

Medicinal Cannabis

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Cannabis and its derivatives



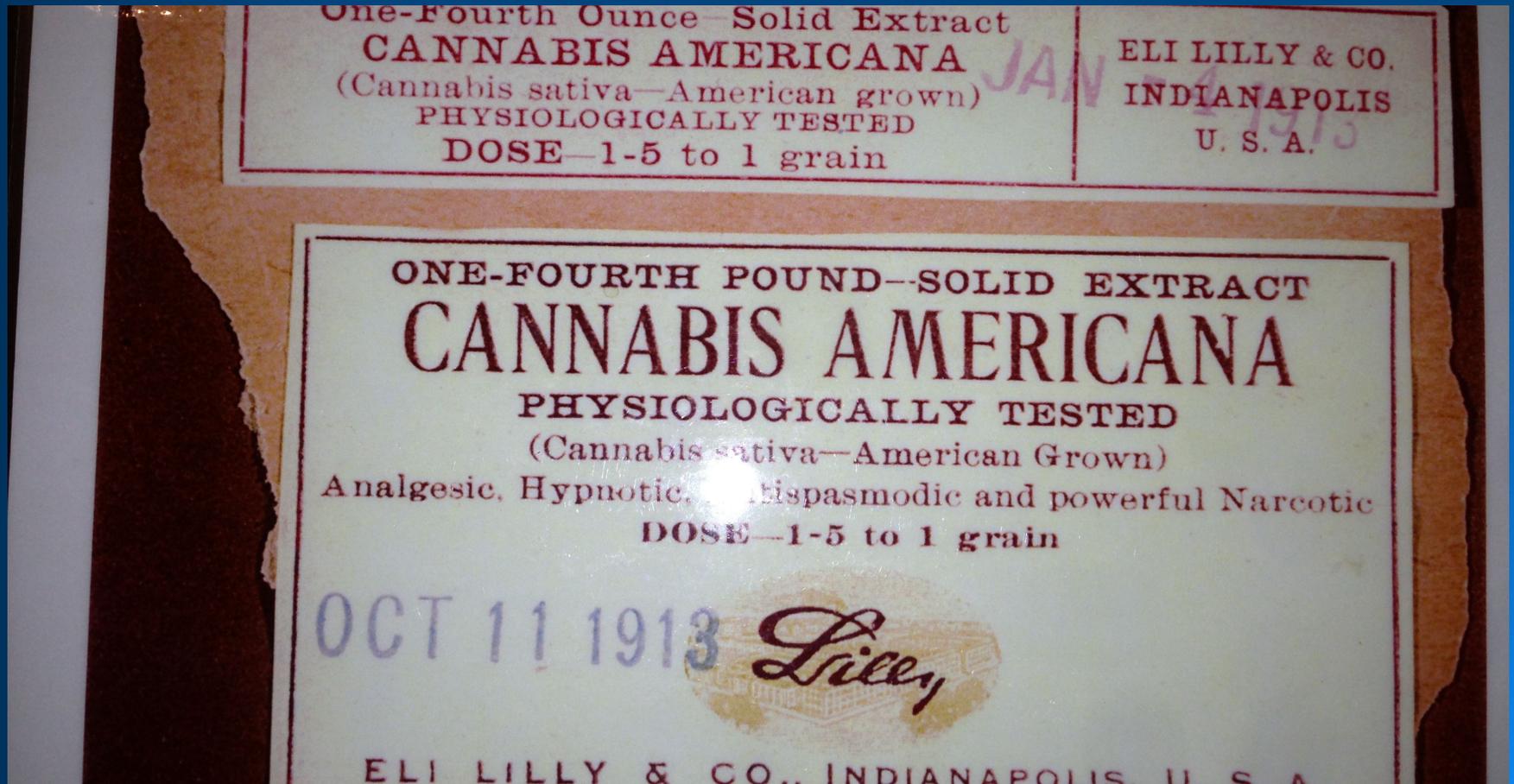
Marijuana



Hashish

Courtesy D. Piomelli, UCI

Cannabis: not a new medicine



Marijuana Compounds



+ 80 cannabinoids

CC1=C(C(=C(C=C1)O)C(=O)OC2=C(C=CC2)C)C

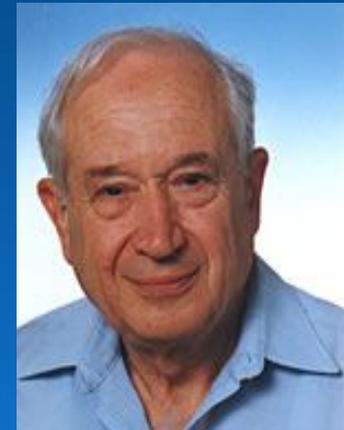
Δ⁹-THC

CC1=C(C(=C(C=C1)O)C(=O)OC2=CC(=CC=C2)C)C

CBD

Isolation, structure and partial synthesis of an active constituent of hashish.

