DC): National Academies Press *(US);* 2017.

No fertilization → high THC/CBD

Seeds ready to harvest as dietary supplement

Bud ready to harvest for cannabinoids

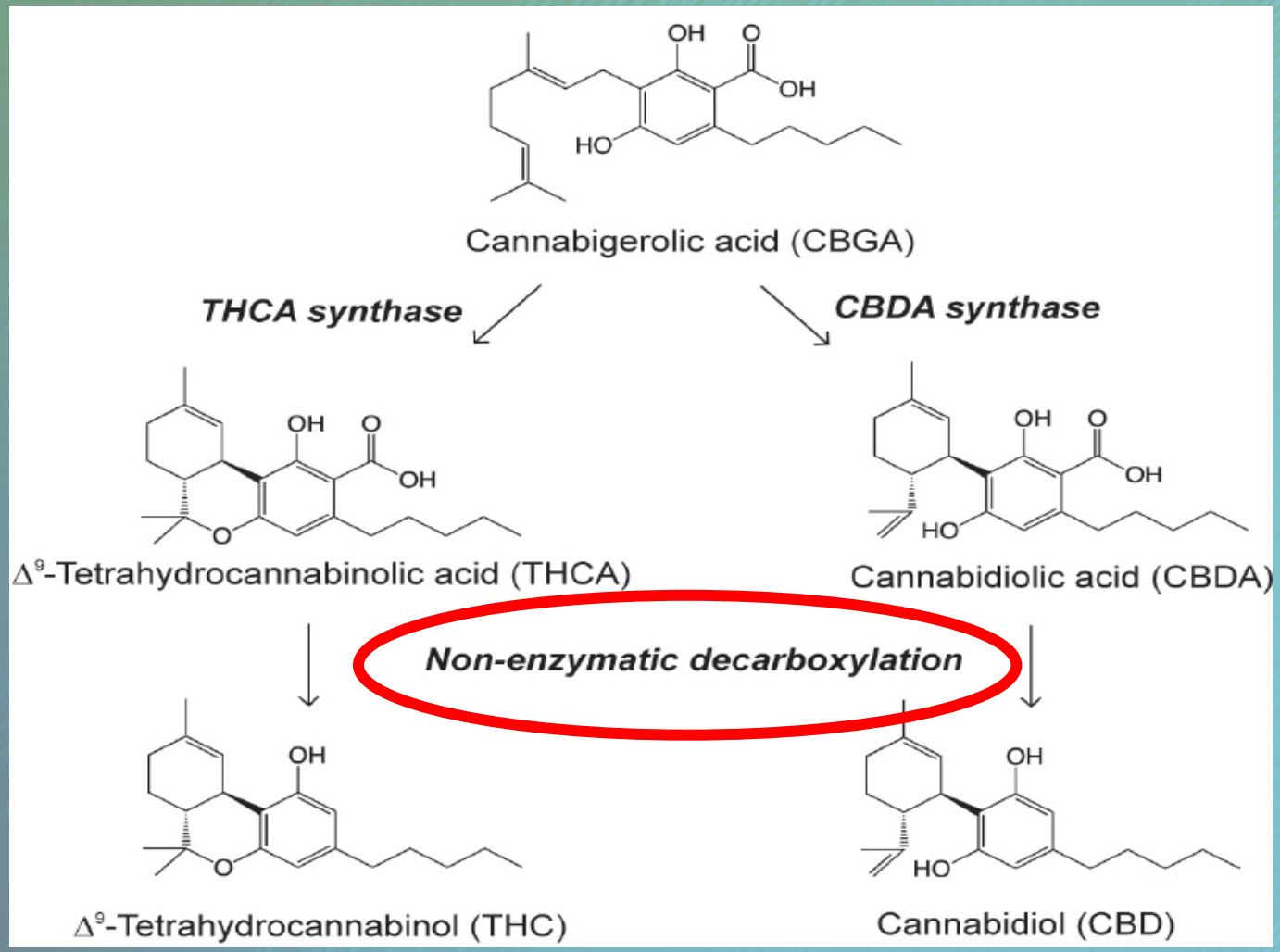
Using the *Cannabis* plant

Does eating marijuana make people sick or high?

According to Phoenix PD Chief Joe Yahner, officers made a man eat a gram of marijuana, which made us ask: How much would someone have to eat before they got sick? What about before they got high?

https://www.12news.com/article/news/local/valley/does-eating-marijuana-make-people-sick-or-high/324090140

Not “activated” until decarboxylated



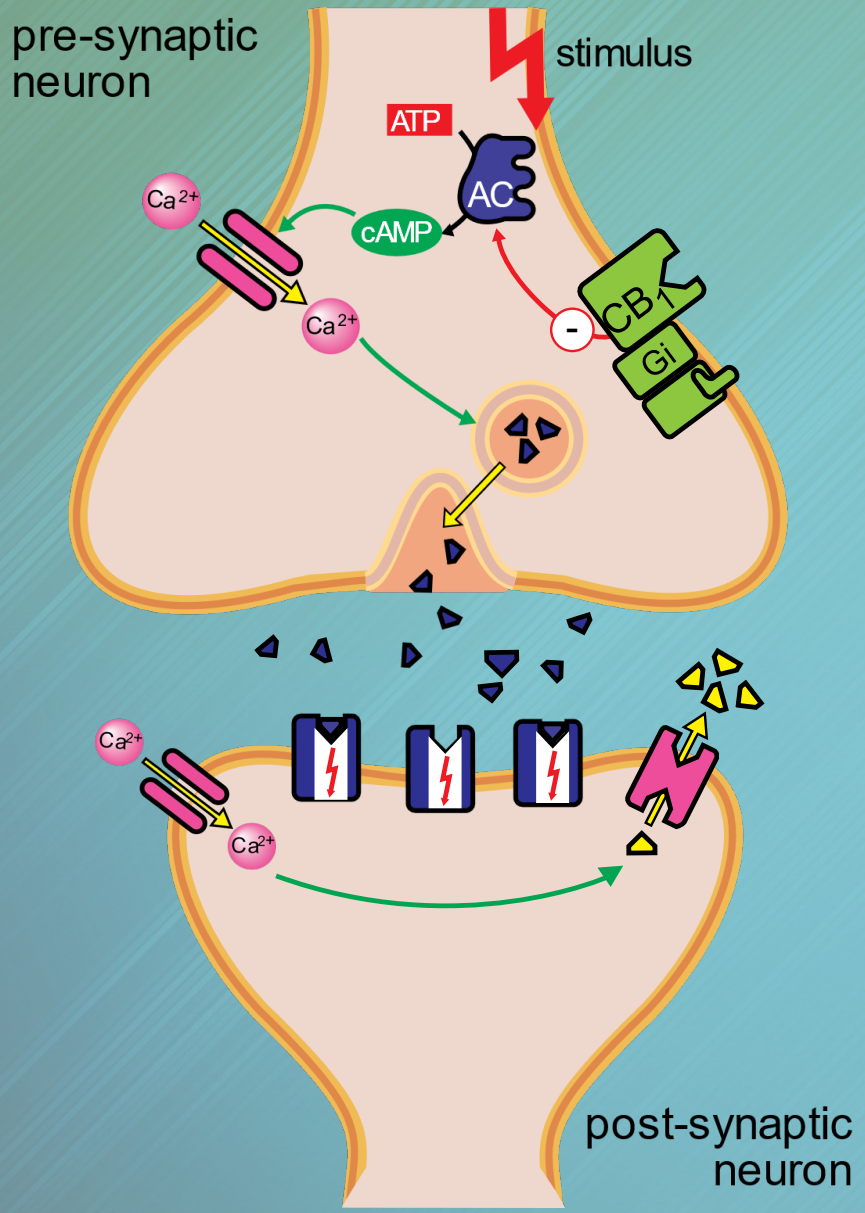
- Heat
- Light
- Cofactors or solvents
- Conversion in the body

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. Washington (DC): National Academies Press (US); 2017.

