



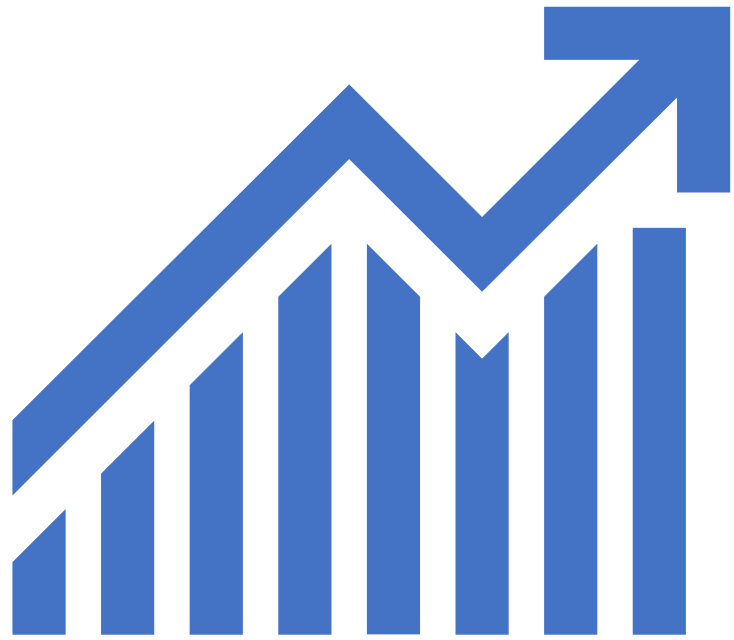
THC and CBD: OMG(osh)!

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October 5, 2019

Objectives

- Provide an overview of Ohio's Medical Marijuana Program
- Illustrate recent updates in Ohio regarding Medical Marijuana and CBD oil
- Differentiate the pharmacology of THC and CBD



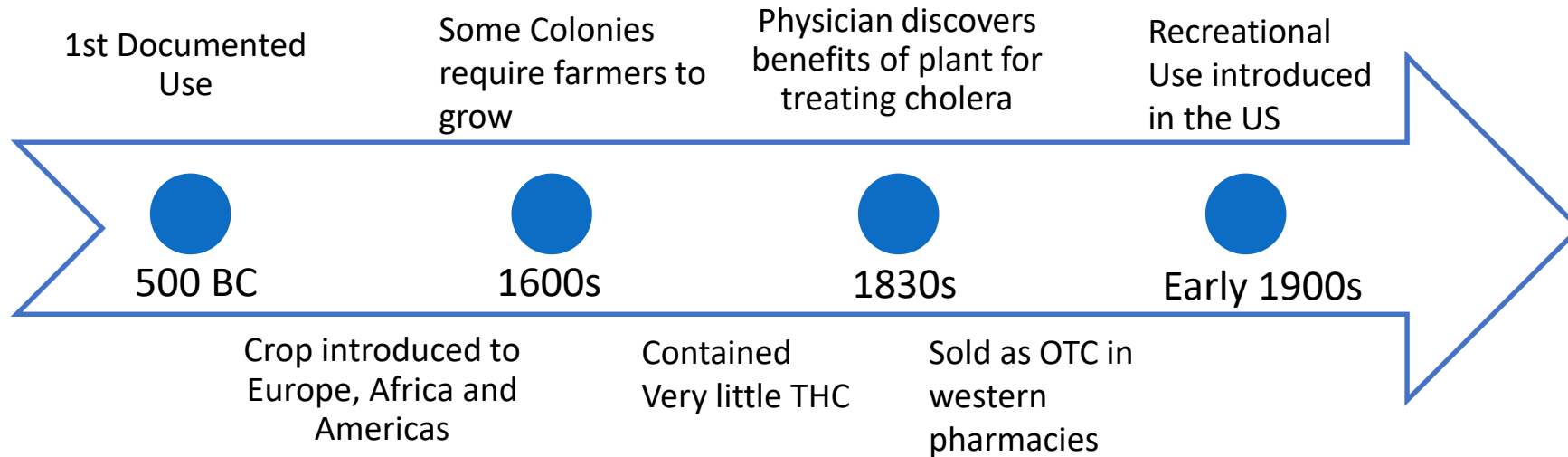
No financial
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Marijuana Vocabulary

