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Business, Consumer Services and Housing Agency
Department of Consumer Affairs
Gavin Newsom, Governor

To: Board Members

Subject: Agenda Item III. Presentation by Dr. Jill Simonian, "Cannabis Therapeutics – High Time for Pharmacy Education"

Background

As part of the January 2020 Board Meeting, members received public comment from Dr. Simonian, requesting the opportunity to provide the Board a presentation on *cannabis*.

During the meeting, Dr. Simonian will provide members with a presentation that will include an overview of *cannabis*, information on the pharmacology of THC and CBD, information on drug interactions, adverse effects, current laws and regulations, and other topics.

Following this memo is a copy of the presentation.

CANNABIS THERAPEUTICS – HIGH TIME FOR PHARMACY EDUCATION

CALIFORNIA STATE BOARD OF PHARMACY

DECEMBER 3, 2020

Jill Simonian, PharmD
Affiliate Faculty Instructor
Skaggs School Pharmacy and Pharmaceutical Sciences
University of California, San Diego
jsimonian@health.ucsd.edu

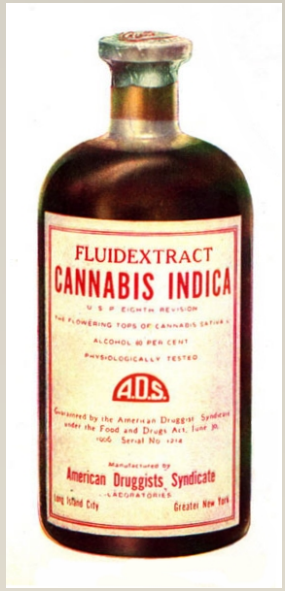
PRESENTATION OVERVIEW

- History and botany of cannabis
- Endocannabinoid system
- Pharmacology and pharmacokinetics of cannabis
- Therapeutic uses
- Public safety
- Current legislation and regulations
- Implications for pharmacist education and involvement

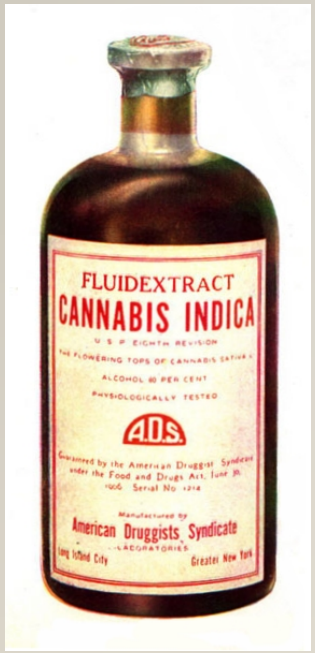
HISTORY AND BOTANY OF CANNABIS

CANNABIS HISTORY

- Indigenous to Central and South Asia
- Used medicinally and for hemp fiber for millennia
- Most well-known compounds
  - △9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
- THC and CBD first isolated in 1960s
- Cannabinoid receptors isolated in 1990s
- Endocannabinoids discovered in later 1990s

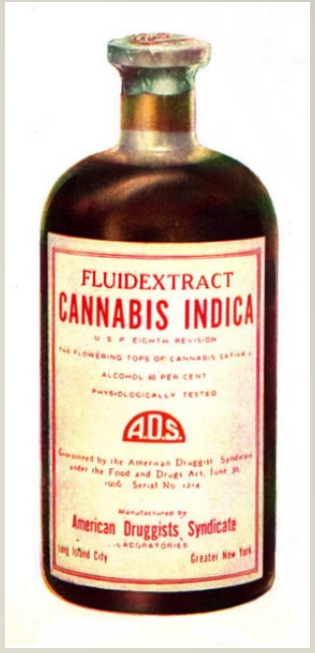


CANNABIS MEDICINE TIMELINE



POLITICS
GREED
MONEY
POWER
RACISM

RESEARCH
SCIENCE
HEALING
MONEY



FOREVER-AGO

1900s

2000s

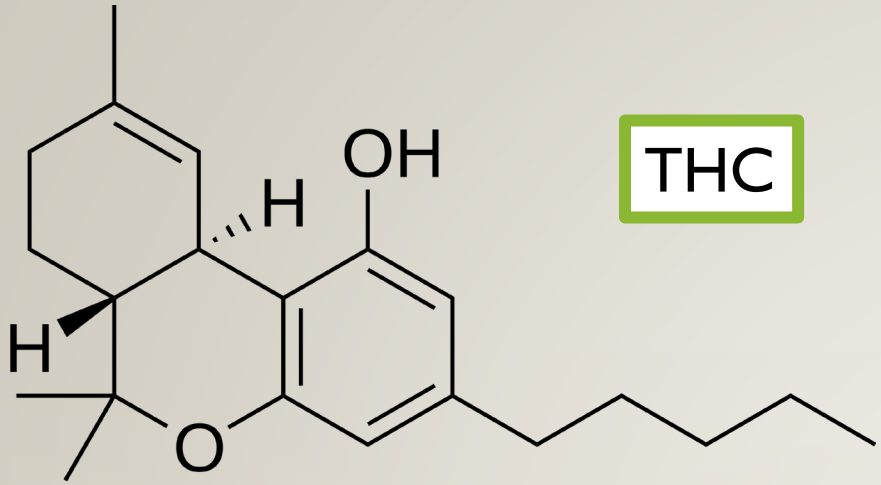
CANNABINOIDS

Molecules that directly or indirectly interact with cannabinoid receptors and modulate neurotransmitter signaling.

<u>Two types:</u>

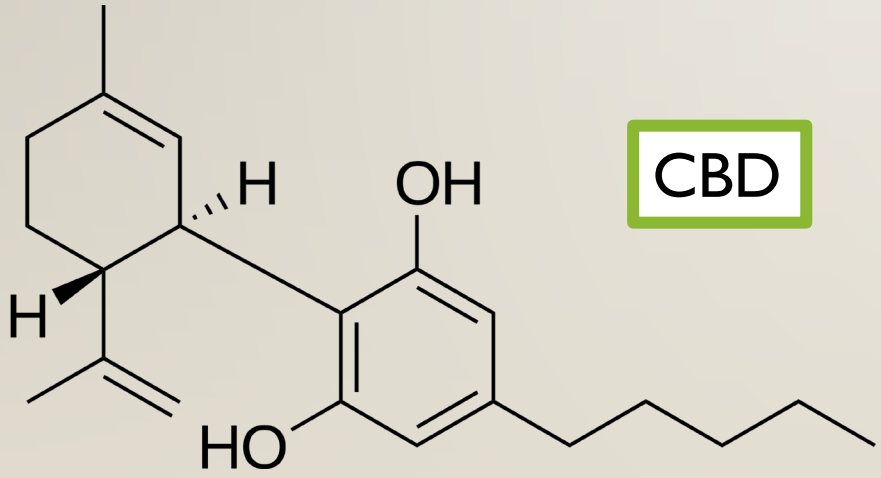
PHYTO – Produced by a plant
ENDO – Produced by the body

Phytocannabinoids



THC

- Naturally occurring
- Biologically active
- Chemical constituents of the cannabis plant

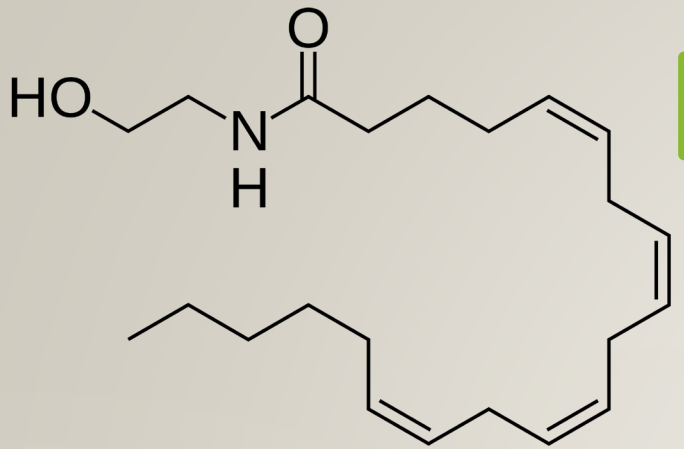


CBD

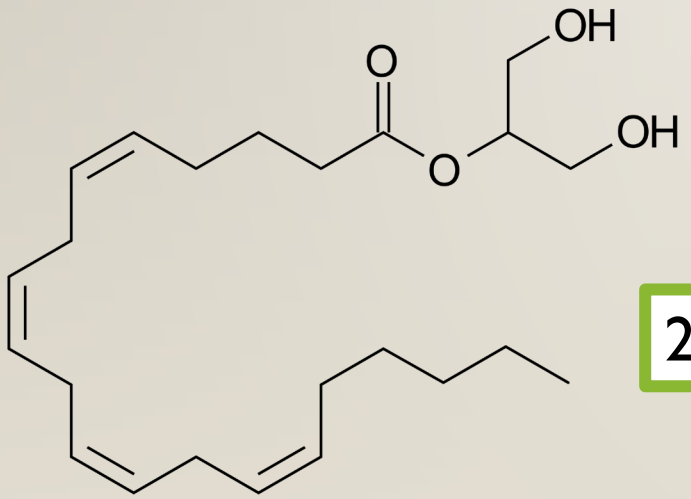
- 122 cannabinoids identified
- Most well known
  - THC
  - CBD
- Lesser known
  - CBC, CBG, CBN, THCV, CBDV

WHERE ARE PHYTOCANNABINOIDS FOUND?