Y. Gaoni, Raphael Mechoulam. J. Am. Chem. Soc. 86, 1964: 1646.

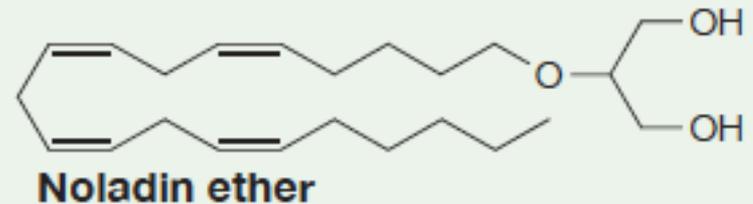
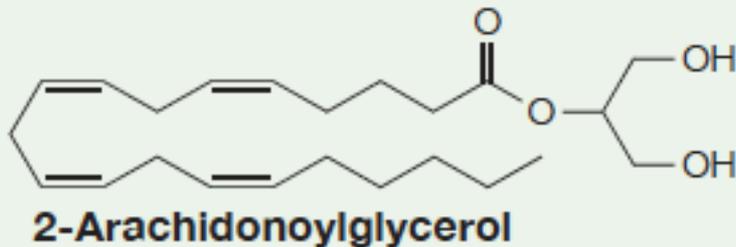
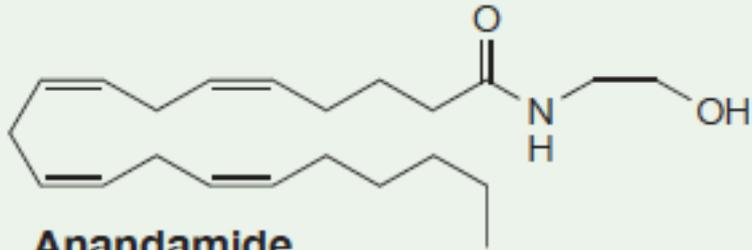


Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

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

- **Persistent anecdotal reports of benefits**
- **Political shifts favoring medicinal access (in USA 18 states now provide for some measure of 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)

