Medicinal Cannabis

University of Cincinnati
Department of Psychiatry & Behavioral Neuroscience
Grand Rounds – Kaplan Endowed Lecture

September 8, 2021

Igor Grant, MD, *Director*

Co-Directors
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www.cmcr.ucsd.edu

UC San Diego
CENTER FOR MEDICINAL CANNABIS RESEARCH

Cannabis sativa (C. sativa)

Cannabis sativa L. A) Flowering male staminate. B) Fruiting female pistillate plant:

1 male staminate flower;

2 stamen (anther and short filament);

3 stamen; 4 pollen grains;

5 female pistillate flower with bract;

6 female flower without bract;

7 female flower showing ovary, longitudinal section;

8 fruit (the fruit is the seed, technically achene) with bract;

9 fruit without bract;

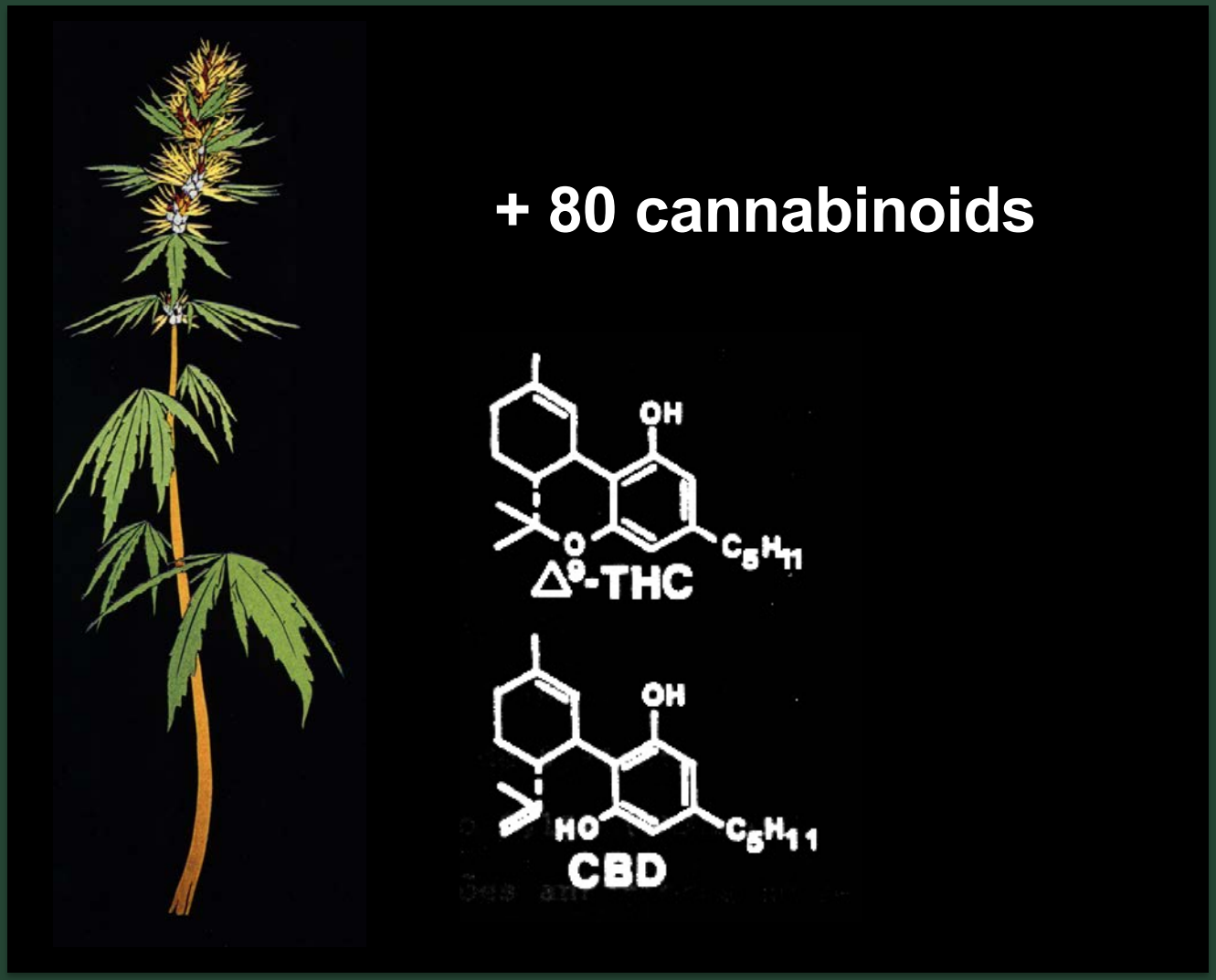
10 fruit (side view);

11 fruit (cross-section);

12 fruit (longitudinal section);

13 fruit without pericarp (hulled).

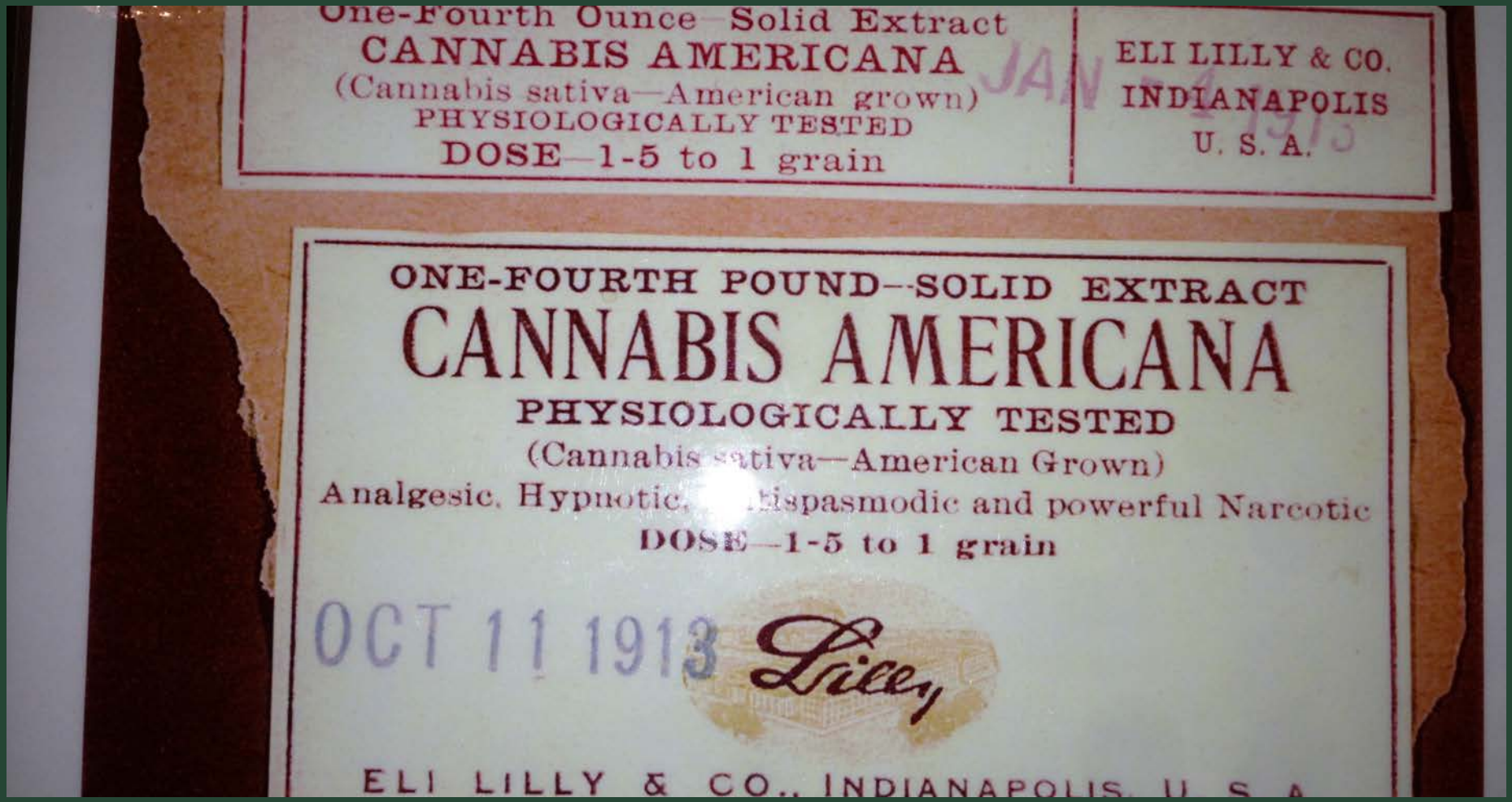
Marijuana Compounds



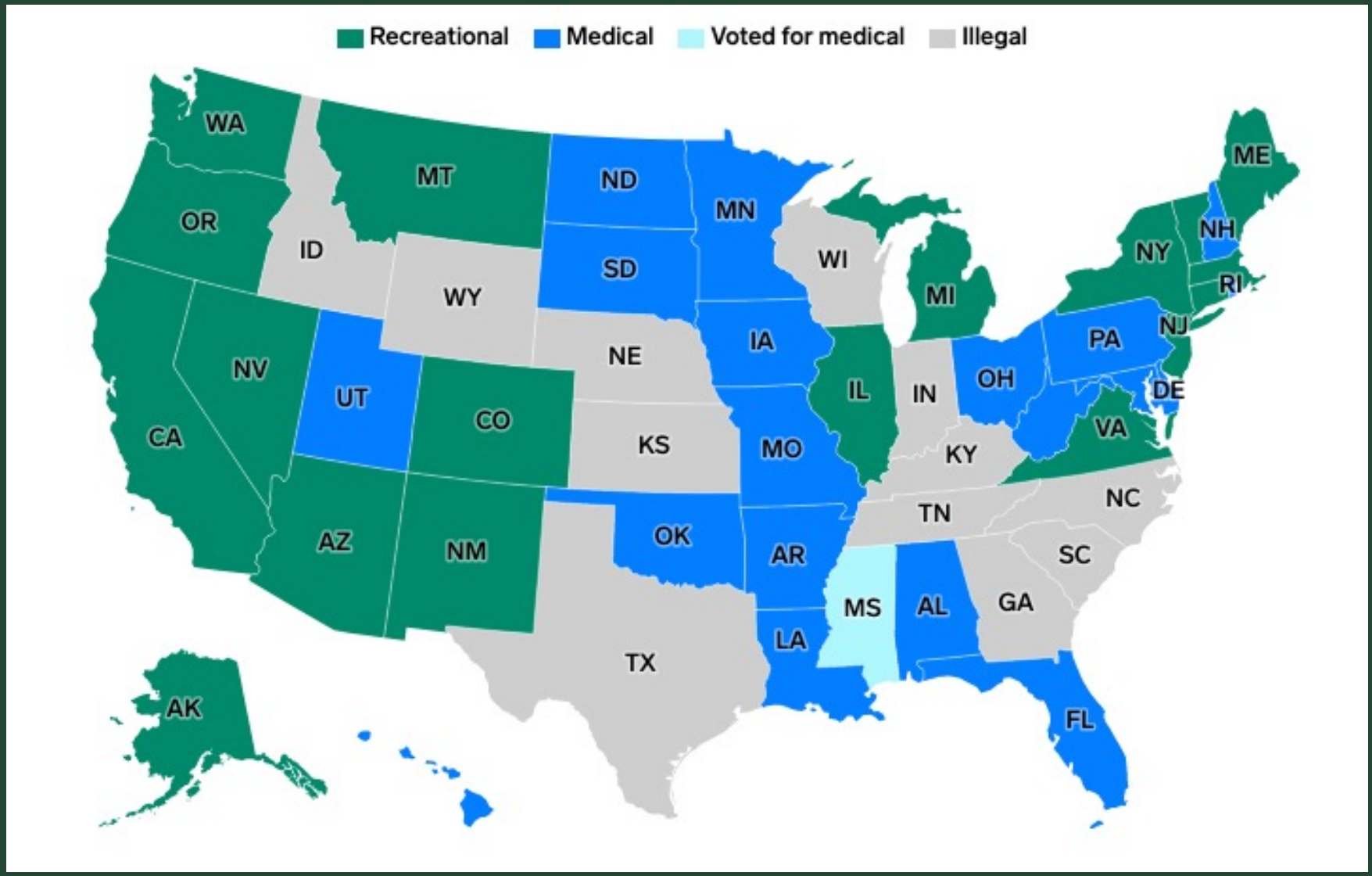
Isolation, structure and partial synthesis of an active constituent of hashish.
Y. Gaoni, Raphael Mechoulam. J. Am. Chem. Soc. 86, 1964: 1646.

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

Cannabis: not a new medicine



Cannabis Legalization by State, July 2021

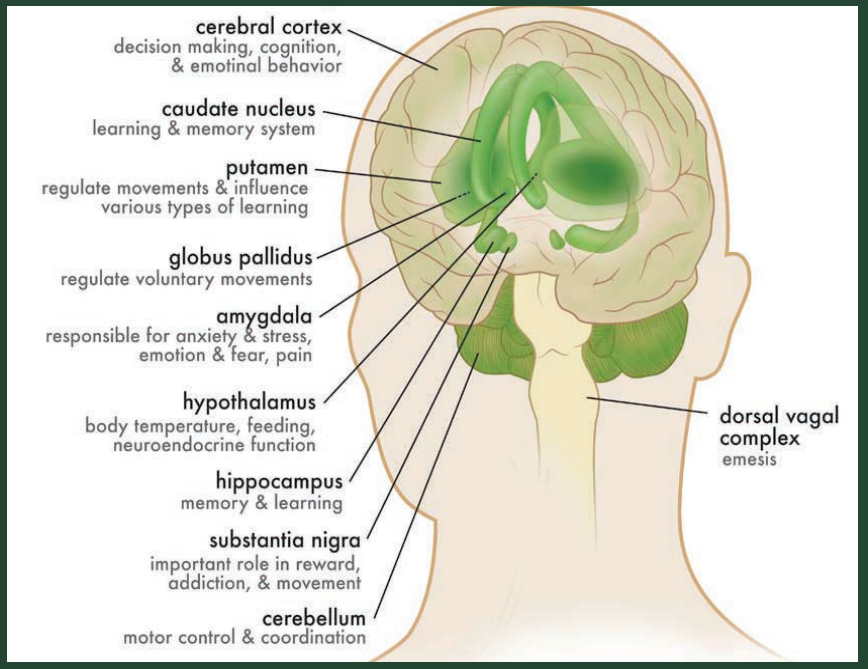


Source: Berke, Gal & Lee/Business Insider, July 2, 2021

Cannabis Comes in from the Cold: A Tale of Science and Politics

- Persistent anecdotal reports of benefits
- Political shifts favoring medicinal access (in the United States, most states now provide for some measure of access)
- Discovery of the endocannabinoid system
  — CB1 and CB2 receptors
  — Anandamide[1]
  — 2-arachidonoylglycerol[2,3] and other signaling molecules
  — Development of synthetic molecules: agonists, partial agonists, antagonists, and other modifiers (e.g., inhibitors of fatty acid amide hydrolase [FAAH]. FAAH breaks down anandamide)