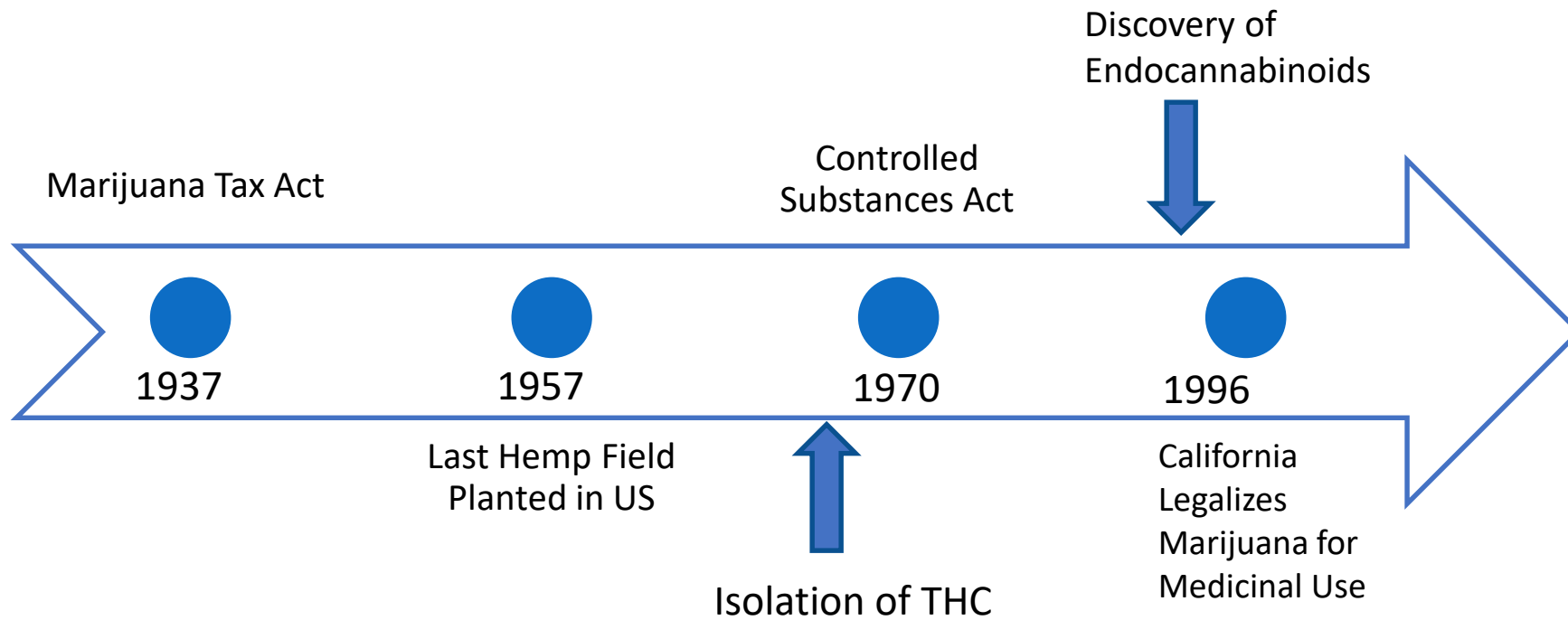
What is Marijuana? National Institute on Drug Abuse [Internet].

