

# MEDICAL MARIJUANA

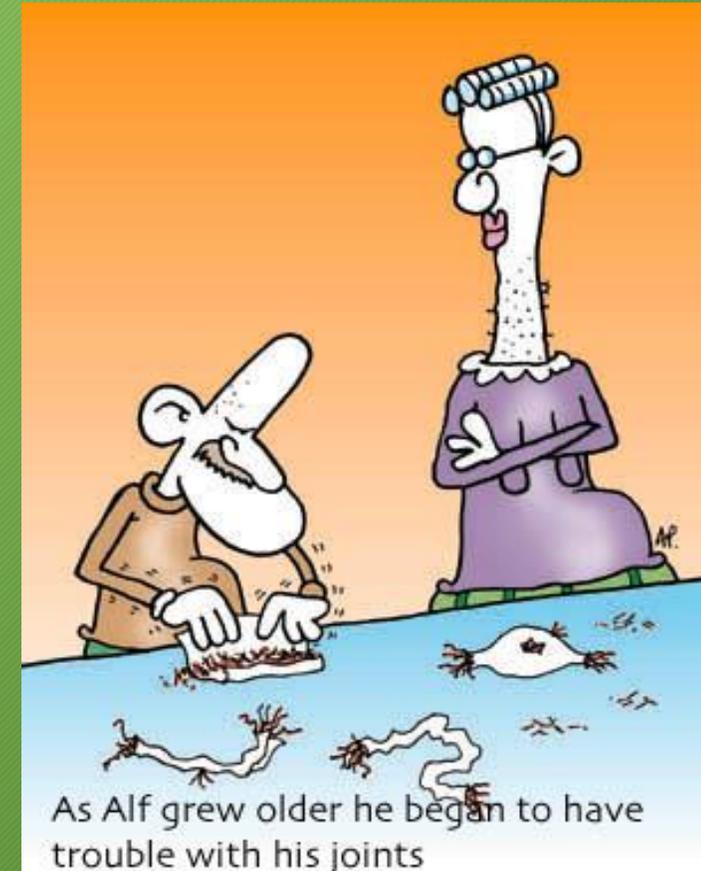


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*Dept. of Consumer Protection*

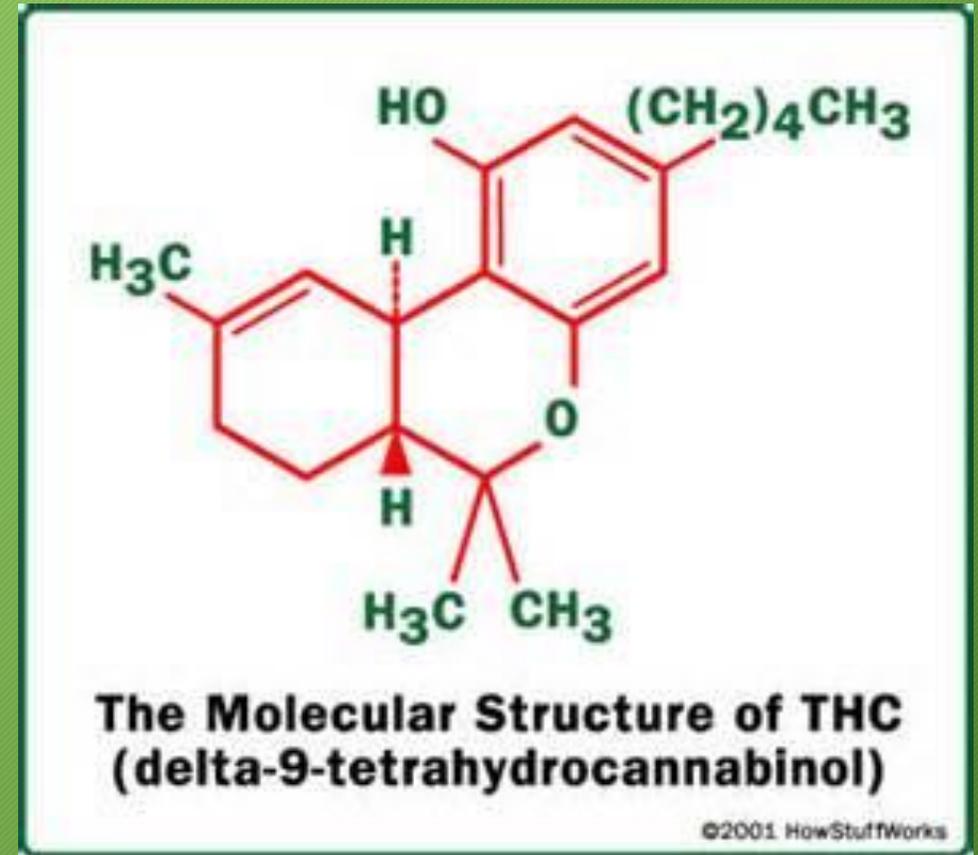
# Goals of Presentation

- When rendering opinions we should avoid our philosophical bias while focusing on efficacy, safety and risk vs benefit
- History
- Epidemiology
- Pharmacokinetics & Pharmacodynamics
- Medical uses
- Prescriber/ medical practice legal exposure of prescribing