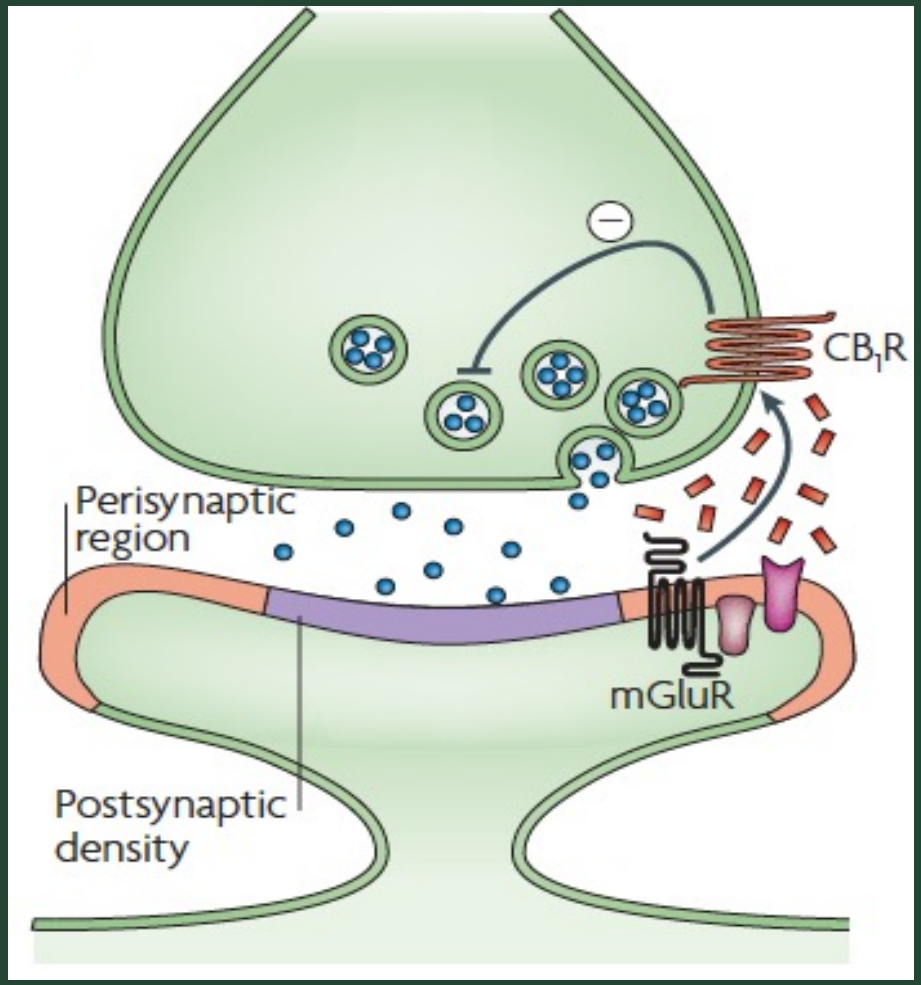
Distribution of CB1 Receptors

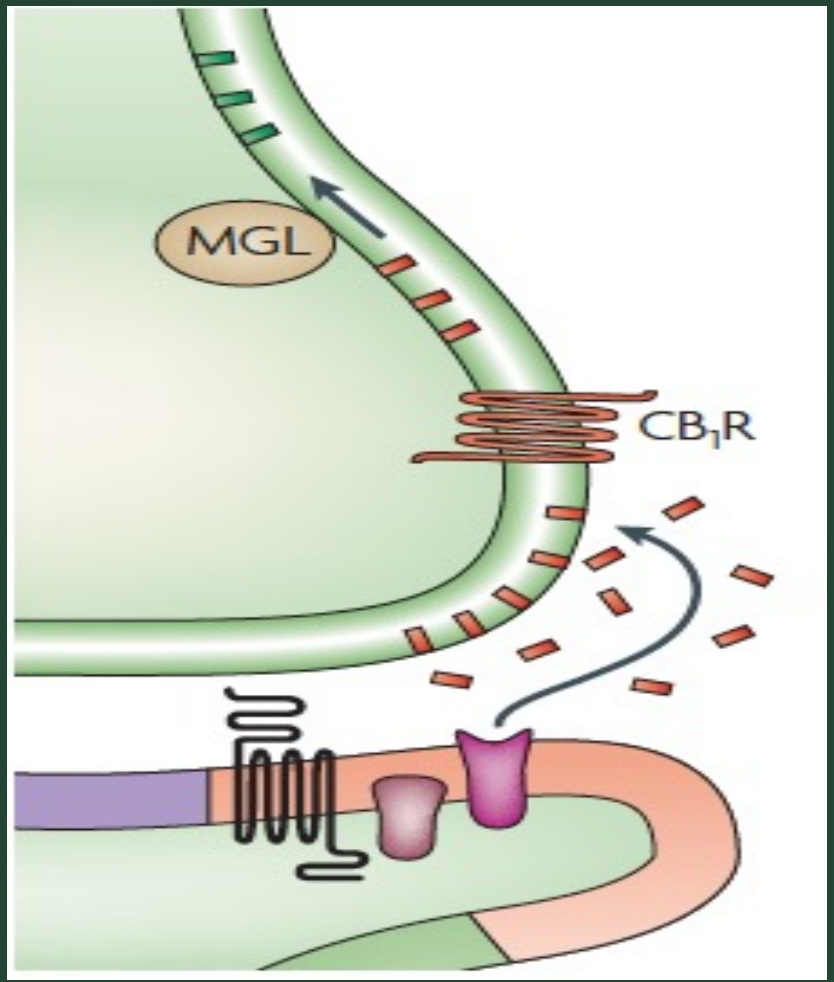


1. Devane, et al. *Science*. 1992;258(5090):1946-1949. 2. Sugiura, et al. *Biochem Biophys Res Commun*. 1995;215:89-97.
3. Mechoulam R. *Biochem Pharmacol*. 1995;50:83-90.

“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)

University of California Center for Medicinal Cannabis Research (CMCR)

Igor Grant, MD, *Director*

Co-Directors

J. Hampton Atkinson, MD & Thomas D. Marcotte, PhD

Investigators

Barth Wilsey, MD; Mark Wallace, MD; Ron Ellis, MD, PhD; David Grelotti, MD; Robert Fitzgerald, PhD; Jeremiah Momper, PhD; Brook Henry, PhD; Alysson Muotri, PhD; William Perry, PhD; Gabriel Silva, PhD; Ji Sun, PharmD; Doris Trauner, MD; Jared Young, PhD

Senior Staff

Jennifer Marquie-Beck, MPH, Felicia Roston, Carla Ingle, Clint Cushman, Debra Cookson, MPH

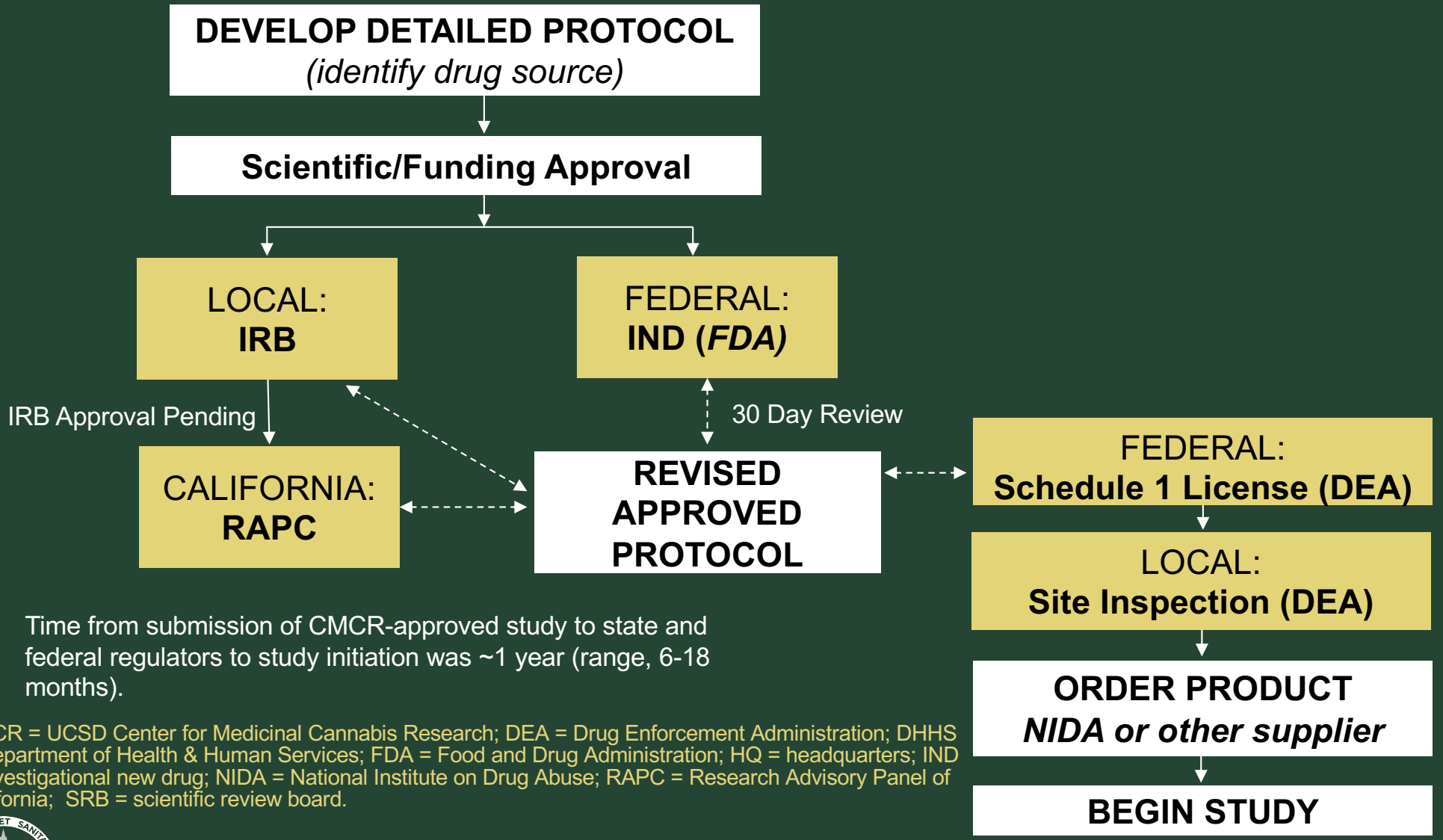
www.cmcr.ucsd.edu

California Events Leading To CMCR

November 1996:	**California passes Prop 215**
September 1999:	**Medical Marijuana Research Act of 1999, (SB 847)**
August 2000:	**Center for Medicinal Cannabis Research established at the Univ of California San Diego**
September 2003:	**Amendment to Medical Marijuana Research Act of 1999, sunset restrictions removed (SB 295)**
November 2016:	**Proposition 64 allocates $2M/yr to CMCR to continue its mission**
February 2021:	**CMCR Reference Lab contracted by California Bureau of Cannabis Control**
Current portfolio	**Total funding ~ 40M combination of NIH, State and Private sources**

Because Cannabis Is a Schedule 1 Drug, and the Only Legal Source Is the Federal Government*, Medical Studies Are Challenging

*As of 2021 DEA may be licensing at least 4 new manufacturers



Time from submission of CMCR-approved study to state and federal regulators to study initiation was ~1 year (range, 6-18 months).

CMCR = UCSD Center for Medicinal Cannabis Research; DEA = Drug Enforcement Administration; DHHS = Department of Health & Human Services; FDA = Food and Drug Administration; HQ = headquarters; IND = investigational new drug; NIDA = National Institute on Drug Abuse; RAPC = Research Advisory Panel of California; SRB = scientific review board.

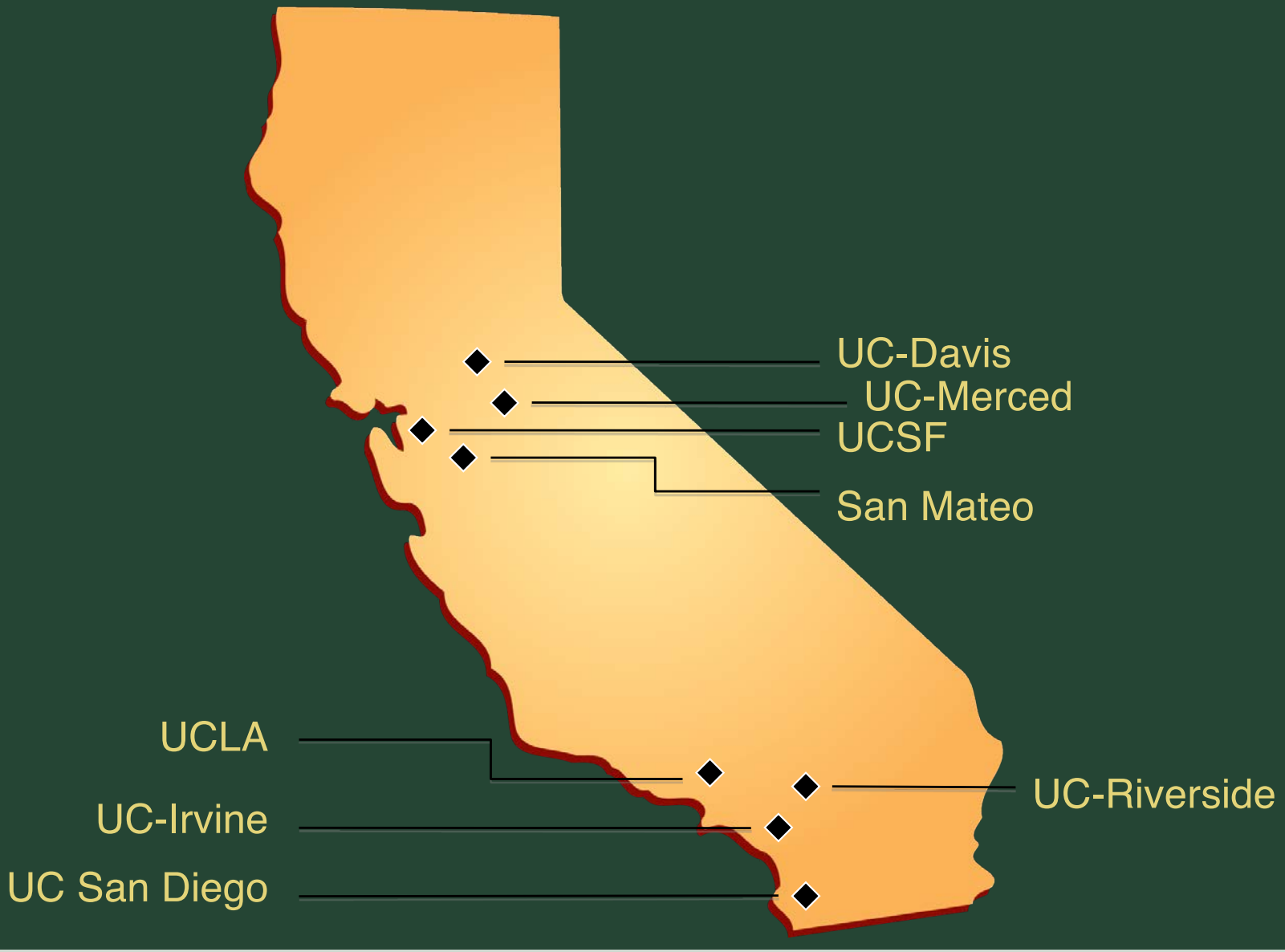
DEA Scheduling

I No currently accepted medical use and high potential for abuse
II High potential for abuse, potentially leading to dependence
III Moderate to low potential for physical and psychological dependence
IV Low potential for abuse or dependence
V Lower abuse risk then IV, limited quantities of narcotics; (antidiarrheal, analgesic)