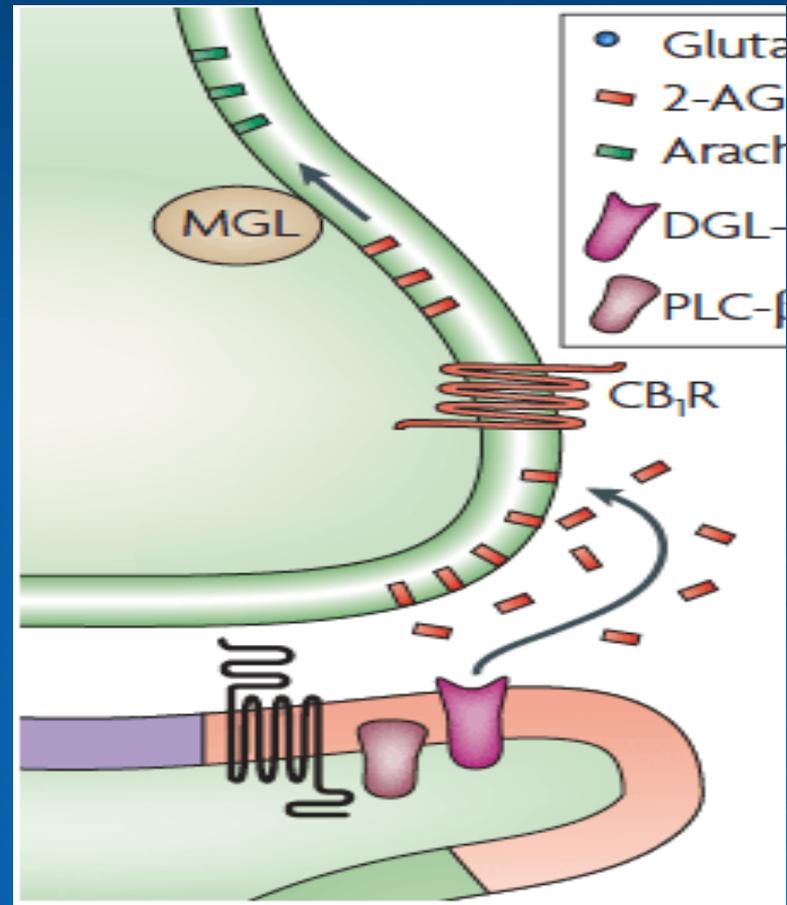
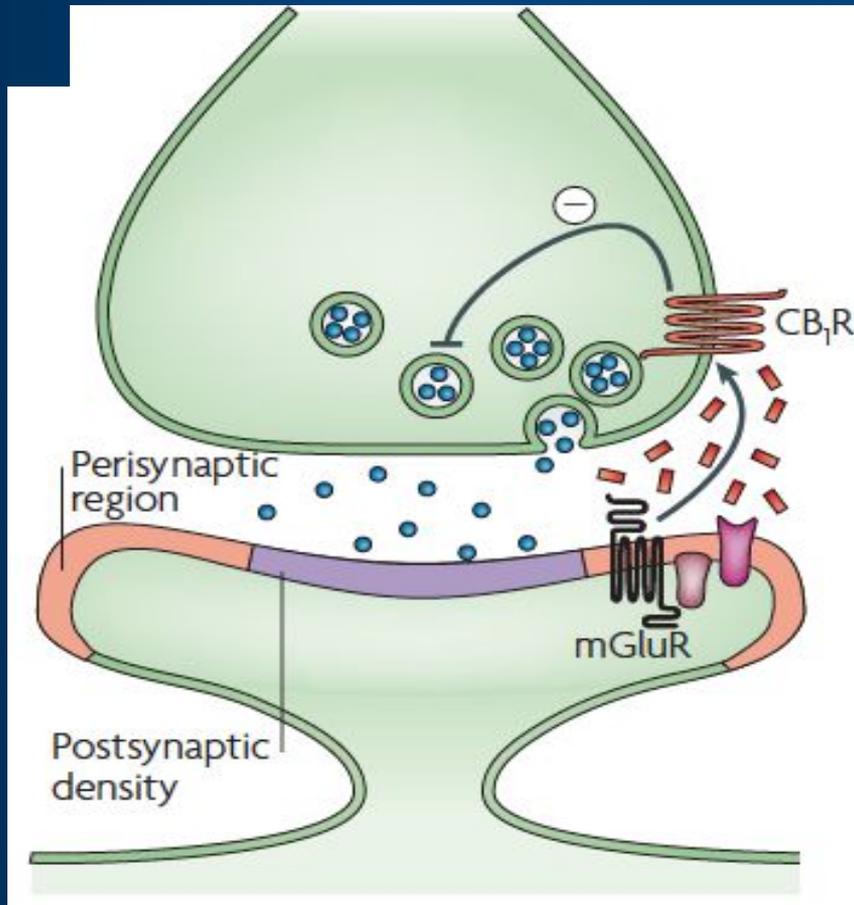
The endogenous cannabinoids



Piomelli, *Nature Rev. Neurosci.*, 2003

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*

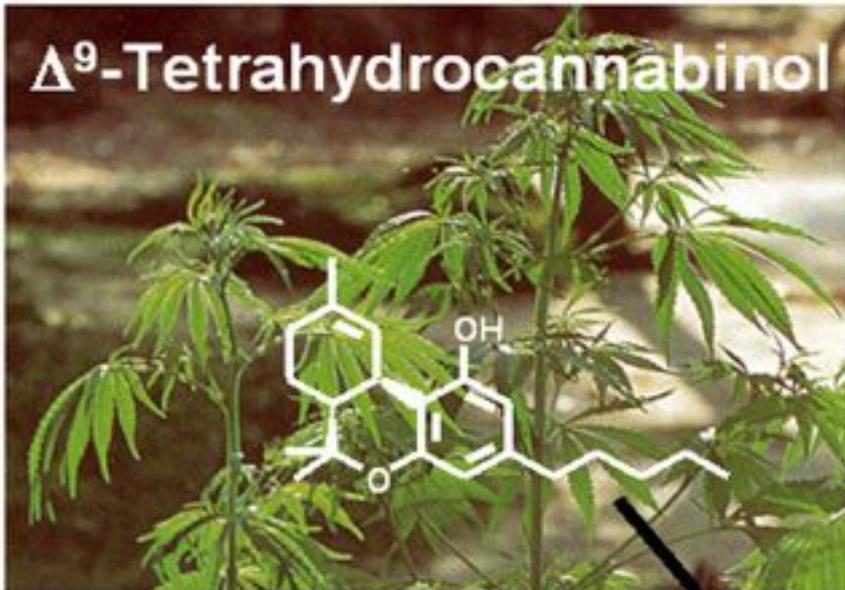


* FAAH = fatty acid amide hydrolase MGL = monoglyceride lipase (Courtesy D. Piomelli, UCI)