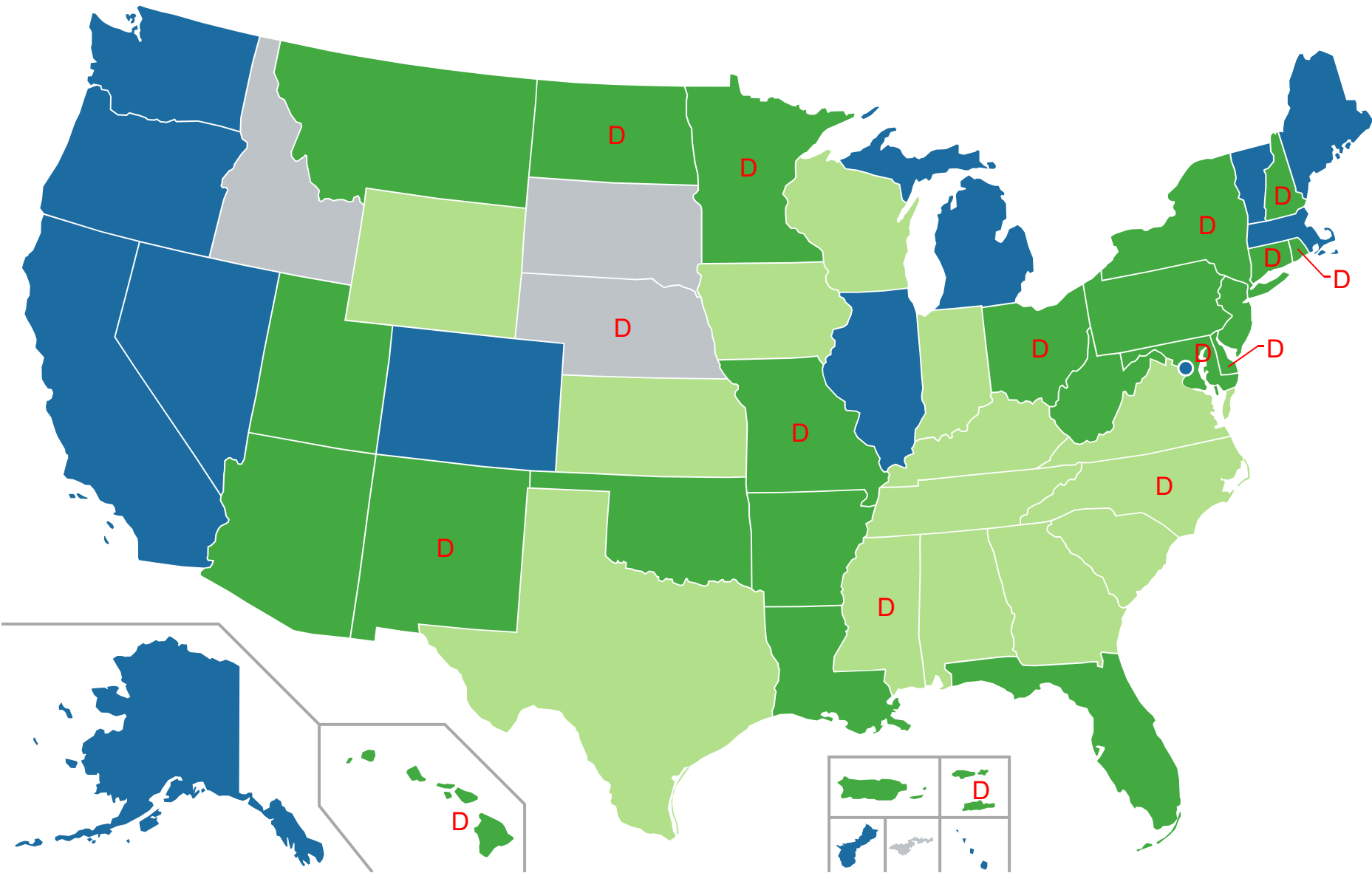
| Term | Definition |
|----------------------|--|
| Marijuana | General name for the mixture of dried leaves and flowers of the <i>C. sativa</i> plant |
| Hemp | Different variety of the <i>C. sativa</i> plant used to make commercial products |
| Cannabis | Umbrella term for the bioactive substances from the cannabis plant |
| Cannabinoid | Compound that binds to or antagonizes cannabinoid receptors (major cannabinoids: THC and CBD) |
| Dabs/Shatter/ Wax | Vaporizing concentrated (50-95% THC) marijuana, usually in the form of a waxy/sticky substance |

Marijuana: A History



Marijuana: A History





By Lokal_Profil, CC BY-SA 2.5,
<https://commons.wikimedia.org/w/index.php?curid=23700>

