Clinical and Legal Considerations in Medical Cannabis

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Objectives

1. Describe key features of the **endocannabinoid system & cannabis pharmacology**, and **non-phytocannabinoid** constitutes of cannabis; including **pharmacokinetics and formulations**.
2. Describe **adverse effects** of cannabis use and distinguish **clinical concerns** associated with selected interactions involving medical marijuana use.
3. Discuss **best practices** in patient evaluation, medical marijuana product choice, dosage and therapeutic monitoring based on the patient's serious medical condition; Discuss risk vs benefits including recognition of **potential drug interactions**, side effects, potential use disorder.
4. Explain the status of cannabis as a controlled substance under **U.S. federal law** & the provisions of **Pennsylvania's Medical Marijuana** Act of 2016.
5. Review practice implications of the most current proposed **USP cannabis monograph**.
6. Have informed discussions with patients about the **risks and benefits of medical cannabis** for the **Pennsylvania approved serious medical conditions**.

Dr. Roussel's Disclosures

- No financial Disclosures Relevant to the Cannabis Industry
- Dr. Roussel is the institutional member and the Vice-Chair of the Pennsylvania Board of Pharmacy, however, this program is not related to the role, and the views expressed are her own
- Dr. Roussel is a member of the Pennsylvania Medical Marijuana Advisory Board and the Chair of the Regulatory Sub-committee, however, this program is not related to the role, and the views expressed are her own
- Program Faculty, Medical Cannabis Education Course, Philadelphia College of Pharmacy, St. Joseph's University

Knowledge Assessment

Which of the following statements about the endocannabinoid system is true?

a) Endocannabiniods are synthesized from amino acids
b) Endocannabinoid receptors are the most concentrated g-protein coupled receptor in the brain
c) Endogenous endocannabinoids have relatively long half lives
d) Cannabinoids only mediate their activity through endocannabinoid receptors

Knowledge Assessment

Which of the following statements a taking cannabis orally is false:

a) The liver metabolizes THC into 11-Hydroxy-THC, (11-OH-THC), which has a longer T1/2and is a more potent analgesic activity
b) Higher blood levels and longer duration of clinical effects following oral administration compared to inhaled
c) Oral administration has a predictable and immediate onset of action

Patient Case

E.D. is a 60 yo truck driver who asks his pharmacist about using medical cannabis to help with his neuropathic pain which significantly disturbs his sleeps?

Medication List

Prilosec 20 mg PO QD

Metformin 100 mg PO BID

Atorvastatin 10 mg PO QD

Losartan 50 mg PO QD

Toprol XL 50 mg PO QD

Warfarin 5 mg PO QD

Gabapentin 600 mg PO TID

Cannabis' Disclosures

- Cannabis is currently not FDA approved for any condition

- **Cannabis is currently DEA Schedule 1 (Federal) under the Controlled Substance Act of 1970**
  - **no currently accepted medical use**
  - **lack of accepted safety for use under medical supervision**
  - **high potential for abuse**

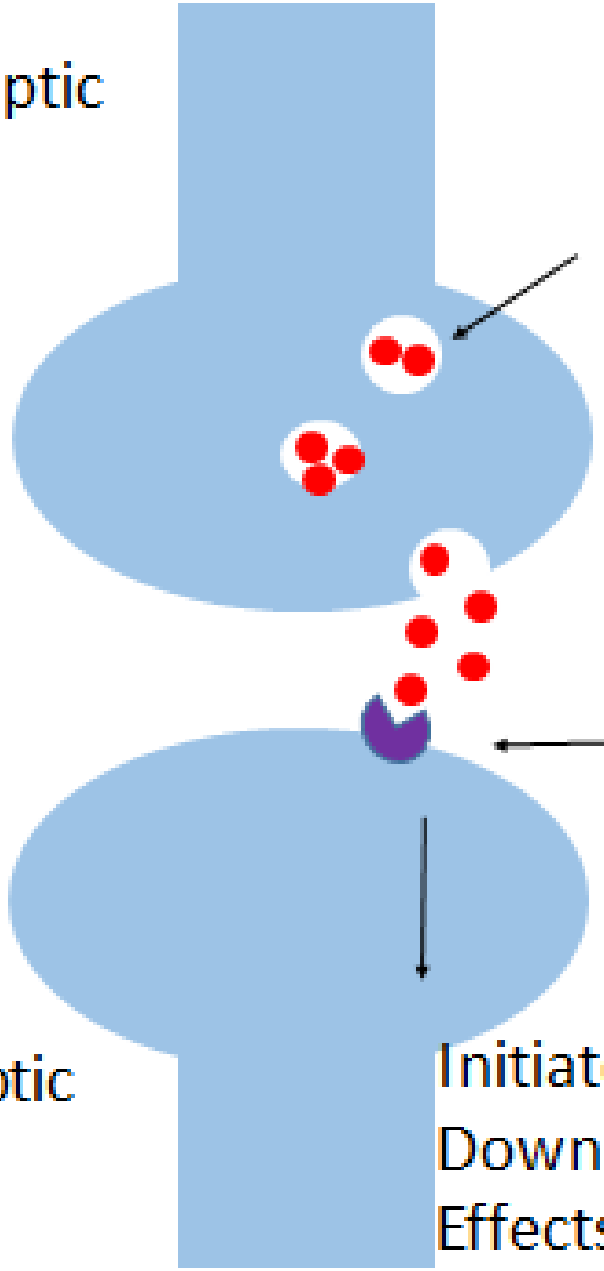
- Investigational use only
  - IND applications must receive triple agency approvals: **National Institute of Drug Abuse (NIDA) / DEA / FDA**

US Government and Cannabis

US Patent

“Cannabinoids are found to have particular application as neuroprotectants, for example limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson’s disease and HIV dimension”

1977 – 1993 Federal Compassionate IND (n=13) Grown by University of Mississippi & NIDA



Neuro Signal Transmission Across the Synaptic Cleft

- Glutamate
- GABA
- Acetylcholine
- Norepinephrine
- Dopamine
- 5-HT3
- Cholecystokinin

Health Canada 2018; Image by C. Roussel

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3. Binding at the CB1 Receptor stabilizes vesicles to decrease neurotransmitter release

Presynaptic Neuron

Neuro Signal Transmission Across the Synaptic Cleft

Endogenous Agonist

- Anandamide N-Arachidonoylethanolamine (AEA)
- 2-Arachidonoylglycerol

2. Endocannabinoids Synthesized on demand for immediate release

1. Too much activity

Postsynaptic Neuron

The Endocannabinoid System Provides Retrograde Inhibition

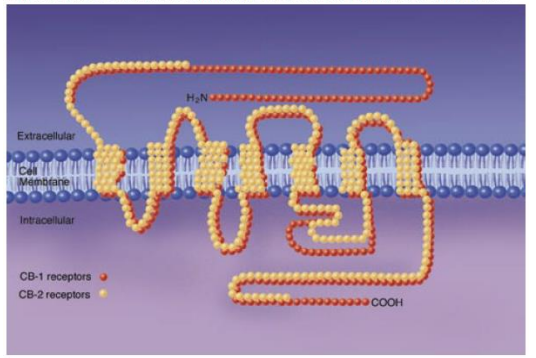
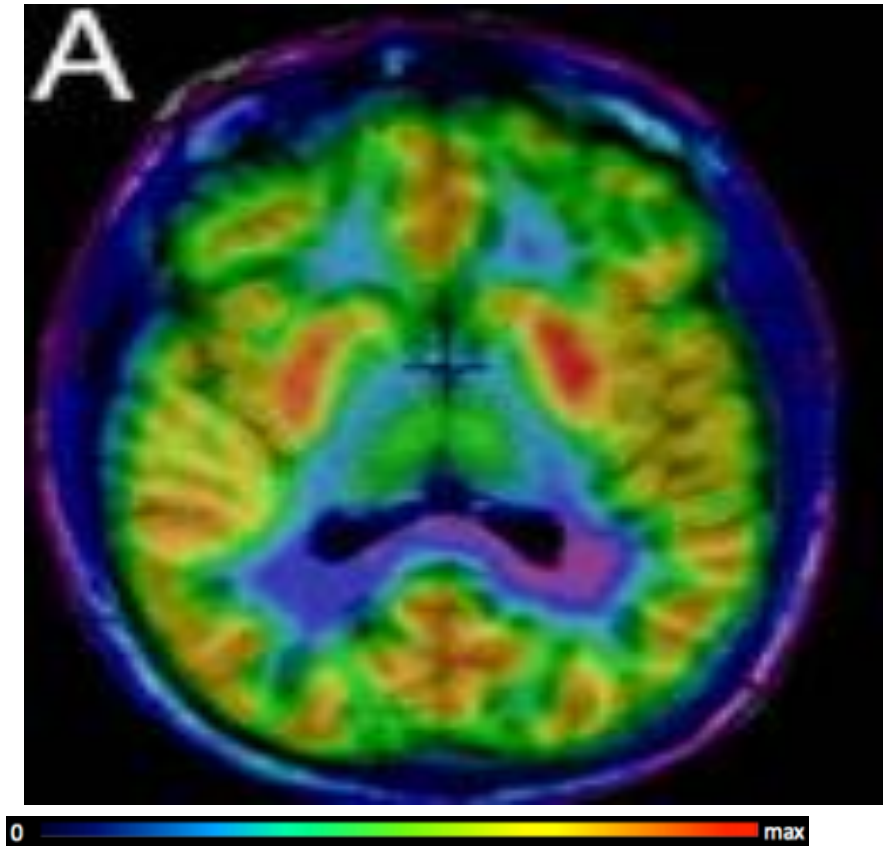


Figure 1. Subtypes of cannabinoid receptors. Cannabinoid-1 (CB-1) receptors primarily modulate psychoactive effects. Cannabinoid-2 (CB-2) receptors primarily modulate immune responses. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from reference 6.

Image by C. Roussel

CB1 Receptors



Human brain after injection of radio tracer to show the regional distribution of CB1R

CB1 – Primarily in Brain

- NOT significant in brainstem (resp drive)

Other Locations

- Adipocytes
- Endocrine and Exocrine Glands
- Hepatocytes

Cannabinoid Pharmacology in CNS

- Anti-nociceptive Effects
- Parasympathetic – antiemetic effects
- Neuroprotection
- Neuroplasticity

Original publication: Burns, et al. [^{18}F]MK-9470, a positron emission tomography (PET) tracer for *in vivo* human PET brain imaging of the cannabinoid-1 receptor. PNAS June 5, 2007, 104, 23. Pg. 9800–9805 © [2007] All rights reserved. Reprinted with permission.
Shohami,E & Horowitz,M (ed). Cannabinoids in Health & Disease. Journal of Basic & Clinical Physiology & Pharmacology 2016; 27(3).

CB2 Receptors:
Signaling ↓ release of activators & sensitizers

Immunomodulation:

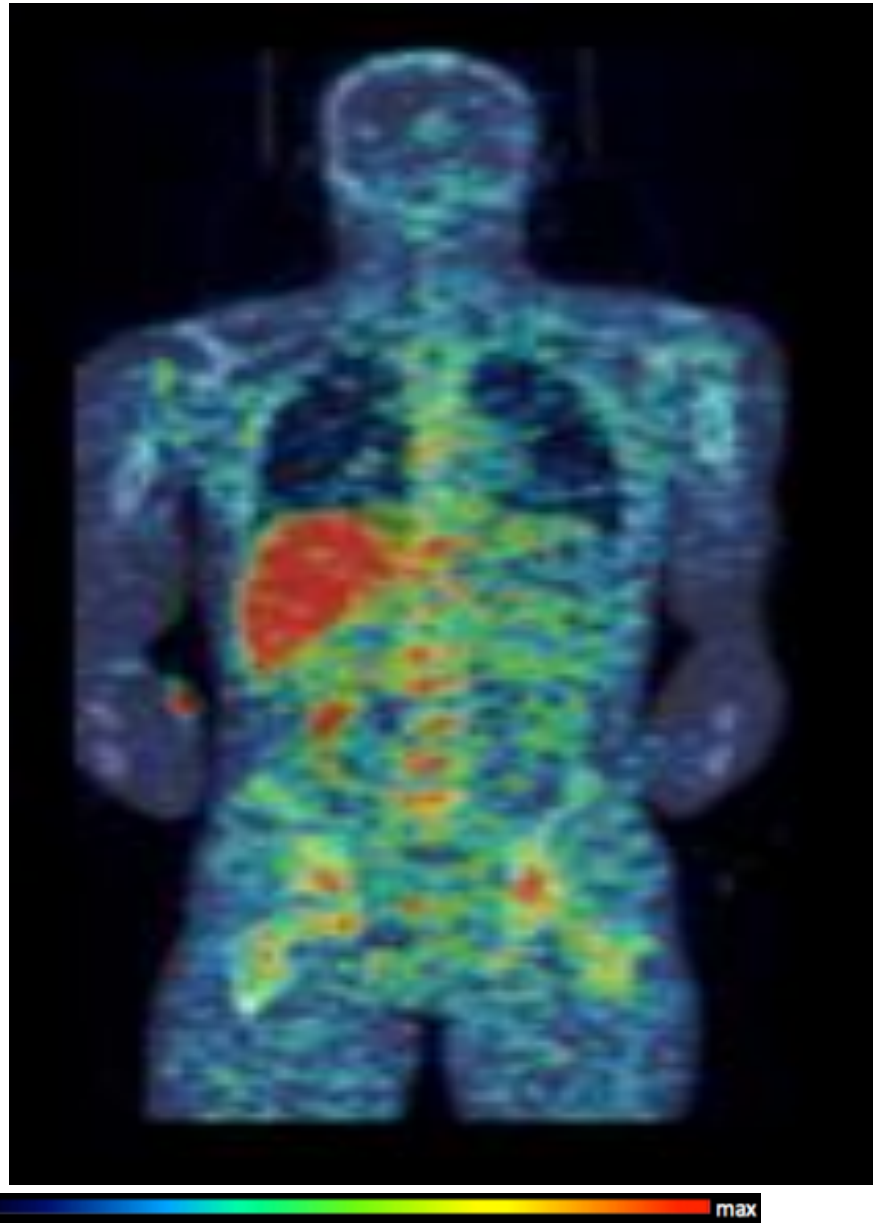
- Monocytes
- Macrophages
- B-cells
- T-cells

Liver, Spleen, Tonsils

Central & Enteric Nervous System

Endocrine & Exocrine Glands

Known to upregulate in tissues where normally not found during inflammation



Original publication: **Ahmad R,, et al. 2016** Whole-body bio-distribution and radiation dosimetry of the cannabinoid type 2 receptor ligand [11C]-NE40 in healthy subjects. Mol.Imaging.Bio 2013 Aug;15(4):384-90© [2013]All rights reserved. Reprinted with permission.

Just Some of the Puzzle Pieces

Receptors

CB1

CB2

TRPV1

TRPV2

(Transient receptor potential vanilloid)

GPR55

PPARα

Ligands

Tetrahydrocannabinol **THC**

Cannabidiol **CBD**

2-arachidonoylglycerol (**2-AG)**

N-arachidonoylethanolamine, arachidonoylethanolamide aka anandamide (**AEA)**

N-oleoylethanolamine, oleoylethanolamide (**OEA)**

N-palmitoylethanolamine, palmitoylethanolamide (**PEA)**

Synthesizing and Degrading Enzymes

fatty acid amide hydrolase (**FAAH)**

monoacylglycerol lipase (**MAGL)**

N-acyl-phosphatidylethanolamine -selective PLD **(NAPE-PLD)**

"The Endocannabinoid System (ECS) seems to be essential in most if not all physiological systems. The ECS is essential to life and it relates messages that affect how we relax, eat, sleep, forget and protect." -Vincenzo Di Marzo, PhD (2008)

Cannabis is a single highly variable species

THC
tetrahydro-cannabinol

CBD
cannabidiol

THCV
Tetrahydro-cannabivarin

THC-A
Tetrahydro-cannabinolic acid

CBC
Cannabi-chromene

CBG
cannabigerol

CBN
Cannabinol

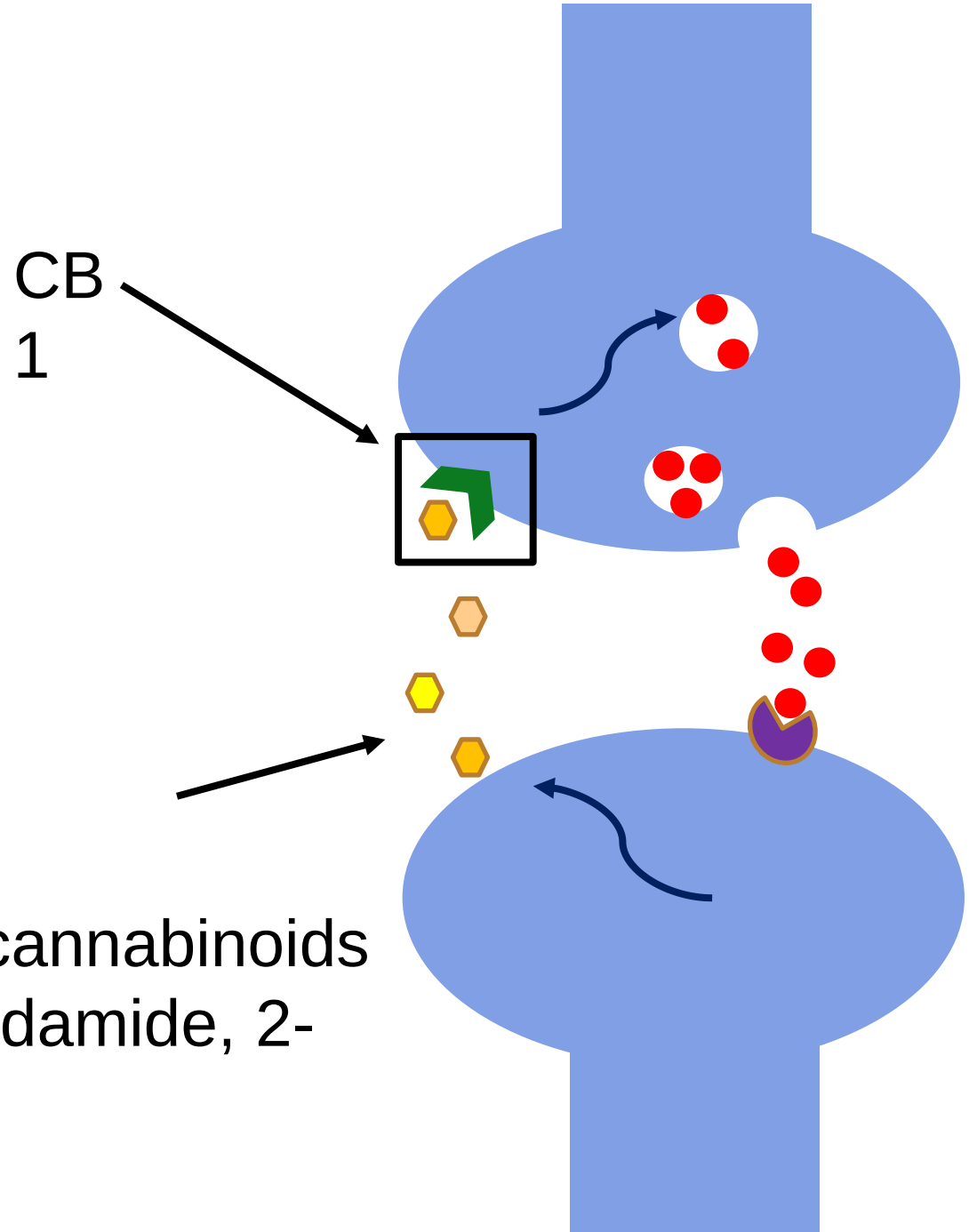
“Entourage Hypothesis”

Cannabinoids
Flavonoids
Lipids
Sterols
Terpenes

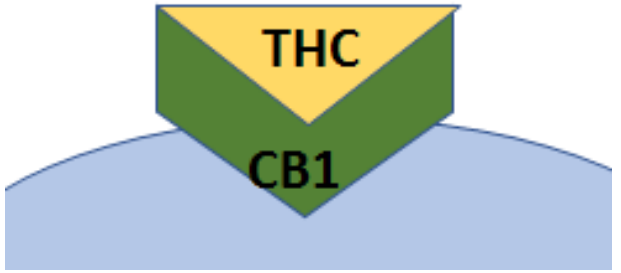
What Should Medical Cannabis Be:

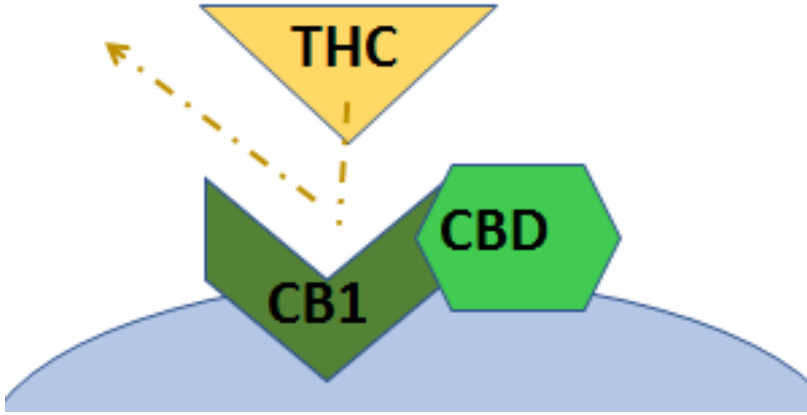
- Cannabis Sativa
- Good Manufacturing Practices applied to grow and processing
- Cannabinoid and Terpenes
  - 3rd Party Assay
  - Labeled with Expiration
    Mold / Yeast
- Contaminants below acceptable levels
  - Pesticides
  - Heavy Metals
  - Residual Solvents

Pictures from Steephill.com/science.