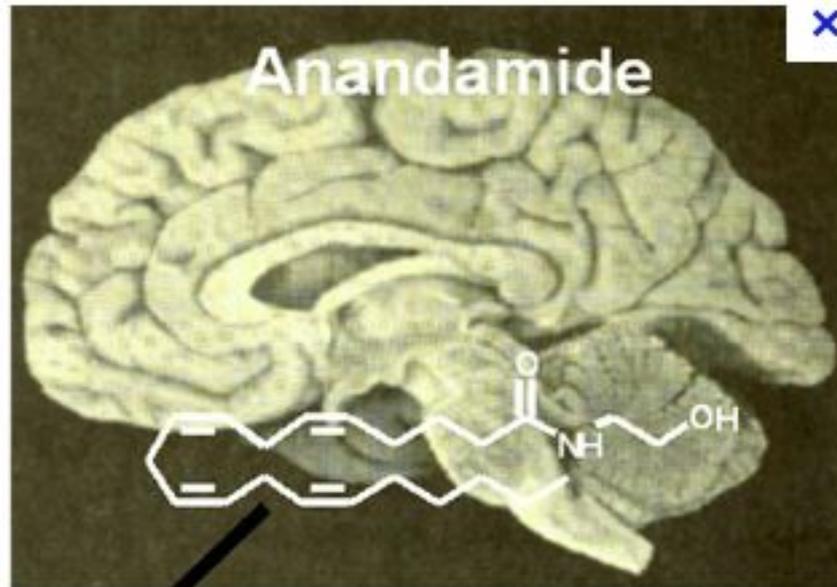
Distribution of Brain CB1 Receptors

- Hippocampus – Memory and Learning
- Amygdala – Novelty, Emotion, Appetitive Behavior
- Basal Ganglia & Motor Cerebellum – Real Time Coordination, Selective Attention and Time Sense
- Nucleus Accumbens - Reward Mechanisms
- Cortex & Frontal Lobe - Executive Function, Judgment, Synthesis, Evaluation

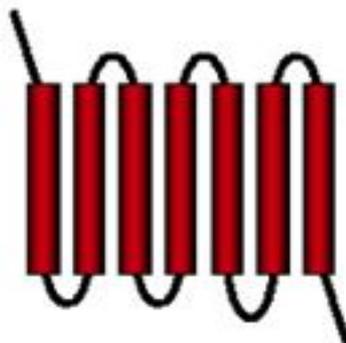
Δ^9 -Tetrahydrocannabinol



Anandamide



Cannabinoid Receptor



Potential Medicinal Uses of Cannabis: NIH & IOM Reviews in late 90s

The NIH Workshop on the Medical Utility of Marijuana (1997) and the Institute of Medicine (1999), following thorough review, identified medical conditions warranting further research regarding the possible therapeutic effects of cannabis.

- Appetite Stimulation
- Nausea and Vomiting
- Analgesia
- Neurological and Movement Disorders

University of California Center for Medicinal Cannabis Research (CMCR)

Igor Grant, M.D.
Director

Thomas J. Coates, Ph.D.

