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The Controversy Around Cannabis as Medicine

J. H. Atkinson MD

9th Annual Primary Care and Behavioral Health Integration Summit

December 6, 2018

Cannabis over the millenia

2900 BC — CHINESE EMPEROR FU HSI REFERENCES MARIJUANA AS A POPULAR MEDICINE

1213 BC — EGYPTIANS USE CANNABIS FOR GLAUCOMA, INFLAMMATION, AND ENEMAS

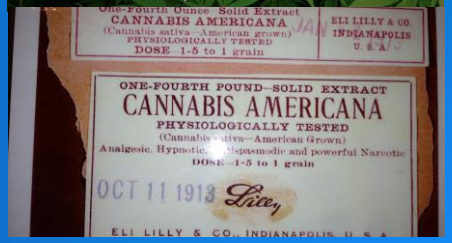
Cannabis pollen is found on the mummy of Ramesses II, who died in 1213 BC. Prescriptions for cannabis in Ancient Egypt include treatment for the eyes (glaucoma), inflammation, and cooling the uterus, as well as administering enemas.

1611 — JAMESTOWN SETTLERS BRING MARIJUANA TO NORTH AMERICA

1850 — Marijuana added to US Pharmacopeia

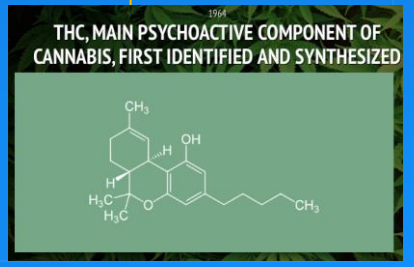
EXTRACTUM CANNABIS. *Extract of Hemp.*
An alcoholic extract of the dried tops of Cannabis sativa—variety *Indica*.

1906 — PURE FOOD AND DRUGS ACT REQUIRES LABELING OF MEDICINE, INCLUDING CANNABIS

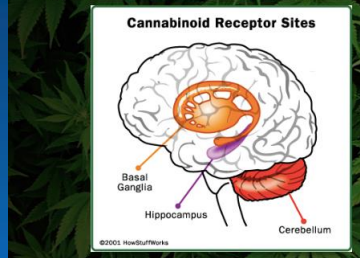


1937 — "MARIHUANA TAX ACT" LEADS TO DECLINE IN MARIJUANA PRESCRIPTIONS

1964 — THC, MAIN PSYCHOACTIVE COMPONENT OF CANNABIS, FIRST IDENTIFIED AND SYNTHESIZED



1990 — SCIENTISTS DISCOVER CANNABINOID RECEPTORS

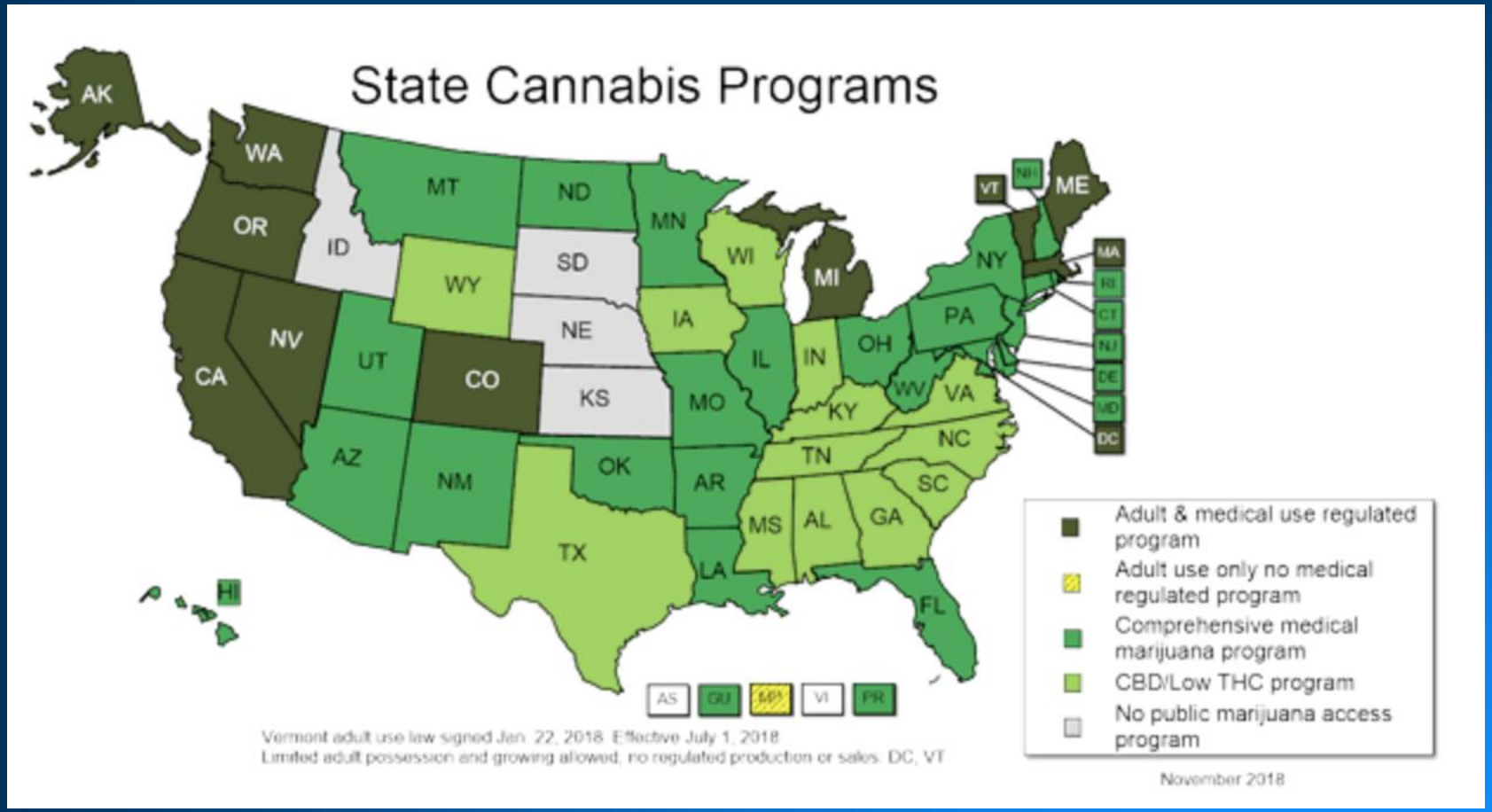


2900 BC | 1213 BC | 1611 | 1850 | 1906 | 1937 | 1964 | 1990

Main Events that Reawakened Interest in Medicinal Cannabis in the 1990s

- **Persistent anecdotal reports of benefits**
- **Political shifts at state level favoring medicinal access**
- **Discovery of the endocannabinoid system**
  - » CB1 and CB2 receptors
  - » Anandamide (Devane, Mechoulam, et al Science 1992)
  - » 2-arachidonoylglycerol (2-AG: Sugiura, et al., Mechoulam et al., 1995), and other signaling molecules
  - » Development of synthetic molecules: agonists, partial agonists, antagonists, and other modifiers (eg., inhibitors of fatty acid amide hydrolase (FAAH). FAAH breaks down anandamide)

Cannabis Legalization by State



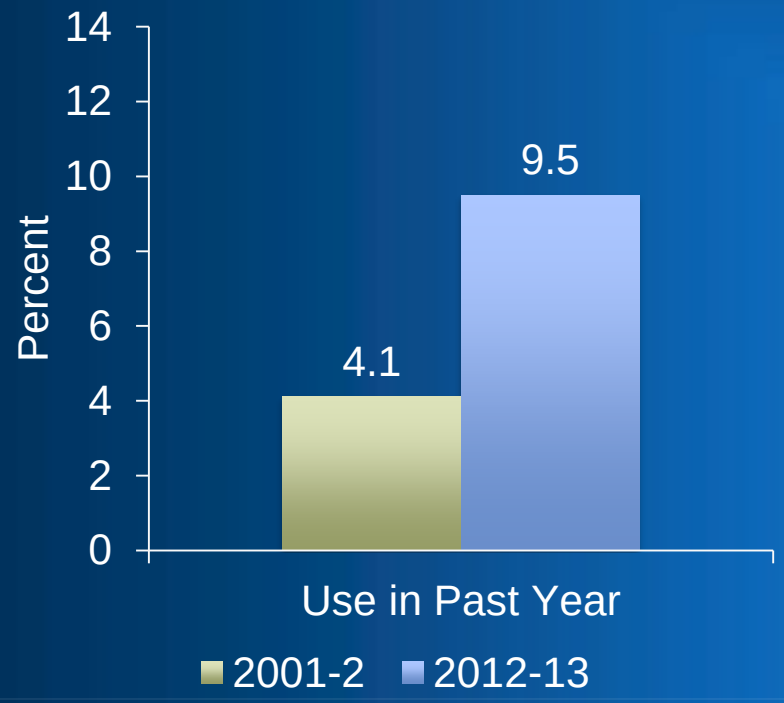
Recreational: 10, D.C. **Medical: 33, D.C** **Low THC/High CBD: 13**

(Source: National Conference of State Legislatures)

Prevalence of Cannabis Use

22.2 million (8.3% of the population) Americans ≥ 12 yo used cannabis in the past month (2015 National Survey on Drug Use and Health)

National Epidemiologic Survey on Alcohol and Related Conditions Use in Past Year (Hasin et al., 2015)

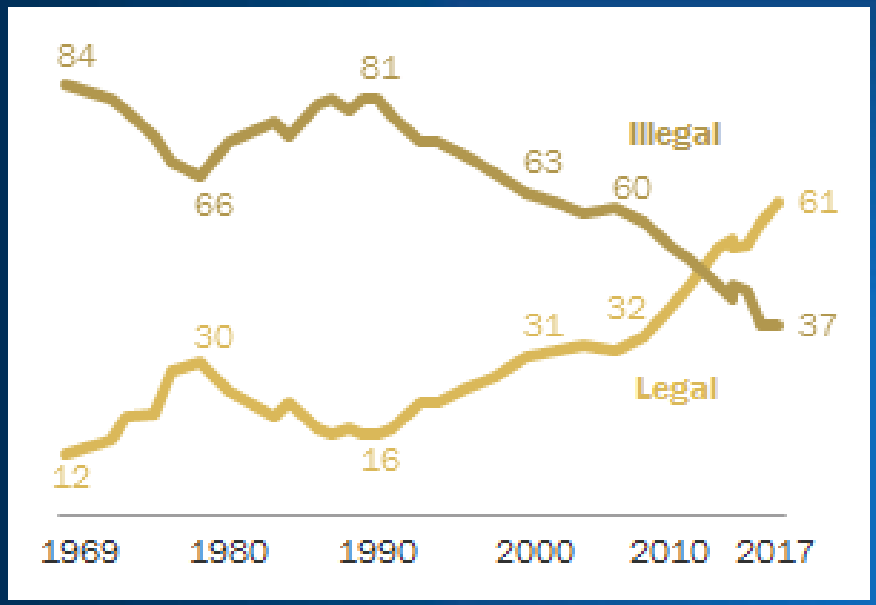


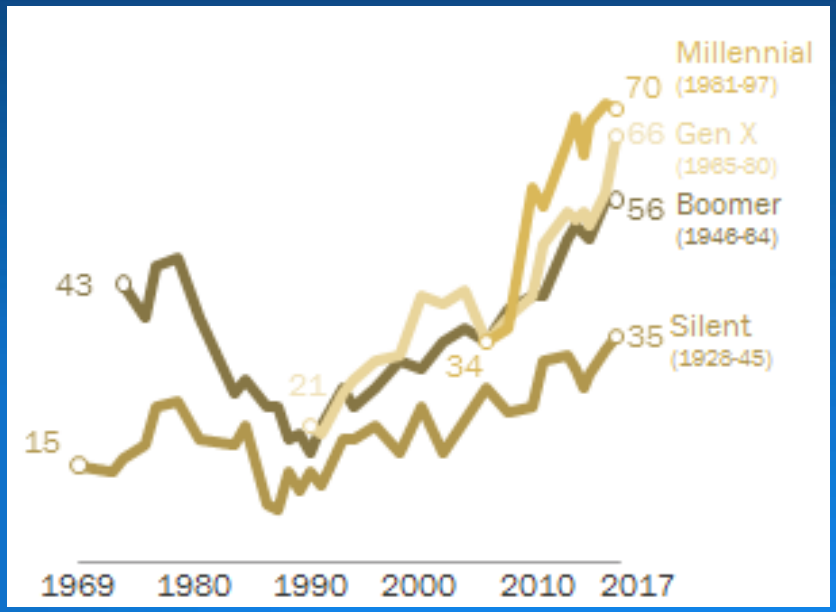
Age	2001-2	2012-13
18-29	10.5%	21.2%
30-34	4.1%	10.1%
45-64	1.6%	5.9%
>65	0.0%	1.3%

Increases across all sex, race/ethnicities, educational levels, income levels, urbanicity, geographic regions

Should Cannabis be Made Legal?