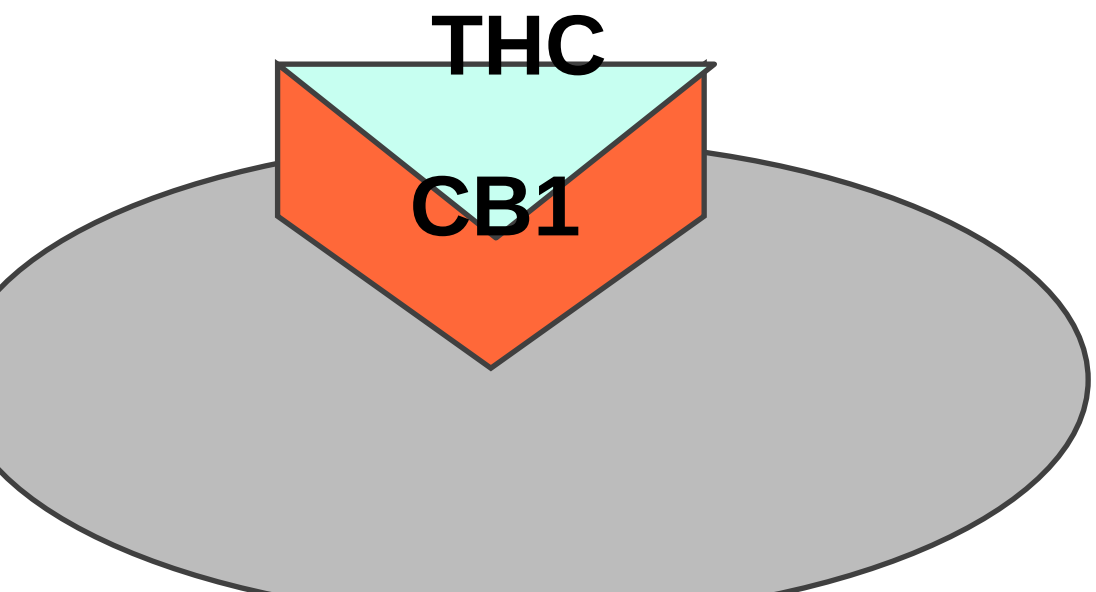
Endocannabinoids (Anandamide, 2-AG)

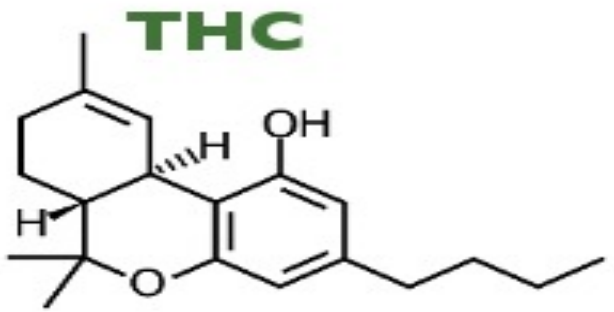


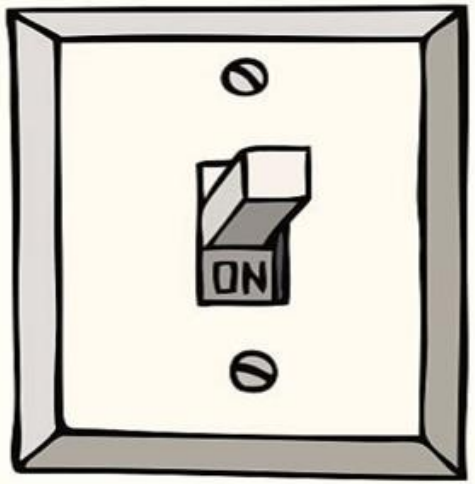


TETRAHYDROCANNABINOL (THC)

- Partial Agonist of CB1 and CB2
- Euphoria
- Analgesia (primary Pain relief molecule)
- Muscle Relaxant
- Anxiolytic (low dose) -> Anxiogenic (higher doses)







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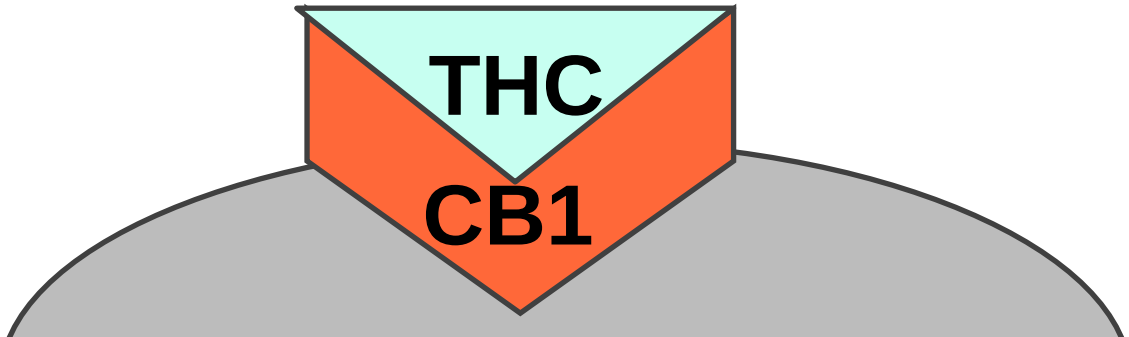
TETRAHYDROCANNABINOL (THC)

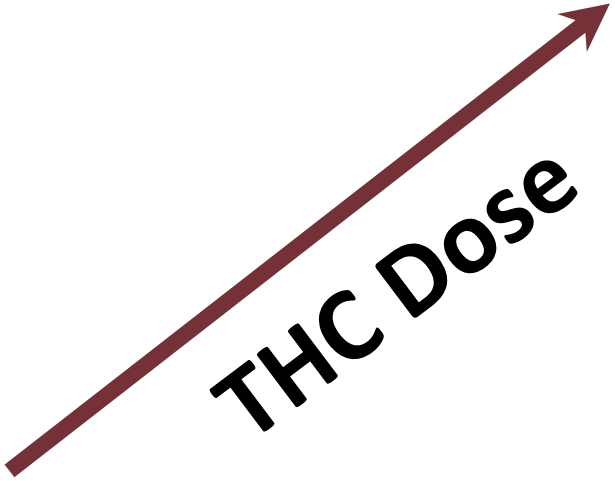
Psychoactivity vs Psychotoxicity

- Impaired cognition
- Difficulty concentrating
- Memory Impairment

Dry mucous membranes
Dizziness
Weakness , increase risk of falls



Anxiogenic / Paranoia
Cannabis Induced Psychosis
Hyperemesis syndrome



Anxiolytic
Anti-emetic

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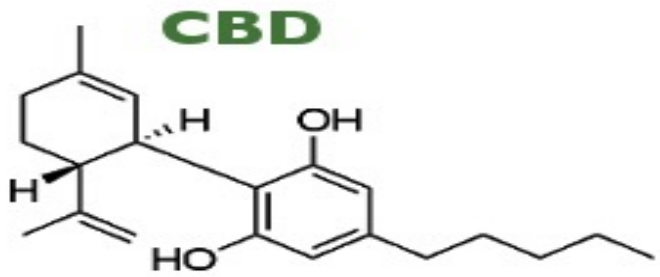
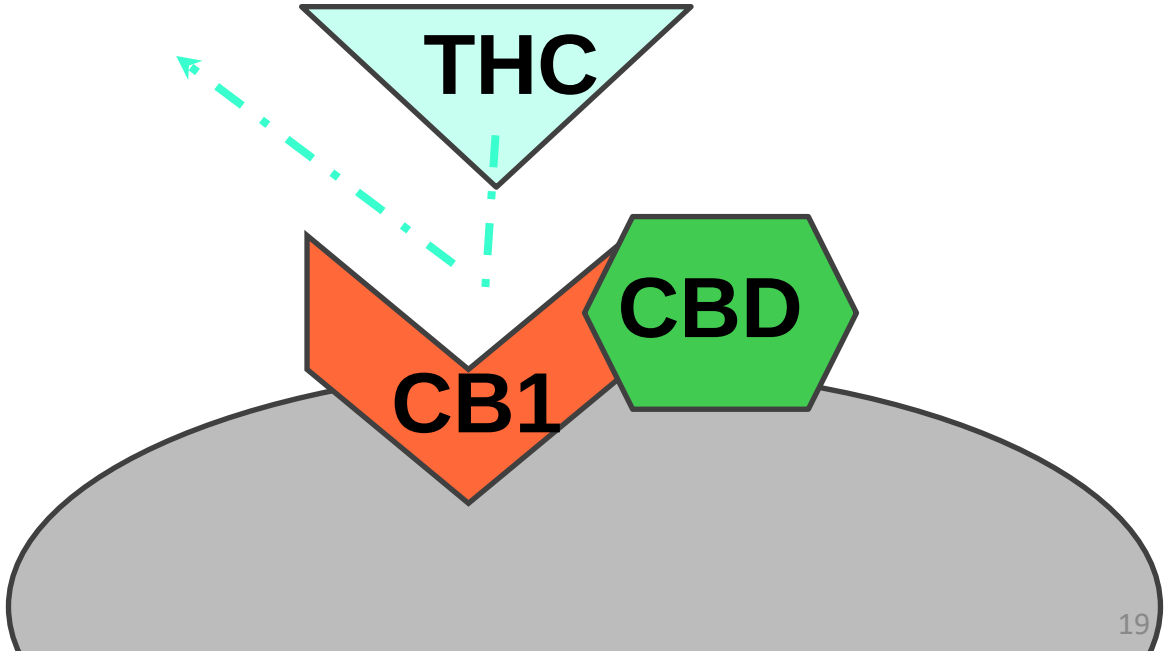
Cannabidiol (CBD)



- Negative Allosteric Modification
- Weak antagonist at CB_2
- Enhances natural endocannabinoid activity via inhibition of degradation
- Agonist at 5-HT_{1A}
- Agonists at TRPV1, TPPV2
- GPR3/6/12/18/55
- Dopamine D_2
- $GABA_A$, TRPA1, PPAR



Cannabidiol (CBD)

- Decreases Seizures (FDA approved)
- Immune Modulary
- Reduce Nausea / Intestinal inflammation
- Non-intoxicating, non-addictive
- "CBD Cushion" - Decrease negative effects of THC (anxiety, memory impairment, psychoactivity)*

<u>UNWANTED EFFECTS</u>

Headache
Diarrhea
Appetite Suppression

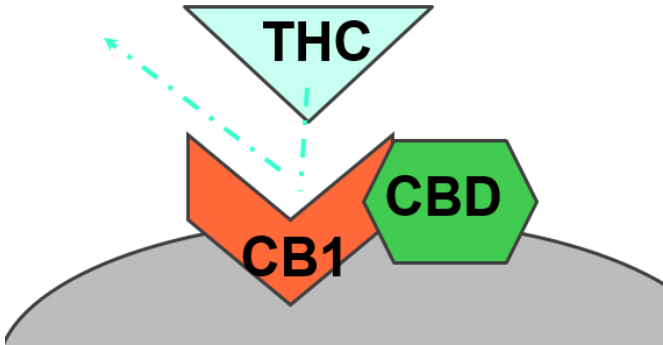
HIGH DOSES

- Drug Interactions
- Liver Enzyme Elevation
- Increased Risk of Infection

"Most of CBD's effects are not directly related to the endocannabinoid system"

- **Dr. Linda Klumpers**

Roussel



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Select Phytocannabinoids & Pharmacology

	Cannabinoid	Areas of Investigation
CBD-A	Cannabidiolic acid	Anti-emetic, anti-anxiety, clinical trial on-going for autism
THC-A	Tetrahydrocannabinolic acid	Anti-inflammatory effects via antagonism of tissue necrosis factor alpha (TNF-α); anti-emetic, anti-convulsant, clinical trial on-going for diabetes
CBN	Cannabinol	1/10th the psychoactive potency, sedative, antibacterial, inhibition of keratinocytes in psoriasis
CBC	Cannabichromene	anti-inflammatory, anti-fungal, anandamide reuptake inhibitor
CBG	Cannabigerol	GABA uptake inhibitor, antibacterial, inhibition of keratinocytes in psoriasis

Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br.J.Pharmacol.* 163: 1344-1364.
Clinicaltrials.gov; Handbook of Cannabis and Related Pathologies, 2017

TERPENES

LINALOOL

Sedative
Anxiolytic
Analgesic
Modulate GABA and Glutamate

MYRCENE

Analgesic
Anti-Inflammatory via PGE-2
Anti-Convulsant
Skeletal Muscle Relaxant

ß CARYOPHYLLENE

Select CB2 Agonist
Analgesic
Gastric Protective
Anti-Inflammatory via PGE-1

Russo, E. B. (2011). Taming THC...*Br.J.Pharmacol.* 163: 1344-1364.

Synthetic Cannabinioids (ie. K2, Spice, Crazy Monkey, Chill Out)

Developed to study the endocannabinioid system

Up to 200 times more potent that plant based cannabis products

- Extreme Potency = Extreme Toxicities

Vaporizers, E-cigarettes, plant products sprayed with chemicals to burn

2015 – 7,797 toxic exposures reported

- 25% of events in children 13 to 18 years old

Neurologic symptoms:

- **Agitation, coma, seizures, toxic psychosis, hallucinations**

Cardiac symptoms

Organ Function

Severe nausea / vomiting, acute kidney injury, respiratory depression, death, Cardiac Symptoms

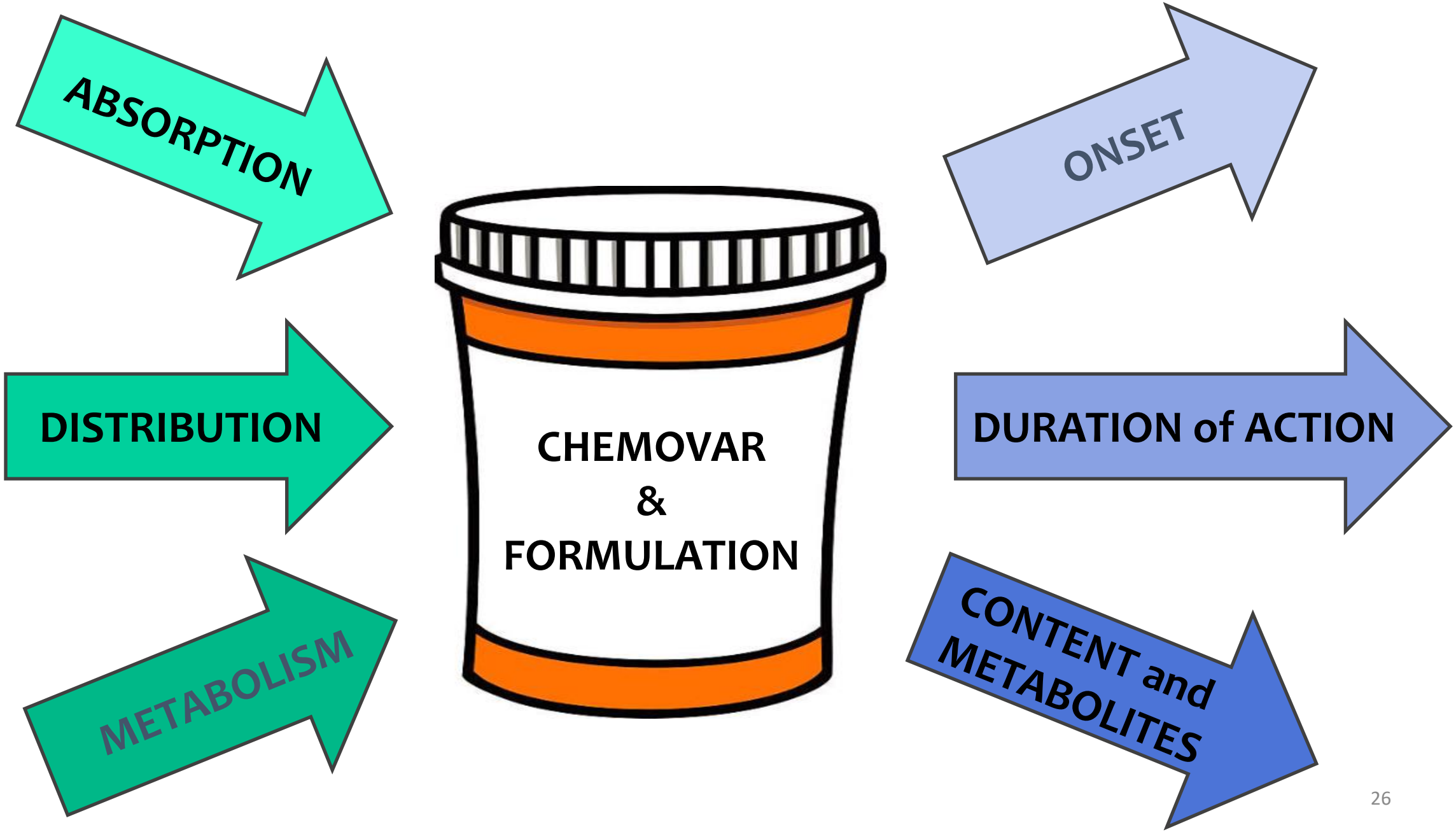
Bleeding … contamination with Brodifacoum

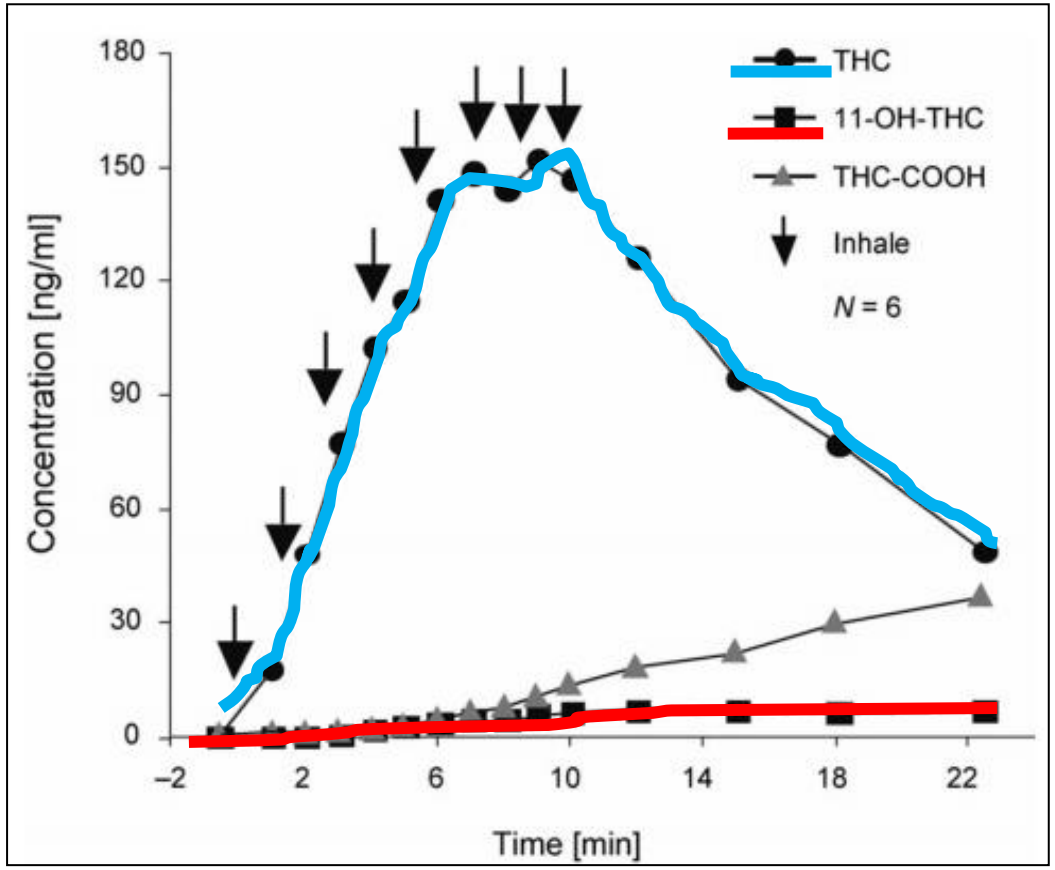
2018 – 320 cases of severe bleeding and abnormal coagulation

Delta 8 THC (aka D8)

- natural amount of delta-8 THC in hemp is very low
- Delta-8 THC alone is not of high concern for safety
- manufacturers employ chemical synthesis to convert other cannabinoids in hemp, like CBD, into delta-8 THC (using household chemicals)
- Chemical manufacturing is generally done illicitly and the products are not purified, thus highly contaminated with a number of chemicals
- Current legality is questionable

https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc


ABSORPTION
DISTRIBUTION
METABOLISM
CHEMOVAR
&
FORMULATION
ONSET
DURATION of ACTION
CONTENT and
METABOLITES



Inhalation

Bioavailability 2 – 60%

- Depth of inhalation
- Duration of Breath Holding
- Temp of Vaporizer

Good For titration & break through because of rapid effects

Important to Teach Proper Technique

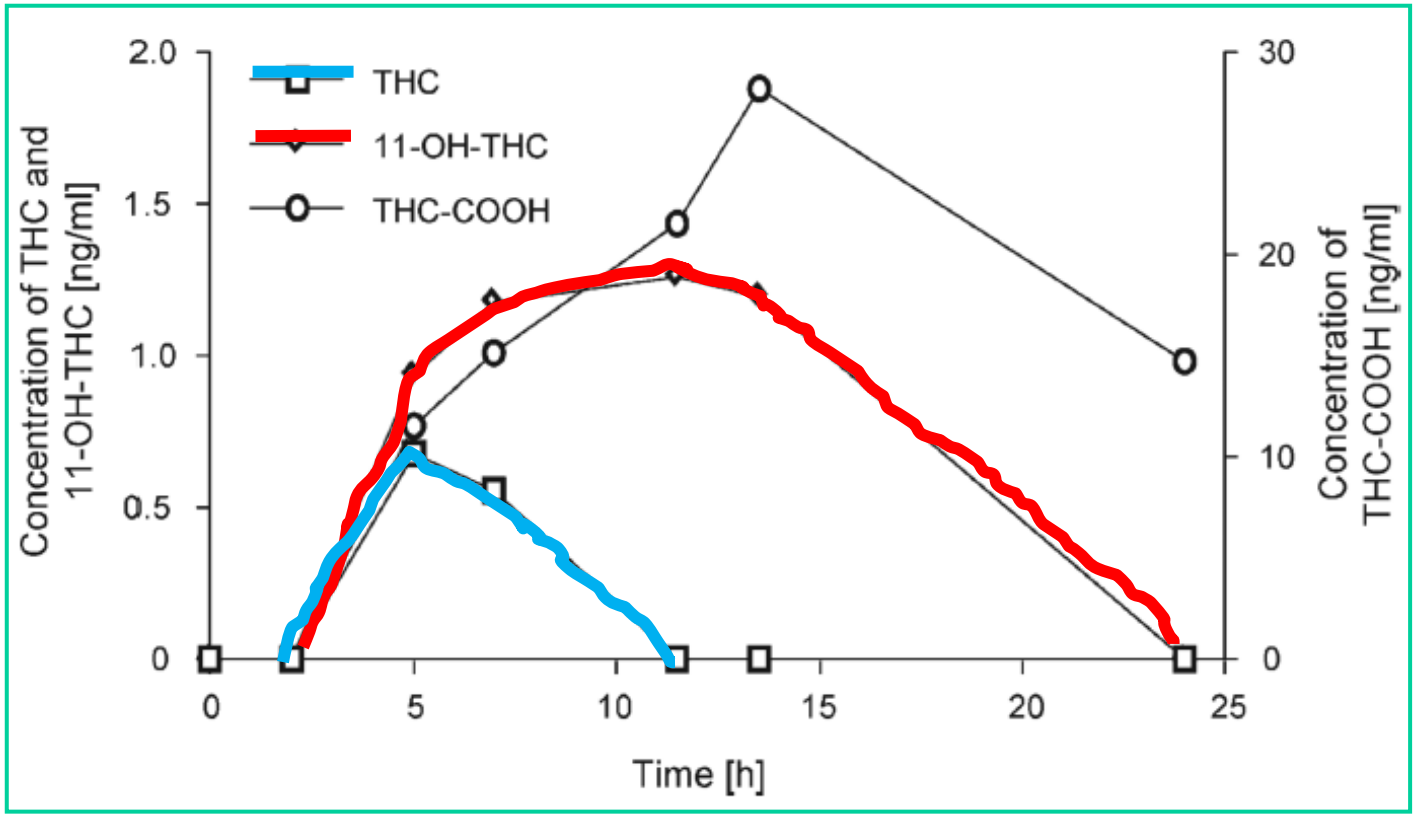
- Wait 5 -10 minutes between inhalations during titration

Typical Onset 0 – 10 min
Duration 2- 4 hours
Intra & Inter Patient Variability due to smoking dynamics

Huestis M. Human Cannabinoid Pharmacokinetics. *Chem Biodivers*. 2007 August ; 4(8): 1770–1804.
MacCullum, Russo, *2018*

Oral Administration

- Onset 30 – 120 min
- ↑ Inter/Intra Pt Variable Absorption
- Absorption ↑ w/ high fat meal
  Contribution of Matrix
- Duration 4 – 8 hours
- *Up to 24 hrs dose dependent
- Lower Peak [THC]
- ↑ [11-Hydroxy-THC]
  -Longer T1/2
  -More potent analgesic activity



After Administration of 2.5 mg Dronabinol

Huestis M. 2007; MacCullum, Russo, 2018.

Oral Administration

Important to Teach Patients:

Ensure ingesting products w. known amount of cannabinoids

Wait at least 2 hours between doses

THC best before meals (appetite.)