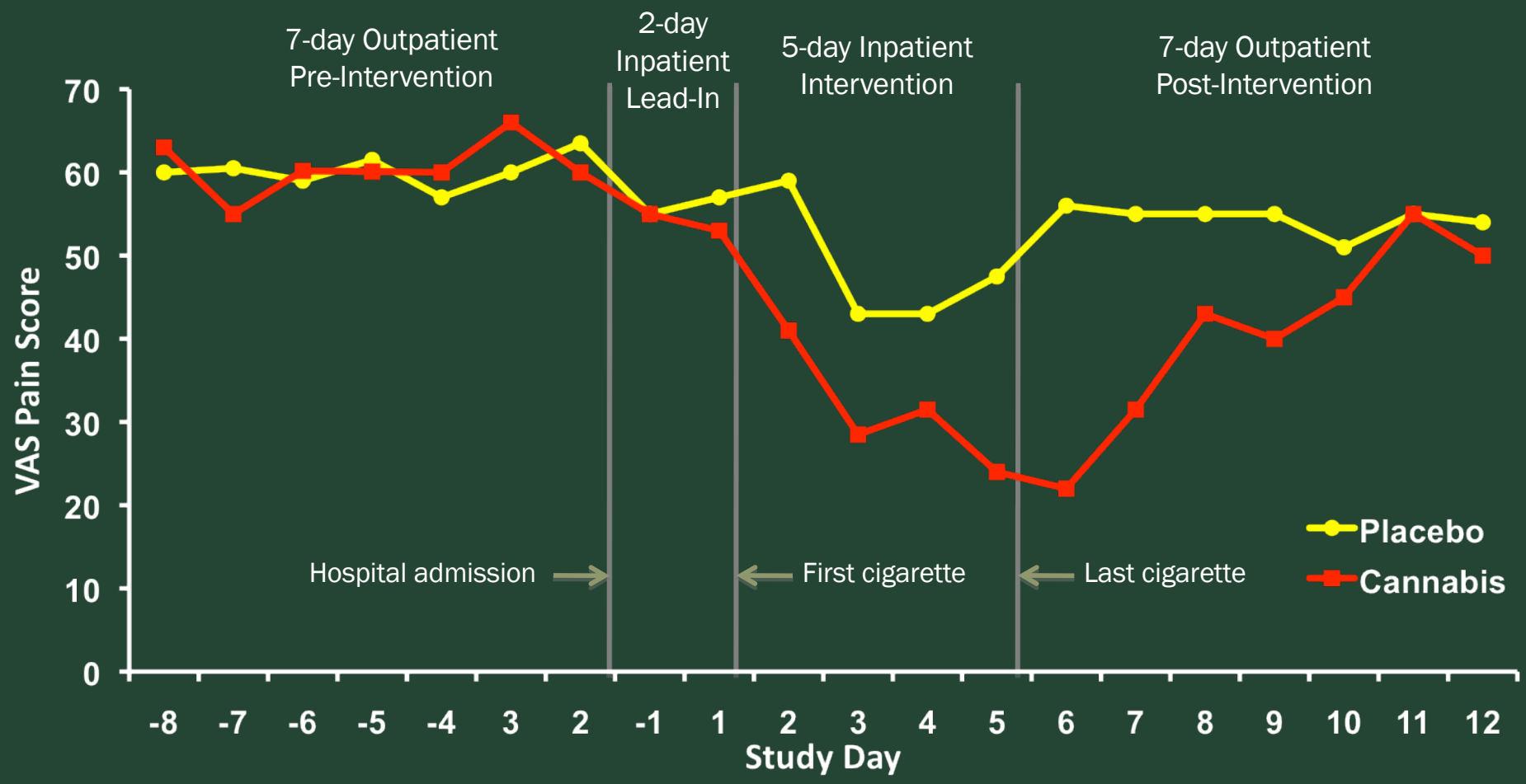
			I	II	III	IV	V
THC	Plant		✓				
	Synthetic	Nabilone (Cesamet)		✓			
	Synthetic	Dronabinol (Syndros)		✓			
	Synthetic	Dronabinol (Marinol)			✓		
CBD	Plant*		✓				
	Synthetic+		-	-	-	-	-
	Plant-based	Epidiolex	-	-	-	-	-
	Hemp^		-	-	-	-	-

* > 0.3% THC content +No detectable THC ^ THC content 0.3% or less

Study Locations



CMCR Abrams et al study: Cannabis reduces HIV Neuropathic Pain



Placebo controlled double blind randomized trial of 4% THC containing vs 0%THC MJ cigarettes administered 3x/day for 5 days.

Source: Abrams, D. I. et al. Neurology 2007;68:515-521

CMCR Clinical Studies completed

SITE	DISORDER	DESIGN	N	DOSE (% THC)	Result
Mark Wallace UCSD	Healthy Volunteers (Experimentally-Induced Pain)	Crossover RCT	15	0%, 2%, 4%, 8%	+
Donald Abrams UCSF	HIV Neuropathy, Experimental Pain	Parallel Groups RCT	50	0%, 3.5%	+
Ronald Ellis UCSD	HIV Neuropathy	Crossover RCT	28	0%, 1-8%	+
Barth Wilsey UC Davis	Neuropathic Pain, Experimental Pain	Crossover RCT	33	0%, 3.5%, 7%	+
Barth Wilsey UC Davis	Neuropathic Pain	Crossover RCT	39	0%, 1.29%, 3.53% (Vaporized)	+
Jody Corey-Bloom UCSD	MS Spasticity	Crossover RCT	30	0%, 4%	+
Mark Wallace UCSD	Diabetic Neuropathy	Crossover RCT	16	0%, 2%, 4%, 7%	+

Current and Pending CMCR Studies

1. Vaporized cannabis and dronabinol in low back pain
2. Oral THC/CBD in essential tremor
3. CBD in severe autism
4. CBD in schizophrenia
5. Vaporized cannabis in neuropathic pain
6. Effects of THC and CBD on endocannabinoids in bipolar
7. CBD in rheumatoid arthritis
8. CBD for sleep disorders
9. CBD for anorexia nervosa
10. Cannabigerol, THC, CBD in pain
11. Cannabis effects on driving
12. CBD to reduce alcohol craving (rodent)
13. CBD effects on blood pressure and metabolic syndrome (rodent)
14. THC effects on Type 2 diabetes
15. THC effects on gut barrier function (rodent)
16. Effects of THC and CBD on attenuating opioid abuse and addiction (rodent)

How effective is cannabis relative to other pain medications? Number-Needed-to-Treat

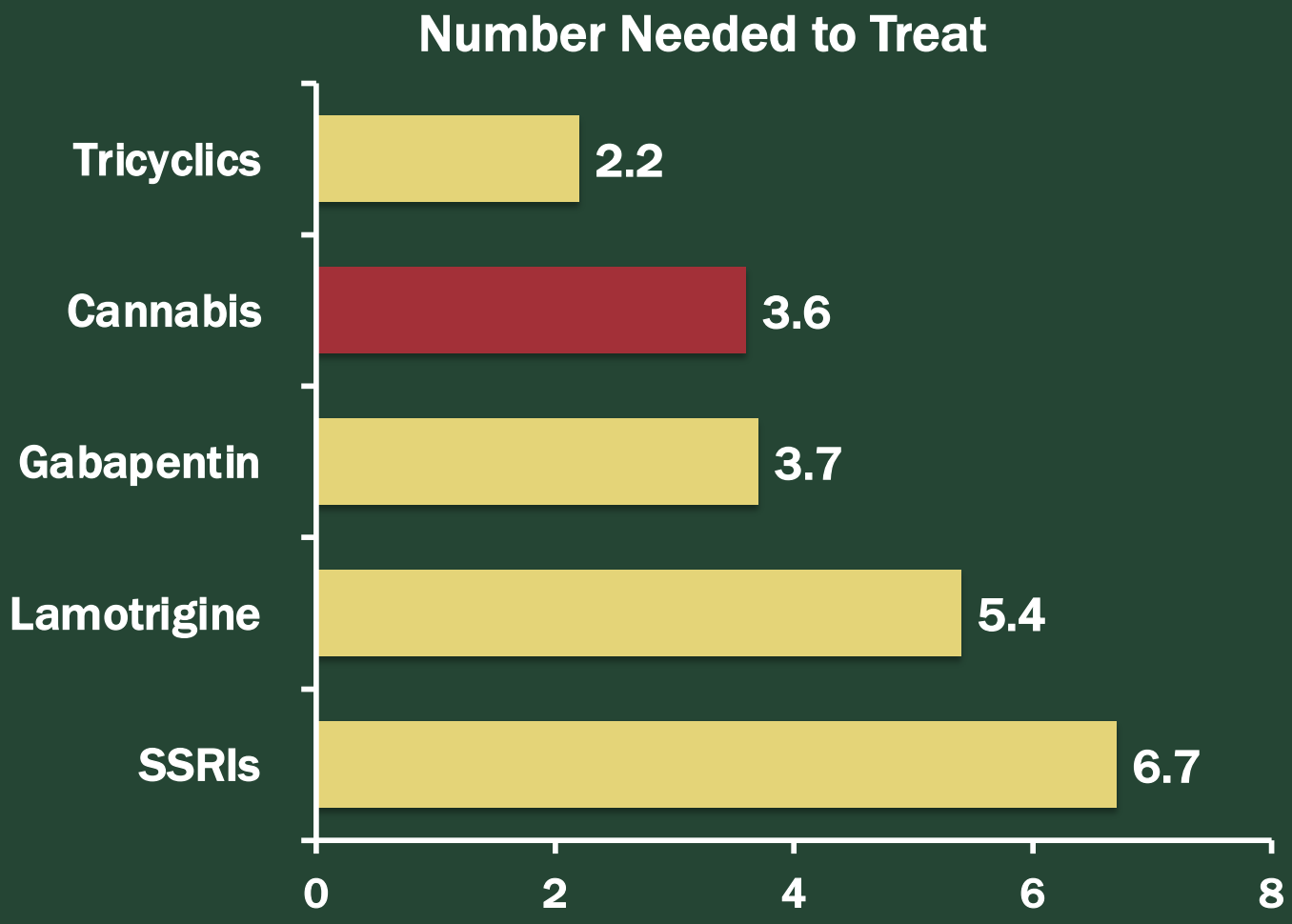
- Number-Needed-to-Treat (NNT) = 1/Proportion improved in experimental condition – Proportion improved on placebo

- Ex: If 30% reduction in pain intensity = "Improved"

  and 60% "improve" in the experimental condition, while 30% "improve" in the placebo condition, then 0.60 – 0.30 = 0.30 and

NNT = 1/.30 = 3.3

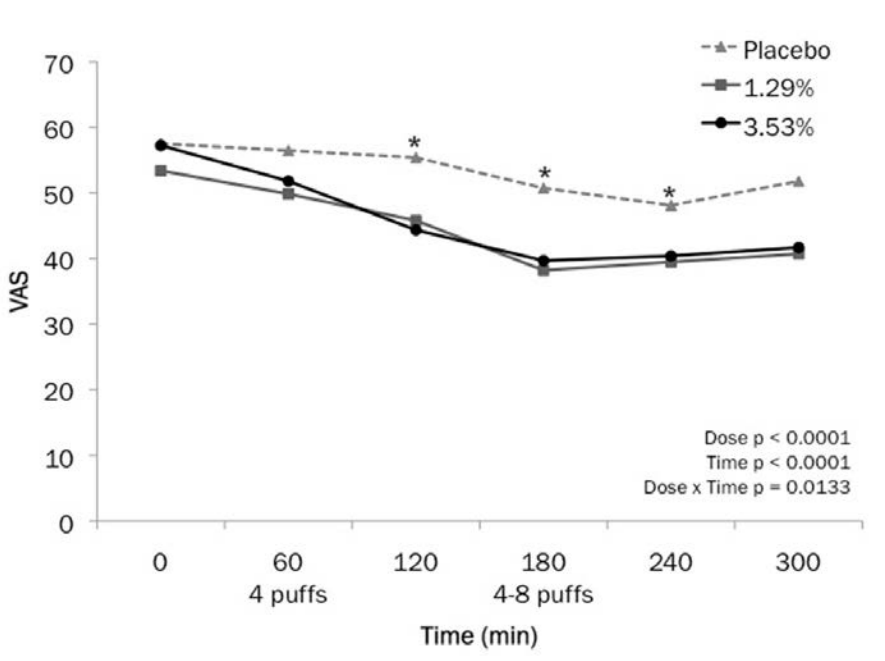
Common Analgesics for Neuropathic Pain



*Number Needed to Treat to to achieve a 30% reduction in pain.

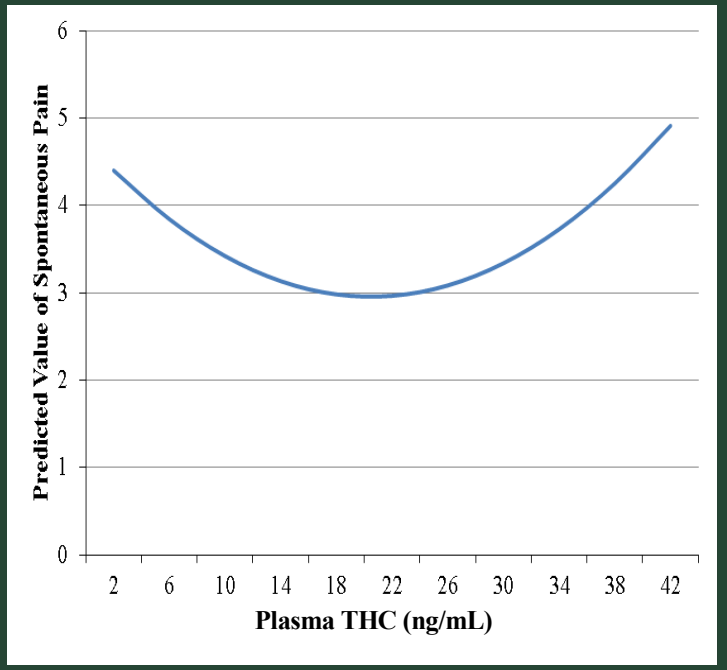
Optimal dosage?: Therapeutic window?