General Population (1,504 adults)





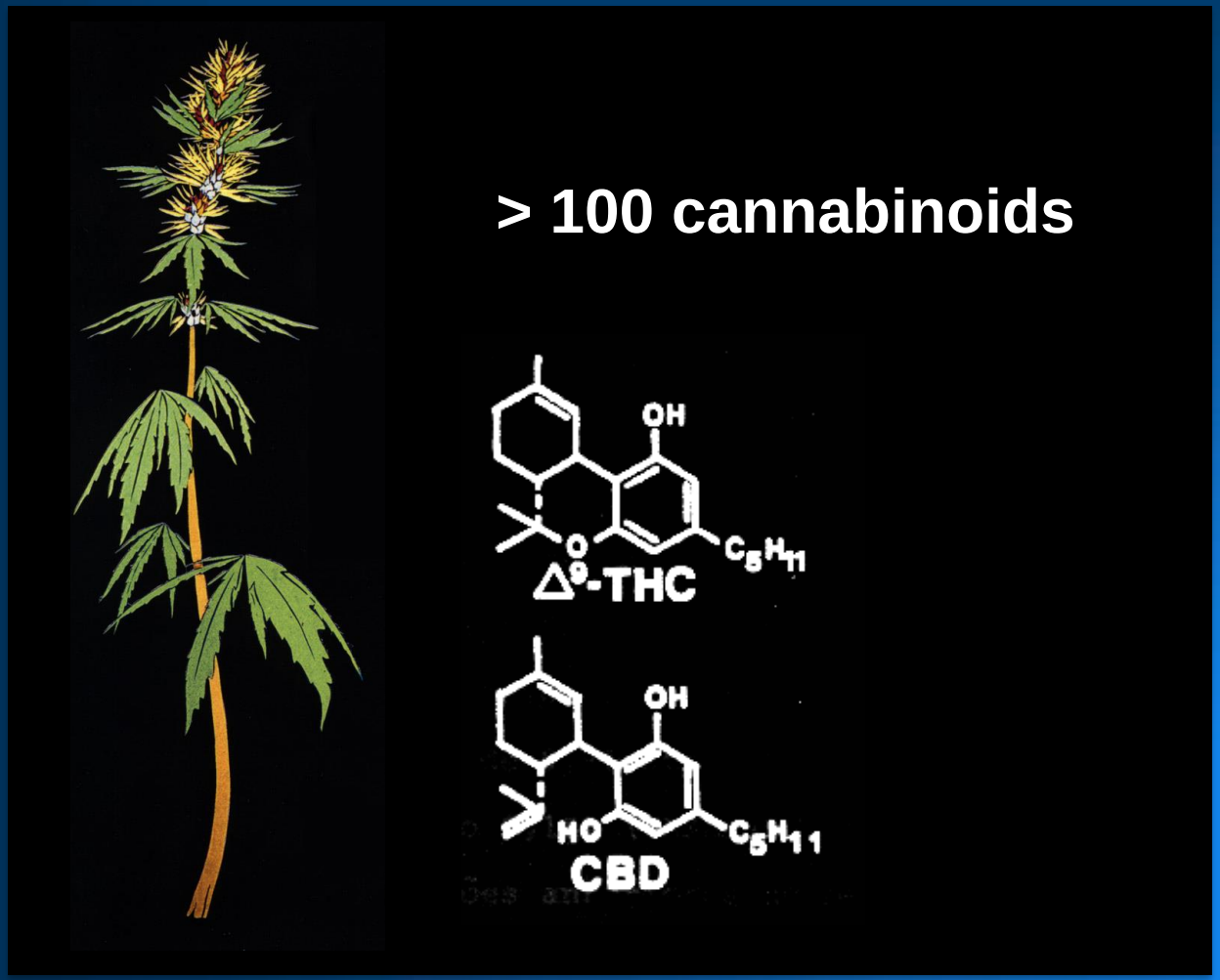
Pew Research Center, 2018

Cannabis Constituents

- 104 different cannabinoids
- Δ-9 THC
  - » Synthesized within the glandular trichomes in the flowers, leaves, and bracts of the female plant

- Terpenoids: aroma, modulate how cannabinoids interact with receptors, may act on serotonin, dopamine, etc.
- Flavonoids: color of plant, anti-oxidants, anti-inflammatory?

Marijuana Compounds



Isolation, structure and partial synthesis of an active constituent of hashish.
Y. Gaoni, Raphael Mechoulam. J. Am. Chem. Soc. 86, 1964: 1646.

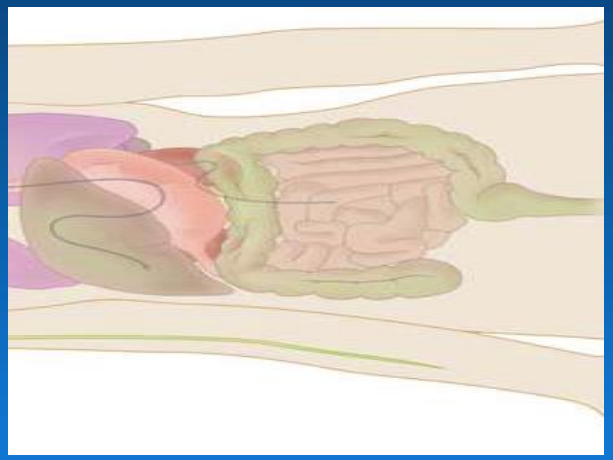
Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

Cannabinoid Receptors

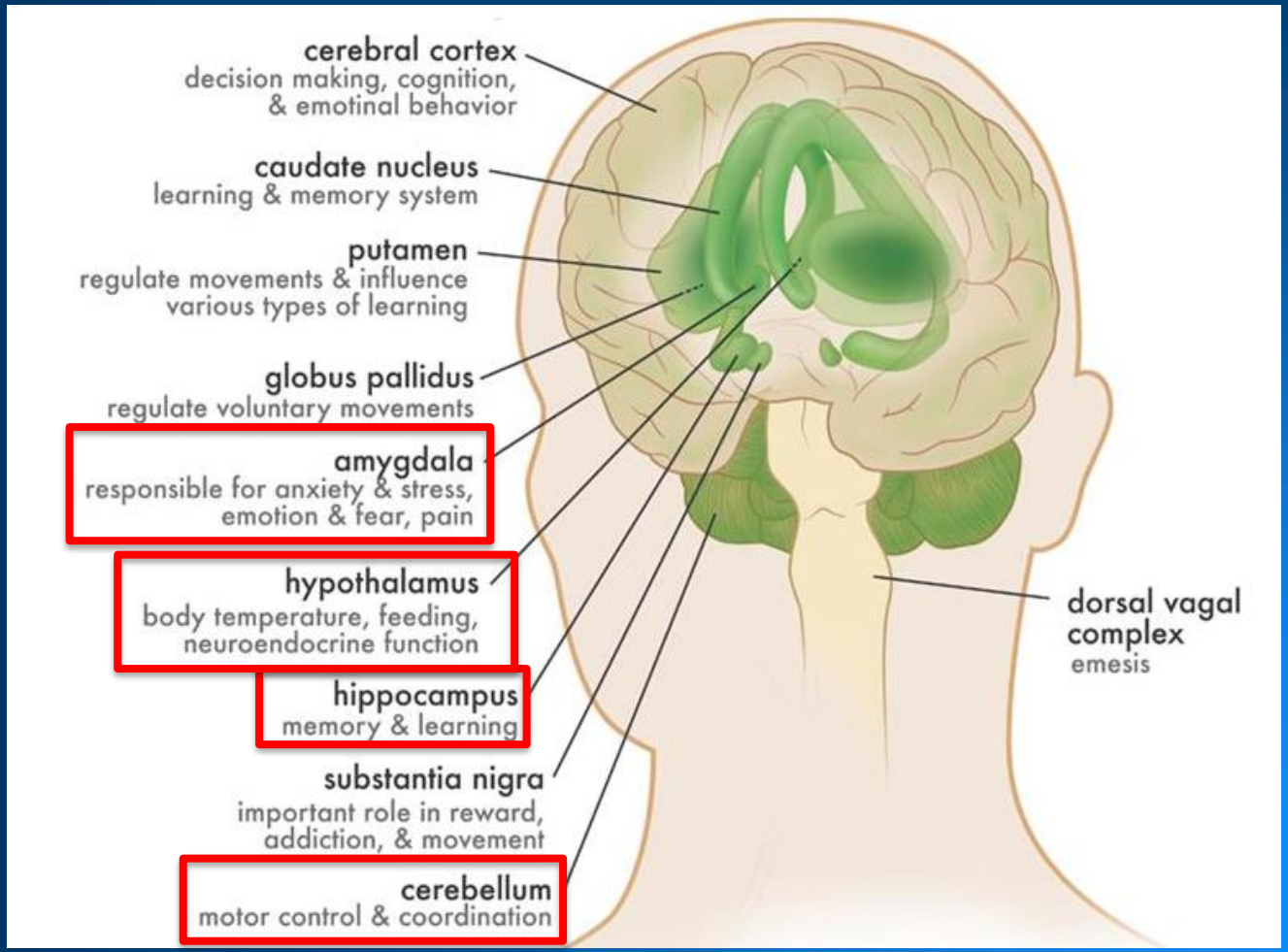
Two types of cannabinoid receptors:

- CB1
  - » Primarily in the brain, intestine, liver
  - » Responsible for the psychoactive effects
- CB2
  - » Immune cells
  - » Reduce inflammation

CB1 Receptors



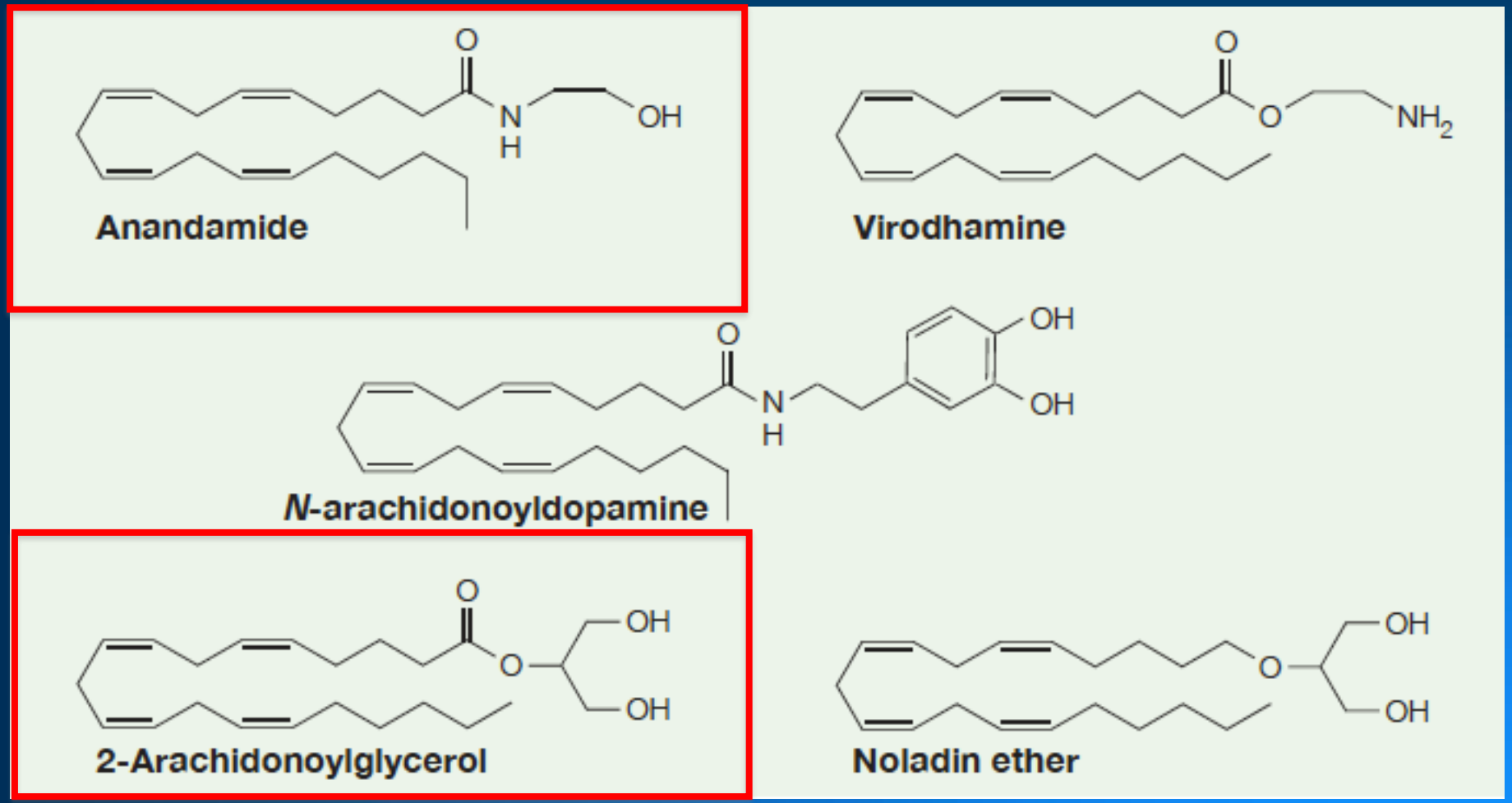
Distribution of CB1 Receptors in the Brain
Acute Effects



Endogenous Cannabinoids (Endocannabinoids)

- Two key ones have been identified (1990s)
  - » Anandamide (ananda [“supreme joy” I Sanskrit])
  - » 2-arachidonylglycerol (2-AG)
- Synthesized on demand
- Primarily neurotransmitter modulators - bring function back to homeostasis
- Feeding, emotion, cognition, pain, reward
- eCBs can be neuroprotective

