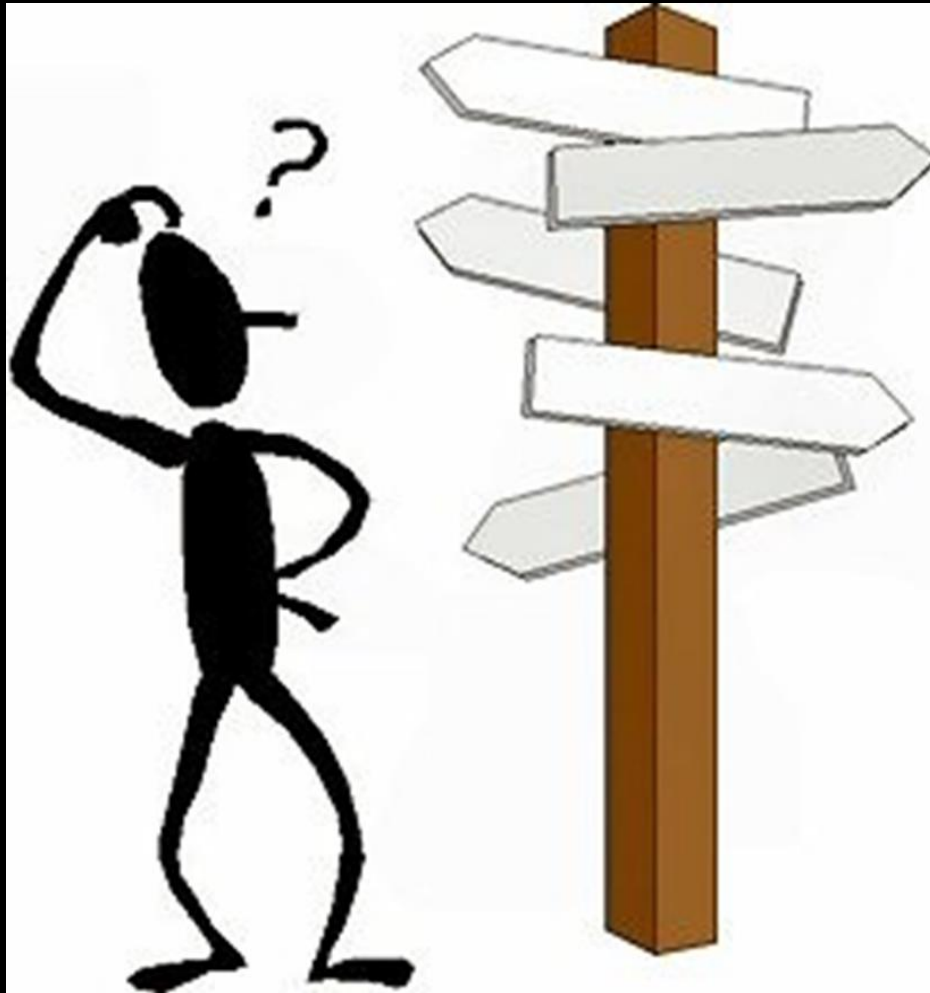


# CANNABIS CONFUSION AND THE HOSPITALIST



- C. Clark Milton, DO, FACOI
- ACOI Clinical Challenges in Hospital Medicine
- 09-12 May 2019

ONLY FDA APPROVED INDICATIONS  
NO "OFF LABEL" RECOMMENDATIONS  
CONFLICT OF INTEREST: NONE TO REPORT



THERE WILL BE NO LABORATORY



# DAZED AND CONFUSED



**MONDAZE  
TUESDAZE  
WEDNESDAZE  
THURSDAZE  
FRIDAZE  
SATURDAZE  
SUNDAZE**

# MEDICAL MARIJUANA ADVOCATES “BELIEVE”



- Therapy for “Intractable Medical Problems”
- Safety
- Effective Treatments



# OPPONENTS “BELIEVE”



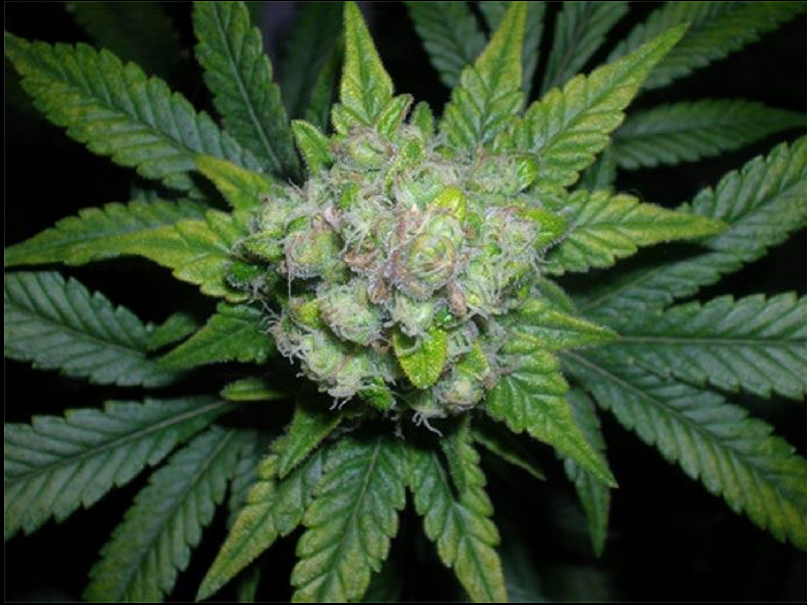
- Benefits are “overblown”
- Ignoring the “Harms” of medical marijuana



# COURT OF PUBLIC OPINION



ACCORDING TO AN AUGUST 2017 QUINNIPIAC  
POLL, WHAT PERCENT OF AMERICANS ARE IN  
FAVOR OF MARIJUANA LEGALIZATION?



- A. 34%
- B. 44%
- C. 54%
- D. 64%

• (94%\* favor MM-was 89% in 2016)

• \* Gallup Oct 2017





The Economist

After New Hampshire: now what?

The great bank scare

Einstein's latest triumph

Don't dam the Mekong

The dismal science of love

FEBRUARY 13TH-19TH 2016

# The right way to do drugs

*fig. 3*



Legalising cannabis safely

# RETAIL CANNABIS



# LEARNING OBJECTIVES

- Medicine by “Popular-vote” vs. Evidence-based and the State-based Cannabis Initiatives:
- Review the History of Botanical/Medicinal Cannabis
- Describe the Components of the Human Endocannabinoid System and Promising Pharmacologic Applications of Phytocannabinoids
- Review the Recent Evidence-based Research of Cannabinoid Compounds
- Discuss Cannabis related Toxicology and Drug Interactions with Resulting Hospital Admissions



“ I AM GOING TO SIGN THIS INTO LAW AND I THINK ALL OF US IN WV FEEL LIKE WE ARE DOING SOMETHING GOOD FOR FAMILIES OUT THERE ”

- WV Medical Cannabis Act
- “Qualified Medical Conditions”
- Certifying Physician
- Regulatory Authority: WV Medical Cannabis Commission
- Limitations: “pills, oils, gels, creams, ointments, tinctures, liquids and **“non-whole plant forms—vaporization”**”
- Access: Home cultivation is prohibited
- DUID
- Medical Cannabis Businesses
- Local Bans/Research Licensees/Taxes and Fees
- 01 July 2019



# OHIO HB 523: “QUALIFYING CONDITIONS”

- AIDS/HIV
- Alzheimer's Disease
- ALS
- Cancer
- Chronic Traumatic Encephalopathy
- Crohn's Disease
- Epilepsy or other Seizure disorder
- Fibromyalgia
- Glaucoma
- HCV
- IBD
- MS
- Pain “either chronic, severe, intractable”
- Parkinson's Disease
- PTSD
- Sickle Cell Anemia
- Spinal Cord Disease or Injury
- Tourette's Syndrome
- TBI
- Ulcerative Colitis
- Any other conditions added by St. Med Board





内容管理系  
DIEDIGMS.COM





# MEDICAL MARIJUANA: POLITICS, MEDICINE, OR COMMERCE





# MONEY, MONEY, MONEY



## U.S. BEER SALES VOLUME GROWTH 2017

OVERALL BEER  
**-1.2%**

196,278,490 BBLs

**5.0%**  
CRAFT

24,868,276 BBLs

**3.2%**  
IMPORT BEER

34,428,490 BBLs

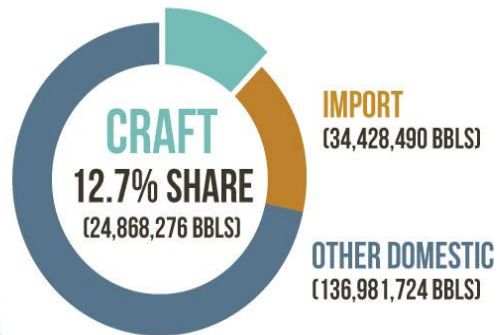
**3.6%**  
EXPORT CRAFT BEER

482,309 BBLs

OVERALL BEER MARKET  
**\$111.4 BILLION**

CRAFT BEER MARKET  
**\$26.0 BILLION**

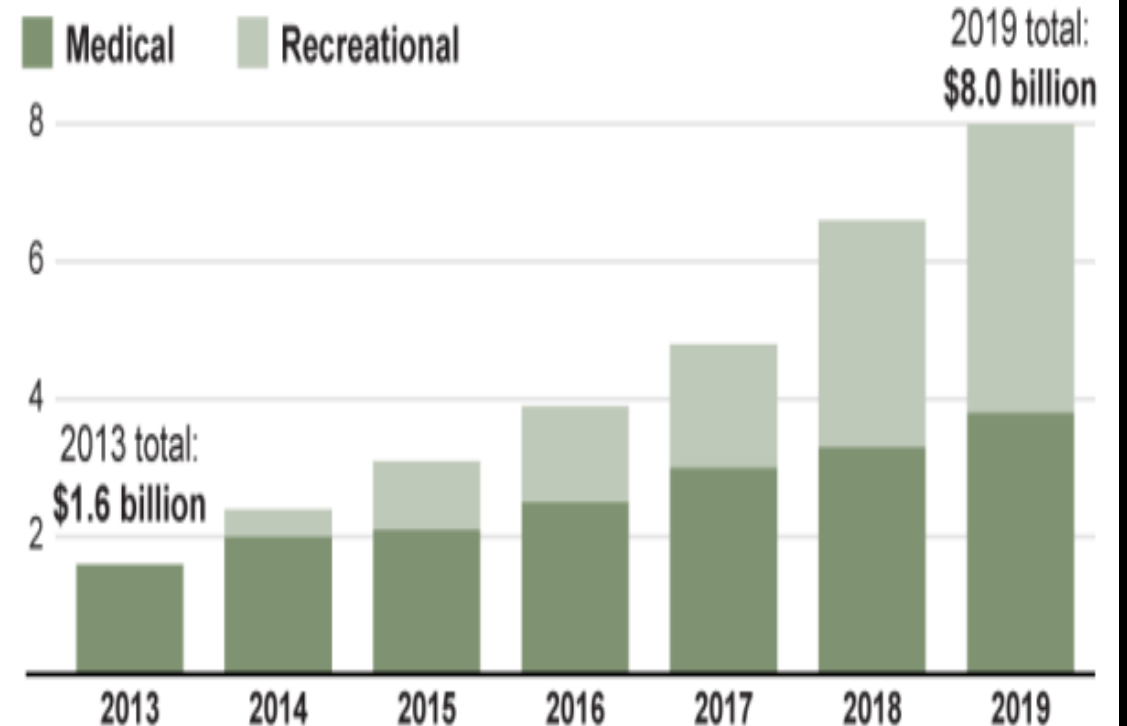
8% DOLLAR SALES GROWTH



SOURCE: BREWERS ASSOCIATION, BOULDER CO

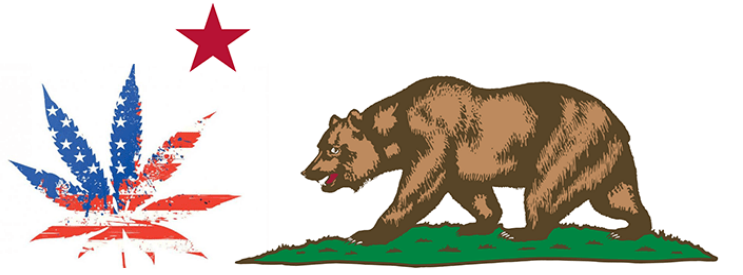
## Legal U.S. marijuana sales estimates

Scale in billions of dollars, largest estimates charted



Source: Marijuana Business Daily

@ChiTribGraphics



CALIFORNIA REPUBLIC

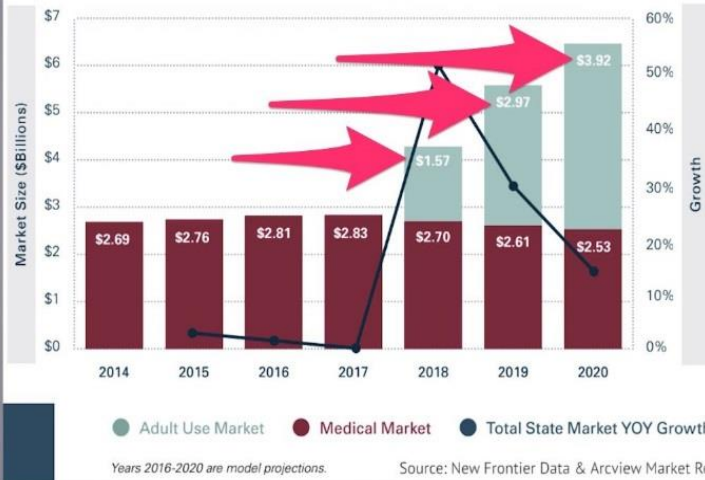
Prop 64

Pot  
Industry

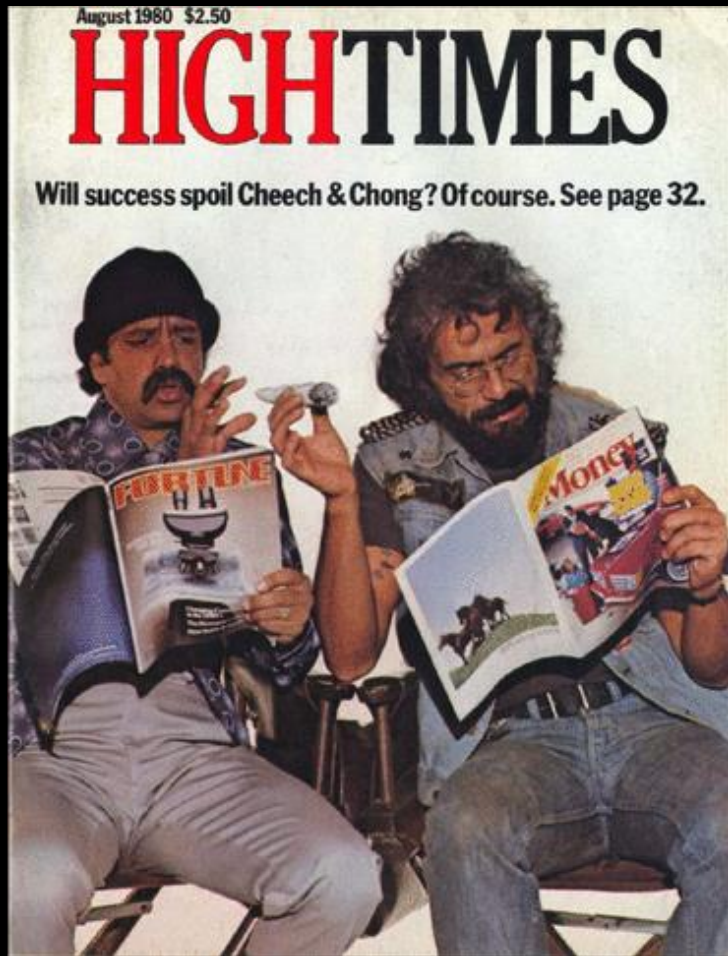
set to  
**Explode**  
in  
CA

- World's 6<sup>th</sup> largest economy
- Economic Output \$2.46 Trillion
- Retail sales to begin 2018
- Tax Revenue: "High hundreds of millions of dollars to over \$1BILLION annually"