J. Hampton Atkinson, M.D.

Andrew Mattison, Ph.D.*

Co-Directors

**(deceased)*

www.cmcr.ucsd.edu

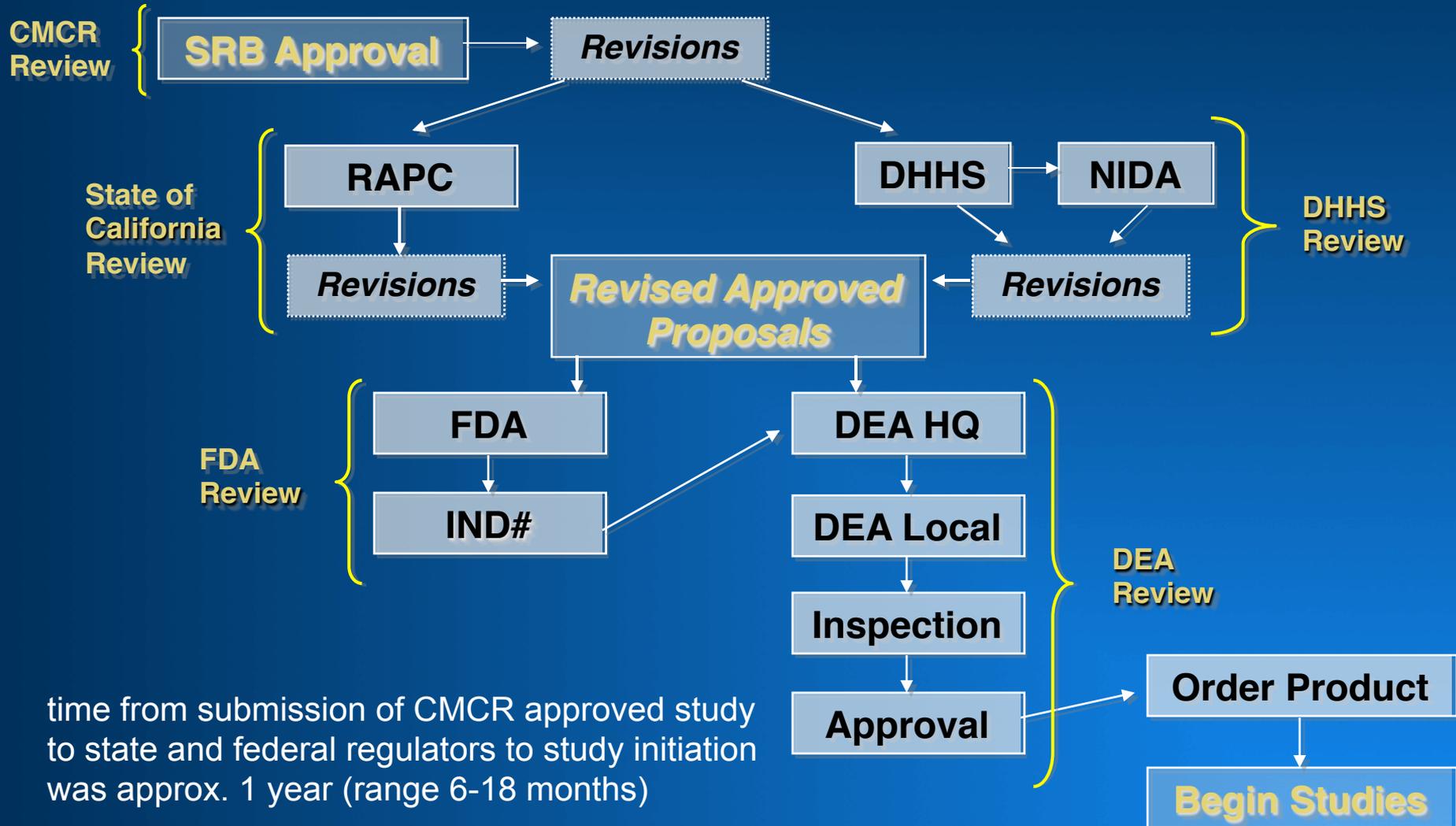
California Events Leading To CMCR

- November 1996:** California Prop 215 passes: Compassionate Use Act
- September 1999:** Medical Marijuana Research Act of 1999, authored by Senator John Vasconcellos.
- August 2000:** Center for Medicinal Cannabis Research established at the University of California.
- September 2003:** Amendment to Medical Marijuana Research Act of 1999, sunset restrictions removed.

