



Stanford
MEDICINE

Northern California Chapter, ACP Update In Medicine

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California
Northern Region

UPDATE ON MARIJUANA

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Outline

- Legal background of marijuana in California
- Current regulatory status
- Current patterns and perceptions among US adults
- Current evidence: health benefits
- Effects on brain
- Health risks of MJ and cannabinoids
- CBD oil
- Special risks in young adults
- Conclusions

Legal background

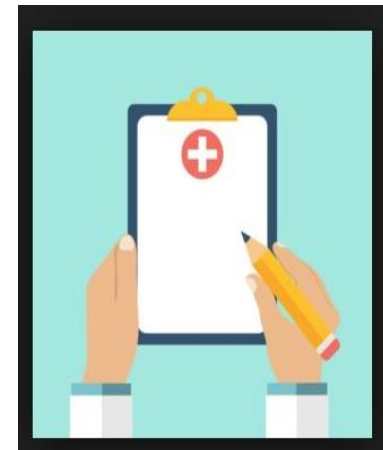
- California [Proposition 215](#), the “Compassionate Use Act,” 1996
- This legalized the use of Marijuana for [medicinal](#) purposes.
- Doctor cannot prescribe marijuana, since remains illegal by federal statute, but can *recommend* for certain conditions

Legal background (continued)

- **Proposition 64**—Legalization of Marijuana in CA. 11/16
- must be over 21 to purchase for ***recreational*** purpose, over 18 for ***medicinal*** purpose.
- 1/1/17. California began issuing licenses to shops throughout the state. Some shops are unlicensed.

Medical Marijuana: doctor's note?

- Advantages of medical recommendation for MJ
 - Persons ages 18-21 may be able to obtain MJ (21 is age limit for recreational MJ purchase)
 - Larger quantities allowed for possession with medical MJ recommendation
 - County-issued medical MJ card exempts purchaser from significant marijuana tax



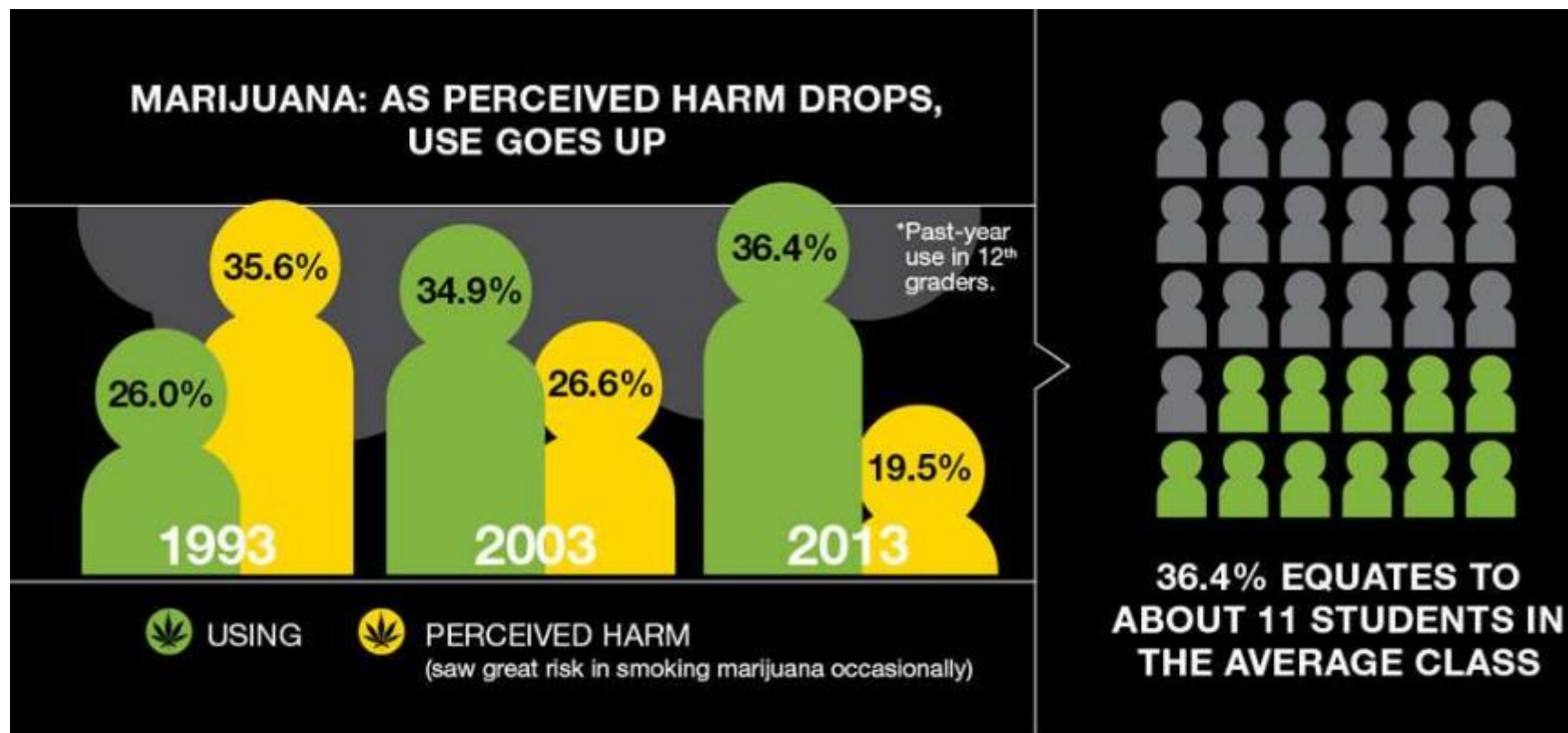
Medical and Adult-Use Cannabis Regulation and Safety Act (“MAUCRSA”) 2018