Before or after meals, depending on food related symptoms

Avoid “Edible” products

- Dosing may not be precise, difficult to dose food

Help patients with the math

Recommend providing written / visual instructions

Huestis, 2007; MacCullum, Russo, 2018

Oral Mucosal Products

? Bypasses Liver Metabolism
Onset 15 – 60 mins
Or is is just swallowing!

Cannabis "Whole Plant Extract" Oil

THC:CBD + Terpenoid, Metered Spray

Other Routes of Administration

Rectal and Vaginal Suppositories

Patches

Topicals

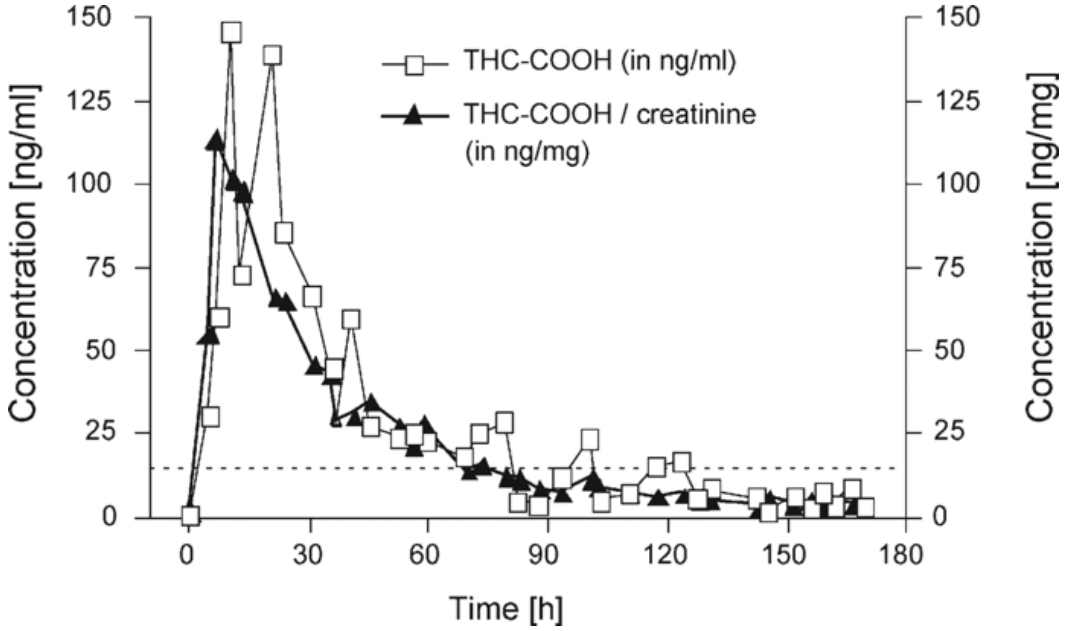
Intravenous

Intraventricular

Insufflation

Cannabis Elimination

- 95-99% protein bound
- Lipophilic – Crosses BBB & placenta; breast milk
- Rapid liver metabolism
- Eliminated in urine and feces
- Inactive metabolites THC-COOH detectable days to weeks after administration in plasma & urine
- oral fluid testing for THC



Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. Clin J Pain. 2013 Feb;29(2):162-71.

Huestis M. Human Cannabinoid Pharmacokinetics. *Chem Biodivers*. 2007 August ; 4(8): 1770–1804.

PA Act 16 Serious Medical Conditions *

1. **Cancer,** *including remission therapy*
2. **Terminal illness**
3. **HIV or AIDS**
4. **Amyotrophic lateral sclerosis (ALS)**
5. **Parkinson's disease**
6. **Multiple sclerosis (MS)**
7. **Huntington's disease**
8. **Neurodegenerative diseases**
9. **Damage to the nervous tissue of the CNS** (brain-spinal cord) w/ objective intractable spasticity & other associated neuropathies
10. **Neuropathies**
11. **Dyskinetic + spastic movement disorders**
12. **Epilepsy**
13. **Intractable seizures**
14. **Post-traumatic stress disorder**
15. **Autism**
16. Anxiety disorders
17. Tourette syndrome
18. **Glaucoma**
19. **Crohn's disease**
20. **Inflammatory bowel disease (IBD)**
21. **Sickle cell anemia**
22. **Severe Pain**
23. **Opioid Use Disorder**- for which conventional therapeutic interventions are contraindicated or ineffective, or adjunctive therapy is indicated in comb. w/primary therapeutic interventions
24. **Hepatitis ****

National Academy of Science 2017

***Beneficial* Associations - Substantial Findings:**

- Chronic pain in adults
- Chemo-induced nausea and vomiting (CINV)
- MS spasticity & improved sleep
- Short-term sleep outcomes associated w/ obstructive sleep apnea syndrome, fibromyalgia & chronic pain

***Harmful* Associations - Substantial Findings:**

- Worsening of respiratory symptoms & chronic bronchitis
- Increased risk of motor vehicle crashes
- Chronic cannabis use in pregnancy = low birth weight
- Frequent user & development of schizophrenia

Adverse Effects of Short Term Use
Dizziness
Impaired motor coordination
Increased Risk of Falls
Altered judgement
Anxiety and Paranoia with high doses (bi-phasic response)
Impaired short term memory

Adverse Effects in Long Term Use
Use Disorder (1 in 10 chronic (daily) RECREATIONAL users)
Chronic Bronchitis
Hyperemesis Syndrome (overuse)

Systematic Review: 23 RCT + 8 observational - Cannabis

Wang et al. CMAJ 2008; 178 (13): 1669-78

Non-Serious Events
(n= 4615)

Serious Events
(n= 164)

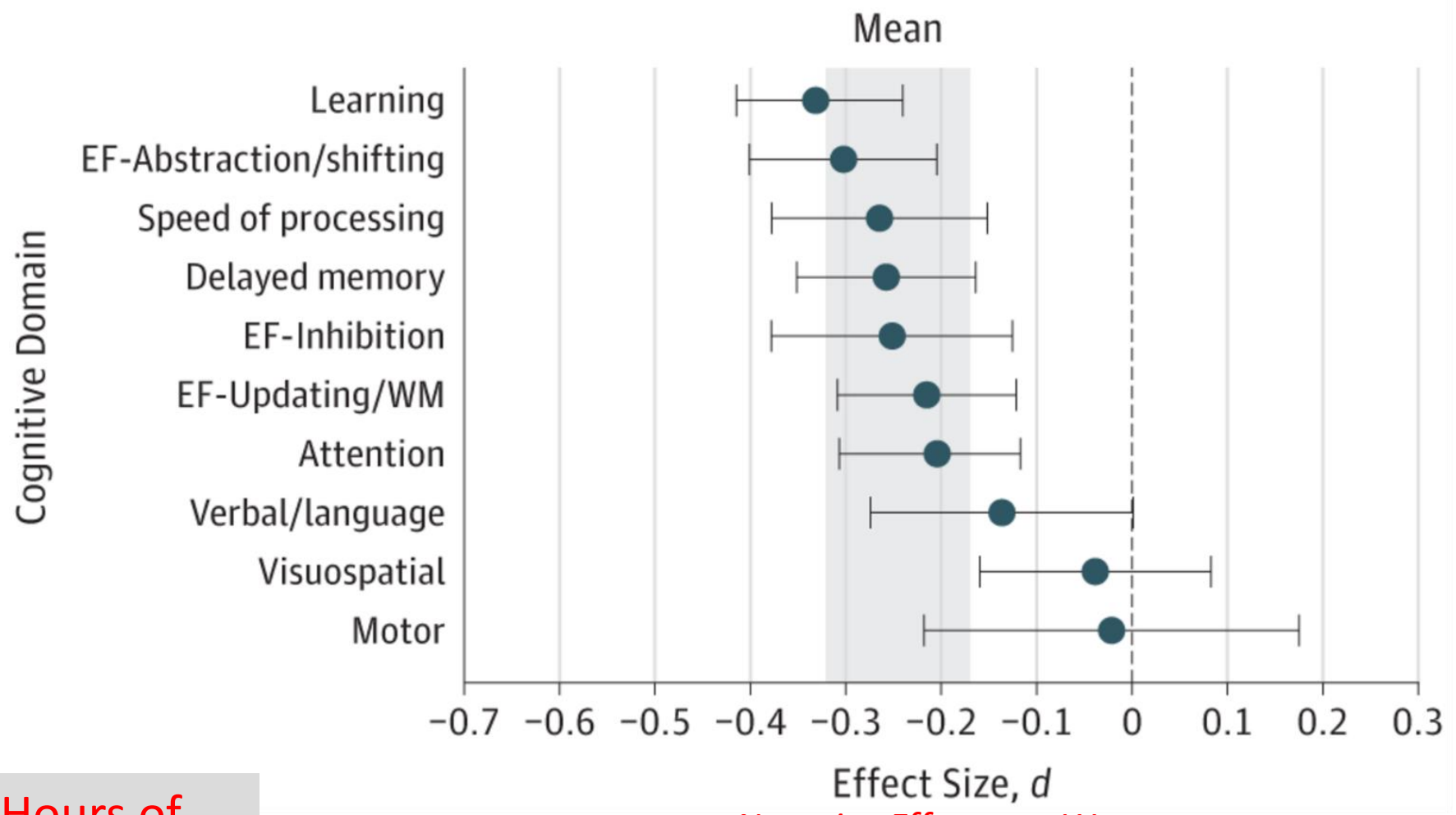
Rates of Non-Serious Events
More Commons with Cannabis
[RR] 1.86 95% CI 1.57-2.21)

Rates of Serious events did NOT
Differ compared to controls
[RR] 1.04. 95% CI 0.78-1.39)

Dizziness

Respiratory
Gastrointestinal
Nervous System

Cannabis (THC) and Cognitive Functioning

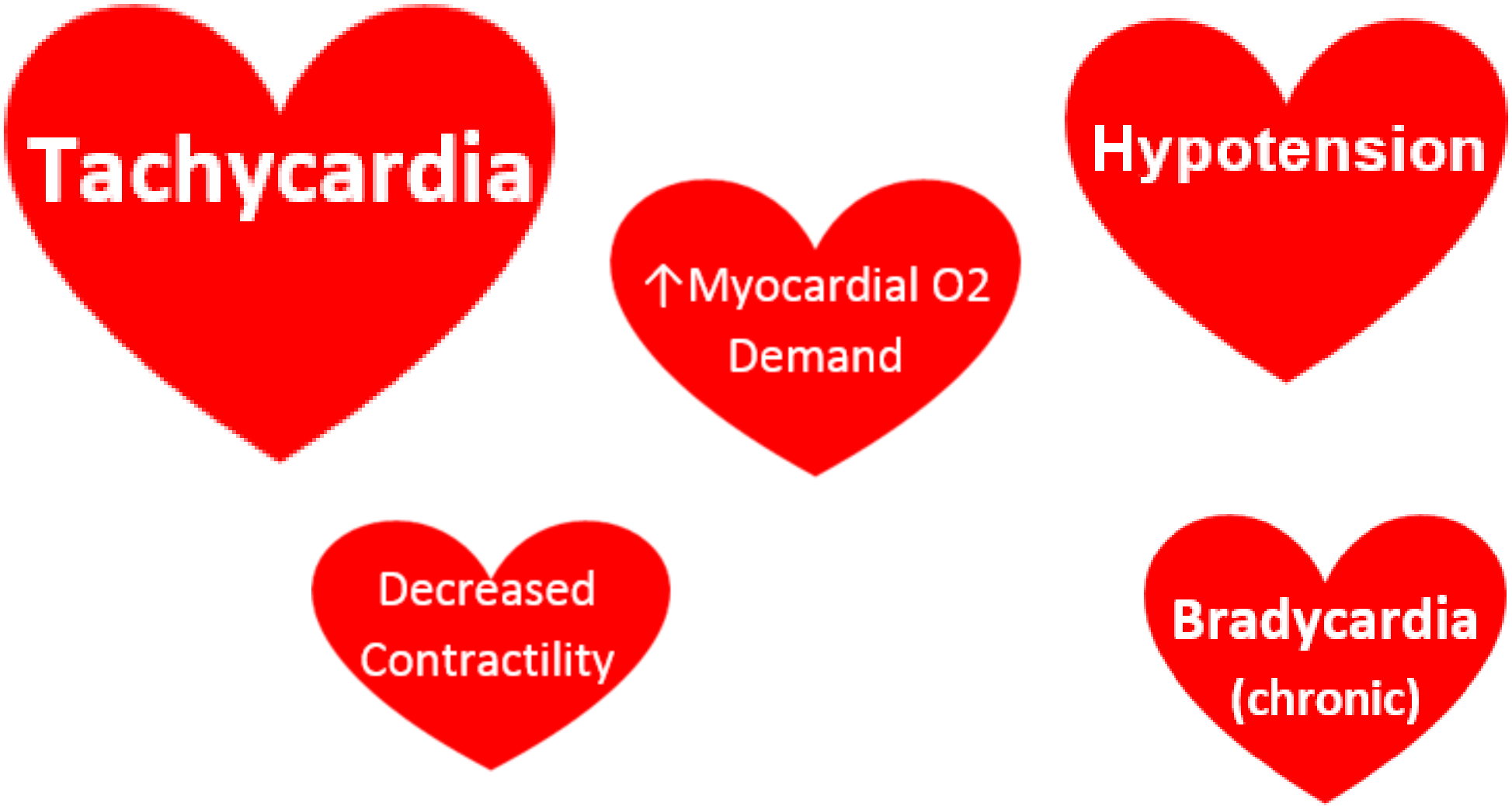


Negative Effect was Worse

AFTER 72 Hours of Abstinence Function Returns to Normal

JAMA Psychiatry. 2018;75(6):585-595. doi:10.1001/jamapsychiatry.2018.0335

Relative contraindications: CV Disease



Pacher, et al. Nature Reviews Cardiology, 2017; Kattoor, Marijuana and Coronary Heart Disease, ACC Expert Analysis Online, 2016

Relative contraindications: CV Disease

Population analysis increased risk of MI with inhaled illegal product … likely a function of the THC

- 4.8-fold higher risk of MI
  - 124 / 3882 patient cohort
- 2.5-fold increased risk of death (weekly use)
  - 54/1913 adults follow-up for h/o MI
- Increased CVD in cannabis users
  - 316,397 of > 20 million
- Cannabis not associated w/ ↑ CVD
  - 4286 with h/o cannabis use

Pacher, et al. Nature Reviews Cardiology, 2017; Kattoor, Marijuana and Coronary Heart Disease, ACC Expert Analysis Online, 2016

Absolute Contraindications: Uncontrolled Psychosis

Cannabis Induced Psychosis (CIP): DSM-5

- Diagnosis of exclusion
- Mood lability & paranoid, 24 hrs - 7 days
- Symptoms precipitated by increased THC potency or use
- Symptoms persist beyond typical intoxication

- Proposed mechanism: Δ9-THC ↑ dopaminergic signal
- Systematic Review: Higher risk psychosis symptoms w/ marijuana
- Case Report in recreational use

Khan, et al., Cannabis-Induced Bipolar Disorder with Psychotic Feature:Psychiatry 2009
Grewal, et al., Cannabis-Induced Psychosis: A Review. Psychiatric Times 2017
Moore, et al., Cannabis use & risk of psychotic or affective mental health outcomes:systematic review. Lancet 2007

Pregnancy- Educate Against Smoking, other Cannabis use

CB receptors role in normal fetal brain development:

- neurotransmitter systems
- neuronal proliferation, migration, differentiation
- [CB receptors] ↑ as gestational age ↑

2-5% Self-Reported Cannabis Use during Pregnancy

- lower maternal age, education, income

Significant ↑ Newborns testing THC +

American College of Obstetricians and Gynecologists – Strongly Recommends Against Cannabis Use During Pregnancy

Lipophilic, Enters Placenta & Breast Milk:

- Fetus plasma levels 10-30% of maternal plasma level
- Accumulates in breast milk, can concentrate 8x > maternal plasma

NASEM 2017, Cannabis Handbook 2014

Cannabis Use During Pregnancy

Chronic use evidence:

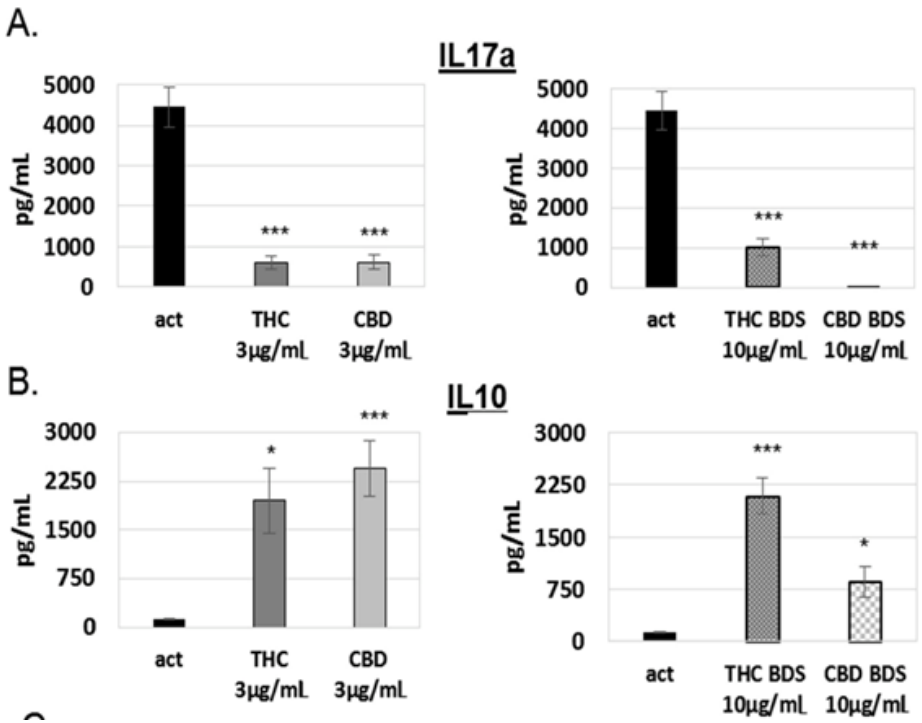
- Substantial: statistical association w/ **Low Birth Weight**
- Limited: **Increased Admission to the NICU**
- confounder: mother's income + education, alcohol/cigarettes

Insufficient Evidence to support or Refute Adverse Developmental Outcomes

- ↑ Hyperactivity, Inattention, Impulsivity
- Conflicting changes on IQ
  - some reporting no change
- confounder: income + education, alcohol/ cigarettes
- Study Heterogeneity, magnitude of use

NASEM 2017, Cannabis Handbook 2014

Cannabinoids and lymphocyte recovery in bone marrow transplantation in MICE



	THC	CBD	THC BDS	CBD BDS
IL-17	↓↓↓	↓↓↓	↓↓↓	↓↓↓↓
IL-10	↑	↑↑↑	↑↑↑	↑
TNFα	↑	↑↑	↑	↑
IL-5	-	↑	↑↑	↓

IL-17 -> epithelial and endothelial to release IL-6 +other pro-inflammatory cytokines

- CBD BDS had the strongest effect with only 0.25% IL-17 expression

IL-10 secretion -> inhibition of IL-2 and interferon gamma

- Pure CBD had the strongest effect with 1806% IL-10 expression

Compare the influence of THC and CBD on lymphocyte activation in vitro and in murine BMT models; pure cannabinoids vs high THC/CBD cannabis extracts

Khuja et al., 2019, *International Journal of Molecular Sciences*, 20(3), p.668

Cannabinoid Cytochrome P450 Metabolism

	Metabolizing Enzyme	Enzyme Inhibition	Enzyme Induction
Smoked Cannabis	2C9, 2C19, 3A4	3A4, 2B6, 2C9, 2D6	1A2
Tetrahydrocannabinol (THC)	2C9, 3A4	3A4,	_
CBD	2C19, 3A4	2B6, 2C9, 2D6, 3A4	_
Nabilone	2C9	-	_
Dronabinol	2C9, 3A4	3A4	_

Maida V. A user's guide to cannabinoid therapies in oncology. *Current Oncology*. Vol. 23, No. 6, Dec. 2016

Drug Interactions: Cannabis Effects on Other Drugs

Potentiate the Effects of Other CNS Depressants

- Alcohol, Opioids, Benzos, Muscle Relaxers

Cardiac Effects

- Amphetamines (Potentiate), ejection fraction

Mechanism Conflict - > Immunotherapy

CYP Interactions 2C19, 2C9, 3A4

- Cancer
- HIV
- Anti-Seizure

Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature *Segal EM 2013*

Cannabidiol Drug Interaction Examples

Case Report

- Patient INR Stable between 2-3 on Warfarin at dose of 7.5 mg/day
- Initiated CBD 15 mg/kg/day and the **INR went to 7** !!
- Warfarin dose was lowered

Dronabinol US Package Insert Contains Cautions when use with warfarin

Grayson,L, et al. An interaction between warfarin and cannabidiol, a case report. Epilepsy & Behavior Case Reports 9 (2018) 10–1.

Multiple Pediatric Patient Study

- Initiation of Cannabidiol led to average 60% in clobazam concentrations and average 500% increase in clobazam's active metabolite concentrations in blood.
- Additional studies show interactions Depakote

Geffrey et al. Drug-Drug Interaction Between Clobazam and Cannabidiol in Children with Refractory Epilepsy. Epilepsia 2015; 56:1246-1251.