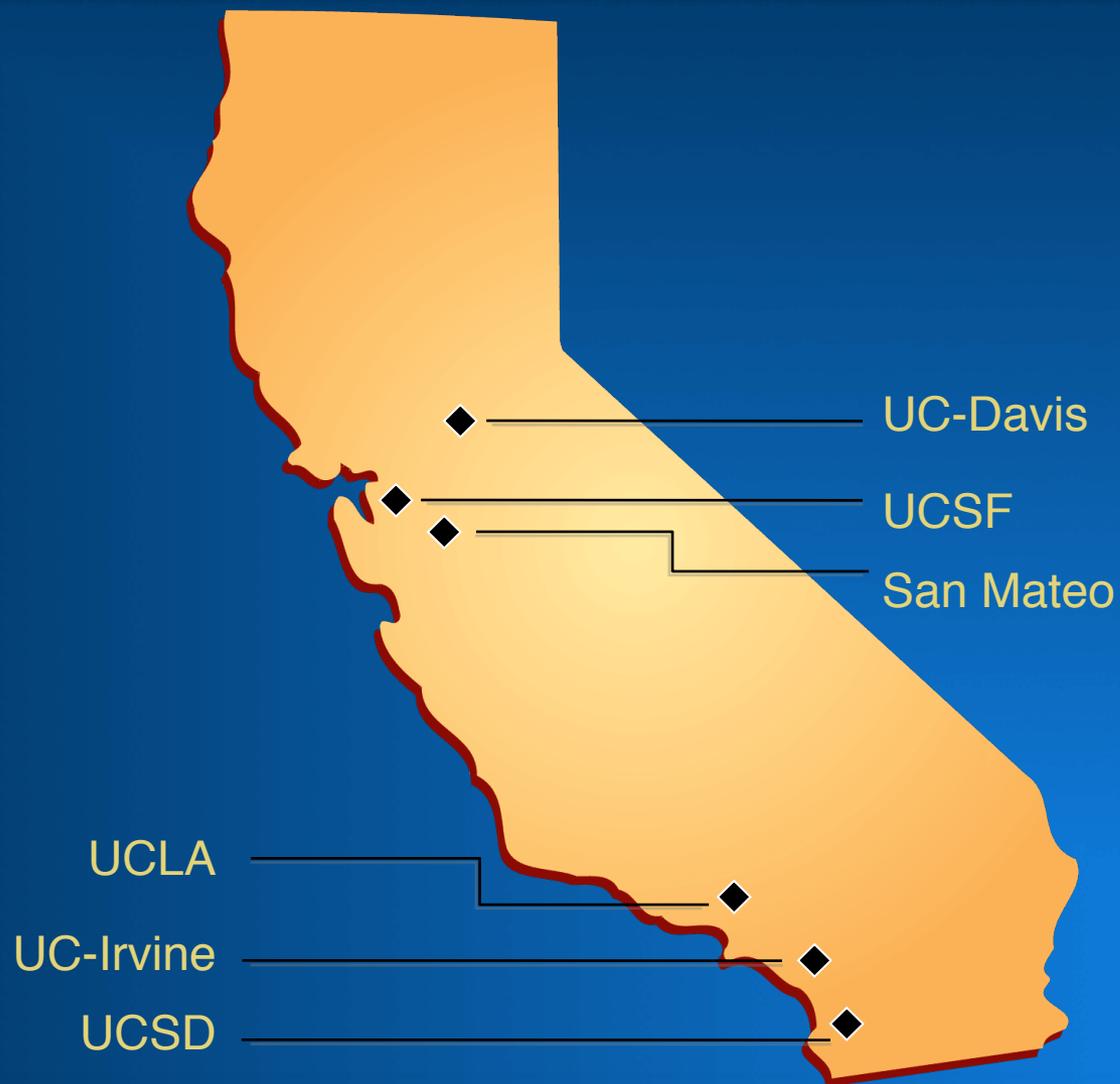
CMCR Mission

The Center for Medicinal Cannabis Research will conduct high quality scientific studies intended to ascertain the general medical safety and efficacy of cannabis products and examine alternative forms of cannabis administration. The Center will be seen as a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities.