- Created a combined regulatory system for both medical and recreational marijuana in State of California.
- Bureau of Cannabis Control, State Dept of Consumer Affairs.
 - responsible for regulating commercial cannabis licenses for retailers, distributors, microbusinesses, testing laboratories, and temporary cannabis events.

Current Usage in U.S.

- Approximately 15% of US adults used marijuana in last year (2017)
- National Institute on Drug Abuse (NIDA) show that 15% of 8th graders have tried marijuana and over 1% use it daily.
- Common perceived benefits:
 - Pain relief 66%
 - Treatment of medical disease (epilepsy, MS, other) 48%
 - Treatment of anxiety/depression 47%
- Perceived risks:
 - Legal problems 52%
 - Addiction 50%
 - Memory impairment 42%

MJ usage is growing among teens



NIDA Data : 2017 update

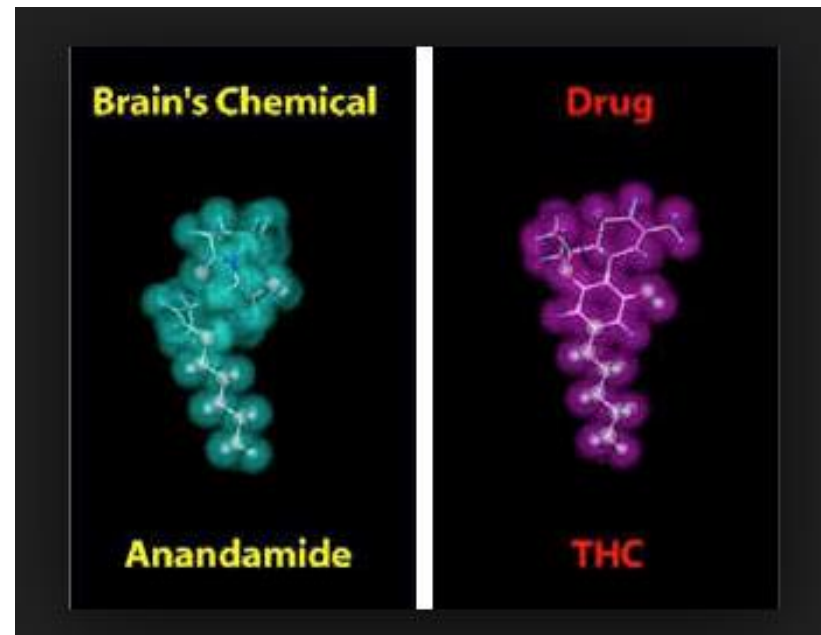
Monitoring the Future Study: Trends in Prevalence of Marijuana/ Hashish for 8th Graders, 10th Graders, and 12th Graders; 2017 (in percent)*