Low-dose inhaled THC (~1.5%) resulted in equivalent analgesia to ~4% with minimal psychotropic effects in patients with neuropathic pain



Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013

Greatest analgesia at mid-range dose (ng/ml) in participants with painful diabetic peripheral neuropathy suggests a therapeutic window



Wallace, M. et al. (In submission)

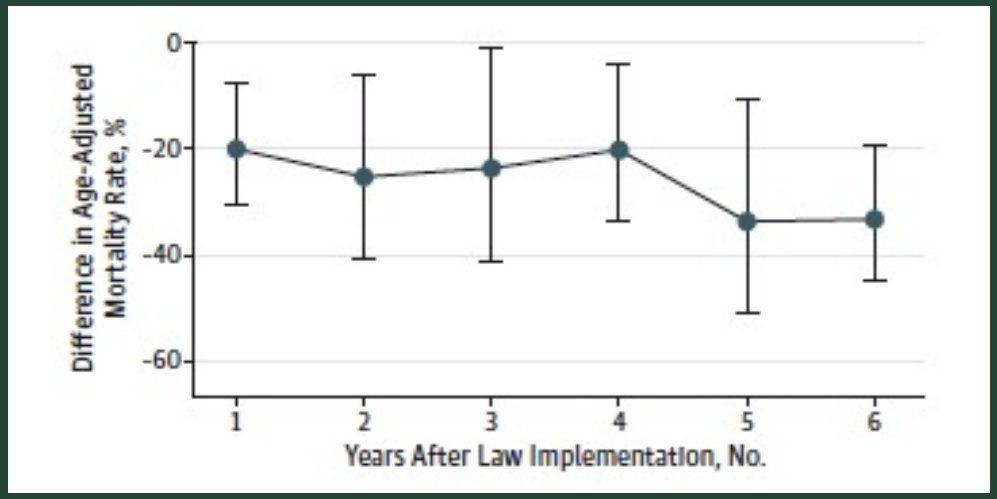
National Academies Report (2017)
Evidence for Therapeutic Benefits of Cannabis

- 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, eg., 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

Ref: The Health Effects of Cannabis and Cannabinoids.
Washington (DC): National Academies Press (US); 2017

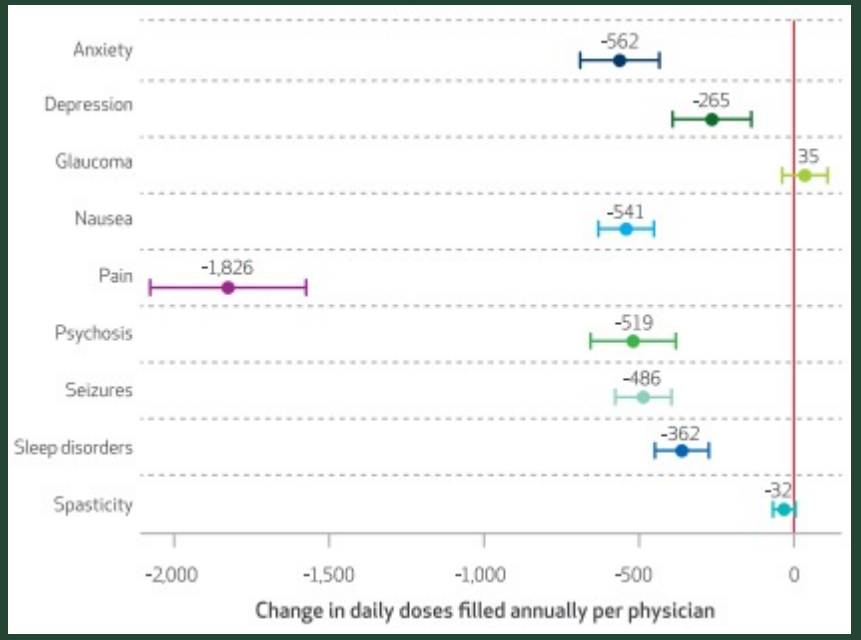
Cannabis May Reduce Opioid Use
States With and Without Medicinal Cannabis

Lower Opioid Overdose Mortality Rates

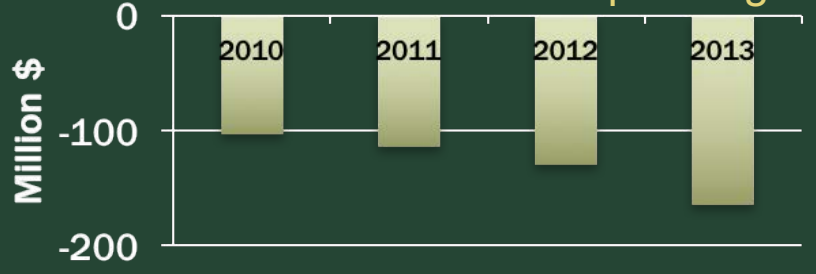


Bachhuber et al., 2014; JAMA Internal Med

Reduced Daily Doses Annually per Physician

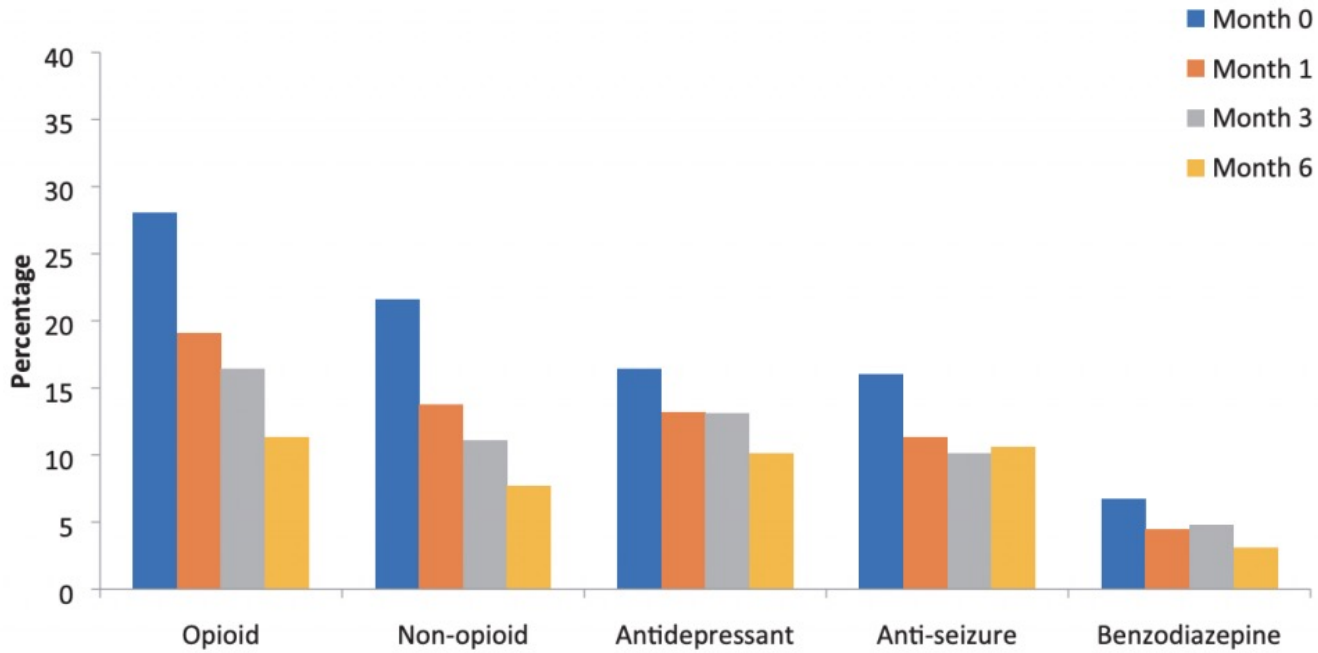


Reduced Annual Medicare Spending



Bradford & Bradford, 2016

Decrease in other prescription drug use over the course of 6 months when cannabis integrated into treatment



% using	Baseline	M1	M3	M6
Opioid	28.1	19.1	16.4	11.3
Non-opioid	21.6	13.8	11.1	7.7
Antidepressant	16.4	13.2	13.1	10.1
Anti-seizure	16	11.3	10.1	10.6
Benzodiazepine	6.7	4.5	4.8	3.1

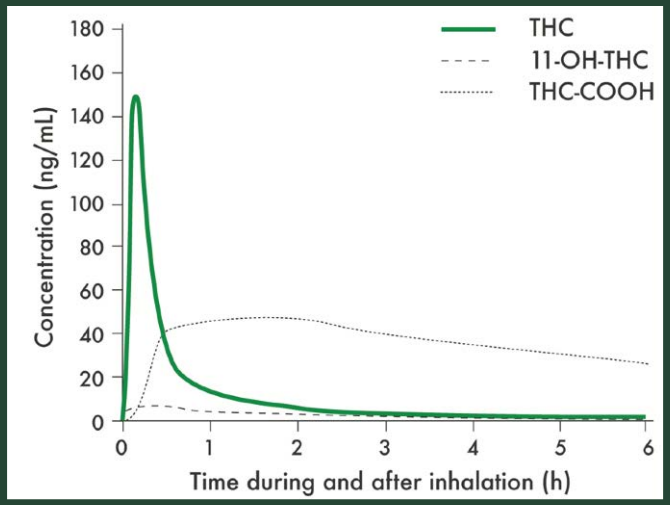
Lucas et al., 2020 Pain Medicine

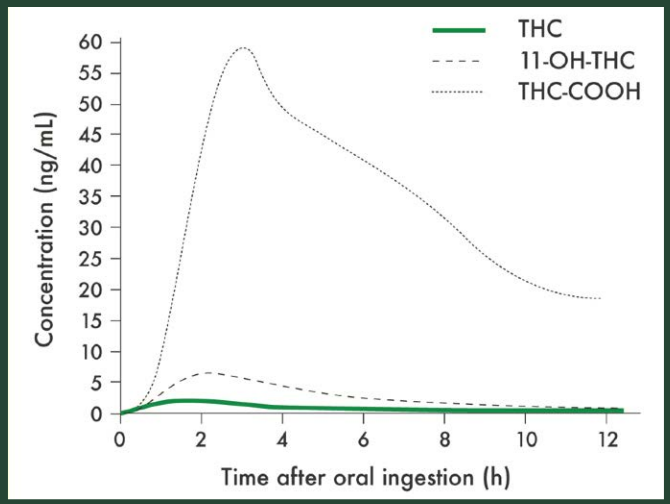
Although it may be effective, smoked marijuana as medicine presents challenges

- 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

Mode of Administration Matters: Need to compare efficacy, duration of beneficial and untoward effects

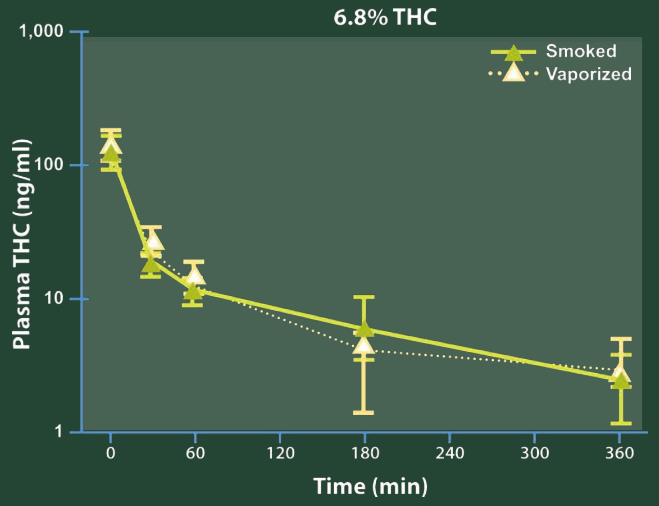
Inhaled vs. Edible

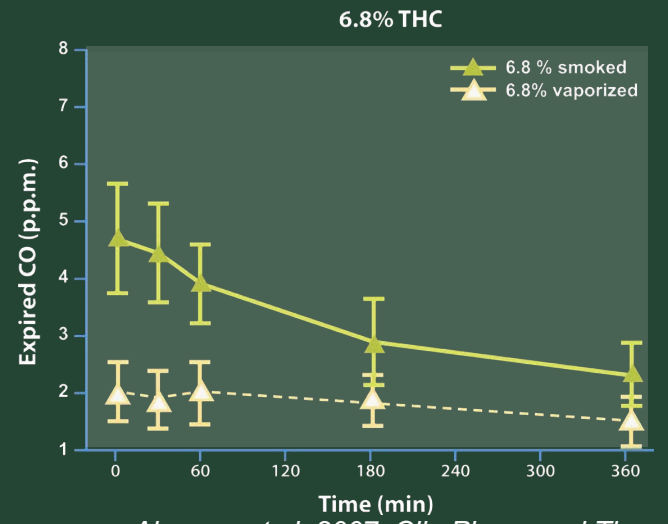




Grotenhermen, et al. 2003. Clin Pharmacokinet 2003; 42 (4): 327-360.

Smoked vs. Vaporized





Abrams, et al. 2007. Clin Pharmacol Ther.

Devices for Marijuana Vaporization

E-cigarettes

Volcano®

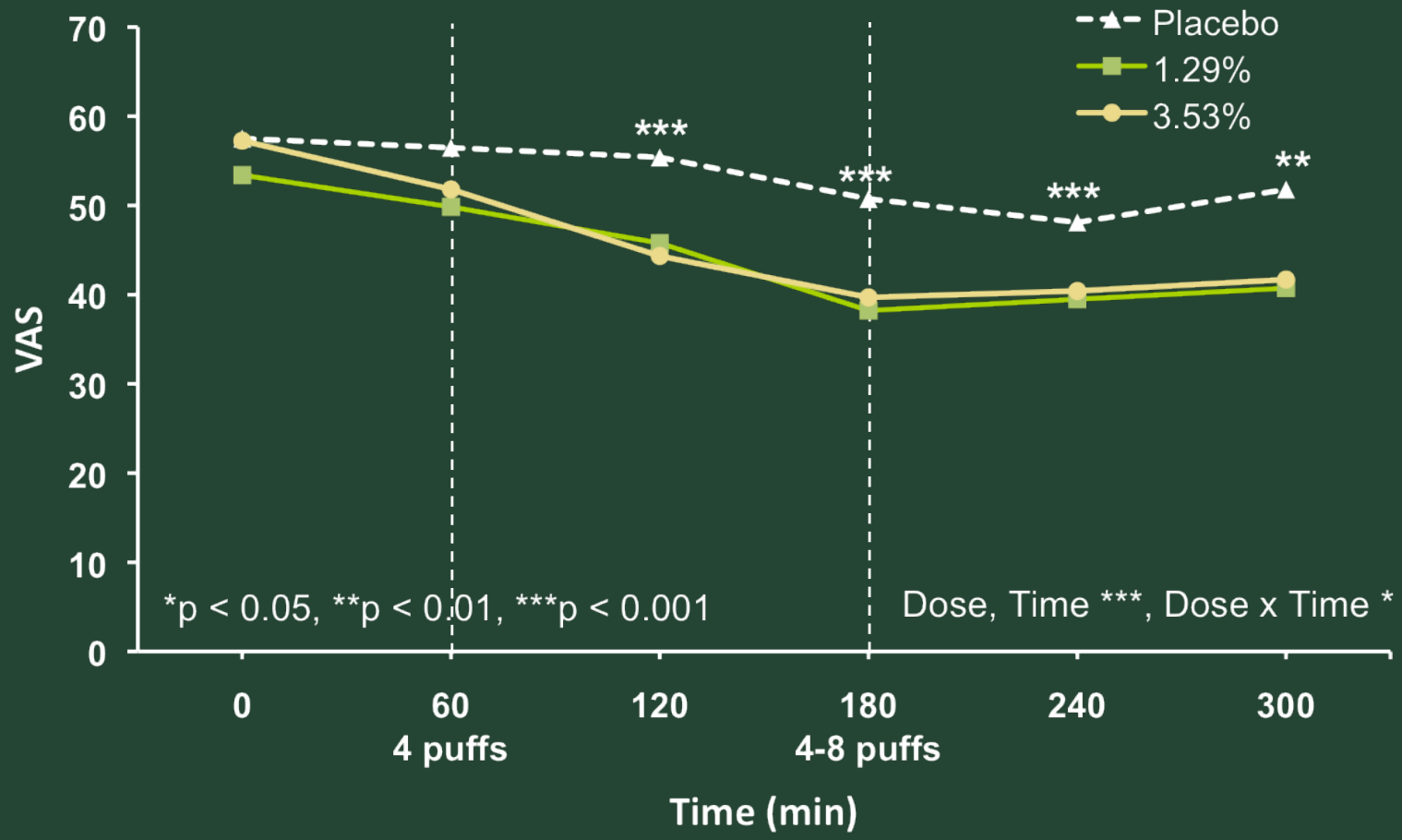
Courtesy David Gorelick, MD

Alternative Delivery Systems: "Volcano"