i California's Legal Cannabis Market



# MARIJUANA MEDICALIZATION/ LEGALIZATION?







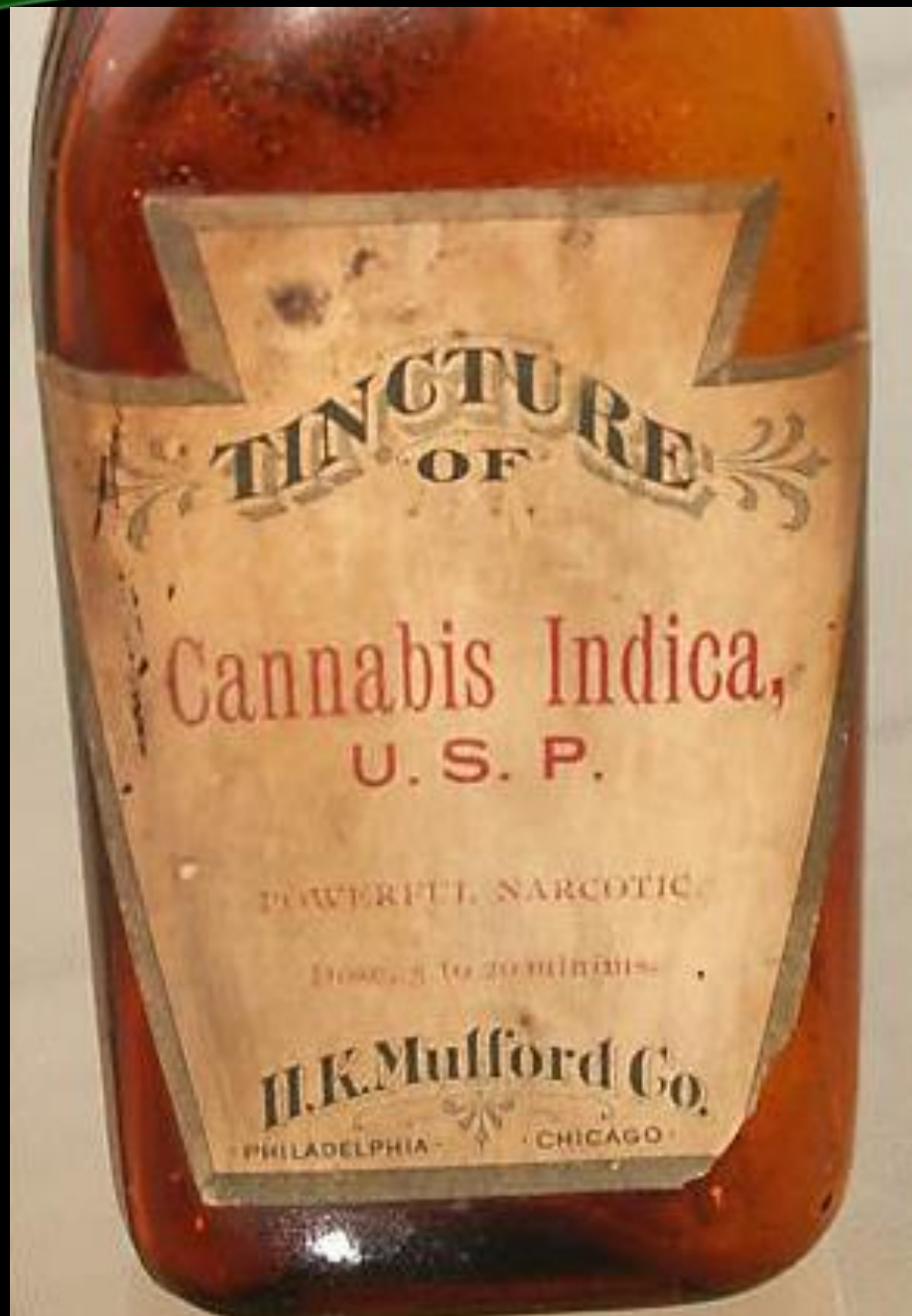
## Budtender Training

- Green CulturED online training provides [budtender training](#) and certification programs in Colorado.
- Become a Budtender and help patients receive the information and medication that they need and stand out from other candidates.
- Budtender Certification educates students on all the important aspects of medical marijuana so that they may make educated decisions for their own health and compassionate recommendations for the patients that they serve.



How To Become A Budtender

[Get Started](#) ▶



# MARIJUANA AS "MEDICINE" IS NOT NEW



# FROM THERAPIES TO PROHIBITION



## DRUG SCHEDULES

I	II	III	IV	V
Heroin Marijuana LSD Ecstasy	Adderall Hydrocodone Cocaine Fentanyl	Tylenol with Codine Ketamine Steroids	Xanax Valium Ambien Tramadol	Robitussin AC Lyrica Lomotil Motofen

NODRUGWAR.ORG



# Marijuana Law

TruthOnPot.com  
 Follow us!

1619



1st N. American marijuana law forces farmers to grow hemp  
 Jamestown Colony, Virginia

1850

Cannabis extract widely recommended & sold over-the-counter in Western pharmacies



1915-1927



Influx of Mexican immigrants into the US...

9 states pass laws outlawing the 'marihuana' they smoked

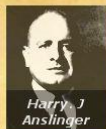
"All Mexicans are crazy and this stuff [marihuana] is what makes them crazy"

-Texas senator on the floor of the Senate

1929-1936

Recreational marijuana use spreads among minorities...

"Reefer makes Darkies think they're as good as white men"



Harry J. Anslinger is appointed as head of the Federal Bureau of Narcotics

1937

Anslinger proposes Marihuana Tax Act to Congress and testifies:

"Marijuana is the most violent drug in the history of mankind"

Act passes...

Marijuana is Prohibited

"I wish I could show you what a small marihuana cigarette can do to one of our degenerate Spanish-speaking residents. That's why our problem is so great"

## Evil Mexican Plants That Drive You Insane.

THE revolution in Mexico has brought with it not only the ravages of war, but also the degradation of the social conditions of soldiers and prisoners. One of the latest forms of dissipation in the ranks of federals and rebels alike is the habit of smoking marihuana, a deadly native plant of Mexico. According to reports many of the Mexican prisoners in the Belem prison in the City of Mexico are losing their minds as a result of smoking this weed.

The dry leaves of marihuana, alone or mixed with tobacco, make the smoker wilder than a wild beast. It is said that after the first three or four draughts of smoke the smoker feels a slight headache, then he sees everything moving, and finally loses all control of his mental faculties.

The next stage of the intoxication is full of terrors. Troops of ferocious wild animals march before the vision of the smoker. Lions, tigers, panthers and other wild beasts occupy his vision. These wild

animals are then attacked by hosts of devils and monsters of unheard-of shapes. The smoker becomes brave and possessed of superhuman strength. It is at this stage of the debauch that murders are committed by smokers of the marihuana weed.

A few Americans have experimented with the weed. A few years ago a well-known citizen of San Antonio purchased a large coffee plantation in southern Mexico. He was induced to try smoking marihuana; he became addicted to the habit, which rendered him insane and finally caused his death.

In another instance the superintendent of a mine in Mexico, who was an American, became the object of hatred of one of the men in his employ. The Mexican mixed marihuana with the American's tobacco. The latter became wildly insane from smoking the mixture, made a vicious attack upon a party of miners, was shot and killed in the affray.

Not long ago a Mexican of the lower

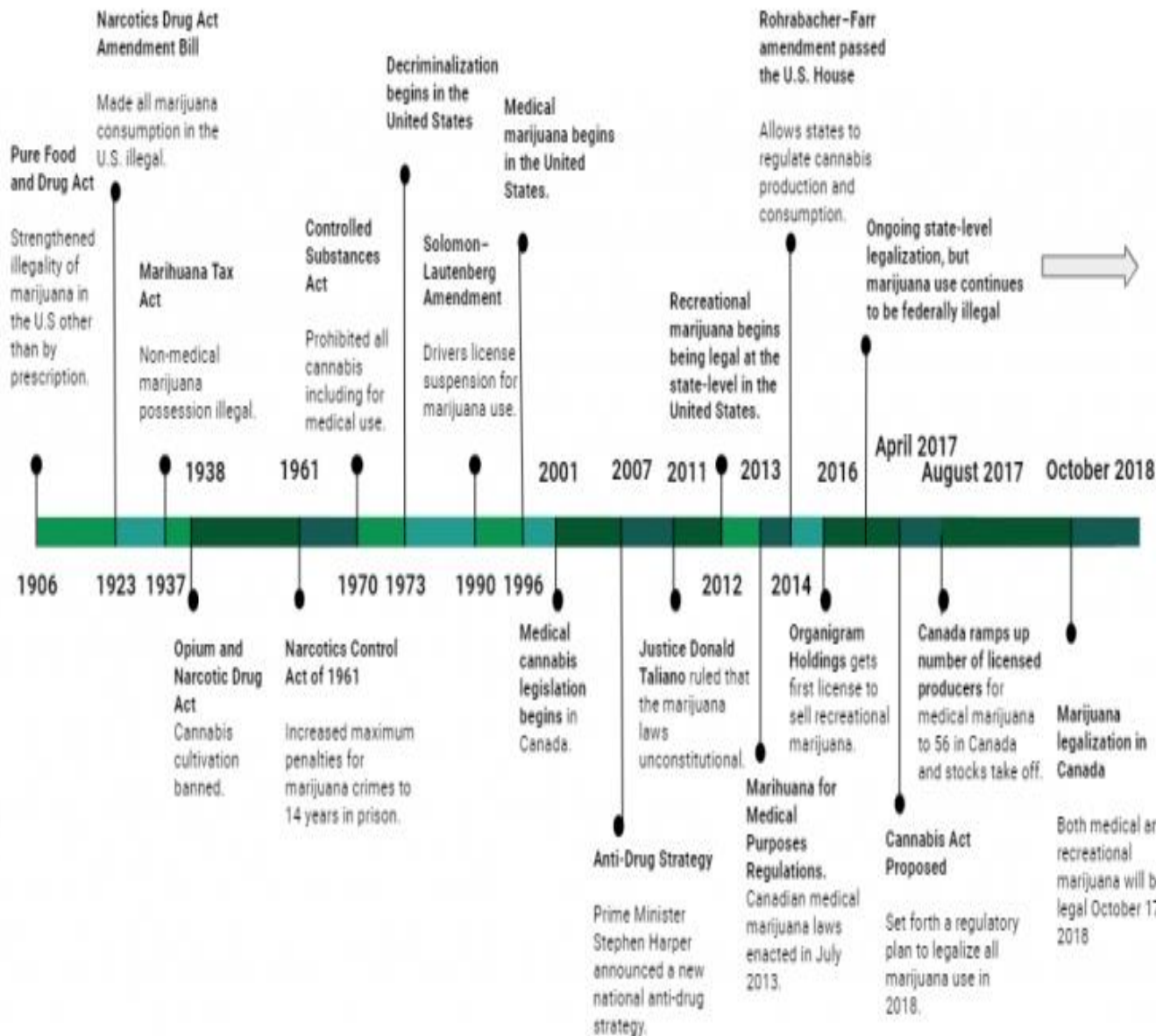
class, living in the City of Mexico, who had smoked a marihuana cigarette, became insane, attacked and killed a policeman and badly wounded three others.

Marihuana is one of the most dangerous drugs found in Mexico. The weed grows wild in many localities in the southern part of that country. Its wonderful powers as an intoxicant have long been known to the natives, and many are the wild orgies it has produced. So dangerous is this weed that in the City of Mexico and other Mexican cities the Government keeps special inspectors constantly employed to see that it is not sold in the markets.

There is in the State of Michoacan, among them the "totrache," a sort of "loco" weed. The seeds of this plant boiled and drunk as tea will make a person insane. Among some classes of Mexicans it is stated that Carlota, the former Empress of Mexico, lost her mind because she was given totrache in a refreshment by her enemies.

United States

Canada





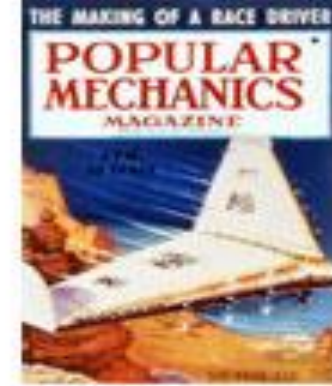
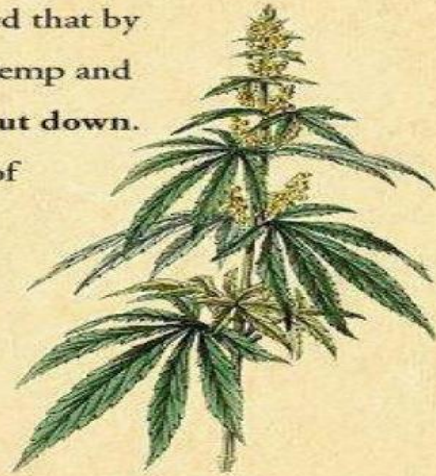
# REEFER MADNESS?

Real or Imaginary in South Alabama?

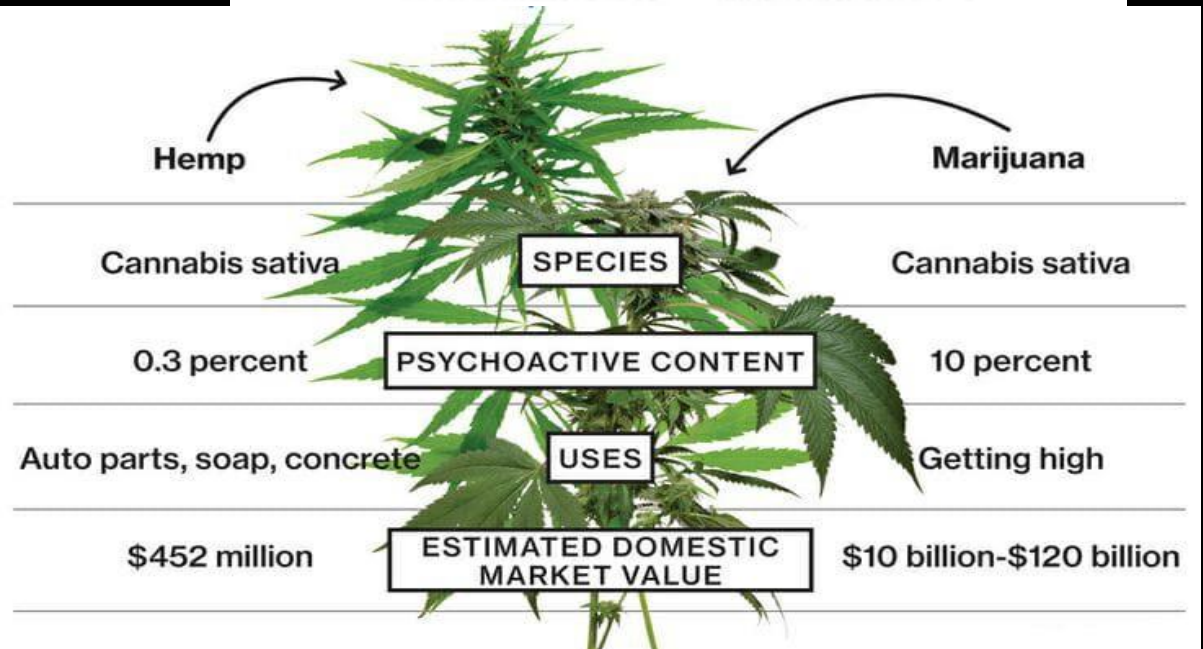
DNES

# 100 YRS MISINFORMATION

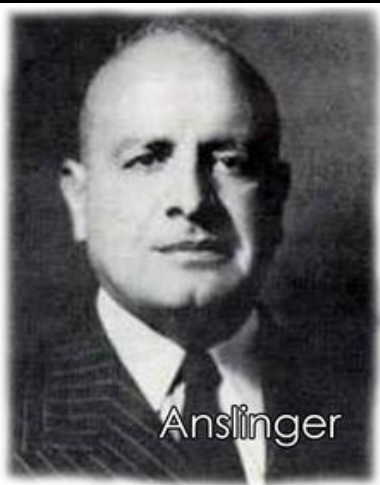
In 1916, the U.S. Government predicted that by the 1940s all paper would come from hemp and that no more trees would need to be cut down. Government studies report that 1 acre of hemp equals 4.1 acres of trees. Hemp production is much more time and resource efficient. Plans were in the works to implement such programs. (U.S. Department of Agriculture)



- 1937: Essentially banned Hemp production (Marihuana Tax Act)
- 2014: President Obama signed Farm Bill to Legalize Hemp for Research Purposes
- 32 States have pro-hemp legislation
- KY very pro-active
- WV: 2016 State Dept. of Agriculture accepting application for permits
- WV Hemp Farmers Cooperative: "WV jobs for a economic downturn"
- 2018 Farm Bill: removed Hemp from Schedule I



**CAUTION**  
**Conspiracy Theory**  
**Ahead**



Anslinger



Hearst

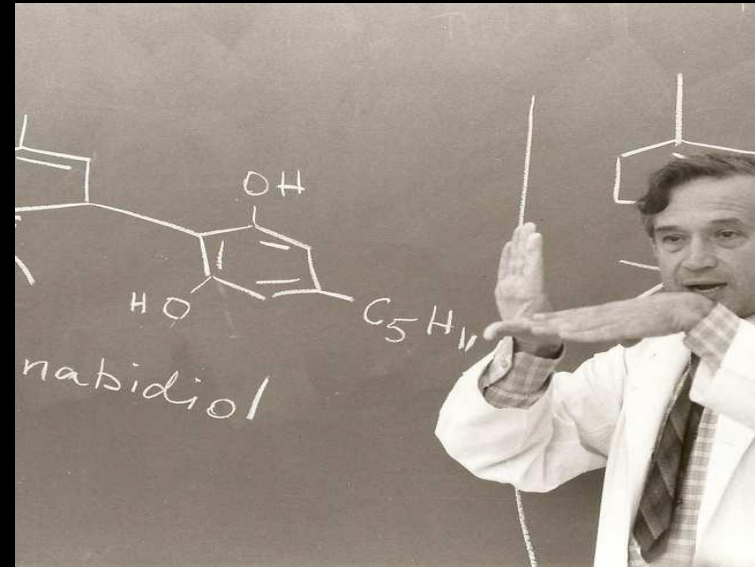
- FBN: Henry Anslinger
- Secretary of Treasury A. Mellon
- William Randolph Hearst
- DuPont, GM, Oil