How do you answer when a patient asks: *"Do you think Cannabis will work for me?"*

- Consider: Why is the patient asking?
  - 2019 Medical and recreational *Cannabis* sales were over $12 billion

The endocannabinoid system



Neurotransmitter (DA, GABA, glutamate)

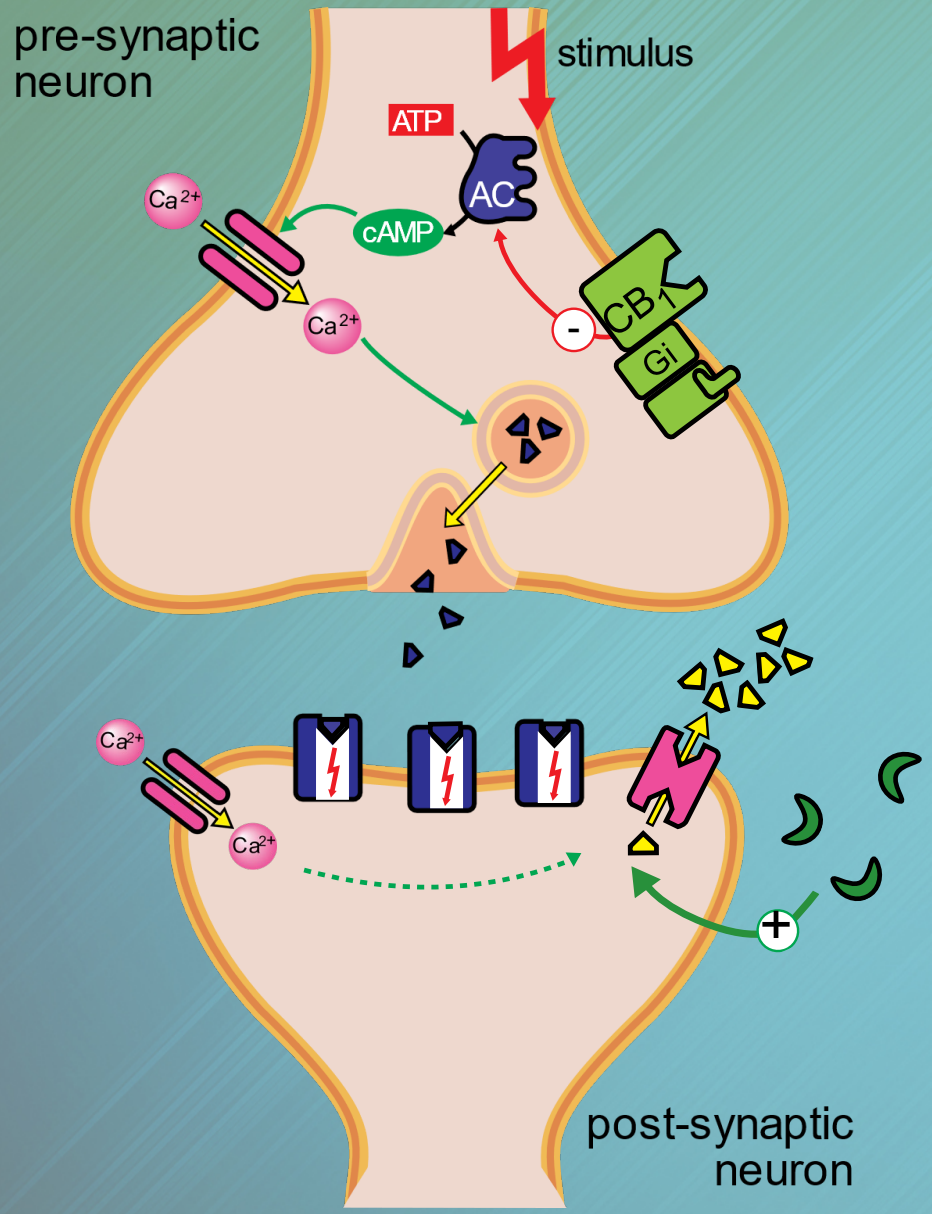
Endocannabinoid (anandamide, 2-AG)

Endocannabinoid membrane transporter

Cannabinoid receptor

Neuromodulation of GLU, Ach, GABA, DA, NE

Mechanism of CBD



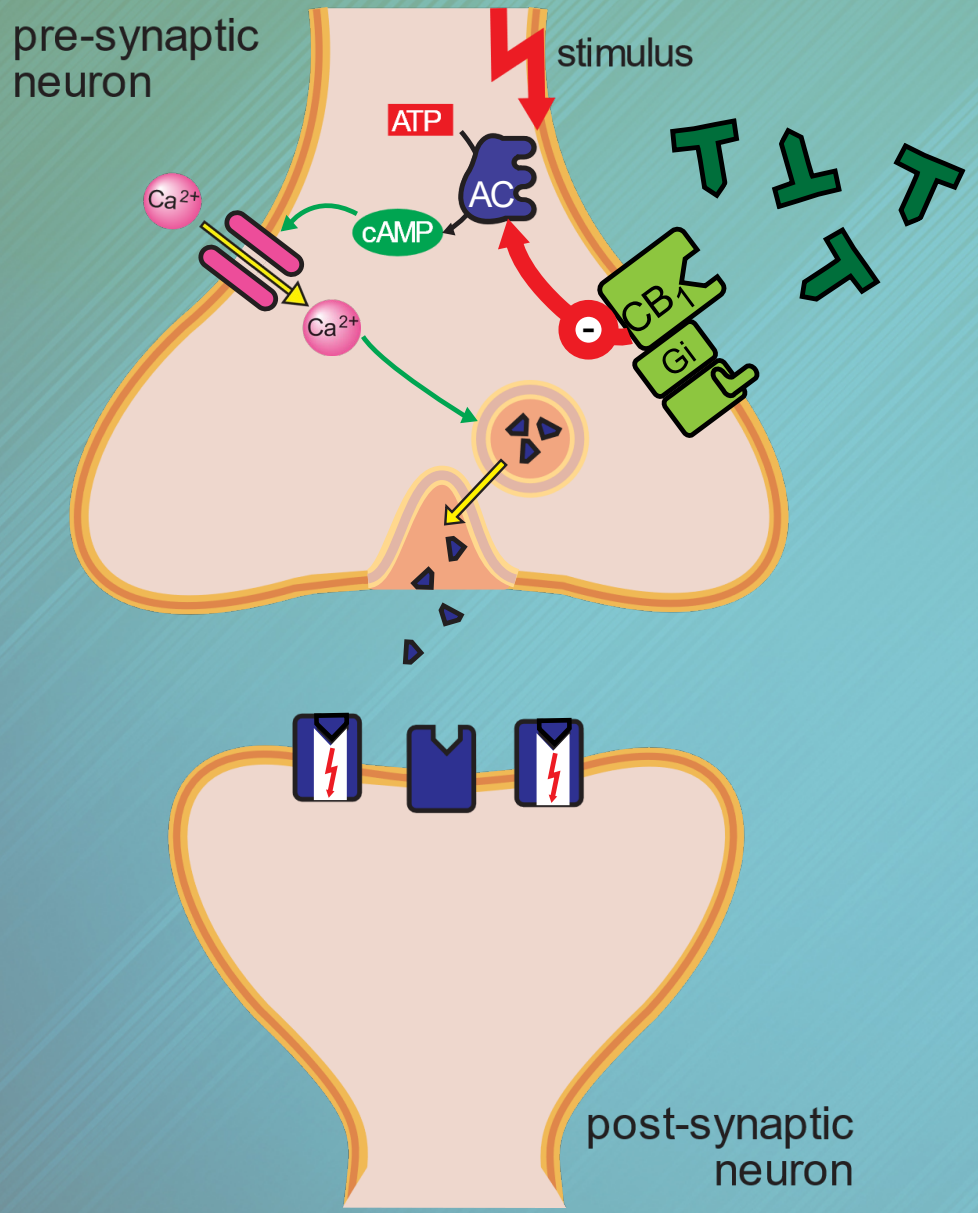
systemic CBD

Other mechanisms:

- Stimulates adenosine A_{2A} → ↓ inflammation & pain
- Agonist at $TRPA_1$ & $TRPV_1$ receptors → ↓ pain
- Agonist at 5-HT_{1A} receptors → ↓ anxiety & depression
- Inhibits voltage dependent anion channels → ↓ seizure activity

Nahler G et al. J Altern Complement Integr Med 2018.

Mechanism of THC



T systemic THC

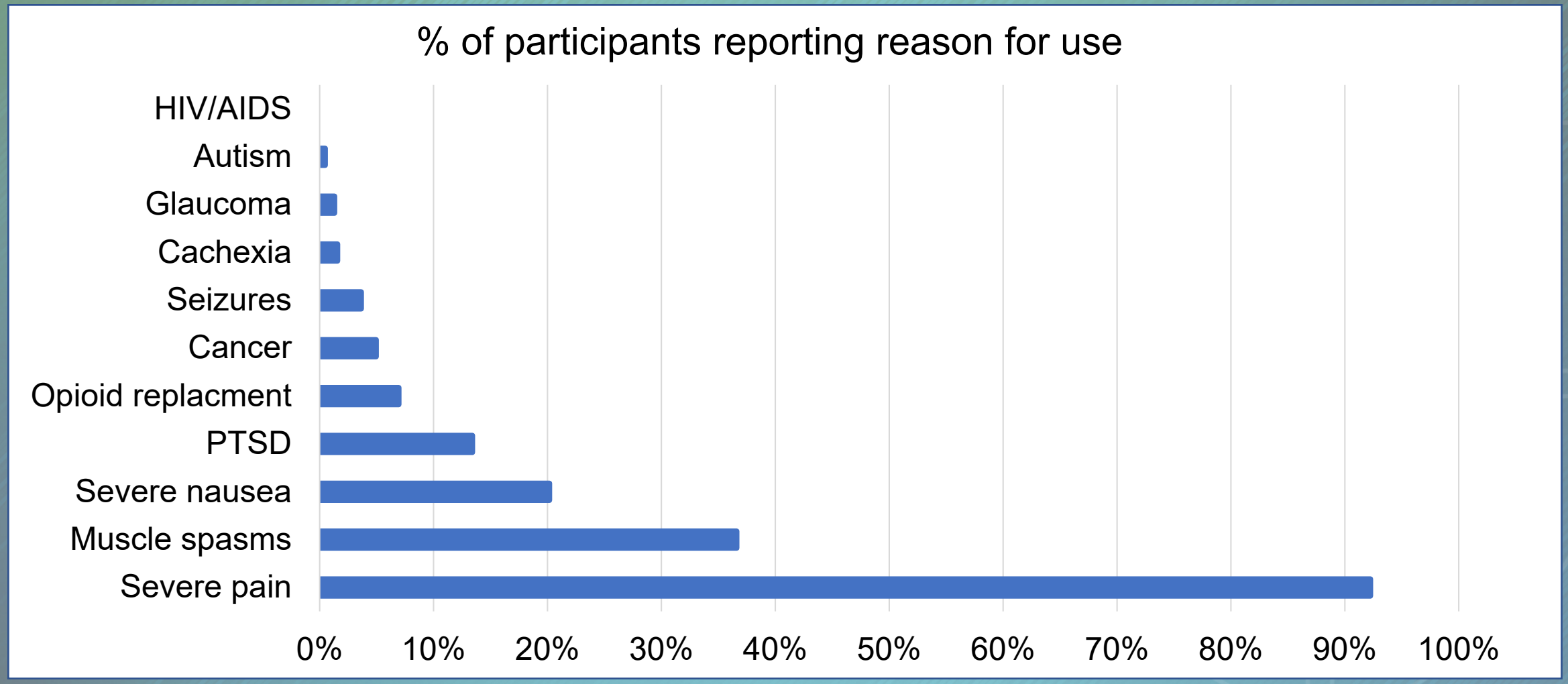
CB_1 agonism → ↓ pain (see below)
↓ memory, ↑ appetite, euphoria