- Cannabis heated to 180° C
- Below the point of combustion (230° C)
- Releases cannabinoids as vapor into balloon
- Inhaled via mouthpiece attached to balloon

STORZ & BICKEL GMBH & CO. KG

CMCR Wilsey vaporizer study: Low dose THC containing cannabis reduces neuropathic pain



Placebo controlled randomized crossover study of 39 patients with neuropathic pain of mixed etiology treated 2x/d. THC conc. = 0%; 1.3%; 3.5%

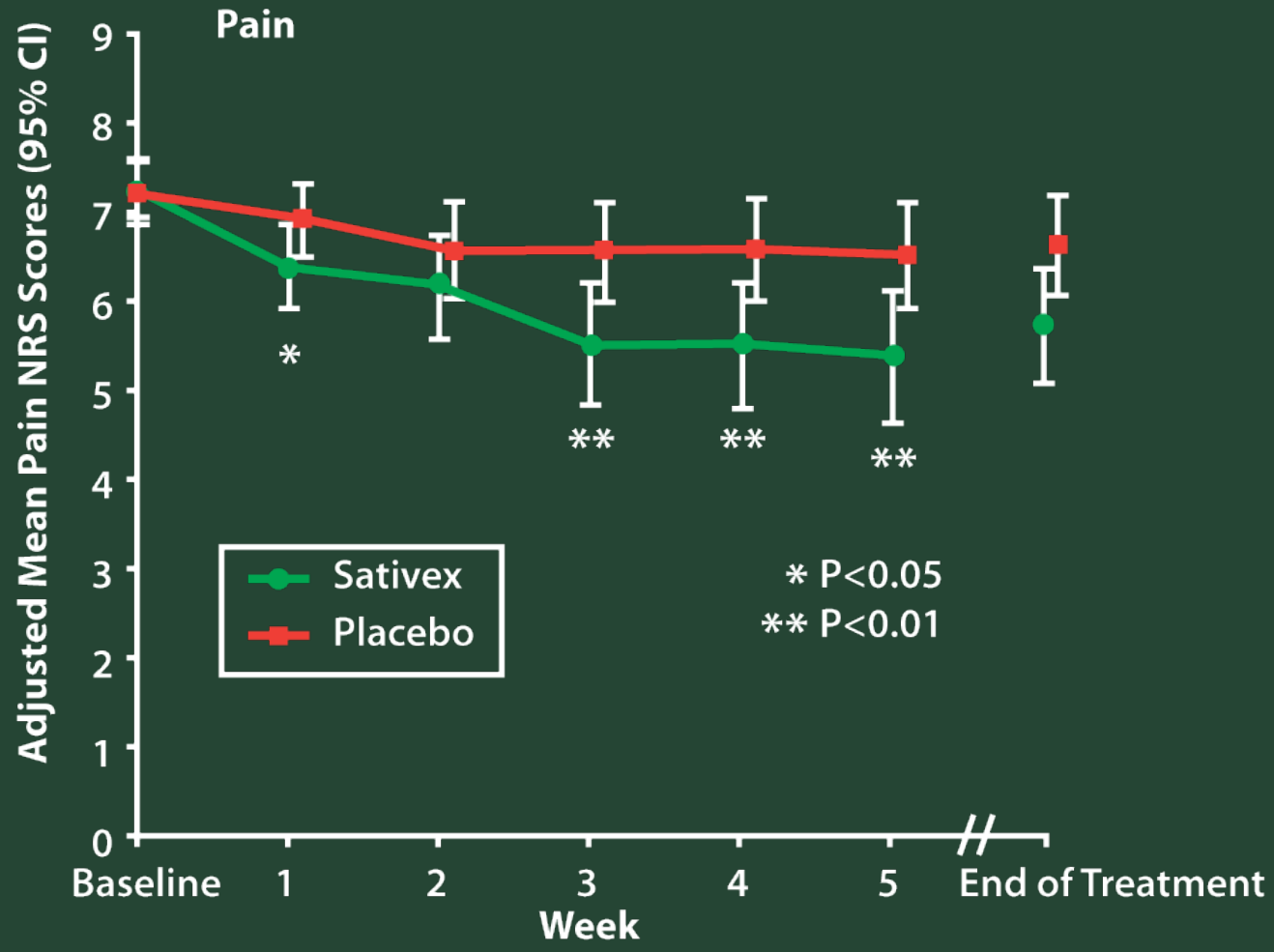
Source: Wilsey, et al. Journal of Pain, 2013.

Nabiximols (Sativex®) oral mucosal spray

- Pump action oral mucosal spray
- Delivers 0.1 ml per spray of solution containing 25 mg/ml THC and 25 mg/ml CBD
- Derived from botanical sources, thus contains other cannabinoids and non cannabinoids (eg., flavonoids; terpenes)

Image courtesy G. Guy, GW Pharmaceuticals

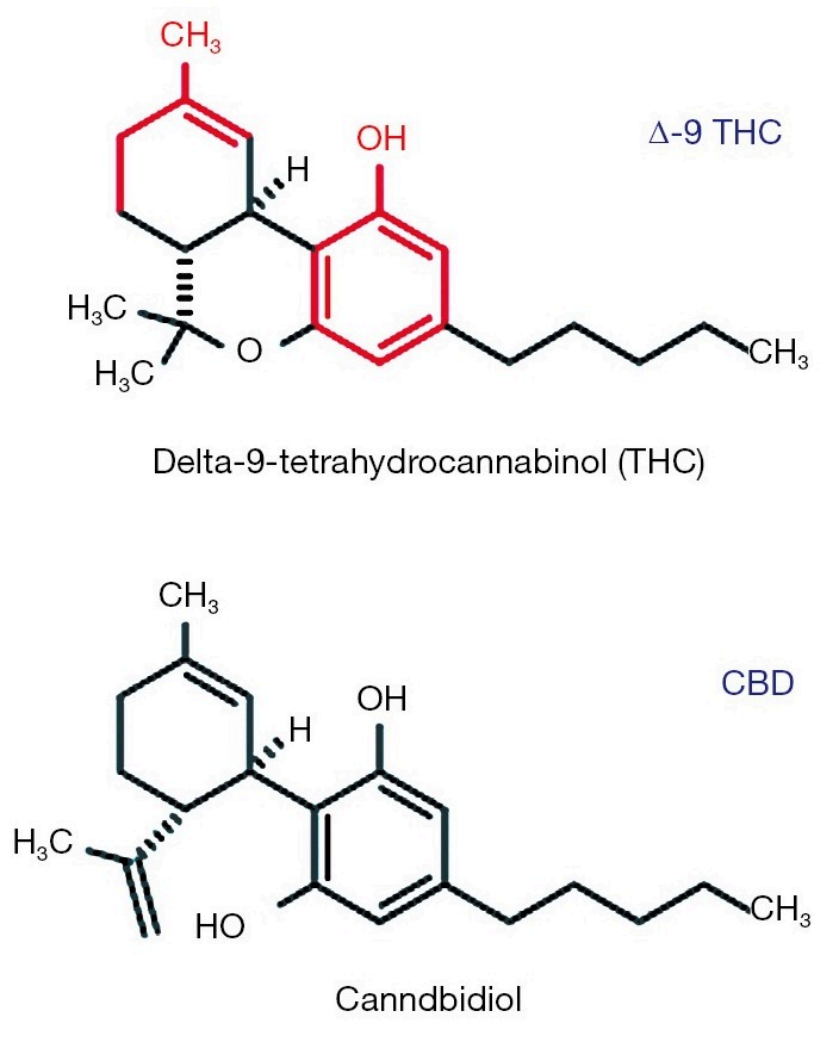
Nabiximols (Sativex®) for Neuropathic Pain



Reduction of global neuropathic pain NRS scores in the two groups during the trial. Weekly mean pain scores were obtained from pain diaries.

Source: Nurmikko, et al. (2007). Pain. 133; 210-220

Other Cannabinoids: Cannabidiol



Terpene phenolic heterocyclic structures of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

*Not active at CB1 or CB2

No psychoactive effect

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

Other Cannabinoids: Minor cannabinoids and suggested therapeutic potentials

Cannabinoid	Examples of potential medical application
CBG-A (Cannabigerolic acid)	Metabolic disorders, colon cancer
THC-A (Tetrahydrocannabinolic acid)	Arthritis, neurodegenerative diseases, nausea, appetite loss
CBD-A (Cannabidiolic acid)	Chemotherapy-induced nausea/vomiting (CINV), depression
CBC-A (Cannabichromene acid)	Fungal diseases
CBG (Cannabigerol)	Crohn's disease, bowel disease, certain cancers
CBD-V (Cannabidivarin)	Seizure prevention, Rett syndrome, Duchenne muscular dystrophy (DMD)
CBC-V (Cannabichromevarin)	Osteoporosis, ALS, Muscular dystrophy
CBC (Cannabichromene)	Could inhibit growth of cancer cells, osteoarthritis, neurological diseases
THC-V (Tetrahydrocannabivarin) *	Diabetes, anxiety, PTSD, Alzheimer's disease
CBN (Cannabinol) *	Bacterial infections, ALS, appetite stimulant

* These are psychoactive. The other minor cannabinoids are not psychoactive.

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
  - » Drug abuse treatment
  - » Antipsychotic
  - » Anticonvulsive
  - » Neuro-protective
  - » Anxiolytic
  - » Others
- Antagonism of THC when both contents are administered concomitantly? FAAH inhibition?

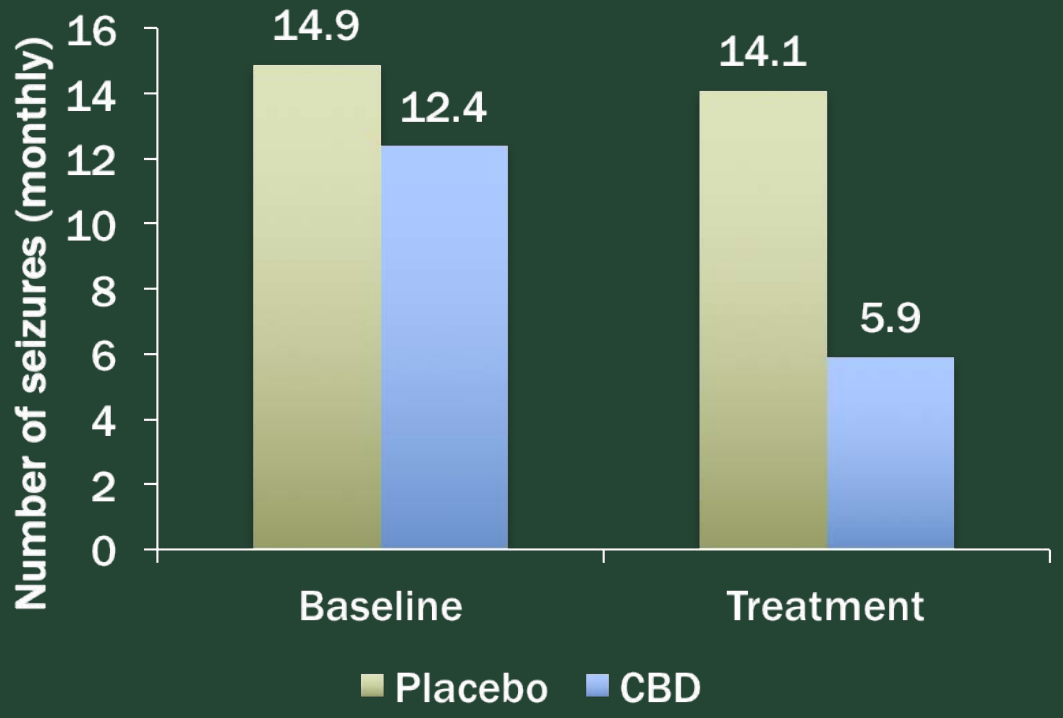
Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

Possible mechanisms of action of CBD

- Does not activate CB1 or CB2
- Desensitizes transient receptor potential channels , eg., TRPV1 : anti-nociceptive to inflammatory pain?
- Blocks GPR55, which may also play a role in neuropathic and inflammatory pain
- Enhances glycine receptor activity: anticonvulsant?
- Inhibits FAAH: increasing availability of anandamide?
- Enhances 5HT1A receptor: anxiolytic effect?
- Modulates cytochrome P4502C metabolism of THC to more psychoactive 11-OH THC?

