



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Innovations in Cannabinoid Medicine

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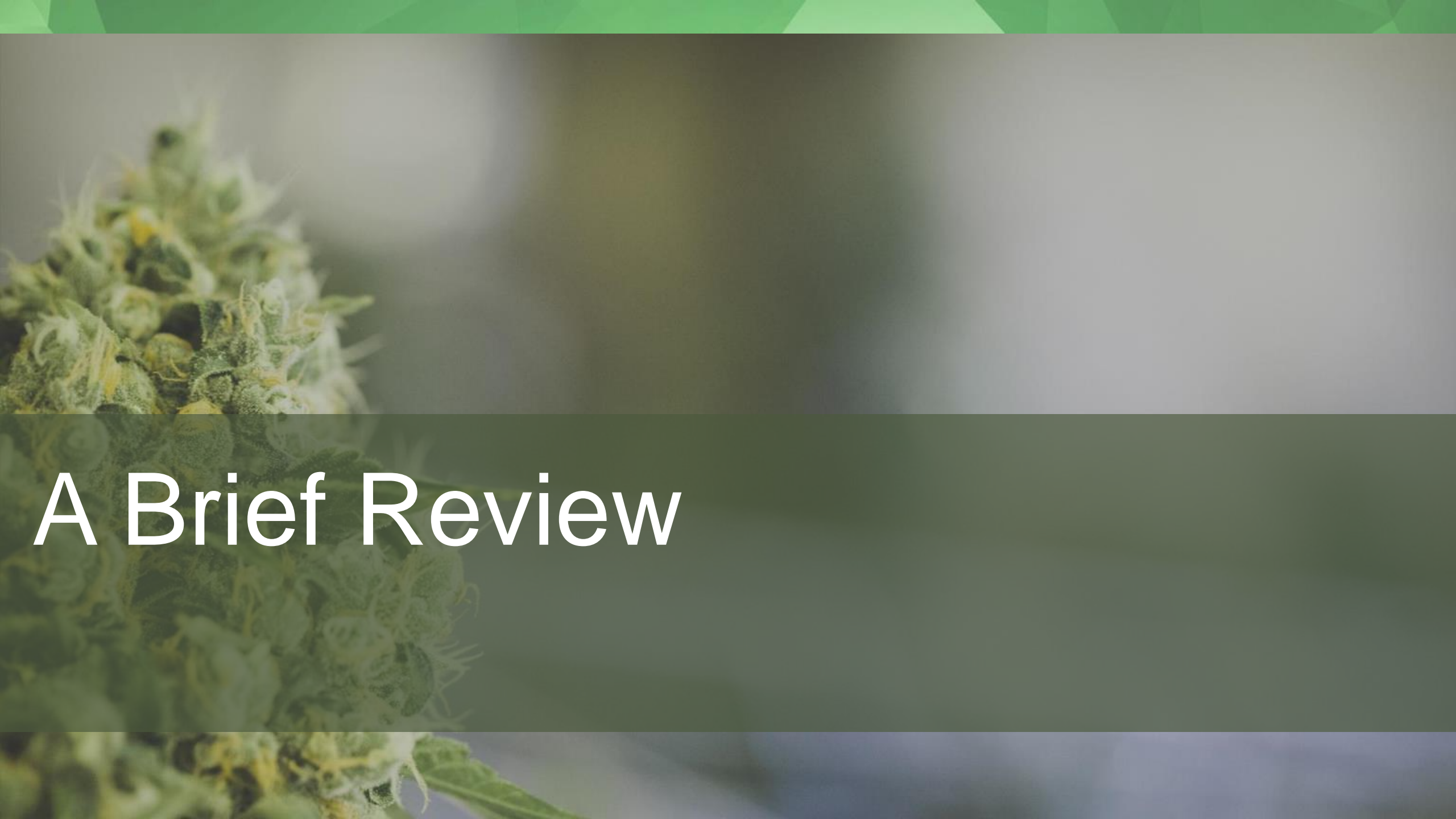
About the Presenter:

- Harvard Medical School
- Brigham and Women's Hospital
- VA Medical Center Emergency Department
- *InhaleMD*
- Association of Cannabinoid Specialists
- No COI to report



Learning Objectives

- Understand that cannabis, if used properly, can be effective medicine for specific problems
- Recognize that many new cannabis products are unregulated and unsubstantiated



A Brief Review

Types of Symptoms Well Treated with Cannabis

1

Pain

4

Anorexia

2

Depression and Anxiety

5

Nausea and vomiting

3

Insomnia

6

Sexual Dysfunction

But, isn't it addictive?

Remember that dependence \neq addiction

Dependence = biological or psychological habituation to a substance such that withdrawal causes symptoms. Air, food, shelter, water, beta blockers, SSRI examples

Addiction (per DSM-V) = dependence that causes adverse effects on patient's life circumstances (trouble with the law or destruction of key relationships)



Lifetime dependence risk of 7% in marijuana users vs 32% for nicotine, 23% for opioids, 17% for cocaine and benzodiazepines, and 15% for alcohol

Cannabis risk “front-loaded”

Typical withdrawal = 3-7 of insomnia and mood instability

Robson P. Abuse potential and psychoactive effects of δ -9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opin Drug Saf.* 2011;10(5):675–685.