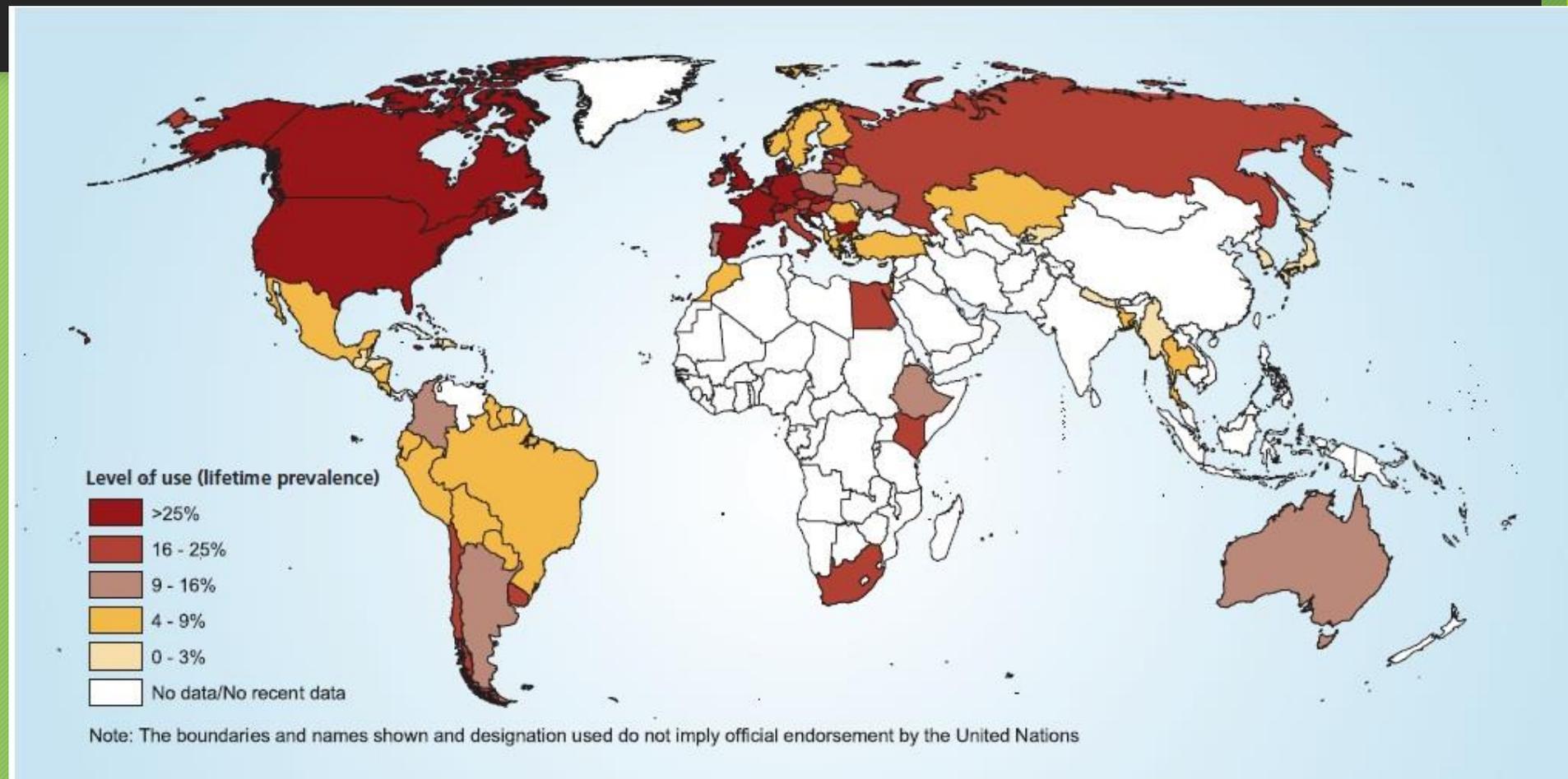


# HISTORY

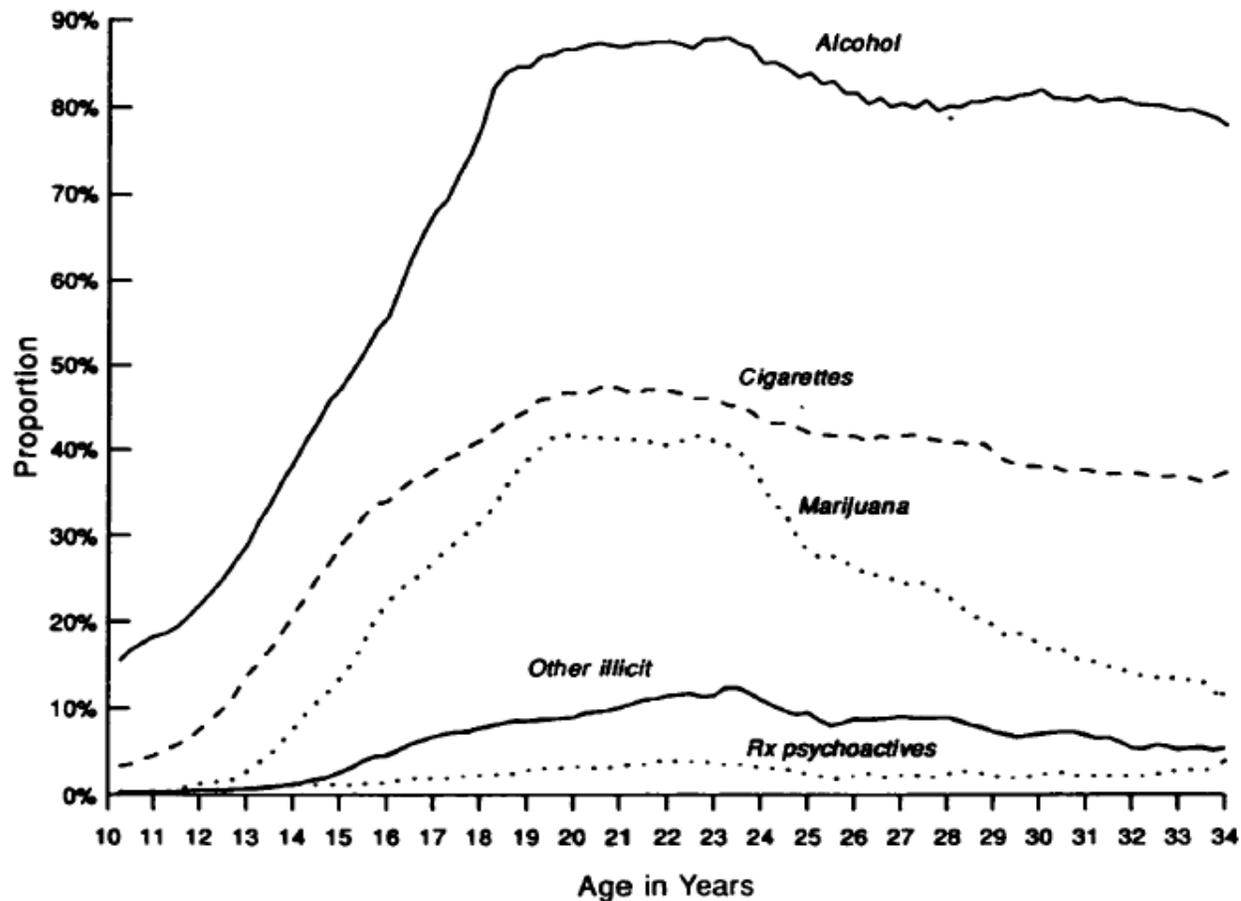
- Professor Raphael Mechoulam in 1964, identified in the plant *Cannabis sativa*, the psychoactive component of marijuana and hashish,  $\Delta^9$ -tetrahydrocannabinol (THC)
- Before 1980's thought was that cannabinoids effect was an indirect interaction w/ cell membrane. The 1<sup>st</sup> cannabinoid receptor discovered in 1980's (CB1 & CB2) and probably more.
- 1970 congress placed into Sched I
- Dronabinol (Marinol) (100% THC); 1985 sched II, 1999 sched III : indications anorexia w/ AIDS, N/V w/ Chemotherapy
- US: Fed.- Sched I, Canada Sched II
- 22 states sched II, as of May 2014