- Cannabis sativa L.
- Trichomes of flowers/leaves of unfertilized female plant
  - Cannabinoids
  - Terpenoids/Flavonoids



AEA



2-AG

Endocannabinoids

- Produced in the body
- Long chain fatty acid lipids
- Retrograde neurotransmitters

- Most well known
  - Anandamide (AEA)
  - 2-AG

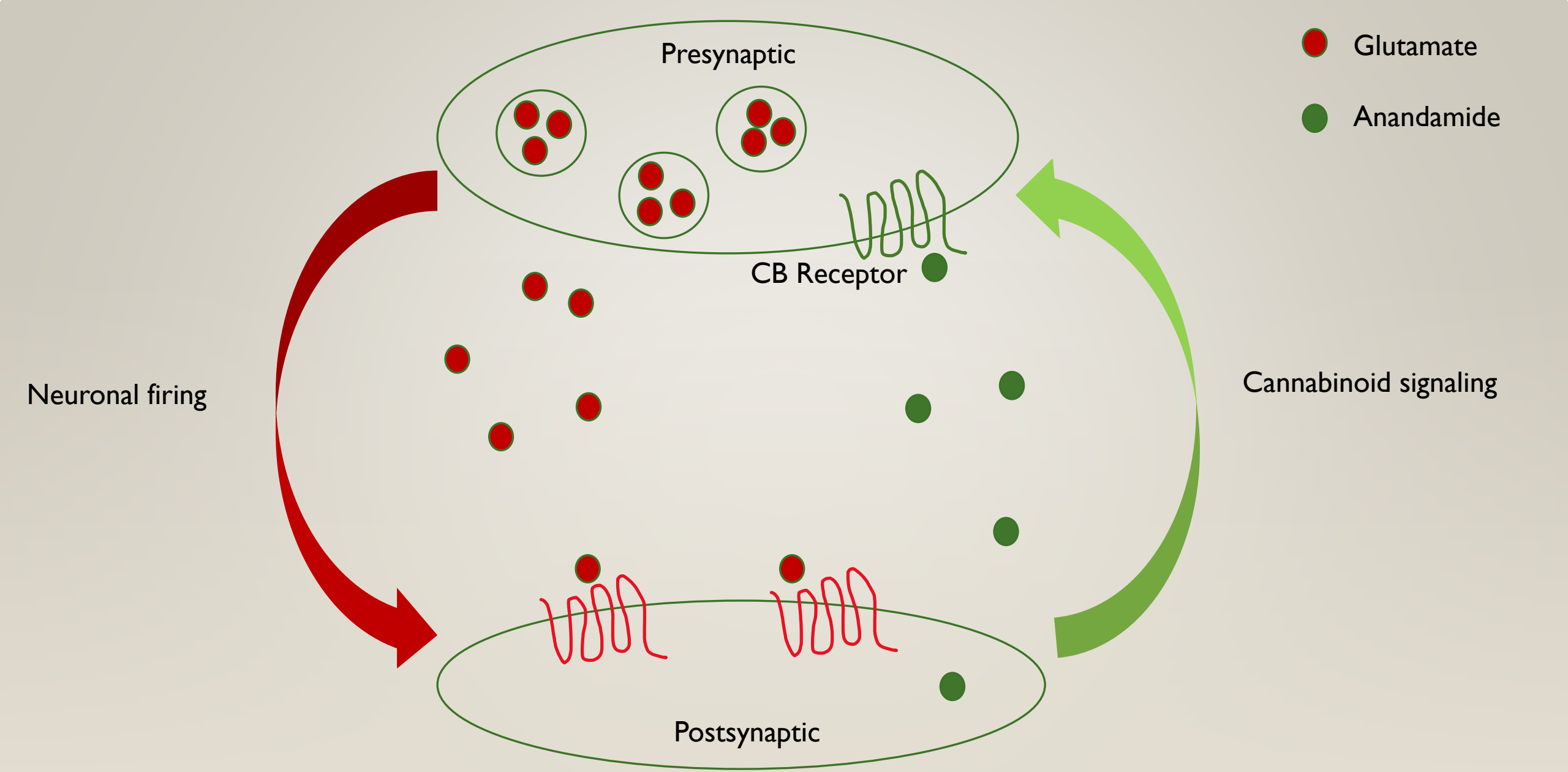
ENDOCANNABINOID SYSTEM (ECS)

ENDOGENOUS CANNABINOID SYSTEM (ECS)

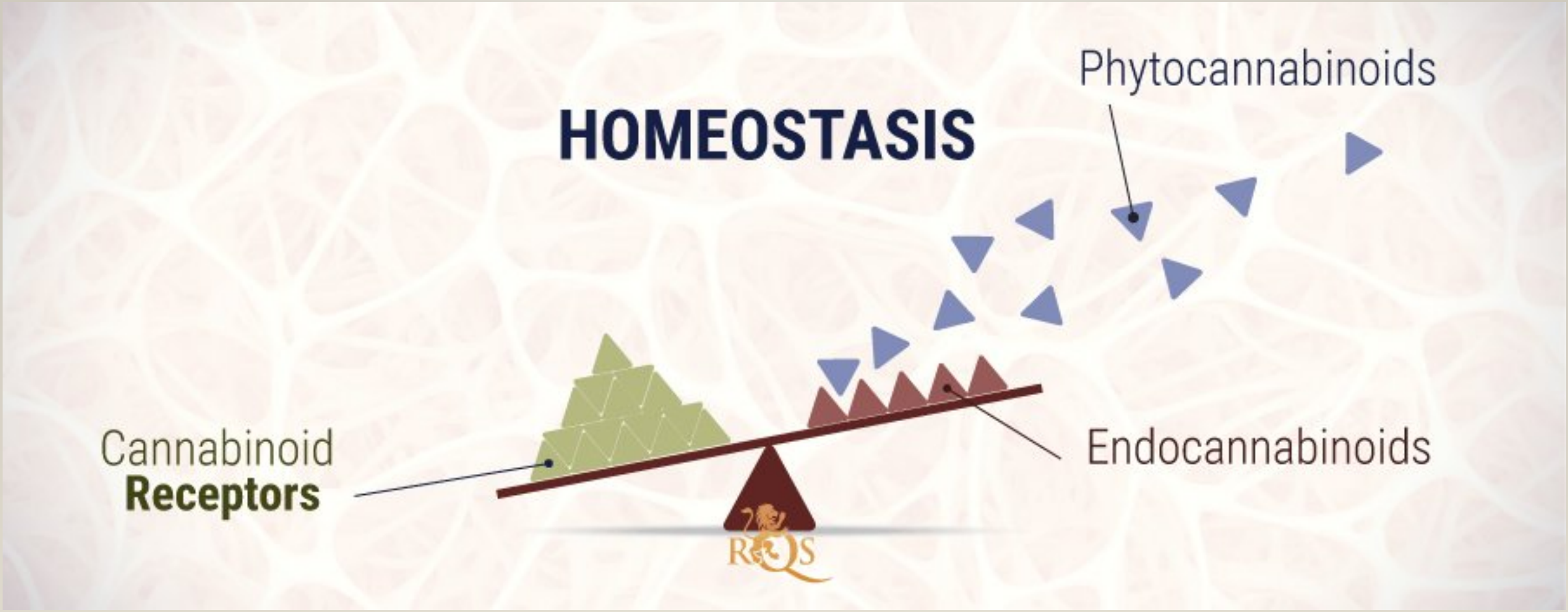
- Major components
  - Receptors – CB1 & CB2
  - Endocannabinoids – AEA & 2-AG
  - Enzymes – FAAH & MAGL

- ECS activity is an adaptive response to stress
- Maintains homeostasis
- Eat, Sleep, Relax, Forget, Protect