Cognitive Issues

Healthy Volunteer (Rec User) Studies:

Several studies using I.Q. and fMRI have shown changes in cognitive function from prolonged use of cannabis

However, these were all done with recreational users with unknown (likely higher than medical) doses.

Best study to date shown ~8 point I.Q. drop in verbal memory function only. None in executive function, spatial or quantitative function. Seen only after 20-30 years “heavy” use.

Patient Studies:

Few studies on actual patients. Studies from Staci Gruber at HMS showed cognitive improvement in patients. Likely b/c illness causes significant cognitive impairment.

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Gonenc, A., Smith, R. T., Lambros, A. M., ... Lukas, S. E. (2018). The Grass Might Be Greener: Medical Marijuana Patients Exhibit Altered Brain Activity and Improved Executive Function after 3 Months of Treatment. *Frontiers in Pharmacology*, 8, 983. <https://doi.org/10.3389/fphar.2017.00983>



Routes of Administration

The Good, the Bad, and the Useless



For symptoms with acute or episodic nature, like nausea or Migraine headache, which would be the preferred modality of treatment?

- A. Tincture
- B. Inhaled vaporized whole flower
- C. Edible
- D. Inhaled oil pen
- E. Topical

Answer:

B. Inhaled vaporized whole flower

Explanation:

Inhalation has most rapid onset to help with acute symptoms and the shortest duration, best for episodic conditions. Oral agents are too slow and too long acting. Oil pens produce carcinogenic byproducts and should be avoided until better technology comes along. Tinctures are not absorbed sublingually and are poorly absorbed in GI. Topicals are not absorbed at all.

The Dose Matters



10-15mg

Not



All About Strains and Strain Types

- Strains: no significant medical differences
- Strain type (Indica vs. Sativa): no significant medical differences and chemically indistinct
- CBD: useful in lab, not in real world, can interact with meds