# World Epidemiology



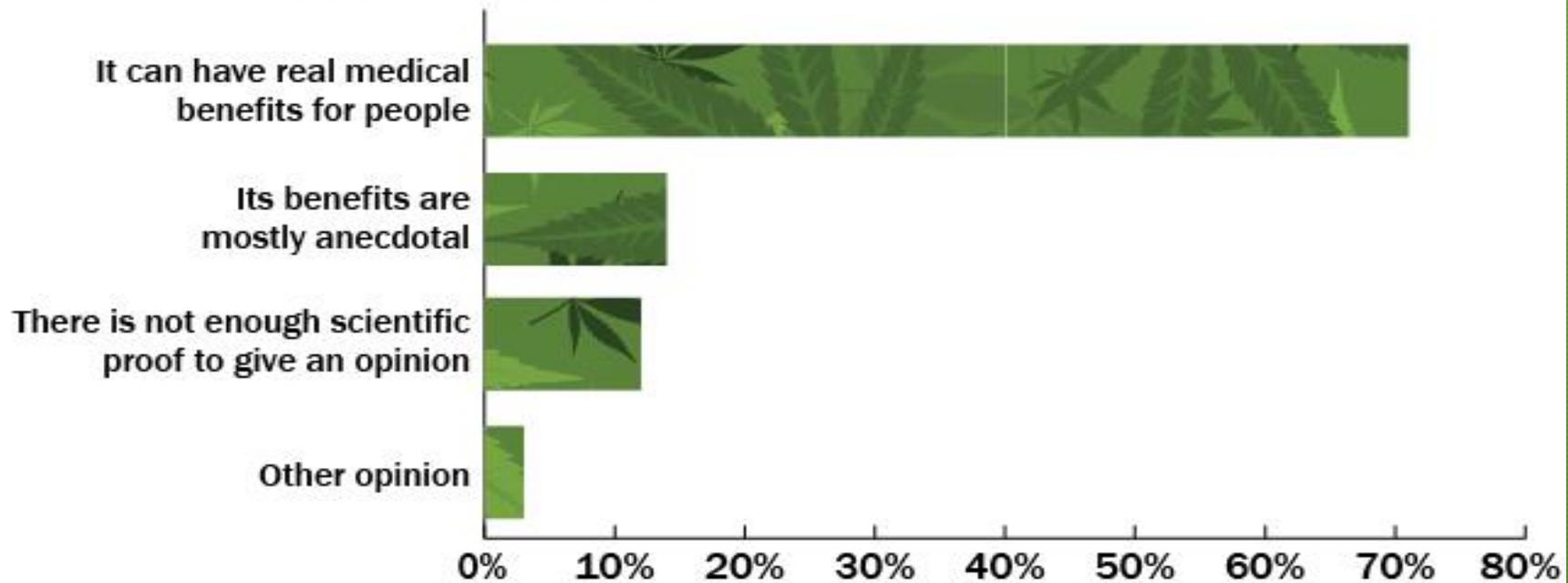
# Drug use with increasing age



Chen, K. & Kandel, D.B.  
1995, *Am J Pub Health*,  
85(1):41-47. © American  
*Journal of Public Health*.

# Medscape Physician Survey

Which of the following statements best reflects your opinion of marijuana's medical benefits?



# N. Engl J Case Survey

Medicinal Use of Marijuana, N Engl J Med 2013; 368:866-868 [February 28, 2013](#)

## CASE VIGNETTE:

Marilyn is a 68-year-old woman with breast cancer metastatic to the lungs and the thoracic and lumbar spine

## Which option would you recommend?

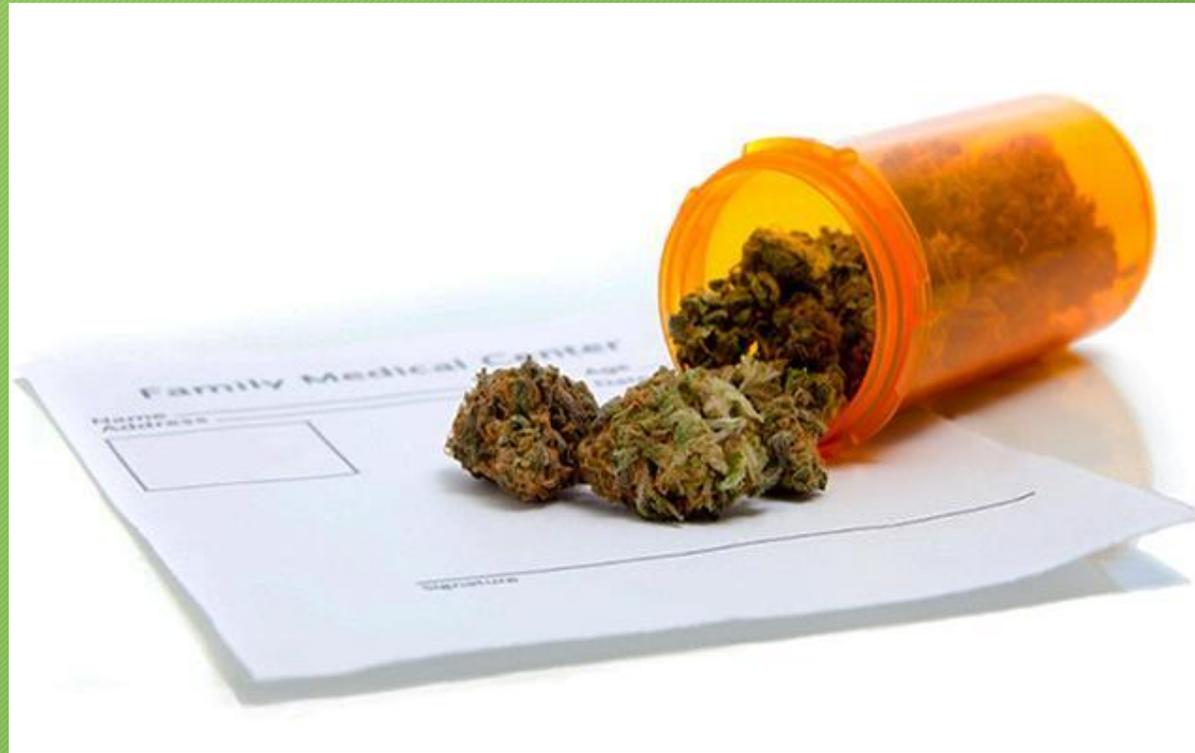
- Recommend the medicinal use of marijuana  
76%
- Recommend against the medicinal use of marijuana  
23%

Poll closed March 7, 2013  
(1446 total Responses)