Di Marzo 2015


Glutamate
Anandamide
Presynaptic
CB Receptor
Neuronal firing
Cannabinoid signaling
Postsynaptic

CANNABIS PHARMACOLOGY


HOMEOSTASIS
Phytocannabinoids
Cannabinoid
Receptors
Endocannabinoids

CANNABIS PHARMACOLOGY

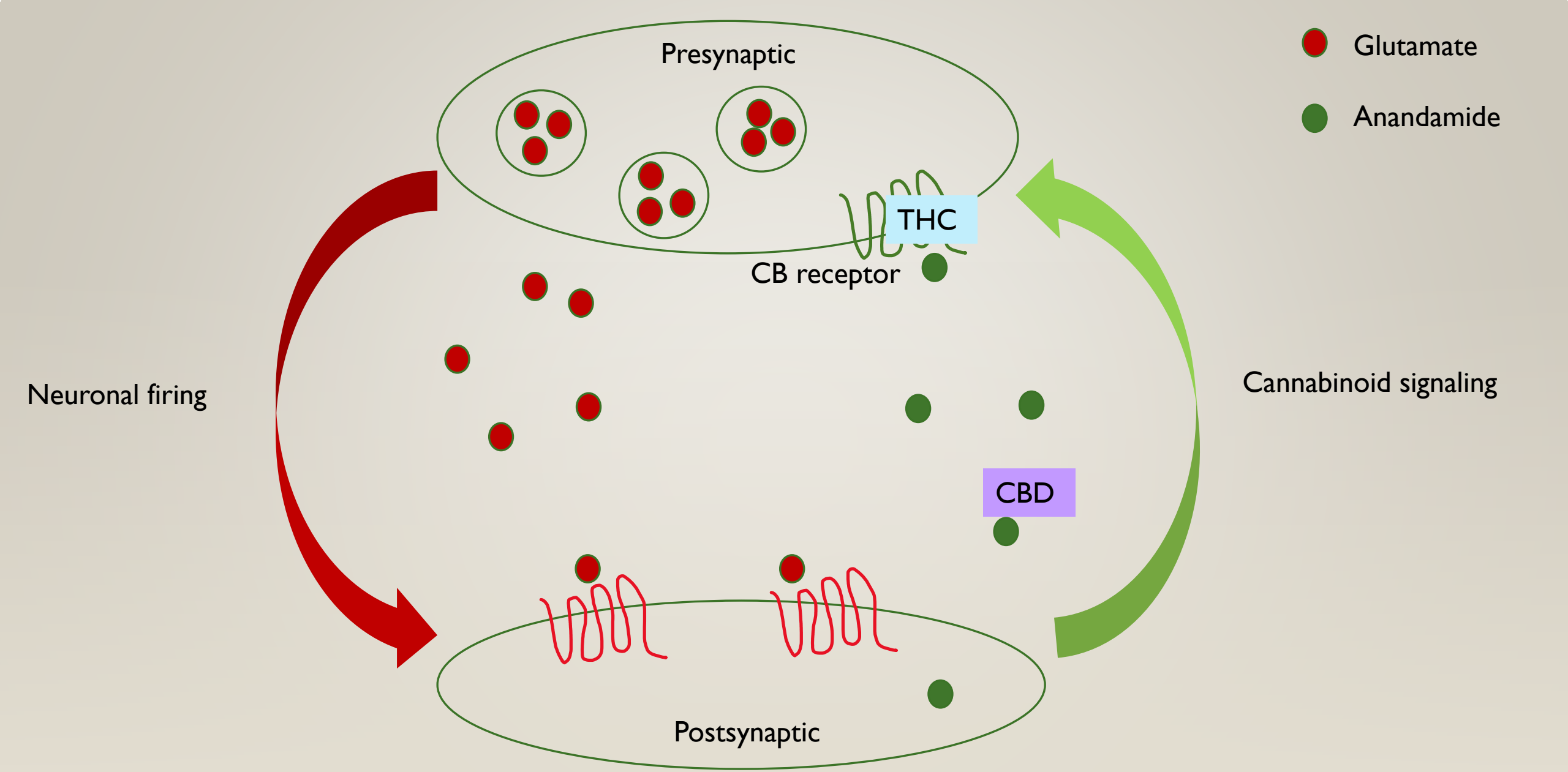
THC

- Intoxicating
- CB1 & CB2 partial agonist

CBD

- Non-intoxicating
- Does not bind to CB1 or CB2
- Increases AEA concentration
- TRPV1, 5HT1A, GPR55

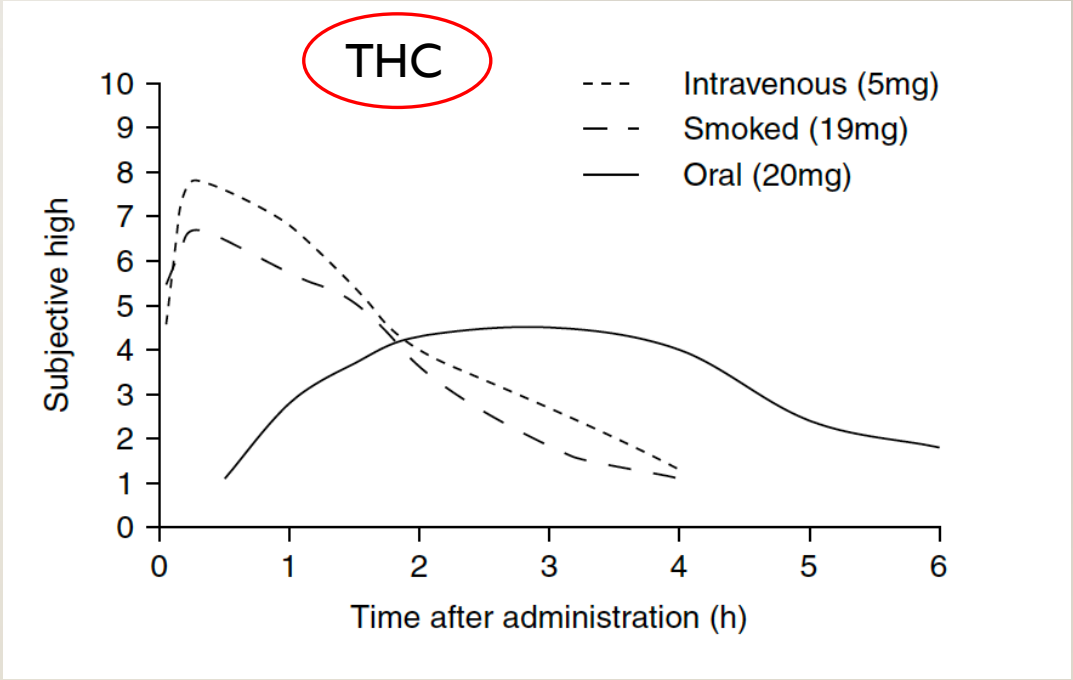
Pertwee 2008; Elmes 2015; Bisogno 2001; Russo 2005


Glutamate
Anandamide
Presynaptic
THC
CB receptor
Neuronal firing
Cannabinoid signaling
CBD
Postsynaptic

CANNABIS PHARMACOKINETICS

GENERAL THC AND CBD PROPERTIES

- Absorption:
  - Inhaled – 5-10 minutes
  - Oral/Sublingual – 1-4 hours
  - Topical – Not systemically absorbed
- Duration of Action:
  - Inhaled – 2-4 hrs
  - Oral/Sublingual – 4-12 hours
- Distribution:
  - Widely distributed into tissues
  - Lipophilic
  - Very long half-life



Huestis 2007; Stott 2013; Grotenhermen 2003

GENERAL THC AND CBD PROPERTIES

- Metabolism
  - Cytochrome P450 (CYP) enzymes
- Extensive gut and liver metabolism
- Oral/Sublingual Formulations
  - Higher liver/gut metabolism
  - Reduced bioavailability
  - Food effects
  - Active THC metabolite
- Potential drug interactions

Huestis 2007; Stott 2013; Grotenhermen 2003

POTENTIAL DRUG INTERACTIONS

- **Considerations**
  - Drugs that utilize CYP P450
    - 3A4, 2C9 and 2C19
  - CYP gene polymorphisms
  - Doses used
  - Liver function

- Examples:
  - Anticonvulsants
  - SSRIs
  - Anticoagulants
  - Macrolide Antibiotics
  - Benzodiazepines

**very few documented

DOCUMENTED DRUG INTERACTIONS

AS CYP INHIBITORS

CBD increases clobazam levels

CBD increases nor-clobazam levels

CBD increases stiripentol levels

CBD increases warfarin (INR)

THC increases warfarin (INR)