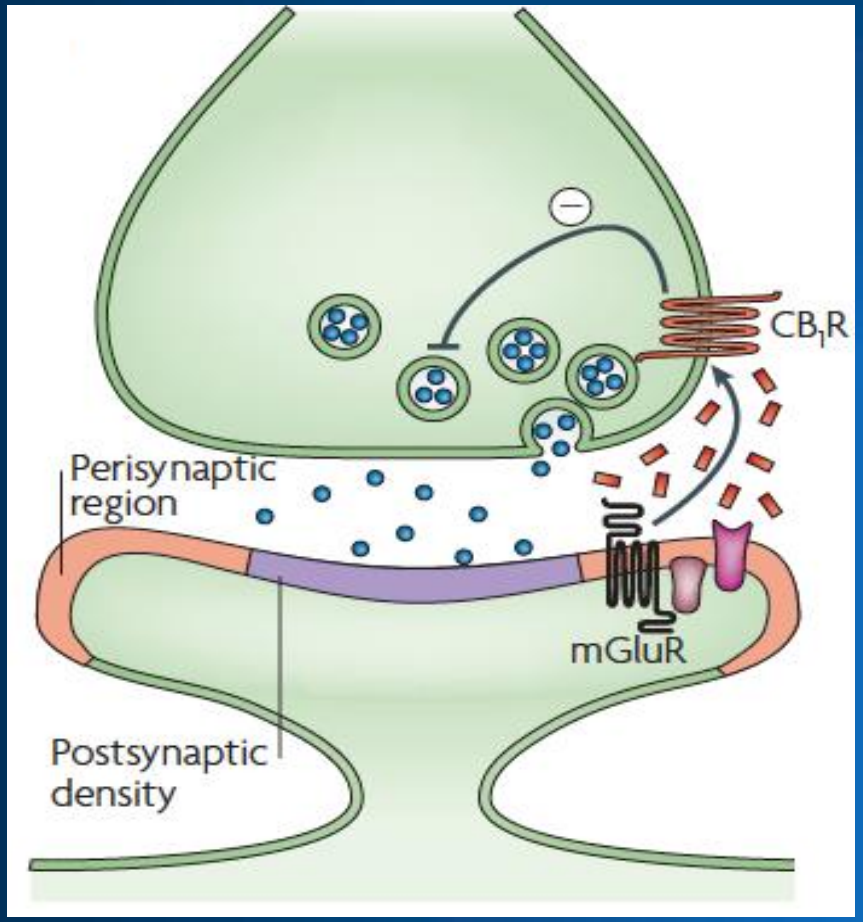
The endogenous cannabinoids

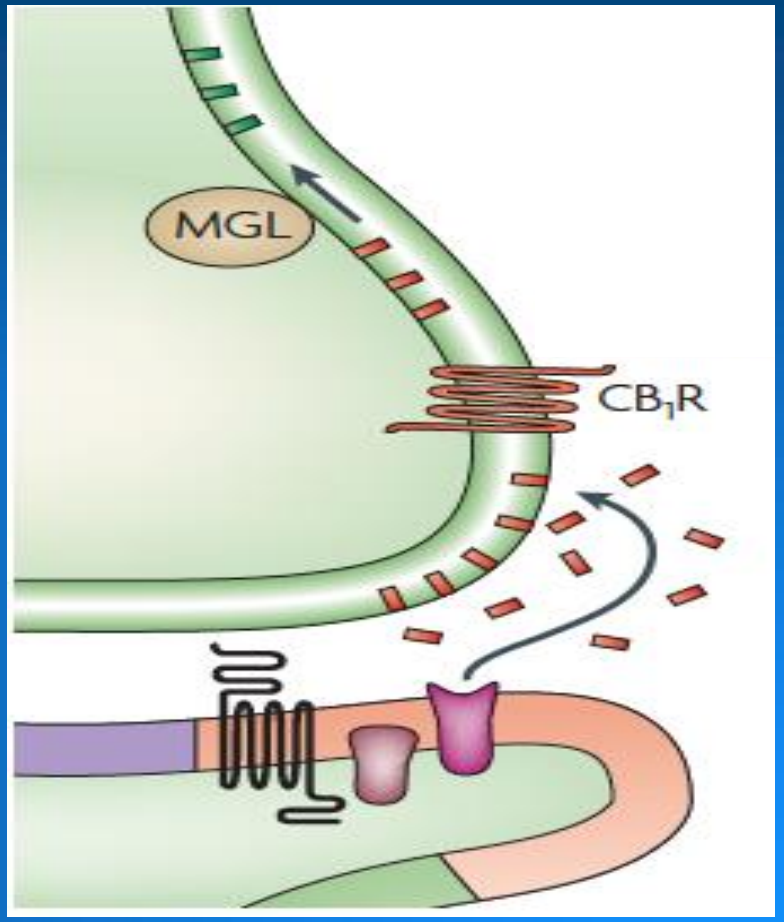


Piomelli, *Nature Rev. Neurosci.*, 2003

“Circuit Breaker” Function of CB Receptors

Neurotransmitter (eg., glutamate) action on post synaptic cells triggers them to release endocannabinoids (EC) that act on presynaptic CB receptors to regulate neurotransmission. The EC are then inactivated by FAAH or MGL*





* FAAH = fatty acid amide hydrolase MGL = monoglyceride lipase (Courtesy D. Piomelli, UCI)

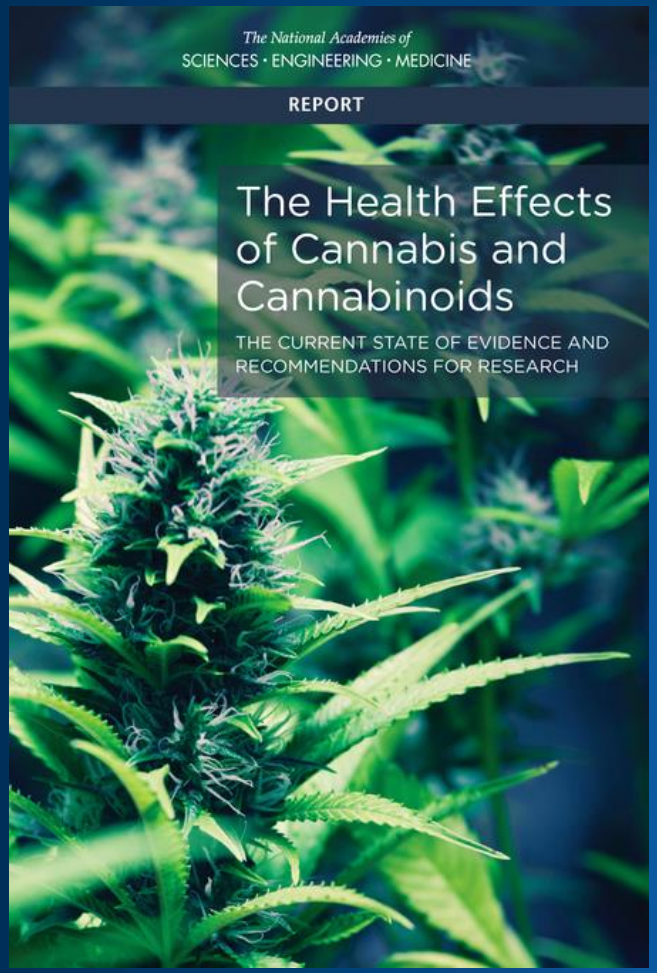
California Developments: Center for Medicinal Cannabis Research

- 1996 - Compassionate Use Act-Proposition 215
- 1999 - Medical Marijuana Research Act
- 2000 - CMCR established (California SB 847; Vasconcellos)
- Mission
  - » Facilitate high quality scientific studies
  - » Ascertain the safety and efficacy of cannabis and cannabinoid products

Center for Medicinal Cannabis Research (Established 2000, SB 847)

- Supported studies at
  - » UCD, UCI, UCLA, UCSD, UCSF and Stanford-affiliated San Mateo Medical Center
  - » 7 randomized, placebo-controlled clinical trials, inhaled cannabis, focusing on pain and muscle spasticity in multiple sclerosis
  - » All studies were Phase II Trials (N < 100), and short-term (weeks) but showed positive effects

The Health Effects of Cannabis and Cannabinoids National Academies Report (2017)

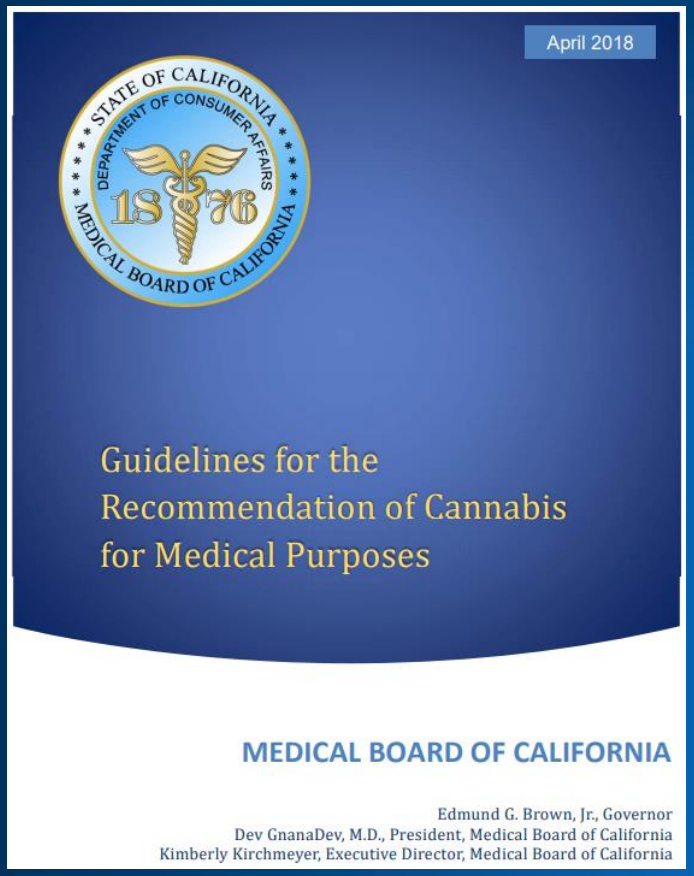


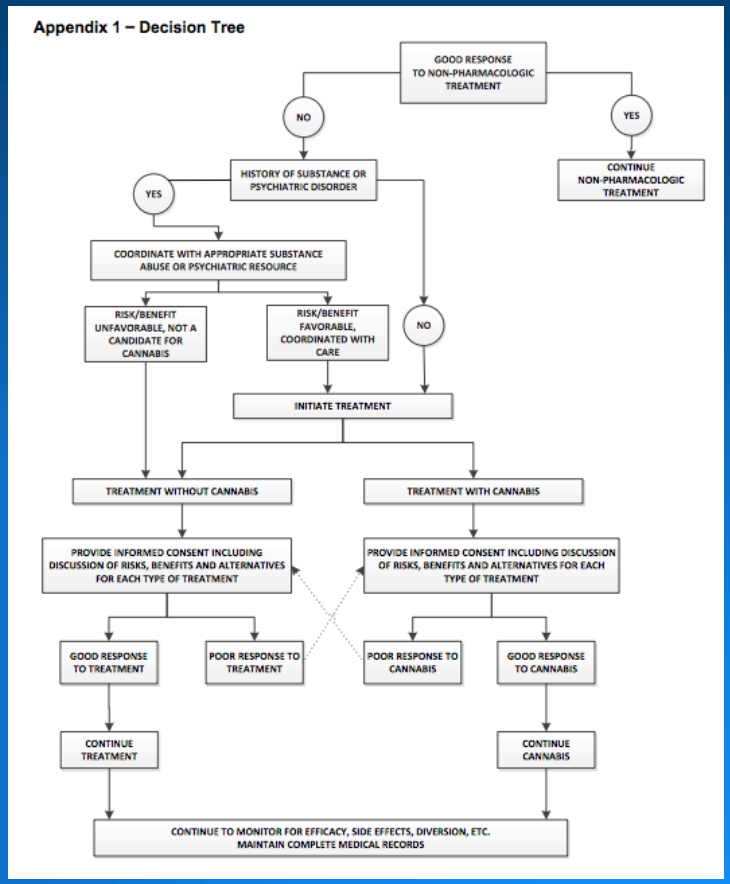
- Cannabis and cannabinoid studies since 1999 IOM report
- Systematic reviews (since 2011) and high-quality primary research
- Human studies (no basic nonhuman research)

Evidence for Therapeutic Benefits of Cannabis National Academies Report (2017)

- **Substantial/conclusive evidence of cannabinoid efficacy in:**
  - Chronic pain
  - Spasticity of multiple sclerosis
  - Control of nausea
- **Moderate evidence of cannabinoid efficacy in:**
  - Improving sleep in those with chronic medical conditions (e.g., chronic pain, fibromyalgia, etc.)
- **Limited evidence of cannabinoid efficacy in:**
  - Treatment of certain anxiety disorders and PTSD
  - Promoting appetite and weight gain
- **No or insufficient evidence of cannabinoid efficacy in:**
  - Treatment of cancers, irritable Bowel Syndrome, epilepsy, movement disorders due to Huntington Disease or Parkinson Disease, Schizophrenia

Medical Board of California





"Physicians who choose to recommend cannabis for medical purposes to their patients as part of their regular practice of medicine… will not be subject to investigation or disciplinary action…if the decision…is within accepted standards of medical responsibility."