Other mechanisms:

- Agonist for CB_2 → ↓ pain
- Agonist for $5HT_3$ → ↓ nausea
- Heteromer with opioid mu & $TRPV_2$ → ↓ pain
- Heteromer with D_2 → ↑ psychosis

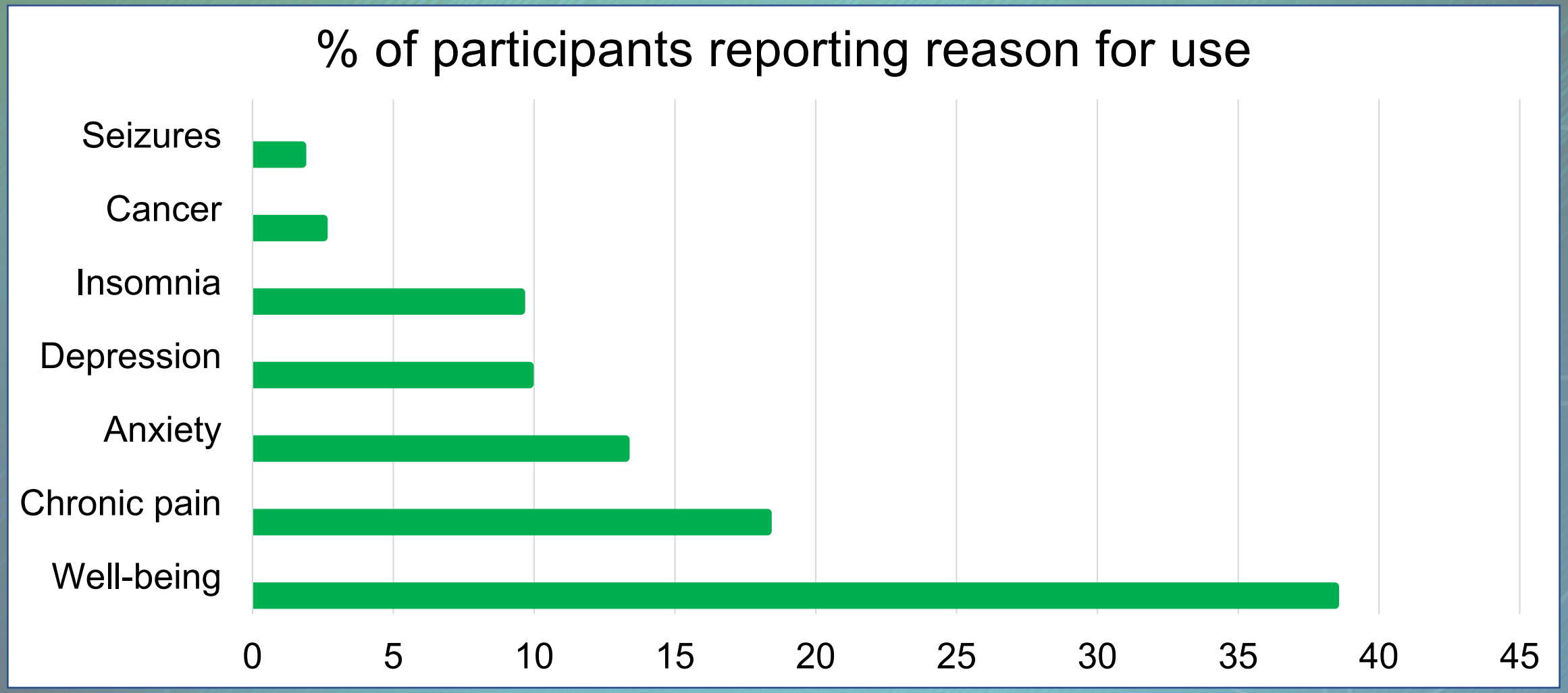
Pertwee RG. Br J Pharmacology 2008.

Why are people using THC-type products?
Will it match the evidence?



Adapted from: www.Colorado.gov/cdphe/medicalmarijuana July 2020 program statistics

Why are people using CBD-type products?
Will it match the evidence?

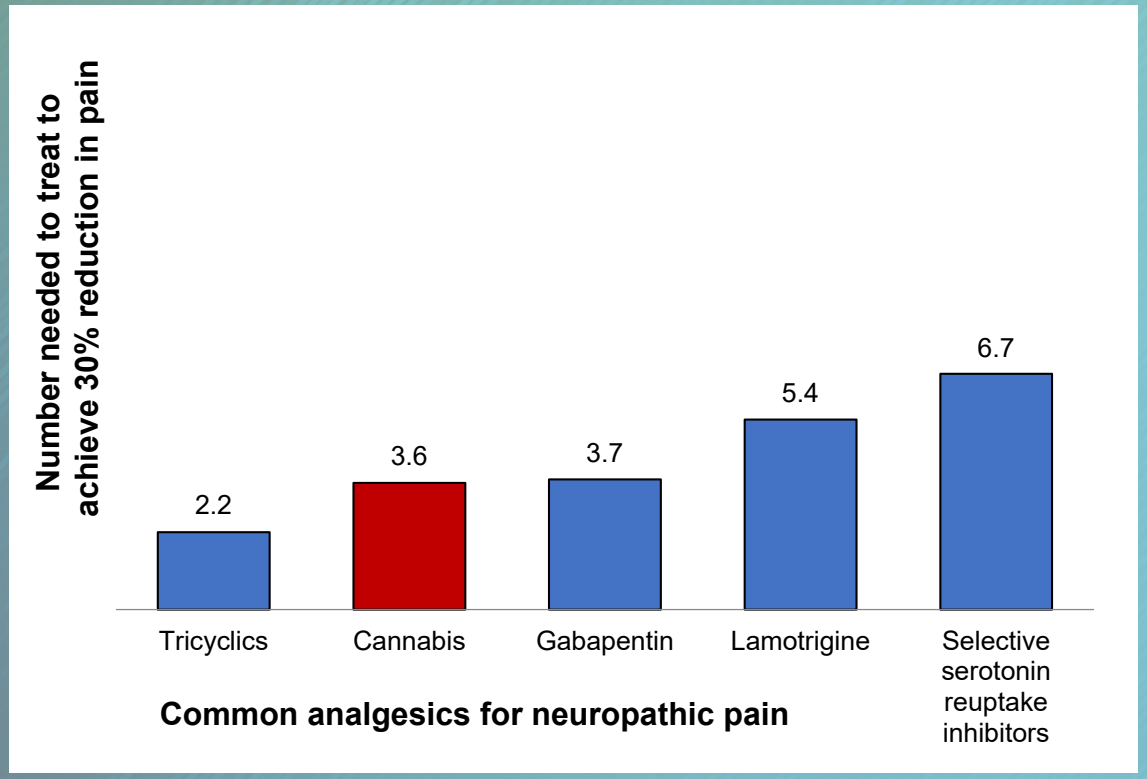


Adapted from: Corroon J, Phillips JA. Cannabis & Cannabinoid Research 2018.