# Controlled Substances Act



# “FATHER OF MODERN CANNABIS

- Raphael Mechoulam, Ph.D.  
Professor of Medicinal Chemistry  
University of Jerusalem
- 1964: Isolates then synthesizes delta-9-THC
- 1992 with others-ID's human endogenous cannabinoid (endocannabinoid) natural “THC”  
Names: ‘anandamide’ Sanskrit: “eternal bliss or supreme joy”
- 1990-Miles Herkebham: NIMH- cannabinoid receptors CB1, CB2
- “Increasing concentrations THC”

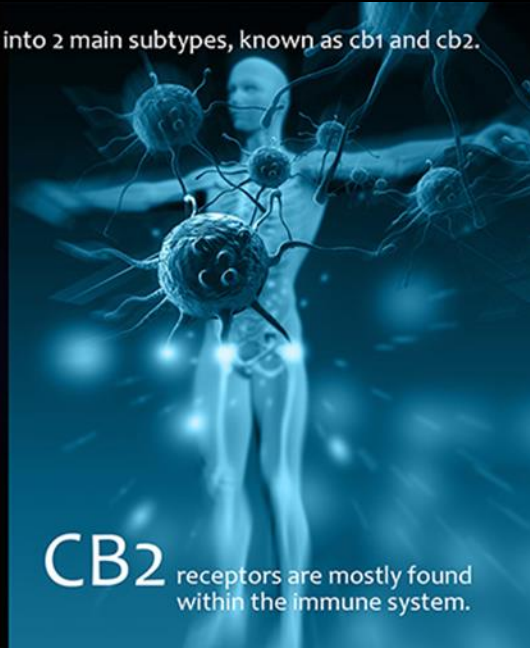


## Vaping oil: ***“Filthy Laboratory”***



# ECS

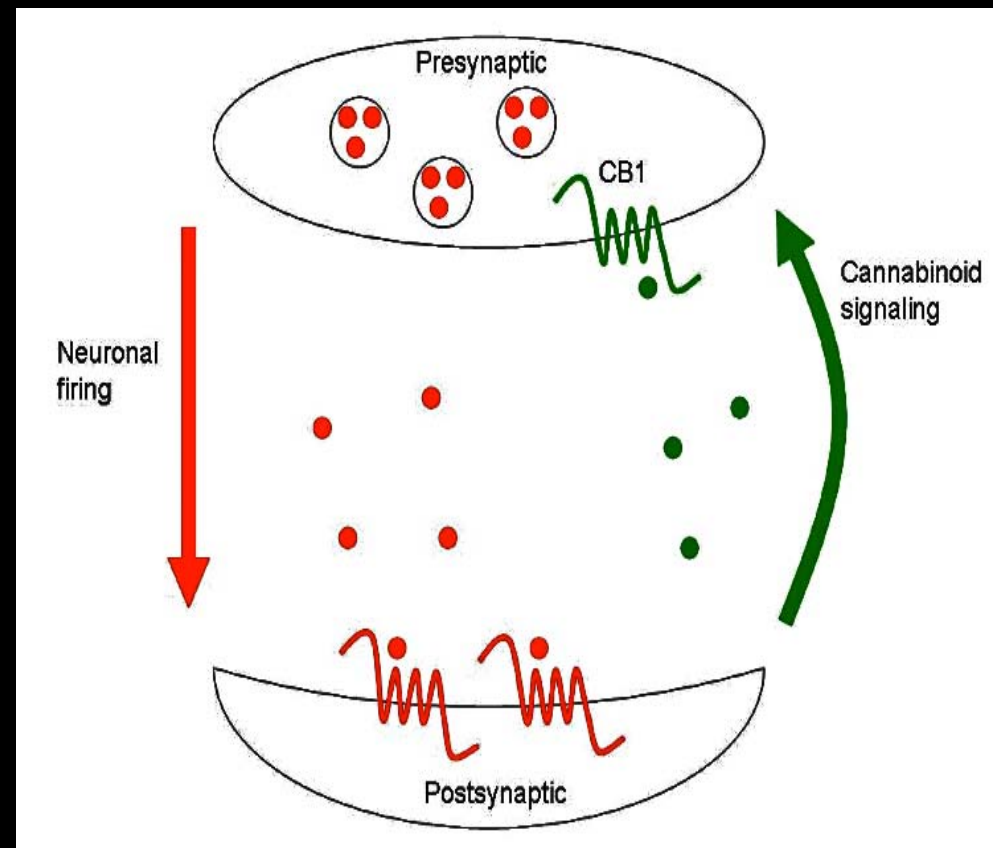
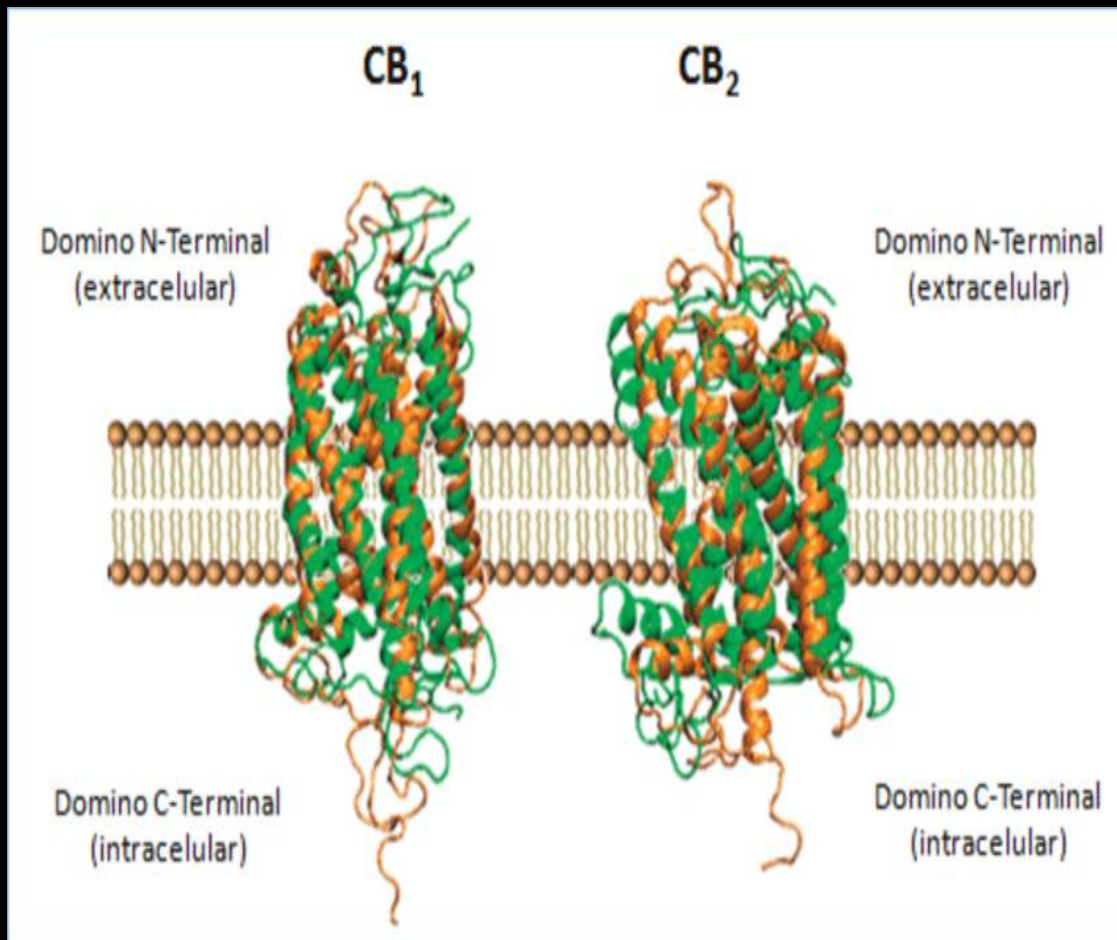
The cannabinoid receptors are further divided into 2 main subtypes, known as cb1 and cb2.



## Endocannabinoid Receptors

- CB1: Brain, spinal cord, connective tissue, reproductive organs, glands, internal organs
- CB2: Spleen, tonsils, GI, thymus gland. White blood cells: T-cells, B-cells, macrophages
- GPR55, GPR18: Regulator of neuroimmune function
- GPR3, GPR6 and GPR12 orphan receptors



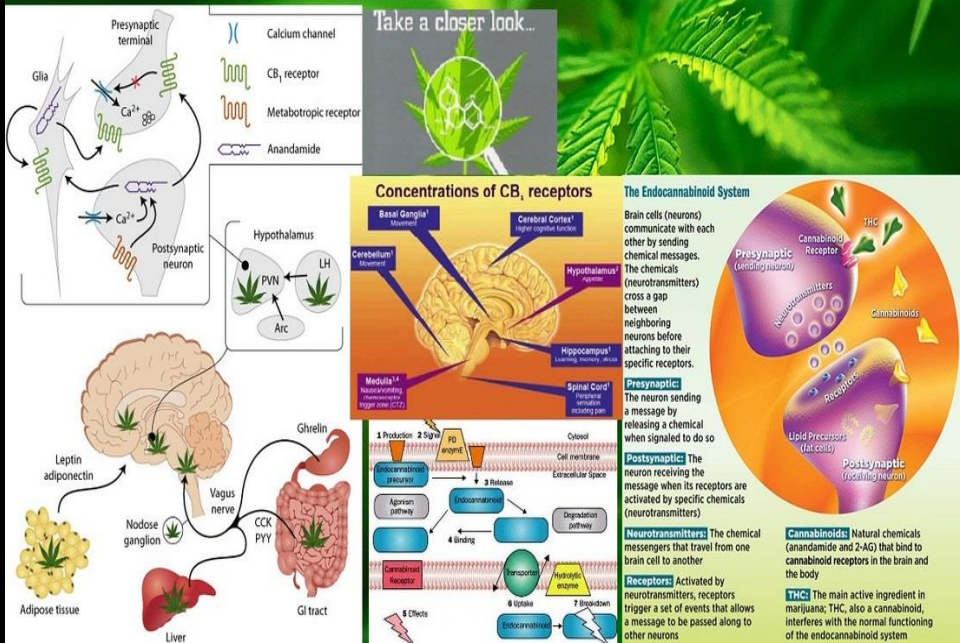


# CANNABINOID BIOLOGY

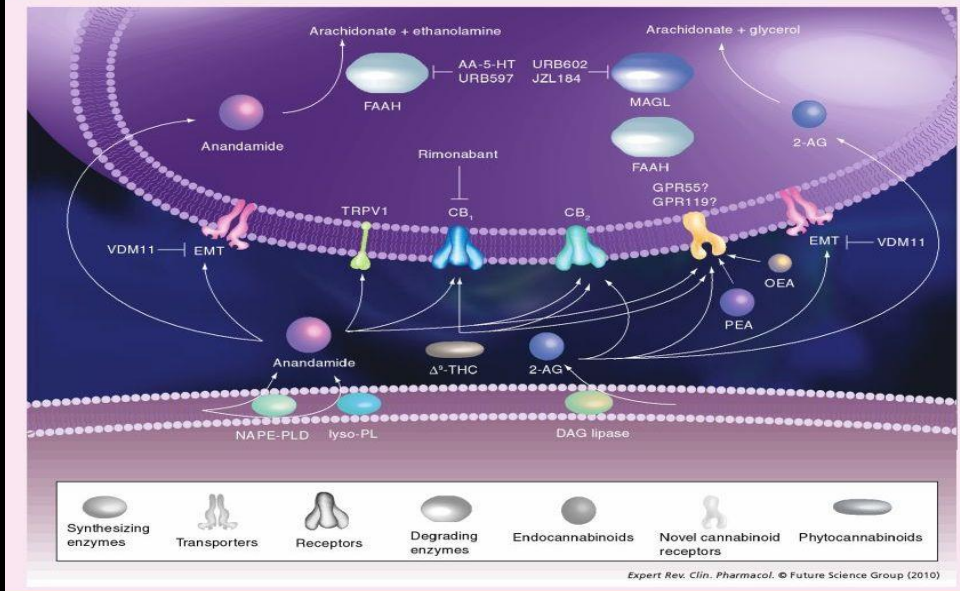
- Cannabinoid receptors characterized in 1980-90's (CB1 and CB2)
- Likely have a natural role in pain modulation, movement control, and memory
- Role in immune systems is likely multi-faceted and remains unclear
- Brain develops tolerance
- Animal research demonstrates potential for dependence
- Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates and benzos



# ENDOCANNABINOID SYSTEM



Medscape

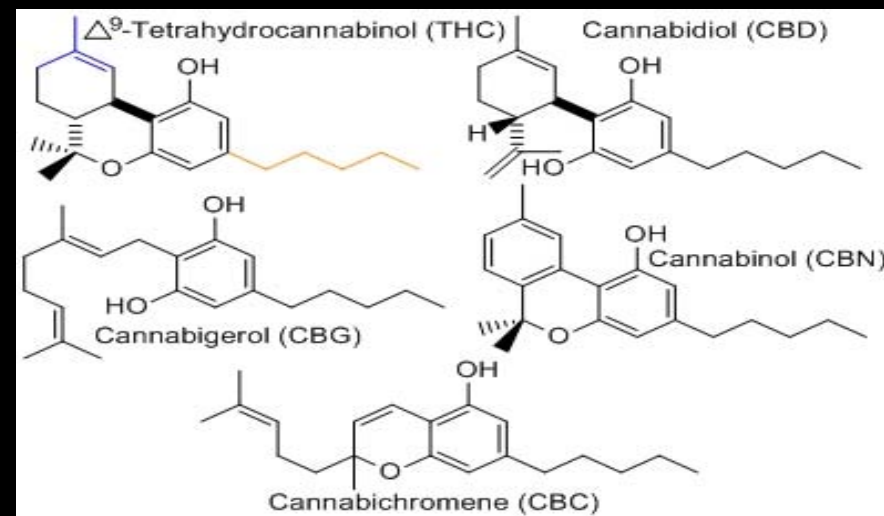


Expert Rev. Clin. Pharmacol. © Future Science Group (2010)

Source: Expert Rev Clin Pharmacol © 2010 Expert Reviews Ltd.

# CANNABIS AND CANNABINOIDS


- *Cannabis sativa/Indica*
- 400 chemical compounds
- 66 different cannabinoids
- 104 Unique to Cannabis Plant
- Phytocannabinoids: delta9-THC: Cannabidiol (CBD)
- Tetrahydrocannabivarin (THCV), Cannabichromene (CBC), Cannabigerol (CBG)
- All are lipophilic
- Amounts vary in growing conditions



# DEFINE: MEDICAL MARIJUANA

- Whole, unprocessed Cannabis plant or its basic extracts
- Used to treat symptoms of illness or other conditions
- FDA: Has NOT recognized or approved the marijuana plant as medicine
- Unprocessed Plant Material
- Liquid or Oils
- Capsules
- Edibles
- Rectal suppositories
- Ointments, Creams, and Lotions

## *Types Of Weed*



**SATIVA**

Cannabis Sativa Sativa is characterized by leaflets that are more narrow, branches that are farther apart, and coloration that tends more toward spring green. Sativa Sativa plants tend to be taller and produce fewer flowers.

**INDICA**

Cannabis Sativa Indica is characterized by broad leaflets that offer overlap, branches that are closer together, and coloration that tends more toward deep olive green. Sativa Indica plants tend to be shorter and bushier, producing fuller, denser flower buds.

**RUDERALIS**

Cannabis Ruderalis is characterized by varied leaflets in the mature leaves, a shorter stature and generally small size. This subspecies is used to create S. Sativa or S. Indica hybrids with select desired traits.