Medical Board of California

- Physician-Patient Relationship – document this has been established; medical examination, etc.
- Patient Evaluation – Hx of illness, social hx, medical/surgical hx, alcohol and substance use hx, documentation of therapies with indequate response, diagnosis requiring cannabis recommendation (paucity of evidence at this time, but allows professional discretion)
- Informed and Shared Decision-Making – discuss risks and benefits; variability and lack of standardization of MJ preparations; use during pregnancy; cognitive changes; driving risks
- Treatment Agreement – measurable goals, track progress, "exit strategy"
- Qualifying Conditions – based upon review of literature; "*a patient need not have failed on all standard medications in order for a physician to recommend or approve the use of cannabis for medical purposes*"
- On-Going Monitoring

Although it may be effective, smoked marijuana as medicine presents challenges

- Safety of combustible material in clinical setting
- Second hand smoke as an irritant, possibly health hazard
- Efficiency and tolerability in smoking naïve
- Availability of cigarettes with standardized dose
- Conflict with anti drug laws
- Possibility of misuse and diversion
- Difficulty in conducting clinical trials on Schedule I substance whose legal availability is limited

Acute and Short Term Adverse Effects of Cannabis Reported in Clinical Trials Literature

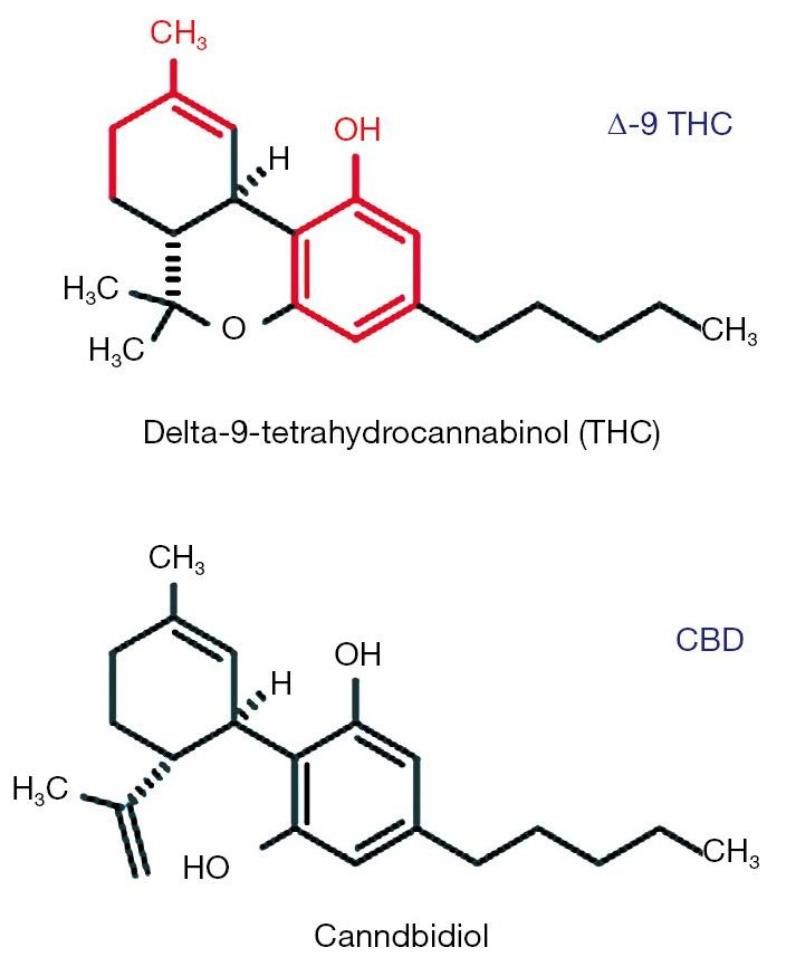
Medical & Neurological

- Dizziness (50%)
- Dry Mouth (25%)
- Fatigue (25%)
- Muscle complaints eg., weakness, myalgia (15%)
- Palpitations (20%)
- Ataxia (10%)
- Syncope (<5%)
- Hypotension (<5%)

Neuropsychiatric

- "High" or Intoxicated (dose dependent)
- Neurocognitive (dose dependent)
  - » processing speed
  - » perceptual (time sense; visual; other senses)
  - » reaction time
  - » attention
  - » recall
- Euphoria (5-25%)
- Anxiety (5-25%)
- Paranoia/Psychosis (< 1%)

Other Cannabinoids: Cannabidiol



Terpene phenolic heterocyclic structures of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Red portions identify basic terpene (left) and phenol (right) backbones.

Cannabidiol actions do not seem to involve endocannabinoid system

No psychoactive effect

Filloux FM. Cannabinoids for pediatric epilepsy? Up in smoke or real science? Transl Pediatr. 2015 Oct;4(4):271-82.

Cannabidiol - CBD

- Natural component of the Cannabis plant
- Constitutes up to 40% of marijuana extracts
- Devoid of typical psychological effects of THC
- Suggested applications as:
  - » Anti-inflammatory
  - » Analgesic
  - » Anti-emetic
  - » Hypnotic and sedative
  - » Antipsychotic
  - » Anticonvulsive
  - » Neuro-protective
  - » Anxiolytic
  - » Others
- Antagonism of THC when both contents are administered concomitantly? FAAH inhibition?

Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

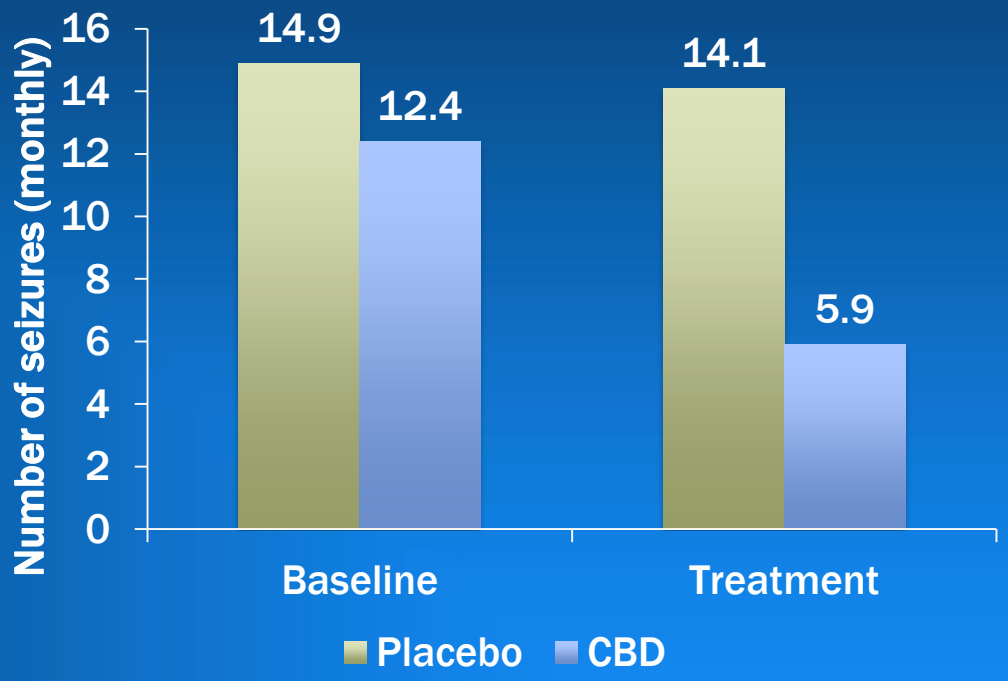
CBD—Enthusiasm or Evidence?

Clinical Trials.Gov 150+ registered trials of CBD (Nov 25, 2018)

- Alcohol, Cannabis, Cocaine, & Tobacco Use disorders
- Anxiety disorders, including PTSD
- Autism spectrum disorders
- Bipolar disorder
- Congestive heart failure
- Crohn's Disease
- Epilepsy
- Essential Tremor
- Infantile spasms
- Irritable bowel syndrome
- Prader-Willi Syndrome
- Sturge-Weber Syndrome
- Tourette's Syndrome

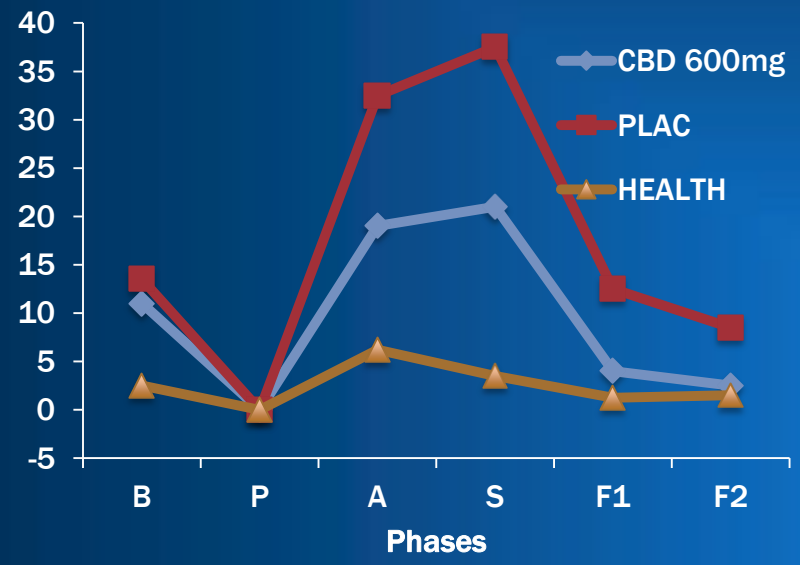
Cannabidiol (CBD) Significantly Reduces Convulsive Seizure Frequency in Lennox-Gastaut Syndrome (LGS)

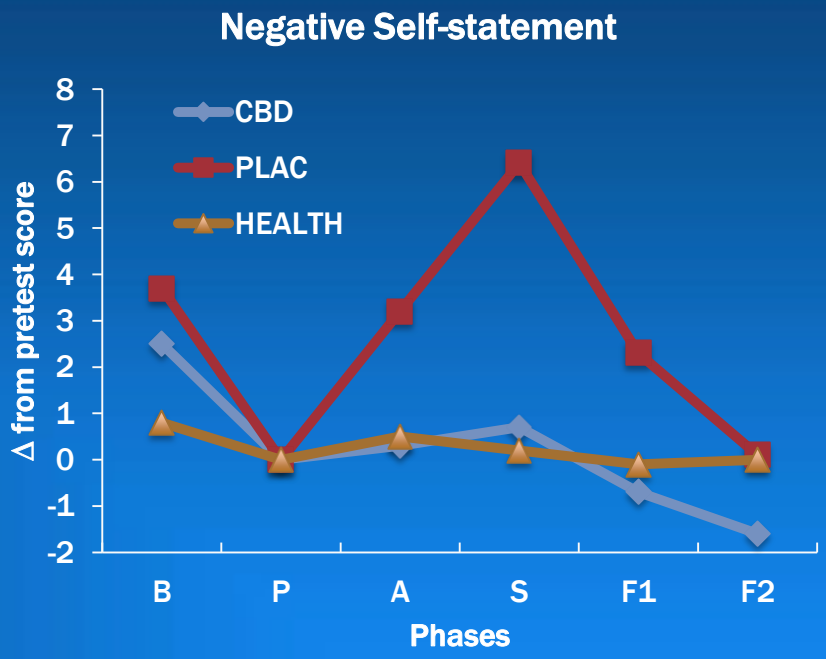
- 120 children/young adults
- 20 mg/kg CBD
- 14-week treatment period
- % with > 50% reduction in frequency (CBD – 43%; Placebo - 27%
- AEs (diarrhea, vomiting, fatigue, etc.