AS CYP SUBSTRATES

Ketoconazole increases THC & CBD levels

Rifampin decreases THC & CBD levels

Stott 2013; Geffrey 2015; Hsu 2019; Gregor 2020; Grayson 2017

PHARMACODYNAMIC DRUG INTERACTIONS

- **Liver Toxicity**
  - Concomitant drugs
  - Doses used
  - Liver function

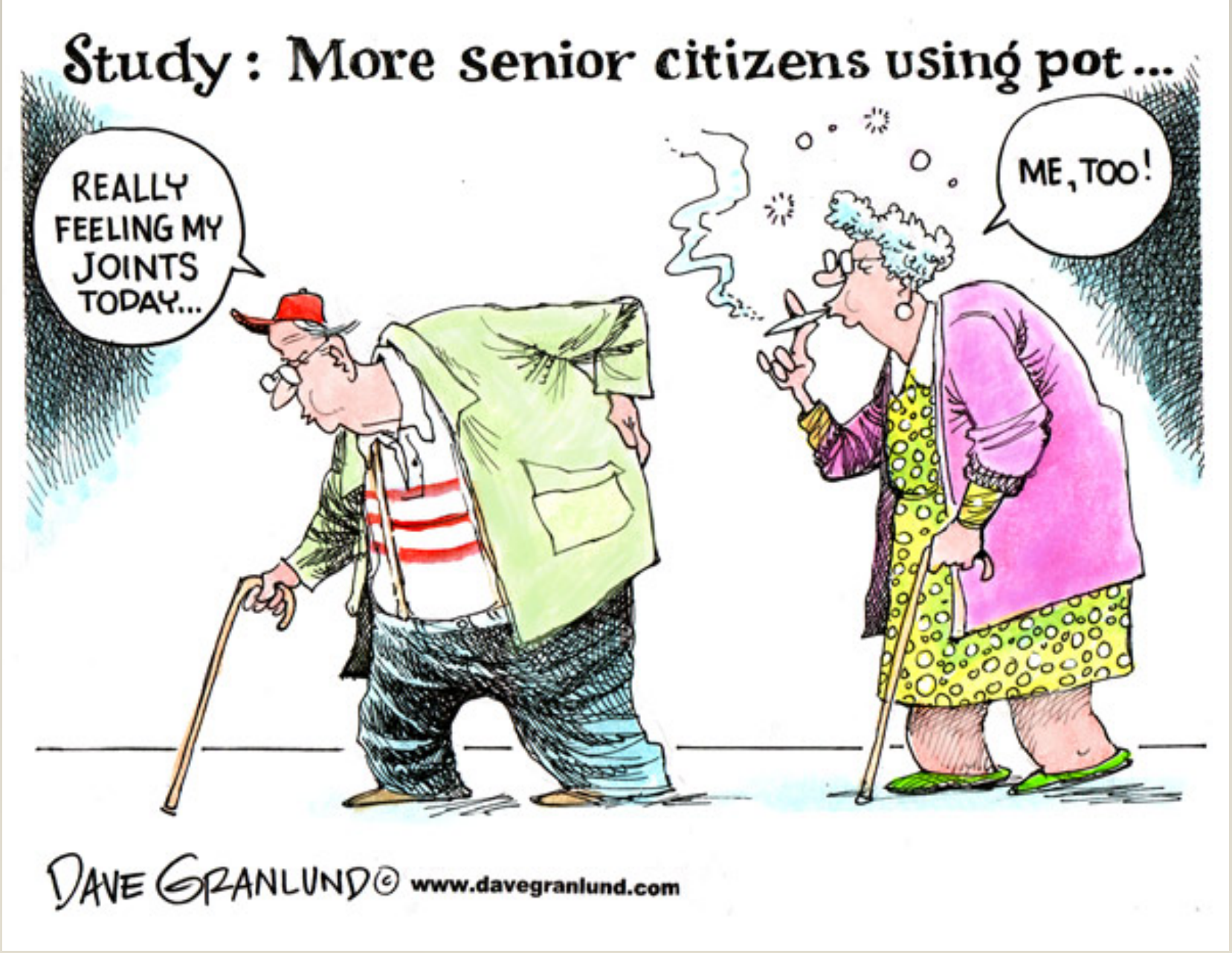
- CBD + valproate *may* increase LFTs

- **Compounded CNS Effects**
  - Concomitant sedative drugs

- THC in combination with:
  - Opioids
  - Alcohol
  - Benzodiazepines
  - Gabapentin

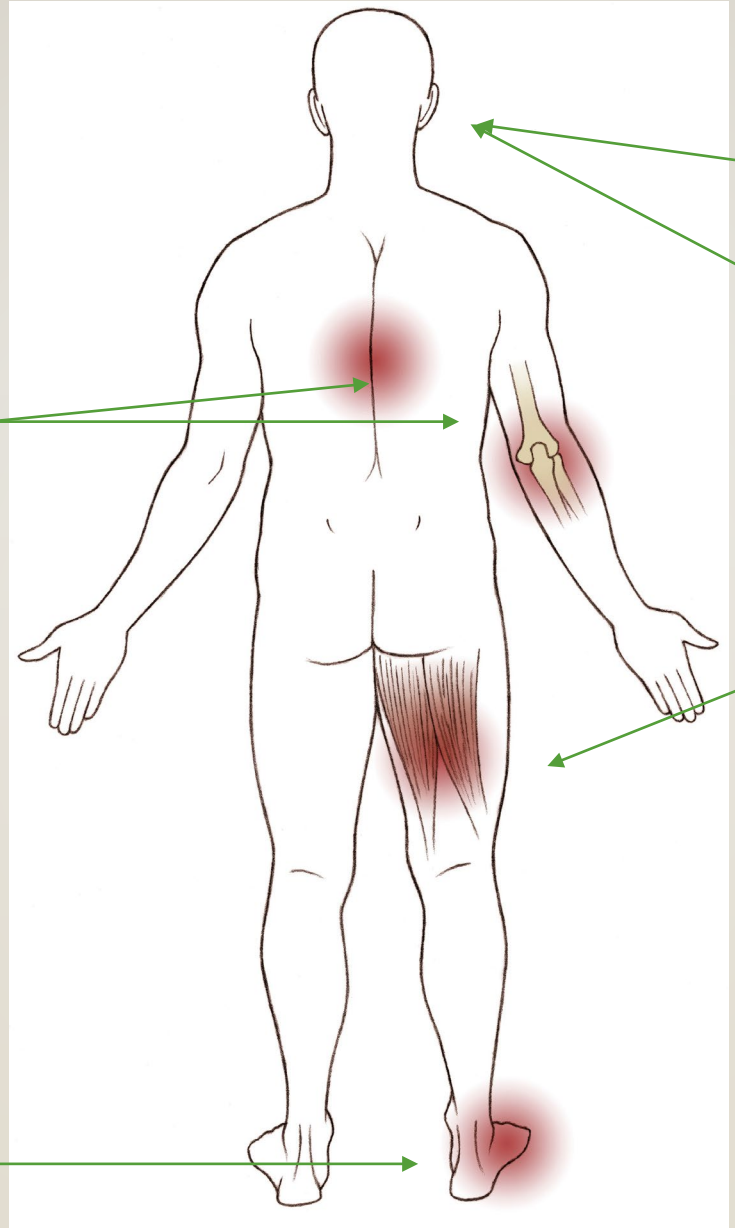
Stott 2013; Taylor CNS Drugs 2018

THERAPEUTIC USES OF CANNABIS


Study : More senior citizens using pot ...
REALLY FEELING MY JOINTS TODAY...
ME, TOO!
DAVE GRANLUND©
www.davegranlund.com

PAIN

- Chronic musculoskeletal pain
- Cancer pain
- Osteoarthritis
- Inflammation
- Neuropathic pain