Drug	Time Period	8th Graders	10th Graders	12th Graders
Marijuana/ Hashish	Lifetime	13.50	30.70	45.00
	Past Year	10.10	25.50	37.10
	Past Month	5.50	[15.70]	22.90
	Daily	0.80	2.90	5.90

Marijuana : cannabinoids

THC identified in mid-1960s. 20 yrs later the cannabinoid receptors are identified—**CB1** and **CB2** found throughout brain and body. (natural ligands are anandamide and AD 2)

- THC (CB1)
- CBD (CB2)



Health benefits of marijuana

Good evidence:

- chronic pain
- antiemetic therapy for chemotherapy induced nausea
- MS associated spasticity, patient-reported

Moderate evidence

- Improved sleep in patients with OSA, fibromyalgia, MS, and chronic pain syndromes

Limited evidence

- Improving appetite in patients with HIV
- MS associated spasticity, Clinician measured

National Academy of Science, Health and Medicine division (former IOM), report published 2017

Health effects of MJ: Lungs

- Microscopic injury to large airways with regular smoking. Symptoms of bronchitis resolve after cessation.
- Inconclusive evidence on risks for pneumonia with regular smoking.
- NO signs of higher risk of COPD
- light to moderate use>>NO higher risk of lung or upper airway cancers.



Health effects of MJ: Brain

- Cannabis lowers activity in ACC (anterior cingulate cortex) and DLPFC (dorsolateral prefrontal cortex)>> probs with exec functioning and decisions, decreased memory, reduced attention.
- For those with psych conditions, these effects can be therapeutic by reducing post traumatic memories and anxiety.
- For the developing brain, may cause structural changes and reduced cognitive function.
- Cannabis increased activity in striatum (caudate/putamen), priming reward circuits and increasing risk of addiction and compulsive behaviors.
- Risk of addiction/cannabis use disorder approximately 8-12%