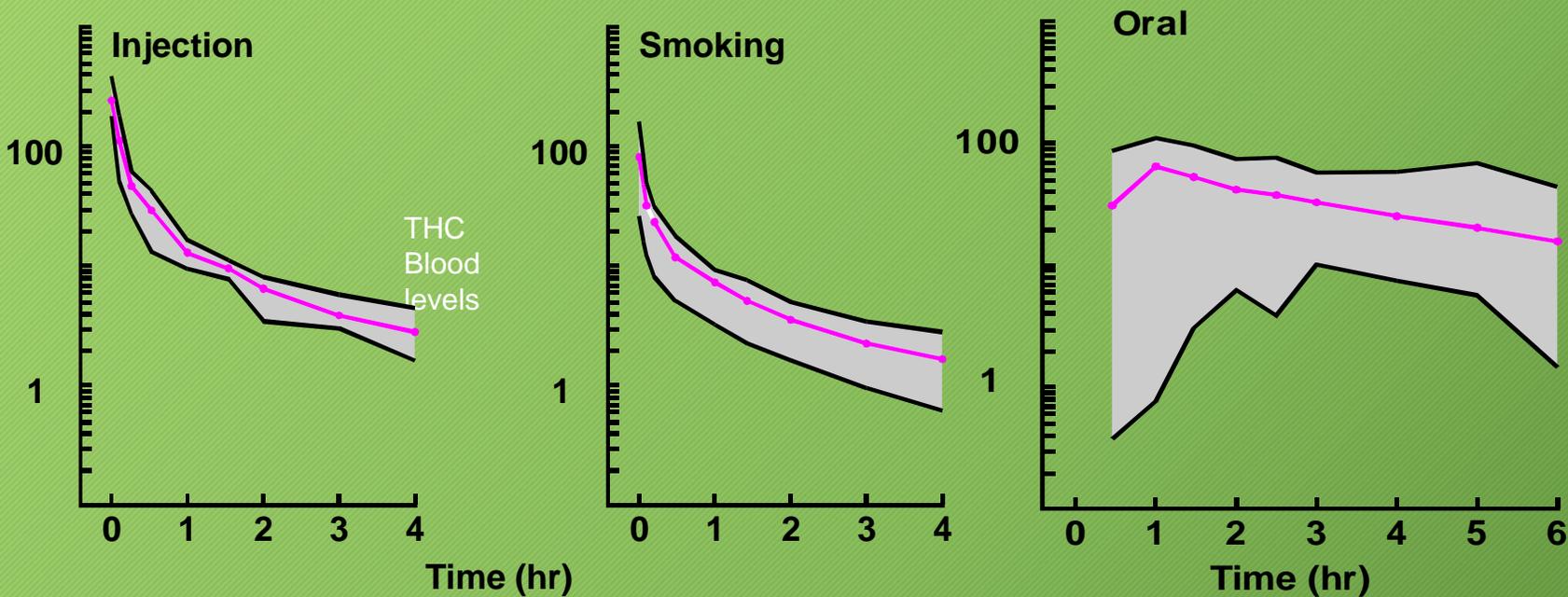
# CT qualifying debilitating medical conditions include:

- Cancer
- Glaucoma
- Positive Status for Human Immunodeficiency Virus or Acquired Immune Deficiency Syndrome
- Parkinson's Disease
- Multiple Sclerosis
- Damage to the Nervous Tissue of the Spinal Cord with Objective Neurological Indication of Intractable Spasticity
- Epilepsy
- Cachexia
- Wasting Syndrome
- Crohn's Disease
- Post-Traumatic Stress Disorder
- ? Future additional dx's

# Pharmacology and mechanism of action

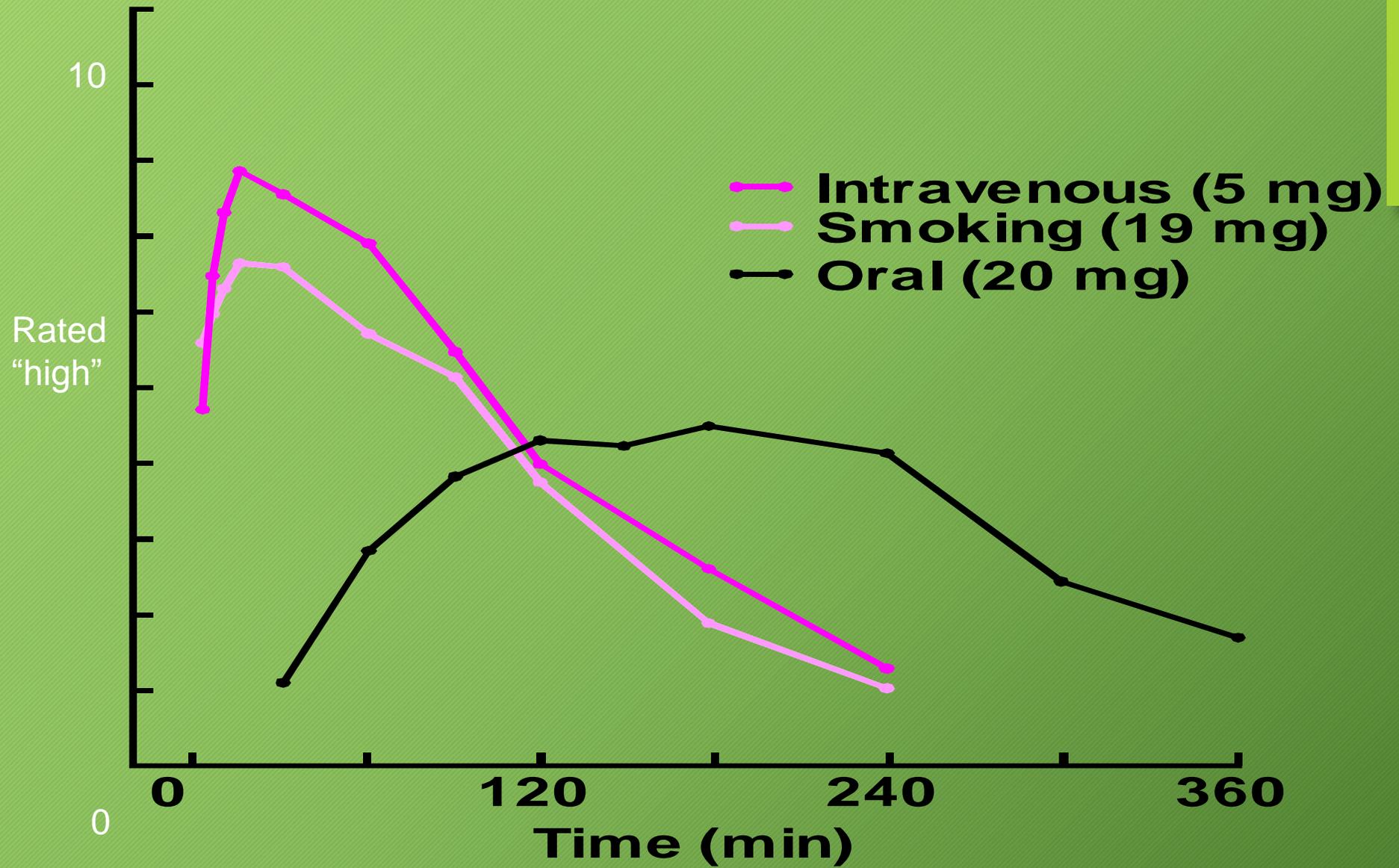


# Pharmacokinetics



$t_{1/2}$  distribution 0.5 hr,  
 $t_{1/2}$  for elimination 30 hr

Route of administration influences THC pharmacokinetics, left = 5 mg i.v. injection, center = smoking 13.0 mg, or right = consuming cookie with 20 mg (Agurell et al. 1986).