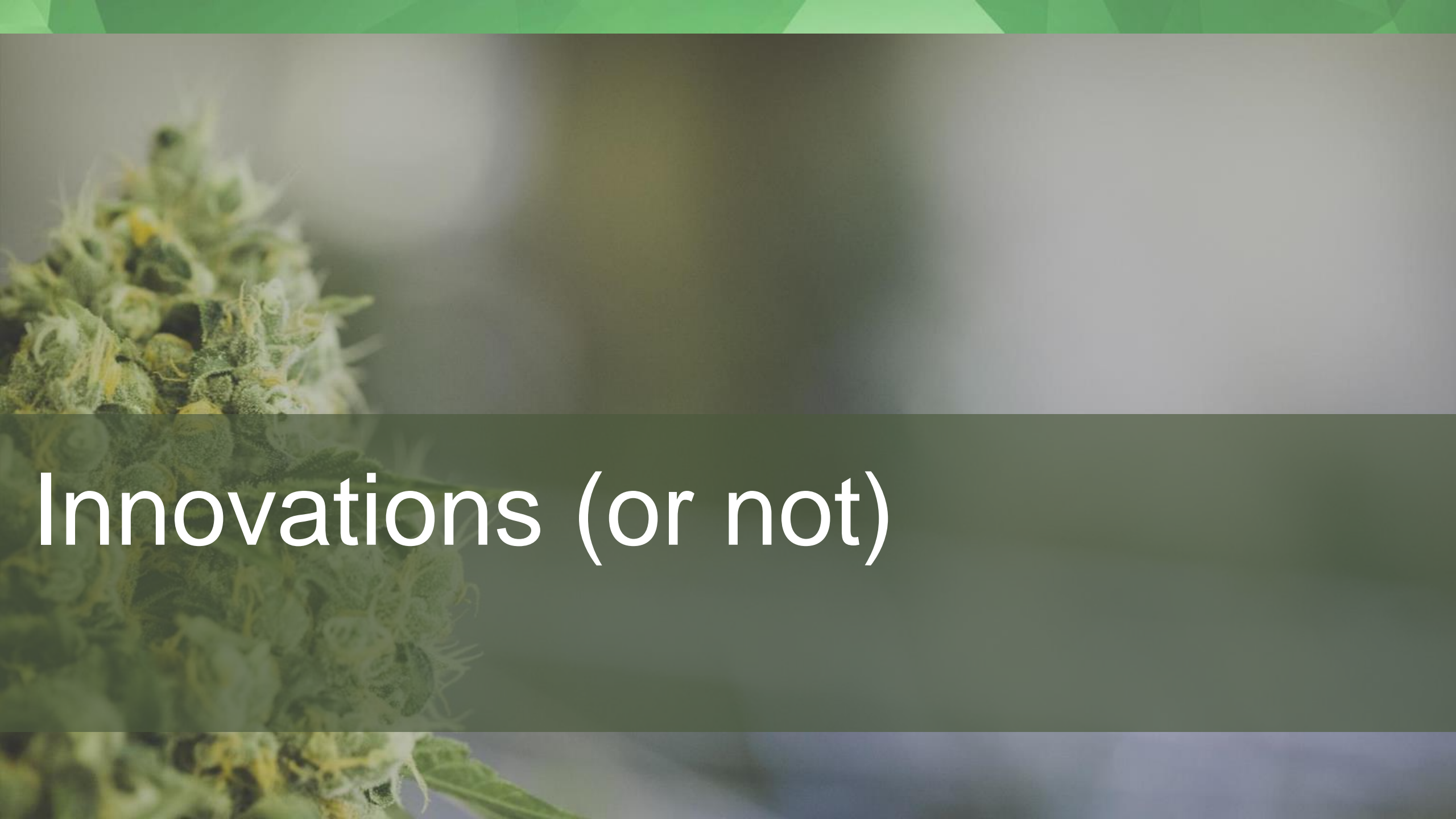
Drug Interactions: Real vs. Theoretical

Medications that concern us:

Medications that are trending on Google:

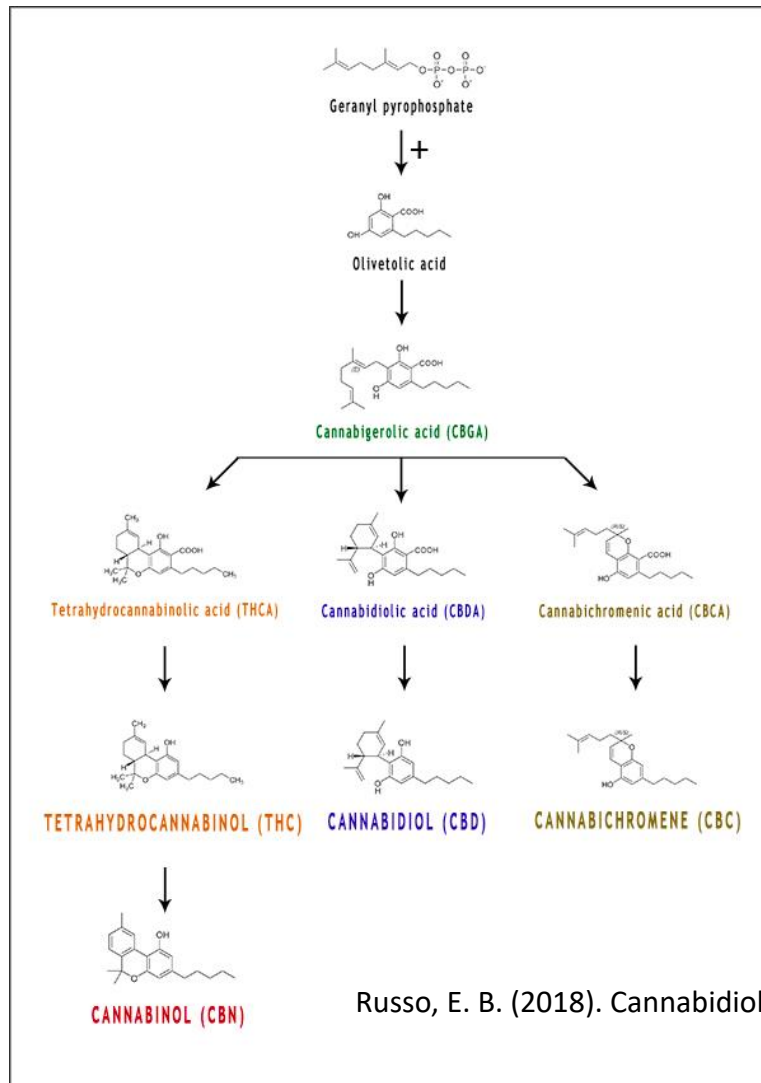
	CBD	THC
Adalimumab (Humira)	N	N
Advair (fluticasone/salmeterol)	N	N
Albuterol (Ventolin)	N	N
Amlodipine (Norvasc)	N	N
Amoxicillin	N	N
Aripiprazole (Abilify)	N	T
Azithromycin (Zithromax, Z-PAK)	N	N
Esomeprazole (Nexium)	Y	N
Etanercept (Enbrel)	N	N
Hydrochlorothiazide	N	N
Infliximab (Remicade)	N	N
Lantus Solostar (insulin glargine)	N	T
Ledipasvir and sofosbuvir (Harvoni)	N	N
Levothyroxine (Synthroid)	N	N
Lisdexamfetamine (Vyvanse)	N	N
Lisinopril (Prinivil, Zestril)	N	N
Metformin (Glucophage)	N	N
Pregabalin (Lyrica)	N	N
Riotropium (Spiriva Handihaler)	N	N
Rosuvastatin (Crestor)	N	N
Simvastatin (Zocor)	N	T
Sitagliptin (Januvia)	N	T
Sofosbuvir (Sovaldi)	N	N