Drug Interactions
Effects of other drugs on Cannabis

Increase Effects of Cannabis (2 -3 times higher levels)	
Amiodarone	Clarithromycin
Antifungal Drugs	Diltiazem
Fluvastatin	Certain HIV Drugs

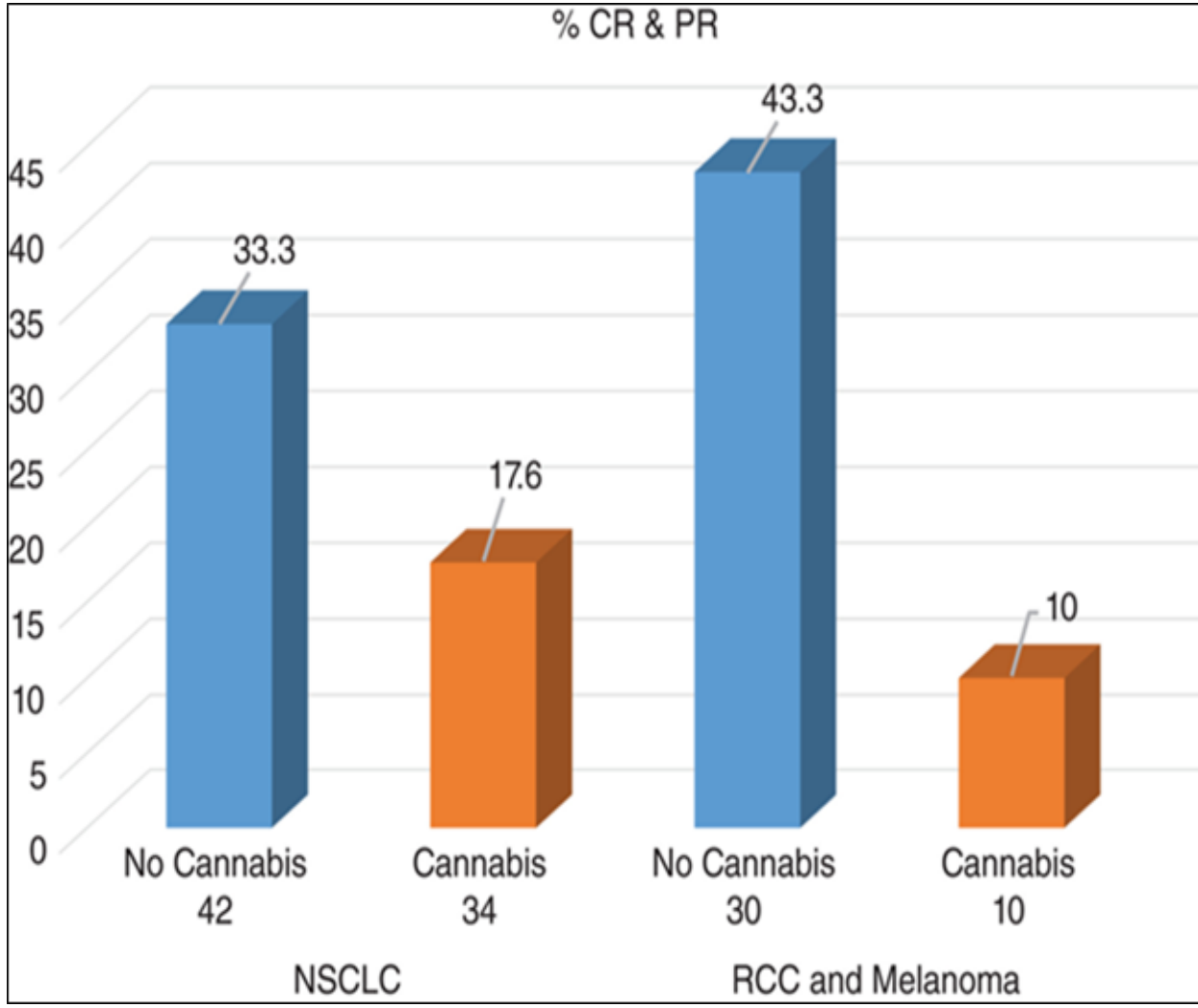
Decrease Effects of Cannabis (50% less Cannabis Effects)	
Carbamazepine	St. Johns Wort
Phenobarbital	Phenytoin

Nabiximols Summary of Medicinal Product Characteristics, European Medicines Agency 3/15

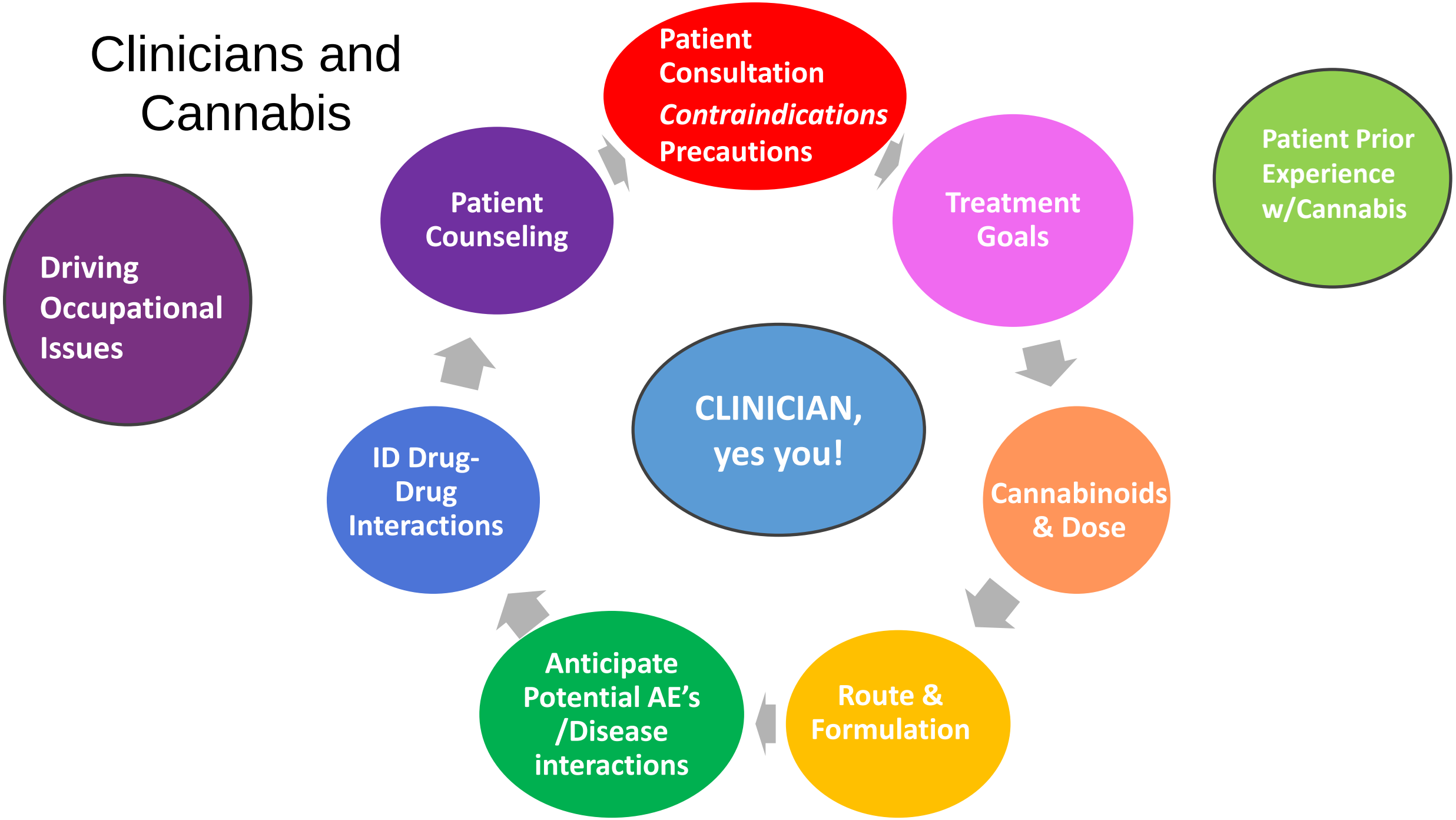
Cannabis and Tumor Response to Nivolumab

Retrospective, observational study of patients using cannabis and initiated therapy with nivolumab

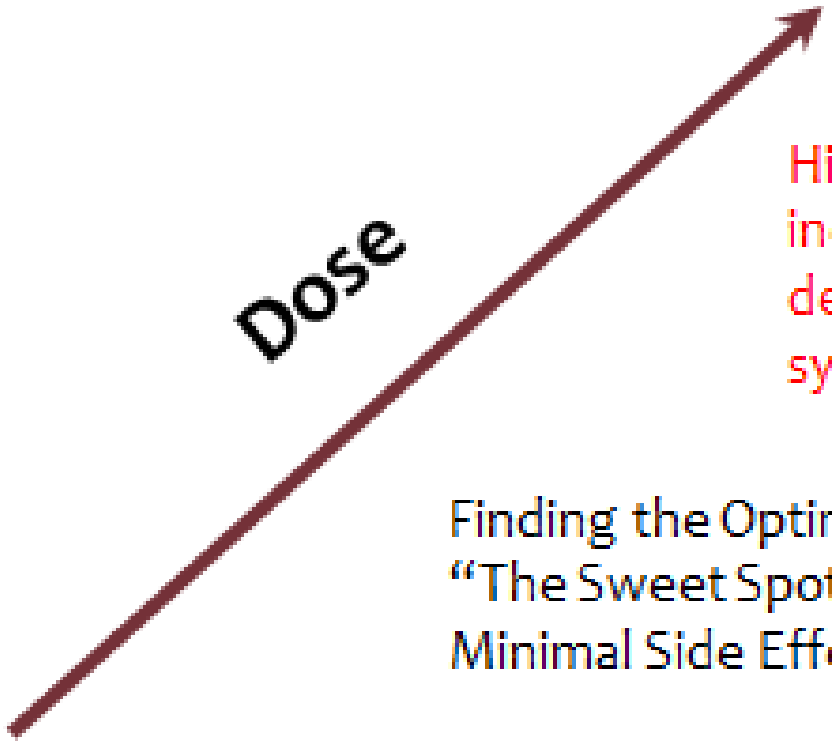
- 140 patients with Stage IV melanoma, non-small cell lung cancer and renal cell carcinoma
- Goal: Evaluate the influence of cannabis during immunotherapy on response rate (RR), progression free survival (PFS), and overall survival (OS)



Clinicians and Cannabis



Considerations in Dosing …. Patient Self-Titration → Patient Education



Higher Doses associated with increased ADRs and possible decrease in efficacy for certain symptoms

Finding the Optimal Dose
"The Sweet Spot"
Minimal Side Effects

Start Low and Go Slow
Cannabis Sensitization Protocols
Sub-Psychoactive Dosing

Want Upregulation of Endocannabinoid Receptors,
Not Down Regulation

Rooted in the Concept:
Less is Really More

Conservative Protocol
from Consensus Dosing Guidelines

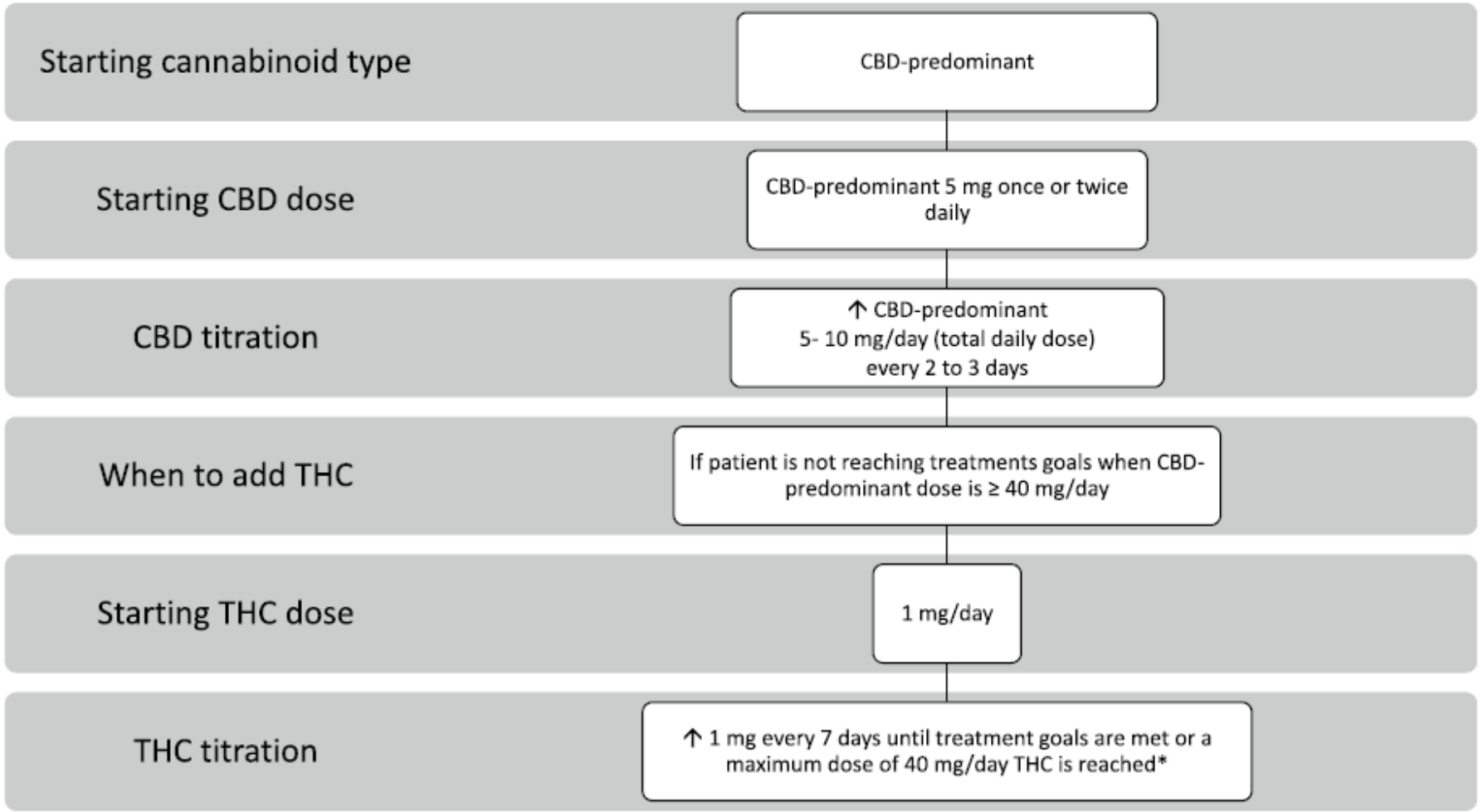


Fig. 3 Conservative protocol for medical cannabis dosing and administration

Bhaskar et al. Journal of Cannabis Research (2021) 3:22
https://doi.org/10.1186/s42238-021-00073-1

“Routine” Protocol
from Consensus Dosing Guidelines

CAUTION

*****

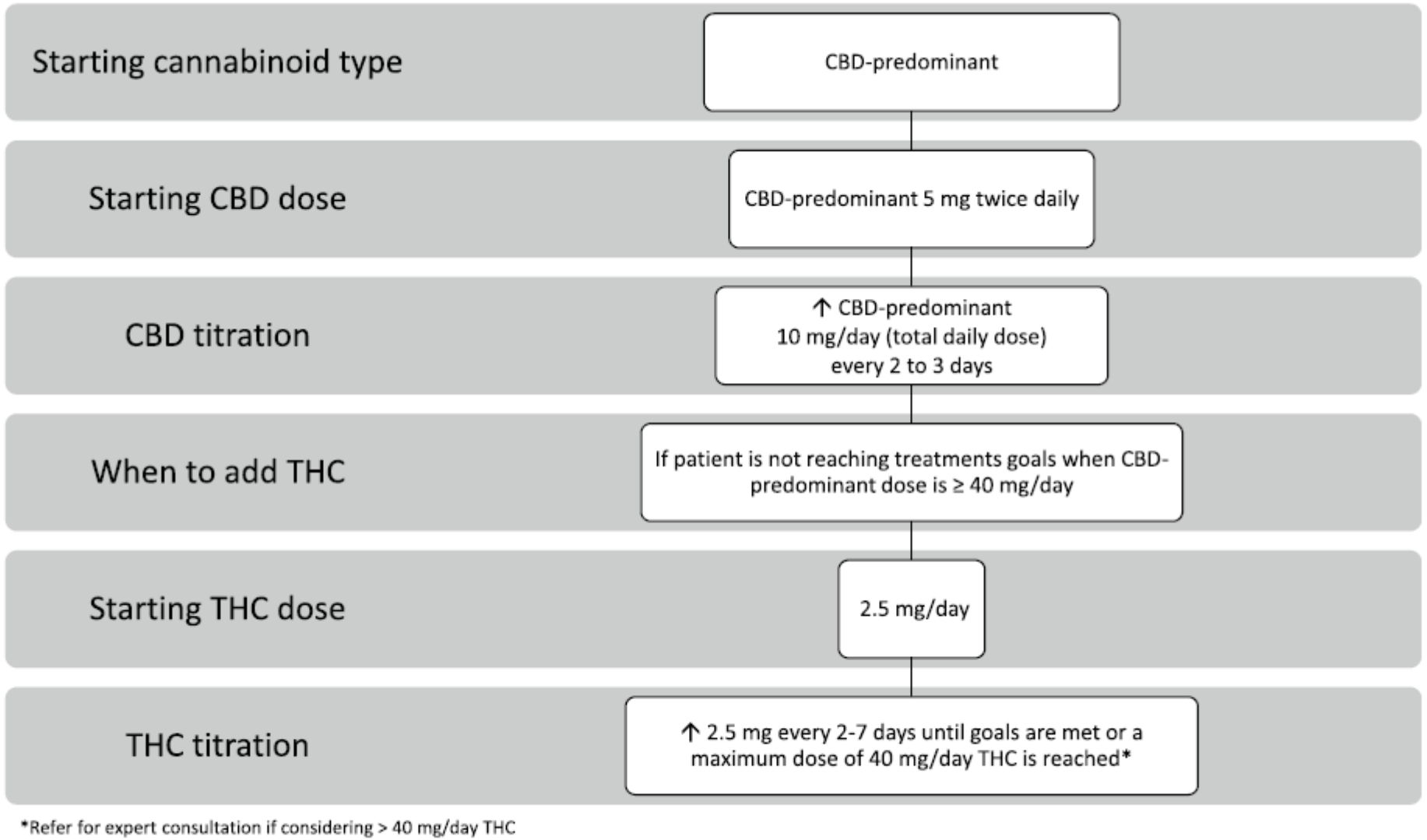
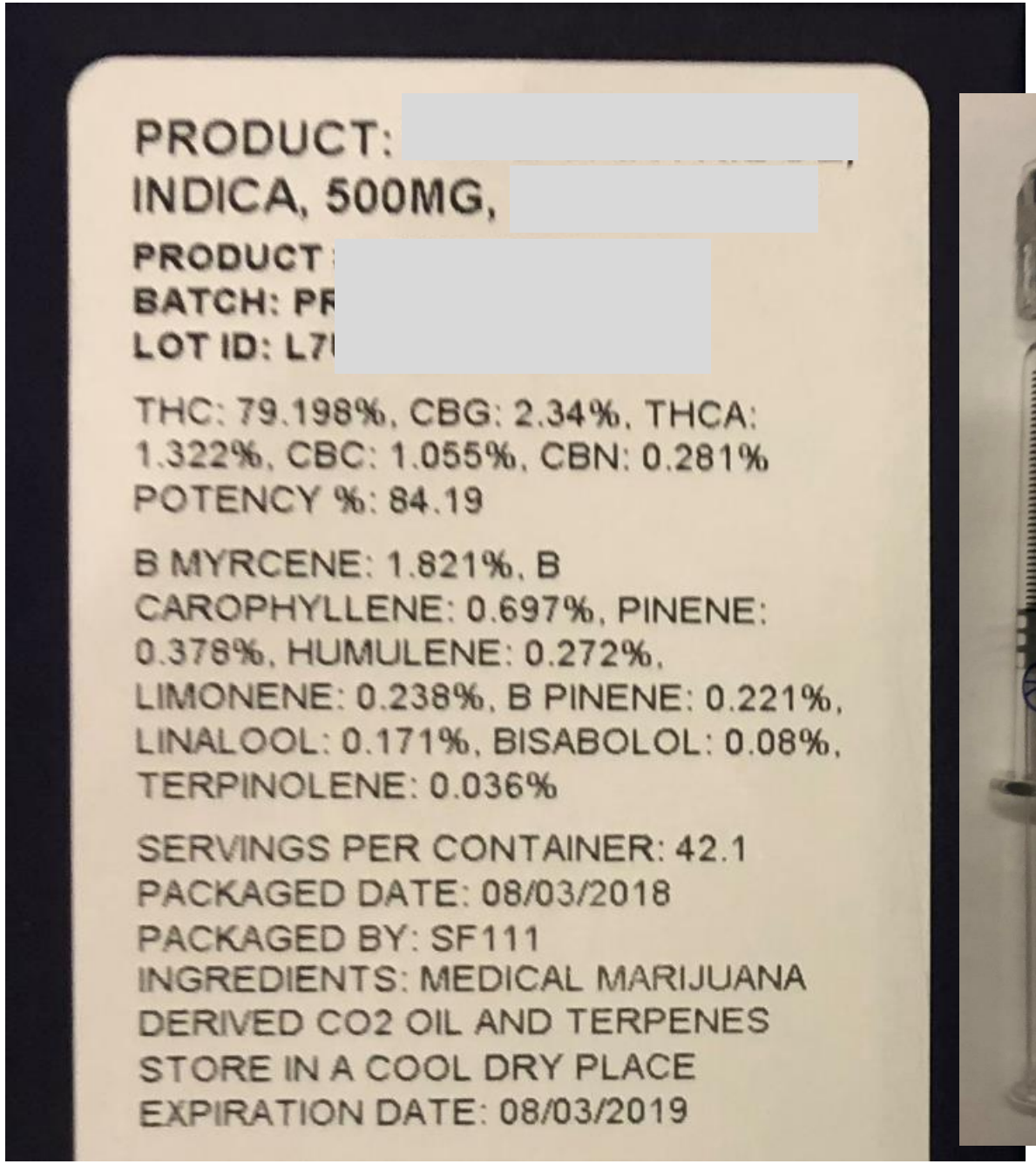
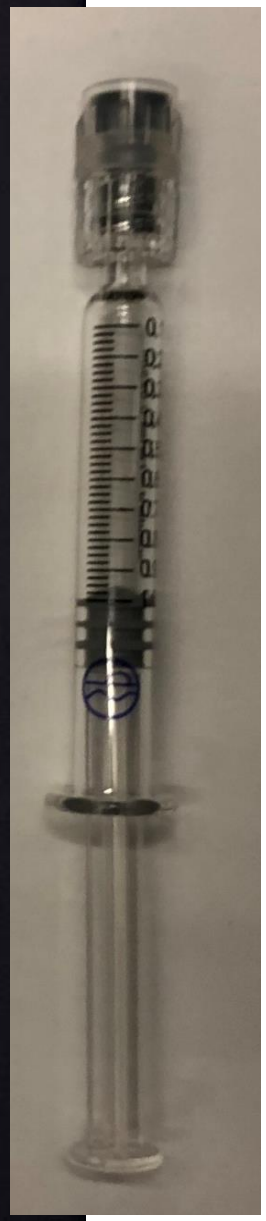


Fig. 2 Routine protocol for medical cannabis dosing and administration

Bhaskar et al. Journal of Cannabis Research (2021) 3:22
https://doi.org/10.1186/s42238-021-00073-1





How much do you give a your Grandma with Cancer?

500 mg Cannabiniods / 1mL
(Volume is only known by reading syringe)

79% THC = >
THC 395 mg / 1 mL

…recommended starting doses ar
between 0.25 - 5 mg THC
(0.0006 mL – 0.012 mL)

Pain Modulation Mechanisms

- Neurotransmitter activity
  - Inhibits release of various neurotransmitters
  - Inhibition of electrical activity
- Natural endocannabinoids are produced on demand as part of a negative feedback loop
  - Endocannabinoid deficiency implicated in many pain conditions
- Exogenous phytocannabinoids activate CB1 receptors for prolonged periods
  - Can temporarily block beneficial inhibitory and excitatory neurotransmitter activity
- Receptor agonists possess antinociceptive and anti-hyperalgesic activity
- Analgesia facilitated at both the neuronal level and non-nervous system tissues
  - Decreases synaptic transmission of the pain signal
  - Anti-inflammatory activity due to both CB1 and CB2 receptor presence on mast cell
  - CB2 receptors may inhibit release of inflammatory substances resulting in anti-nociceptive activity
  - CB2 receptors may stimulate opioid receptors in the periphery

Vuckovic S, et al. *Front. Pharmacol* 2018

Controversial Use

- Controversial efficacy in various types of pain, opioid use disorder
  - Better evidence for reduction of opioids in chronic pain vs. opioid use disorder
  - No robust evidence for acute pain
  - Third line recommendations in neuropathic pain guidelines
- Recent study (2018): >1500 patients, 4-year prospective cohort did *not* show improved outcomes re: pain/ opioid use
- Mass. online survey (2017): n= 1,513 patients, self-reports: 76% ↓ opioids, 71% ↓anti-anxiety meds, 42% ↓alcohol, 37% ↓antidepressants
- *Randomized trials needed*

Cambell, et.al. *The Lancet Public Health* 2018. Piper BJ. *Journal Psychopharmacology* 2017.