Ohio Medical Marijuana Program

- 2015: Ohio Issue 3
 - Sought to legalize medicinal and recreational use (>21 years) of marijuana in Ohio
 - Voted down in election (63% no/36% yes)
- 2016: Ohio HB 523
 - Passed September 8, 2016, Effective September 2018
 - Legalized medical marijuana in the state of Ohio for patients with certain medical conditions upon recommendation by an approved physician
 - Established the framework for the Ohio Medical Marijuana Control Program (MMCP)

Ohio Medical Marijuana Program

- June 2018- Epidiolex (cannabidiol) is approved by the FDA
 - 1st marijuana derived CBD product
- August 2018- State Board of Pharmacy issues a statement that they consider all CBD products (except FDA approved ones) to only be legal if sold through the medical marijuana program
- September 2018 MMCP was expected to be operational (it was not)
- December 2018- Farm Bill – removed Hemp from the CSA
 - Defined it as <0.3%THC
 - {products} that are derived from hemp will be legal, *if and only if* that hemp is produced in a manner consistent with the Farm Bill, associated federal regulations, association state regulations, and by a licensed grower

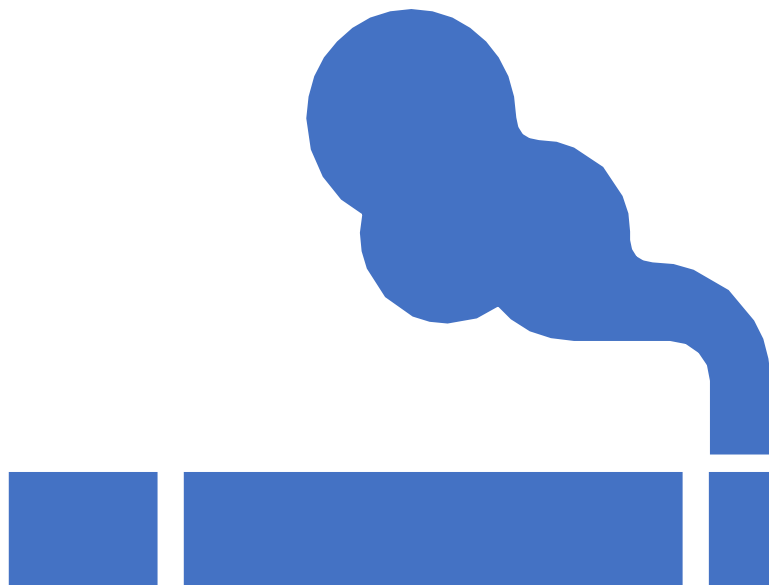
Ohio Medical Marijuana Program

- January 2019- 1st dispensary opens in Ohio
 - Currently 30 open and operating
- July 2019- Ohio Senate Bill 57 signed into law
 - Removed CBD from Ohio's CSA if it is hemp-derived
 - Allows interstate transfer of legally produced product
 - Ohio Department of Agriculture will determine rules/regulations for growth
- September 2019
 - Currently 30 dispensaries are open and operating with product slowly rolling in
 - 55K+ registered patients
 - 261 Registered physicians
 - \$26+ mill in sales