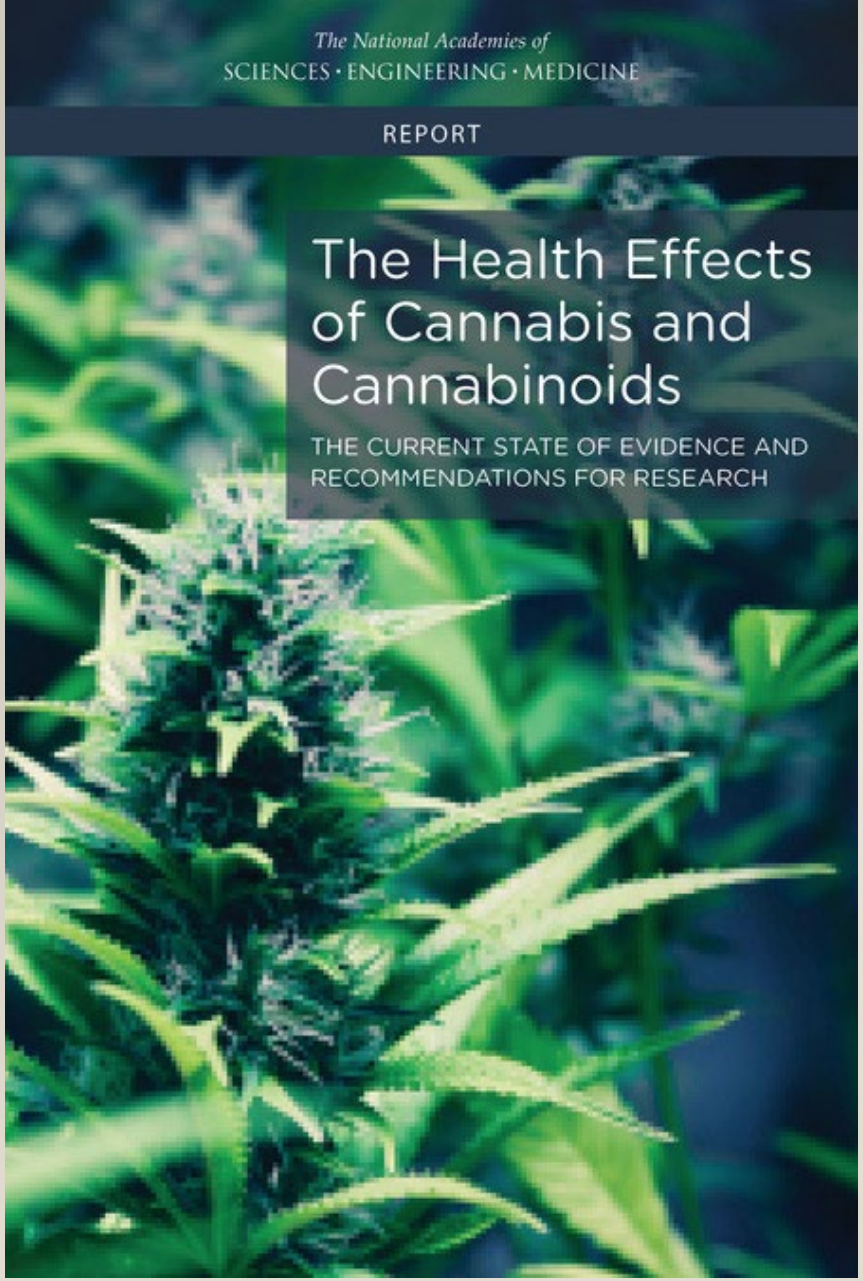


ANXIETY

SLEEP

SPASTICITY (MS)

OPIOID – SPARING ?



National Academies of Sciences, Engineering, and Medicine (NASEM)

Health and Medicine Division

2017 Report, 440 pages

NASEM 2017

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea, fibromyalgia, chronic pain, and MS (cannabinoids, nabiximols)

The National Academies of Sciences, Engineering and Medicine 2017

PUBLIC SAFETY

PUBLIC SAFETY CONSIDERATIONS

- Dosing/Therapeutics
- Potential Drug Interactions
- Adverse Drug Reactions
- Lack of Product Standardization

ADVERSE DRUG REACTIONS

- **THC**
  - Cognition, sedation, dizziness, headache, cough, impaired driving
  - Tachycardia, orthostatic hypotension (rare)
  - Acute psychosis (high doses)
- **CBD**
  - Diarrhea, sedation at high doses
  - Liver toxicity? (not likely)

NO FATAL DOSE

CDC REPORT ON DRUG RELATED RISKS

TABLE 2B

Self-reported prevalence of illicit drug use[a] and prescription drug misuse[b] in the past year, persons 12+ years old, numbers in thousands — United States, 2016

CONTINUED

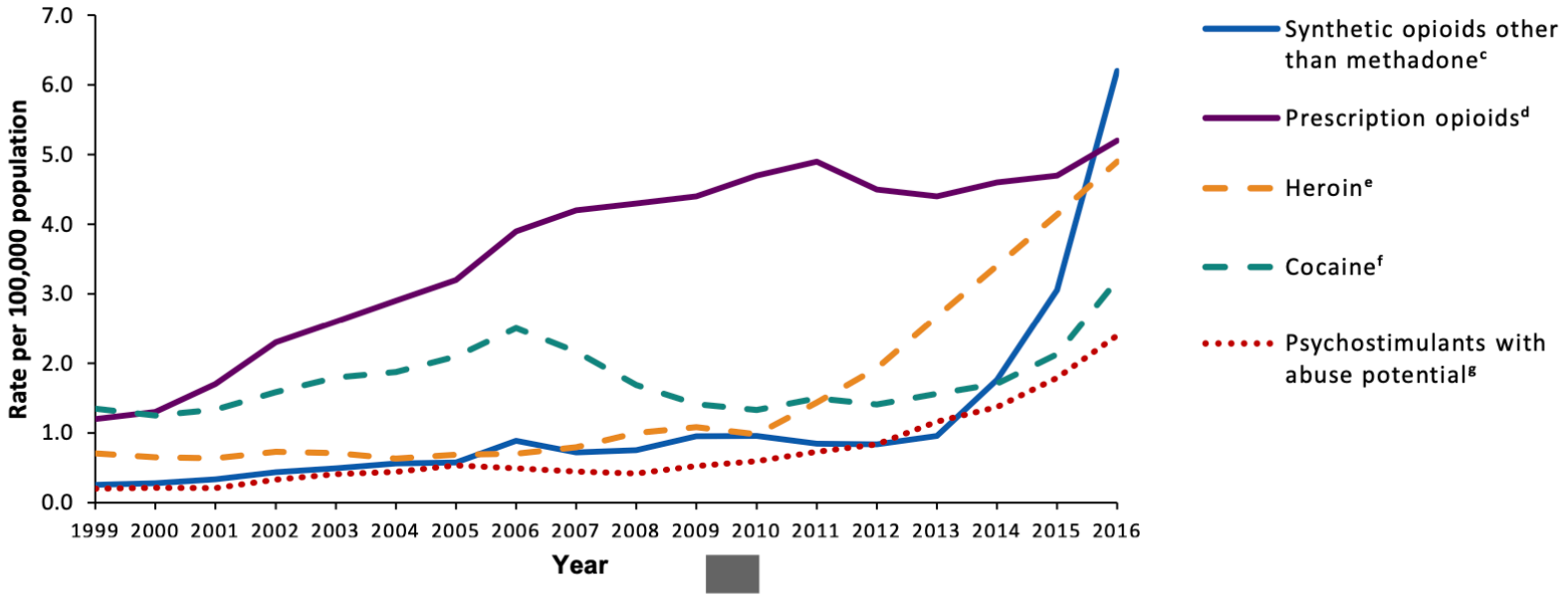
Socio-demographic characteristic	Marijuana			Heroin			Opioids[e] (heroin or prescription pain relievers)			Cocaine			Methamphetamine		
	Number	%	SE	Number	%	SE	Number	%	SE	Number	%	SE	Number	%	SE
All	37,570	13.9	0.2	948	0.4	0.03	11,824	4.4	0.11	5,071	1.9	0.07	1,391	0.5	0.04
Gender															
Male	21,839	16.7	0.30	596	0.5	0.05	6,420	4.9	0.16	3,238	2.5	0.11	782	0.6	0.06
Female	15,731	11.3	0.24	352	0.3	0.03	5,403	3.9	0.14	1,833	1.3	0.08	609	0.4	0.04

Center for Disease Control and Prevention 2018

CDC REPORT ON DRUG RELATED RISKS

FIGURE 2B

Age-adjusted rates[a] of drug overdose deaths[b] by drug or drug class and year — United States, 1999–2016



Center for Disease Control and Prevention 2018

CDC FAQ ON MARIJUANA AND PUBLIC HEALTH

A fatal overdose is unlikely, but that doesn't mean marijuana is harmless. The signs of using too much marijuana are similar to the typical effects of using marijuana but more severe. These signs may include extreme confusion, anxiety, paranoia, panic, fast heart rate, delusions or hallucinations, increased blood pressure, and severe nausea or vomiting. In some cases, these reactions can lead to unintentional injury such as a motor vehicle crash, fall, or poisoning.