Chronic Pain

Chronic pain onset is when the pain persists beyond the expected healing time

- Untreated acute pain may develop into a chronic pain state

Complex and difficult to treat, with biopsychosocial issues influencing individual pain experiences

- Source of pain may not be identified

Often associated with heightened pain processes leading to allodynia/hyperalgesia

- Allodynia – pain from stimuli that should not be painful
- Hyperalgesia – severe pain from a minor pain stimulus

Endo and phytocannabinoids have demonstrated anti-nociceptive and anti-hyperalgesic effects

Clinical Evidence for Medical Use

- Meta-analysis of 28 RCT's demonstrated moderate quality evidence for use of cannabinoids for treatment of various neuropathic and chronic pain conditions
  - Smoked cannabis had greatest effect
- Reduction of pain demonstrated in peripheral and central pain conditions in patients receiving traditional analgesics
- Side effect profile is comparable to existing pharmacologic treatments
- Adverse effects can be minimized by starting with low doses and titrating to effect

Whiting PF, et al.. *JAMA* 2015

Neuropathic Pain

- Cannabis for neuropathic pain demonstrated efficacy similarly to traditional pharmaceutical options
- Mixture of cannabinoids and non-cannabinoid components may offer more effective analgesia than single components
  - THC:CBD combinations recommended
  - Terpene profile influences
- CB1 and CB2 receptors upregulated in the presence of nerve damage
- 2018 Cochrane Review Nerve Pain
  - 1750 people within 16 studies with use of different cannabis formulations
  - Improvements in pain, sleep, and psychologic distress seen
  - Similar frequency in side effects demonstrated

Mucke, et.al.. *Cochrane Database of Systematic Reviews* 2018.

Antinociceptive Synergy with Opioids

Synergy is when the combined benefit of two substances gives more added benefit than each individual agent

- Morphine and THC synergy demonstrated

Cannabinoids and opioids provide analgesia by different pharmacologic mechanisms of action in the dorsal horn

- Glutamate release inhibition from primary afferent neurons in spinal cord with opioid agonists
- Spinal cord inhibition of excitatory transmission by CB1 receptors

CB2 receptors may offer pain modulatory activity through facilitation of b-endorphin release when activated

- Provides antinociceptive activity

Care Plan Considerations

- Tolerance
  - Cannabis naïve vs. experienced users
- Patient age
- Patient preference
- Persistent vs intermittent symptoms
  - Appropriate formulation
- Pain Management Considerations
  - Nociceptive vs. neuropathic
  - Acute vs. chronic
  - Temporal pattern

ECS & the Gastrointestinal Tract

ECS regulates energy balance & food intake, both in brain & GI tract

- ECS involved in processes that include hunger, GI motility, pain perception and immune response
- CB1 and CB2 receptors widely distributed in the GI tract
- Additional GI system targets in gastric mucosa, enteric nervous system and immune system including TRPV1, PPARs, orphan GPR55 receptors

ECS modulates visceral sensation and pain signaling

- Cannabinoid receptors agonists may be used to alleviate abdominal pain
- CB1 receptor agonists inhibit small intestine peristalsis and reduce relaxation of the esophageal sphincter

Carvalho, et al. *Int. J. Mol. Sci.* 2020

CB receptors in the GI Tract

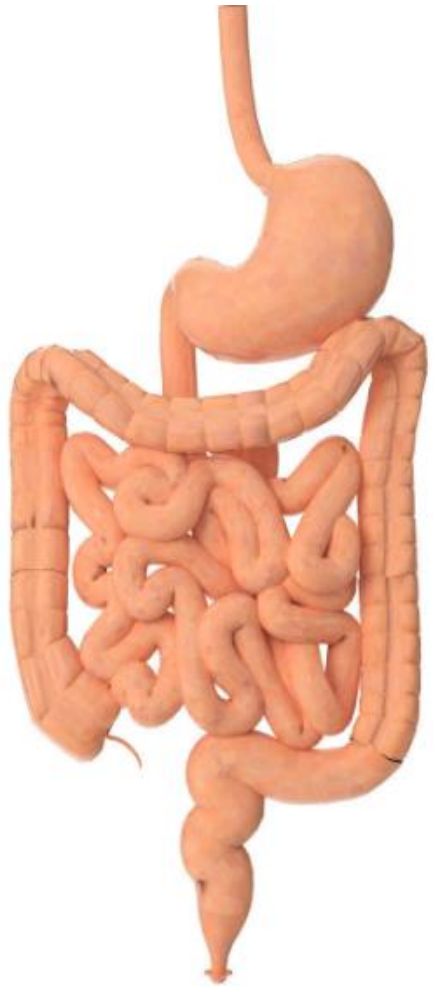
- CB1 receptors are in mucosa & neuromuscular layers of colon & expressed in plasma cells & influence mucosal inflammation
- CB1 receptors upregulated in experimental IBD models
- AEA upregulated in submucosal layer with no effect in the mucosal layer

Modulates physiological functions from esophagus to large Intestines

- ↓ contractility
- ↓ motility

Direct activation of CB 1 receptors by THC

- ↓ gastric acid secretion
- ↓ gastric motor activity
- ↓ formation of gastric mucosal lesions
- Stimulates hunger



CB2 receptors mainly expressed by subepithelial immune cells (i.e. macrophages & plasma cells) & also by enteric neurons

CB2 receptors on endocrine & immune cells upregulated in Inflammation

Cannabinoid modulation:

- Anti-inflammatory
- Controls fluid accumulation

Caution:

- May control hunger
- May cause diarrhea

Abalo R & Martin-Fontelles I. *Handbook of Cannabis & Related Pathologies* 2017; NASEM 2017; Gyires K & Zadori Z. *Current Neuropharmacology* 2016; Hasenoehrl C, et al.. *Expert Review of Gastroenterology & Hepatology* 2017; Wright et al., 2005

Inflammatory Bowel Disease (IBD)

IBD

- Chronic, relapsing inflammation of GI tract
- Crohn's disease (CD) & ulcerative colitis (UC)
- Similar symptoms: i.e. diarrhea, abdominal pain & weight loss

Both CB receptors & at least 1 of 2 major endocannabinoids (AEA) show altered intestinal levels in IBD.

- Upregulation of CB receptors & their activation by AEA & 2-AG promotes epithelial healing & tempers inflammation

Gyires K & Zadori Z. *Current Neuropharmacology* 2016

Therapeutic Dosing Options

- Preparation used depends on symptom onset and duration
  - Oral therapy for persistent symptoms
  - Inhalation/tinctures for immediate/quick symptom relief
  - Suppository option for local pain/inflammation
- Always start w/ lowest possible dose
  - lower doses of THC likely effective - appetite stimulation
  - Anecdotally higher doses needed - nausea
- CBD calms inflammation in the gut
  - Gut transit increases - helps w/ constipation
- THC inhibits gut transit - helpful for diarrhea
- CBG - non-intoxicating cannabinoid may be helpful for pain

Abalo R & Martin-Fontelles I. *Handbook of Cannabis & Related Pathologies* 2017

Nausea/Vomiting (N/V)

- High quality evidence for prevention and treatment of n/v not available
- Australian guidelines recommend cannabis only after traditional modalities have failed
  - Consider risk/benefits of therapy and monitor for adverse effects
- Most benefit seen in patients with cancer or AIDS

- Cochrane Review including 23 RCT's concluded that cannabis may be useful in treating chemotherapy induced nausea/vomiting
  - More effective than placebo and similar efficacy to traditional nausea therapies
  - No difference in reported n/v between those using cannabis and traditional anti-emetics (prochlorperazine as the main comparator)
  - Combination with traditional antiemetics may offer more benefit vs. monotherapy

Smith LA, et al. *Cochrane Database Syst Rev* 2016

Insomnia

- Short term use may be beneficial for sleep disturbances of sleep latency and sleep/wake cycle
- Chronic THC administration associated with tolerance to sedative effects, daytime sleepiness, delayed sleep onset latency
- Sleep disruption is associated with cannabis withdrawal
- High dose CBD and low dose THC potentially efficacious
- Formulation used based on difficulty with onset vs. duration of sleep vs. both
  - Inhalation for quick onset
  - Oral use for maintaining sleep
  - Indica, various terpenes (myrcene, linalool)

Babson, et al. *Curr Psychiatry Rep.* 2017

Risk of problem cannabis use ?

⇧ Greater frequency of cannabis use
⇧ Initiating cannabis use at a younger age

Risk of Cannabis Use Disorder increases with:

Male cigarette smokers
Use at early age (< age 18 4-7x ⇧ risk)
High use frequency

In a human physical dependence study, administration of cannabidiol (CBD) 1500 mg/day (750 mg 2x daily) to adults for 28 days did not produce signs or symptoms of withdrawal over 6-week period after drug discontinuation

- Suggests that **CBD** does not produce physical dependence

***Cannabis* dependence & withdrawal symptoms** are reported in the literature.

Thus THC (and/or minor cannabinoids) are driving the neuroadaptation that results in a withdrawal syndrome

NASEM, 2017; NIDA, 2018; Hasin et al, 2015, Epidiolex package insert. June 2018.

Cannabis Use Disorder (CUDIT-SF)

How often in the past 6 months:

1. Did you find you were unable to stop using cannabis once you had started?
2. Have you devoted a great deal of your time to getting, using or recovering from cannabis?
3. Have you had a problem with memory or conversation after using cannabis?

Never(0) Less than monthly (1) Monthly (2) Weekly (3) Daily (4)

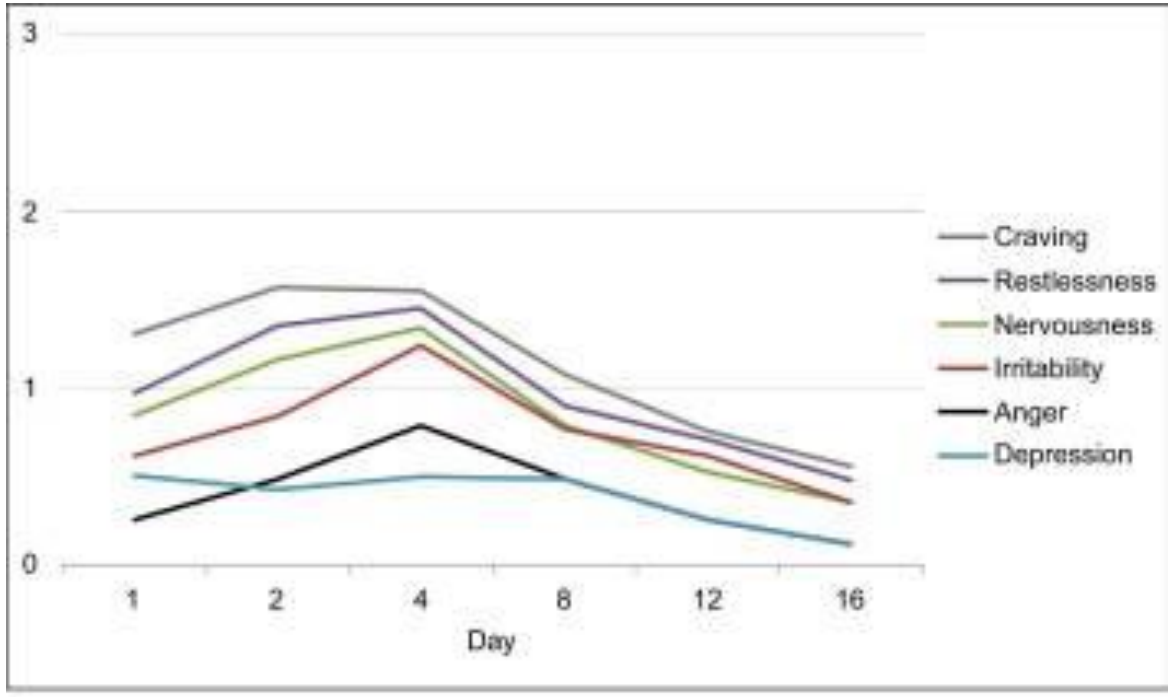
CUD present with ≥ 2

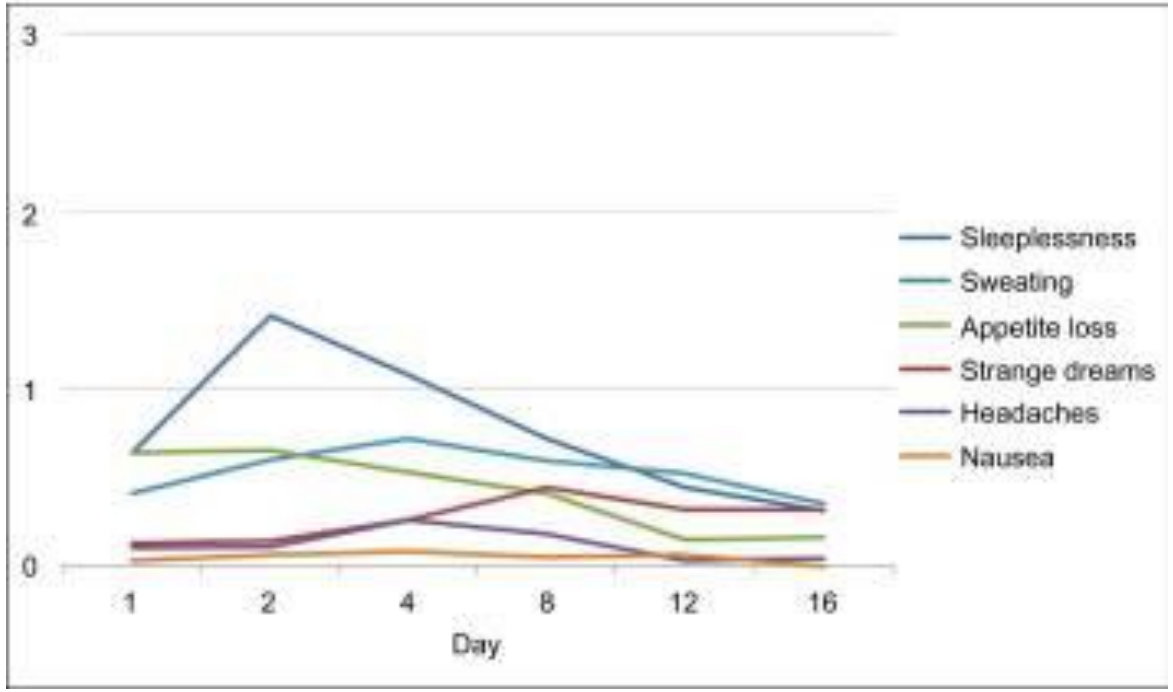
Bonn-Miller M. et al., Cannabis Cannabinoid Res. 2016, 1 :252-261.

Cannabis Withdrawal Symptoms

DSM-5 Cannabis withdrawal (ICD-10: F12.23)

- Anxiety, restlessness
- Depression, irritability
- Insomnia, odd dreams
- Tremors/Headache
- Decreased appetite
- Peak day 4





Gorelick DA et al, Diagnostic Criteria for Cannabis Withdrawal Syndrome, *Drug & Alcohol Dependence*, 2012

Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil*. 2017;8:9-37.

Medical States Approve Access for Serious Medical Conditions …
Symptom Management vs. Disease Modification

THC

- Chronic Pain
- Nausea and Vomiting (specific disorders, including cancer related) **
- Multiple Sclerosis (MS) related symptom management
- Improved Sleep (short term use)

CBD

- Seizure Disorders**
- Inflammation

Symptom Management

- Pain
- Nausea / Vomiting
- Appetite
- Spasticity
- Inflammation
- Sleep Disorders
- Anxiety / Depression

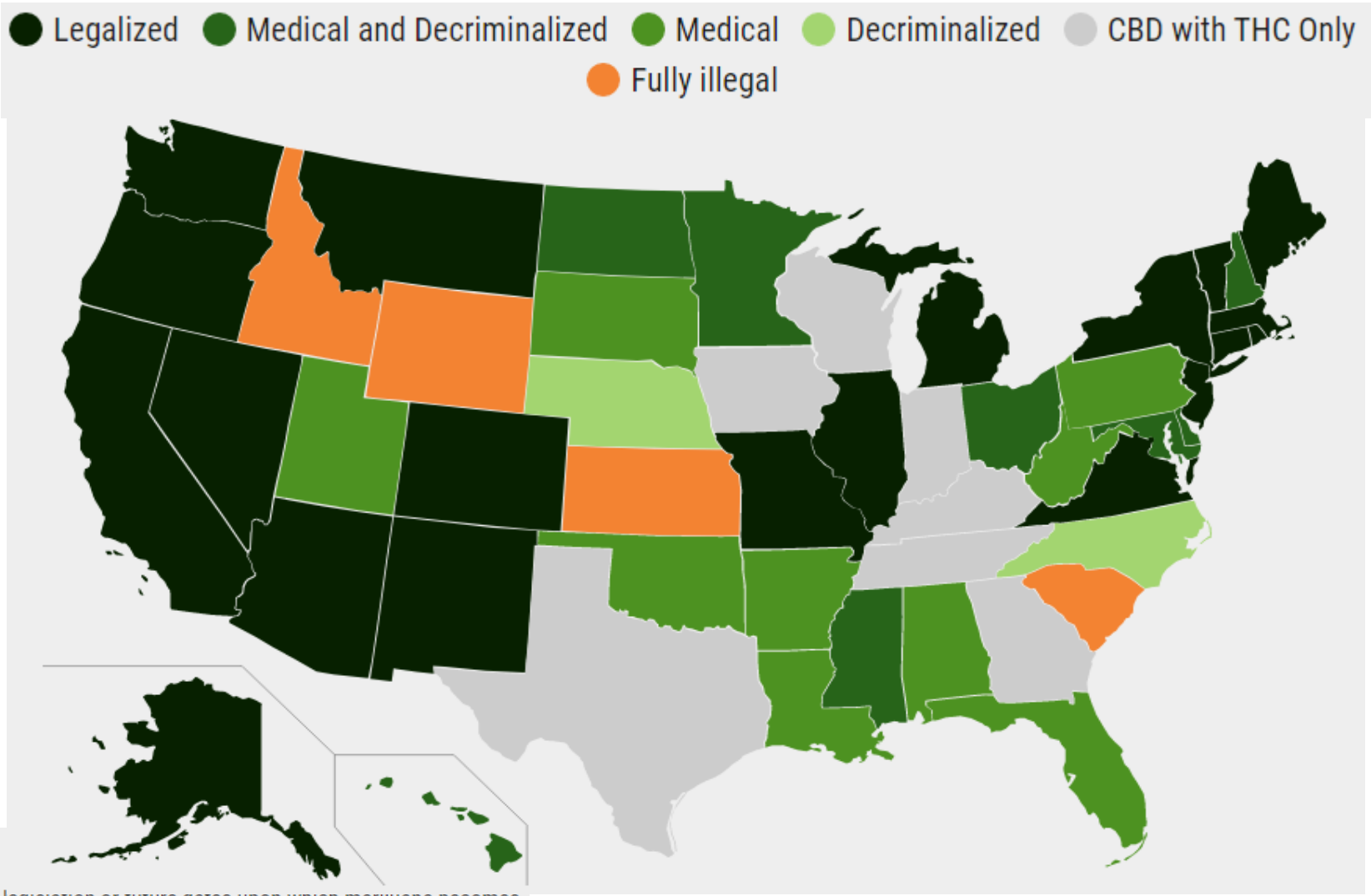
Cannabis NOT FDA approved for any condition

** Marinol – synthetic THC; FDA approved

** Epidiolex – cannabis derived CBD; FDA approved

Cannabis Legality By State …

Lack of Federal Regulations Leads to Heterogeneous State Regs



Last Updated: February 2023

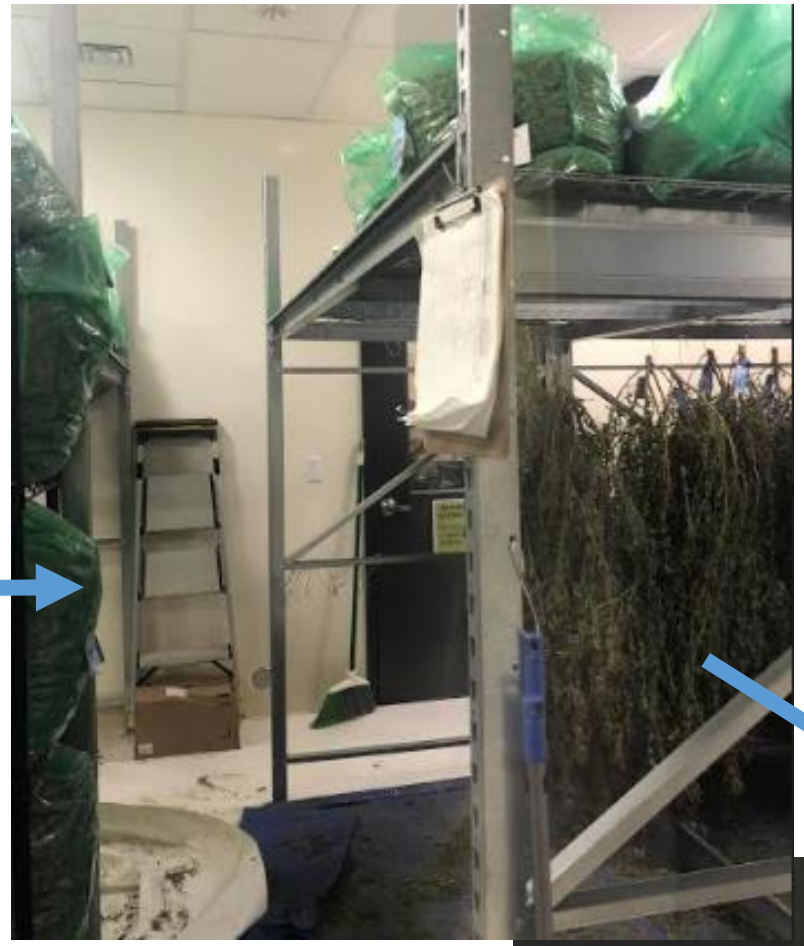
- State status reflects current laws at the time of update, not pending legislation or future dates upon which marijuana becomes available medicinally or recreationally. States with legislation that has passed but has a future enactment date will be marked with an asterisk *.
- CBD oil can be made with or without THC. This chart is specifically referring to CBD Oil with THC as an ingredient. CBD oil with THC is illegal in states marked as "Fully Illegal".
- All "statuses" are subject to state limits. E.g., CBD Oil may only be legal to 0.5% THC or marijuana may only be legal to one ounce. Please consult state laws.
- **Effective July 1, 2022 in Minnesota, it will be legal to consume, manufacture, distribute, and sell edibles in packages containing up to 50 milligrams of any form of THC, so long as it's derived from hemp.

https://disa.com/maps/marijuana-legality-by-state

Growing Operations

- Mother Plant and Clones
- Seed to Sale Tracking
- Light and Dark Cycles
- Micro-organism Control