[www.Types-of-Weed.ORG](http://www.Types-of-Weed.ORG)

# WHICH OF THE FOLLOWING PLANTS IS MOST CLOSELY RELATED TO CANNABIS



- A. Tobacco
- B. Coca
- C. Hops
- D. Sage


# TERPENES

- Aromatic compounds produced in the glandular flower bud
- Not phytocannabinoids
- Limonene, pinene, myrcene, etc
- Responsible for aromatic/odorous character
- *May involve modulating effects of THC and CBD*
- *Content ? Related to distinction of sativa vs indica*

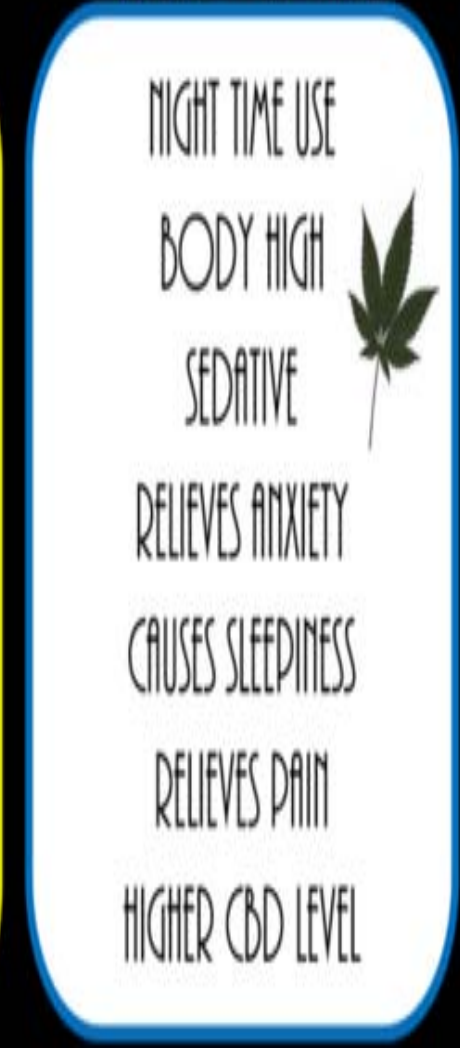
## SATIVA




DAY TIME USE  
CEREBRAL HIGH  
ENERGETIC  
STIMULATE APPETITE  
ENHANCES CREATIVITY  
RELIEVES DEPRESSION  
HIGHER THC LEVEL



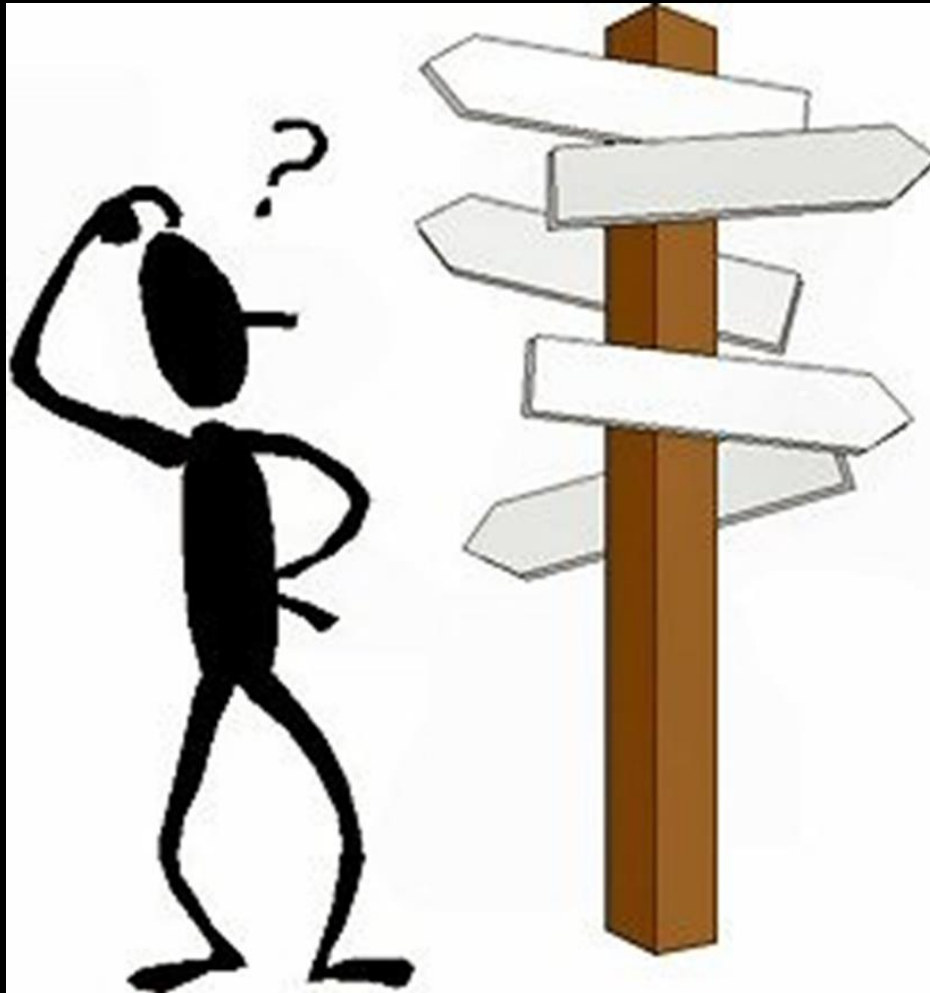
## INDICA



NIGHT TIME USE  
BODY HIGH  
SEDATIVE  
RELIEVES ANXIETY  
CAUSES SLEEPINESS  
RELIEVES PAIN  
HIGHER CBD LEVEL



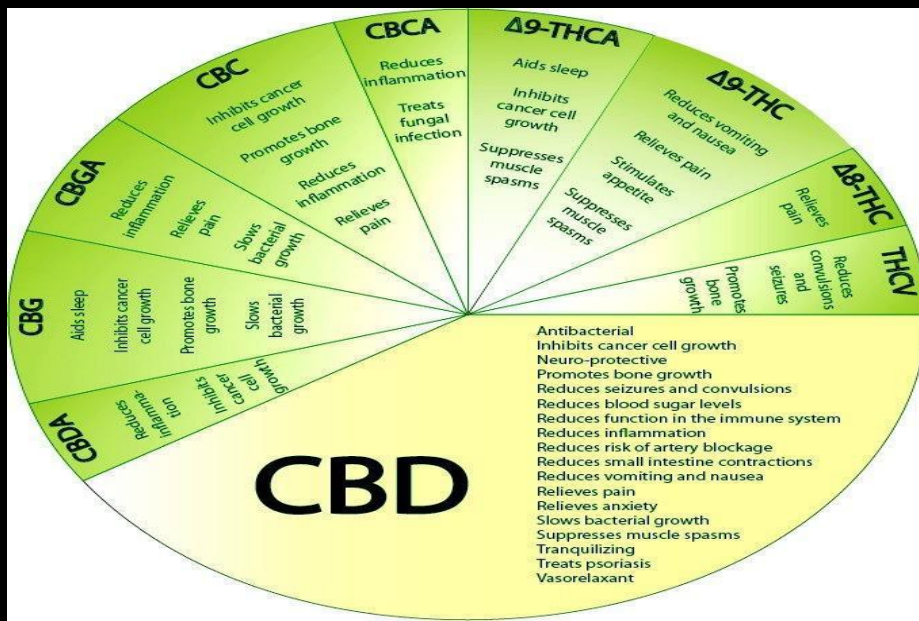
# CANNABIS CONFUSION AND THE HOSPITALIST



- C. Clark Milton, DO, FACOI
- ACOI Clinical Challenges in Hospital Medicine
- 09-12 May 2019



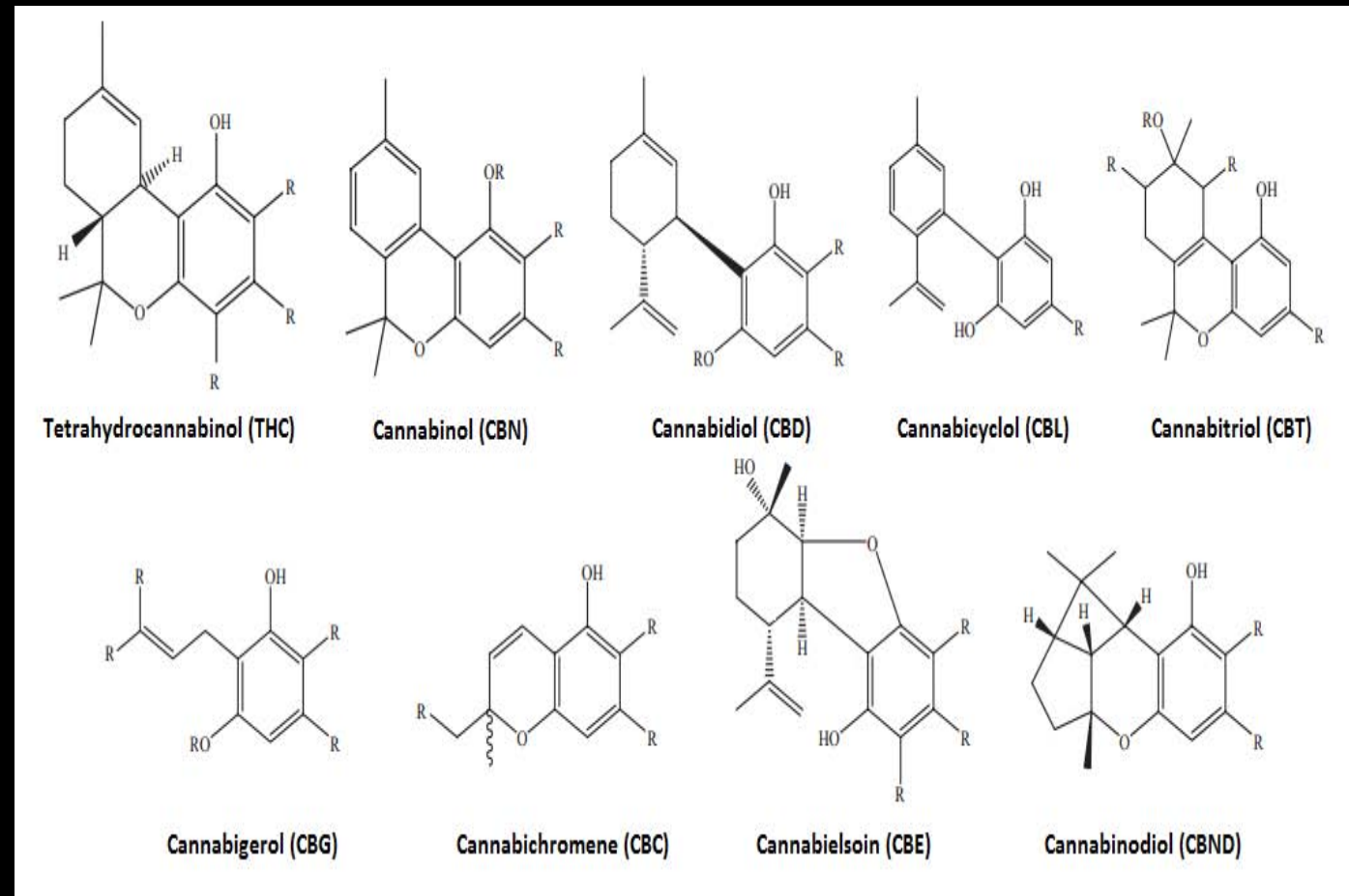
# “MEDICAL MARIJUANA”: PHARMACOLOGY



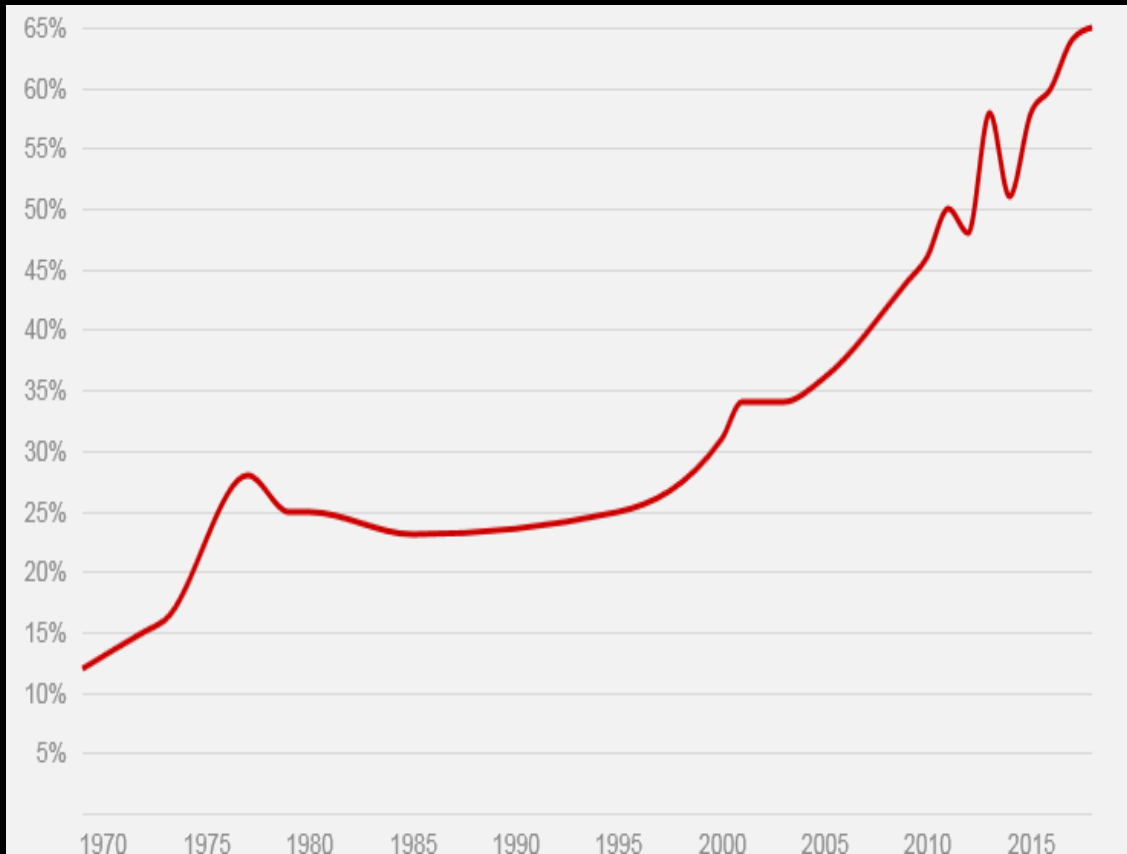
- 2 of 3 forms of cannabinoids
- 1. Endocannabinoids: arachadonic acid neurotransmitter
- 2. Phytocannabinoids: of *C. sativa*/*C. Indica* (hundreds) THC and CBD
- 3. Synthetic cannabinoids: and THC analogues: foundation of the pharmaceutical industry
- THC concentration : 0.2%-30% in hybridized sinsemilla
- 2% 1980: 4.5% 1997: 8.5% 2006

# PHYTOCANNABINOIDS

THC	vs	CBD
<b>PSYCHOACTIVE</b>		<b>NON-PSYCHOACTIVE</b> <small>THROUGH MODULATE NEUROCHEMISTRY</small>
<b>STRONG CB1 &amp; CB2 RECEPTOR AGONIST</b>		<b>WEAK CB1 &amp; CB2 AGONIST</b> <small>STRONGLY INFLUENCES EFFECT OF OTHER AGONISTS (ANANDAMIDE)</small>
<b>WEAK GENE TRANSCRIPTION MODULATOR</b>		<b>STRONG GENE TRANSCRIPTION MODULATOR</b>
<b>ILLEGAL</b> <small>MEDICALLY LEGAL IN 29 STATES. RECREATIONALLY LEGAL IN 7 STATES</small>		<b>FEDERALLY LEGAL</b> <small>IN ALL 50 STATES</small>



# SUPPORT OF US LEGALIZATION



## THE FEDERAL DRUG SCHEDULE

Different drugs are given classifications on the national level. These classifications are called "schedules." Here's how it breaks down:

### Schedule 1

Drugs with no accepted medical use.  
(*Marijuana, heroin, LSD, ecstasy, peyote..*)

### Schedule 3

Drugs that have a low risk of dependency.  
(*anabolic steroid, testosterone and ketamine..*)

### Schedule 2

Drugs that often do have medical use.  
(*Vicodin, methadone, methamphetamine..*)

### Schedule 3

Drugs that have a low risk of dependency.  
(*anabolic steroid, testosterone and ketamine..*)

### Schedule 4

Drugs with a very low risk of abuse.  
(*valium, ambien, tramadol, talwin..*)