	CBD	THC
Amiodarone (Pacerone)	Y	N
Cetirizine (Zyrtec)	N	N
Clonazepam (Klonopin)	N	N
Clopidogrel (Plavix)	N	T
Eszopiclone (Lunesta)	N	N
Everolimus (Afinitor)	Y	T
Loratadine (Claritin)	Y	T
Lorazepam (Ativan)	Y	T
Quetiapine (Seroquel)	N	T
Remeron (Mirtazapine)	Y	N
Tacrolimus (Protopic, Prograf)	Y	Y
Trazadone (Desyrel)	N	N
Warfarin (Coumadin)	Y	T
Zolpidem (Ambien)	N	N



Innovations (or not)

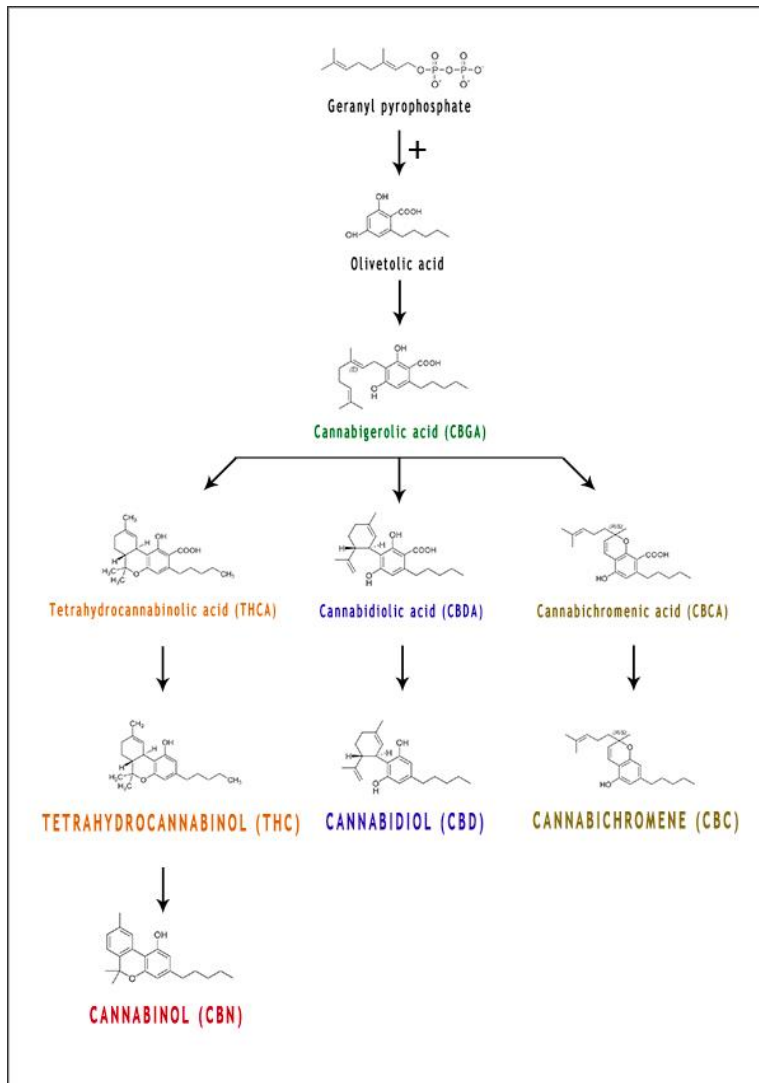
New Cannabinoids on the Market



Cannabidiol (CBD)

- Other than THC, only FDA approved cannabinoid - Epidiolex
- Human RCT data for other uses not positive
- Most likely to interact with conventional medications
- Not regulated federally: online & store sources not safe