Qualifying Conditions in Ohio

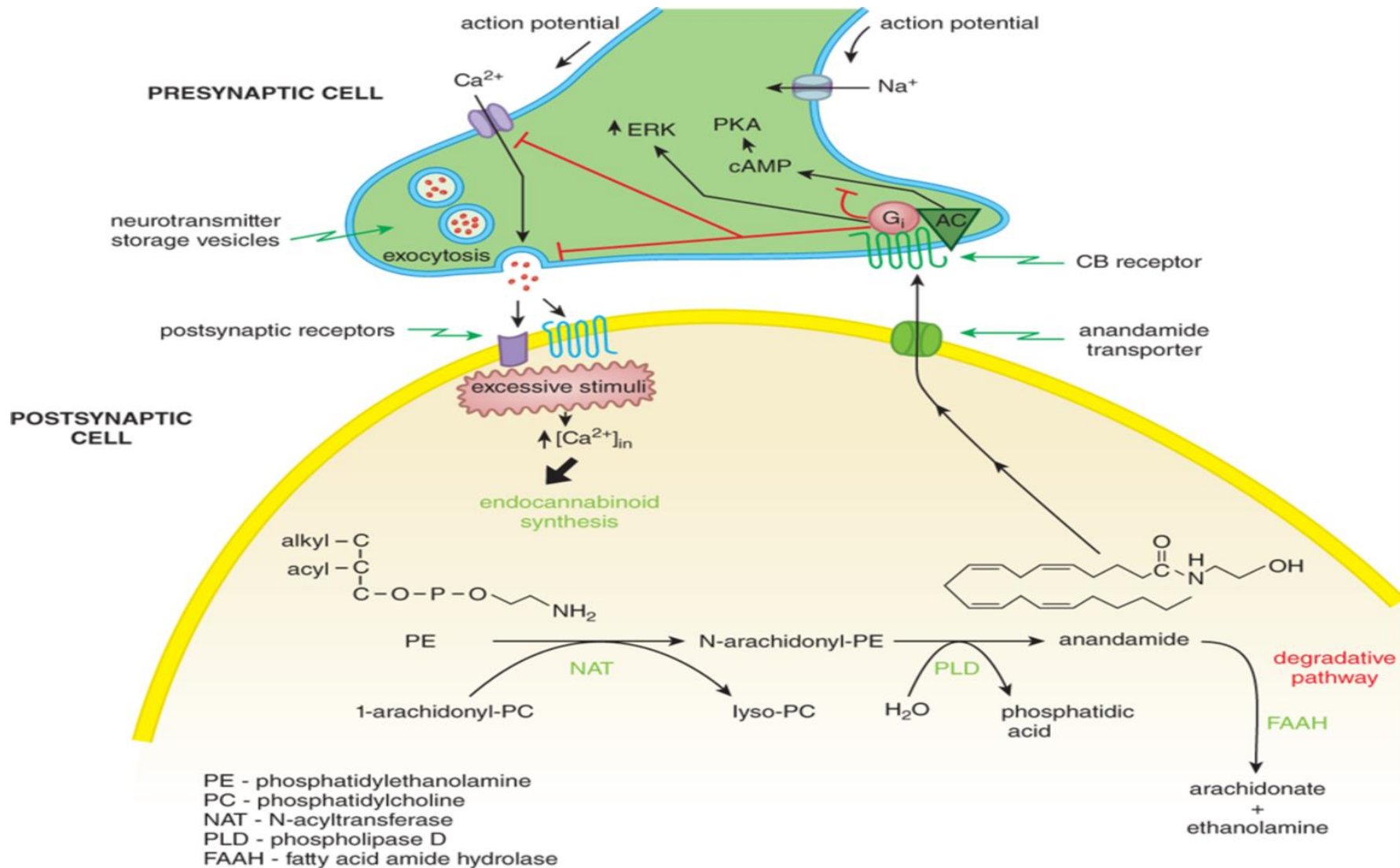
| | |
|-------------------------------------|--|
| AIDS | Amyotrophic lateral sclerosis |
| Alzheimer's disease | Cancer |
| Chronic traumatic encephalopathy | Crohn's disease and Ulcerative colitis |
| Epilepsy | Fibromyalgia |
| Glaucoma | Hepatitis C |
| Inflammatory bowel disease | Multiple sclerosis |
| Pain (chronic/ severe/ intractable) | Parkinson's disease |
| Positive status for HIV | Post-traumatic stress disorder |
| Sickle cell anemia | Spinal cord disease/injury |
| Tourette's syndrome | Traumatic brain injury |

Marijuana and the Endocannabinoid System



Endocannabinoid System

- Consists of the cannabinoid receptors, endocannabinoids, and the enzymes that synthesize and degrade endocannabinoids
 - 2 major endocannabinoids: Anandamide and 2-AG (2-arachinoalglycerol)
 - 2 G-protein coupled receptors: CB1 and CB2, CB3?
- Mechanism of signaling:
 - Inhibit the presynaptic release of neurotransmitters in both the CNS and periphery by decreasing NT release
 - Have been linked to a variety of neuronal processes:
 - Pain sensation, stress, anxiety, appetite, motor learning
- Pacher P, Bátkai S, Kunos G. Pharmacol Rev. 2006 Sep;58(3)389-462.