MAY 25, 2018

# TIME

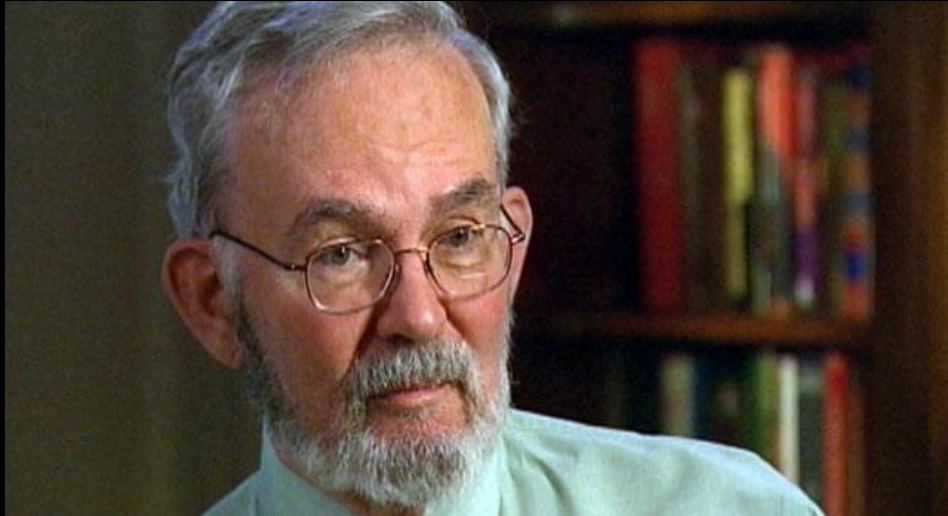
The Highly Divisive,  
Curiously Underfunded  
and Strangely Promising  
**World of Pot Science**

BY BRUCE BARCOTT & MICHAEL SCHERER



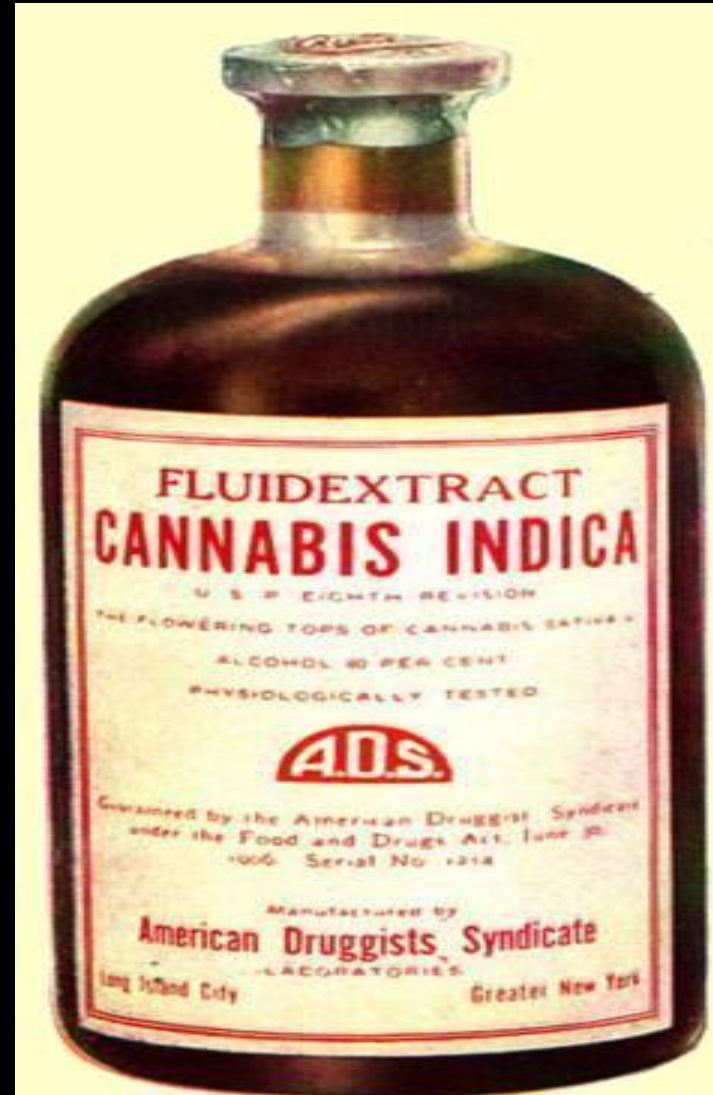
time.com

# SCHEDULE I AND RESEARCH

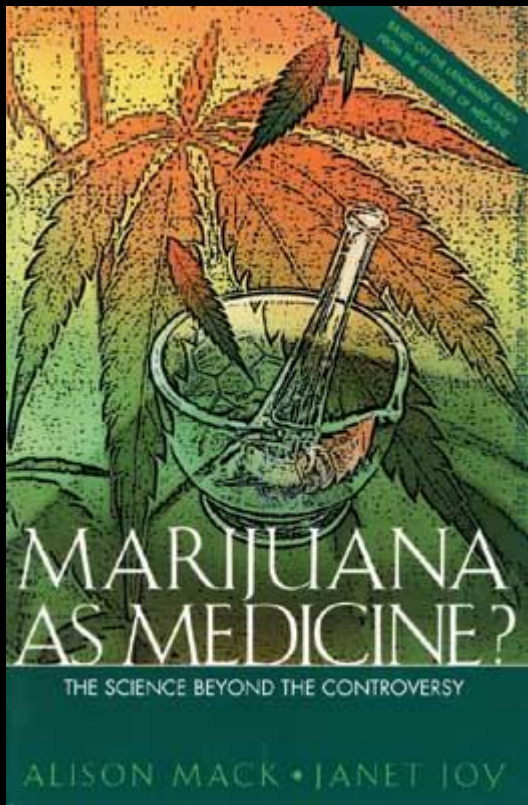


- John W. Huffman, PhD
- NIDA research 1984
- 450 synthetic compounds
- JWH-007 to JWH-424
- In 2000 2 compounds were being sold in Germany
- “....I figured it would spread....I’m concerned it would hurt someone”
- April 2018: IL: Bleeding according CDC ( 4-hydroxycoumarin)

# SCIENCE OF CANNABIS



# INSTITUTE OF MEDICINE: 1997 & 2003



## SUMMARY OF RESEARCH

- More than 30 yrs of clinical research
- Only small number of randomized, controlled trials of "smoked cannabis"
- Short term with a total of about 300 patients
- Indicate: reduction in neuropathic pain
- Improves appetite and caloric intake
- Spasticity relief in MS
- Better alternatives are available to Rx glaucoma and chemo-induced N & V

# CANNABINOIDS FOR MEDICAL USE: 23 JUNE 2015



- Systemic Review and Meta-Analysis
- 79 Trials: (6462 participants)
- Study Selection: “Randomized clinical trials of cannabinoids for the following indications:

  - 1. Nausea and vomiting associated with ChemoRX
  - 2. Appetite Stimulation in HIV/AIDS
  - 3. Chronic Pain
  - 4. Spasticity due to MS/paraplegia
  - 5. Anxiety/Depression: Sleep Disorder
  - 6. Psychosis: glaucoma, Tourette Syndrome



# CANNABINOIDS FOR MEDICAL USE (CONT)



- Most trials showed improvement in “SYMPTOMS” ...Did NOT meet statically significance in all trials
- N&V: greater than average showing response comp. with placebo
- Pain: greater than average reduction in numerical pain scale rating
- Spascity: Average reduction

# CONCLUSIONS AND RELEVANCE

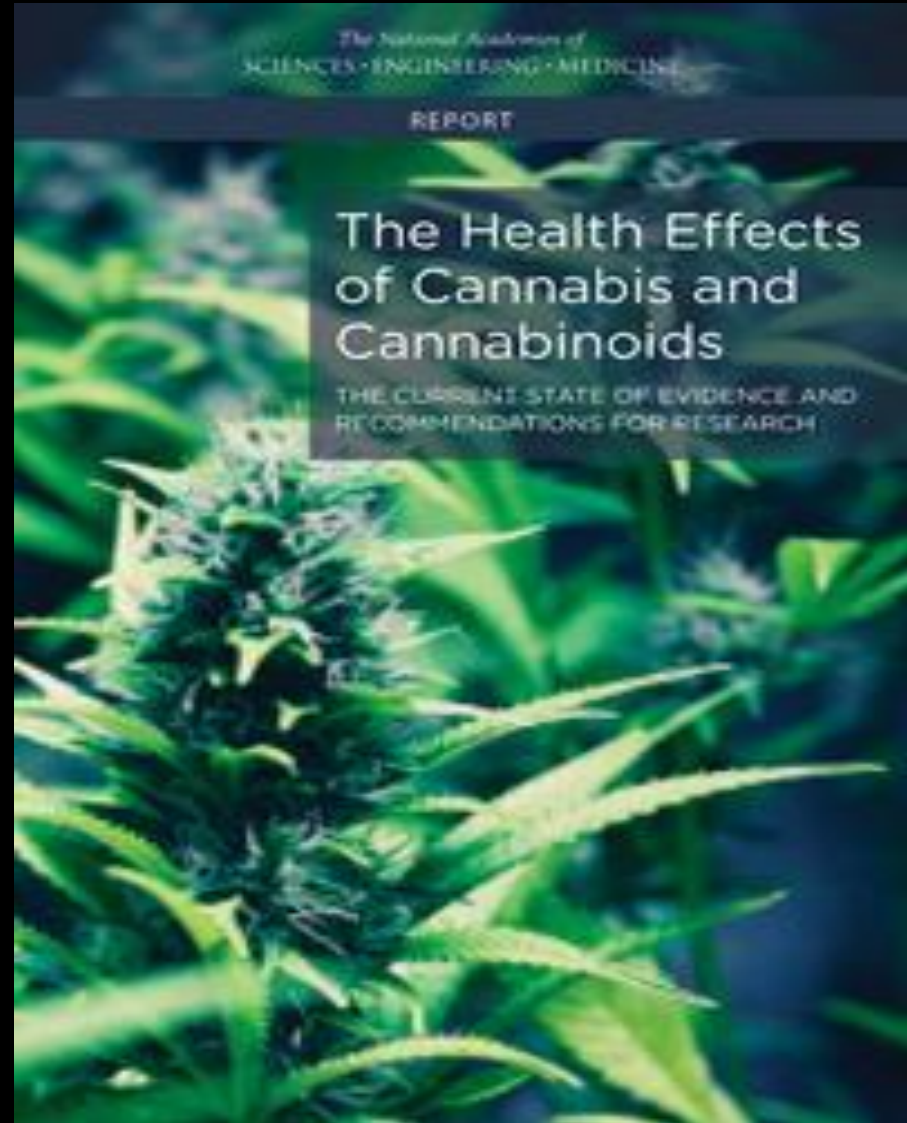


- Moderate-quality evidence to Support cannabinoid use for Chronic Pain and Spascity
- Low-Quality evidence: Suggesting that Cannabinoids were associated with Improvements in N&V due to ChemoRx, Weight gain in HIV, Sleep Disorders, and Tourettes
- Cannabinoids were associated with an Increase risk of short term AE



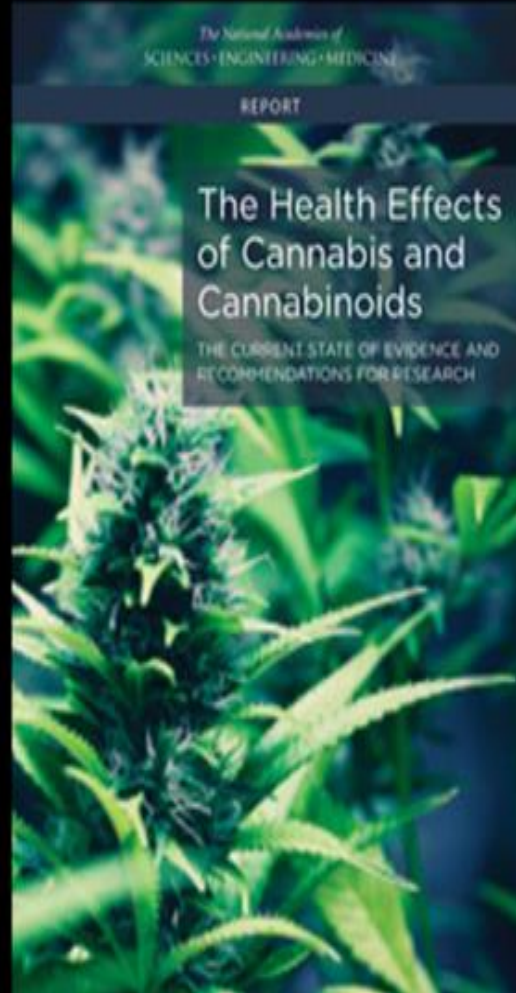
12 JANUARY 2017

*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE



12 JANUARY 2017

*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE



- Review more than 10,700 Abstracts
- Close to 100 different research conclusions
- Health Effects
- Potential Therapeutic Uses
- Risks: Mental Health, CA, Immunity
- ? Therapeutic Use of Cannabis and Cannabinoids
- Chronic Pain, CA, HIV-related anorexia, HD, PD

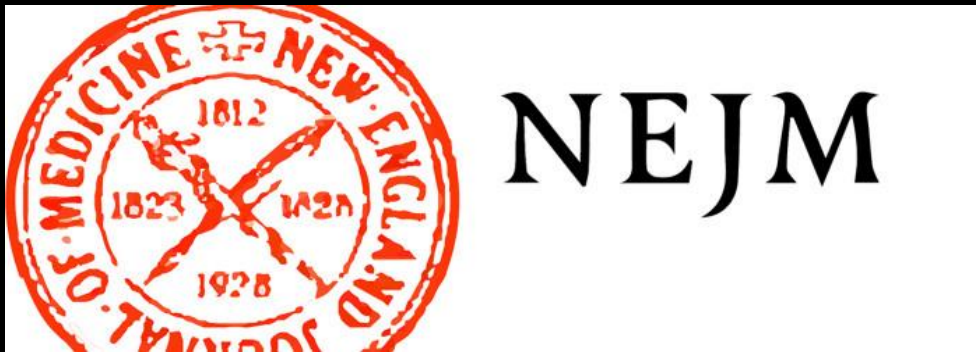
*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE

- “Conclusive or Substantial”: Can treat chronic pain in adults  
Nausea and vomiting in ChemoRx  
Improve reported MS spasticity
- “Substantial Evidence”
  - Smoking: worse respiratory S/S
  - Increase bronchitis
  - Risk MVC
  - Low Birth weight pregnancy
  - Increase psychosis/frequent use
  - Use at “earlier age” problematic

*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE

- “Conclusive or Substantial”: Can treat chronic pain in adults  
Nausea and vomiting in ChemoRx  
Improve reported MS spasticity
- “Substantial Evidence”
  - Smoking: worse respiratory S/S
  - Increase bronchitis
  - Risk MVC
  - Low Birth weight pregnancy
  - Increase psychosis/frequent use
  - Use at “earlier age” problematic

# TRIAL OF CBD FOR DRUG-RESISTENT SEIZURES IN DRAVET SYNDROME



- 31 May 2017
- Complex childhood epilepsy disorder
- Double blind placebo controlled
- 120 participants: 20mg/kg
- 14 weeks
- With CBD decreased seizures/month 12.5 to 9
- Placebo 14.9 to 14.1
- AE: CBD diarrhea, vomiting, fatigue, pyrexia, somnolence, LFT
- More withdrawals in CBD
- Greater reduction in seizure frequency
- Funded by GW Pharm



# CANNABINOID RX AVAILABLE IN US AND CANADA

**Table. Some Cannabinoid Products**

Drug	Available Formulations	Usual Adult Dosage	Cost <sup>a</sup>
Dronabinol - generic			\$235.20 <sup>b</sup>
Marinol (Abbvie)	2.5, 5, 10 mg capsules	5 mg/m <sup>2</sup> , 4-6 x/d <sup>c</sup>	545.30 <sup>b</sup>
Syndros (Insys)	5 mg/mL PO solution	4.2 mg/m <sup>2</sup> , 4-6 x/d <sup>c</sup>	NA
Nabilone-Cesamet (Meda)	1 mg capsules	1-2 mg bid	216.20
Nabiximols <sup>d</sup> -Sativex (GW Pharma)	10 mL oromucosal spray <sup>e</sup>	4-8 sprays/d	221.50 <sup>f</sup>

NA = Cost will be updated when drug becomes available. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers.

<sup>a</sup> Approximate WAC for 3 days treatment with the lowest usual adult dosage. WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource<sup>®</sup> Monthly. July 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. [www.fdbhealth.com/policies/drug-pricing-policy](http://www.fdbhealth.com/policies/drug-pricing-policy).

<sup>b</sup> Cost for a patient with a body surface area of 1.8 m<sup>2</sup>.

<sup>c</sup> Usual dosage for treatment of chemotherapy-induced nausea and vomiting.

<sup>d</sup> Not available in the US.

<sup>e</sup> Each 10-mL vial contains up to 90 sprays. Each 100-mL spray contains 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

<sup>f</sup> Approximate WAC for one 10-mL vial, based on price from a national wholesaler in Canada (price in Ontario, July 2016).