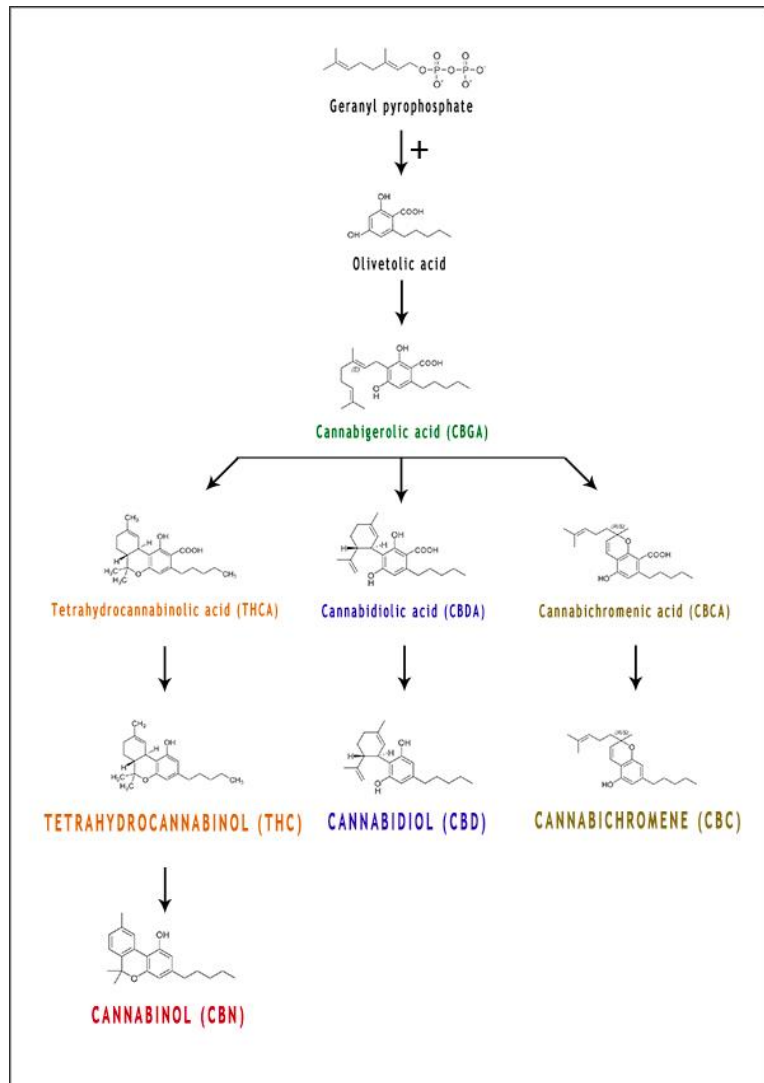
New Cannabinoids on the Market



Cannabinol (CBN)

- Breakdown product of THC
- Thought to cause drowsiness
- One human RTC but not THC arm
- In clinical practice, no advantage over THC
- Not regulated federally: online & store sources not safe

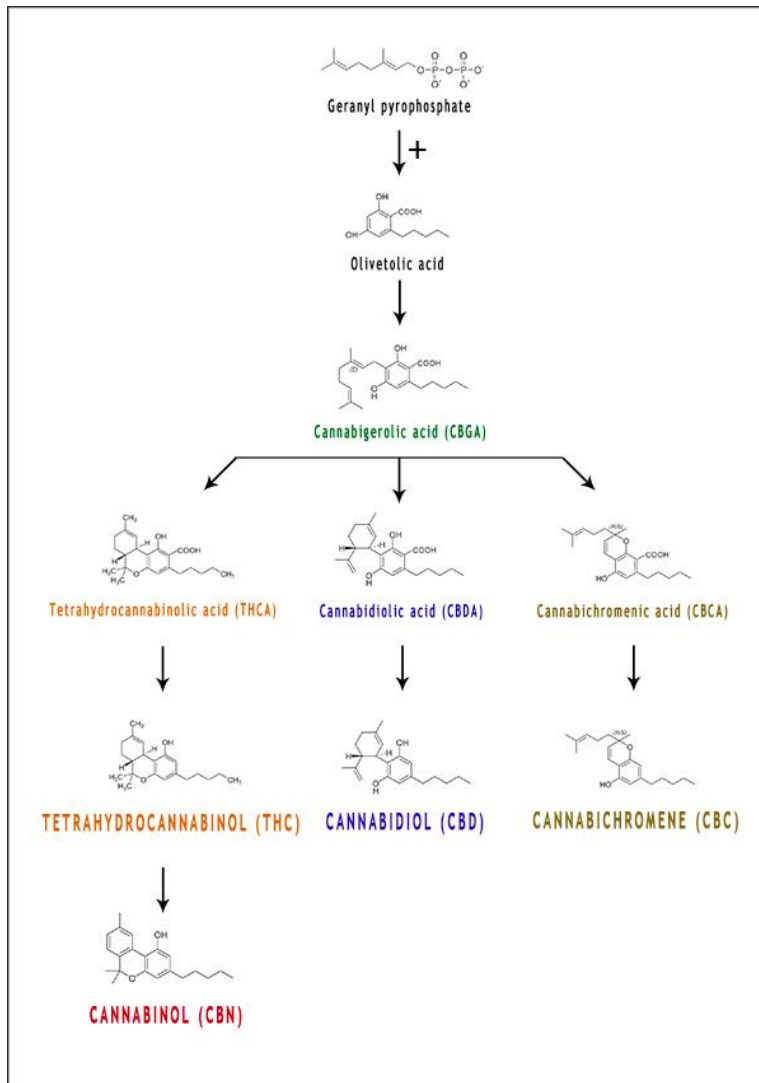
New Cannabinoids on the Market



Cannabigerol (CBG)

- The “mother” cannabinoid
- Thought to be anti-oxidant, “neuro-protective” and anti-inflammatory
- No human data
- In clinical practice, unclear use case
- Not regulated federally: online & store sources not safe

New Cannabinoids on the Market



Tetrahydrocannabivarin (THC-V)

- Rare, not directly related to THC
- Short half-life, very intoxicating at high doses, at low dose felt to suppress appetite
- No human data to support use
- In clinical practice, no decreased munchies seen
- Despite being sold OTC, is clearly federally illegal

New Cannabinoids on the Market



Saved
the Best
for Last

Tetrahydrocannabinolic Acid (THC-A)

- Abundant precursor of THC, non-intoxicating
- Potent anti-inflammatory 10-20x CBD
- Both mouse and human ex-vivo data in IBD
- In clinical practice, sig benefit to Crohn's, UC, and RA
- Available at some dispensaries, and easy to make at home

In a 35 yo woman s/p renal transplant on Tacrolimus, which of the following components of cannabis would be contraindicated?