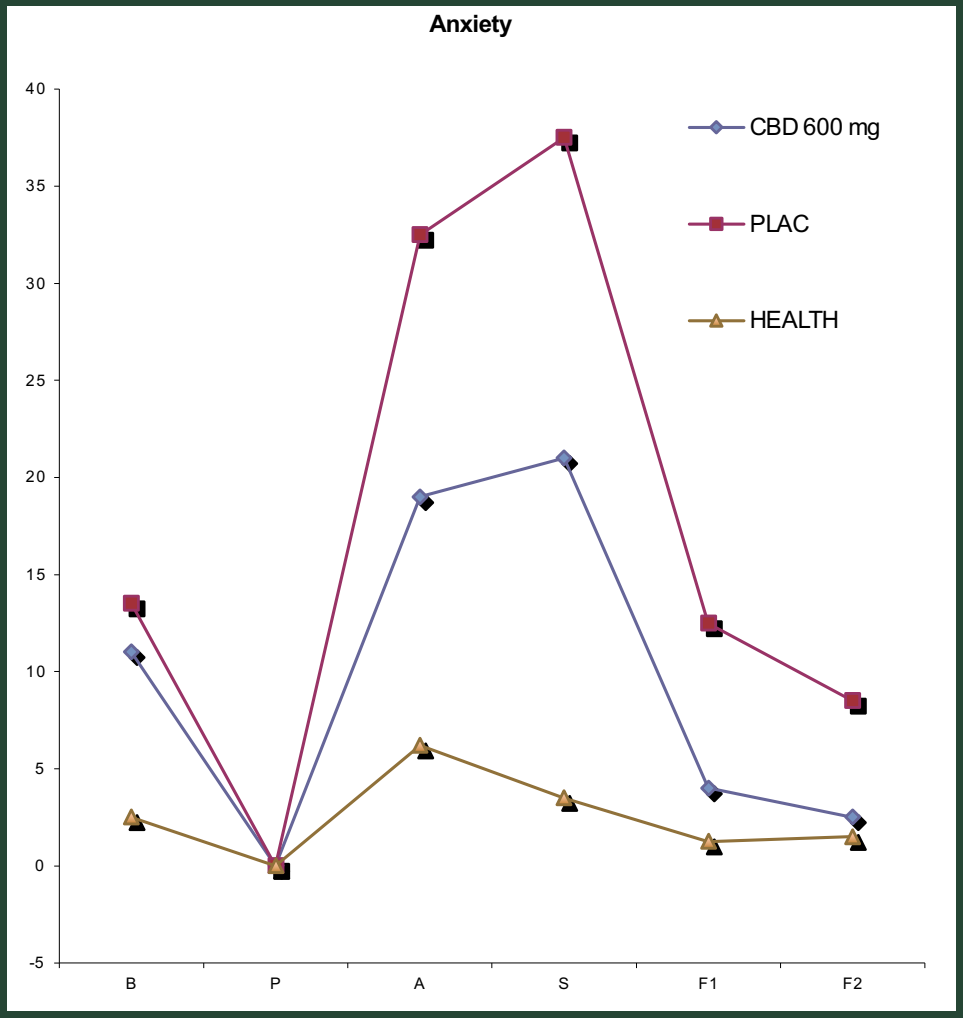
Cannabidiol (CBD) Significantly Reduces Convulsive Seizure Frequency in Lennox-Gastaut Syndrome (LGS)

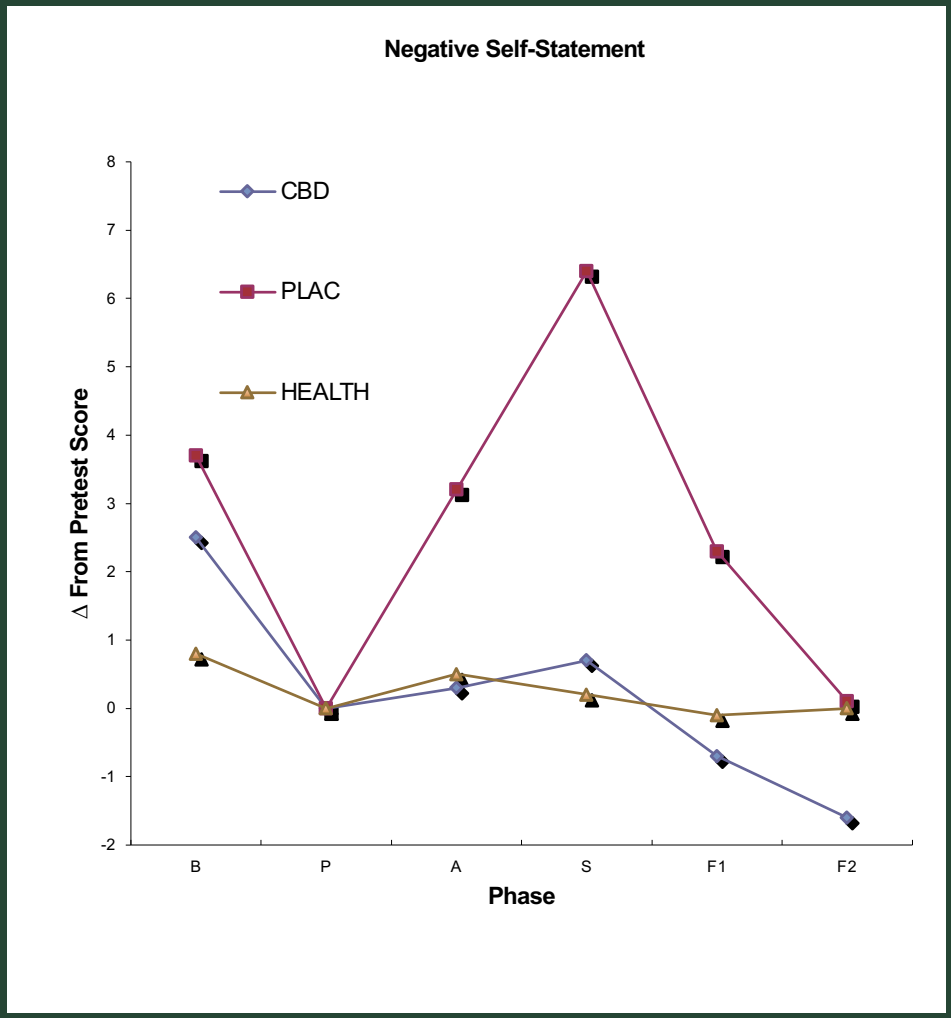
- 120 children/young adults
- 20 mg/kg CBD
- 14-week treatment period
- % with > 50% reduction in frequency (CBD – 43%; Placebo - 27%
- AEs (diarrhea, vomiting, fatigue, etc.



Devinsky et al., 2017 (NEJM)

Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

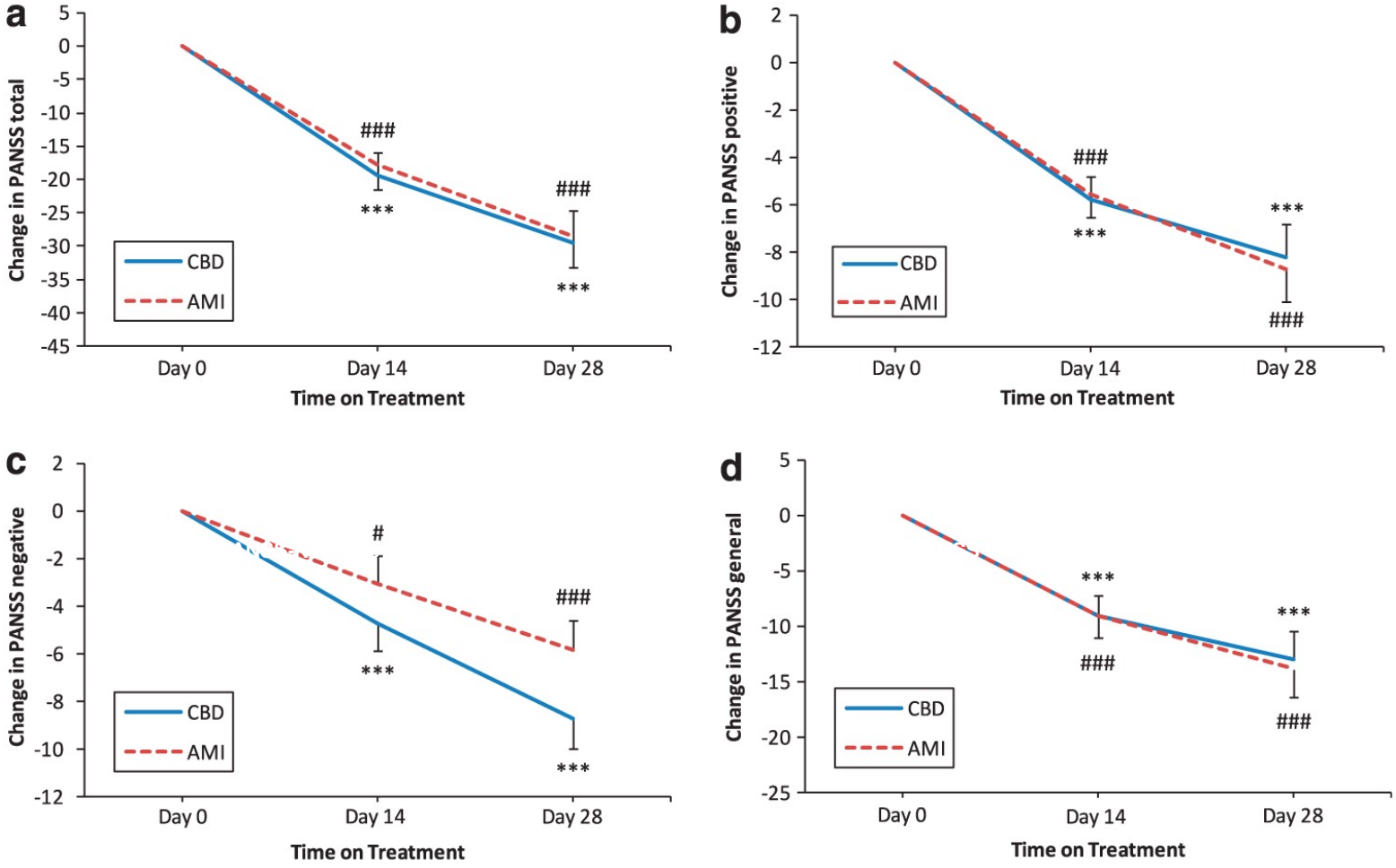




Bergamaschi, et al. *Neuropsychopharmacology*. 2001;36(6)1219-1226.
Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil.

CBD Improves Positive and Negative Symptoms of Schizophrenia

42 cases randomized to receive 800 mg/d CBD or amisulpride



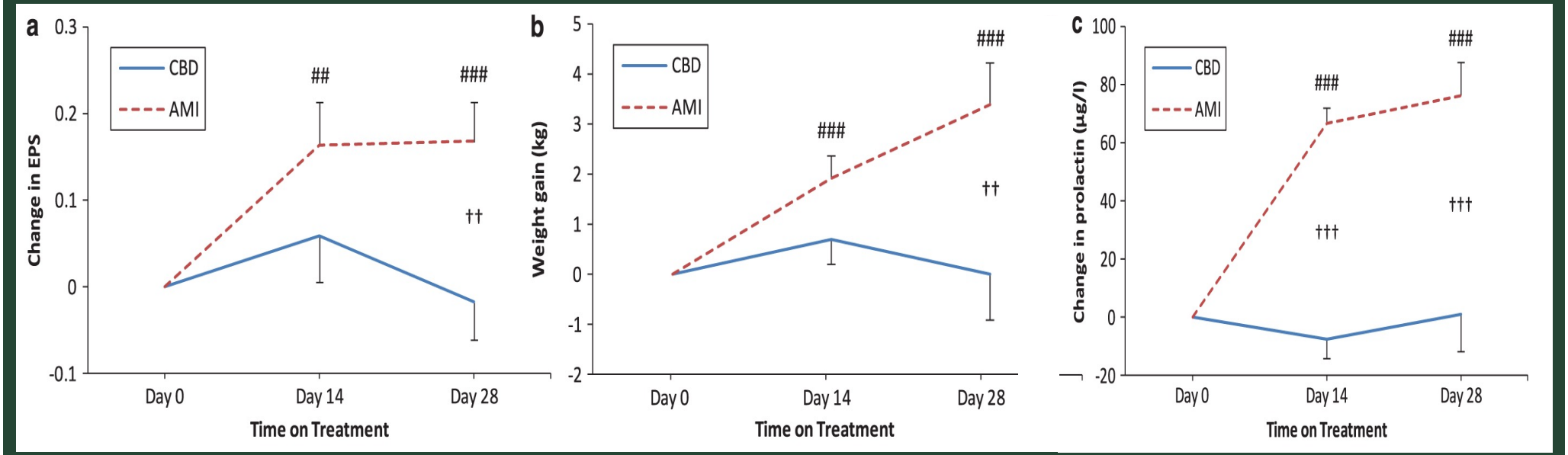
PANSS = Positive and Negative Syndrome Scale.

Data show predicted means and side effects. Statistical significance is calculated between groups and versus baseline, that is,0 (*CBD, #AMI; #$P \leqslant 0.001$; ***/###$P \leqslant 0.05$).

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

Compared to Atypical Antipsychotic Amisulpride, CBD Does Not Worsen Extrapyramidal Symptoms, and Is Not Associated with Weight Gain or Elevated Prolactin

Extrapyramidal Symptom Scale (EPS) | **Weight Gain** | **Prolactin**



Data show predicted means and side effects. Statistical significance is calculated between groups ($^{††}P \leqslant 0.01$, $^{†††}P \leqslant 0.001$ and versus baseline, that is, 0 (*CBD, $^{\#}$AMI; $^{\#\#}P \leqslant 0.01$; $^{\#\#\#}P \leqslant 0.05$; */$^{\#}$P $\leqslant 0.001$).

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

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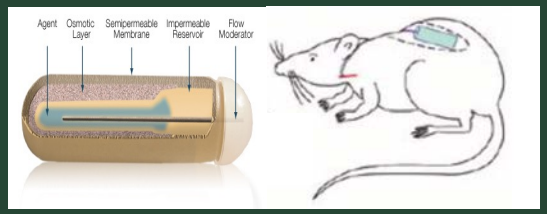
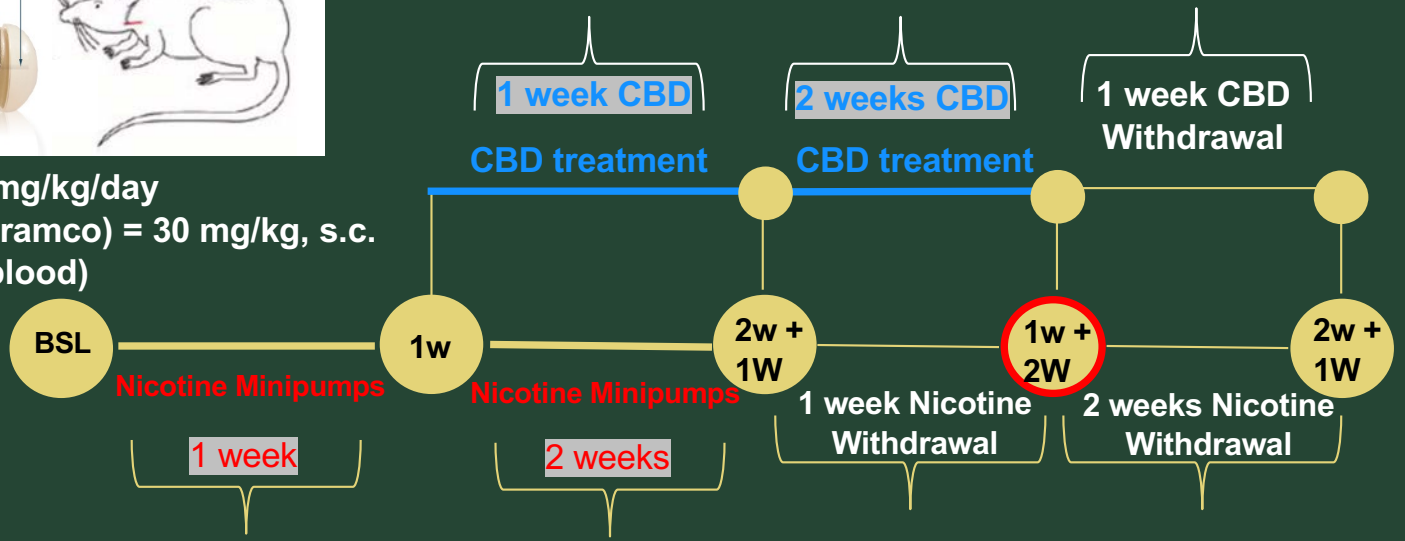
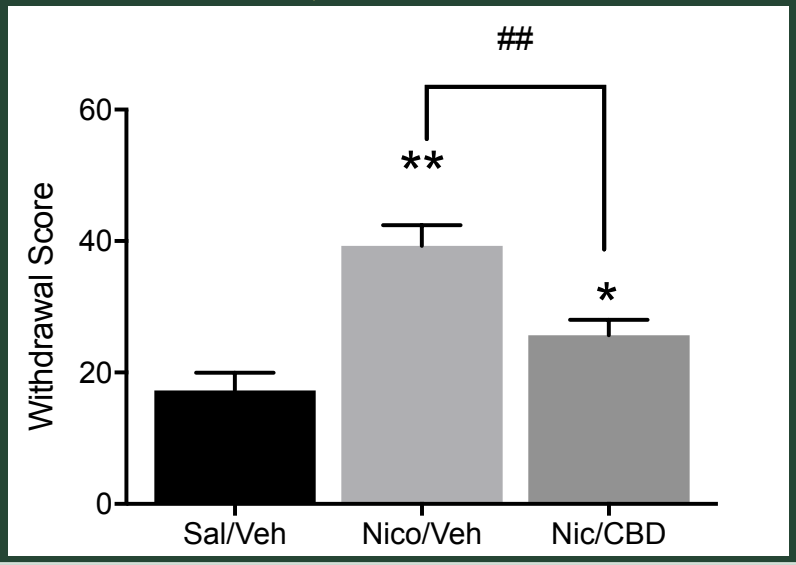
CBD attenuates nicotine withdrawal