Other Health Effects of MJ

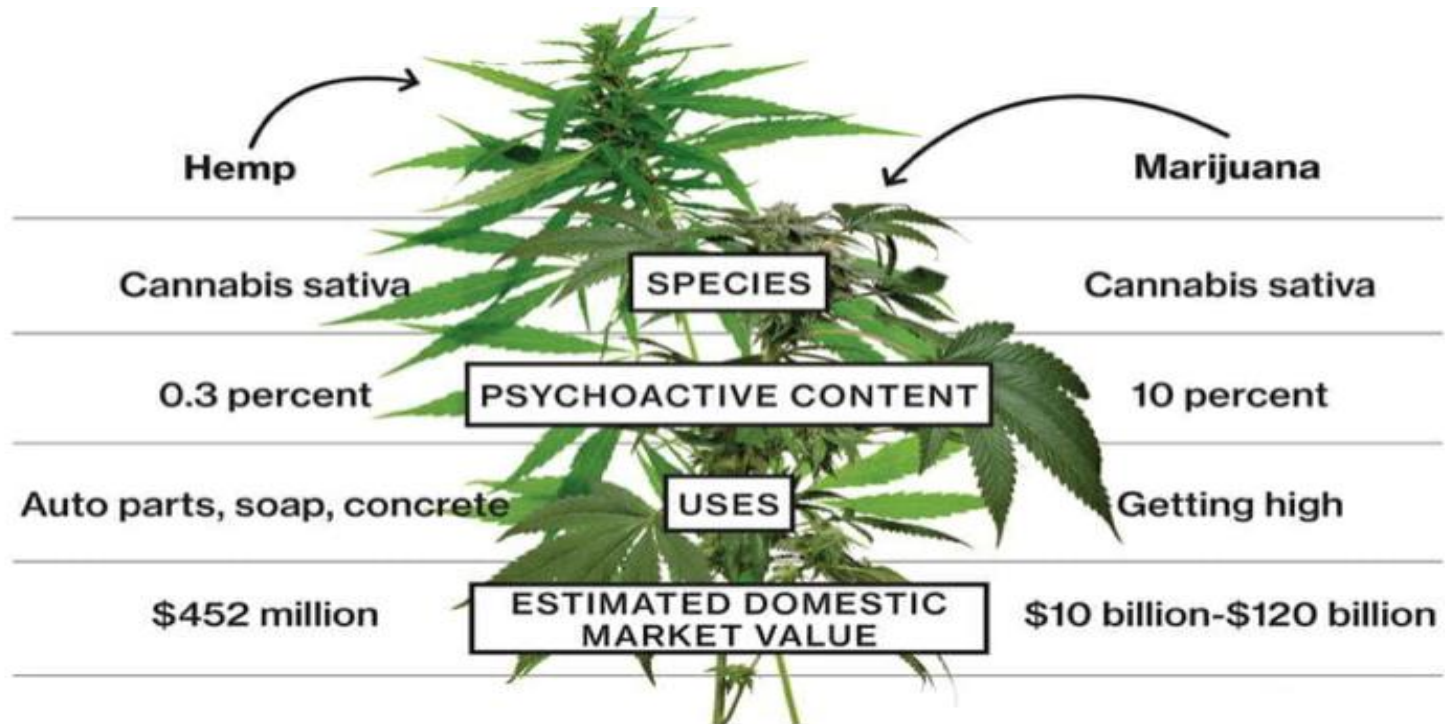
- higher rate of MVA
- augments alcohol intoxication effects
- increases heart rate/sympathetics
with increased myocardial oxygen demand
(small excess risk MI/CVA acutely)
- hyperemesis syndrome
- lower sperm counts
- oral disease: gingivitis, periodontitis, thrush

What about CBD oil?

- CBD is another cannabinoid from the cannabis plant, often manufactured as “oil”. No euphoria or “high” associated with CBD use. If THC content is under 0.3% and if CBD is derived from hemp then legal across most states of US.
- CB2 receptors are more common in the immune system. They modulate inflammation and pain.

DEA says Hemp Derived CBD Oil Products are Federally Legal

Hemp versus marijuana



WHO: "...in humans, CBD exhibits no effects indicative of any abuse or dependence potential...well tolerated with a good safety profile...no evidence of any public health-related problems."