# NATURAL EXTRACT FROM PLANT SOURCE



- THC and CBD (nabiximols)  
Oromucosal spray
- 2.7mgTHC/2.5mg CBD: 2.5-120mg in divided doses
- Neuropathic pain/spasticity of MS
- Analgesia: advanced CA-mod/severe
- UK, Canada 2010: First Cannabis based med
- US: Phase III trials in CA pain initial results in 2014
- GW Pharm/ Otsuka
- New Drug app: 2013 spasticity of MS

# SIMILAR COMPOUND: NOT IN CANNABIS PLANT

- Synthetic Analogue: similar to THC
- N/V (Refractory) associated the CA Rx
- 1985 approved but withdrawn 1989: re-approved 2006
- Warning: “Potential to affect mental state of patients”
- Rx: CII
- 1-2mg TID: Max 6mg/day
- Months supply \$2250



# SYNTHETIC VERSIONS OF CANNABIS EXTRACTS

- Dronabinol (Synthetic 9-THC)
- N/V CA Rx
- Appetite stim. HIV
- Analgesia neuropathic pain/MS: OFF LABEL
- Approved 1985 CII
- 1999 CIII
- \$150 million/yr
- 2.5-10mg/day in divided doses
- \$3000/month: Generic \$1351

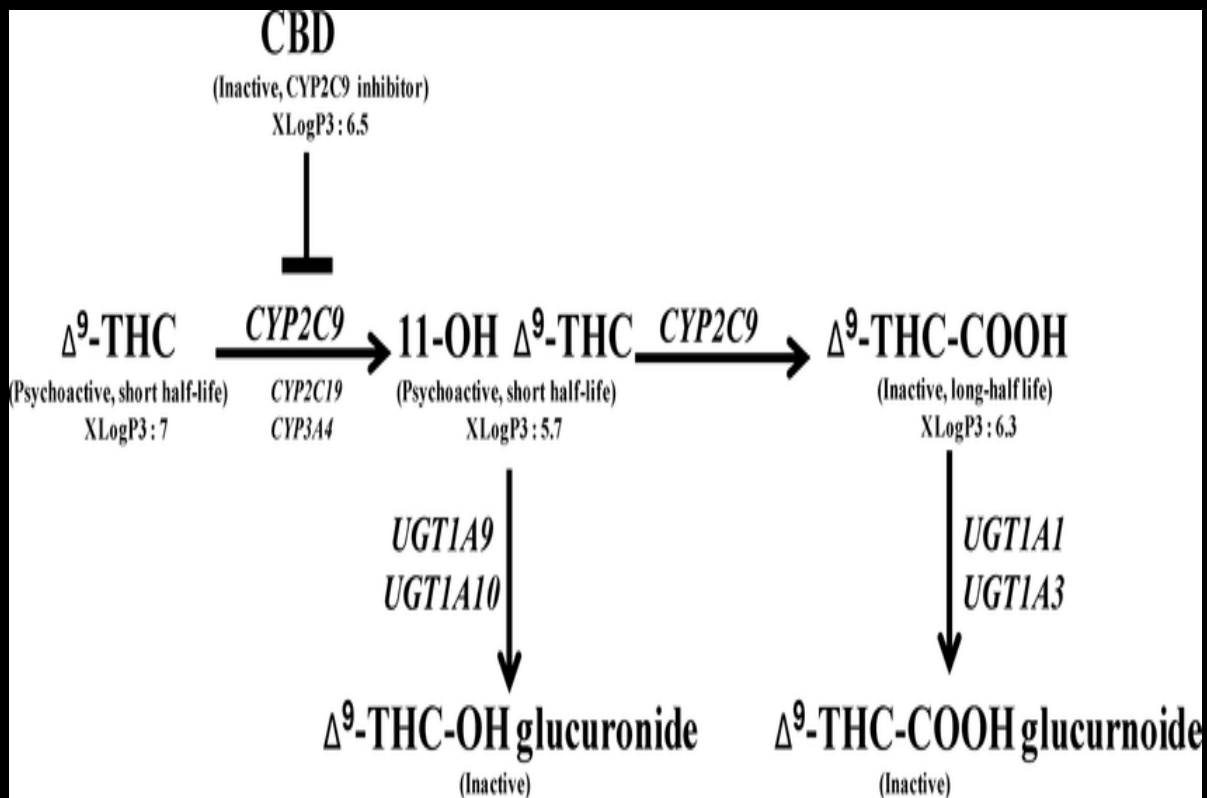


# BIOAVAILABILITY THC

- Smoking (Inhalation): Onset almost immediate: Negative Pulmonary: Cardiovascular: Toxins/Health Effects
- Vaporizing (warm air not flame-180-200 C): ? More efficient cannabinoid extraction: Fewer Negative Pulmonary adverse Effects
- Infused Edibles: Variability: Cannabinoid Ratio, Absorption, Fatty meals,
- Juicing:
- Topical/Transdermal: Creams, Balms, Patches: (Hydrophobic-Not easily skin penetrating) ? Subjective local relief—CBD/CBDN 10X's THC
- Oromucosal:

Mode of Administration	Time of Onset of Effects	Time of Peak Effects	Duration of Effects
Vaporization or Smoking	90 seconds	15 – 30 minutes	2 - 3 hours
Oral Administration	90 minutes	2 – 6 hours (There is considerable variability among patients.)	4 – 12 hours
Oromucosal Spray	0.5 – 2.5 hours	1.5 – 4.25 hours	

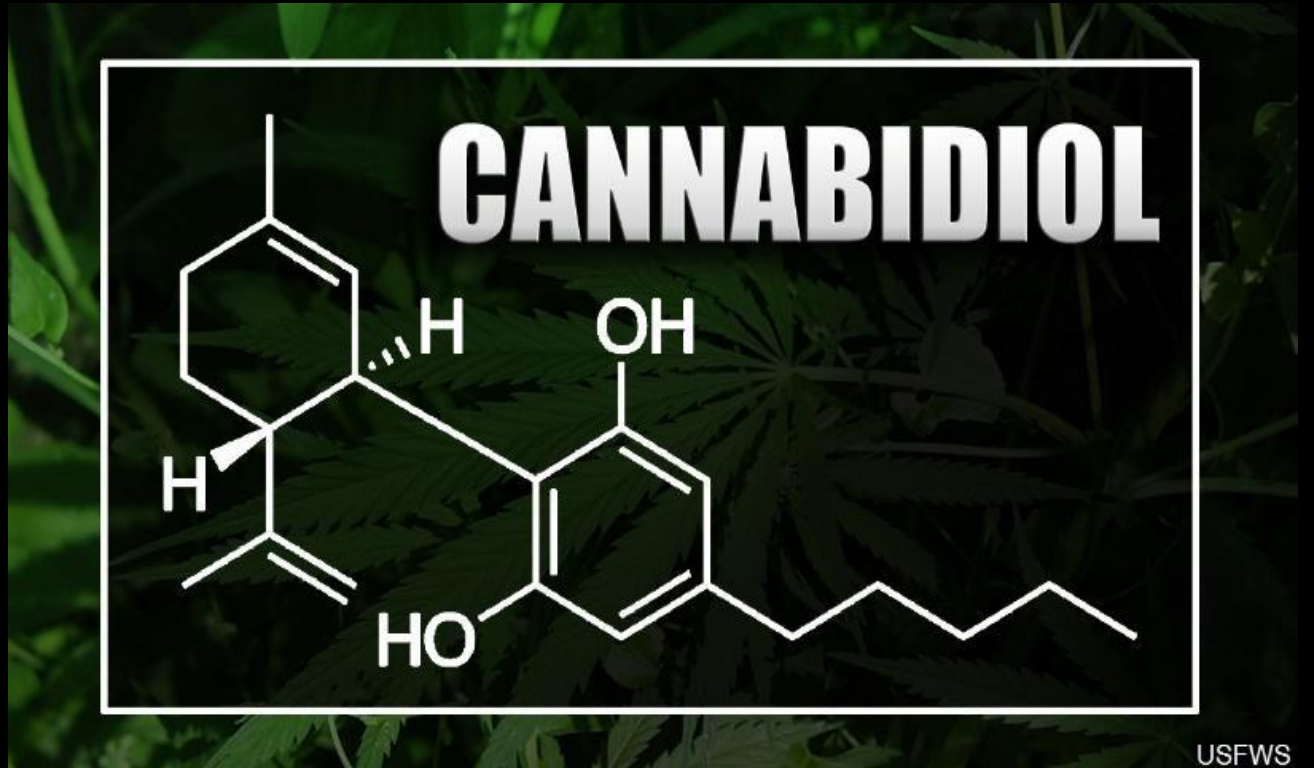
# METABOLISM OF THC



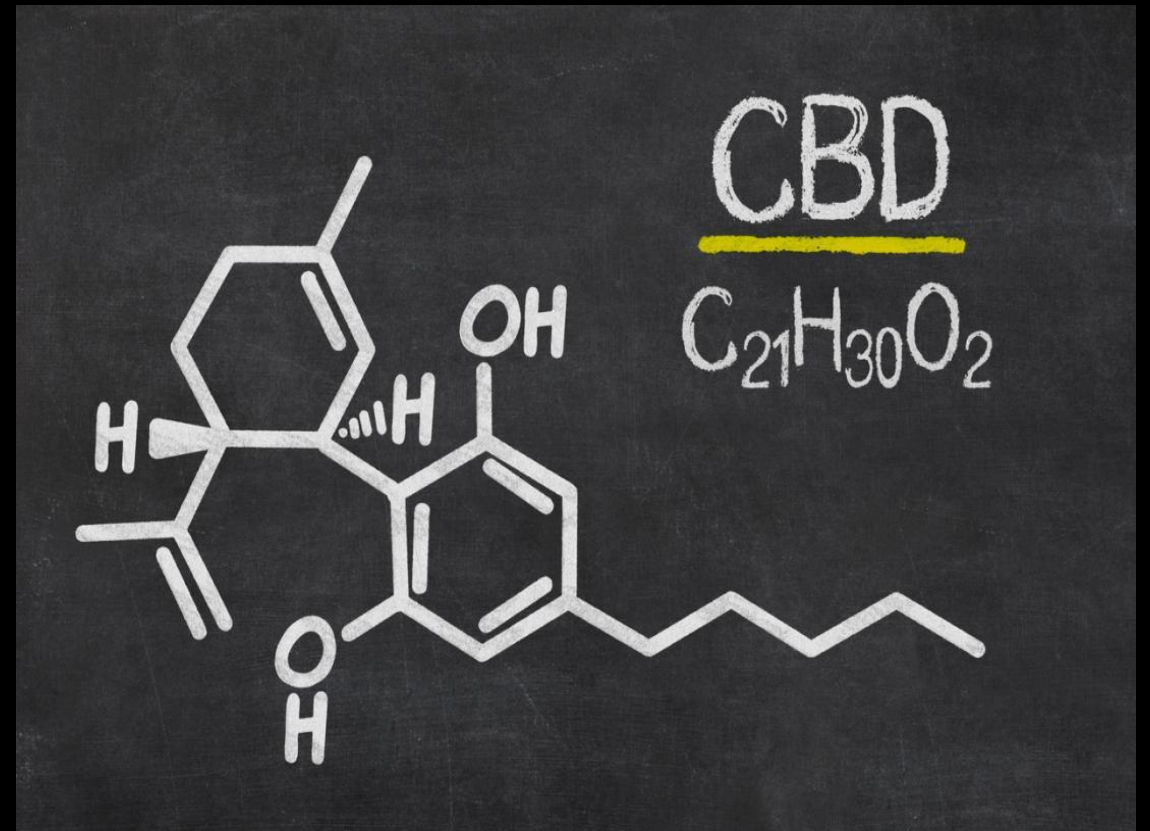
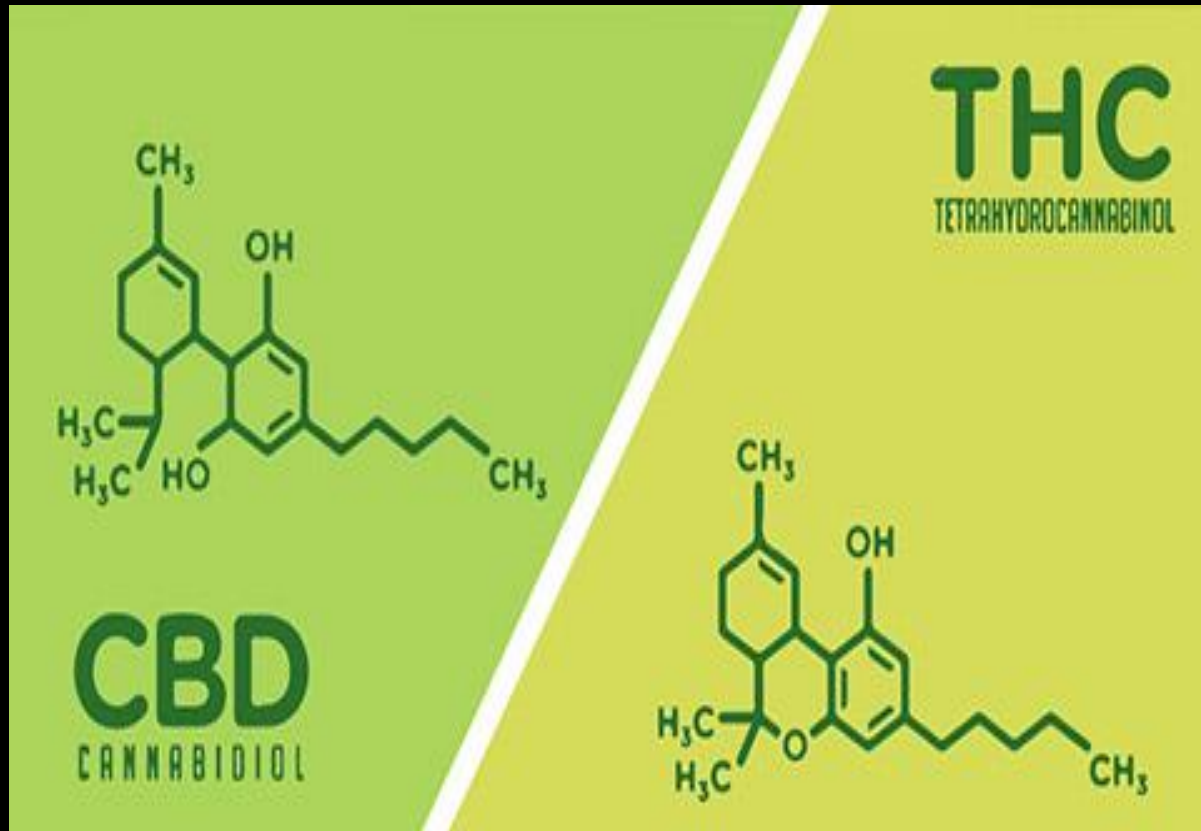
- Occurs mainly in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of cytochrome P450 (CYP) complex
- Nearly 100 metabolites have been identified
- Other tissues are also able to metabolize yet to a lesser degree

IT'S EVERYWHERE

CBD



# STEREISOMERS



# FDA CHIEF CLARIFIES ENFORCEMENT PRIORITIES FOR CBD PRODUCTS: 28 MARCH 2019



- “Regulatory and Enforcement Uncertainty”
- Discretion
- Only if “Over-the-line” claims; e.g.-  
“it can cure cancer or prevent Alzheimer’s disease”
- Exists as approved drug: Epidiolex
- May take years to enact CBD regulations
- Food vs drug: certain concentrations, potency, purity: Fish Oil





# COLORADO "SCHOLARLY ACTIVITY"

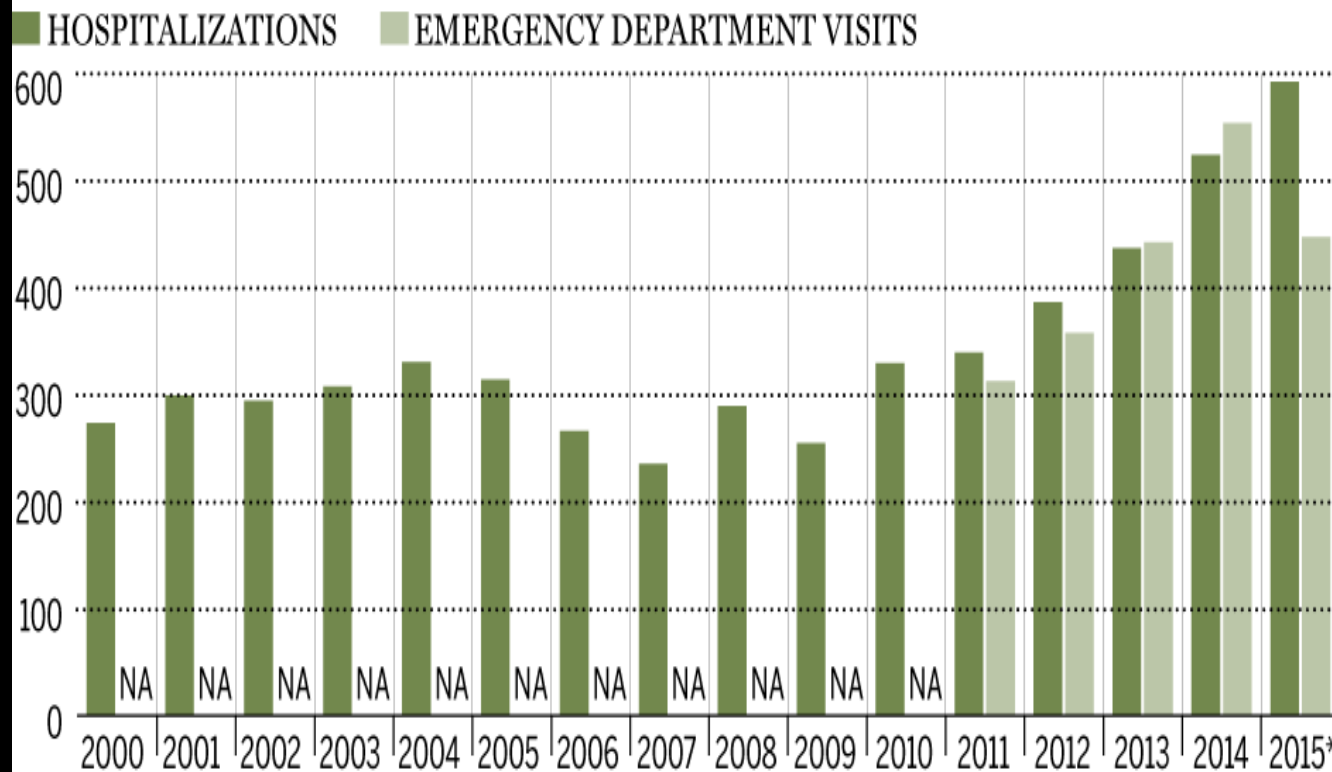


## LEGALIZED POT LINKED TO SPIKE IN COLORADO HOSPITAL VISITS

*Despite marijuana's medical properties, users are increasingly seeking medical help for rapid heart rates, vomiting and anxiety.*