Nicotine = 3.14 mg/kg/day
Cannabidiol (Noramco) = 30 mg/kg, s.c.
180-300 ng/ml (blood)





Data courtesy of
Giordano de Guglielmo, PharmD, PhD
and Olivier George, PhD, UCSD

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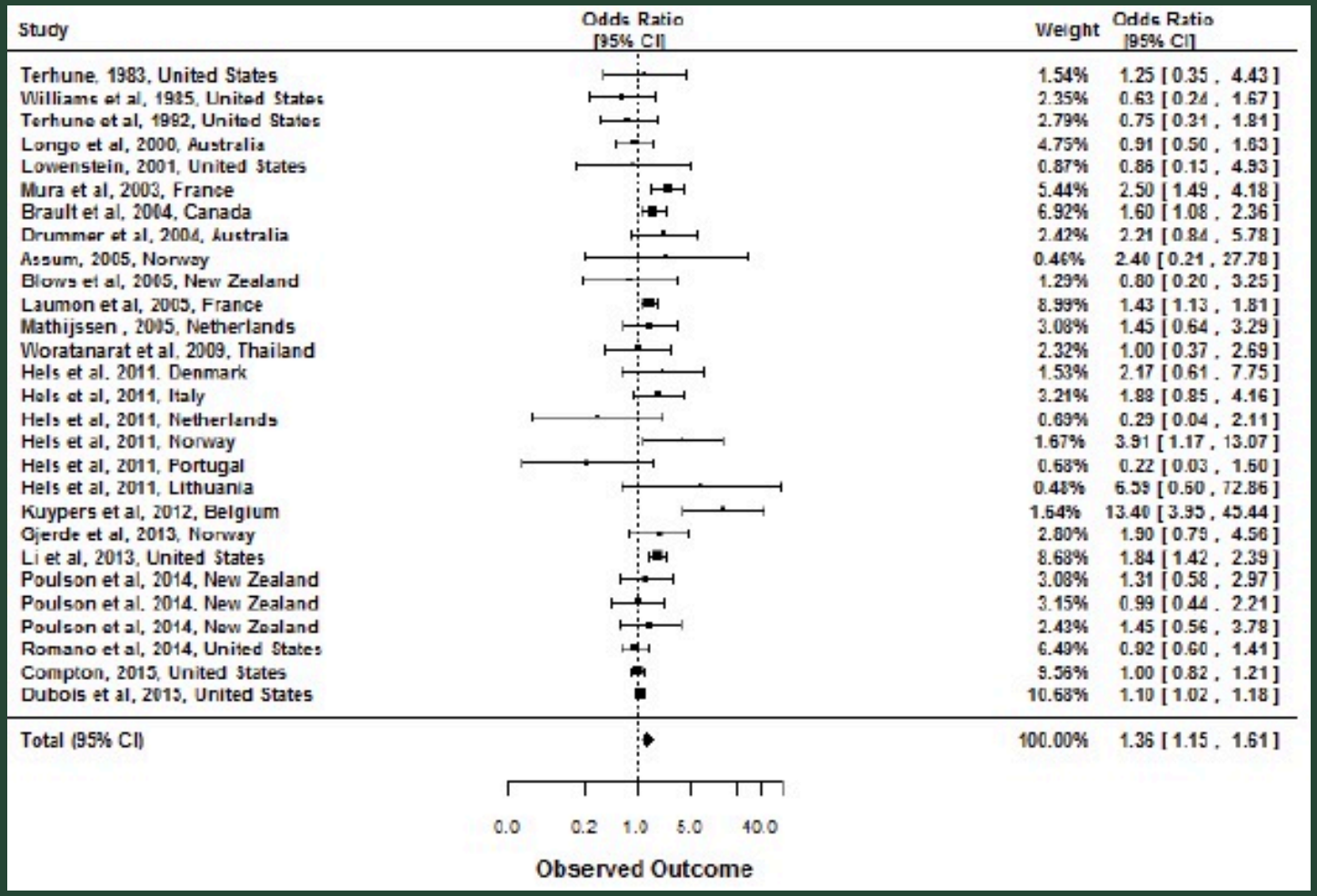
What are the downsides of medicinal cannabis?

- Acute effects: alertness; cognitive; mood; cardiovascular
  - Effects on driving, work, studying?
  - Some of these effects wear off (habituation) with regular use
- Longer term use: long term effects of cannabinoids as medicines unknown. Data from recreational use:
  - Moderate use in adults not associated with organ system injury* based on 2017 National Academies review. However:
  - Effects on youth, eg., developing brain, unclear. Many negative effects reported, eg., IQ loss, psychosis risk, but “chicken vs egg” conundrum
  - Effects in other groups? eg., elderly, underlying conditions
- Interactions with other medicines/drugs: clear amplification of neurocognitive effects; other pharmacologic interactions unclear.

Meta-analyses of cannabis intoxication and automobile crashes (Rogeberg et al., 2016)



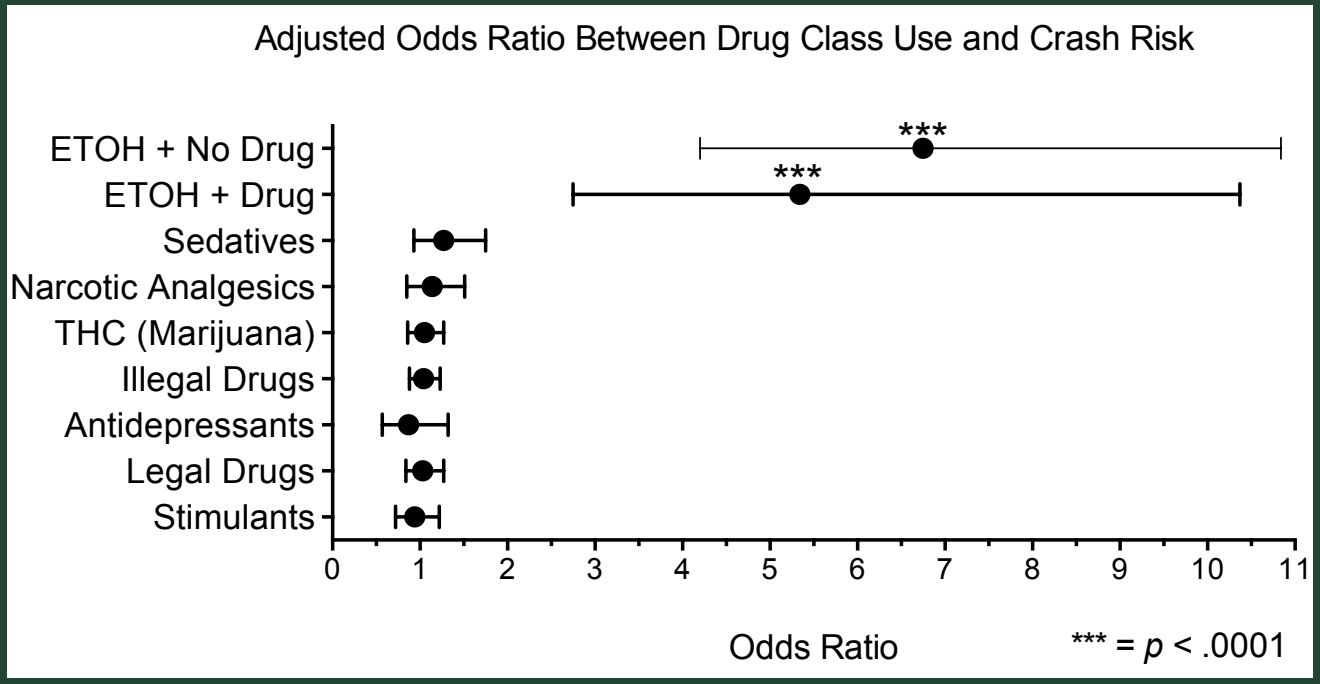
Random effects: OR 1.36 (1.15-1.61

Meta-regression: OR 1.22 (1.1-1.36)

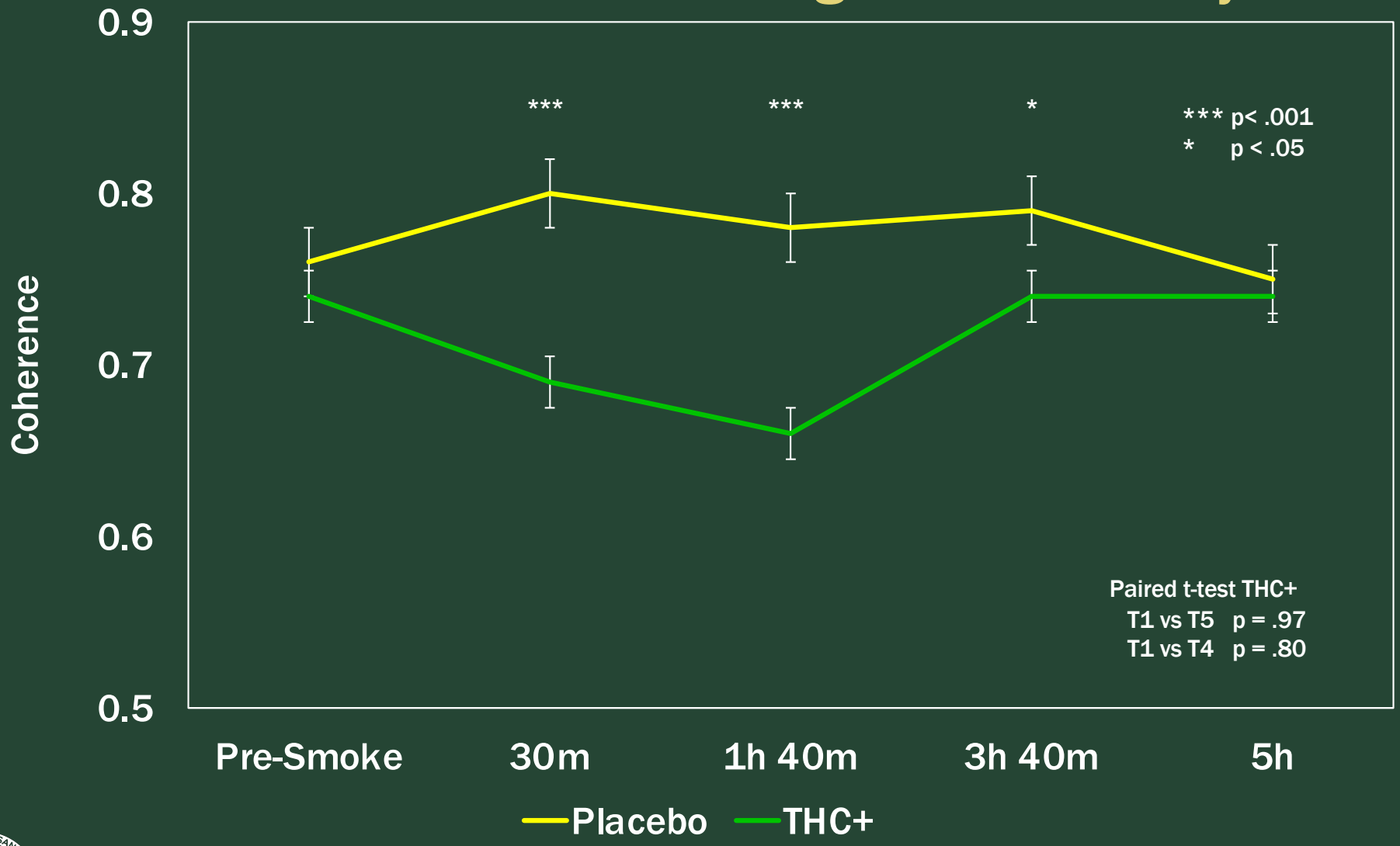
NHTSA Crash Risk Study (Compton and Berning, 2015)

- First large scale U.S. study to include drugs other than alcohol
- 3,000 crash-involved and 6,000 control drivers in Virginia Beach, VA
- 24h/7 days per week response to crashes over 20 month period
- Match crashes by visiting site one week later, same time of day
- THC+ in blood