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann:
 Goodman & Gilman's: The Pharmacological Basis of Therapeutics,
 Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

CB1 vs CB2 Receptors

CB1 Receptors

- Increase concentration in areas of the brain associated with movement, cognition and emotions
- Sparse CB1 receptors in the brainstem
 - Lack of coma and respiratory depression
- Subject to genetic variation

CB2 Receptors

- Typically found peripherally
 - Mainly affect immune and inflammatory response:
 - mRNA found in spleen, thymus, tonsils, GI tract and immune cells
- Possible site of action for CBD derivatives

What exactly is THC?

Pharmacology

- Partial agonist at CB1 receptors
- Responsible for psychogenic effects and cognitive impairment

Pharmacokinetics

- Absorption:
 - Absorption via inhalation: very rapid with a bioavailability of 18-50% of the THC in a cigarette
 - Psychotropic effects in 15-20 minutes, taper off in 1-2 hours
 - Oral absorption: much slower, difficult to predict
 - Psychotropic effects in 30-90 min, taper off in 4-12 hours
- Metabolism
 - Extensive hepatic first pass metabolism

What exactly is CBD?

Pharmacology

- Allosteric modulator of CB receptors
- Antagonism of GR55 receptor
- Desensitization of TRPV1 receptor (aka capsaicin receptor)
- Agonism at 5HT1A/2A/3A receptors
- Broad and varied anti-inflammatory effects

Pharmacokinetics

- Bioavailability hindered by prominent first-pass effect
- 4x increase in bioavailability when administered with a high-fat/high-calorie meal

Drug Interactions

- CYP interferences with CYP2C19 and CYP3A4
- Studies reflect a low risk of clinically significant drug interactions but lack specific human data

Franco V, Perucca E. *Drugs*. 2019 Aug 1. doi: 10.1007/s40265-019-01171-4.

Lauckner JE, Jensen JB, Chen HY, Lu HC, Hille B, Mackie K. *Proc Natl Acad Sci USA*. 2008 Feb 19;105(7):2699–2704.

Stout SM, Cimino NM. *Drug Met Rev*. 25 Oct 2013;46(1):86-95.

What are marijuana “strains”?