CMCR Regulatory Pathway



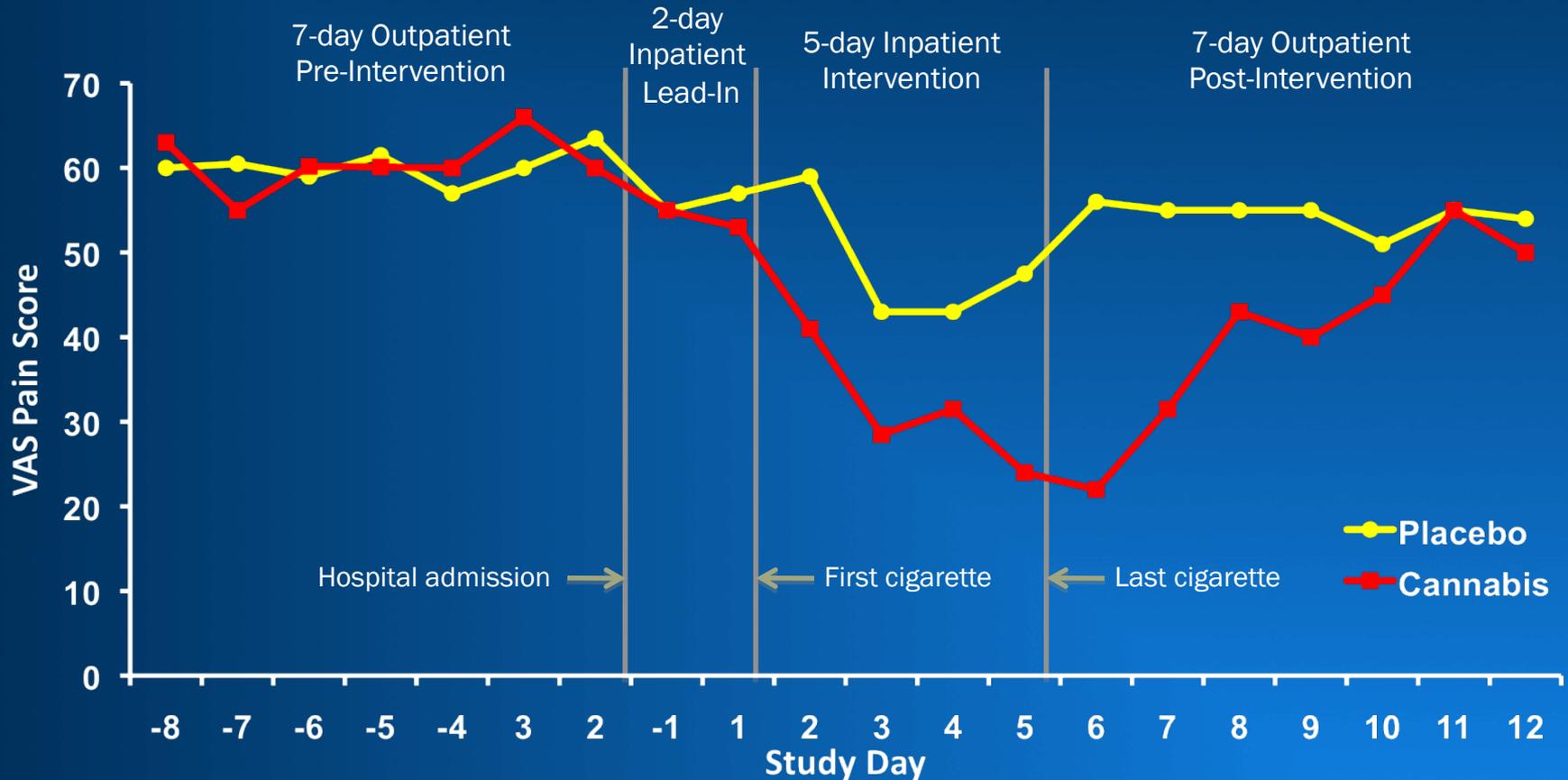
Study Locations



CMCR Clinical Studies completed

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

CMCR Abrams et al study: Cannabis reduces HIV Neuropathic Pain

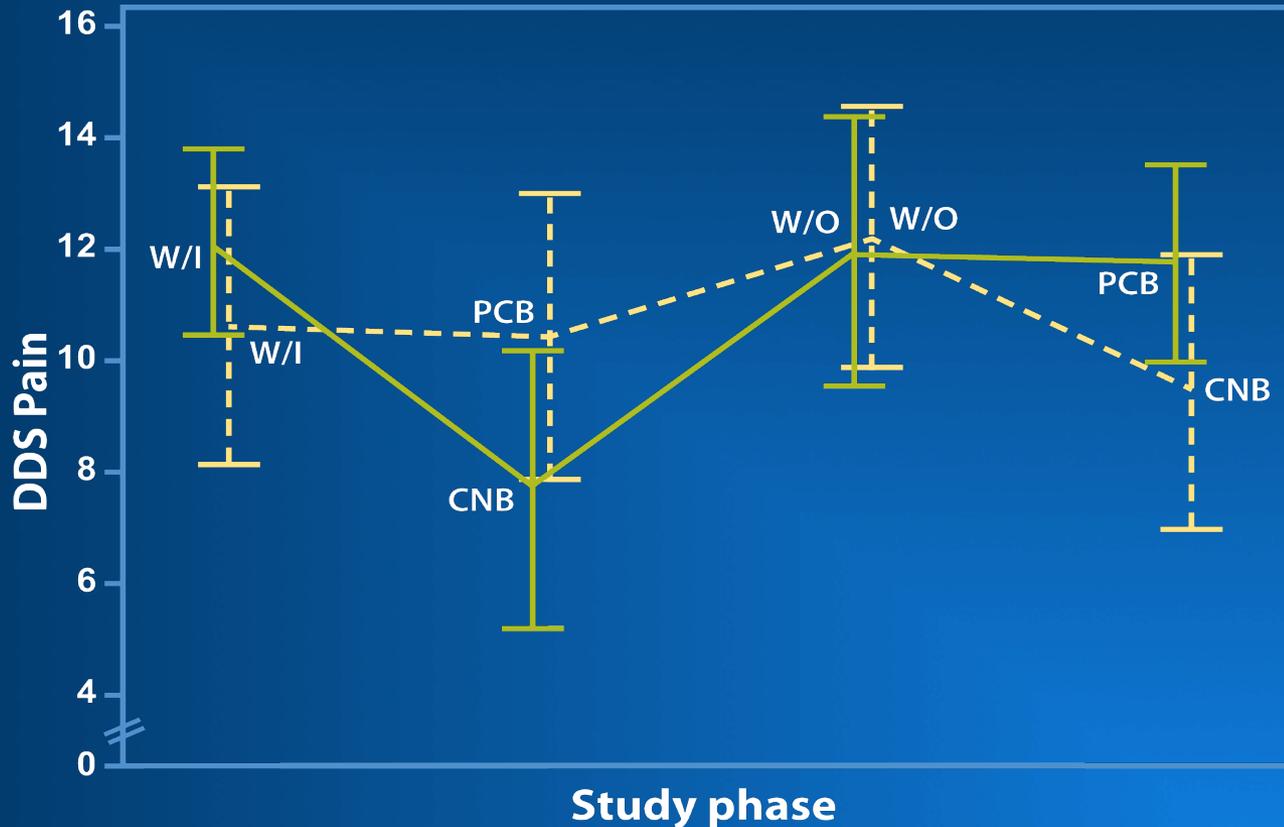


Placebo controlled double blind randomized trial of 4% THC containing vs 0%THC MJ cigarettes administered 3x/day for 5 days.