# Mode of cannabis action



- Two specific primary cannabinoid receptors
  - CB1 - brain and peripheral tissues
  - CB2 - immune system
  - CB?
- CB1 activation blocks TNF induced inflammation, protecting neurons from damage (ie reduce damage to motor neurons i.e. in ALS)
- CB2 receptors are upregulated in inflamed neural tissue (CNS disorders - ALS, MS)
- CB2 agonist AM-1241 at sx onset inc. mouse ALS survival 56% J Neurochem 2007;101:87-98
- Endocannabinoid sys might be involved in pathophysiology of ALS

## The Human Endocannabinoid System

THC and CBN are known for "fit" like lock and key into network of existing receptors. The Endocannabinoid System exists to receive cannabinoids produced inside the body called "Anandamide" and "2-Arachidonylglycerol". Stimulating the ECS with plant-based cannabinoids restores balance and helps maintain symptoms.

CB1 receptors are concentrated in the brain and central nervous system but also sparsely populates other parts of the human body.

Receptors are found on cell surfaces

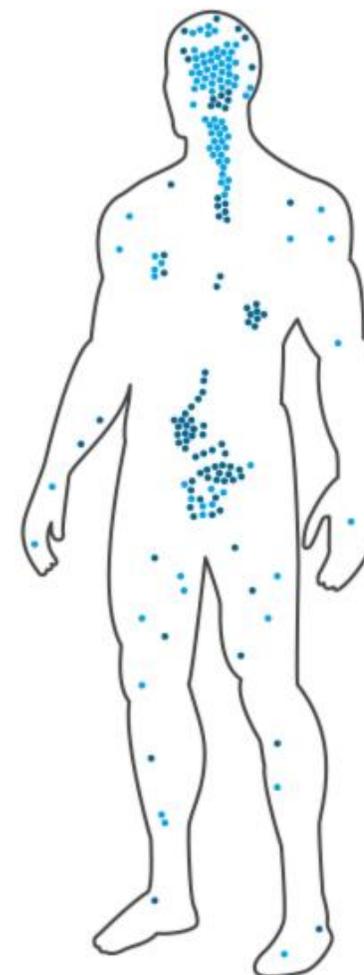


Cannabidiol

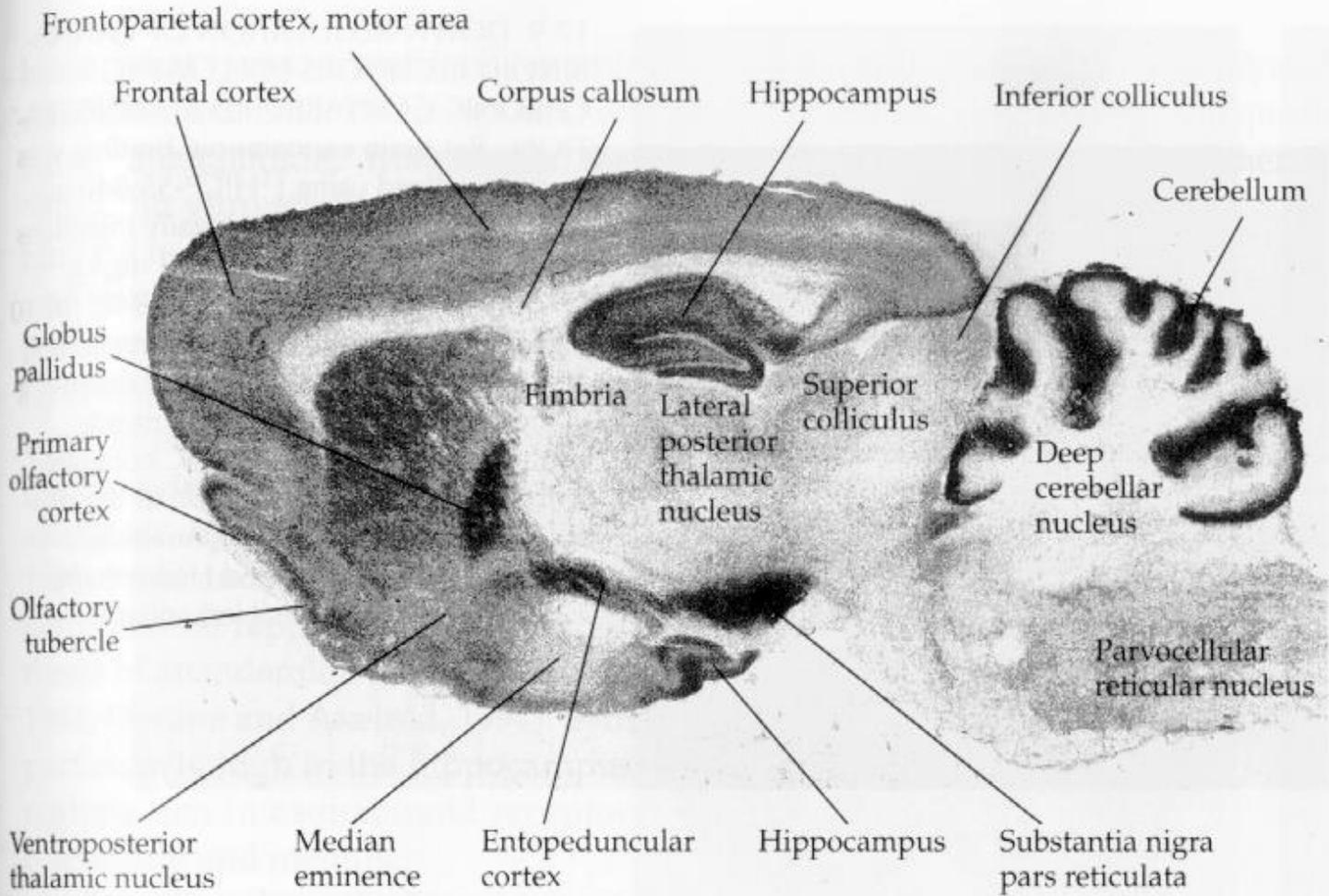
CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied



CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system



# Density of Cannabinoid Receptor 1 (Increased Darkness = more receptors labeled with [<sup>3</sup>H]CP-55,940)



- Hypothalamus- short term memory
- Hypothalamus- regulates appetite

# THC is the most psychoactive component of cannabis

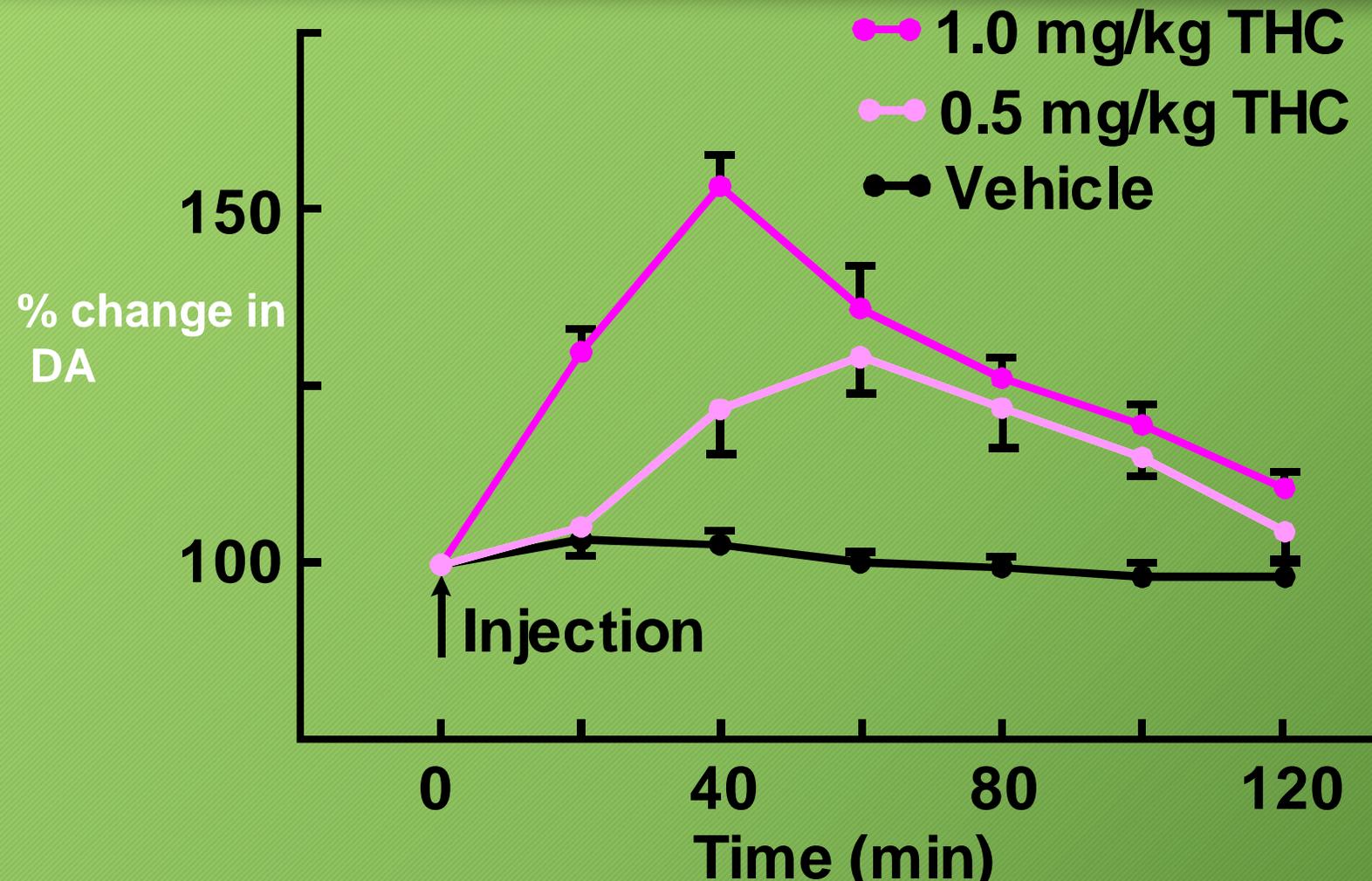
## Typical “effective” dosing of THC

- Low dose < 7 mg
- Medium dose = 7 - 18 mg
- High dose > 18 mg

There is a known tolerance to THC via down regulation of CB1 receptors

High probability of tolerance with chronic use, and low with intermittent

# Effects of THC on dopamine



- Cannabis Abuse/Dependence : assoc. w/ chronically lower Dopamine levels and is a possible marker for Addiction

# Research

- cannabinoid research has had its main focus on pathophysiology of the central nervous system
- neurotoxic effects of cannabinoids *in vitro* and *in vivo* were also described
- extremely low doses of THC, several days before or after brain injury, provides effective long-term cognitive neuroprotection
- treating chronic liver disease with CB<sub>1</sub> antagonists and CB<sub>2</sub> agonists ([Mallat et al., 2011](#))
- therapeutic potential of cannabinoids for cancer, as identified in clinical trials ([Guindon and Hohmann, 2011](#))
- cannabinoids are safe and modestly effective, particularly in neuropathic pain ([Lynch and Campbell, 2011](#))

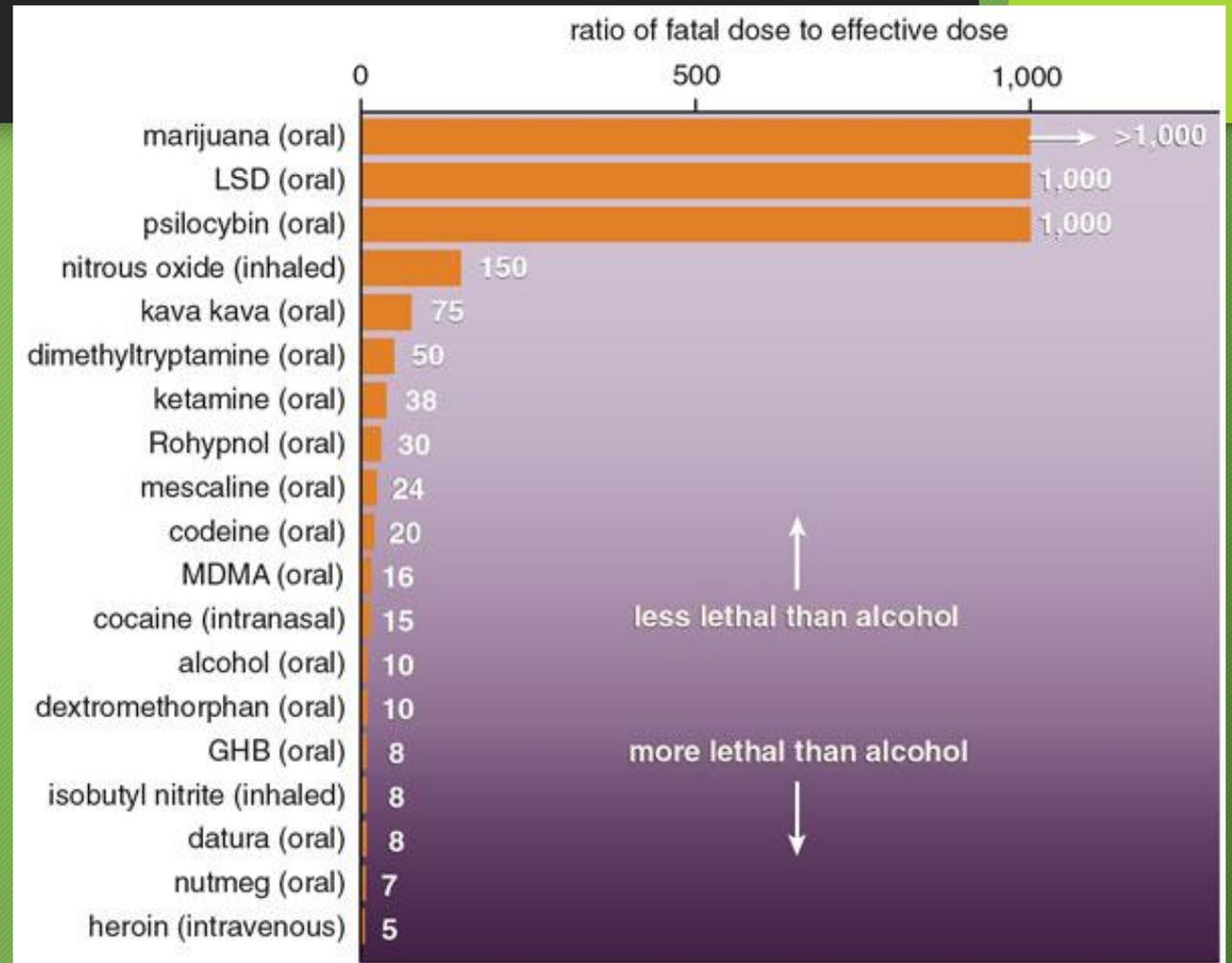
# Research cont.