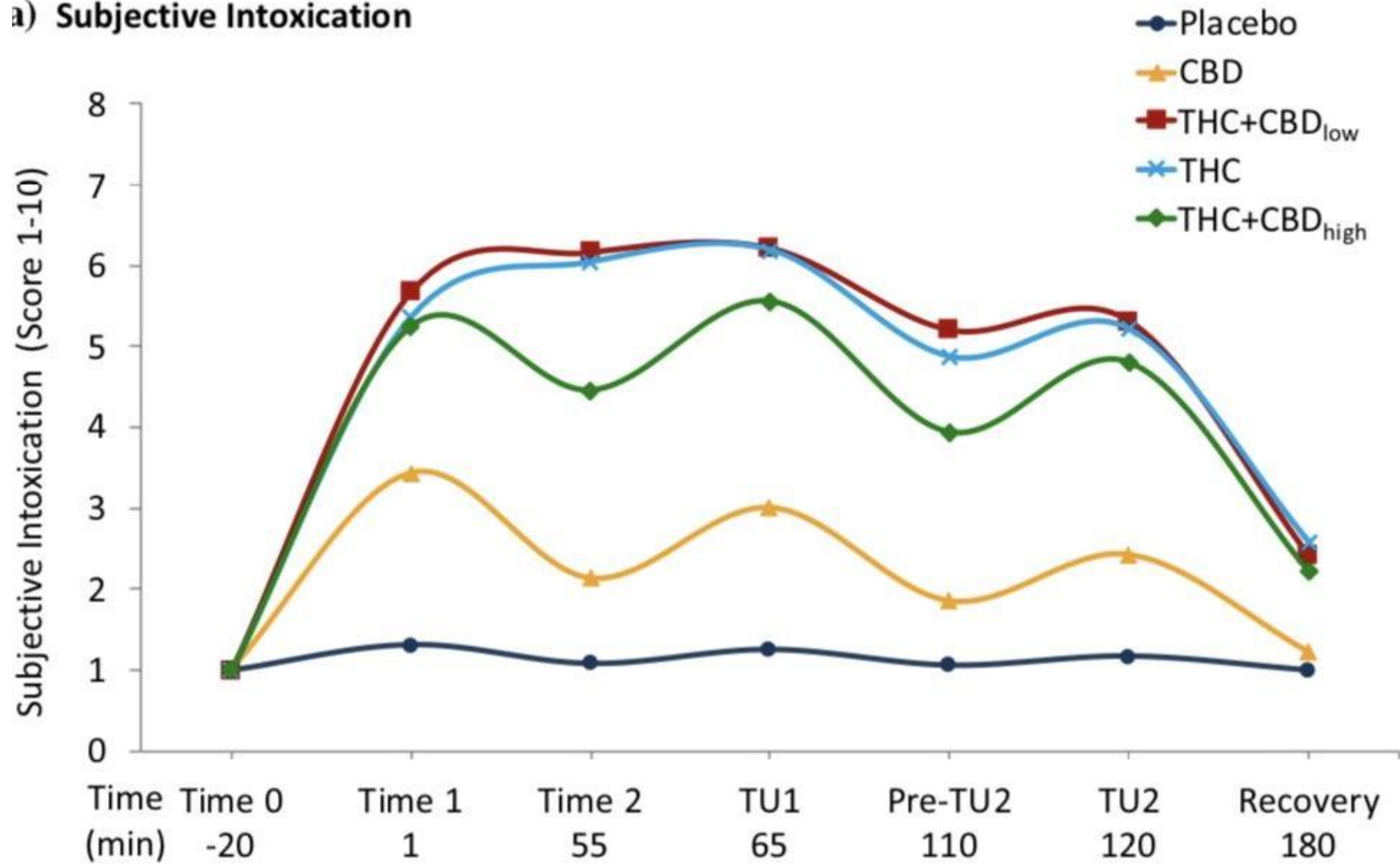
- Marijuana cultivators can manipulate amounts and ratios of CBD and THC
 - Colorado cannabis dispensaries
 - 1990's: <2% THC
 - 1995: 4% THC
 - 2017: “Girl Scout Cookie Strain”
 - 17-28% THC/ 0.09-0.2% CBD
 - Dabs/Shatter/Wax: Concentrations of 50-95% THC
 - Historical data
 - Levels of CBD in illegal marijuana dropped from 0.28% (2001) to <0.15% (2014)
 - THC/CBD levels have increased over time:
 - 1995: THC levels 14 times CBD levels
 - 2014: THC levels 80 times CBD levels
- A Rise in Marijuana's THC Levels. National Institute on Drug Abuse [Internet].
- Stuyt E. Mo Med. 2018 Nov-Dec;115(6):482-486.

What are marijuana “strains”? cont.

- Researchers in Australia conducted a randomized controlled trial comparing the effects of vaporized THC and CBD, alone and in combination in infrequent and frequent cannabis users
 - THC alone: 8 mg
 - High-dose CBD alone: 400 mg
 - Equivalent to doses that have shown antipsychotic effects in previous studies
 - THC + low-dose CBD: 8 mg + 4 mg, respectively
 - Mimics 2:1 ratio previously found in illegal street marijuana before potent THC strains
 - THC + high-dose CBD: 12 mg + 400 mg, respectively

- Solowij N, Broyd S, Greenwood L, et al. Eur Arch Psychiatry Clin Neurosci. 2019 Feb;269(1):17-35.

a) Subjective Intoxication



The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
RECOMMENDATIONS FOR RESEARCH

Does medical marijuana actually work?

- Substantial evidence that it is effective for:
 - Adult cancer pain
 - Chemotherapy-induced nausea and vomiting (CINV)
 - Patient-reported spasticity in MS
 - Epilepsy*
- Moderate evidence that it is effective for:
 - Improving sleep outcomes in patients with OSA, MS, chronic pain, and fibromyalgia



Medical Marijuana Concerns

FDA reports inconsistencies in CBD products

- Between 2015 and 2016, the FDA tested 38 CBD products for the amount of CBD actually contained in the product vs the amount that was labeled
 - 34/38 products contained very little CBD
 - 7 products did not contain any CBD
 - 4 products contained more than the allowed 0.3% THC
-
- FDA testing of CBD products. CBD stasis [Internet].