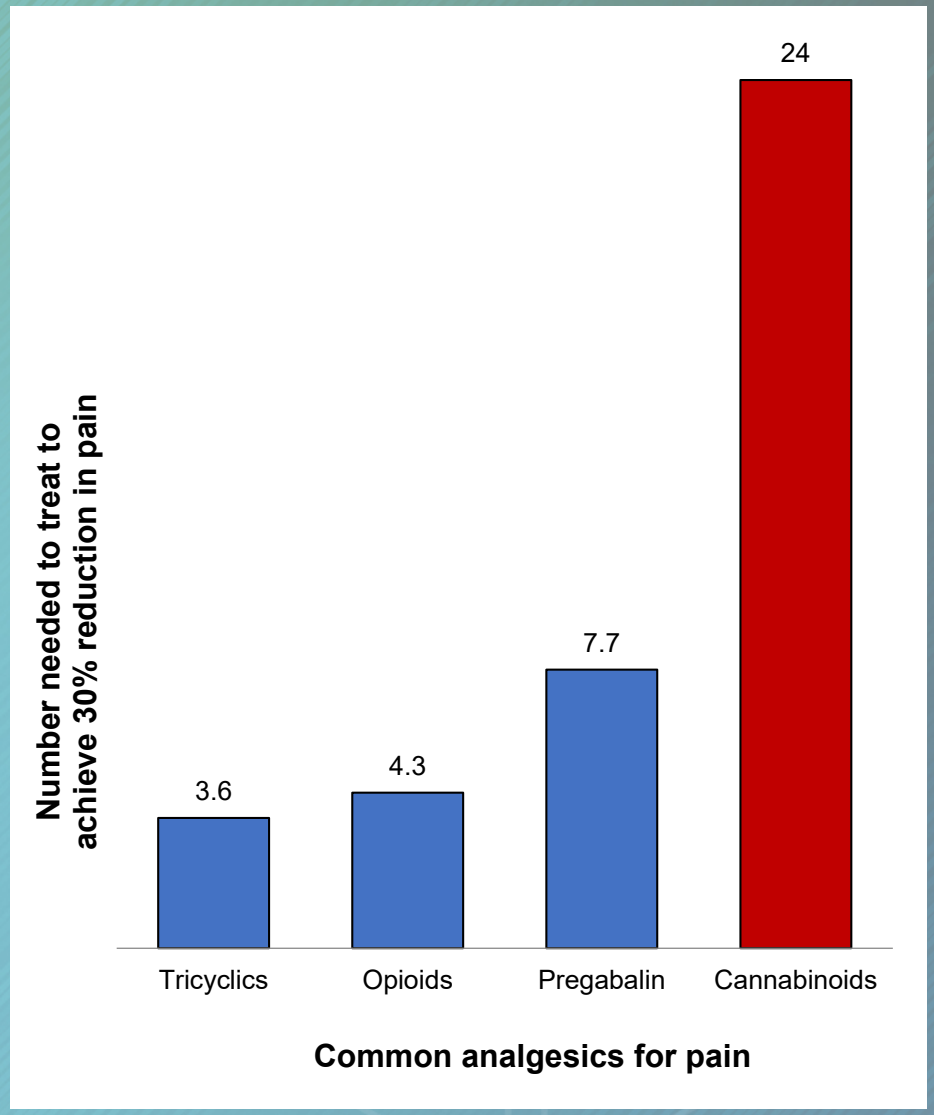
THC-type pain evidence

2 meta-analyses with >30% reduction in pain

- 6 neuropathic pain trials (Grant)
- 48 neuropathic & 48 CNCP trials (Stockings)



Adapted from Grant I et al. Virtual Mentor 2013.



Adapted from Stockings E et al. Pain 2018.

Hybrid-type pain evidence

- Trials with neuropathic pain due to MS
  - Compared nabiximols, placebo x 4 weeks using NRS (N = 64)
    - dose (26mg THC: 24mg CBD) → greater reduction in pain than placebo
  - Compared nabiximols, placebo x 14 weeks using NRS (N = 339)
    - dose (24mg THC: 22mg CBD) → improved QOL, did not improve NRS ≥ 30%
  - Retrospective EHR patient self-rating efficacy to reduce neuropathic pain
    - increased THC:CBD ratio was associated with increased response for neuropathic pain (OR of 3.58, 95% CI: 1.32-9.68; p=0.012)

- RCTs to achieve >30% reduction in cancer pain
  - Compared nabiximols, THC-type, placebo x 2 weeks (N = 177)
    - dose (23mg THC:22mg CBD) → better than placebo, THC-type → not better
  - Compared nabiximols, placebo x 5 and 7 weeks (N = 805)
    - dose (27mg THC:25mg CBD) → No change in average daily NRS

Rog DJ et al. 2005; Langford RM et al. 2013; Johnson JR et al. 2010; Fallon MT et al. 2017; Casarett DJ et al. 2019.

CBD-type pain evidence

- 4-way crossover in females with fibromyalgia
  - Compared hybrid, THC-type, CBD-type (N = 20)
    - Hybrid ↓ pain symptoms; hybrid & THC-type ↓ evoked pain; CBD-type no effect
- Case study: neurofibromatosis type 1
  - CBD-type oil (CBD:THC 20:1) 4 mg SL twice daily → 8 mg twice daily
    - ↓ pain (6/10 to 1/10), ↓ anxiety (9/10 to 3 - 4/10), and ↓ migraines (15/mo to 5/mo)
- Case series 7 kidney-transplant patients' chronic pain
  - CBD 50 to 150 mg twice a day for 3 weeks
    - Total pain improvement (2), partial response (4), no change (1)

van de Donk T et al. 2019; Hegazy O et al. 2019; Cunetti L et al. 2018;

Impact of *Cannabis* on opioid use & harms

- Pre-clinical studies → CBs have opioid-sparing effect
- Patient self-reports support this finding
- Open-label cohort studies are divided: some show patients with chronic pain discontinued/decreased opioid use
  - NM medical cannabis program enrollees
    - OR 17 of stopping opiates; OR 5 of lowering dose
    - Significant for stopping all medications
  - Medical Marijuana permissive laws (presence of dispensaries)
    - ↓ opioid use, chronic use, and high-risk use, however, small at <1%
    - ↓ hospitalization rates for dependence, abuse, and overdose
    - Initial ↓ opioid deaths, but now ↑ opioid deaths

Nielsen S et al. 2017; Boehnke KF et al. 2016; O'Connell M et al. 2019; Campbell G et al. 2018; Vigil JM et al. 2017.

Post-Traumatic Stress Disorder (PTSD)

- 650 veterans with PTSD report improvement of symptoms with THC
- A few randomized controlled trials (RCTs) show improved symptoms
- Observational study >2200 Veterans from 1992–2011
  - Never users, stoppers, continuing users, and starters
  - Adjusted for covariates of baseline symptoms, drug & alcohol use, violent behavior, and employment
  - *Cannabis* use associated with worsening of PTSD symptom severity, violent behavior, and alcohol & drug use
- 11 PTSD patients used 49mg CBD capsule/spray
  - After 8 weeks 28% of patients had reduction in symptoms

Earlywine & Bowles JR. J Psychoact Drugs 2014; Wilkinson ST et al. J Clin Psychiatry 2015; Elms L et al. J Altern Complement Med 2019.

Depression

- Naturalist study of changes in depression, anxiety, and stress symptoms from THC and CBD from tracking app
  - Results: after 20 minutes, 50% ↓ depression and 58% ↓ in anxiety
  - CBD-type was associated with the largest changes in depression ratings
  - But! Baseline symptoms of depression exacerbated across time
- Meta-analysis of 11 longitudinal and prospective studies
  - The OR of adolescent *Cannabis* use risk compared to non-users:
    - 3.46 (95% CI, 1.53–7.84, I2 = 61.3%) suicidal attempt
    - 1.50 (95% CI, 1.11–2.03; I2 = 0%) suicidal ideation
    - 1.37 (95% CI, 1.16–1.62; I2 = 0%) developing depression
    - 1.18 (95% CI, 0.84–1.67; I2 = 42%) developing anxiety

Who's heard of rimonabant?

Cuttler C et al. J Affect Disord 2018; Gobbi G et al. JAMA Psychiatry 2019.

Improving short-term sleep outcomes

Acute: THC decreases sleep onset latency & REM sleep
Chronic: THC habituation, daytime sleepiness, ↓ mood, & memory

- Multiple Sclerosis patients sleep quality
  - % of patients reporting relief from *Cannabis* ↓ from week 4–12

Low-dose CBD stimulating; high-dose CBD sedating

- Parkinson's disease starting dose 400mg
  - CBD ↓ symptoms (e.g., nightmares) of REM sleep behavior disorder
- 72 adults with anxiety & sleep complaints given 25mg capsules for 3 months
  - 79% had ↓ HAMA months 1–3, 67% had ↓ PSQI month 1

Babson KA et al. Curr Psychiatry Rep 2017; Zajicek JP et al. J Neurol Neurosurg Psychiatry 2012; Shannon S et al. Perm J 2019 .

Other psychiatric disorders

- 12 SAD & 12 control subject randomized trial
  - 600 mg CBD vs. placebo vs. control subject response
  - Simulated public speaking test, after CBD, SAD patients had improvements in anxiety and cognitive impairment

- Two 6-week trials in schizophrenia
  - 600 & 1000mg CBD led to no change and improvement

Bergamaschi MM et al. Neuropsychophar 2011; Boggs DL et al. Psychophar 2018; McGuire P et al. Am J Psych 2018.