Photos, C. Roussel



Harvesting and Drying

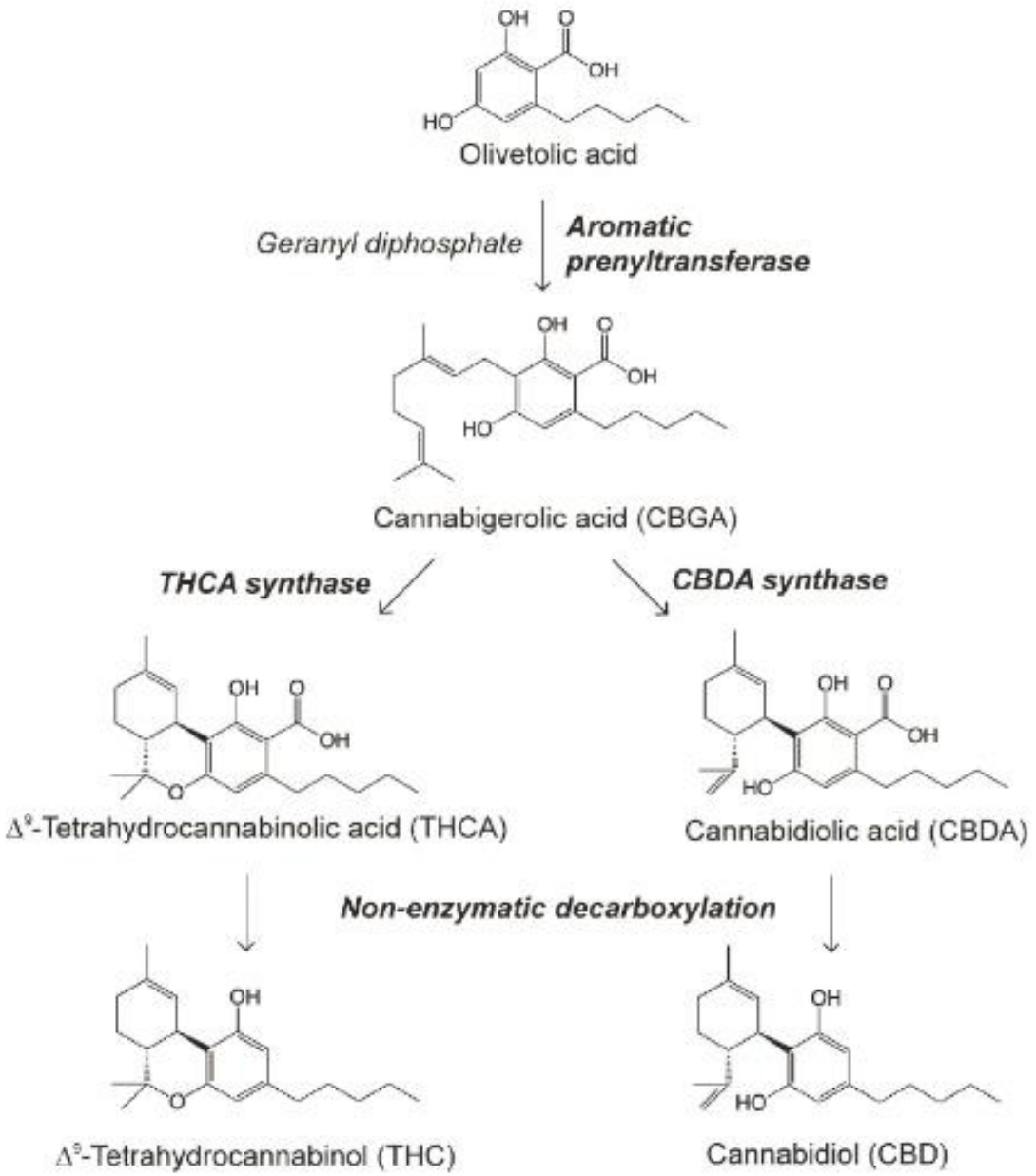
Photos, C. Roussel

Extraction

Photos by C. Roussel

Photos, C. Roussel

Cannabaceae



Natural Synthesis of Cannabinoids (NAS 2017)

- Unfertilized female flower
- Acidic cannabinoids
- Chemovars
- THC-predominant (Type I)
- THC:CBD mix (Type II)
- CBD-predominant (Type III)
- **Indica vs Sativa vs Hybrids vs Hemp**

No official mechanism to register Cannabis strains -- potential for incorrect identification & labeling

INDICA ("In da couch")

- Short, bushy, wide leaves
- Grow faster, higher yield
- Higher CBD & lower THC

CHEMOVAR QUALITIES (traditionally)

- Nightime. Muscle & mental relaxation
- For nausea, appetite, pain, sleep

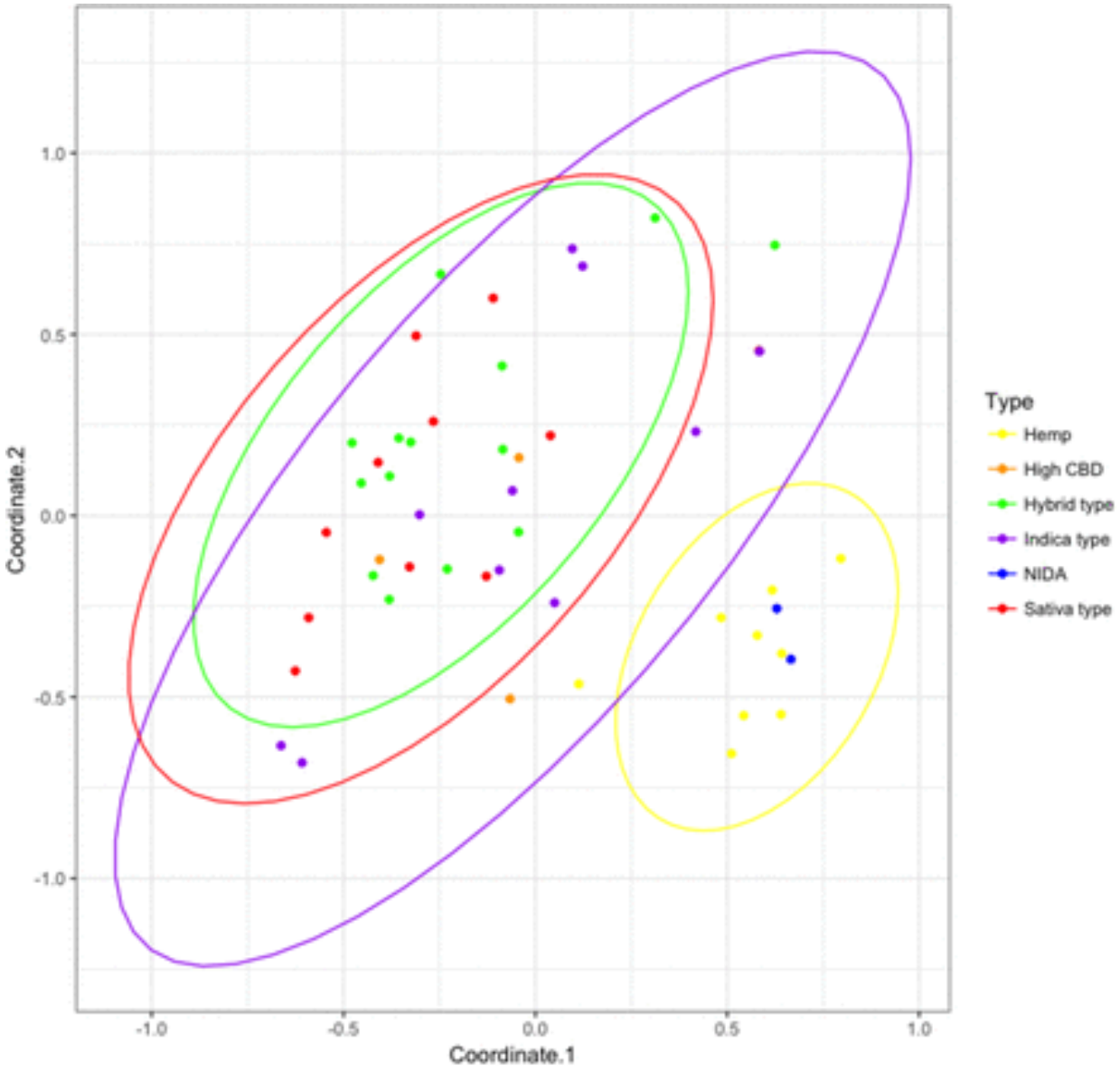
SATIVA (stimulating)

- Tall, thin w. narrow leaves
- Longer to mature, requires more light
- Lower CBD, higher THC counts

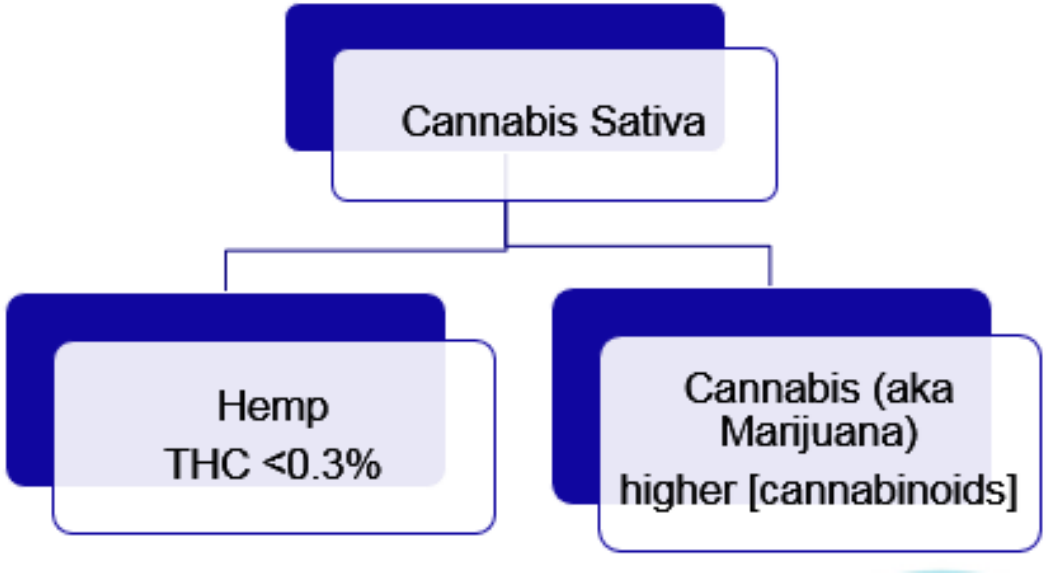
CHEMOVAR QUALITIES (traditionally)

- Daytime. Increase focus & creativity, uplifting, invigorating,
- for fatigue/depression

Piomelli D, Russo EB (2016)

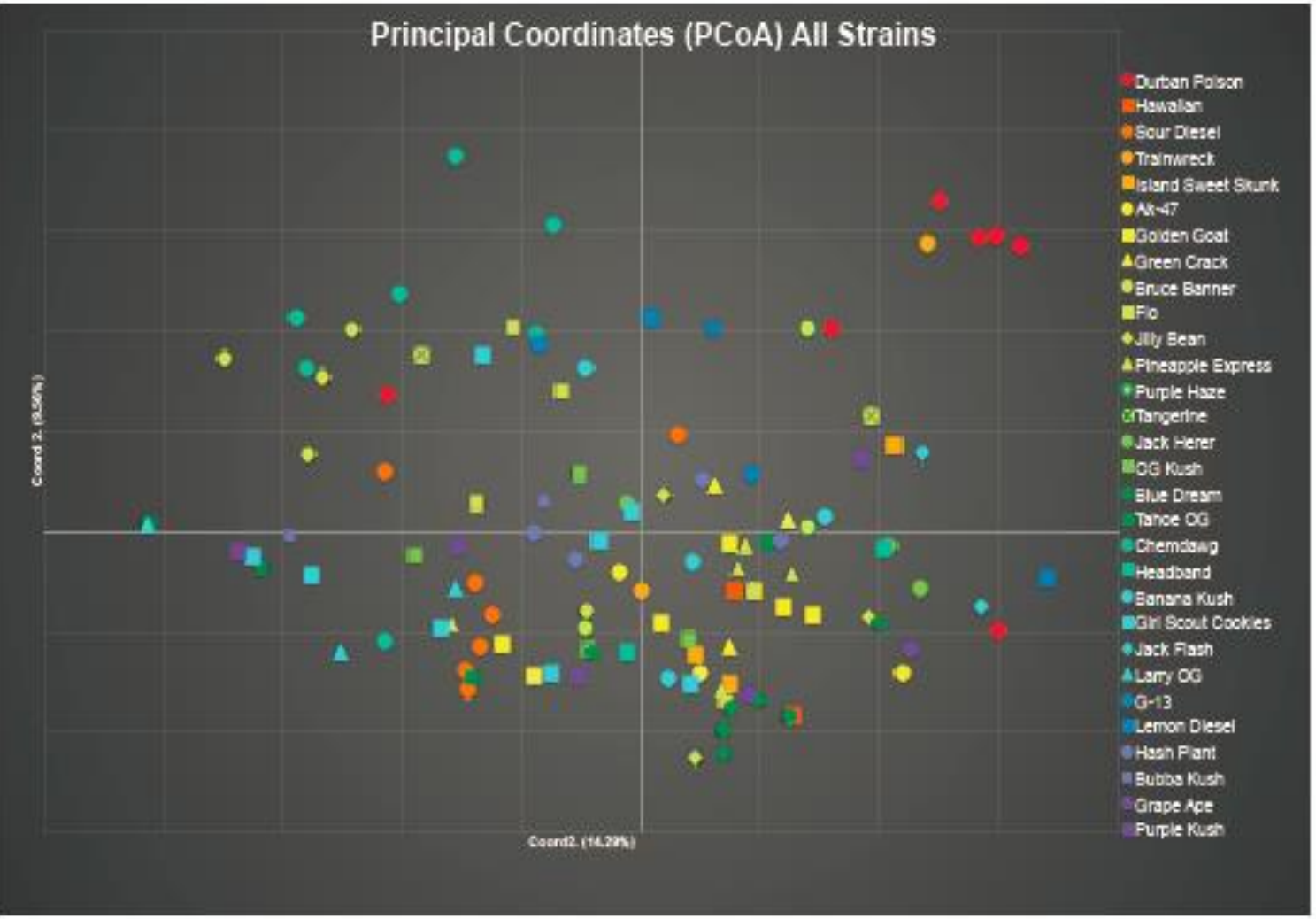


Research grade marijuana supplied by the National Institute on Drug Abuse is genetically divergent from commercially available Cannabis



A.L. Schwabe, et al. 3/28/1, pre-print. Not yet peer reviewed. DO - 10.1101/592725

"Genetic tools weed out misconceptions of strain reliability in *Cannabis sativa*"



No consistent genetic differentiation between Sativa & Indica *Cannabis* types

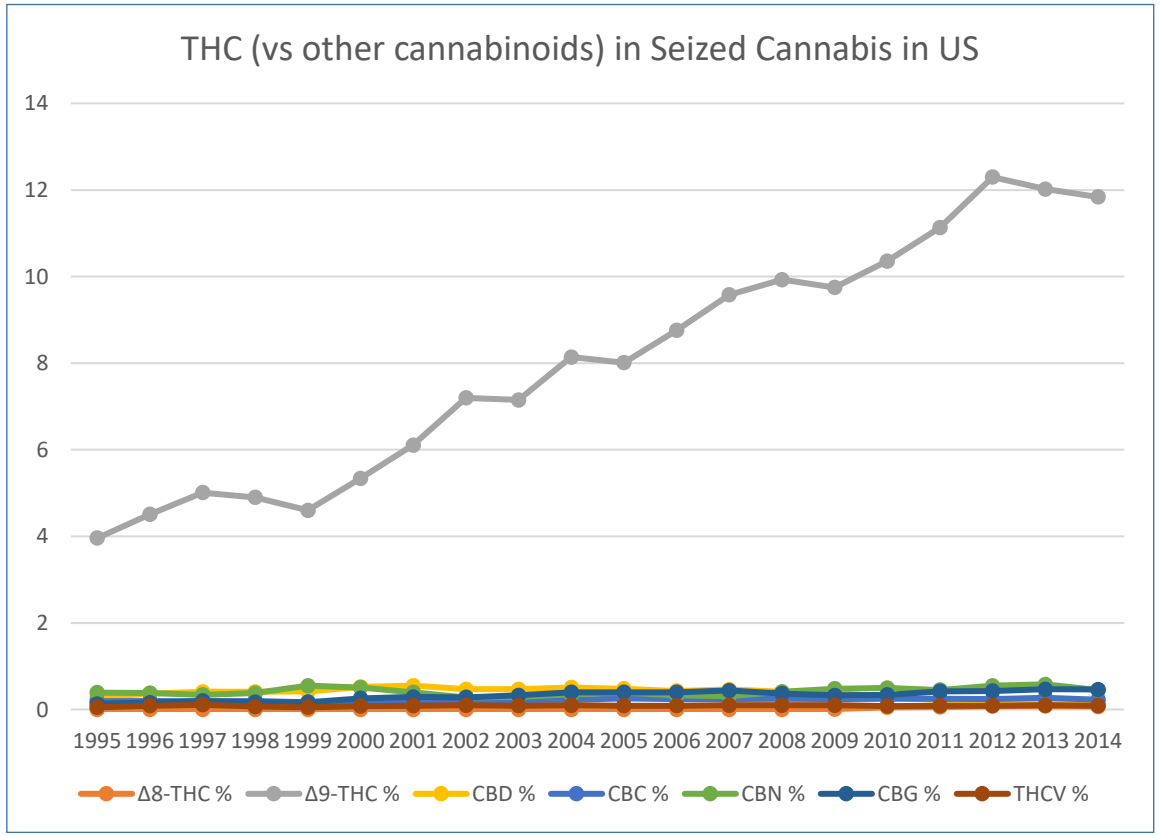
Samples within strains *not* genetically similar

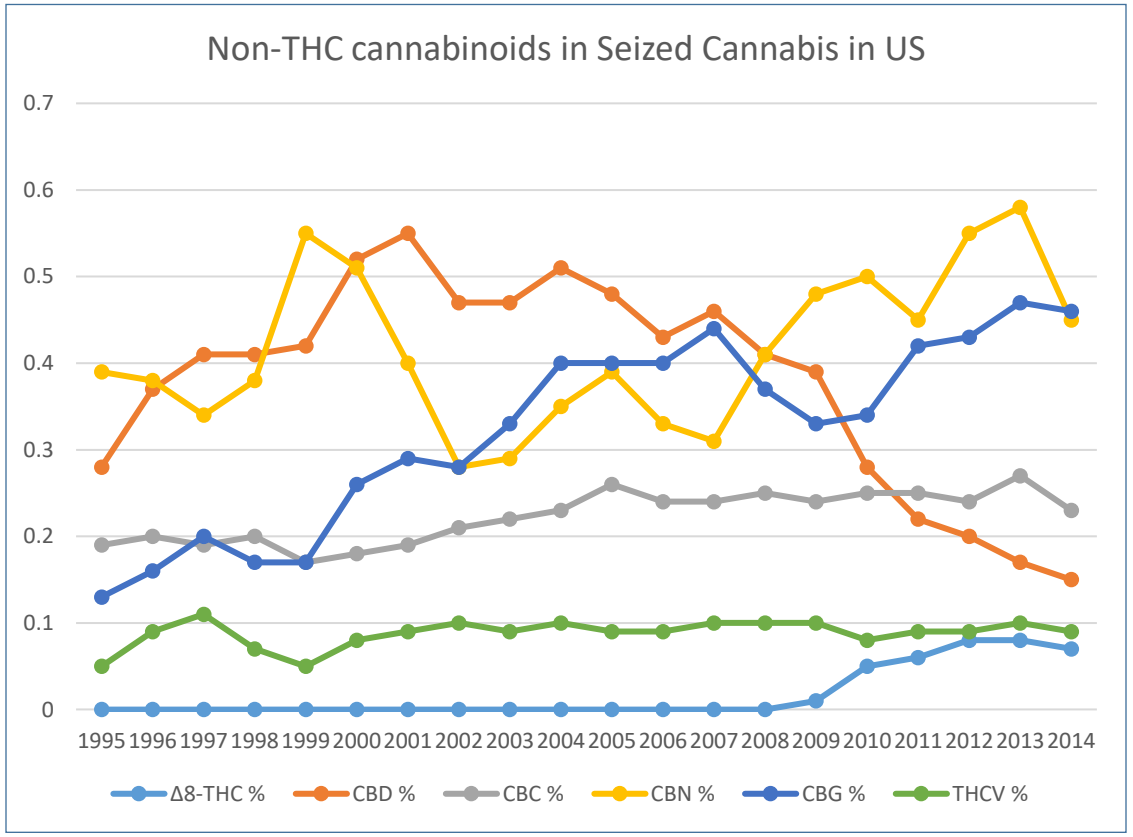
We should **"abandon the *sativa*/*indica* nomenclature** &… **insist that accurate biochemical assays** on cannabinoid & terpenoid profiles be available…in both the medical & recreational markets. Scientific accuracy & the public health demand no less than this."

- Dr. Ethan Russo

Schwabe, A., McGlaughlin, M., Genetic tools weed out misconceptions of strain reliability in 1 *Cannabis sativa:* Implications for a budding industry. bioRxiv preprint, online May. 28, 2018. NOT PEER REVIEWED

Cannabis Evolution





Graphs developed using data from: ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. *Biol Psychiatry*. 2016;79(7):613-9.

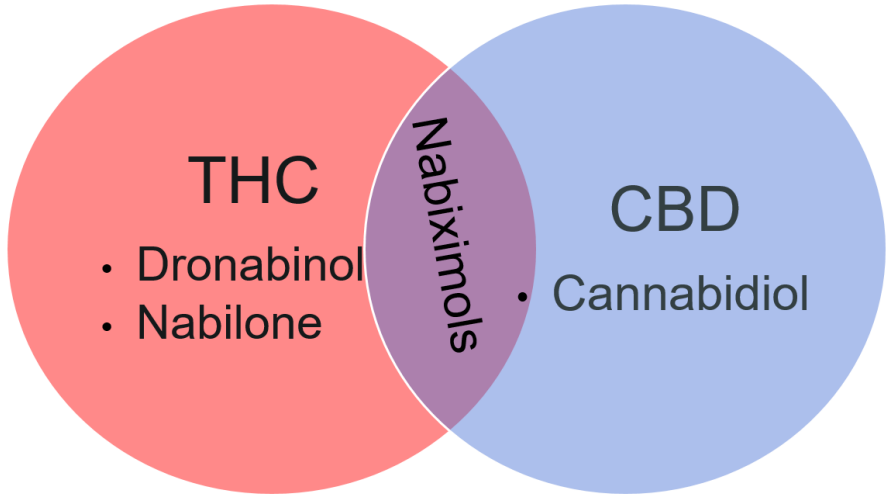
Agriculture Improvement Act (AIA) of 2018 (commonly known as the 2018 Farm Bill)

- "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% on a dry weight basis"
- Amended the Controlled Substances Act to exclude hemp from the definition of marihuana and to remove it from Schedule I status, thereby providing for regulated cultivation of hemp as an agricultural commodity.

FDA Authority - Food, Drug & Cosmetics Act has authority

Both CBD & THC = active ingredients in FDA-approved drugs

- Synthetic THC – marinol, nabilone
- CBD – cannabis derived CBD



Unlawful to:

- introduce food w/ added CBD or THC into interstate commerce
- market CBD or THC products as, or in, dietary supplements, (whether or not hemp-derived)

True Content of Cannabidiol (CBD) Products Sold with out a prescription (Internet, food stores – technically illegal)

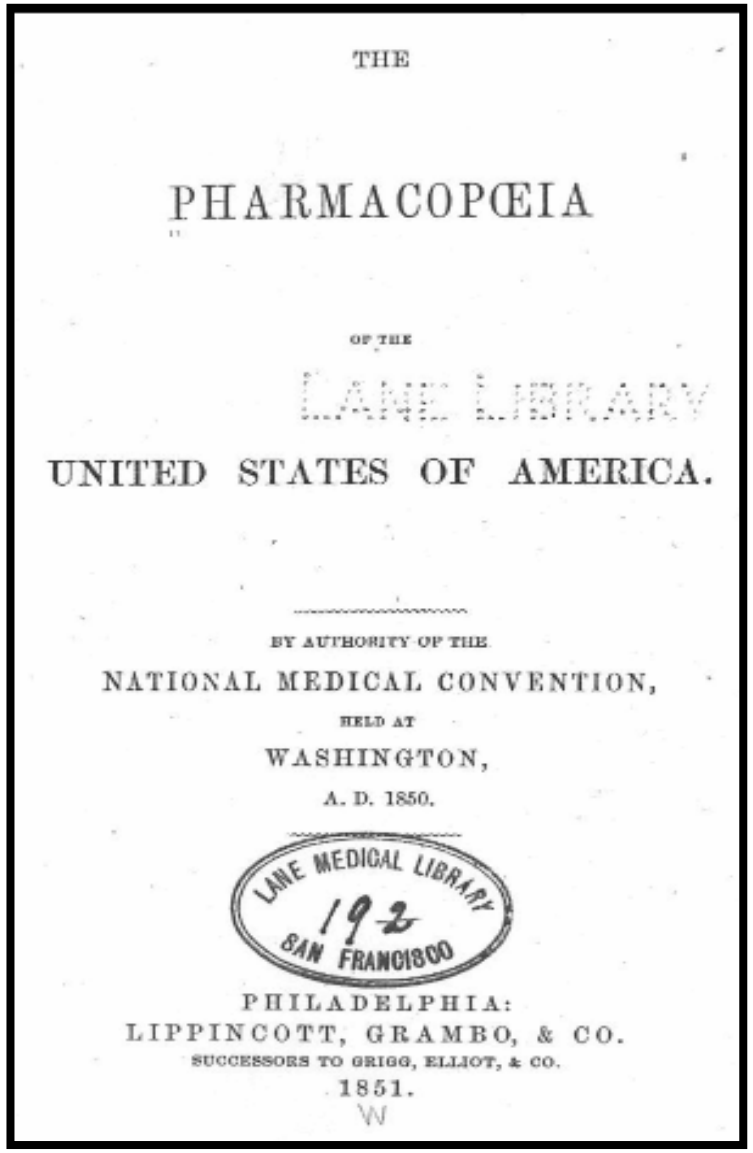
- Almost 50% of products had more than on the label
- A quarter had way less than on the label

- ~ 25% contained THC without it being on the Label (18 / 84)
- THC contamination detected as high as 6.43 mg/mL

- FDA has cited companies for having NO CBD in their products as well as high amounts of substances like LEAD

Using +/- 10% for label accuracy of CBD content (n=84)

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA 2017;318:1708-1709.