Side Effects of CBD

- Epidiolex: (Approved 2018)
 - Seizure disorders: treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older
- Administration: Oral
- Effectiveness:
 - 50% reduction in frequency of drug-resistant seizures in 43% of pediatric patients in Epidiolex 20 mg/kg/day vs 27% with placebo (P=0.08)
 - Median percent reduction from baseline in drop seizure frequency:
 - 41.9% in 20mg CBD group (P=0.005)
 - 37.2% in 10mg CBD group (P=0.002)
 - 17.2 in placebo group

Side Effects

- RCTS of Epidiolex found that 84-94% of patients in the treatment group experienced side effects in comparison to 69-75% of patients in the placebo group
 - Adverse effects were **dose-dependent**
 - $\geq 10\%$ of patients experienced **pyrexia, URIs, somnolence, decreased appetite, diarrhea, vomiting, nasopharyngitis, fatigue, convulsions, and lethargy**
 - Observed increase in liver aminotransferases; 80% of the patients in which this occurred were on concurrent therapy with valproate
 - Liver enzymes spontaneously returned to normal after discontinuation of valproate or a dosage decrease of valproate

Sekar K, Pack A. F1000 Res. 2019 Feb 28;8:F1000.

Are there side effects? (CBD)

- Somnolence and sedation increase with dose escalation
 - 23% and 25% of patients receiving 10 mg/kg/day CBD and 20 mg/kg/day CBD, respectively, experienced somnolence
 - 11% and 12% experienced fatigue
 - 4% and 8% experienced lethargy
 - 3% and 6% experienced sedation
 - *These side effects are potentiated by coadministration of CBD with other sedatives*
- Insomnia and sleep disturbances decrease with dose escalation
 - Inverse dose relationship
 - 11% and 5% experienced sleep disturbances
- Weight loss increases with dose escalation
 - 16% and 22% vs. 5% placebo

Are there side effects? (CBD) con't

- Diarrhea more likely with dose escalation
 - 9% and 20% vs. 9% placebo
 - *Diarrhea can be complicated by stimulants, antidepressants, antibiotics, etc.*
- Hematologic abnormalities
 - Increased occurrences of lab-defined anemia
 - 30% of patients treated with CBD vs. 13% of patients treated with placebo
 - Exact cause is unknown
- Infection risk
 - Patients treated with CBD have 10% higher risk of developing an infection
 - Thought to be attributed to CBD modulation of immune system

Are there side effects? (THC)

Subramaniam VN, Menezes AR, DeSchutter A, Lavie CJ. Mo Med. 2019;116(2):146-153.

- Cardiovascular and cerebrovascular effects
 - Acute dose-dependent increase in blood pressure and heart rate
- Anxiety, psychosis
 - Chronic cannabis use increases the risk of later psychotic symptoms and disorders 2-3x
- Inflammatory effects in the peripheral vascular system
 - Similar to Buerger's Disease
- In vitro studies associated with platelet aggregation via CB2 effects
- Cannabinoid Hyperemesis syndrome

Can Patients Afford It?

- Marijuana flower bought illegally
 - Approx. \$8.25/gm
- Medicinal marijuana flower
 - Approx \$18.50/gm
- Edibles
 - \$80 for 11 gummies
- Concentrated oil for vaporization
 - Oil syringe: \$135-175
- Tinctures
 - \$80-120 depending on mg of THC
- Topical products
 - 21 mg transdermal patch: \$17

How much
does it cost in
other states?

- Cost varies depending on supply and demand state to state:
- Examples of costs of medicinal marijuana in other states:
 - Oregon: \$210.18
 - Washington: \$232.90
 - Colorado: \$241.74
 - Ohio: \$260
 - National Average: \$326.06

- Lautieri A, Thomas S, Stein S. The Average Cost of Marijuana by State. Oxford Treatment Center [Internet].

Summary

Medical marijuana is now legal in the state of Ohio, with over 20 operating dispensaries

- Cost and access remain a concern
- Legality of CBD operates in shades of gray

Various medical marijuana products are available with ranging concentrations of THC and CBD

Phytocannabinoid pharmacology and endogenous cannabinoid pharmacology is evolving

- Will likely produce new lines of FDA-approved agents in the future



Questions?

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