Treatment of cancer

- Systematic review of literature on preclinical evidence
  - Inhibition of cell growth and tumor angioneogenesis
- Case study of lung cancer tumor response
  - 81-year-old adenocarcinoma
  - Refused chemotherapy and radiotherapy
  - After 2 and 7 months mass increased in size
  - Then started 1.32mg CBD twice daily and within 2 months total resolution of mass

Sule-Suso J. Open Med Case Reports 2019; Guzman M. Br J Cancer 2006; Creative Commons: https://2.bp.blogspot.com/-KNO0FdBVgIM/TwfDq1bBnmI/AAAAAAAAAUg/Je5eOXNB44c/s1600/angels+choir.png

Treatment of cancer

- Pharmacokinetic drug interactions
  - **Inhibit P-gp:** methotrexate, tyrosine kinase (TK) inhibitors, taxanes, vinca-alkaloids, topoisomerase inhibitors, intercalants
  - **Inhibit BCRP:** methotrexate, cyclophosphamide, paclitaxel, topotecan, TK inhibitors
  - **Inhibit 2C19**: cyclophosphamide, imatinib, lapatinib
  - **Inhibit 3A4:** cyclophosphamide, taxanes, anastrozole, TK inhibitors
- Pharmacodynamic drug interactions
  - ↓ paclitaxel induced peripheral neuropathy
  - Cytotoxic synergy with temozolomide, carmustine, cisplatin in GBM cells
  - Cytotoxic synergy with bortexomib in MM cells

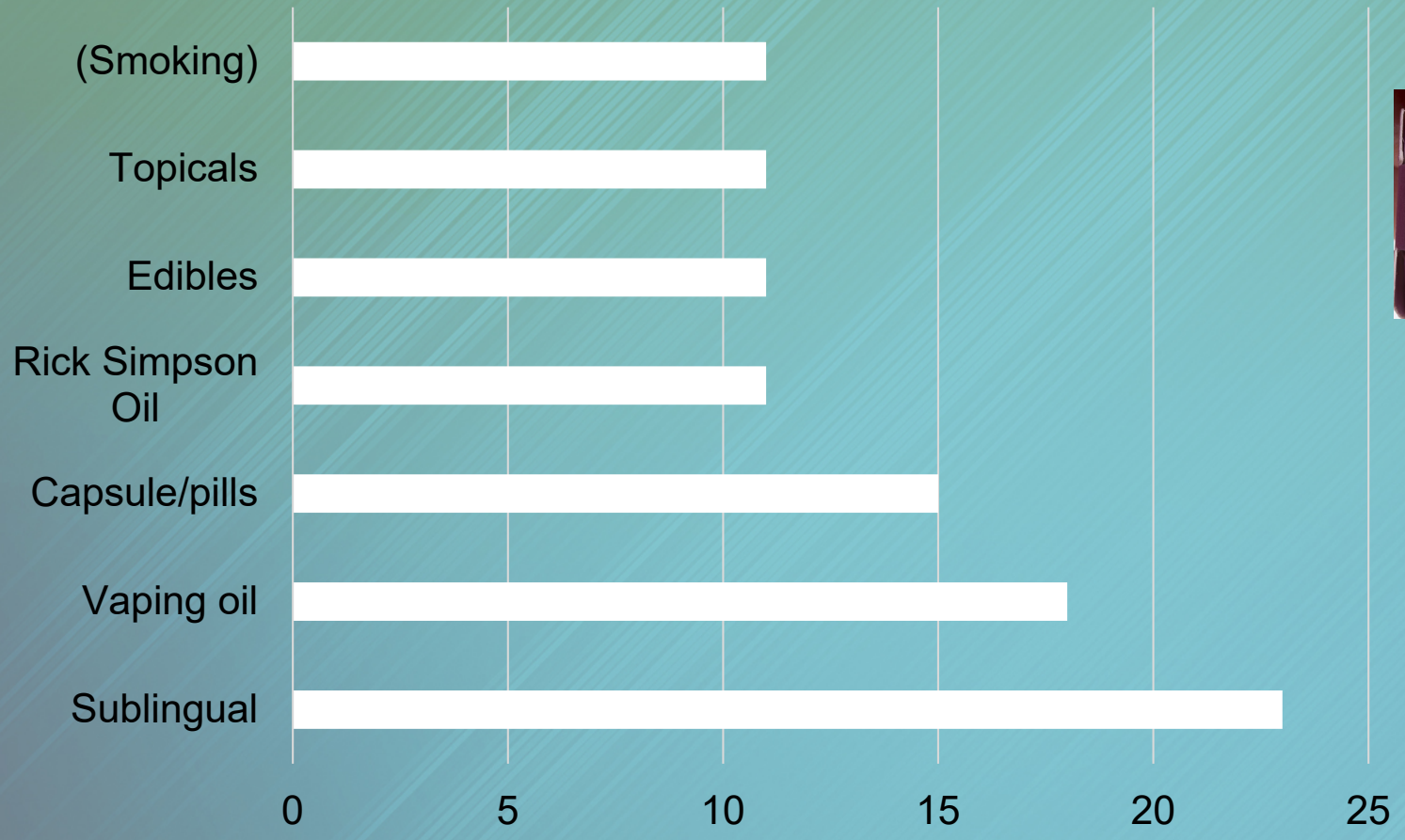
Opitz BJ, Ostroff ML, Whitman AC. J Pharmacy Practice 2019.

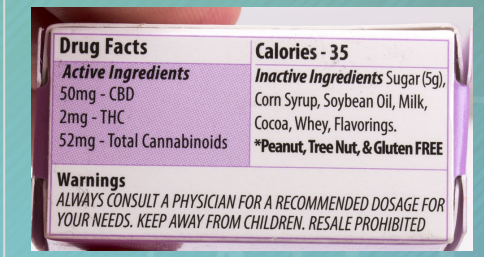
Seizure disorders

- Clinical trials in intractable epilepsy syndromes
  - 120 children (2–18 years) with Dravet syndrome
    - 29% CBD vs. 9% placebo (PBO) total drop in seizure frequency
  - 225 patients (2–55 years) with Lennox-Gastaut 10 & 20mg/kg CBD
    - 36% 10mg/kg CBD vs. 38% 20mg/kg CBD vs. 19% PBO total drop in seizure frequency
  - 171 patients (2–55 years) with Lennox-Gastaut
    - 41% CBD vs. 14% PBO total drop in seizure frequency
- Pharmacokinetic drug interactions
  - CBD inhibits CYP2C19 and 3A4, ↑ 300–500% levels of clobazam N-desmethyl metabolite, → CBD efficacy?

Devinsky O et al. N Engl J Med 2017; Devinsky O et al. N Engl J Med 2018; Thiele EA et al. Lancet 2018; Qian Y, Gurley BJ, Markowitz J. J Clin Psychopharmacol 2019.

CBD oil products percent use
Is this a good way to take the product?

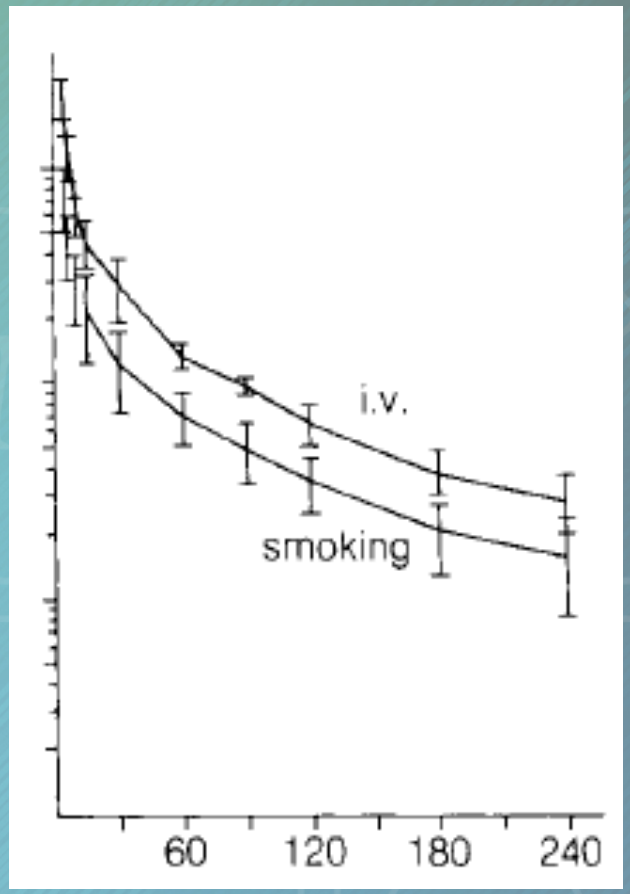




Adapted from: Corroon J, Phillips JA. Cannabis & Cannabinoid Research 2018; Image from: https://spendabit.co/go?q=vape&offset=0; http://www.leafscience.com/2015/10/27/beginners-guide-marijuana-edibles/; http://www.leafscience.com/2015/10/27/beginners-guide-marijuana-edibles/; http://uploads.medicaljane.com/wp-content/uploads/2015/11/cbdtopical_0.png http://uploads.medicaljane.com/wp-content/uploads/2014/06/cbdHD2.jpg