- Neurology March, 2014;82;1083-1092: 2 well-powered class I studies of patients with relapsing-remitting (RR), secondary progressive (SP), and primary progressive (PP) types of MS, the panel concluded that oral cannabis extracts is effective for reducing both patient-reported spasticity symptoms and pain unrelated to central neuropathic pain.
- [FASEB J.](#) 2006 May;20(7):1003-5. Epub 2006 Mar 29.  
Increasing cannabinoid levels by pharmacological and genetic manipulation delayed disease progression in SOD1 ALS mice (56% inc. survival).
- Some beginning evidence: NMDA receptor modulation to reduce motor tone, increase seizure threshold, neuronal injury protection, decrease perception of pain & elevation of mood.
- [Pain Med.](#) 2009 Nov;10(8):1353-68. doi: 10.1111/j.1526-4637.2009.00703.x. Epub 2009 Sep 1.  
Systematic review and meta-analysis of cannabis treatment(18 trials). At 2008, evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms. More evidence from larger, well-designed trials is needed to clarify the true balance of benefits to harm.

# Acute toxicities

- Hallucinations
- Tachycardia
- Labored breathing
- Obtundation
- Any toxicity deaths are very rare

Wang GS JAMA Pediatrics, 2013



[http://opiophilia.blogspot.com/2013\\_04\\_01\\_archive.html](http://opiophilia.blogspot.com/2013_04_01_archive.html)

Gable (2006) Amer Scientist 94:206.

# 'Cannabis Psychoses'

**TABLE**  
**SIGNS AND SYMPTOMS RELATED TO MARIJUANA USE THAT MAY INDICATE FUTURE RISK OF PSYCHOSIS**

***Marijuana Withdrawal***

- Irritability
- Insomnia
- Anorexia
- Restlessness
- Aggressivity

***Anomalous Marijuana-related Symptoms***

- Anxiety
- Fear
- Panic attack symptoms
- Suspiciousness and paranoia
- Hallucinations (visual, auditory)

Anomalous symptoms usually manifest early in the course of marijuana use, either during the first marijuana use or shortly after continued use. These are distinguished from signs and symptoms of marijuana withdrawal that may develop after abruptly ceasing smoking marijuana after dependence has developed.

Raby WN. *Primary Psychiatry*. Vol 16, No 4. 2009.

- marijuana-smoking patients with these symptoms frequently have a family history of psychiatric illness as well (depression, bipolar disorder, anxiety disorders, or schizophrenia)
- these anomalous effects of marijuana may go on to develop autonomous psychotic disorders from not stopping their marijuana use in time.
- symptoms contrary to the usual effects of marijuana may signal that continued use of marijuana may possibly and seriously jeopardize their future mental health

# Comorbid Cannabis Misuse in Psychotic Disorders:

Primary Psychiatry | May 21, 2013

- Swedish study examined a cohort of 50,087 conscripts:
  - “heavy marijuana users” were **2.3** times more likely than non-users to have a schizophrenia diagnosis **15** year later, When the analysis was extended to **27** years, heavy users were **6.7** times more likely than non-users to carry a schizophrenia diagnosis
- marijuana-induced psychosis could be an early sign of schizophrenia rather than a distinct form of psychosis
- Possible Genetic predisposition: Caspi and colleagues reported that individuals with a functional polymorphism in the catechol-O-methyltransferase (COMT) gene were at increased risk of schizophreniform disorder after use of marijuana during adolescence as compared with those who did not carry this polymorphism

# Role of endocannabinoid system in schizophrenia

- Schizophrenics have heightened levels of anandamide (endogenous cannabinoid neurotransmitter) in their CSF than control
- Schizophrenics (that have never taken cannabis) have increased CB<sub>1</sub> receptors in their forebrain compared to matched controls.

# Suggested Message

- Communicate the risk while acknowledging the uncertainties that remain
- people with psychosis or a first degree relative with psychosis avoid using cannabis
- one in seven people who use cannabis report unpleasant, psychotic-like symptoms; avoid use
- discouraging young people from using cannabis

# Smokeless cannabis delivery device found efficient and less toxic

- UCSF study, "Clinical Pharmacology and Therapeutics"
- looked at the effectiveness of a device that heats cannabis to a temperature between 180 and 200 degrees C, just short of combustion, which occurs at 230 degrees C
- Plasma concentrations of THC were measured along with the exhaled levels of carbon monoxide, a marker for the many other combustion-generated toxins inhaled when smoking
- there was virtually no exposure to harmful combustion products using the vaporizing devices
- carcinogenic polynuclear aromatic hydrocarbons, a suspect in cigarette-related cancers, these toxins are essentially a byproduct of combustion
- no evidence that marijuana smoking causes cancer, chronic smoking has been shown to elevate the risk of bronchitis and respiratory infections

# State Medical Marijuana Laws Linked to Lower Prescription Overdose Deaths

Released: 21-Aug-2014



Report on the research appears in the August 25 issue of *JAMA Internal Medicine*

- number of deaths from prescription drug overdose is 25 percent lower than in states where medical marijuana remains illegal
- states with a medical marijuana law had about 1,700 fewer opioid painkiller overdose deaths in 2010 than would be expected based on trends before the laws were passed
- California, Oregon and Washington – legalized medical marijuana prior to 1999
- may have unintended benefits
- Obviously very controversial and opponents have raised concerns that they may promote cannabis use among children

# WHAT IS IN IT?

Find out what's in your meds so you can understand what you're buying before you buy it.