THE

PHARMACOPŒIA

OF THE

UNITED STATES OF AMERICA.

BY AUTHORITY OF THE

NATIONAL MEDICAL CONVENTION,

HELD AT

WASHINGTON,

A. D. 1850.

PHILADELPHIA:
LIPPINCOTT, GRAMBO, & CO.
SUCCESSORS TO GRIGG, ELLIOT, & CO.
1851.

9th edition, published in 1916
-> USP required biologic assays

- analysis performed on dogs
- fluid extracts $\leq$ 0.03 mL/kg
- tinctures $\leq$ 0.3 mL/kg of preparation
- This practice helped ascertain the dose of preparation needed to produce the desired “muscular incoordination” effect without overt toxicity
- USP outlined that there was a significant difference in response to the drug between dog breeds

- Determined that Fox Terriers were particularly susceptible to the effects of cannabis, making them a great marker for efficacy and safety of the drug for the biological assay.

The Pure Food & Drug Act of 1906

Labeling requirement: products w/ cannabis & 7 other drugs

Harrison Narcotic Act of 1914

Regulated & taxed opium, coca leaves, derivatives, & preparations.
EXCLUDED CANNABIS

Federal Bureau of Narcotics (1930)

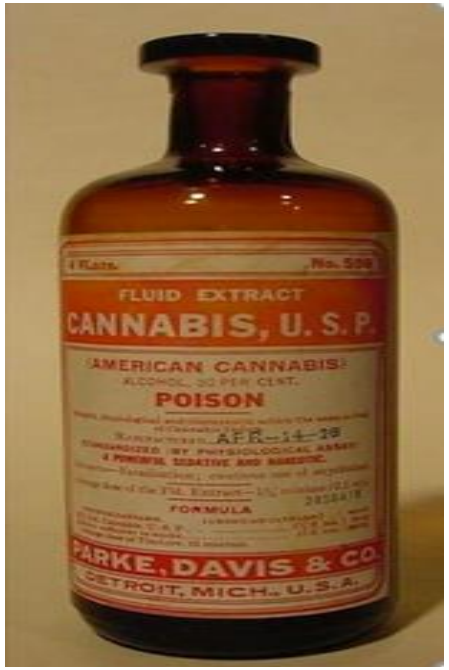
Marijuana “causes violence and insanity”

Marijuana Tax Act – 1937 Criminalized marijuana & hemp

AMA and hemp farmers not consulted; opposed it

Controlled Substances Act (CSA) - 1970

Formalized hemp & cannabis= Schedule 1 (of 5 classes)



FDA and the US Pharmacopeia

- **1906 Pure Food and Drug Act** deemed the United States Pharmacopeia and the National Formulary (USP-NF) official compendia under federal law

- USP develops and publishes standards for drug substances, drug products, excipients, and dietary supplements in the USP–NF

- **1938 Federal Food, Drug and Cosmetic (FD&C) Act** expressly recognizes USP quality standards for Medicine
  - defines the term "official compendium" as the official USP, the official NF,
  - the official Homeopathic Pharmacopeia of US, or any supplement to them.
  - binding for dietary supplement manufacturers that label their products as compliant with USP specifications.

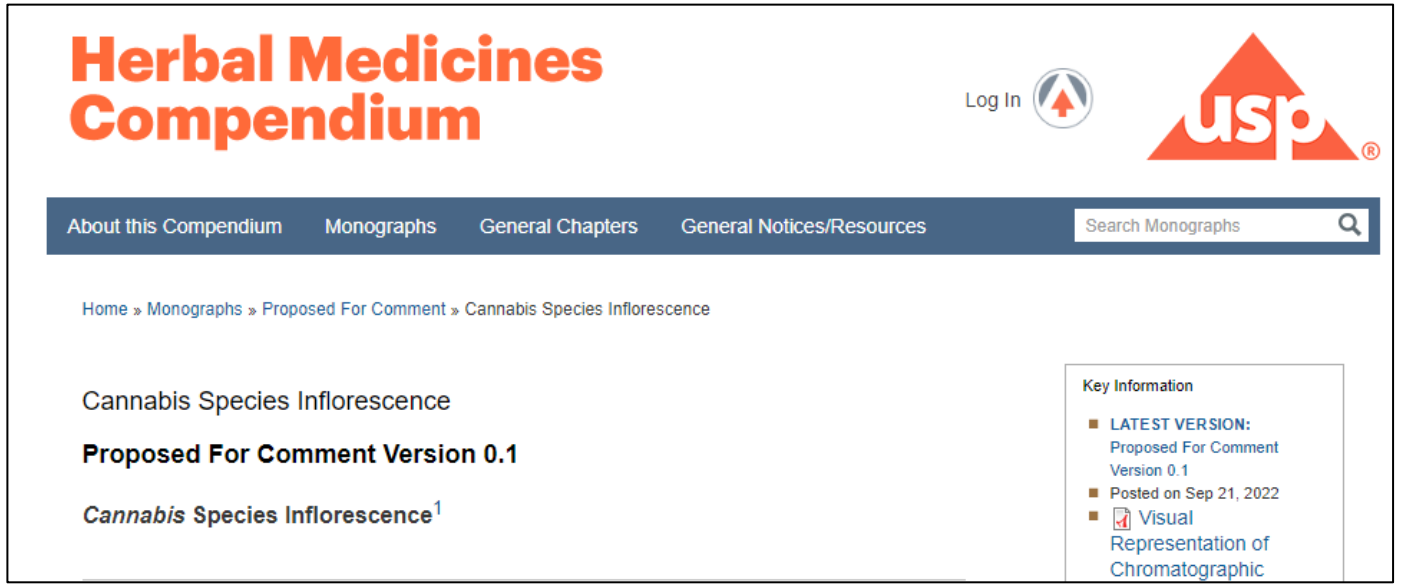
https://www.usp.org/about/legal-recognition/standard-categories;
https://www.usp.org/sites/default/files/usp/document/about/public-policy/USP-and-US-FDA-a-partnership.pdf

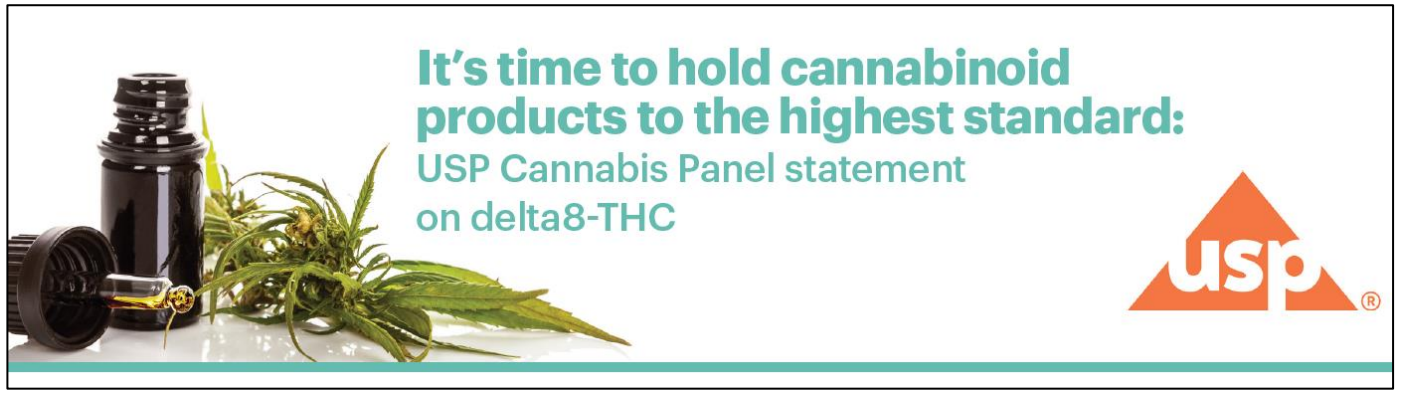

U.S. FOOD & DRUG ADMINISTRATION
Home / Regulatory Information / Search for FDA Guidance Documents / Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research Guidance for Industry
GUIDANCE DOCUMENT
Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research Guidance for Industry
Guidance for Industry
JANUARY 2023
Download the Final Guidance Document
Read the Federal Register Notice
Final
Level 1 Guidance


FDA STATEMENT
FDA Concludes that Existing Regulatory Frameworks for Foods and Supplements are Not Appropriate for Cannabidiol, Will Work with Congress on a New Way Forward
Share
Tweet
Linkedin
Email
Print
For Immediate Release: January 26, 2023
Statement From: Janet Woodcock, M.D.
Principal Deputy Commissioner - Office of the Commissioner


DEA United States Drug Enforcement Administration
Law Enforcement
Drug Scheduling
Although some states within the United States have allowed the use of marijuana for medicinal purpose, it is the U.S. Food and Drug Administration that has the federal authority to approve drugs for medicinal use in the U.S. To date, the FDA has not approved a marketing application for any marijuana product for any clinical indication. Consistent therewith, the FDA and DEA have concluded that marijuana has no federally approved medical use for treatment in the U.S. and thus it remains as a Schedule I controlled substance under federal law.

Marihuana Growers Information (usdoj.gov)





Limits for Contaminants

The limits for contaminants in cannabis — including pesticide residues, microbial load, aflatoxin levels, and elemental contaminants — should be based on scientific considerations. The USP *JNP* article provides appropriate tests, also contained in USP General Chapters and criteria to control contaminants and which may be useful for quality assurance.

- **USP General Chapter <61>** *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*
- **USP General Chapter <62>** *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*
- **USP General Chapter <232>** *Elemental Impurities—Limits*
- **USP General Chapter <561>** *Articles of Botanical Origin: Pesticide Residue Analysis; Test for Aflatoxins*
- **USP General Chapter <1111>** *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use: Microbial limits for products that conform to limits for inhalation use.*

https://www.usp.org/dietary-supplements-herbal-medicines/cannabis

Cannabis Species Inflorescence Proposed For Comment Version 0.1. Herbal Medicines Compendium. Sep 21, 2022. https://hmc.usp.org/monographs/cannabis-species-inflorescence-0-1

Highlights from the Purposed USP Cannabis Monograph

Treat Cannabis as a single highly variable species
THC:CBD Ratio – Establishing Formal Order of Expression
List the labeled amount of all cannabinoids measured (mg/g) where contents is NLT 80% and NMT 120% of the labeled amount.
Labelling Standards
Microbial Contamination Limits
Definitions of THC dominant, CBD dominant and Intermediate chemotypes
Products must be labelled if they have undergone microbial remediation

THC:CBD Chemotypes or Ratios

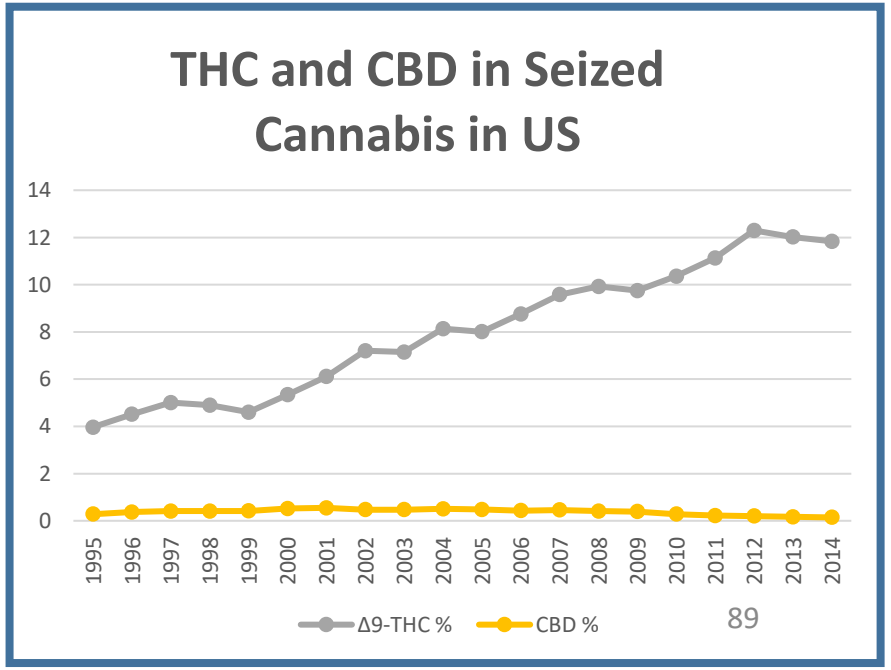
Psychoactivity

THC-dominant NLT 5:1

Intermediate (aka balanced)

NLT 0.2:1 and NMT 5:1

CBD-dominant - NMT 1:5



Chemo type Acceptance Criteria (ratio expresses THC:CBD)

THC-dominant	THC/CBD intermediate	CBD-dominant
NLT 5:1	NLT 0.2:1 and NMT 5:1.	NMT 1:5
NMT 10 mg/g total CBD and NLT 10 mg/g total THC.		Contains less than 10 mg/g of total THC.
CBN content is NMT 2% of the total content of THC. No unidentified peak in the Sample solution chromatogram exceeds the area of the CBN peak.		

NLT = not less than; NMT = not more than
must to contain NLT 80% and NMT 120% of the labeled amount (in mg/g) of the total tetrahydrocannabinol (THC) including Δ 9 -THC and THCA
and NLT 80% and NMT 120% of the labeled amount (in mg/g) of the total cannabidiol (CBD) including CBD and CBDA

What Else is your Cannabis?

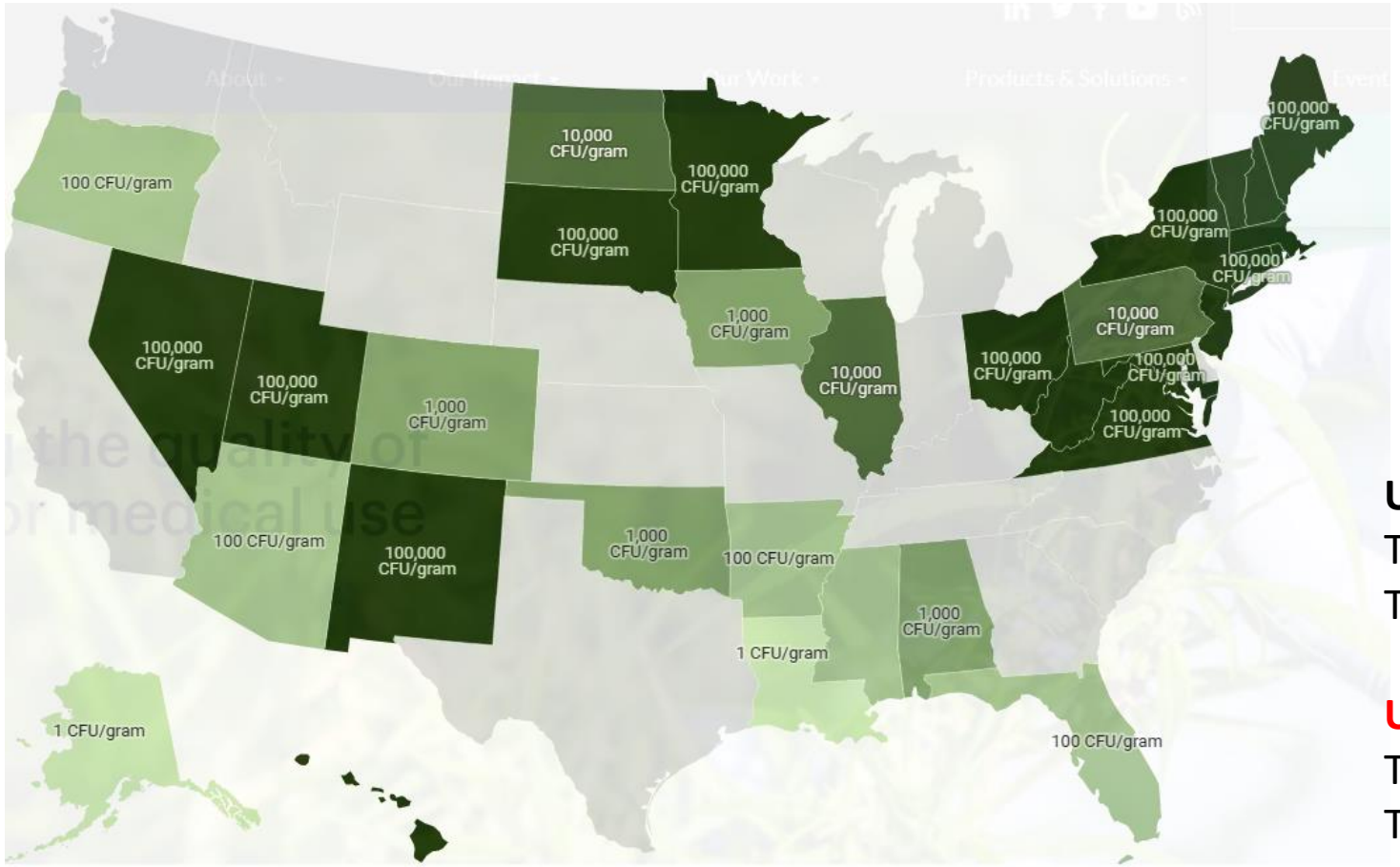
USP General Chapter <232> on Elemental Impurities - Limits and USP General Chapter <561> Articles of Botanical Origin,

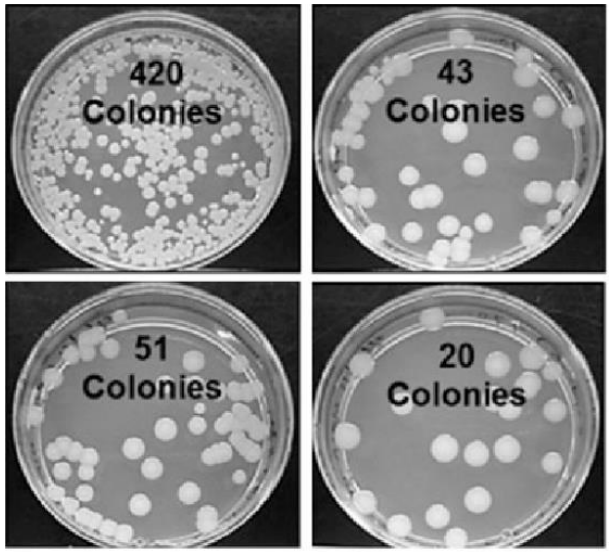
- arsenic (NMT 0.2 µg/g)
- cadmium (NMT 0.3 µg/g)
- lead (NMT 0.5 µg/g)
- mercury (NMT 0.1 µg/g)

USP on Pesticides -> “the relevant regulatory body requirements.”

Aerobic Bacteria Count Limits for Cannabis by State

Colony Forming Unit / Gram of Cannabis





Gram of Cannabis ~ size of Grape

USP < 61 > Microbial Testing

Total Aerobic Bacteria Count < 100,000 cfu/gram

Total Combined Yeast and Mold < 10,000 cfu/gram

USP <1111> Acceptance Criteria Non-Sterile Products

Total Aerobic Bacteria Count < 100 cfu/gram

Total Combined Yeast and Mold < 10 cfu/gram

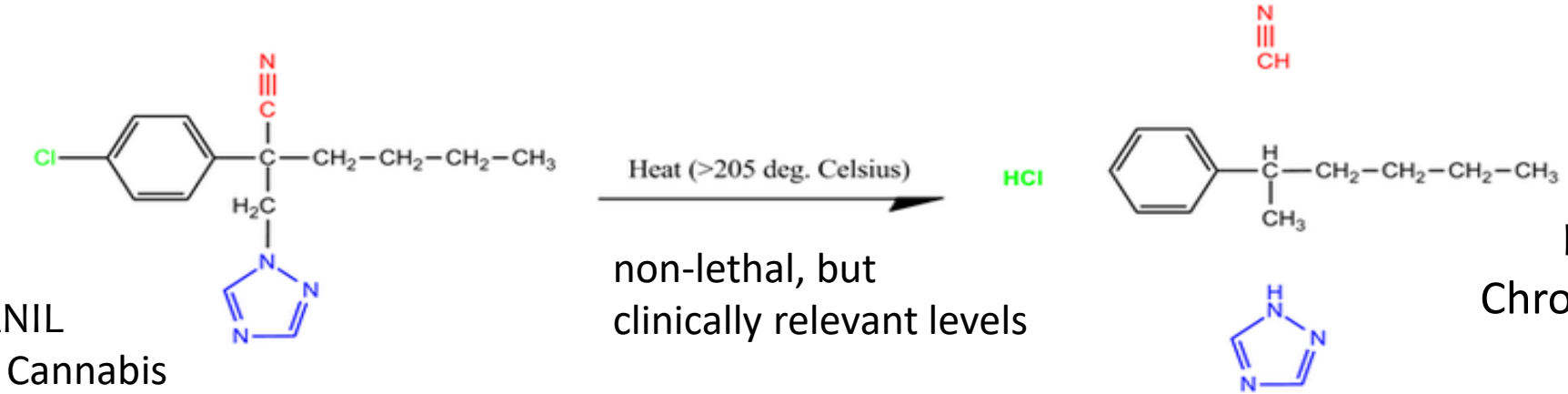
The map below outlines different Total Aerobic Count acceptable limits each state requires for microbial cannabis testing. States in gray either do not require a Total Aerobic Count limit or cannabis is outlawed.

1 CFU/gram 1,000 CFU/gram 10,000 CFU/gram 100 CFU/gram 100,000 CFU/gram

Pesticide Use on Cannabis

15 labs across 13 states detecting 80 different pesticides in cannabis flower samples.