PK profile of smoked THC

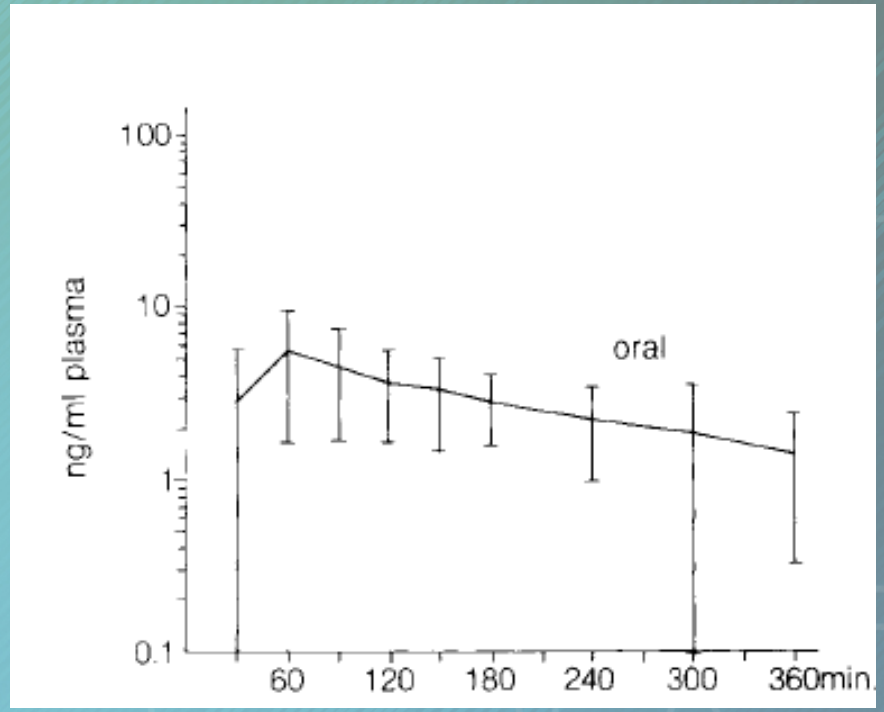
- Smoking cannabis turns ~50% of the THC content into smoke
- Up to 50% of inhaled smoke is exhaled again, and some undergoes localized metabolism in the lung
- Resulting bioavailability of an inhaled dose of THC is between 10–25%
- Effects are perceptible within seconds and fully apparent in a few minutes
- Effects last about 3 hours



Strougo A et al. J Psychopharmacology 2008.

PK profile of oral THC

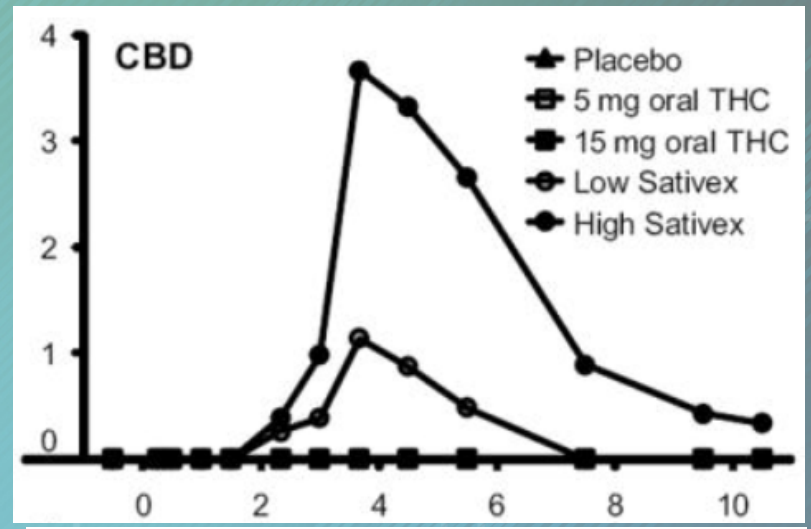
- Bioavailability of THC after oral ingestion ranges from 5–20% in the controlled environment of clinical studies
- Onset of effect is delayed 1–3 hours due to slow absorption from the gut
- Weight, metabolism, gender, and eating habits also play a role in absorption
- Effects last about 6–12 hours

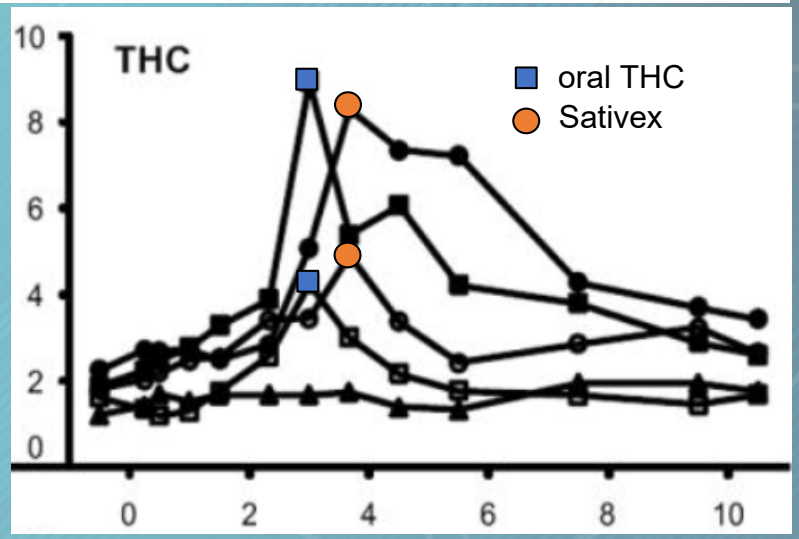


Agurell S, Halldin M, Lindgren JE et al. Pharmacological reviews 1986.

PK profile of oromucosal THC/CBD—Sativex

- Sativex study did not find difference between oral THC and oromucosal spray PK
- Peak concentration THC 1.5 hours
- Peak concentration CBD 1.3 hours
- 2-fold inter-patient variability in peak THC and CBD levels





Karschner EL. Clin Chem 2011.

PK profiles of ingestible CBD

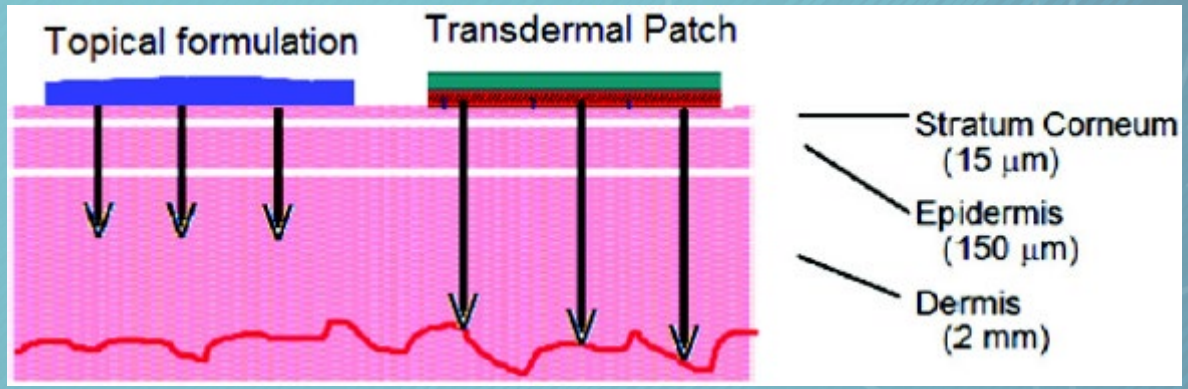
CBD route	Cmax	min	max	Tmax	min	max	T ½
Sublingual	2.5	0.27	6.55	97.5	45	180	86
Oro-pharyngeal	2.61	0.41	6.36	122.5	45	300	105
Buccal	3.02	0.29	9.91	167.5	60	270	108
Oral	2.47	0.47	7.55	76.3	30	180	65
Inhaled	2			15	15	30	

C_{max} are 5- and 3-fold higher during fed conditions; T_{max} is also delayed under the fed state (nearly 4-fold)

Guy GW, Robson PJ. The Haworth Press 2003; Millar SA et al. Front Pharmacol 2018.

Cannabis infused creams, lotions, and oils

- CBs not charged, but lipophilic properties limit it getting to site of action
- Most products claim no psychoactive effects, so CBs not getting absorbed
- Patch with occlusion and vehicle to enhance absorption



Images from: http://dailyleafdeals.com/apothecanna-product-review ; http://www.americanpharmaceuticalreview.com/Featured-Articles/170872-Lipids-in-Transdermal-and-Topical-Drug-Delivery

Topical use of *Cannabis* products

www.pbs.org › newshour › health › whoopi-goldbergs-...

Can Whoopi Goldberg's pot-infused bath soaks soothe ... - PBS

Apr 1, 2016 - But psychopharmacologist **Kari Franson** of the University of Colorado, Denver, said taking a bath to soak up THC — the chemical that produces ...