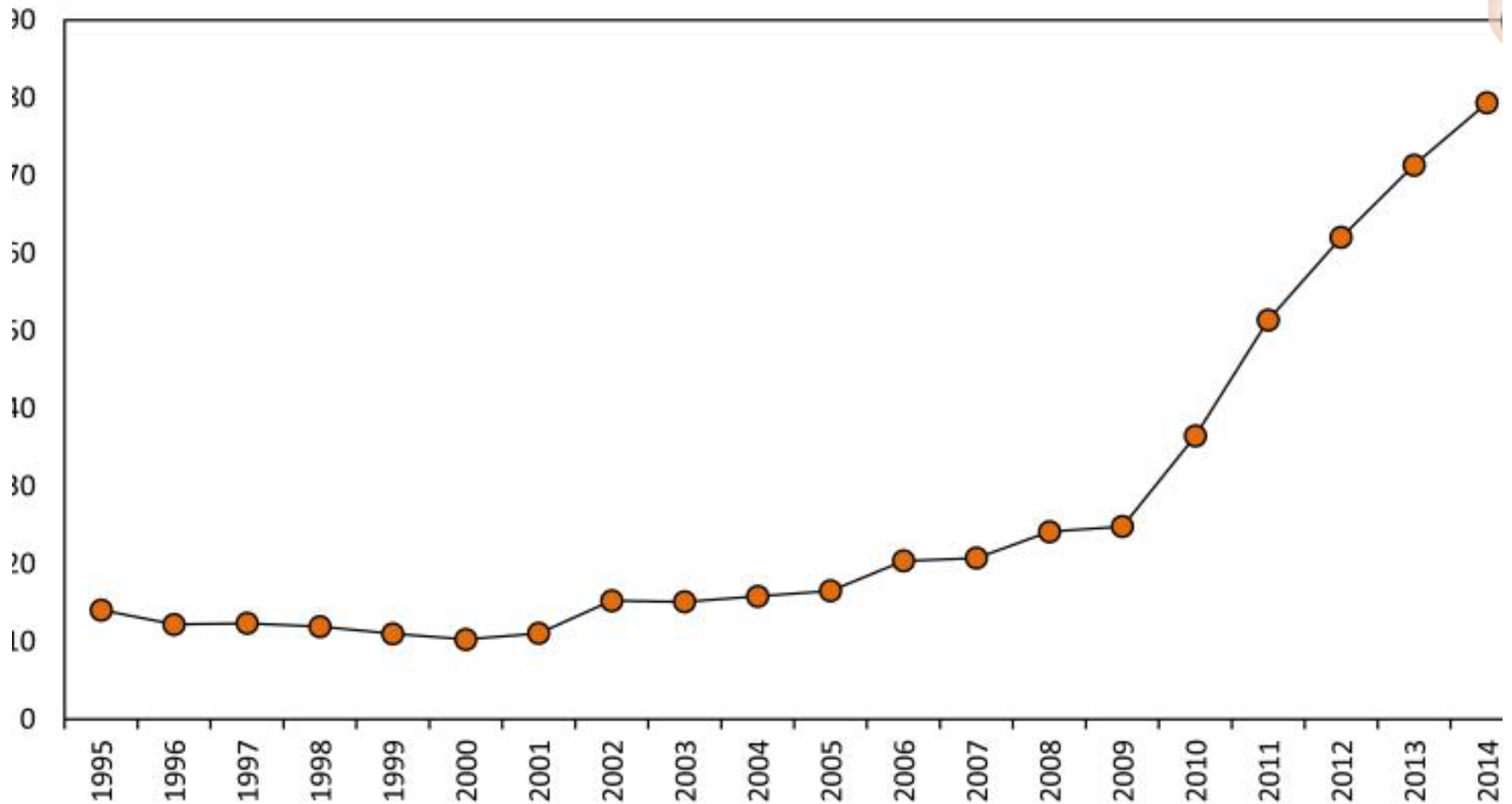
Clinical uses for CBD oil

- Benefit in controlling 2 forms of childhood epilepsy. Dravet syndrome and Lennox-Gastaut. Drug [Epidiolex](#) approved by FDA in 2018.
- Studies have shown *possible* benefit in :
Alzheimers disease, cancer, smoking cessation, addiction, insomnia, anxiety, OCD, neurodegenerative disorders, TBI, stroke, CTE, psychotic disorders, arthritis/pain conditions.

-
- Is current usage of marijuana a higher risk “HIGH” than it used to be?



Marijuana: Higher potency (1995-2014)



Synthetic “Marijuana”: Tainted product risks

FDA issues warning after synthetic marijuana tainted with rat poison sickens hundreds (USA Today, 2018)

California outlaws possession of synthetic drug 'spice' amid overdoses on L.A.'s Skid Row (LA Times, 9/16)

- Synthetic MJ also known as “Spice”, “K2”, and “AK 47”.
- Most synthetic cannabinoids are **full agonists for the CB1 receptor** rather than **partial agonist** as with THC.
- Several people have died and many have become ill with bleeding and other complications. (no overdoses from MJ)

Special risks to youth and the developing brain.