29 pesticides were detected in cannabis flower samples from 3 or more states



MYCLOBUTANIL
Inhalation of Cannabis
w/ MYC at 0.03 ppm

non-lethal, but
clinically relevant levels

HYDROGEN CYANIDE
Chronic exposure to dilute
HCN (ex. 0.008 ppm)

- Serious neurological, respiratory, cardiovascular, & thyroid problems
- **Myclobutanil (**tebuconazole & propiconazole) **co-extracted w/cannabinoids in concentrate production** -> Accumulate at levels 250x ↑than starting material

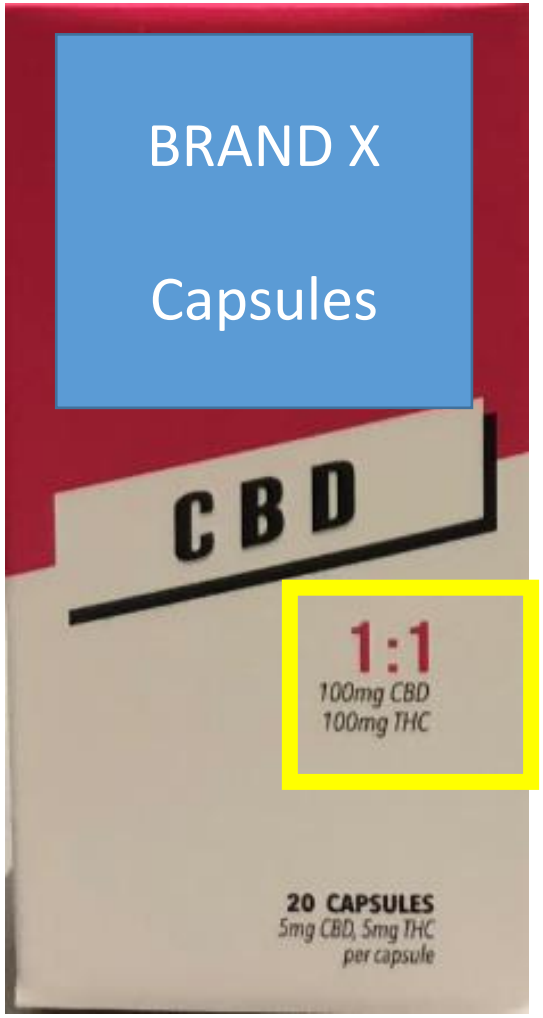
 National Cannabis Laboratory Council (NCLC). Standardizing Cannabis Lab Testing Nationally. NCLC website. 2022. Accessed February 16, 2023. https://www.perkinscoie.com/images/content/2/5/253590/Standardizing-Cannabis-Lab-Testing-Nationally-FINAL-7-1-1.pdf; Pinkhasova D, Jameson LE, Conrow KD, et al. Regulatory status of pesticide residues in cannabis: Implications to medical use in neurological diseases. *Current Research in Toxicology 2*. 2021;140-148.

Who Regulates Pesticides and Insecticides on Cannabis???

- US Environmental Protection Agency (EPA) to define this type of contamination, as granted by the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) of 1996.
  - "There are currently **no pesticides** registered by EPA specifically for use on cannabis. Some pesticide labels do list industrial hemp among listed crops. Currently, there are no tolerances established for marijuana or hemp."
  - EPA has approved adding hemp to the labels of 98 pesticides products (as of 12/2022)
- At least 6 states have adopted the EPA's pesticide residue action levels for food commodities (decent start but does not adequately address the effects of inhalation nor processing and incineration)
- One study identified that on average the action levels for top 50 pesticides were "32-fold higher than the most stringent tolerances for food commodities by the US EPA."

US EPA - Hemp
Pinkhasova D, Jameson LE, Conrow KD, et al. Regulatory status of pesticide residues in cannabis: Implications to medical use in neurological diseases. *Current Research in Toxicology 2*. 2021;140-148
USP, FDA Propose Quality Standards for Cannabis, Highlighting its Role as Medicine (pharmacytimes.com).

EXAMPLES OF PRODUCT LABELLING IN PENNSYLVANIA PROGRAM APPROVED PRODUCTS



https://www.pacode.com/secure/data/028/chapter1141/chap1141toc.html

Patient Registers
Physician Certified Patient based on Serious Qualifying Medical Conditions
Patient Pays for Care
Patient visits Dispensary (Ideally meets with Dispensary Pharmacist)

Physicians Cannot Prescribe Medical Marijuana

"Prescription" - written or oral order issued by a duly licensed medical practitioner in the course of his professional practice for a controlled substance, other drug or device or medication…dispensed for use by a consumer

Physicians may NOT:

- Order a patient to consume/obtain a Schedule 1 Controlled Substance
- Order the dispense of a Schedule 1 Controlled Substance
- Specify specific amount to consume (dose)

PA Physicians can:

- Put limitations on the recommended forms and time on the certification

justice.gov/osg/brief/walters-v-conant-petition

Physicians *CAN Recommend* Medical Marijuana

Physicians Can:

- Discuss treatment options (inc. cannabis or cannabis products)
- Discuss pros & cons of treatment w/ medical cannabis.
- Recommend that a patient consider the use of medical cannabis for symptoms

The court held that what it regarded as physicians' "legitimate need to discuss with and to recommend to their patients all medically acceptable forms of treatment" outweighs the government's "legitimate interest in suppressing and controlling the flow of dangerous drugs and controlled substances within the United States."

https://www.justice.gov/osg/brief/walters-v-conant-petition

Serious Medical Condition	Percent
Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain.	45.02%
Anxiety Disorders.	14.94%
Post-traumatic stress disorder.	12.33%
Cancer, including remission therapy.	6.47%
Neuropathies.	6.28%
Opioid use disorder for which conventional therapeutic interventions are contraindicated or ineffective, or for which adjunctive therapy is indicated in combination with primary therapeutic interventions.	3.01%
Damage to the nervous tissue of the central nervous system (brain-spinal cord) with objective neurological indication of intractable spasticity, and other associated neuropathies.	2.12%
Inflammatory bowel disease.	2.00%
Multiple sclerosis.	1.56%
Epilepsy.	1.20%
Crohn's disease.	1.16%
Autism.	< 1%
Glaucoma.	< 1%
Positive status for Human Immunodeficiency Virus or Acquired Immune Deficiency Syndrome.	< 1%
Parkinson's disease.	< 1%
Intractable seizures.	< 1%
Dyskinetic and spastic movement disorders.	< 1%
Neurodegenerative diseases.	< 1%
Amyotrophic lateral sclerosis.	< 1%
Tourette Syndrome.	< 1%
Sickle cell anemia.	< 1%
Terminal illness.	< 1%
Huntington's disease.	< 1%

Publically Presented at MMAB Meeting in Feb 2020

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Certifying Physician Signs Off: “I have”

- **conducted a patient consultation** in manner... to make a medical determination as to the patient’s serious medical condition(s)
- **made a diagnosis of a serious medical condition** for which the *patient will receive a therapeutic or palliative medical benefit*
- **established a medical record** & **shall maintain** medical record while patient is under my *continuing care*
- **consulted the PDMP database.. was** patient dispensed any controlled substances that would prohibit or pose a risk re: MM?
- **received informed consent statement** from patient, or if applicable from caregiver, custodial parent, legal guardian or spouse

Informed Consent (should include but not limited to)

- Investigational - Not FDA Approved
- Inability to predict or guarantee effects / response

Legal Considerations

Department of Justice (DOJ) “has authority to enforce civil & criminal federal laws relating to marijuana possession & use, regardless of state law.” Selective enforcement to date, but patients need to know implications.

Understand Legal Constraints

- Don’t take across state lines
- Ensure Proper storage
- Don’t Share
- Don’t Drive

Informed Consent/ Risks

- Side effects
- Psych conditions - from anxiety & depression to psychosis
- Cannabis use disorder/ addiction
- Short & long-term cognitive effects
- Chronic Obstructive Lung Disease (COPD)
- Reproductive risks (pregnant? plan to become pregnant?)
- Drug Interactions
- Increased Risk of Falls
- Lower Blood Pressure /Alter Heart Rate
- Temporary memory impairment/paranoia
- Drug testing: potential + cannabis (THC) drug screen

PA Dispensaries

1st location: physician or pharmacist must be available on site or remotely during the time the dispensary is open

- 2nd & 3rd locations may have NP or PA on site
- Medical Marijuana
  - can be dispensed
  - can *not* be administered
- Can obtain MM products from any Grower / Processor licensed by the Commonwealth

PA Dispensing Regulations

- Review Dept. Database prior to each dispense
- Products dispensed to the patient/caregiver “must” conform to the limitations set by the practitioner
  - States “medical professionals should consider the recommendations”
  - (ie. dosage form specified by certifying physician)
- If no practitioner requirements/ limitations: Dispensary clinician “Shall consult with the patient or the caregiver regarding the appropriate form & dose of medical marijuana to be provided”
- Dispense ≤ 90 day supply, but not until all but 7 days remain
- Report Adverse Events

Medical Marijuana Final-Form Regulations Update

Product limitations – 90 day supply of 192 medical marijuana units

- 1 unit: 3.5 g dry leaf, 1 g concentrate, 100 mg THC infused into pill, capsule, oil, tincture, liquid, tincture or topical

Health care professional requirements on site

- Dispensary is required to have physician/pharmacist available at all times during operating hours
- Each dispensary must have no less than one medical professional present (physician, pharmacist, PA, NP) and cannot cover more than one dispensary facility location at a given time
- In dispensaries with more than one license, the PA or NP may provide services at any of the facilities as long as one facility has a physician or pharmacist present

Dispensary access

- Only to employees, caregivers or children <18 accompanied by parent/guardian
- Exceptions for individuals providing goods/services, assist patient with product selection as the certifying practitioner, or potential employment

Medical Marijuana Advisory Board Meeting

Tuesday, November 22, 2022
10am - noon

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Metrics Are Presented at Medical Marijuana Advisory Board Meetings and Available online to the Public

https://www.health.pa.gov/topics/Documents/Programs/Medical%20Marijuana/MMAB%20Slides%20-%20November%2022,%202022.pdf

Medical Marijuana Program Update

- Program to date:
  - 842,021 Patients and Caregivers Registered;
  - 423,443 Active Patient Certifications;
  - 1,870 Approved Practitioners;
  - 26.5 Million Patient Dispensing Events;
  - 75.9 Million Products Dispensed
  - $6.3 Billion in Total Sales;
  - $2.5 Billion by G/Ps to Dispensaries; and
  - $3.8 Billion by Dispensaries
  - 171 Operational Dispensaries

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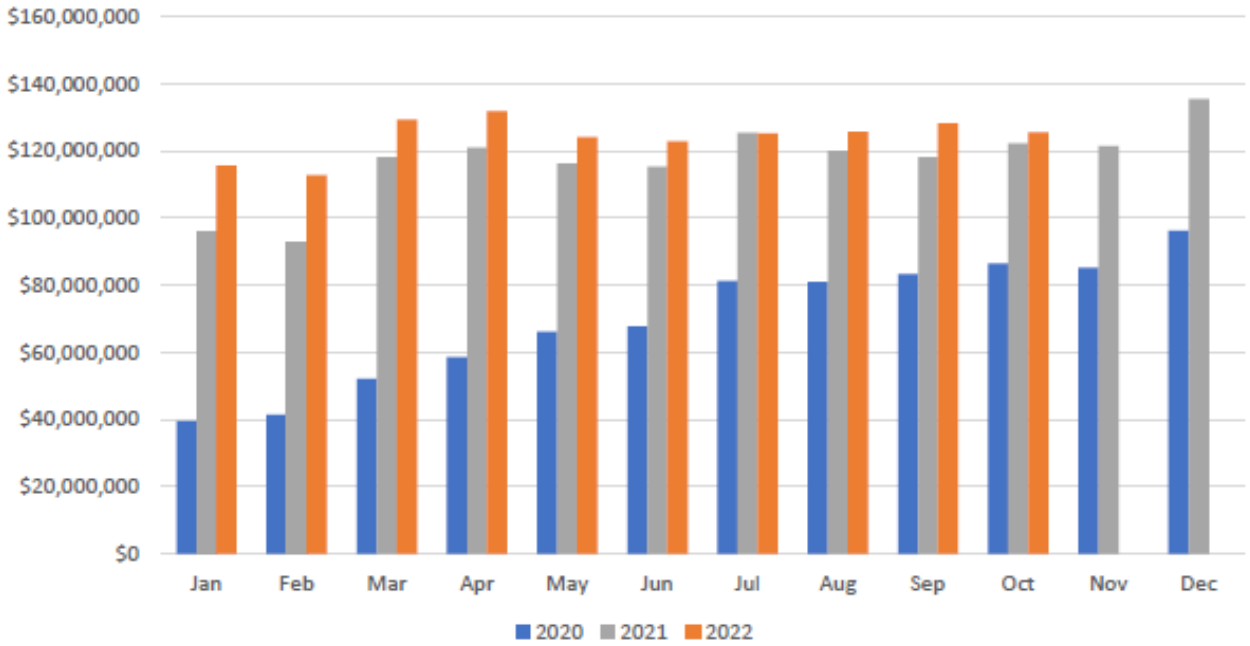
Medical Marijuana Program Update

Dispensary Sales by Month Since Jan 2020



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Medical Marijuana Program Update

Current and Planned Medical Marijuana Assistance

	Full Cost	Current Cost After Benefits	MMAP Phase 1	MMAP Phase 2	MMAP Phase 3 Pilot	MMAP Phase 3 Expansion
MM Identification Card	$50.00	$25.00 *50% discount*	No Cost Implemented March 1, 2022!		Implemented November 14, 2022!	
Caregiver Background Checks	$20.85	$7.60 *65% discount*		No Cost		
Patient Product Cost	Retail Price				$50/month *For PACE/PACENET Patients*	*Timing, patient applicability, and monthly benefit amount dependent on future funding*

35 P.S. Section 10231.902

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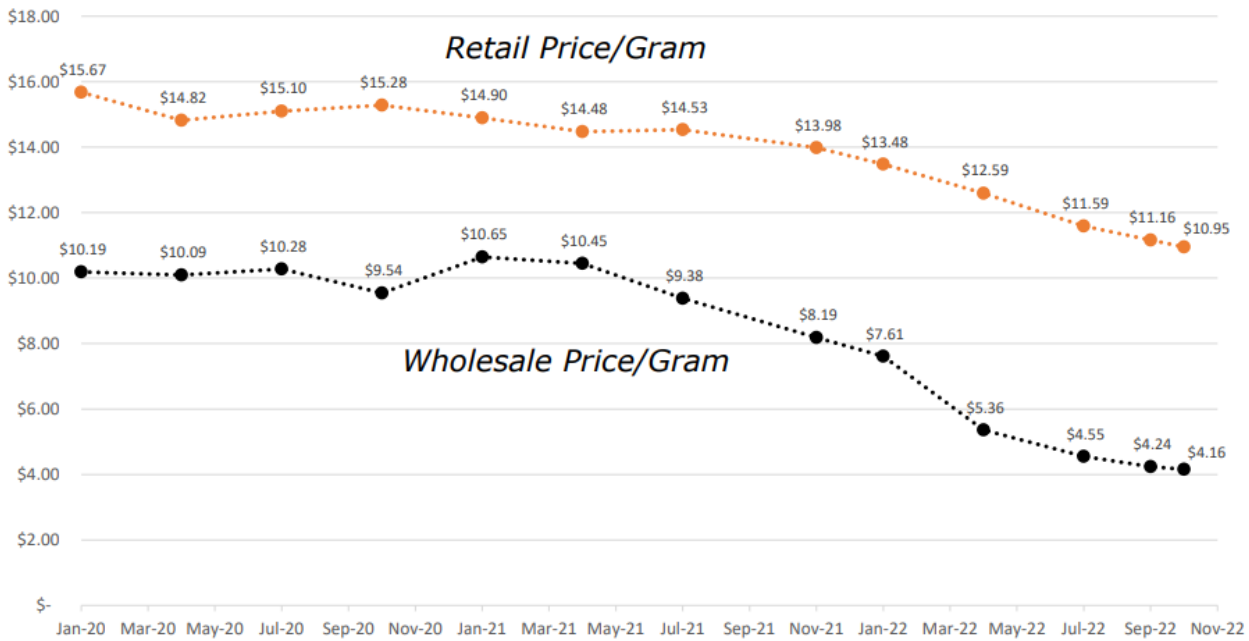
Medical Marijuana Program Update

Dry Leaf Retail and Wholesale Pricing Details



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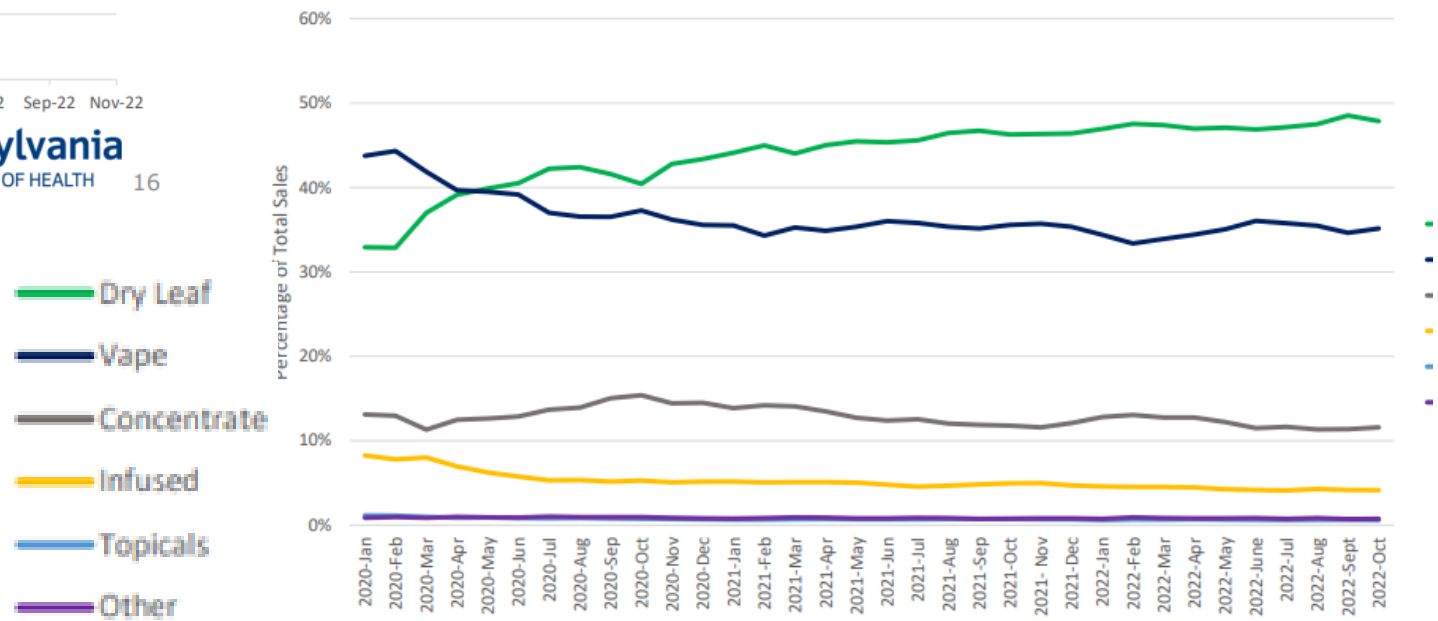
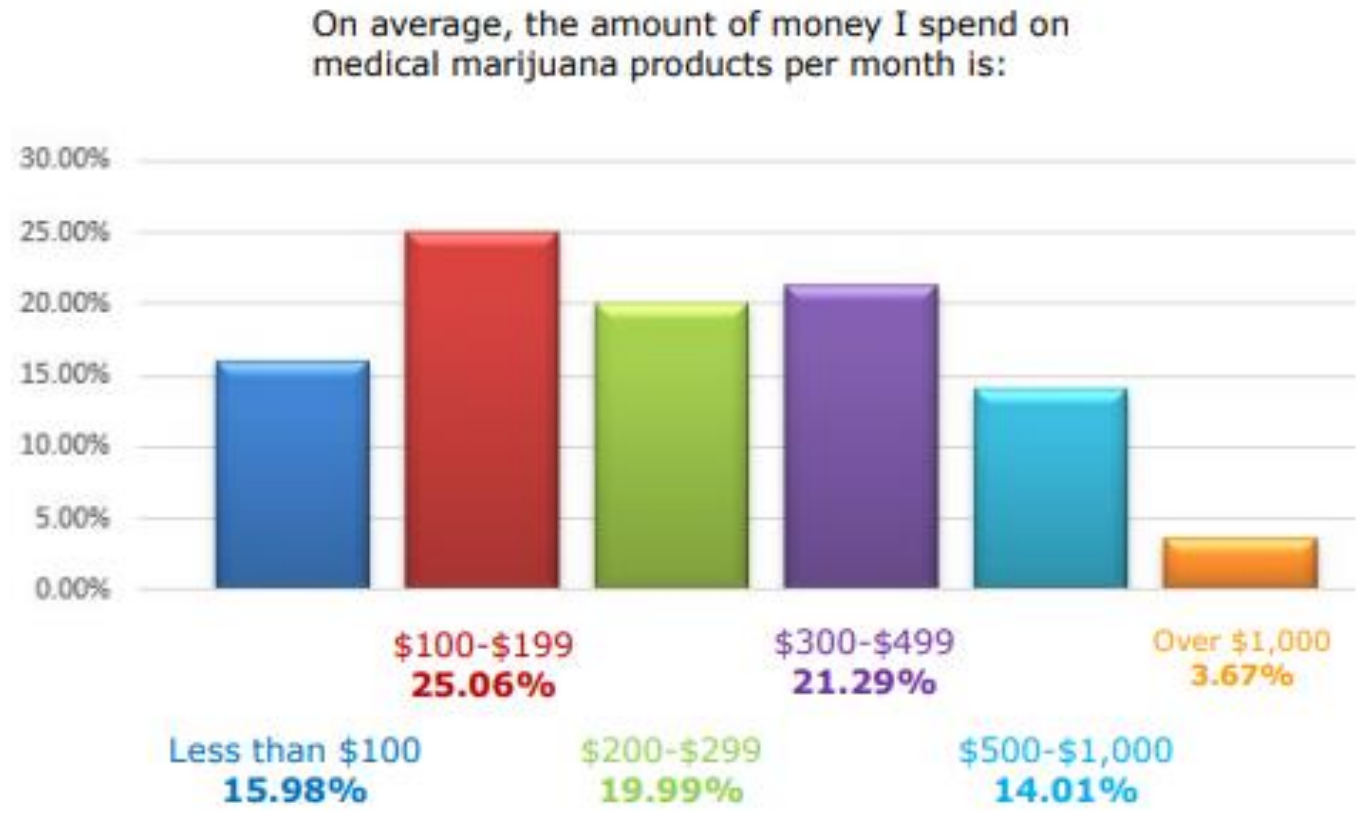
Medical Marijuana Program Update

Patient Purchasing Trends by Product Category



Program Feedback Survey



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- Dry Leaf (~ 50%)
- Vaporization Cartridges (~ 22%)
- Concentrates (~ 15%)
- RSO Syringes (~7.5 %)
- Tinctures (5 %)
- Capsules (< 5%)
- Topicals (< 5%)

Publically Presented at MMAB Meeting in Feb 2020

Knowledge Assessment

Which of the following statements about the endocannabinoid system is true?

a) Endocannabiniods are synthesized from amino acids

b) Endocannabinoid receptors are the most concentrated g-protein coupled receptor in the brain

c) Endogenous endocannabinoids have relatively long half lives

d) Cannabinoids only mediate their activity through endocannabinoid receptors

Knowledge Assessment

Which of the following statements a taking cannabis orally is false:

a) The liver metabolizes THC into 11-Hydroxy-THC, (11-OH-THC), which has a longer T1/2and is a more potent analgesic activity
b) Higher blood levels and longer duration of clinical effects following oral administration compared to inhaled
c) **Oral administration has a predictable and immediate onset of action**

Knowledge Assessment

Which of the following statements about the endocannabinoid system is true?

a) Endocannabiniods are synthesized from amino acids
b) Endocannabinoid receptors are the most concentrated g-protein coupled receptor in the brain
c) Endogenous endocannabinoids have relatively long half lives
d) Cannabinoids only mediate their activity through endocannabinoid receptors