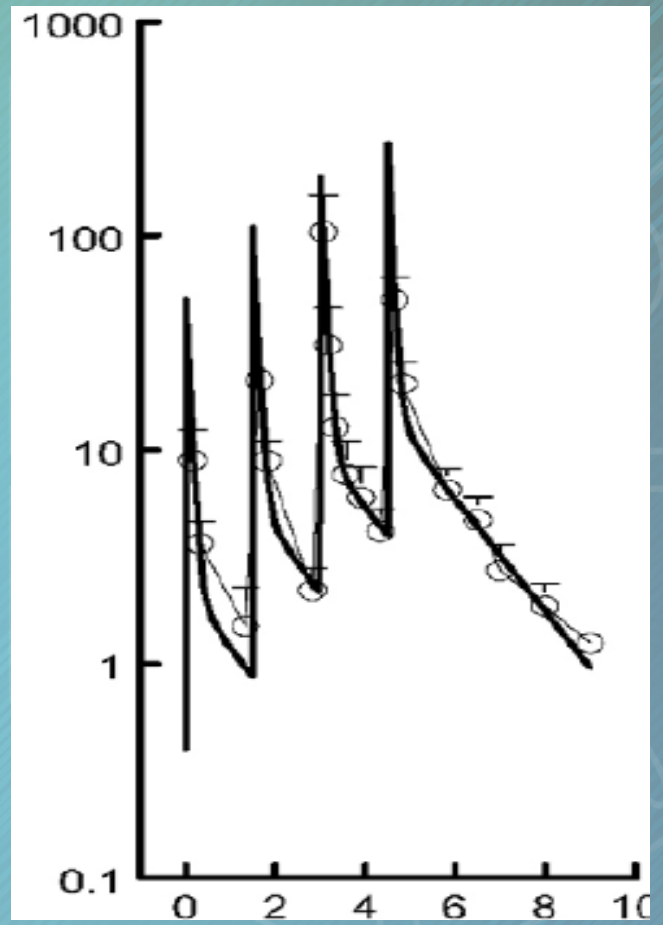
Whoopi Goldberg's New Cannabis Company For Women | THCU Insider

insider.thcuniversity.org/whoopi-goldbergs-new-cannabis-company/

Apr 14, 2016 - Psychopharmacologist Karl **Franson** of the University of Colorado, Denver, says that soaking up THC topically through your skin is not the most effective way to treat pain, not to mention the sticky tub. Inhaling THC is a very fast acting and effective method at treating pain and controlling your dose is easy, ...

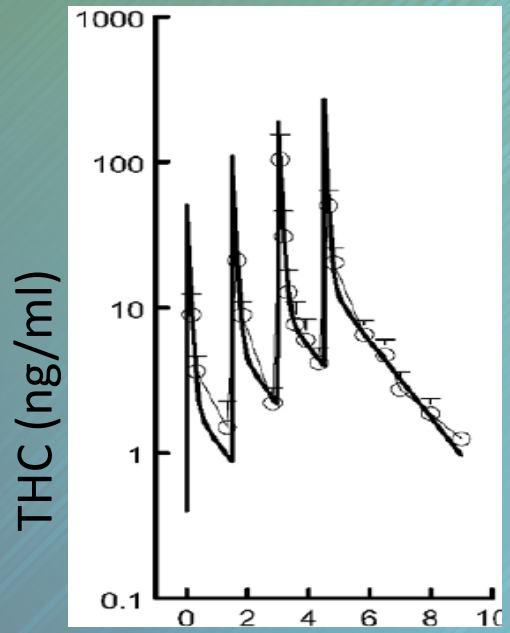
Evaluating dose/response effect of *Cannabis*
How much Cannabis do our patients need?

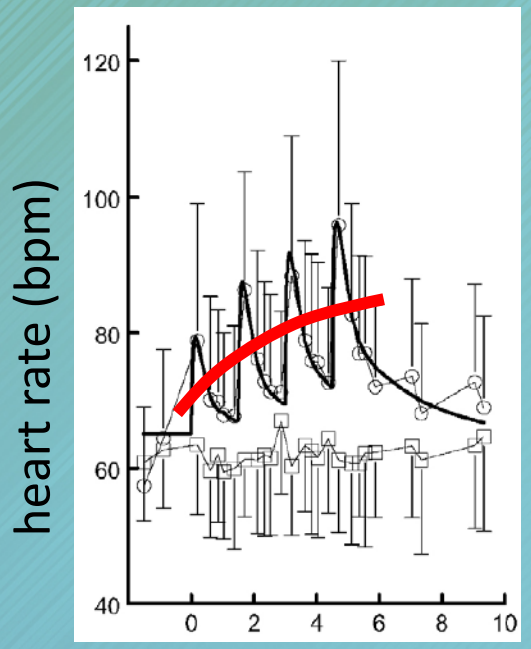
Subjects given increasing doses (2, 4, 6, 8 mg) of THC via Volcano vaporizer at 1.5-hour intervals

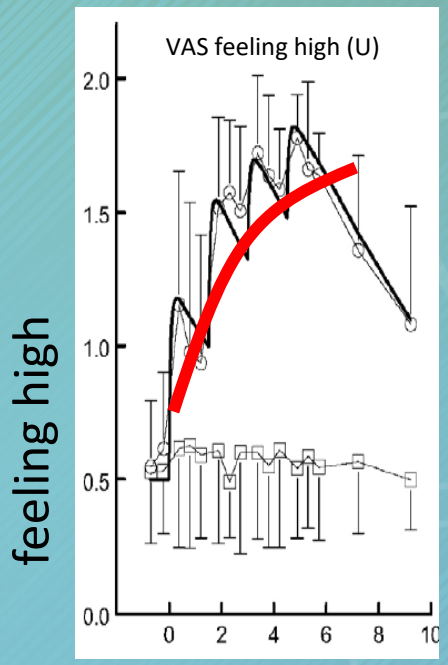


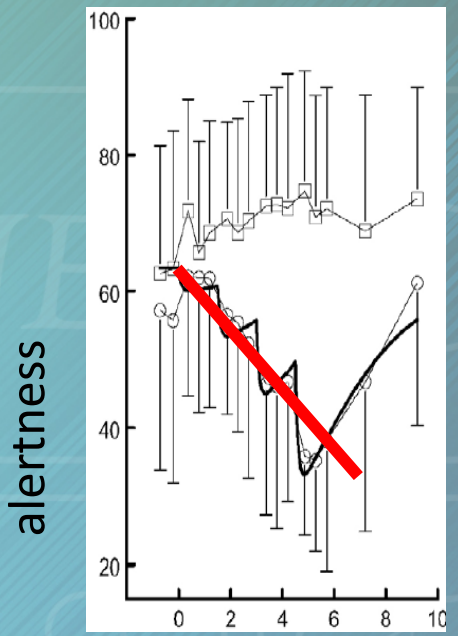
Zuurman L et al. Br J Clinical Pharmacology 2008.

Concentration vs. THC pharmacological effect





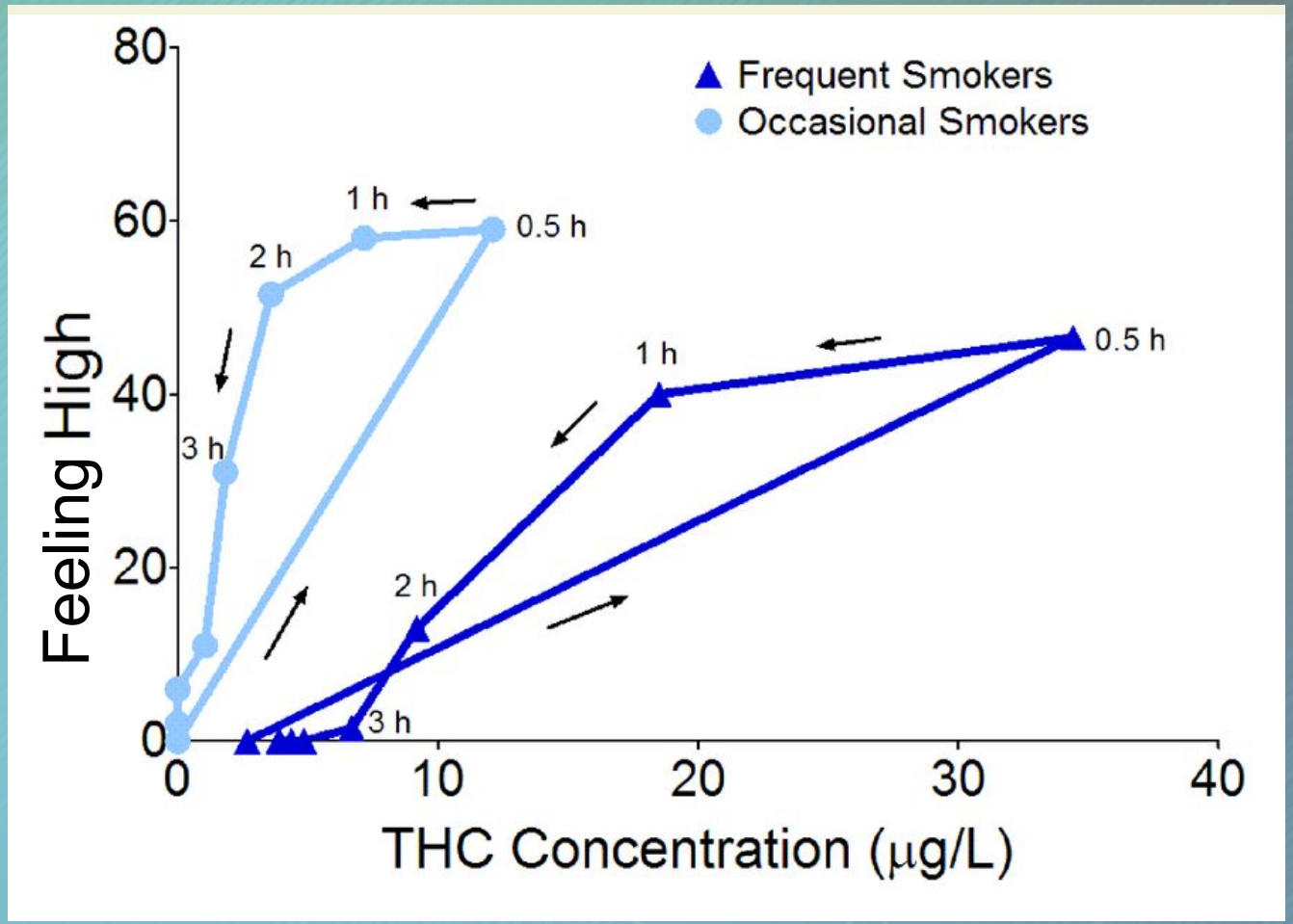




Zuurman L et al. Br J Clinical Pharmacology 2008.