- Adolescent Brain Cognitive Development (ABCD) study (NIH)
 - 10-year project in process, following 10,000 children from age 9-10, acquiring data from brain scans, genetic and psychological tests, academic records and surveys.
- Studies show higher risk of schizophrenia particularly in younger users (both epidemiologic studies and animal biological model support link)

JAMA Study of MJ and risk to young adults (2018)

Metaanalysis of 69 cross sectional studies, compared ~2100 cannabis users and ~6600 comparison participants.

Small effect showing reduced cognitive functioning in young adults with frequent cannabis use.

Studies in which users were abstinent for 72 hours or more showed a NON significant effect size.

Memory changes reverse

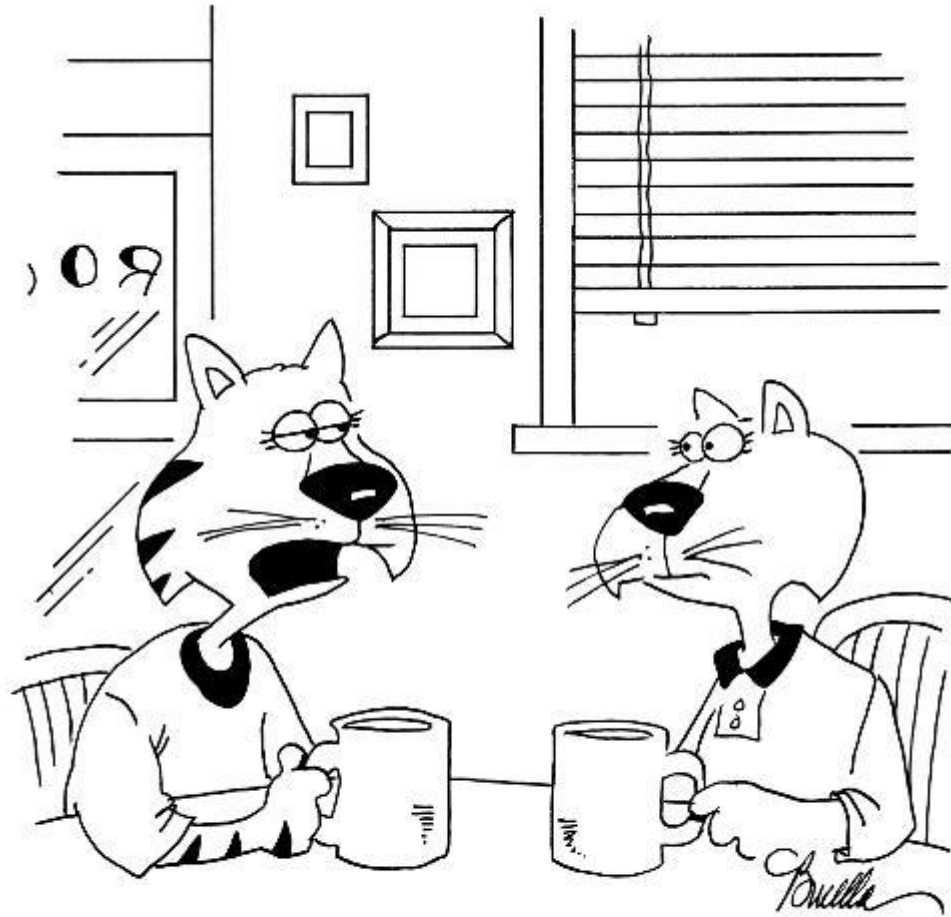
- RCT, 88 participants, regular MJ users
- Half randomized to 30 day abstinence, other half to continued use
- Memory scores at baseline and repeated at 30 days
- Abstinent group had significant memory improvement compared to control group.

My takeaways....