Devinsky et al., 2017 (NEJM)

Cannabidiol Reduced Anxiety in Simulated Public Speaking in Social Phobia Patients

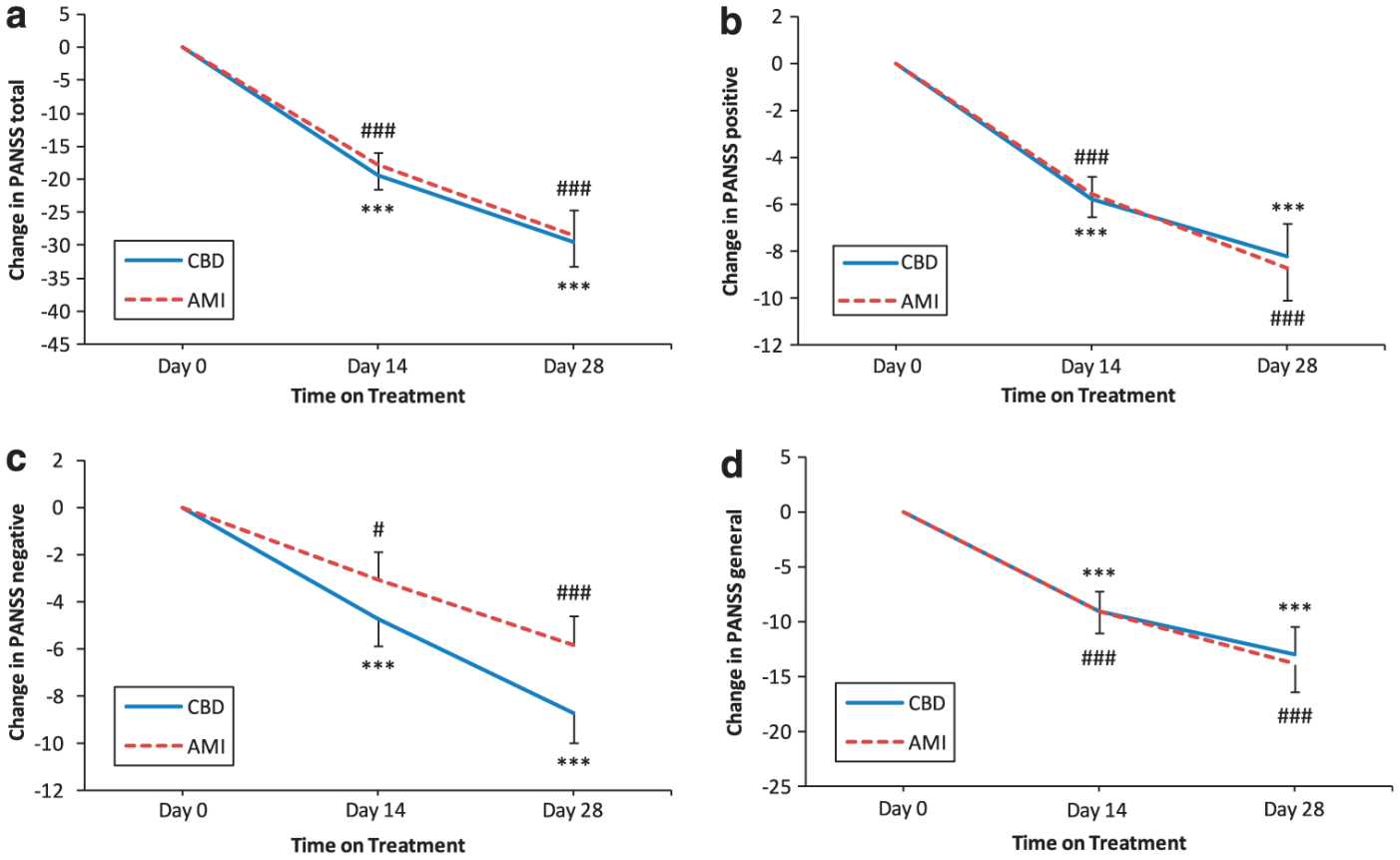




B (basal); P (pretest), A (anticipation), S (speech performance), F1 (post-speech measures 1), F2 (post-speech measures 2)

Bergamaschi et al., 2011

CBD improves positive and negative symptoms of schizophrenia: (42 cases randomized to receive 800 mg/d cannabidiol or amisulpride)



Leweke FM, Transl Psychiatry. 2012 Mar 20;2:e94.

Does CBD Mitigate the Effects of THC?

- CBD reduces THC activation of CB1 receptor in cells
- Results in humans are mixed
- Most studies conclude that there is no effect on the psychoactive or cardiovascular effects of THC
- May reduce anxiety or transient psychosis-like side-effects of THC seen in infrequent users

Acute and Short Term Adverse Effects of CBD Reported in Clinical Trials Literature

Medical & Neurological

- Viral infection-pneumonia (4%)
- Liver toxicity (2%)

Neuropsychiatric

- Lethargy-somnolence (2%)

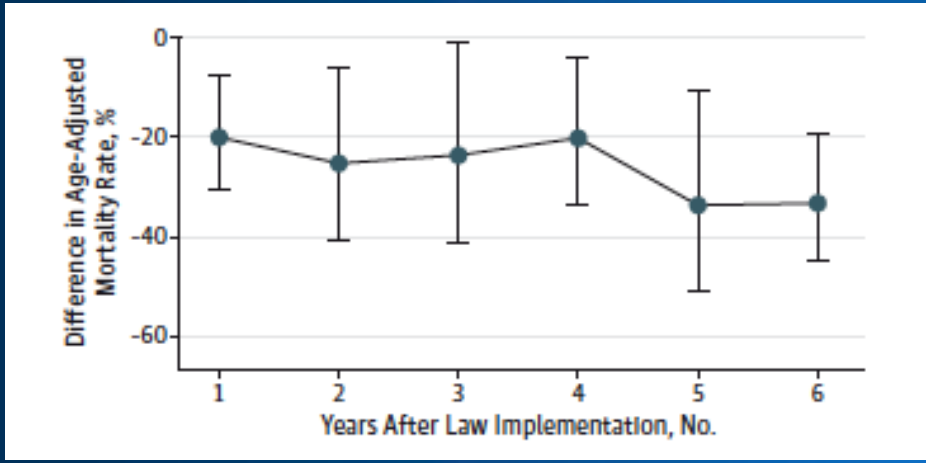
Medical Cannabis: Potential Public Health Benefits

- Decreased opioid analgesic overdose deaths
  - » Mean 25% decrease in states with medical cannabis (Bachhuber, et al., *JAMA Int Med*, 2014)
- Decreased opioid analgesic misuse
  - » Decreased treatment admissions for prescription opioid misuse
- Decreased obesity
  - » Associated with 2-6% decreased probability of obesity
- Decreased alcohol use
  - » Mixed findings

Courtesy David Gorelick, MD

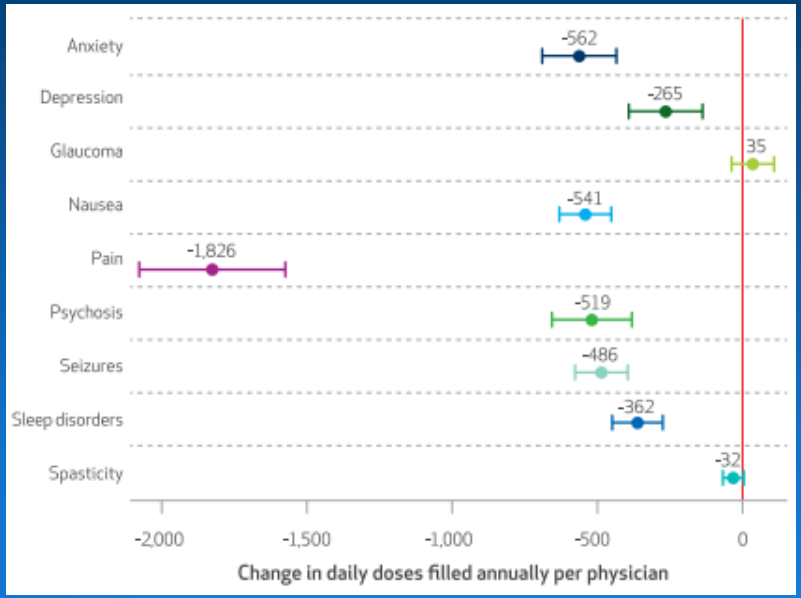
Cannabis May Reduce Opioid Use
States With and Without Medicinal Cannabis

Lower Opioid Overdose Mortality Rates

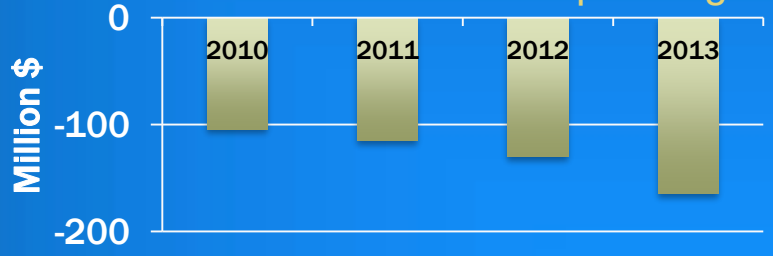


Bachhuber et al., 2014; JAMA Internal Med

Reduced Daily Doses Annually per Physician



Reduced Annual Medicare Spending



Bradford & Bradford, 2016

Medical Cannabis: Potential Public Health Harms

- Increased cannabis use
  - » Found in some, but not all, epidemiological analyses
- Increased incidence of cannabis use disorders
  - » Small increase in recent epidemiological analysis (Hasin et al., *JAMA Psychiatry*, 2017)
- Increased alcohol use
  - » Some evidence for both increased and decreased use (substitution)
- Increased cannabis-associated motor vehicle accidents
  - » Assessed in 3 states: CA, HI, WA (Masten & Guenzburger, *J Safety Res*, 2014)
- Increased unintended cannabis overdoses
  - » in Colorado, especially among children (e.g., Davis et al., *JAMA Psychiatry*, 2017)
- Increased crime around cannabis dispensaries
  - » Only in immediate vicinity (Long Beach, CA study)

Courtesy David Gorelick, MD

Potential Medical and Public Health Harms of Cannabis

Medical

- Respiratory Infection; chronic lung disease?
- Cancers ?
- Myocardial Infarction
- Teratogenicity?
- Fatal Overdose Not Reported

Neuropsychiatric

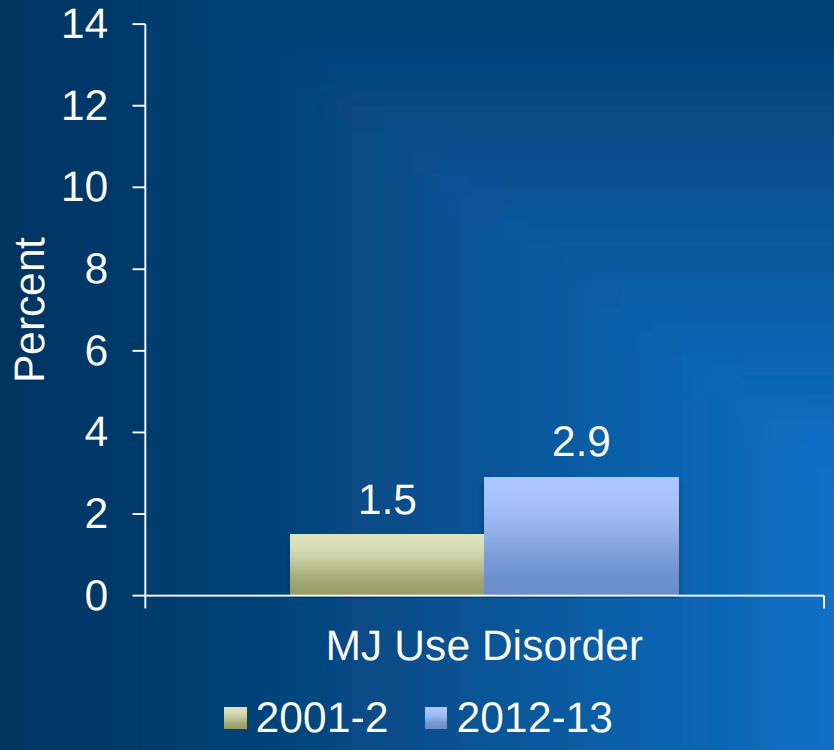
- Dependence
- Persisting Neurocognitive impairment?
- Psychotic disorder?
- Neurodevelopmental maturation

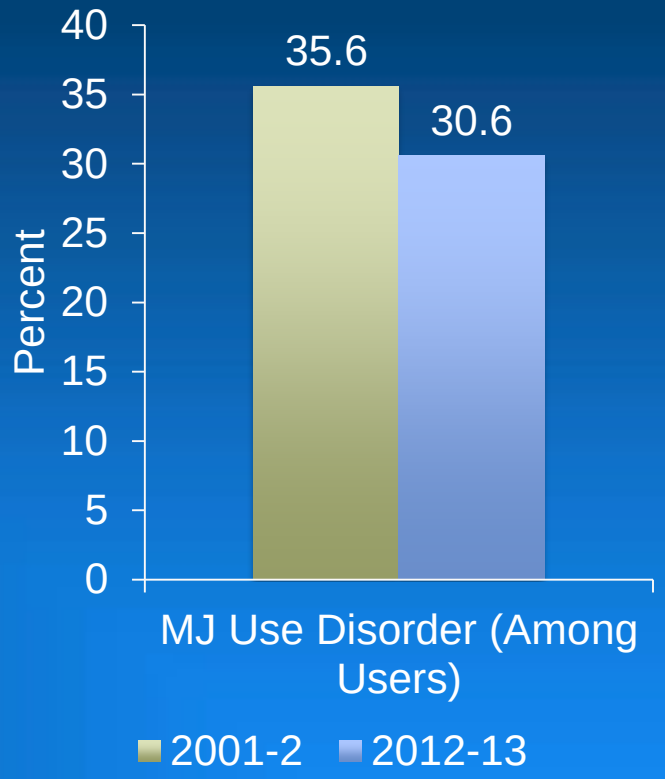
Public Health

- Traffic Accidents
  - Cannabis
  - Alcohol
  - Cannabis + Alcohol
- Scholastic and occupational difficulties
- "Gateway drug"?