Blood concentration and tolerance

- Frequent and occasional smokers smoked one 6.8% THC *Cannabis* cigarette ad libitum
- Blood cannabinoids were quantified 1 h before, and up to 15 times (0.5–30 h) after smoking
- Average 3- to 4-fold differences in concentration → effect



Adapted from Desrosiers NA et al. Clinical Chemistry 2014.

Interpreting *Cannabis* dosing

THC	Inconsistent user studied doses	*Frequent user extrapolated doses*	Experienced effects
Low	<1–5mg	*<3–20mg*	Inconsistently experienced: Increased HR Intensified visual and auditory perception Decreased attention Impaired cognition on sequential tasks Mood effects—euphoria, laughter
Typical	5–15mg	*15–60mg*	Reliably experienced the effects listed above, and inconsistently experienced: Dry mouth Reduced nausea and vomiting (anti-emetic action) Impaired decision-making Decreased BP Reduced/increased anxiety Increased alpha brain wave activity Reduced REM sleep Blood glucose levels drop—“munchies”
High	>15–30mg	*>45–120mg*	Toxicity or undesirable effects: Delusions Hallucinations Paranoia Confused, disorganized thought Anxiety/panic Depersonalization—feelings of separation from self

Zuurman L et al. Br J Clinical Pharmacology 2008; https://www.latimes.com/projects/la-me-weed-101-thc-calculator/

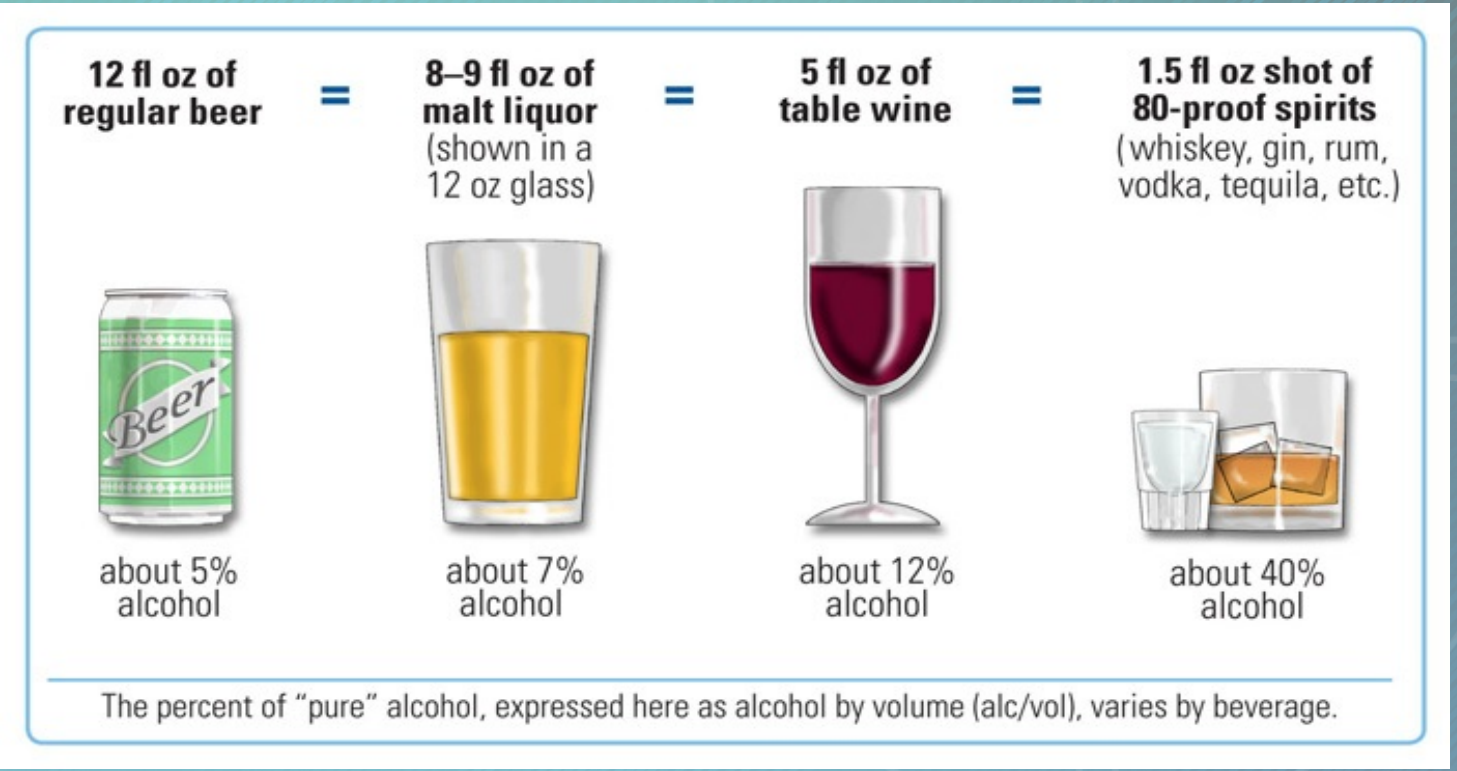
Interpreting *Cannabis* dosing

CBD	Dose	Experienced effects
Approved	5–20mg/kg/day given twice daily	Approved for treatment of seizures associated with Dravet and Lennox-Gastaut syndrome
Low	2–100mg	Anecdotal evidence in cancer case studies, pain, and sleep disorder studies
High	400–1000mg	Given to Parkinson's patients daily x 6 months (some side effects and improved sleep)
Highest safely given	1200 mg	Given to bipolar patients x 4 weeks (tolerated but no effect)

Understanding dosing (% versus mg)

Patients need assistance converting %THC or %CBD they buy into mg dose is based on weight of serving size

Compare to alcohol serving sizes which are based on % alcohol to volume



Understanding dosing (% versus mg)

Patients need assistance converting %THC or %CBD into mg dose is based on weight of serving size

If the patient needs a typical dose of 10mg of THC:

250mg of 4% product

500mg of 2% product

1000mg of 1% product

Remembering our PK when dosing *Cannabis*

To convert how much is in the cigarette to how much will get into the patient, assume 10–25% bioavailability

So, if the patient needs a typical dose of 10mg of THC:

250mg of 16% product

500mg of 8% product

1000mg of 4% product

How would you respond?

- To a 58-yo male patient who asks for a typical dose to try THC or CBD for his pain?

- To a 58-yo male patient who states his 1/8 oz of 15% THC cannabis is the only thing that reduces his anxiety?

Summary

- Discussed the purported mechanisms of various components of *Cannabis*
- Interpreted clinical studies discussing the efficacy of *Cannabis* for treating various syndromes
- Described doses patients could use based on the differences in how quickly, how long, and how reliably various *Cannabis* formulations get into the body

Posttest Question 1

Which product is cultivated in a manner to produce an FDA-recognized dietary supplement?

1. Cannabis-derived oil extracts
2. CBD oil
3. Inhaled hemp
4. Hemp seed oil

Posttest Question 2

Cannabidiol's likely mechanism for the treatment of pain is…

1. Agonism of adenosine A_{2A} receptors
2. Agonism of CB_1 receptors
3. Antagonism of CB_2 receptors
4. Agonism of serotonin 5-HT_{1A} receptors

Posttest Question 3

Which product has the most evidence for reducing neuropathic pain?

1. CBD
2. CBD:THC hybrid
3. High CBD:HighTHC
4. THC

Posttest Question 4

Which of the following CBD routes of administration has been found to have the shortest time to maximum concentration (Tmax)?

1. Buccal spray
2. Oral capsule
3. Oro-pharyngeal spray
4. Sublingual spray

Posttest Question 5

How many mg of THC would *reach the blood* of a patient who vaporized a 500 mg bowl of 10% THC *Cannabis*?

1. 10 mg
2. 12.5 mg
3. 50 mg
4. 500 mg