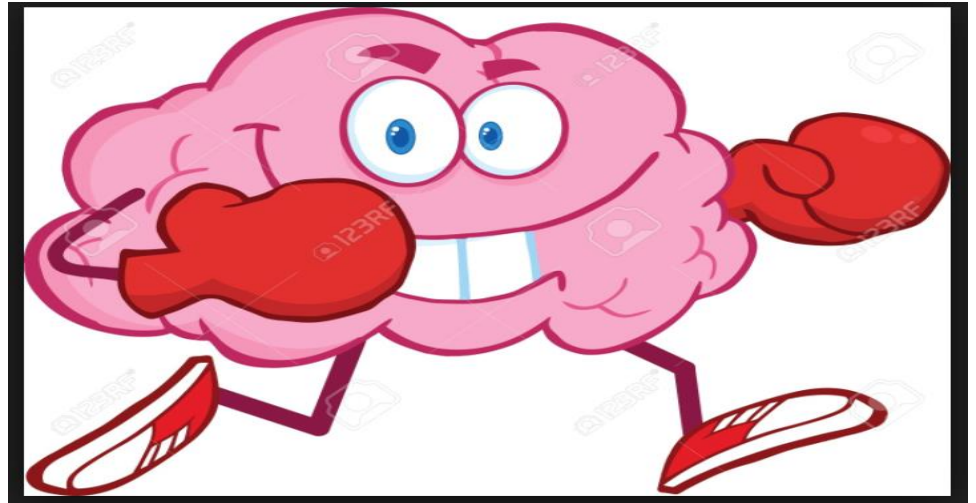
- MJ use is highly prevalent in US—about 1/6 adults used in the last year.
- MJ is now legal in CA but patients must avoid driving and performing other critical functions when using.
- MJ remains a potentially addictive drug—in up to 10% of users.
- Synthetic cannabinoids should be avoided, with their unique risks. Today's MJ is much more potent than before and patients should be counseled.
- Marijuana should not be used by young adults.
- We need more study on the safety and efficacy of THC and CBD for treatment of chronic conditions to properly advise patients. CBD oil is an interesting compound for further study—pain, anxiety, and neuroprotective? Industry messaging is outpacing science.



Take a breath and stretch....



"I use catnip, too, but only for medical purposes."



SPRINT-MIND Trial

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SPRINT study: overview

- RCT funded by NIH, ~9400 persons
 - Age over 50
 - SBP >130
 - Increased CV risk
 - No diabetes
 - Intensive (<120) vs Standard (<140)
- Outcome: composite of MI, ACS, stroke, Heart failure, CV death.

SPRINT Study: outcomes

- At year 1, mean **SBP 121.4 mm** vs **SBP 136.2 mm**
- Study stopped early after median f/u 3.26 years
- Composite outcome 1.65%/yr vs 2.19%/yr

HR composite **0.75** (0.64 to 0.89 p<0.001)

HR all cause mort **0.73** (0.60 to 0.90 p=0.003)

SPRINT Study: Practical issues





- With a prior goal BP of 140/90, BP control only achieved ~50% of the time in US.
- On average, one additional drug for BP needed to achieve more intensive target BP in the SPRINT trial.
- New 2017 guideline from AHA; BP >130/80=hypertension. Start drugs immediately in those with DM, CKD, CVD or 10 yr CV risk >10%. For others can start with lifestyle until 140/90.
- Note that society guidelines differ. ACP 2017 retains the goal <150/90 for those older than 60.

SPRINT MIND Study: Outcomes (AAIC meeting 2018)

	MCI	Dementia	MCI or dementia
SBP <120 vs SBP <140	HR= 0.81 (0.70 to 0.95), p=0.01	HR = 0.83 (0.67 to 1.04), p=0.10	HR = 0.86 p=0.02

Absolute risk reduction was 1.34% for cog impairment; 1.38% for either MCI Or dementia