Center for Disease Control and Prevention 2018

Fatal dose of Heroin and Fentanyl

Fatal dose of Marijuana

PRODUCT STANDARDIZATION ISSUES

Schedule III
Synthetic THC

Schedule II
Synthetic THC

Schedule II
Synthetic THC analogue
Off-Market

Descheduled
Whole Plant CBD

Not FDA approved – available in UK etc
Whole Plant THC:CBD

WHOLE PLANT

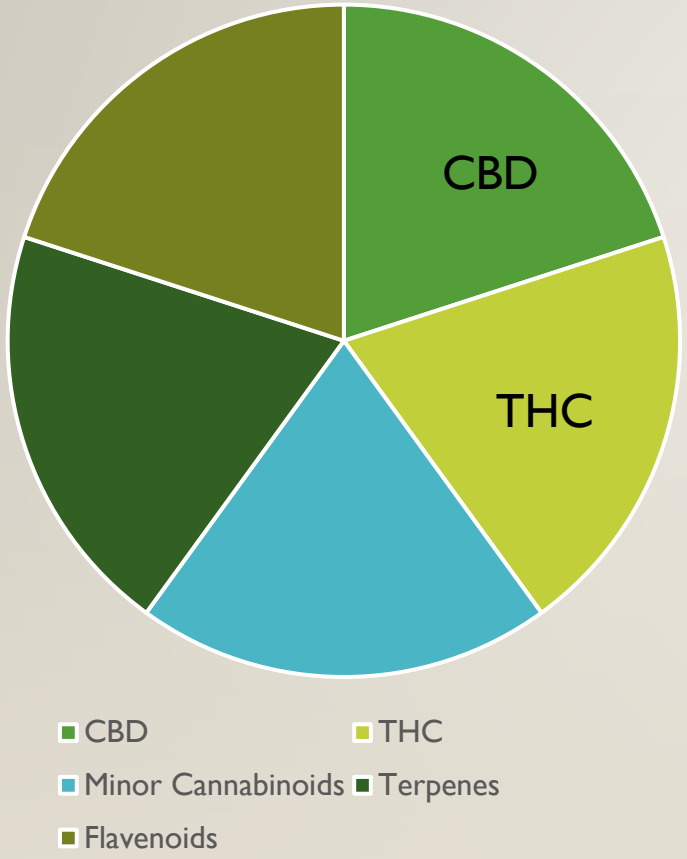
VS

ISOLATE

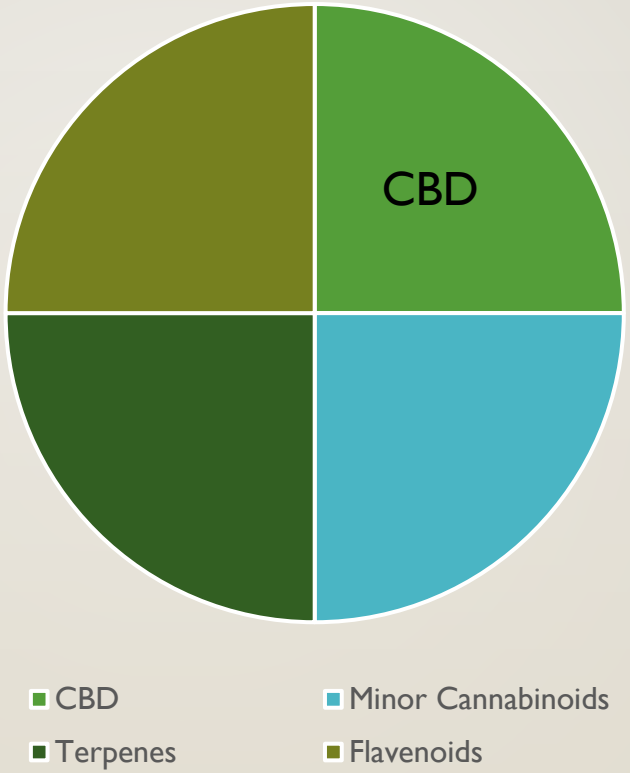
???

CBD PRODUCT COMPOSITION

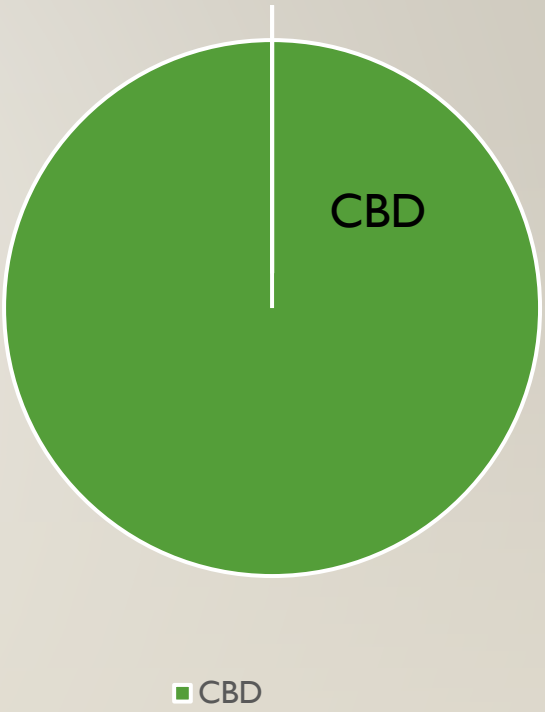
Full Spectrum



Broad Spectrum



Isolate

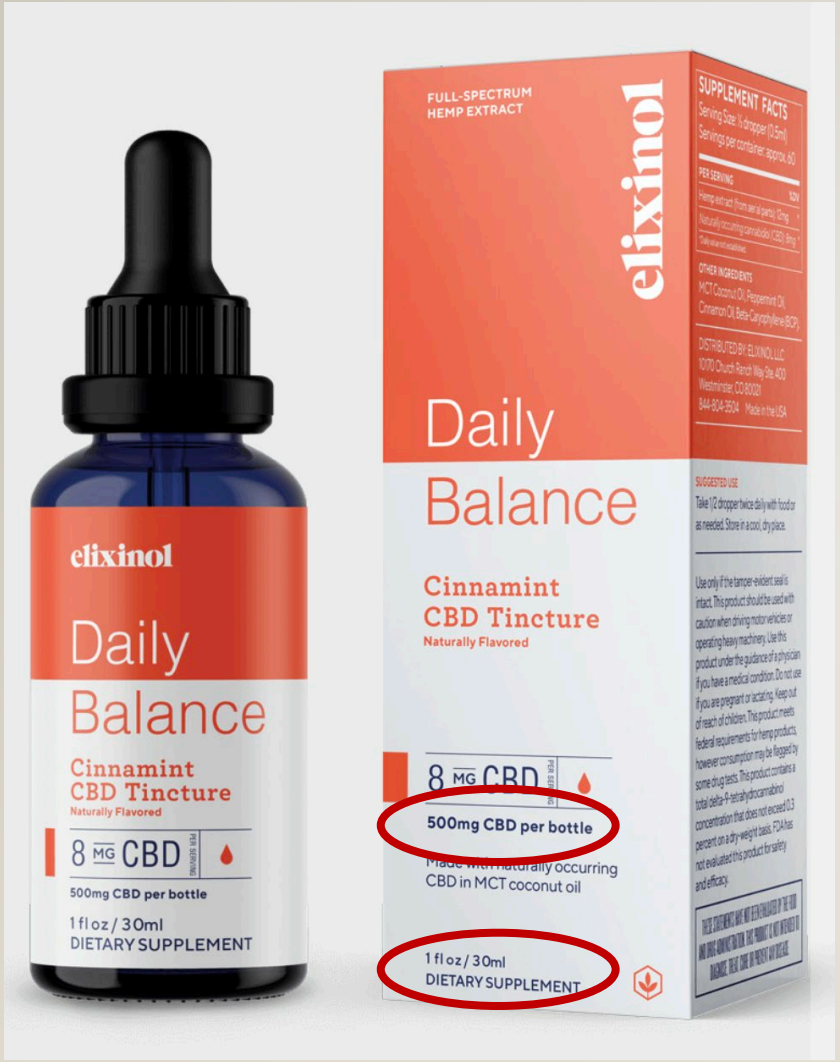


2020 CBD Product Sampling and Testing by FDA

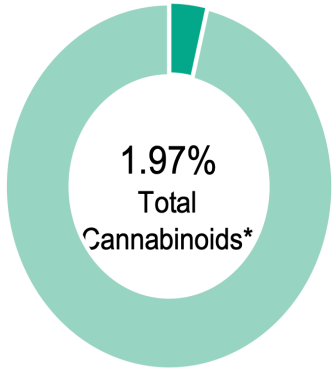
	PRODUCTS (tincture, oil, gummy, edible, beverage, pet)	
Products Tested	147	
CBD Amount Indicated on Label	102	(48%)
+/- 20% of CBD as Labeled	46/102	(45%)
<80% of CBD as Labeled	18/102	(17%)
>120% of CBD as Labeled	38/102	(37%)
Contained THC	72/147	(49%)
Heavy Metals Detected	0	