- ? = Harm unclear

Prevalence of Past-Year Cannabis Use
National Epidemiologic Survey on Alcohol and Related Conditions





- *Increase MJUD prevalence is due to increase in number of users*
- *Higher potency in 2013, but perhaps once certain strength is reached, there are no additional reinforcing effects (self-titrating)*

Hasin et al., 2015

Cannabis Withdrawal

- Commonly seen in chronic, heavy marijuana users following abrupt discontinuation
- Often mild to moderate intensity
- Occurs in first couple of days of abstinence, resolves within 4 weeks
  - » Irritability
  - » Anxiety/nervousness
  - » Sleep difficulty
  - » Decreased appetite or weight loss
  - » Depressed mood
  - » Physical symptoms: abdominal pain, shakiness/tremors, sweating, fever, chills, headache
- May be more severe in females

Bonnet & Preuss, 2017

Comparative Risks of Substance Use Disorders

National Comorbidity Study 1994; National Epidemiologic Study of Alcohol and Related Disorders (2015)

Lifetime Dependence

- Tobacco 24%
- Alcohol 14%
- Cannabis 4%
- Cocaine 3%
- Methamphetamine 2%
- Heroin 0.5%

Conditional Dependence*

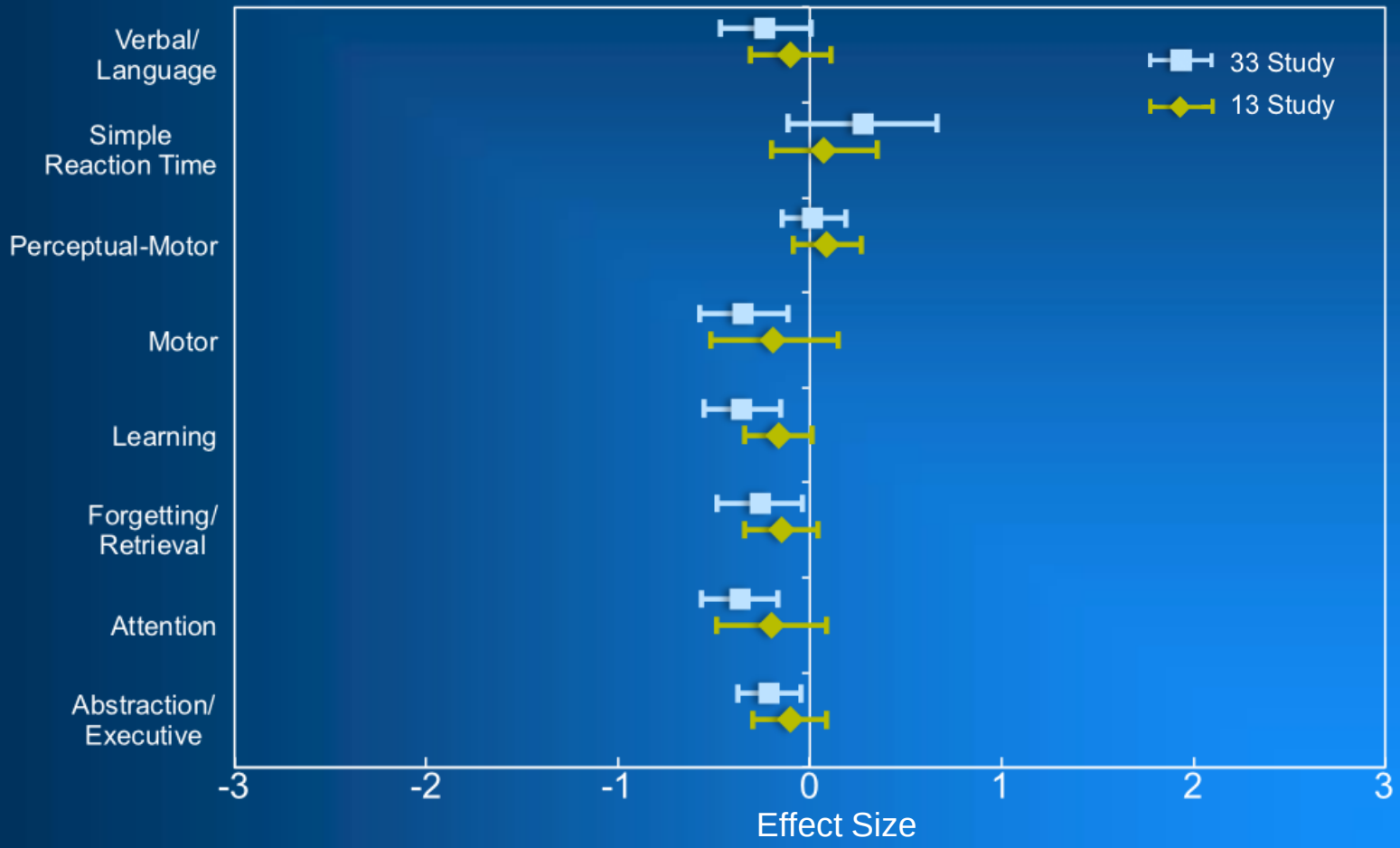
Tobacco 32%
Heroin 23%
Cocaine 16%
Alcohol 15%
Methamphetamine 11%
Cannabis 9%

» *Conditional = % of those who ever used at least once

Does Cannabis Use Cause Declines in NP Functioning? (Gonzalez et al., 2017)

- Reviewed studies with and without data before cannabis use initiation
- Long-term use results in neuropsychological decline
- Associations were
  - » Modest (1/5 to 1/2 standard deviation)
  - » Present only for heaviest users (often only 5 – 20% of participants)
  - » Often attenuated (or not significant) after controlling for confounding variables
- Future studies should:
  - » Control for “third variables”
  - » Examine impact in vulnerable populations
  - » Explore more potent products (extracts, wax, shatter)

Persisting neurocognitive deficits? Meta-analyses based on 33 Studies of nonintoxicated MJ users and subset of 13 studies with minimum 25 days abstinent

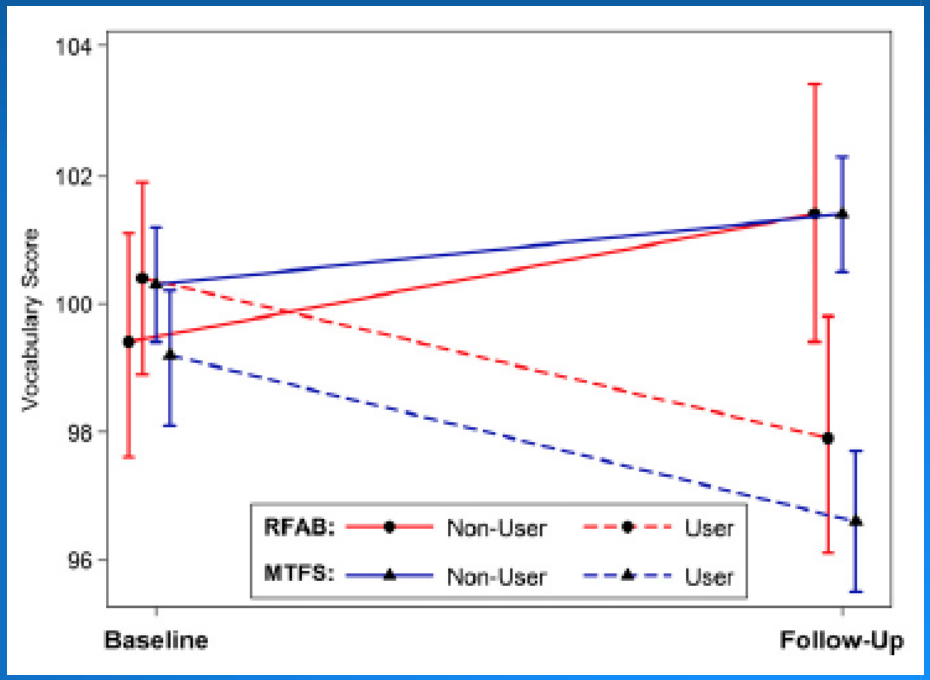


Schreiner & Dunn, Experimental and Clinical Psychopharmacology, 2012, 20(5):420-429.

Impact of Adolescent Cannabis Use on Intelligence (Jackson et al., 2017)

- Two longitudinal studies (RFAB, MTFS) of adolescent twins (n = 789; n = 2,277)
- Adjusted for family background characteristics and genetic propensities
- IQ assessed at 9-12 yo (before MJ use) and 17-20 yo

- MJ users had baseline IQ scores
- Significant decline in crystallized intelligence (attenuated when adjusting for binge drinking)
- No dose-response between frequency of use and IQ change
- MJ-using twins did not show greater decline compared to non-using siblings across most tests
- Declines in IQ not due to MJ exposure, but rather familial factors



Vocabulary Score Decline

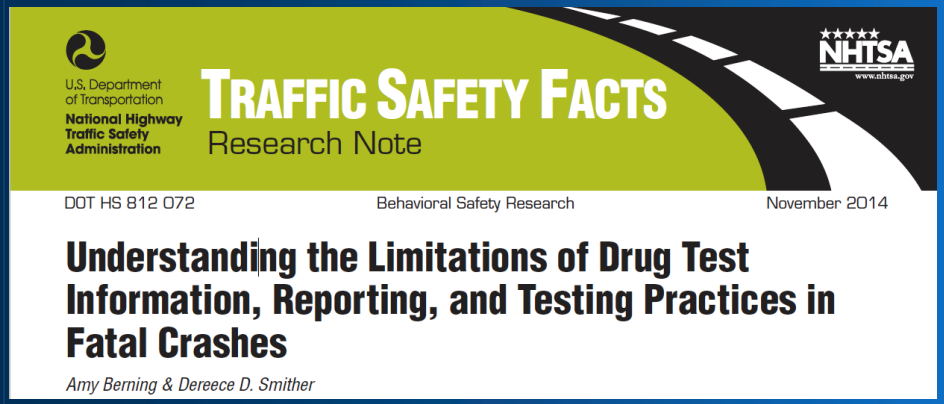
Summary

- Dose-related acute effects of MJ on attention, learning/memory, perception
- Chronic users develop some degree of tolerance to the impairing effects of cannabis
- Upon cessation of chronic heavy use neurocognitive effects may persist for days to weeks, and may be accompanied by a mild withdrawal syndrome
- Long term brain effects of chronic MJ use in adults not clearly demonstrated in those beyond residual MJ effect period. If present, they may be subtle and of unclear clinical significance
- Bodily fluids are of limited utility in determining cannabis-related impairment. Physiological signs may be indicative of recent use. Behavioral/cognitive assessments would more directly establish impairment status

She said marijuana makes her a better driver. "The weed makes me feel much more relaxed, and I don't feel rushed."

Cannabis and Fatal Crashes

- *"Marijuana-related traffic deaths more than doubled from 2013 to 2016…"* (RMHIDTA, 2017)
- *"Three years after recreational marijuana legalization, changes in motor vehicle crash rates for WA and CO were not statistically different from [states without legalization]"* (Aydelotte et al., 2017)
- *"Traffic deaths in Nevada dropped over 10 percent in the first year of recreational marijuana"* (News4, Reno, 2018)


U.S. Department of Transportation
National Highway Traffic Safety Administration

NHTSA
www.nhtsa.gov

TRAFFIC SAFETY FACTS
Research Note

DOT HS 812 072 | Behavioral Safety Research | November 2014

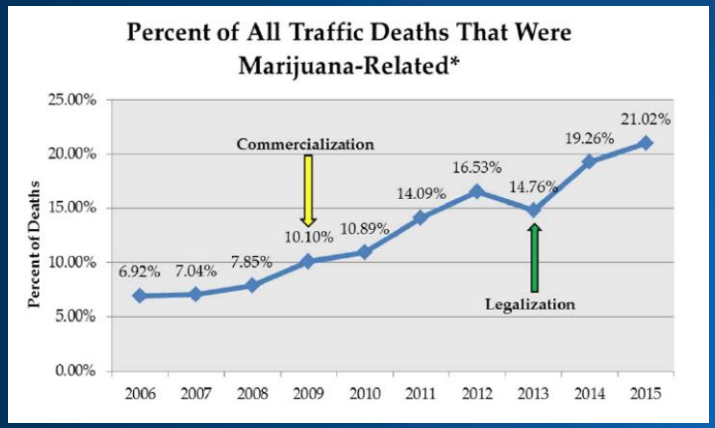
Understanding the Limitations of Drug Test Information, Reporting, and Testing Practices in Fatal Crashes

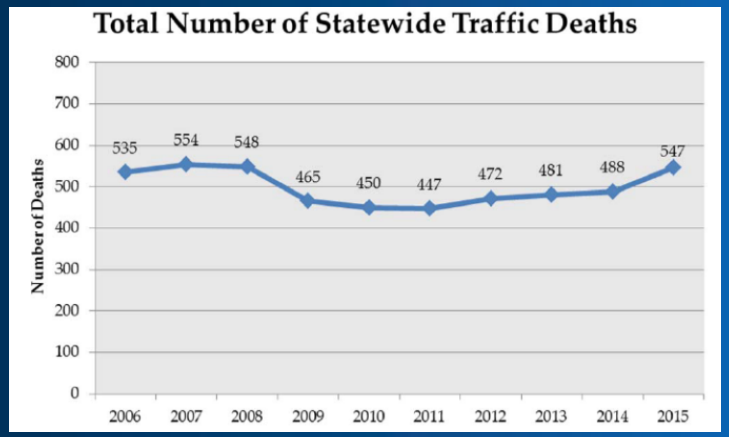
Amy Berning & Dereece D. Smither

- Inconsistent testing methods (who, which drugs, when, cut-points, equipment, bodily fluid)
- *FARS data is insufficient to allow comparisons of drug use across years, or across States…or inferences about impairment, crash causation…."*