- A. THC
- B. CBD
- C. CBG
- D. THC-A

Answer:

B. CBD

Explanation:

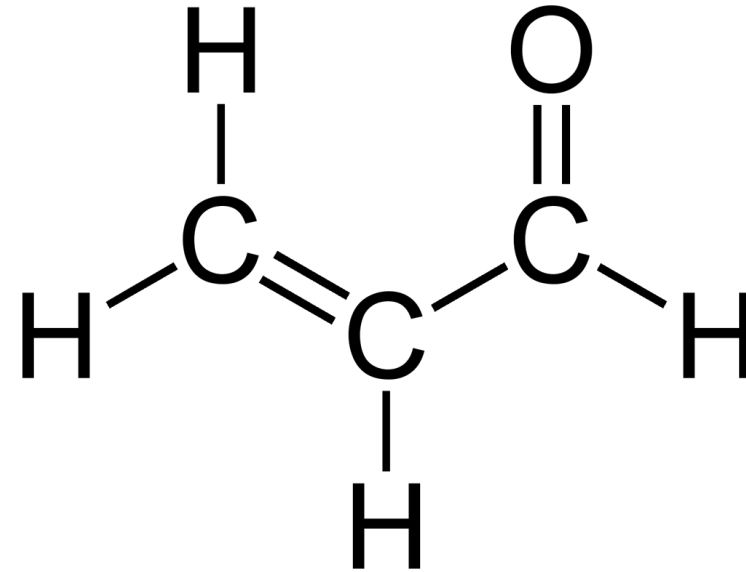
CBD has been shown to interact with many conventional Medications, including Tacrolimus, via the P450 system. Other components, like THC, can interact with various isoenzymes, but do not usually show interaction with medications due to abundant availability of most isoenzymes.



Scary New Stuff – Vape Pens and Hemp Derived Cannabinoids

Oil-Pen (Vape Pen) Associated Risks

- Medium Chain Triglyceride oil (MCT), typically coconut oil, has been associated with Lipoid Pneumonitis
- Terpene combustion produces a wide array of carcinogens at low temperatures, including Benzene, Acrolein, and Metacrolein.
- Devices leach heavy metals into oil then inhaled.



Troutt, W. D., & DiDonato, M. D. (2017). Carbonyl Compounds Produced by Vaporizing Cannabis Oil Thinning Agents. *The Journal of Alternative and Complementary Medicine*, acm.2016.0337.
<https://doi.org/10.1089/acm.2016.0337>

McDaniel, C., Mallampati, S. R., & Wise, A. (2021). Metals in Cannabis Vaporizer Aerosols: Sources, Possible Mechanisms, and Exposure Profiles. *Chemical Research in Toxicology*, 34(11), 2331–2342.
<https://doi.org/10.1021/acs.chemrestox.1c00230>

New Cannabinoids on the Market

2018 Farm Bill legalized hemp and CBD along with all derivatives therefrom

Hemp = cannabis bred to produce <0.3% THC but makes all other natural cannabinoids

Industry selling novel “derivative” cannabinoids from CBD (for intoxication)

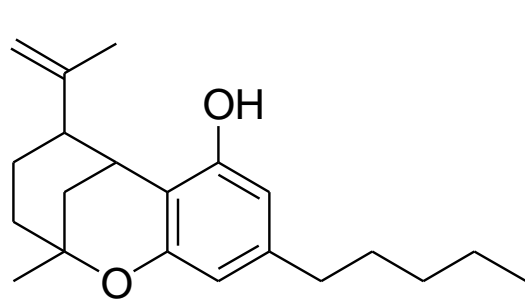
Chemistry of making derivatives is actually complex

- Boron trifluoride, sulfuric acid, and hydrochloric acid
- Dangerous side products

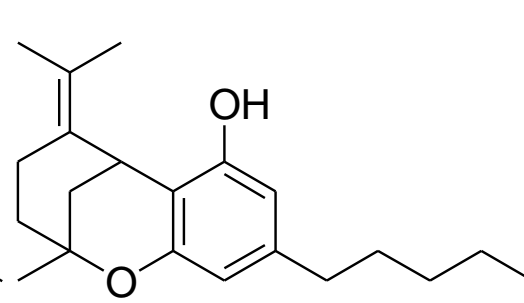
Safety analysis not easy and most labs not equipped to detect isomers and enantiomers