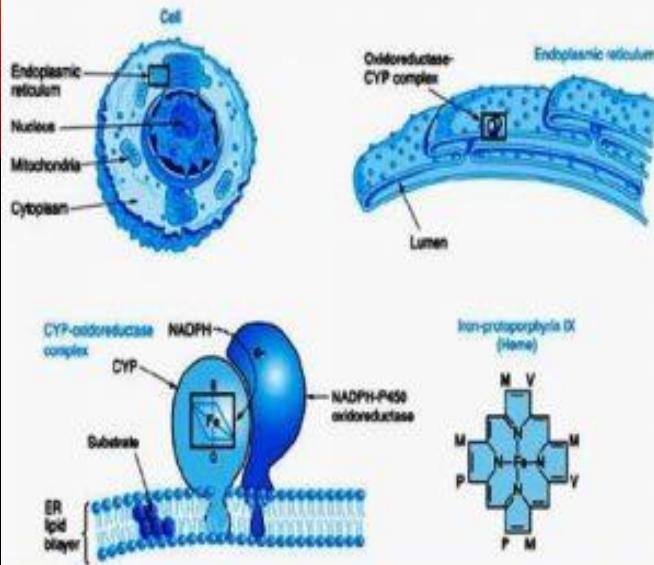
### RATES OF HOSPITALIZATION AND EMERGENCY DEPARTMENT VISITS

WITH POSSIBLE MARIJUANA EXPOSURES AND DIAGNOSES, PER 100,000, IN COLORADO



\*Jan.-June

## Location of Cytochrome P450

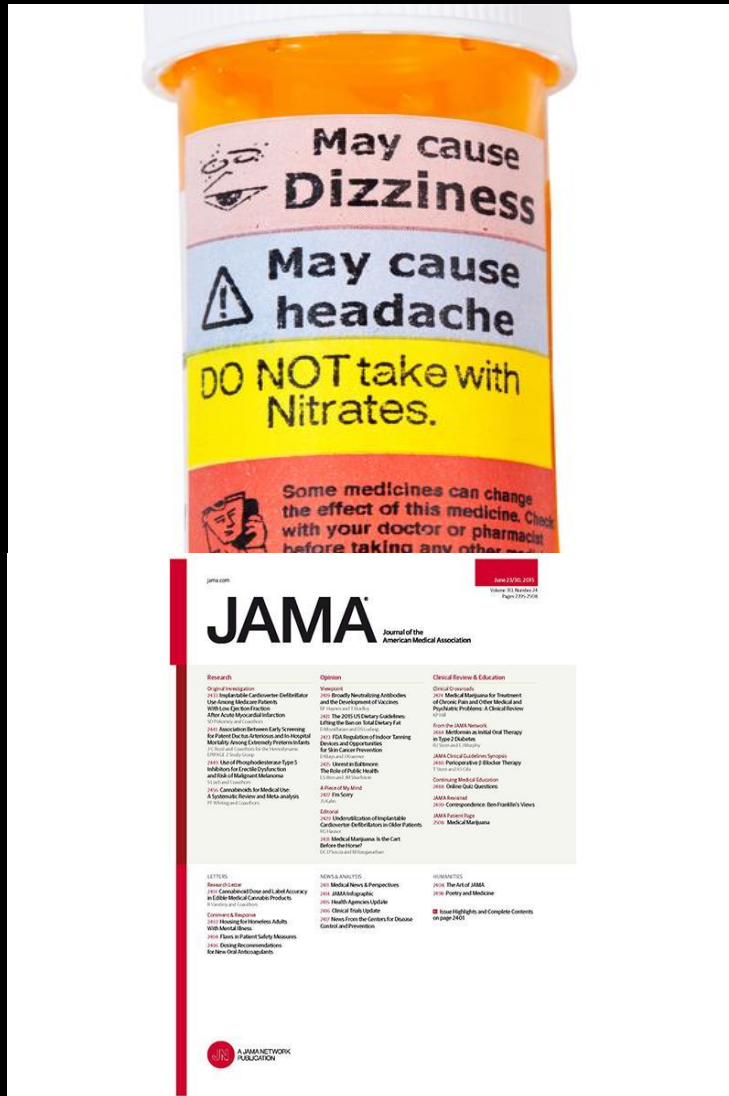


# DRUG INTERACTIONS

- CYP450 Inhibition
- Warfarin, most Statins, Erythromycin
- Azole antifungals, clobazam, other AEDs
- ETOH, Benzodiazepines
  
- NSAID, particularly indomethacin, can antagonize some effects of TCH
- Cholinergic drugs can modulate the effects of cannabis.
- Anticholinergics may increase the psychoactive side effects



# CANNABINOIDS FOR MEDICAL USE: ADVERSE EFFECTS (AE)



- Common AE:
- Dizziness
- Dry Mouth
- Nausea
- Fatigue
- Somnolence
- Euphoria
- Vomiting
- Disorientation, Drowsiness
- Confusion, Loss of Balance
- Hallucination

26 MARCH 2019



# Annals of Internal Medicine®

LATEST ISSUES CHANNELS CME/MOC IN THE CLINIC JOURNAL CLUB WEB EXCLUSIVES AUTHOR INFO

ORIGINAL RESEARCH | 26 MARCH 2019

## Acute Illness Associated With Cannabis Use, by Route of Exposure: An Observational Study

Andrew A. Monte, MD, PhD; Shelby K. Shelton, MPH; Eleanor Mills, BS; Jessica Saben, PhD; Andrew Hopkinson, BS; Brandon Sonn, MS; Michael Devivo, BA; Tae Chang, MD; Jacob Fox, BA; Cody Brevik, MD; Kayla Williamson, MS; Diana Abbott, PhD

Article, Author, and Disclosure Information

**FULL ARTICLE**

- Abstract
- Methods
- Results
- Discussion
- References
- Figures
- Tables
- Comments

### Abstract

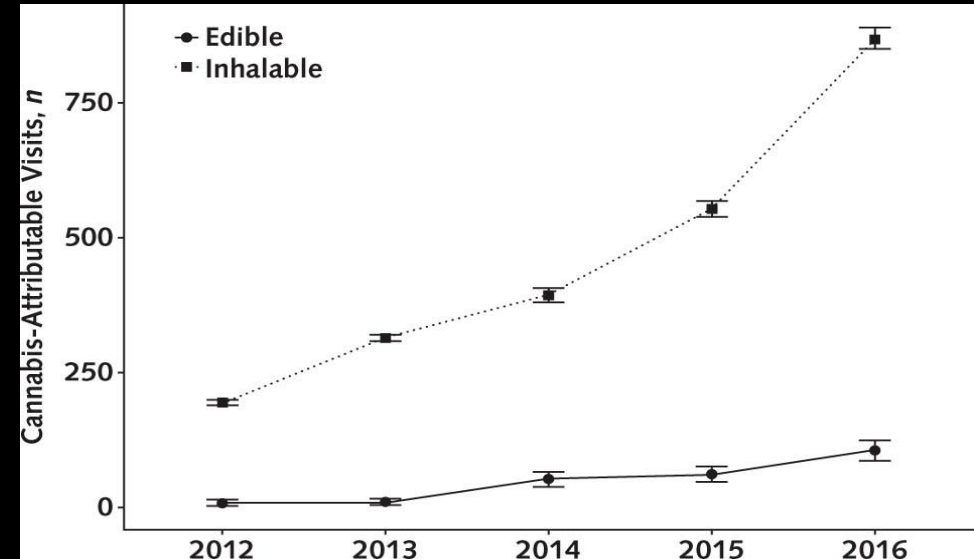
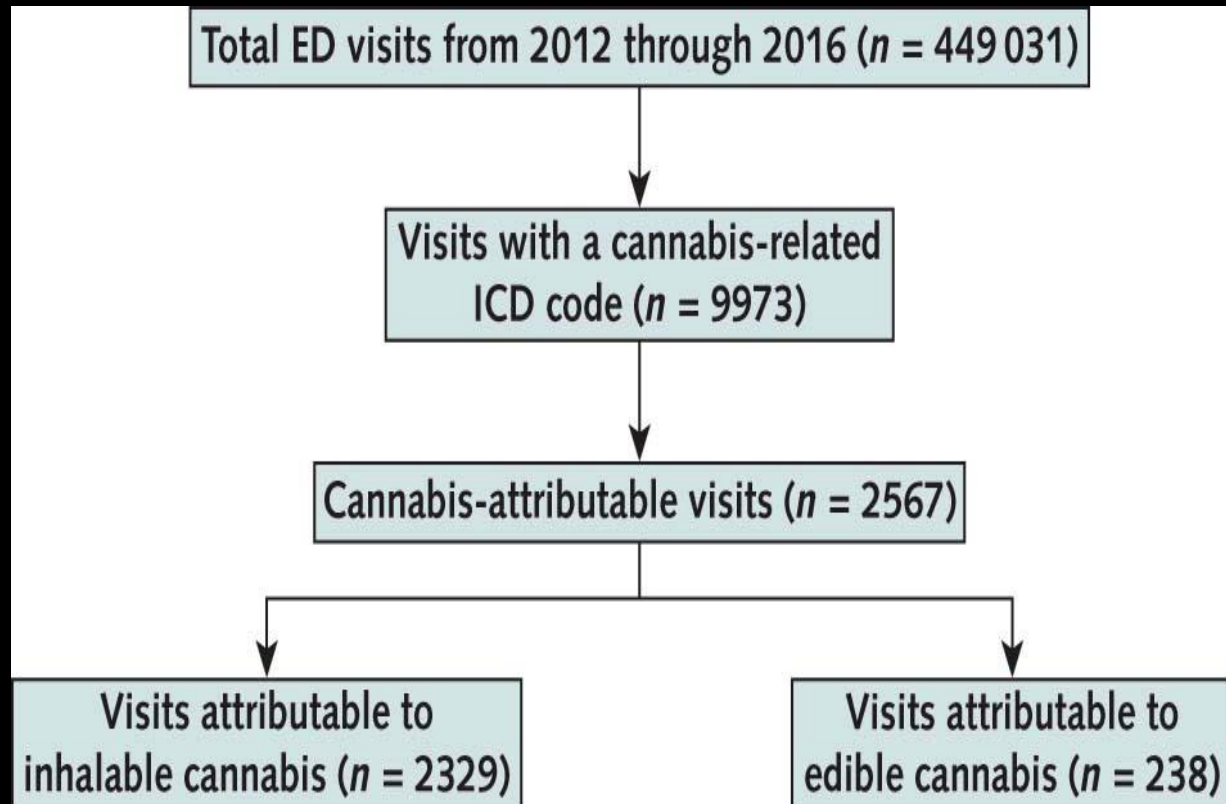
**Background:** Little is known about the relative harms of edible and inhalable cannabis products.

**Objective:** To describe and compare adult emergency department (ED) visits related to edible and inhaled cannabis exposure.

**Design:** Chart review of ED visits between 1 January 2012 and 31 December 2016.

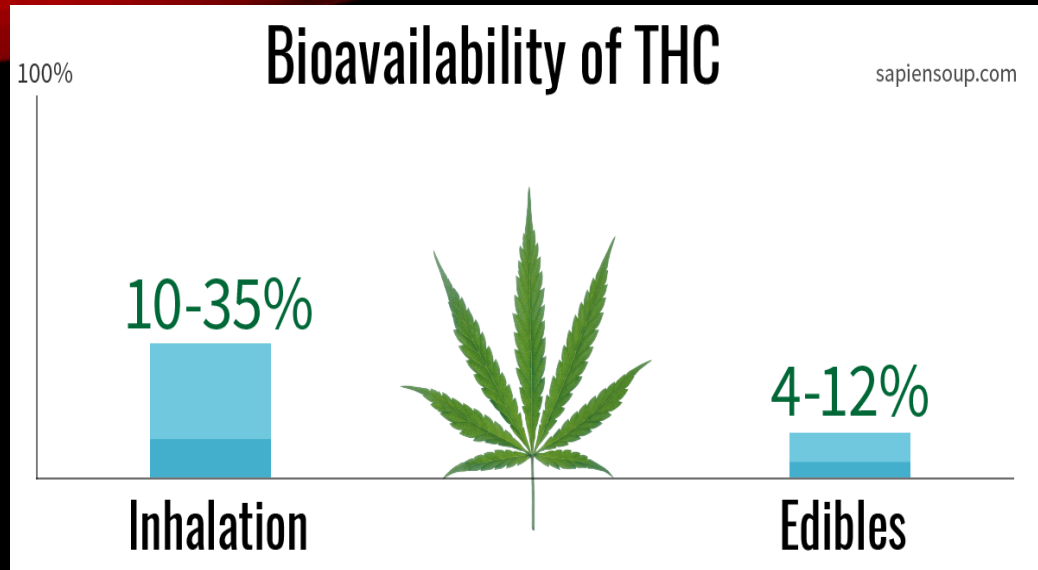
**Setting:** A large urban academic hospital in Colorado.

# LITTLE IS KNOWN ABOUT THE RELATIVE HARMS OF EDIBLE AND INHALABLE CANNABIS



- Inhaled: Cannabinoid Hyperemesis Syndrome
- Edible: 1% total cannabis sales: 11% of ED visits
- Acute psychiatric, intoxication, and cardiovascular symptoms
- UC Hospital ED

# EDIBLES



- Slow rate of absorption; 3 hours blood peak vs inhaled 30 min
- Slower clearance (12h vs 4)
- Escape first-pass
- Labeling
- More intense and unpleasant psychiatric symptoms
- Psychosis with violence, Cardiovascular
- Deaths 3: suicide, killed by husband, suicide at the ski resort

# INHALABLE CANNABIS: HOSPITAL ADMISSIONS



- 309 times more THC sold as flower
- GI: Cannabinoid Hyperemesis Syndrome (chronic use)
- Acute intoxication and AE
- 39% hospitalization inhaled vs 19% edible



**Table 2. Most Common Clinical Conditions Associated With Cannabis-Attributable Visits, Stratified by Route of Exposure**

Condition	Edible Exposure (n = 238), n (%)	Inhalable Exposure (n = 2329), n (%)	Absolute Difference (Edible – Inhalable) (95% CI), percentage points	Total Visits, n (%)
Gastrointestinal symptoms	36 (15.1)	752 (32.3)	-17.2 (-12.2 to -22.1)	788 (30.7)
Cannabinoid hyperemesis syndrome	20 (8.4)	420 (18.0)	-9.6 (-5.7 to -13.5)	440 (17.1)
Intoxication	115 (48.3)	647 (27.8)	20.5 (13.9 to 27.1)	762 (29.7)
Psychiatric symptoms	62 (26.1)	571 (24.5)	1.6 (-4.2 to 7.4)	633 (24.7)
Acute psychiatric symptoms	43 (18.0)	254 (10.9)	7.1 (2.1 to 12.1)	297 (46.9)
Acute exacerbation of underlying chronic disease	1 (0.4)	93 (4.0)	-3.6 (-2.5 to -4.7)	94 (14.1)
Chronic psychiatric condition	1 (0.4)	99 (4.3)	-3.9 (-2.8 to -5.0)	100 (15.8)
Cardiovascular symptoms	19 (8.0)	73 (3.1)	4.9 (1.4 to 8.4)	92 (3.6)

- Medical Cannabis 2009: Recreational 2014
- 10,00 ED cannabis related ED visits
- Pub Med search: ED visits associated with cannabis; increasing
- Edibles: Unintentional pediatric exposure:

# CANNABINOID HYPEREMESIS SYNDROME



- Most common ED visits 31%
- Chronic Use
- Cyclic nausea and vomiting (Cyclic vomiting syndrome)
- Compulsive hot baths and showers
- Resolution after cessation of cannabis use
- 41 per 113,262 to 87 per 125,095 ED visits
- Admissions: imaging, lab work, endoscopies

# cannabis intoxication

## What are the signs & symptoms of acute Cannabis Intoxication ?

- Physical
  - Tachycardia
  - Postural hypotension
  - Conjunctival injection
  - Dry mouth
  - Increased appetite
- Cognitive
  - Suspiciousness or Paranoid ideation
  - Impaired judgment
  - Impaired Attention
  - Impaired Reaction Time
- Affective
  - Euphoria
  - Disinhibition
  - Anxiety
- Perceptual
  - Temporal Slowing
  - Auditory, Visual or Tactile Illusions or Hallucinations
  - De-personalisation & De-realisation

DEPT OF PSYCHIATRY 19/11/2016

- Second most common
- Cannabis tourism
- THC content: edibles
- 29.6%



# PSYCHIATRIC SYMPTOMS

- 24% of Ed visits
- Acute symptoms: Anxiety and Psychosis
- *Lancet Psychiatry*: March 2019: correlation “between daily use and psychosis
- Reviewed in the 2017 *National Academy of SEM*
- Medicinal: avoidance in psychiatric history: close family history

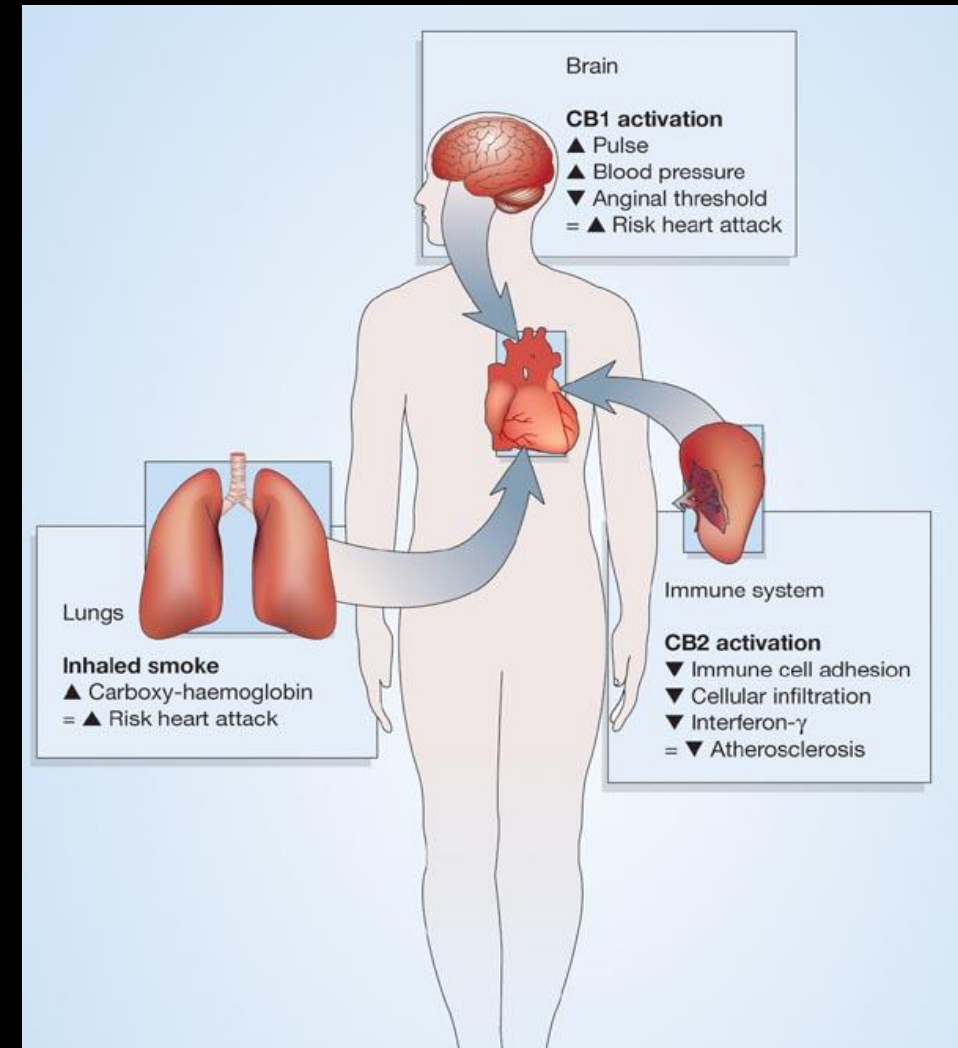


# MOTOR VEHICLE



- Highway deaths in CO 2017 “marijuana in their system” increasing
- Drivers intoxicated “5ng/ml: down
- Science of Impairment--lacking
- Irregular use 10mg THC likely to impair( typical cannabis cigarette 60-115 mg THC

# CARDIO-PULMONARY



# SPECIAL CONCERNS AND CONTRAINDICATIONS

- Concerns: Liver and Kidney Disease
- COPD: Delivery via Inhalation
- History of Substance Abuse
- Drug with other sedating meds
- ? History Seizure disorder THC vs CBD
- Fall risk: orthostasis, sedation, visual-spatial disorientation
- History of psychotic illness (family history schizophrenia-1<sup>st</sup> degree)
- Ischemic Heart disease—vasodilator, increase cardiac demand: 4-fold increase in ACS in first hour
- Hypersensitive to cannabis constituents
- Pregnancy/breast-feeding: LBW
- Exposure to children

# DETERMINE DOSE



Handwritten mathematical notes and formulas surrounding the word "Potency".

**Potency**

Surrounding formulas include:

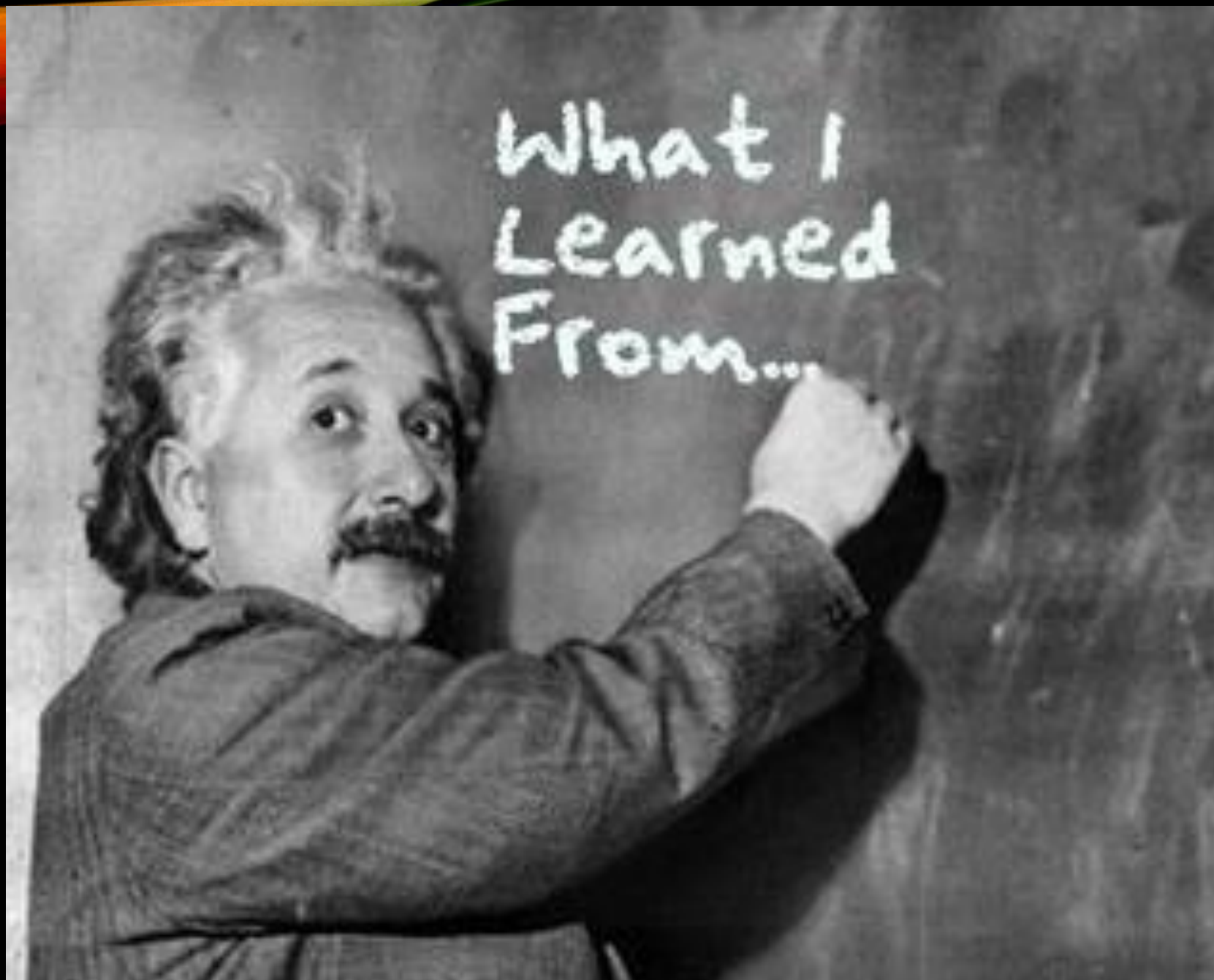
- $S_n = A_n U^n A_n$
- $|A_n| = \frac{n!}{2} \left| \int f(x) \log_2 \frac{1}{f(x)} dx \right| < \epsilon \quad g^{-1} \cdot g = e$
- $\int dG_n(x) \approx \frac{1}{2} \sum_{k=0}^{\infty} e^{-\frac{kx}{2}} = H(k)$
- $\prod_{k \in b} \prod_{i=1}^{n-1} H_i; \prod_{n=0}^{\infty} X_n$
- $f_n(t) = \frac{2^k n! e^{-2t}}{(n-1)!}$
- $f_n(x) = \frac{G_n(x)}{1+G_n(x)}$
- $U_n^+(n) = (2n) - (2n - c)$
- $\lim_{n \rightarrow \infty} \frac{f_n(x)}{n} = P_e$
- $R = \int p(t) dt$
- $[p(t) e^{-itx} + p(t e^i)]$
- $\frac{1}{n} \psi(t) = \psi\left(\frac{n}{m} t\right)$
- $g_n(x) = \frac{P_e^n}{\sum_{j=1}^n P_e^j}$
- $P(n) = \frac{1}{2^n} (1 - \sqrt{1 - e^{-2n}})$
- $\lim_{n \rightarrow \infty} \frac{1}{n} \ln \left( \frac{x}{n} \right) = \frac{1}{2^n} e^{-\frac{x}{2^n}}$
- $P_n(t) = P_n^{(c)}$
- $P(\lim_{n \rightarrow \infty})$
- $f(x) = \sum_{j=1}^n a_j \left( \sum_{k=1}^{n_j} b_{kj} x^k \right) \left( \frac{2t}{2t} \right) \approx \frac{1}{\Gamma(t)}$
- $Q(x) = \int_1^x f(w) dP$
- $f(x) = -\log_2 \left( \frac{\sum_{k=1}^n P_k^k \log_2 \frac{1}{P_k}}{\sum_{k=1}^n P_k} - \left( \frac{\sum_{k=1}^n P_k \log_2 \frac{1}{P_k}}{\sum_{k=1}^n P_k} \right)^2 \right)$
- $P_n^{(m)} = \sum_{i=1}^m P_i^{(m)} P_i^{(m-r)} \frac{1}{2^m} \int \operatorname{Re} \left\{ p(t) \frac{e^{itx} - e^{itb}}{it} \right\} dt$



# CHALLENGES OF “RECOMMENDATION”



- Recreational vs Medicinal Use
- Mode of Administration
- Purity and Quality of the Cannabis product
- Medical Grade Cannabis: Impurities, molds, additives, others
- Concentrations/ratios of various cannabinoids
- Recreational: High THC
- Medicinal: High CBD
- JAMA 2016: 17% accurately labeled; 23% overestimate THC and 60% underestimate



What I  
Learned  
From...

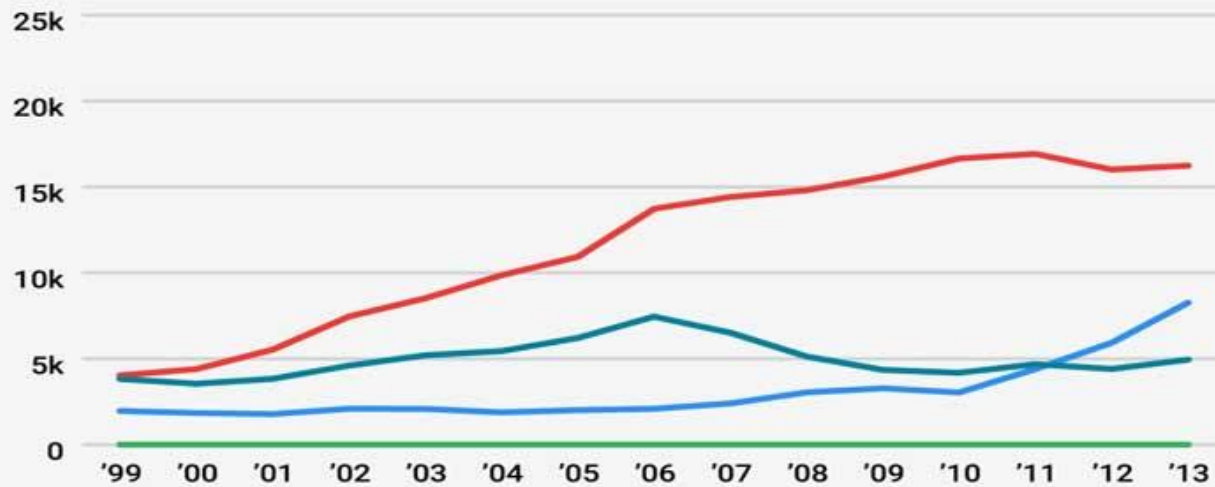


# THE TAKE-HOME MESSAGE

## OVERDOSE DEATH RATES IN AMERICA

Opioid Pain Relievers Heroin Cocaine Marijuana

All underlying causes of death\*



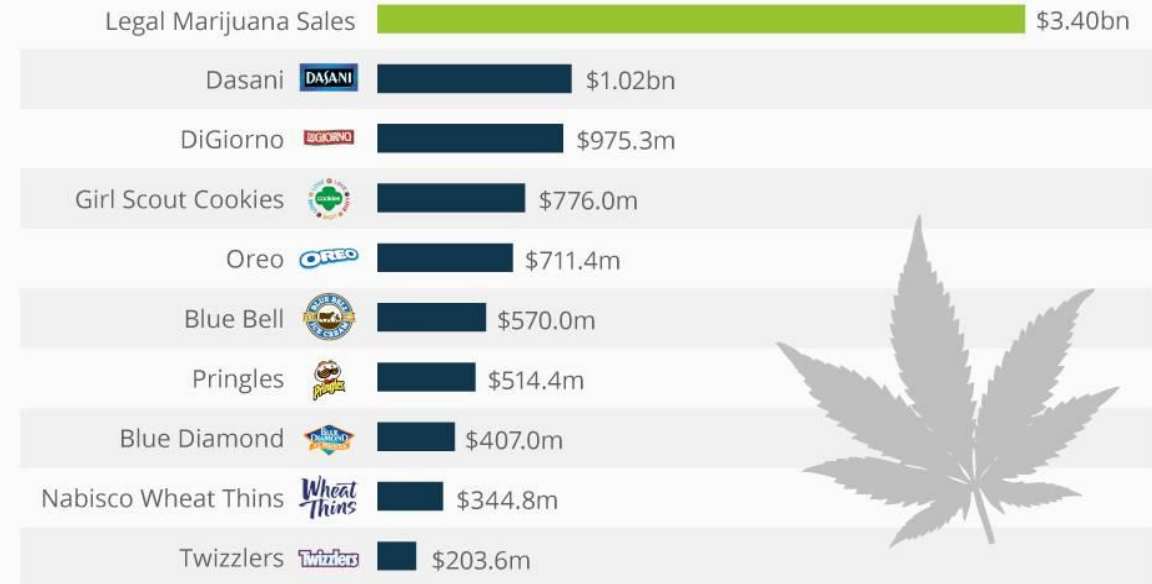
\*Includes deaths from unintentional drug poisoning, suicide drug poisoning, homicide drug poisoning or drug poisoning of undetermined intent.

SOURCE: Wonder.cdc.gov

BUSINESS INSIDER

## America's 2015 Marijuana Sales In Context

2015 legal marijuana sales and selected 2014 company sales in the U.S.\*



@StatistaCharts

\*52 weeks ending Jan 2015. Oreo & Dasani fiscal year ended April & May 2015 respectively

Source: Company Reports

statista

“SHARE YOUR KNOWLEDGE. IT IS A  
WAY TO ACHIEVE IMMORTALITY”