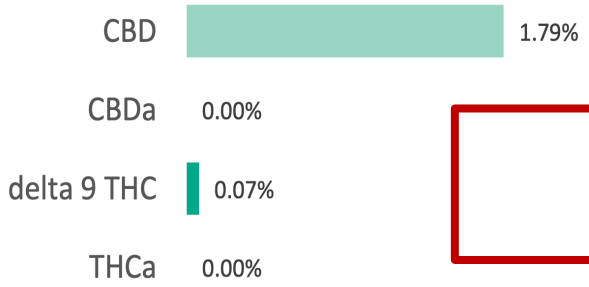
Report to the US House Committee on Appropriations and the US Senate Committee on Appropriations; US FDA 2020

30ml bottle



CANNABINOID PROFILE





Compound	LOQ (%)	Result (%)	Result (mg/g)
Delta 9-Tetrahydrocannabinolic acid (THCA-A)	0.06	ND	ND
Delta 9-Tetrahydrocannabinol (Delta 9THC)	0.03	0.07	0.7
Cannabidiolic acid (CBDA)	0.05	ND	ND
Cannabidiol (CBD)	0.03	1.79	17.9
Delta 8-Tetrahydrocannabinol (Delta 8THC)	0.03	ND	ND
Cannabinolic Acid (CBNA)	0.09	ND	ND
Cannabinol (CBN)	0.04	ND	ND
Cannabigerolic acid (CBGA)	0.06	ND	ND
Cannabigerol (CBG)	0.03	0.04	0.4
Tetrahydrocannabivarinic Acid (THCVA)	0.05	ND	ND
Tetrahydrocannabivarin (THCV)	0.03	ND	ND
Cannabidivarinic Acid (CBDVA)	0.05	ND	ND
Cannabidivarin (CBDV)	0.03	ND	ND
Cannabichromenic Acid (CBCA)	0.05	ND	ND
Cannabichromene (CBC)	0.06	0.07	0.7
Total Cannabinoids		**1.97**	**19.70**
Total Potential THC**		0.07	0.70
Total Potential CBD**		1.79	17.90

$40 = 8 cents/mg CBD

CBD = 537 mg
THC = 21 mg

30ml bottle

$40 =
4 cents/mg

$50 =
5 cents/mg

Locate a batch report by entering your product's batch number below. A Hyperlinked URL will appear.Click on the picture to view hyperlink, download, or print your Batch Report. Labs we use are ISO 17025:2017 and AOAC accreditation
Please Include The Dashes.

Search here... FIND CERTIFICATE

?? CBD & THC

15ml bottle

Content:	
CBD	29.6 mg/serving
CBC	1.56 mg/serving
CBG	1.07 mg/serving
THC	0.97 mg/serving
CBDV	0.47 mg/serving
Total CBD	29.72 mg/serving
0.3% THC Compliant	✓
Total THC	0.97 mg/serving

CBD = 450mg
THC = 15mg

$34 = 3 cents/mg

Dispensary

CBD = 900mg
THC = 30mg
$94 = 10 cents/mg

HEMP PRODUCTION & THE 2018 FARM BILL

FARM BILL 2018, SEC. 297A.

The 2018 Farm Bill removed hemp from Schedule I of the Federal Controlled Substances Act. Thus, hemp is no longer federally regulated as a controlled substance.

Federal Register 10/2019

FARM BILL 2018, SEC. 297A.

(1) HEMP.—The term 'hemp' means 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 percent on a dry weight basis.

Federal Register 10/2019

FDA REGULATIONS ON CANNABIS-DERIVED COMPOUNDS

What the law *didn't* change:

Congress explicitly preserved the FDA's current authority to regulate products containing cannabis or cannabis-derived compounds under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and section 351 of the Public Health Service Act.

FDA Statement 12/2018

FDA REGULATIONS ON FOOD PRODUCTS/DIETARY SUPPLEMENTS

It is unlawful under the FD&C Act to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived.

FDA Statement 12/2018

MARIJUANA V. HEMP

CANNABIS BRED FOR HEMP

- C. sativa L.
- < 0.3% THC
- Hemp Seed (Oil)
- Hemp Stalks (Fiber/Materials)