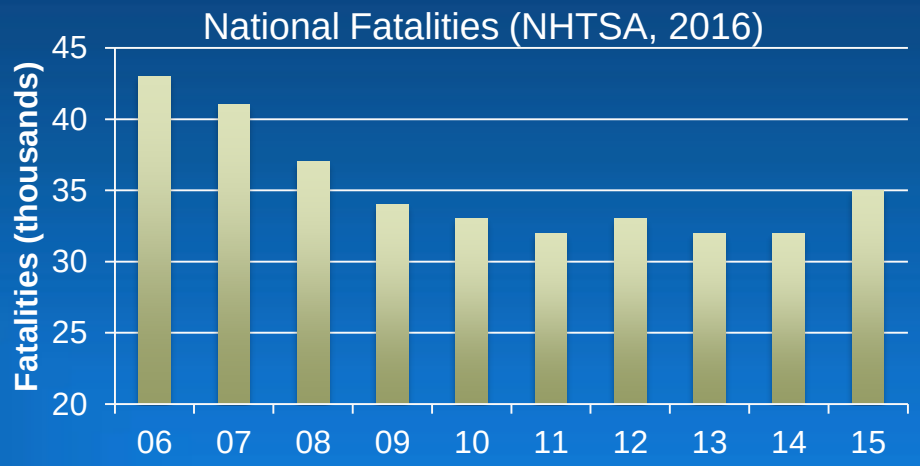
Impact of Legalization in Colorado

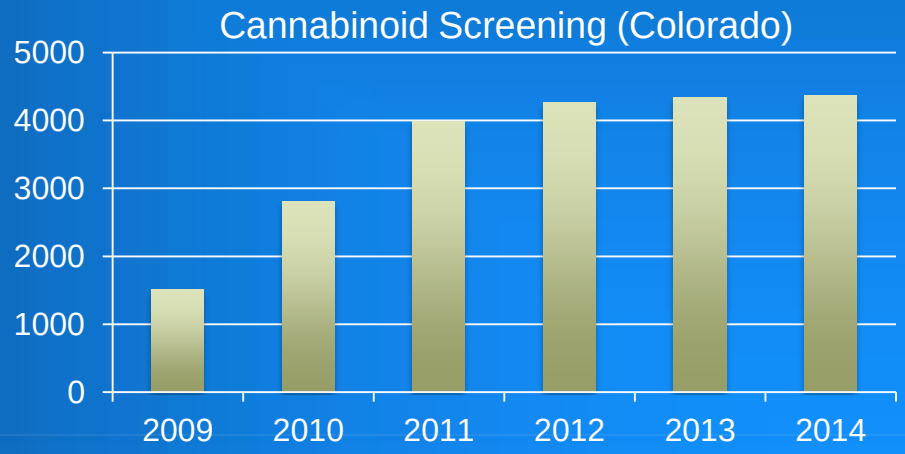
- **Marijuana-related traffic deaths (marijuana "mentioned"; includes other substances) increased 48% (2013-15) compared to 2010-2012; All traffic deaths increased 11%.**



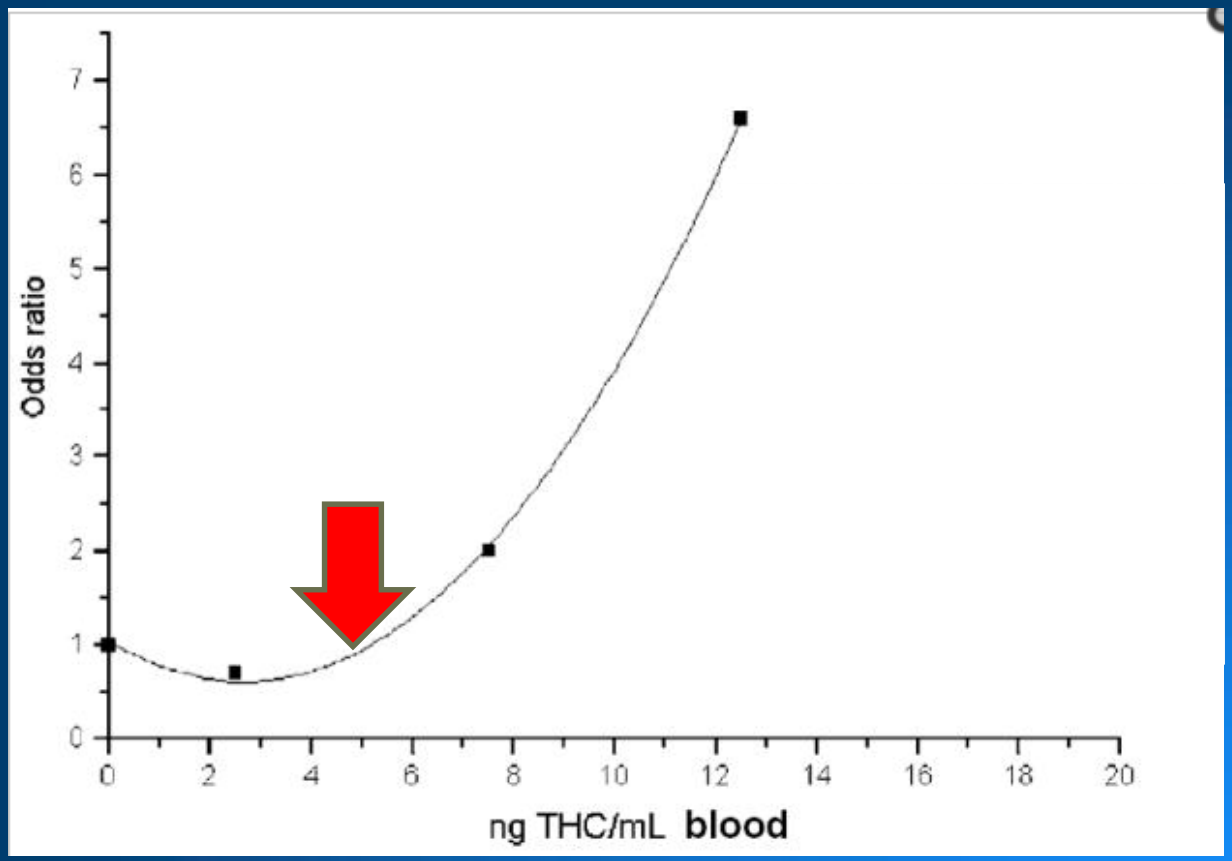


RMHIDTA, 2015





Increased crash risk if > 5 ng/mL

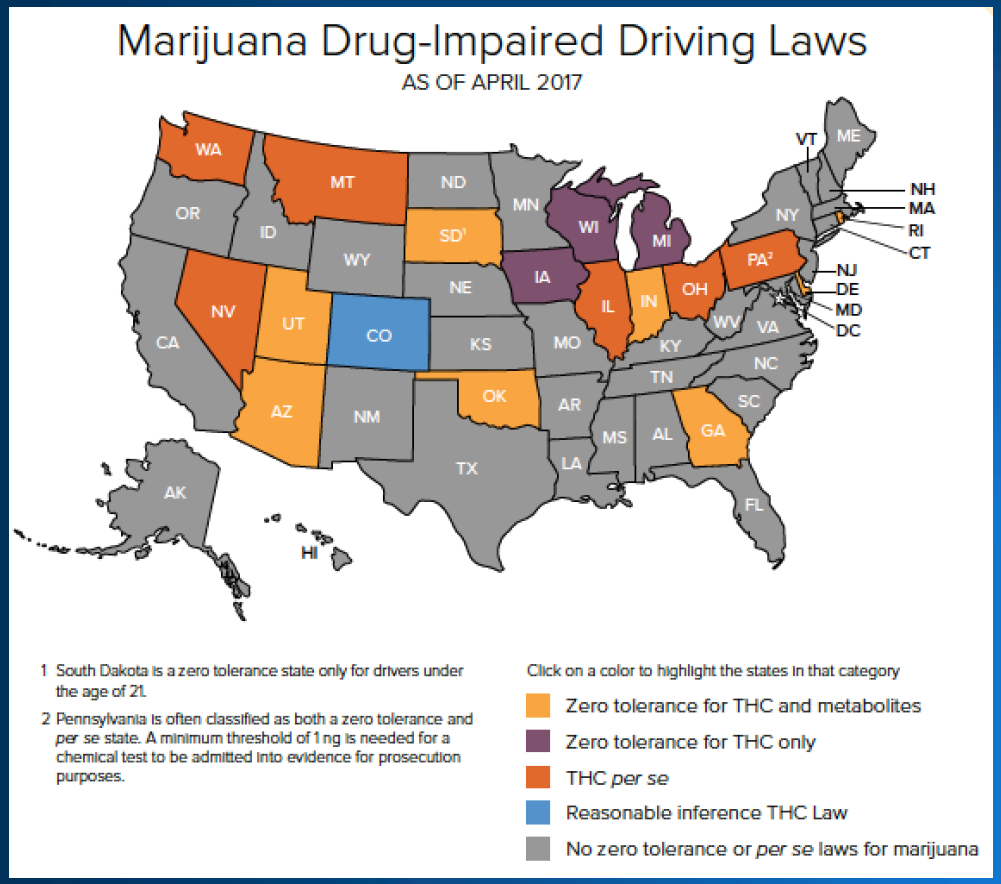


Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. Am J Addict. May-Jun 2009;18(3):185-193.

Cannabis and Driving

- What are the effects of cannabis combined with alcohol, other drugs, including prescription medications?
- Impact of other administration methods: Vape pens, dabbing, edibles, transdermal, salves, topicals, lip balm, sublingual, suppository
- Impact of concentrates (up to 90% THC; Wax, shatter, budder, dabs)
- Do regular cannabis users develop tolerance to the driver impairing aspects of cannabis?
- Synthetic THC: Spice, K2, etc.
- Impact in older users

THC levels and *per se* Laws



18 States with zero tolerance on non-zero *per se* laws

Zero tolerance (THC/metabolite)

AZ, DE, GA, IN, OK, RI, SD, UT

Zero tolerance (THC)

IA, MI, WI

Per se

1 ng (PA), 2 ng (NV, OH), 5 ng (IL, MT, WA); non-zero metabolites (NV, OH, PA)

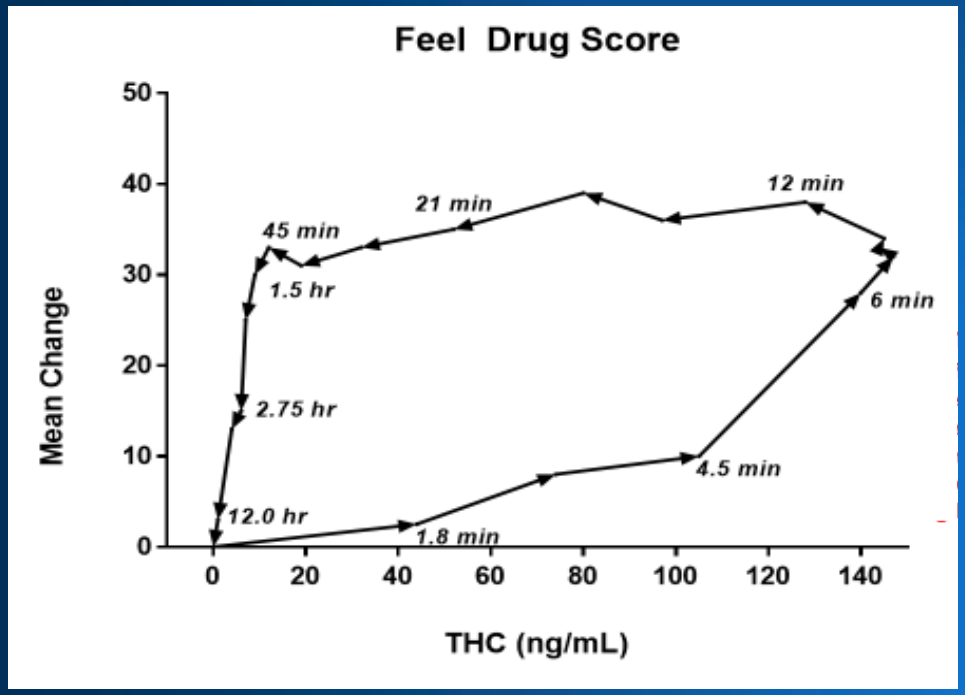
Reasonable inference

5 ng (CO)

Governors Highway Safety Administration (GHSA) (2017)

Complex Pharmacodynamics of THC

Poor correlation of being "high" and blood THC concentrations



Counter-clockwise Hysteresis (M. Huestis)

THC is detectable days after smoking (in chronic users; ~30 people)

Day	% detect	Median	Max
Admit	90%	1.4ng	6.3ng
1	68%	1.8	2.9
2	80%	1.2	2.2
3	79%	1.3	2.6
4	79%	1.1	2.3
5	77%	1.0	1.9
6	72%	1.0	2.2
7	79%	0.9	2.0

Bergamaschi et al., 2013

Medicinal Cannabis Challenges Research and Implementation

- Drug Enforcement Agency (DEA) scheduling
- Access to different constituents; single source for plant material
- Access to real-world cannabis

DEA Scheduling

I No currently accepted medical use and high potential for abuse:
Heroin, LSD, Ecstasy