Next slide shows only 1 of 4 pages of possible products of these reactions, about the safety of which we know absolutely nothing:

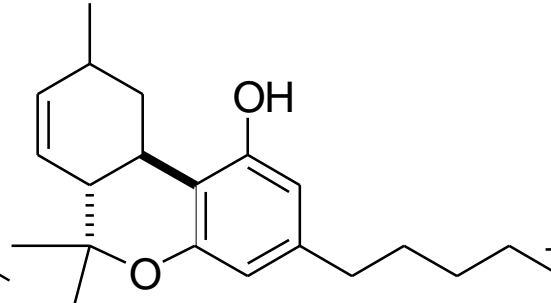
THC Isomers formed in the ACRCC reaction



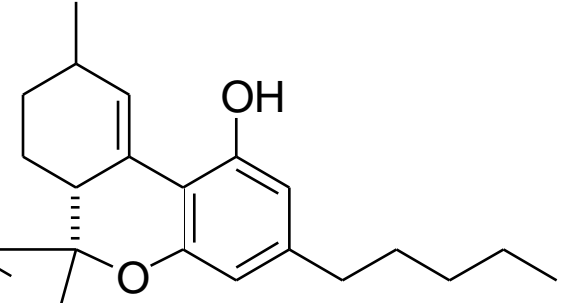
iso Δ^8 -THC



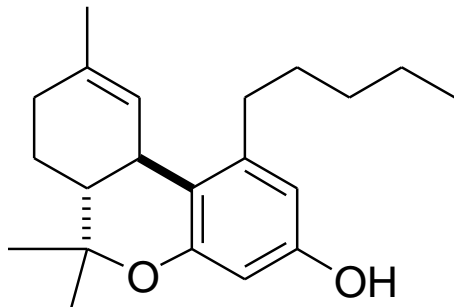
iso $\Delta^{4(8)}$ -THC



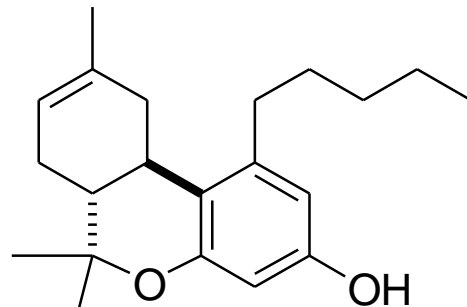
Δ^7 -THC



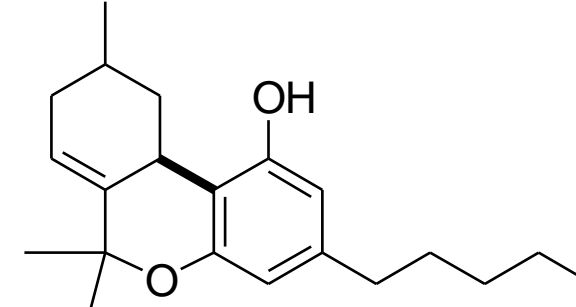
Δ^{10} -THC



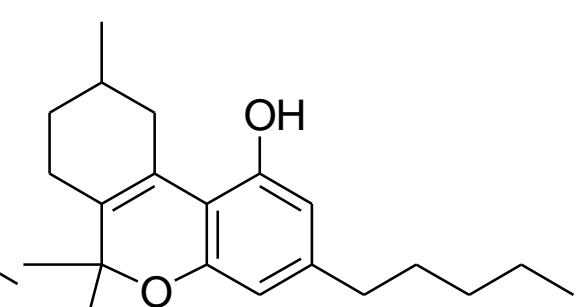
ortho Δ^9 -THC



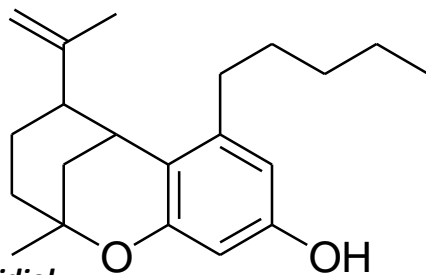
ortho Δ^8 -THC



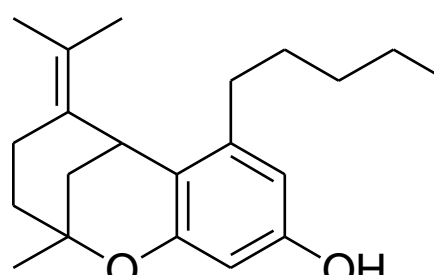
Δ^6 -THC



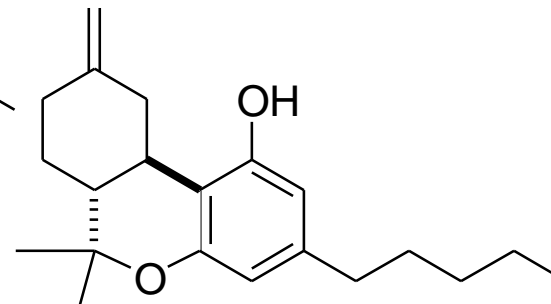
$\Delta^{6a(10a)}$ -THC



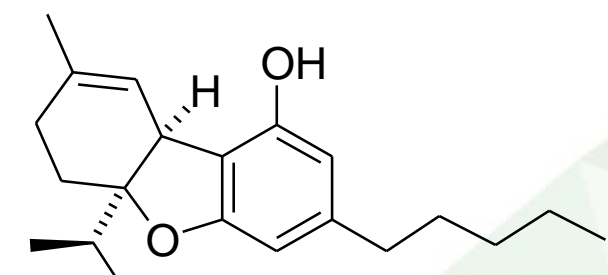
ortho iso Δ^8 -THC



ortho iso $\Delta^{4(8)}$ -THC

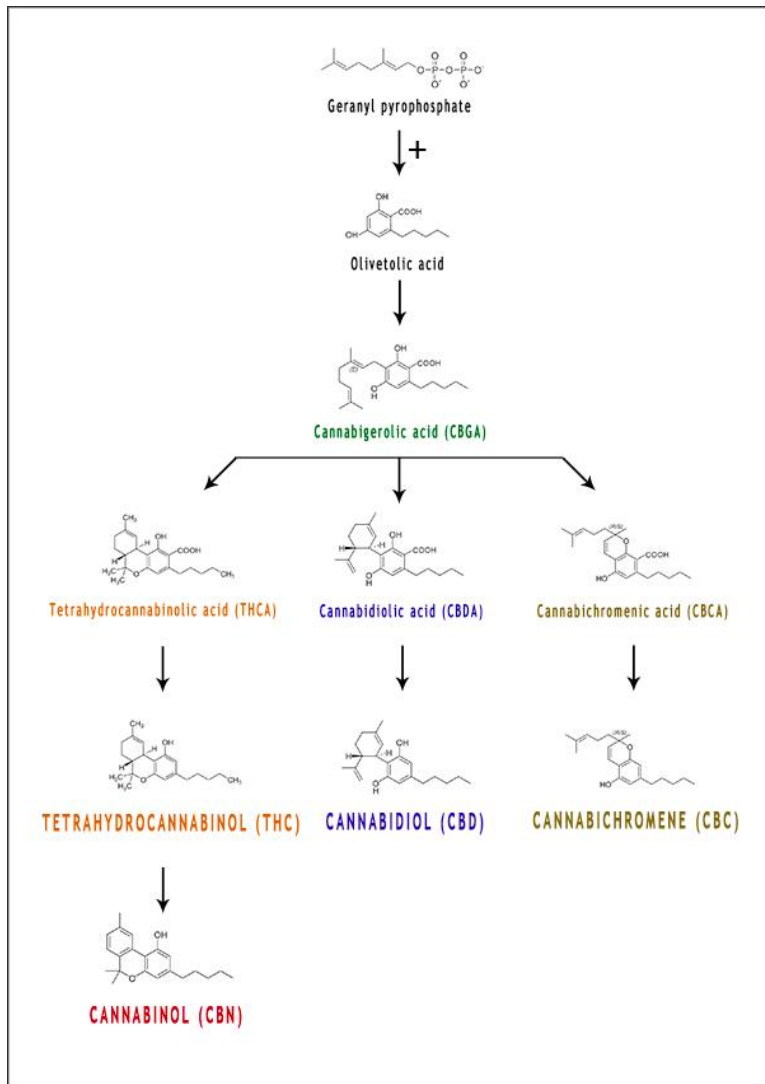


Δ^{11} -THC



iso Δ^9 -THCBF

New Cannabinoids on the Market



d8-Tetrahydrocannabinol (d8-THC)

- A natural variant of d9-THC
- Binds less avidly to CB receptors, causes less intoxication, perhaps less benefit
- No human data in isolation from d9
- In clinical practice, unclear use case
- Despite being sold OTC, is clearly federally illegal

Certification Is Not the Goal

- Effective and Safe Medical Care
- Dispensaries provide misinformation and take advantage of patients
- Close medical guidance and availability of doctor key

About the Association of Cannabinoid Specialists (ACS)



- **International organization** of healthcare professionals at the forefront of cannabinoid medicine
- **Membership benefits** include:
 - Advocacy
 - Education
 - Networking
 - Events

Visit cannaspecialists.org to learn more



Requirements For A Federal Medical Cannabis System

- Exact prescriptions
- Medical claims
- State-to-state interoperability
- Common safety standards
- Clinical Discretion
- Purchase feedback
- Recreational system overlap
- Research agenda

Legalization as currently discussed will accomplish none of this!

SUMMARY



- Cannabis can be effective for pain, anxiety and depression, insomnia, anorexia, nausea, and sexuality
- Dose, timing, and route of administration are key
- Think INH vs. PO
- Strain is irrelevant
- Many new cannabinoids on market without adequate data
- CBD unproven in humans and can interact dangerously with common medications
- THC-A has best data so far



References

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