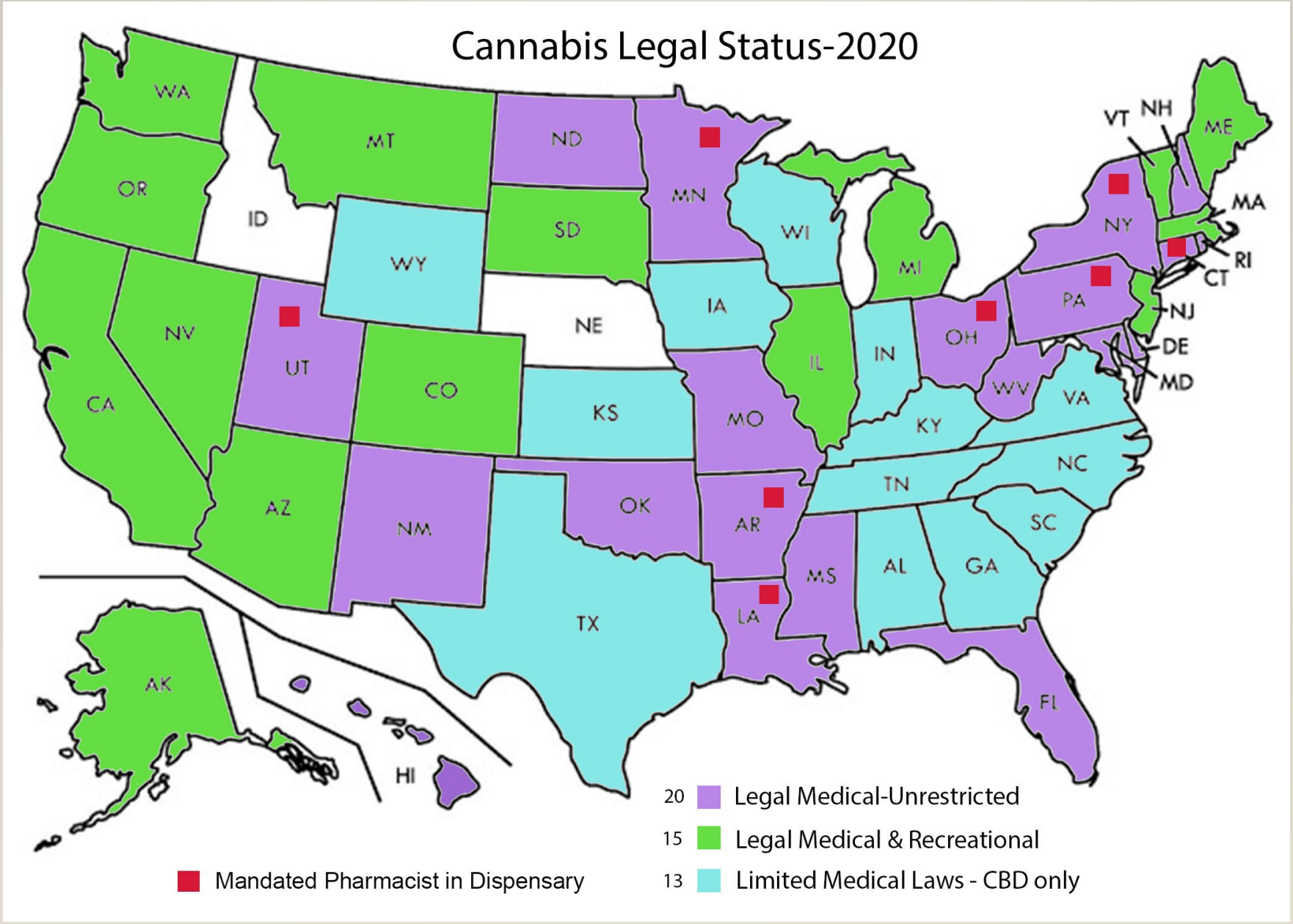
Low THC:CBD

CANNABIS BRED FOR DRUG

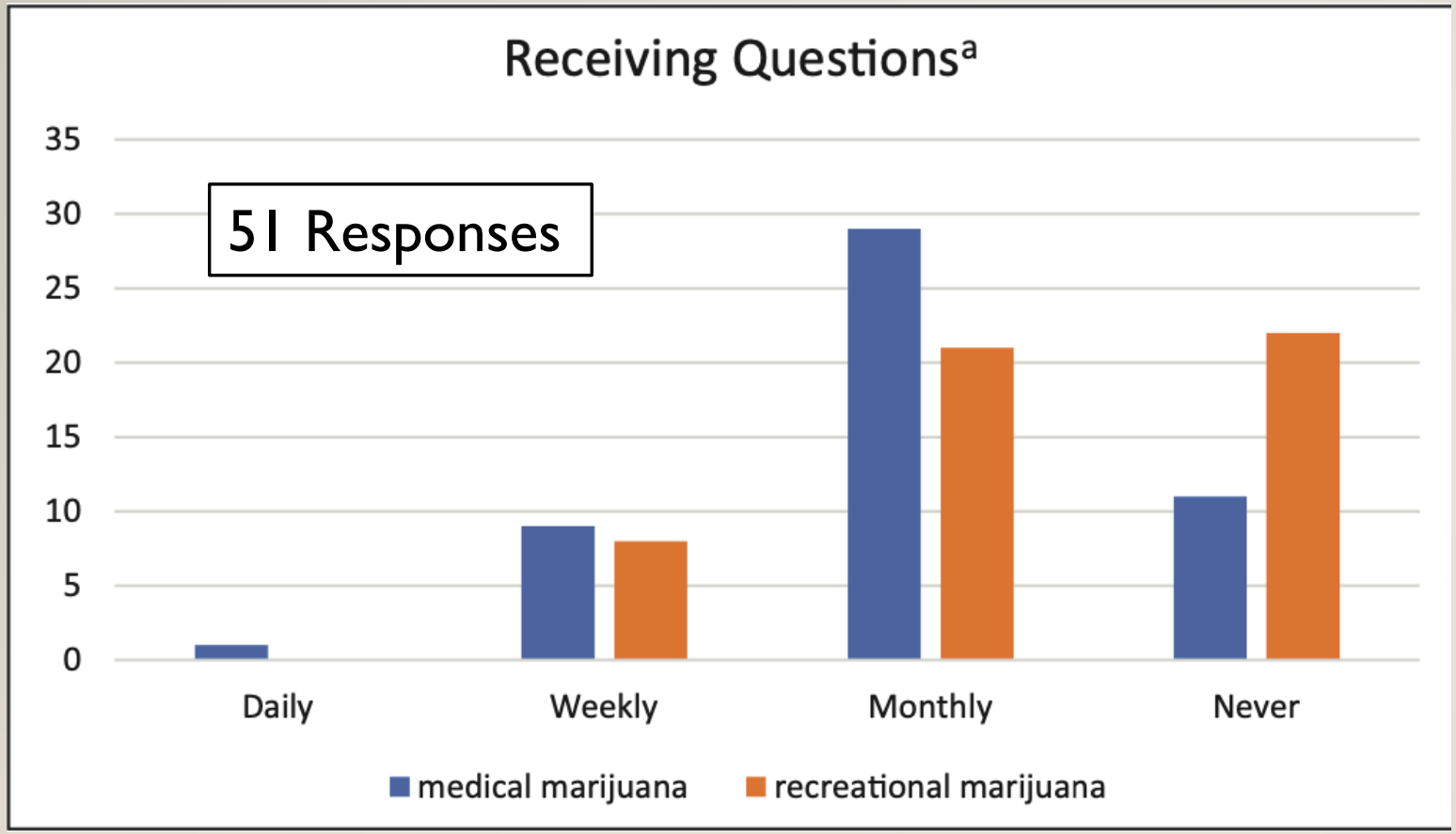
- C. sativa L.
- 5-30% THC
- Medical and Recreational Uses

High THC:CBD

CANNABIS EDUCATION


Cannabis Legal Status-2020
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
VT
NH
ME
MA
RI
CT
NJ
DE
MD
AK
HI
20 Legal Medical-Unrestricted
15 Legal Medical & Recreational
13 Limited Medical Laws - CBD only
Mandated Pharmacist in Dispensary

Colorado Community Pharmacists' Survey 2018



[a]How often do you receive questions about medical/recreational marijuana?

53% - not comfortable answering questions:

- Indications
- Efficacy
- Drug Interactions
- Where to buy
- Detected in body

California Pharmacists Association Survey on Cannabis Knowledge and Attitudes – October 2017

Total: 474 surveys completed

Knowledge, n (%)	No Knowledge	Very Little Knowledge	Some Knowledge	Moderate Knowledge	Substantial Knowledge	High Level of Knowledge	Professional Level of knowledge	P
How much knowledge do you have about medical marijuana?	18 (5.64)	104 (32.60)	80 (25.08)	59 (18.50)	25 (7.84)	18 (5.64)	15 (4.70)	.000
How much knowledge do you have about the risks and side-effects of marijuana?	13 (4.06)	60 (18.75)	89 (27.81)	82 (25.62)	34 (10.63)	27 (8.77)	15 (4.69)	.000
How much knowledge do you have about marijuana dosage?	106 (33.44)	114 (35.96)	41 (12.93)	26 (8.20)	12 (3.79)	8 (2.52)	10 (3.15)	.000
How much knowledge do you have about the different types/forms of marijuana products	48 (52.96)	122 (38.01)	65 (20.25)	37 (11.53)	25 (7.79)	12 (3.74)	12 (3.74)	.000

Attitudes, n (%)	Strongly Disagree	Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Agree	Strongly Agree	P
I know where to find info about medical marijuana	24 (7.50)	39 (12.19)	45 (14.06)	37 (11.56)	85 (26.56)	62 (19.38)	28 (8.75)	.00
Medical marijuana has medical efficacy	4 (1.25)	11 (3.43)	7 (2.18)	60 (18.69)	99 (30.84)	100 (31.15)	40 (12.46)	.00
There needs to be more education about marijuana	0 (0.00)	1 (0.33)	5 (1.65)	18 (5.94)	18 (5.94)	90 (29.70)	171 (56.44)	.00
Continuing education credits should be available for marijuana related education	2 (0.67)	0 (0.00)	4 (1.33)	20 (6.67)	22 (7.33)	92 (30.67)	160 (53.33)	.00

Szyliowicz 2019

CANNABIS EDUCATION IN COLLEGES

- UCSD, USC, Rosalind Franklin Univ IL, UW Madison, UM Ann Arbor, Concordia Univ WI
  - Electives or classes offered
- University of Maryland School of Pharmacy
  - Two electives on Medical Cannabis - Pharmacology and Therapeutics (PY3 & 4)
  - MS: Medical Cannabis Science and Therapeutics (2 year)
- Univ of CO Skaggs School of Pharmacy
  - Graduate certificate in Cannabis Science and Medicine (1 year)
  - MS in pharmaceutical sciences: Cannabis Science and Medicine Specialty Track (2 year)

College	State	State Status	Type of Institution	Program Type
Northern Michigan University	Michigan	Full Legalization	Four-Year	Bachelors in Medicinal Plant Chemistry
Southern University	Louisiana	Medical Legalization	Four-Year	Pending Medical Marijuana Program
Stockton University[29]	New Jersey	Medical Legalization	Four-Year	Undergraduate Minor
University of Denver Sturm College of Law	Colorado	Full Legalization	Law	Class (Law) Representing the Marijuana Client Marijuana Regulatory Drafting and Policy
University of California-Davis	California	Full Legalization	Four-Year	Class (Graduate)[30] Cannabis Sativa: The Plant and its Impact on People Class (Undergraduate)[31] Physiology of Cannabis
The Ohio State University Moritz College of Law	Ohio	Medical Legalization	Law	Class (Law) Cannabiz: Exploring the "Legalized Cannabis Industry"
Vanderbilt University[32]	Tennessee		Law	Class (Law) Marijuana Law and Policy
The University of Washington School of Medicine[33]	Washington	Full Legalization	Medicine	Training Medicinal Cannabis and Chronic Pain
Thomas Jefferson University	Pennsylvania	Medical Legalization	Four-Year	Graduate-Level Certification Cannabinoid Pharmacology Cannabis Medicine Cannabinoid Chemistry and Toxicology
The University of Vermont, Larner College of Medicine[34]	Vermont	Full Legalization	Medicine	Class Pharmacology 200: Cannabis Past, Present and Future Online Modules
Southern Illinois University[35]	Illinois	Medical Legalization	Four-Year	In Progress Medicinal Cannabis Science Certification in Medicinal Cannabis Production

RECOMMENDATIONS

- Education
  - California Pharmacy Schools
  - NABP collaboration
- Protection from liability for pharmacists
- Greater access to primary literature in community pharmacies
- Allow patients in hospitals to use personal medical marijuana
- Create task force committee with CPHA and CSHP

Q & A