II High potential for abuse, potentially leading to dependence:
Vicodin, cocaine, methamphetamine, methadone, fentanyl, Adderall

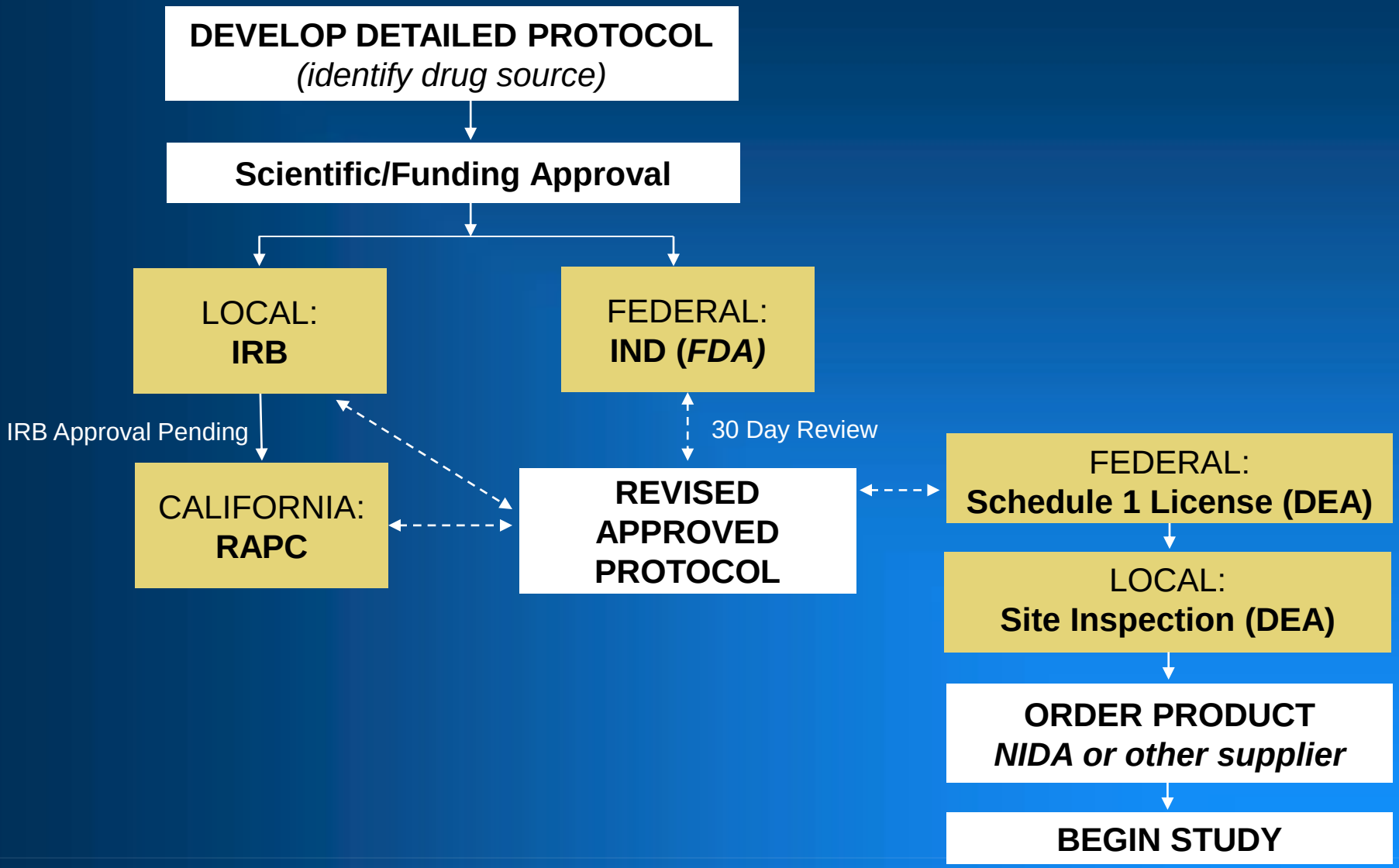
III Moderate to low potential for physical and psychological dependence:
Tylenol with codeine, ketamine, anabolic steroids, testosterone

IV Low potential for abuse or dependence:
Xanax, Darvocet, Valium, Ativan, Ambien

V Lower abuse risk then IV, limited quantities of narcotics; (antidiarrheal, analgesic)
Robitussin AC, Lomotil, Lyrica

			I	II	III	IV	V
THC	Synthetic	Nabilone (Cesamet)		✓			
	Synthetic	Dronabinol (Marinol)			✓		
	Synthetic	Dronabinol (Syndros)		✓			
	Plant		✓				
CBD	Plant-based	Epidiolex					✓
	Plant		✓				

Regulatory Approval Pathway



FDA Investigational New Drug Application

Federal Food, Drug & Cosmetic Act: Scientific/regulatory support for research on therapeutic uses; regulation of drug development (under INDs); enforcement regarding human health risks, illegal labeling claims

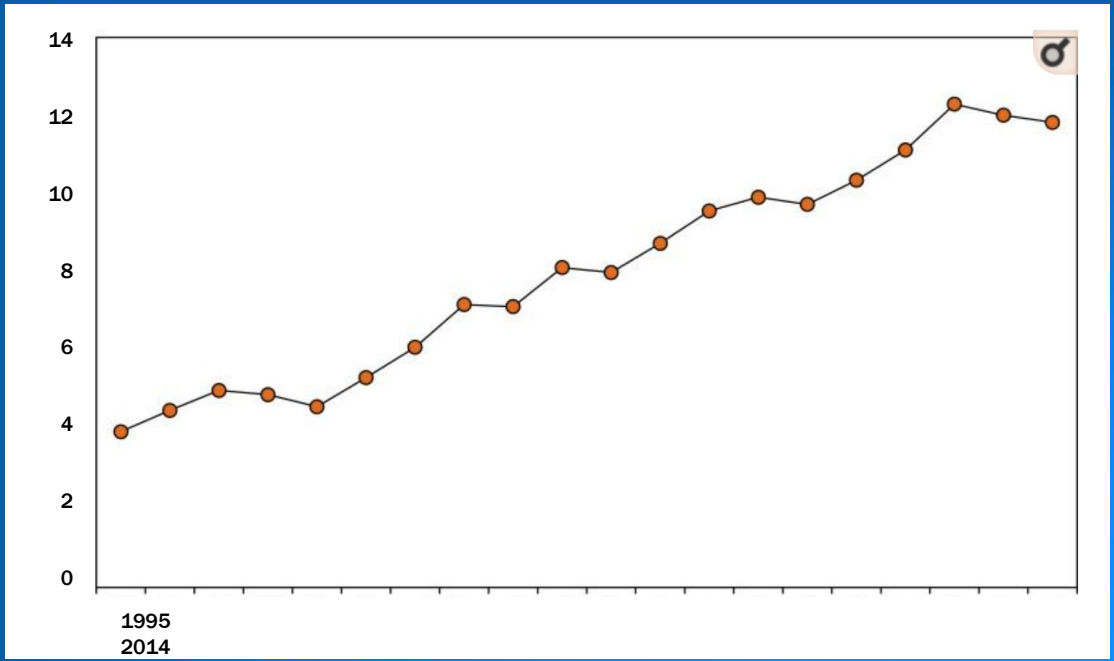
Controlled Substances Act: Scientific assessment on appropriate controls to recommend to HHS and DEA; assisting DEA on protocol for Schedule I research

Seven-Step Process

1. Secure communications (email, web access)
2. Obtain information on available product
   a) NIDA (strains, etc.)
   b) DEA-registered source (synthetic, etc.)
3. Contact DEA to apply for Schedule I license
4. Obtain Letter of Authorization (LOA) to reference all necessary information in the Drug Master File (DMF) on file with the FDA
5. Submit IND application, protocol, and LOA to FDA
6. FDA review and response within 30 days
7. Contact NIDA or other source after FDA review of IND completed and DEA registration is received

Challenges
Access to Product with Cannabinoids of Interest

NIDA has limited ability to provide cannabis with the cannabinoid ratios that are of scientific interest (e.g., THC levels representative of current markets; high CBD/low THC)



ElSohly et al, 2016

Challenge:
Accessing Real World Cannabis

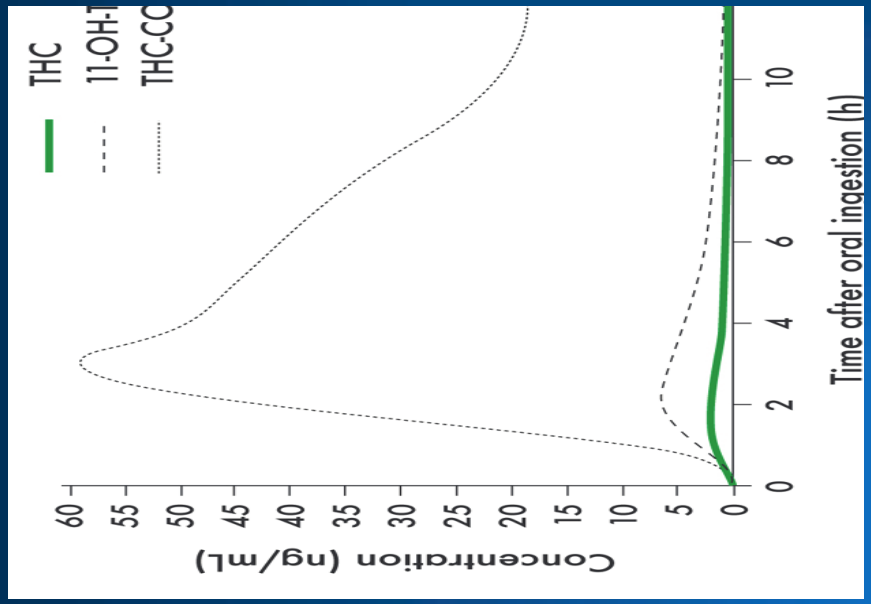
- Non-flower products are in wide use (edibles, wax, oils, concentrates) but cannot be accessed for research. Many are promoted as possibly have medicinal value.
  - In some products the THC levels approach 95%, but there is no research on the physiologic/cognitive effects this might have on individuals
  - We are unable to even analyze (e.g., true THC levels, contaminants) what is currently in use in the community, since by receiving any of the above we would be in violation of Federal law.

Research Options:
Potential Medicinal Benefits

Plasma THC Levels – Smoked vs. Oral

inhaled cannabis ~34mg THC

15mg oral THC (dronabinol)



- THC-COOH does not exhibit CNS effects

Mean plasma concentrations of Δ9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) following administration smoked cannabis vs. oral dronabinol.

Source: Grotenhermen, et al. 2003. Clin Pharmacokinet 2003; 42 (4): 327-360.

Current Sources of Material

- Plant
  - » NIDA/University of Mississippi
- Plant-derived cannabinoids
  - » Greenwich Biosciences (GW) – Epidiolex (CBD)
  - » Tilray/Canada - CBD-rich (20:1 CBD:THC) – recently approved import license (Fatah Nahab, MD – UCSD/CMCR)
- Synthetic
  - » Dronabinol/Marinol – THC
  - » INSYS– Syndros (THC), CBD

Examples of future research directions on medicinal cannabis

- Patient diversity, treatment response and adverse effects
  - » Sex; Age; prior experience with cannabis; co-occurring conditions eg., psychiatric; non cannabis substance disorders; medical, eg.,heart disease; liver disease
- Differential effectiveness, adverse effects, of various delivery systems
  - » eg., inhaled; oral; transdermal; oral-mucosal; suppositories
- Differential effects of specific cannabinoids
  - » ,eg., THC, CBD, their combination. Other cannabinoids and terpines?
- Cannabinoid synergistic or sparing effects
  - » Reduce or replace opioids, benzodiazepines, or other medications?
- Studies on dosing, duration of effect, tolerance:
  - » eg., are therapeutic [such as analgesic] effects gained at lower doses than psychoactive? Effects of cannabinoid combinations? Longer term outcome?

New CMCR-Associated Projects

- *"Randomized Controlled Trial of Dronabinol and Vaporized Cannabis in Low Back Pain"* (B. Wilsey & T. Marcotte; NIH)
- *"Effect of cannabis and endocannabinoids on HIV Neuropathic Pain"* (B. Henry; NIH)
- *"Cannabis Use and the Endocannabinoid System in Bipolar Disorder"* (W. Perry & J Young; NIH)
- *"Cannabidiol for the Treatment of Behavioral Abnormalities in Children with Autism Spectrum Disorders"* (D. Trauner, Noorda Foundation)
- *Cannabidiol/THC for the Treatment of Essential Tremor* (F. Nahab, Essential Tremor Foundation)
- *Cannabidiol as an Adjunct to Antipsychotics in Early Psychosis* (K. Cadenhead, Krupp Family Foundation)
- *"Assessing Cannabis-Related Driving Impairment"* (T. Marcotte; State of California)

Medicinal Cannabis

Thank you!

Igor Grant, M.D.

Director

J. Hampton Atkinson, MD & Tom Marcotte, PhD, Co-Directors

Barth Wilsey, MD, Ron Ellis, MD, PhD, Mark Wallace, MD, Robert Fitzgerald, PhD, Investigators; Ben Gouaux and Jennifer Marquie Beck, Senior Staff

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