SPRINT MIND Study: Outcomes

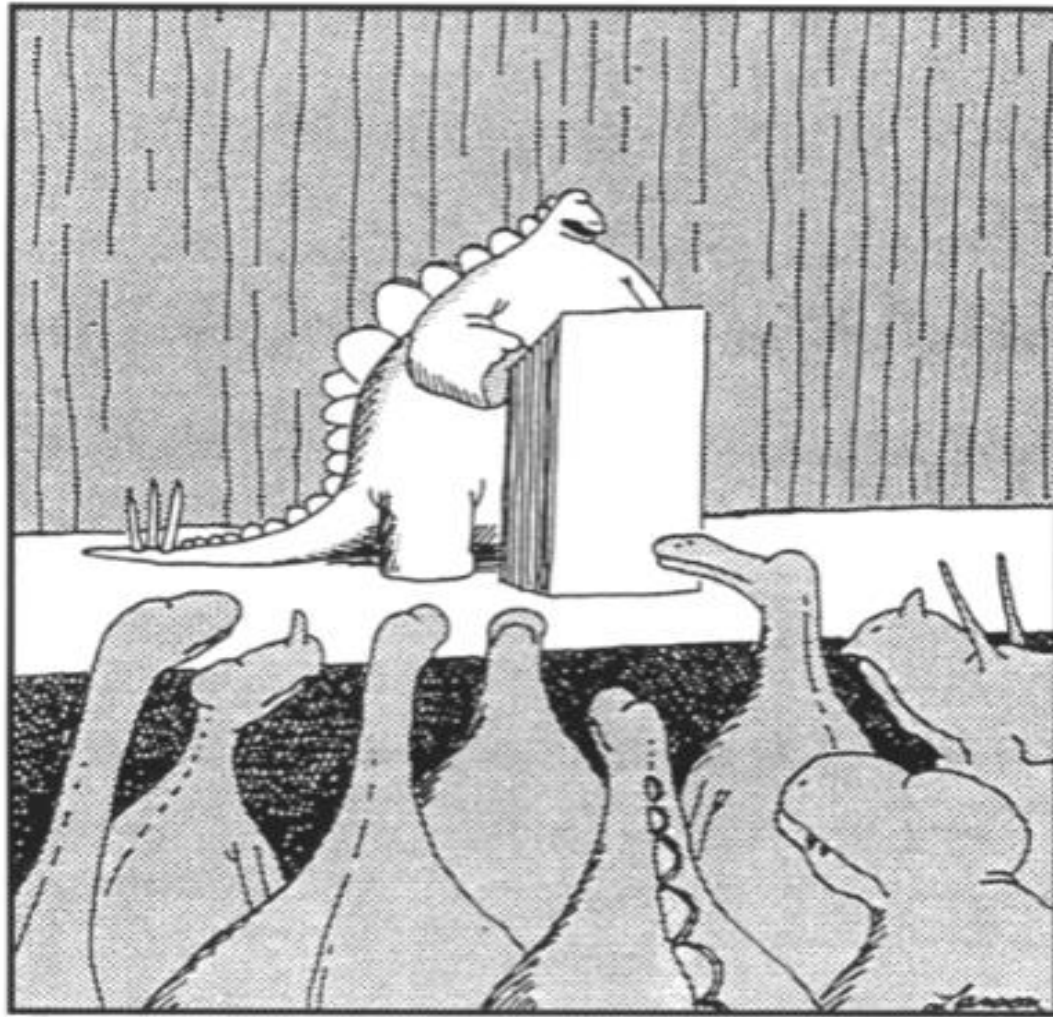
	WML	Brain volume
SBP < 120	 0.28 cm ³ (ss)	 24.8 cm ³ (not ss)
SBP < 140	 0.92 cm ³	 27.3 cm ³

Subset of 454 participants who had follow up brain MRIs,
median 3.9 yrs after randomization

Summary of SPRINT and SPRINT MIND

- SPRINT trial : ~25% reduction of CV endpoints and mortality with aggressive SBP target of 120 vs 140 in a group of high-CV risk individuals.
- Costs: one extra drug on average, and more syncope/hypotension, electrolyte issues and AKI in the intensive group
- SPRINT-MIND shows reduction in MCI of 18% and non significant reduction in dementia. Brain WML and volume studies also correlate with the clinical outcomes.
- How will you translate this to your clinical practice??

Questions? (...and a final word from Gary Larson)



"The picture's pretty bleak, gentlemen. . . .
The world's climates are changing, the mammals
are taking over, and we all have a brain
about the size of a walnut."