Like 915

twitter

## Strain: White Widow

Primary Cannabinoid: THC Ratio Rarity: 4%



### Calculated Active Cannabinoids

- CBD: 0.49%
- CBC: 0.02%
- CBN: %
- THCV: 0%
- THC: 15.33%

Total Active Cannabinoids: 15.95%



FULLSPECTRUMLABS  
White Widow

Recommend

## Strain Reviews

## Find Your Perfect Strain

### TESTED PRODUCTS

Strain

Cannabinoid  >  %

Ratio  >

Type

Suitable For

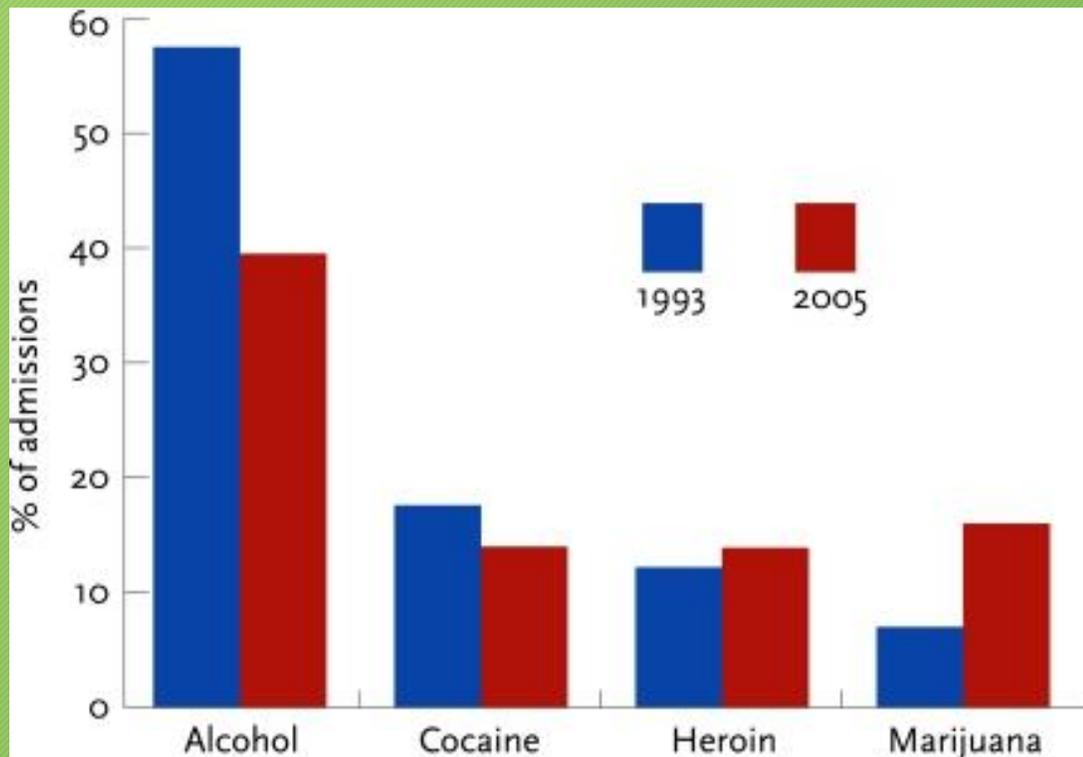
Search

### DISPENSARIES

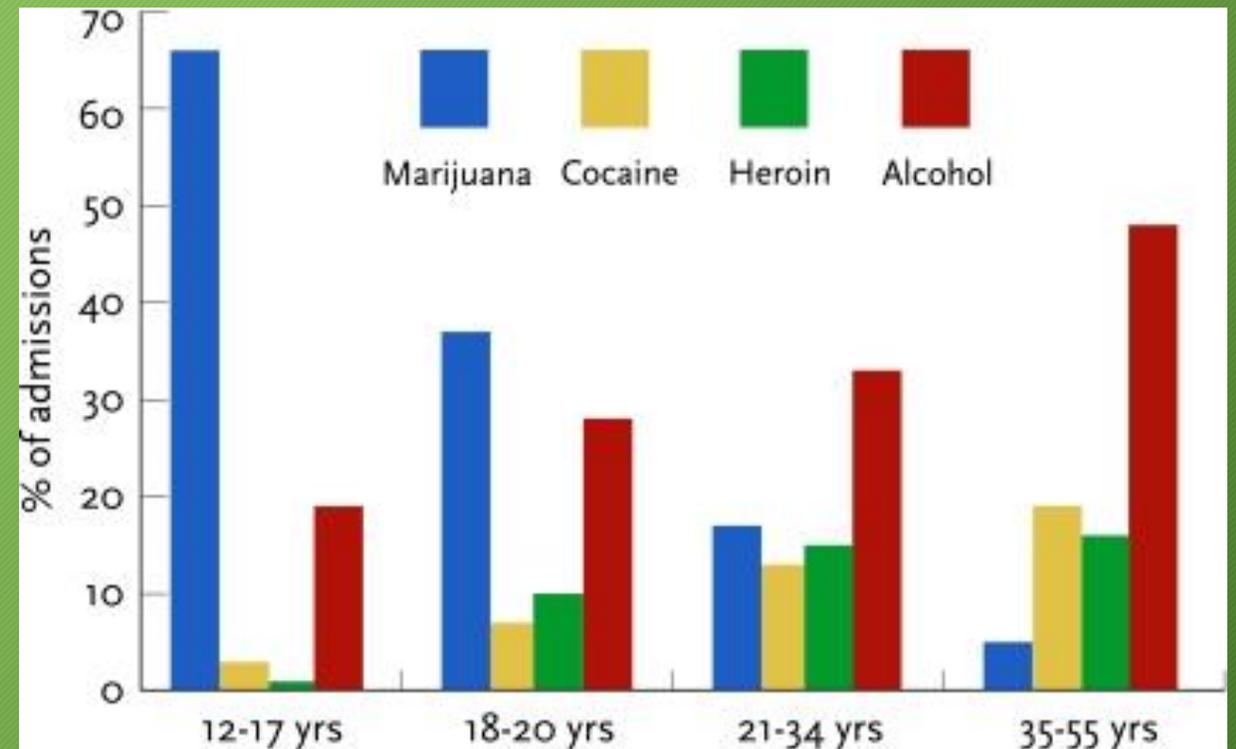
# Clinical features of dependence

- Withdrawal syndrome: common in users seeking help
- Compulsive use: common in problem users
  - Impaired control
  - Strong desire to use
- Tolerance
- Large amounts of day spent using
- ?? Continued use despite clear evidence of harm:
  - less common than for alcohol
- May continue use despite self reported paranoia, or past exacerbation of schizophrenia; despite social conflict arising from use, wheeze; all known to be associated with use

# Primary Marijuana Dependence



The percentage of substance abuse treatment admissions that were due to marijuana nearly doubled from 1993 to 2005 ([SAMHSA, 2006b](#))



Marijuana accounts for most adolescent drug treatment admissions and progressively smaller proportions of admissions in each successive higher age group ([SAMHSA, 2006b](#))

# psychosocial treatments for marijuana abuse or dependence

- Behavioral treatments, such as motivational enhancement therapy (MET), cognitive-behavioral therapy (CBT), and contingency management (CM), as well as family-based treatments

# Withdrawal

- Symptoms worse in first week
- Symptoms (rarely life-threatening):
  - irritability, anger
  - restlessness, anxiety
  - sleep difficulties, including strange dreams
  - craving, weight/appetite change, depressed mood, physical discomfort
- To some extent still controversial
- No validated rating scale

## To review:

### What does the human body do to THC?

- Smoking THC mimics IV, but with 10-25% bioavailability, quick effect → easy to titrate
- Ingesting THC, 1/3 bioavailability, high variability and delayed effect → increased toxicities
- Medium dose: 10mg, giving rise to ↑HR, ↑high, ↓alertness, ↓stability, but tolerance quickly develops
- Acute THC ingestions are relatively safe