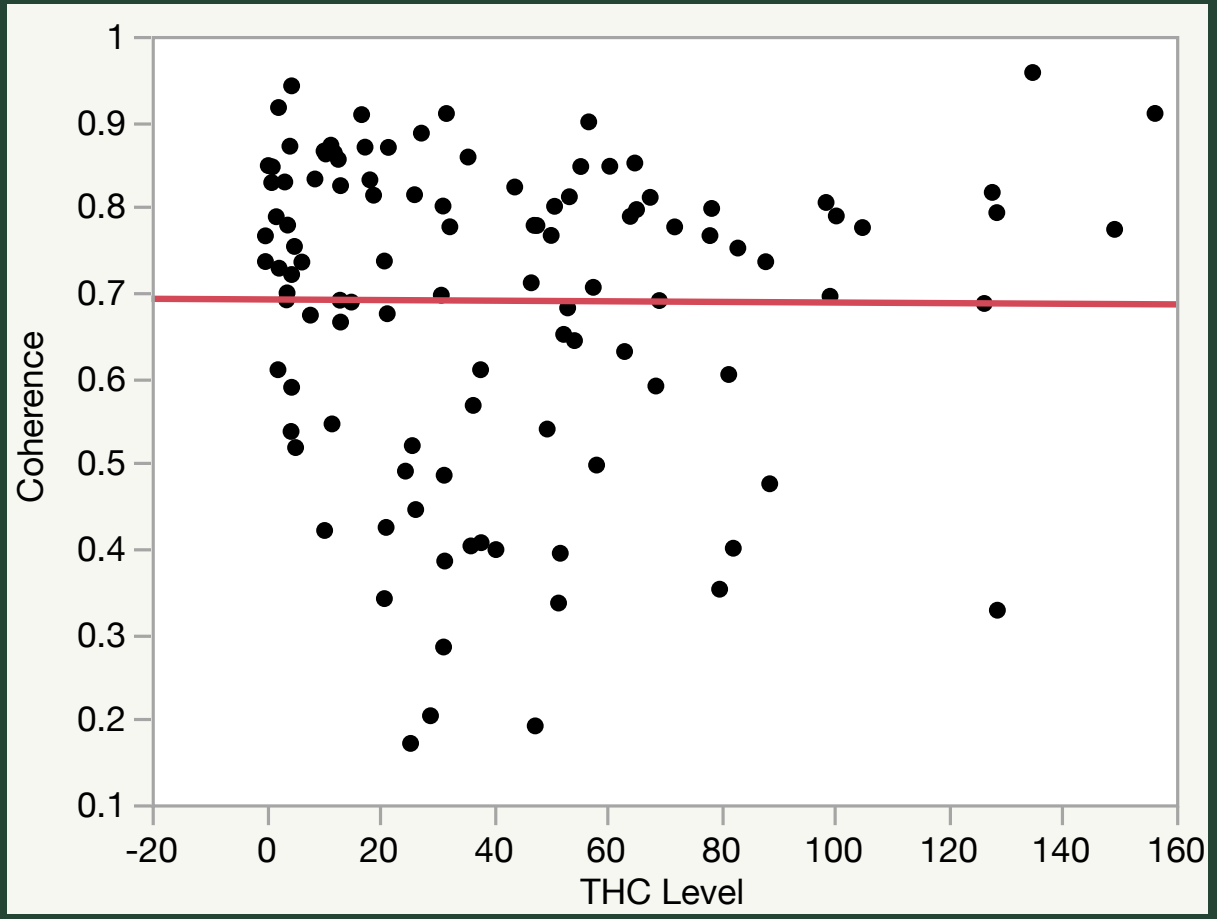
- Unadjusted OR = 1.25
- Adjusted OR = 1.05
- Low substance use prevalence: ~7% drivers were THC+; National Roadside Survey found 12.6% with THC



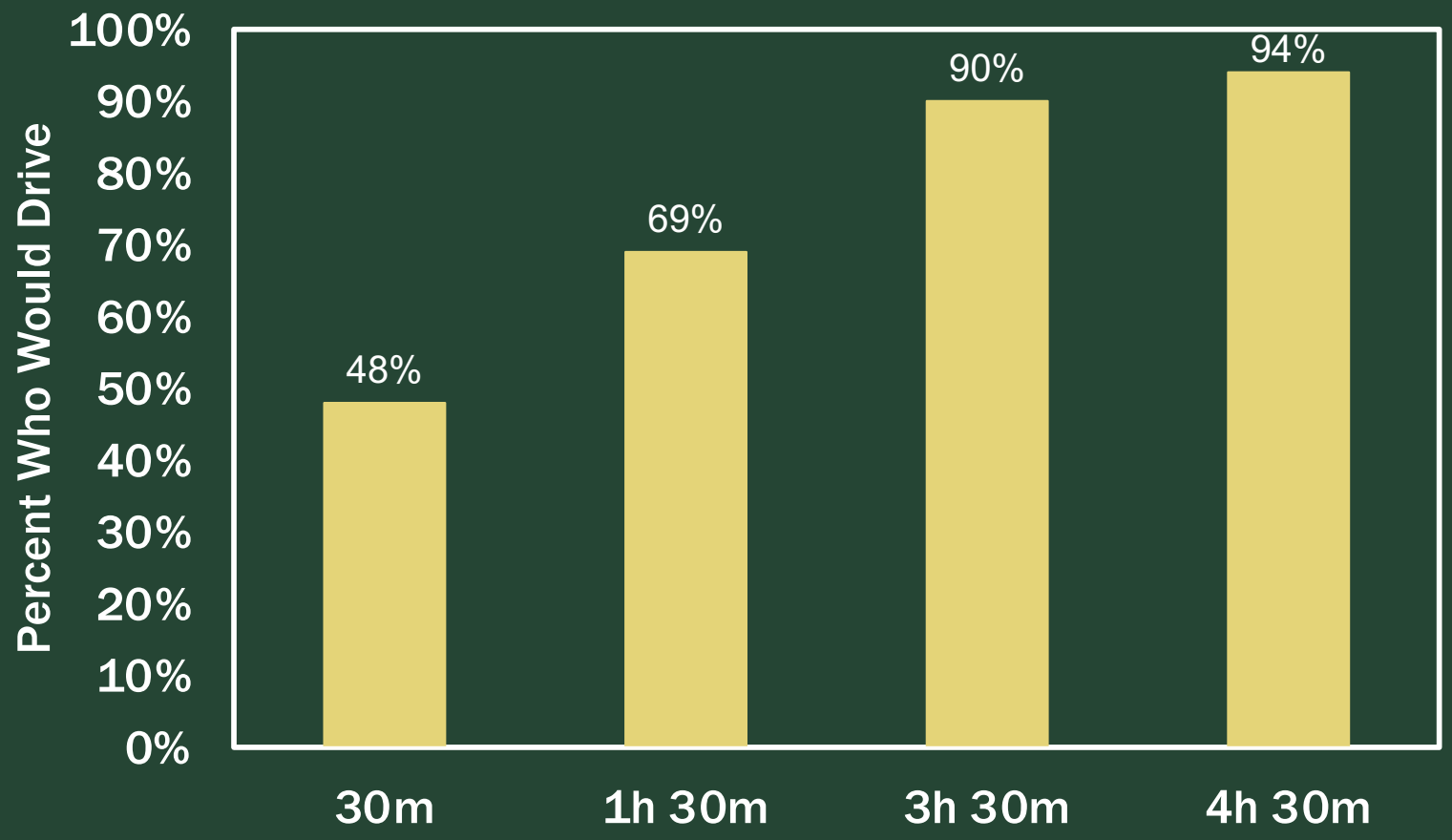
Car Following – Coherence Reduced by MJ*
(*ability to adjust to movement of car ahead of you)
30 minutes Post-Smoking in CMCR study



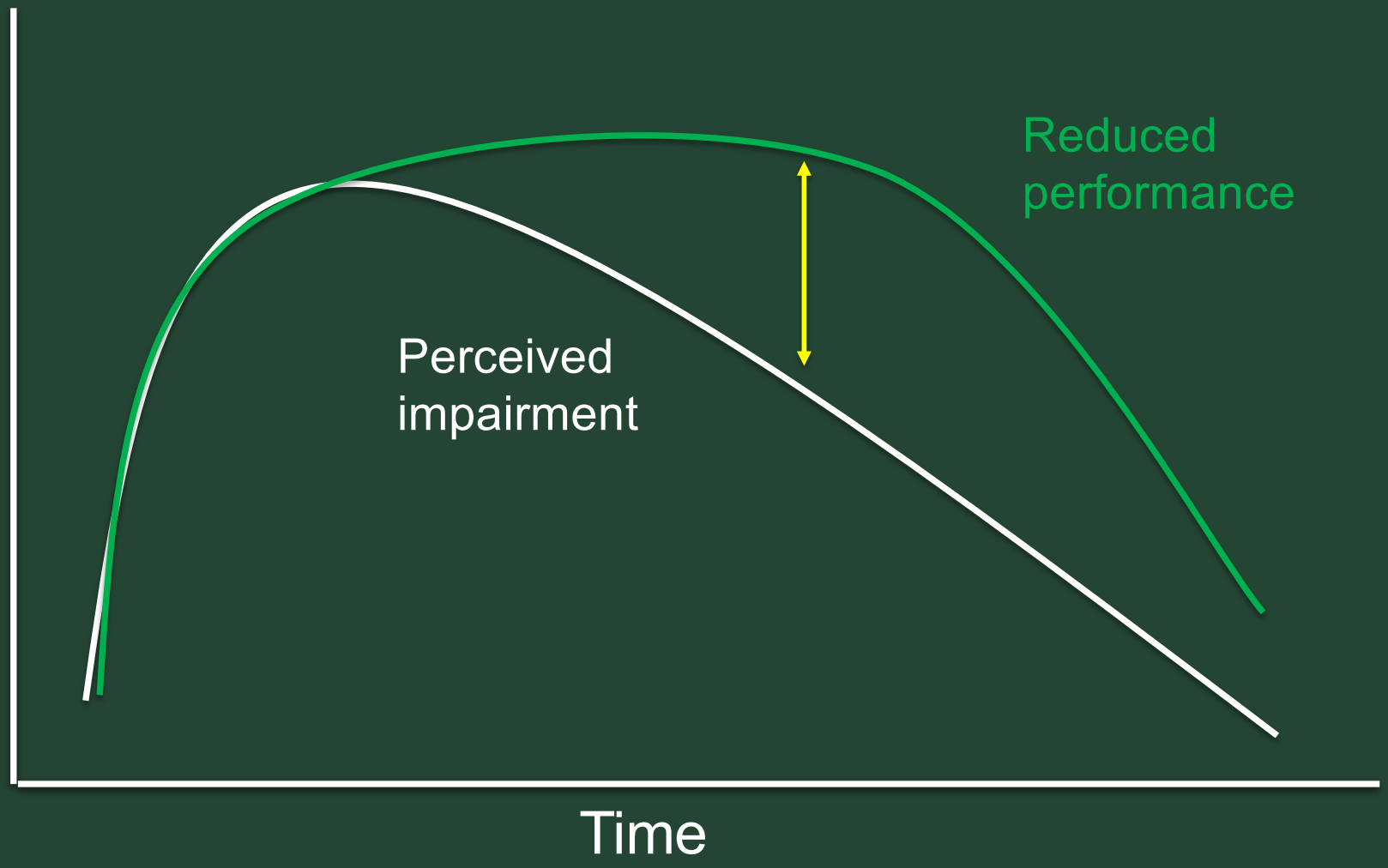
Relationship Between Car Following Coherence and Whole Blood THC Levels Immediately Post-Smoking THC containing cannabis



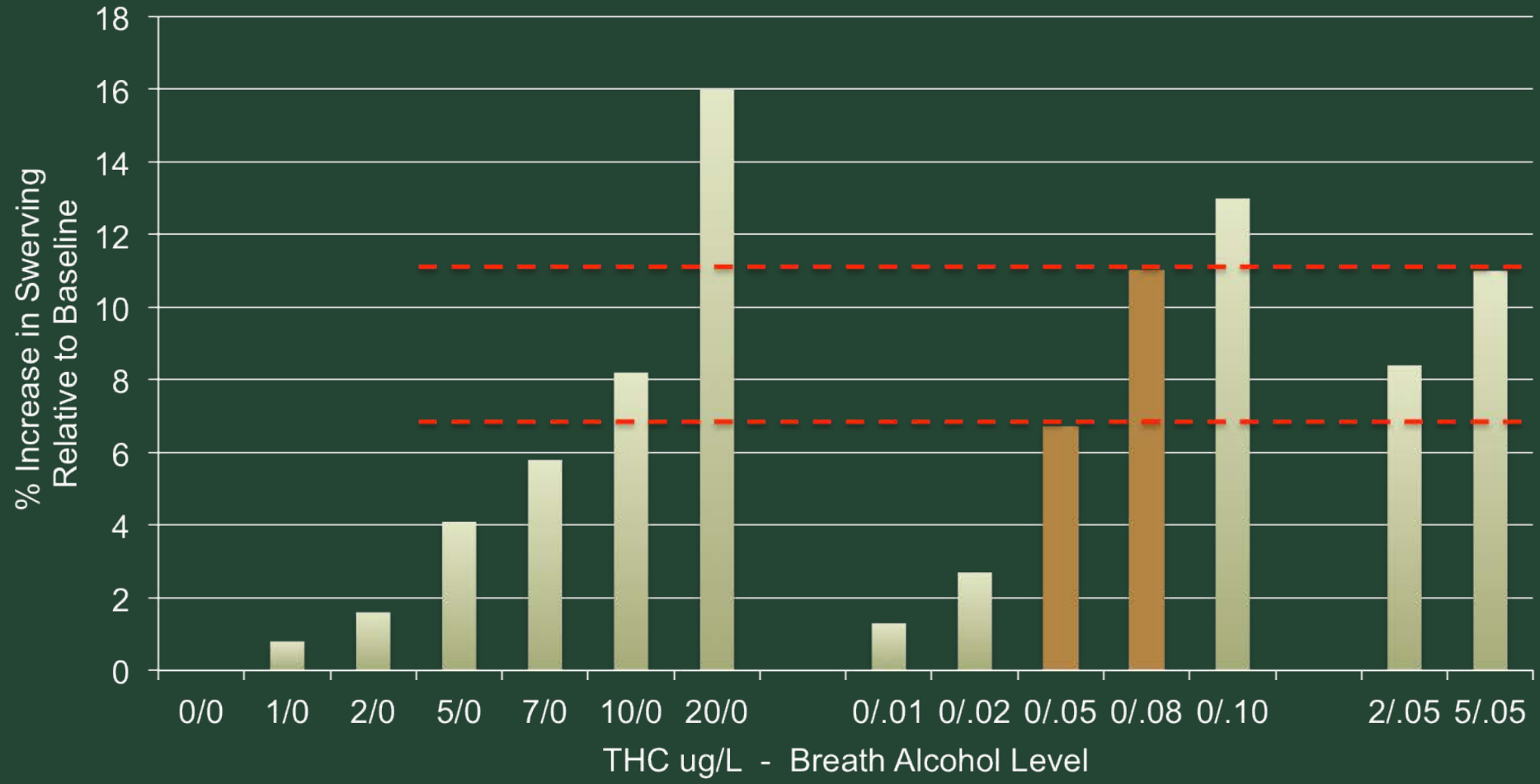
Proportion of those receiving THC containing cannabis saying they would drive in their current state



Self-perception vs. Performance



Cannabis blood levels/Breath alcohol level and simulator swerving



Hartman et al., Drug Alcohol Depend. 2015

Summary of current status of Medicinal Cannabis/Cannabinoid Modulators

- Smoked/vaporized cannabis, and extracts containing THC/CBD mix probably efficacious in neuropathic pain and spasticity from MS
- Cannabidiol showing initial promise in treatment of anxiety, psychosis, and intractable epilepsy (eg., FDA approved Epidiolex for seizures in Dravet; Lennox Gastaud; Tuberous Sclerosis)
- CBD may have anti-craving actions: addictions treatment?
- Cannabis with THC content may have opioid sparing effects
- Possible efficacy in sleep disorders treatment :THC, CBD or both?

Possible Roles of Cannabinoid Modulators

- Synthetic THC-like molecules efficacious in appetite stimulation and control of nausea. Potential safety & utility of other synthetic CB1 agonists not yet established
- CB1 antagonists, partial agonists may be useful in appetite suppression, but adverse psychiatric effects have been problematic, eg., rimonabant
- Fatty Acid Amide Hydrolase [FAAH] inhibitors promising in animal models of chronic pain [caution re neuro complications, eg., BIA 10-2474?]
- Anti-inflammatory actions of cannabinoids, including natural and synthetic, deserve further exploration

Once we clear the smoke: Examples of future research directions on medicinal cannabis

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

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Medical Cannabis

Thank you!

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