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

CMCR Ellis et al Study:

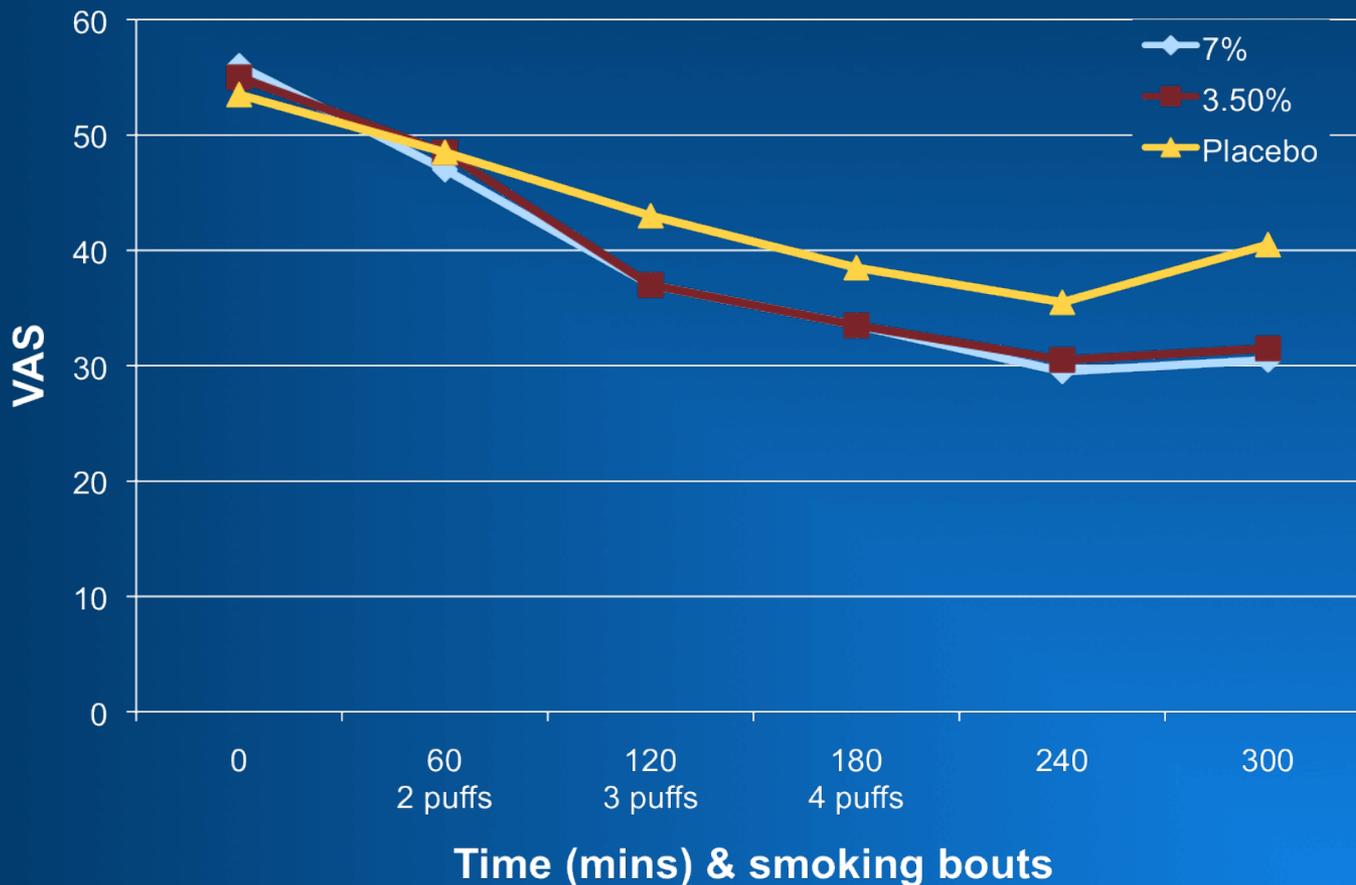
Reduction in HIV Neuropathic Pain in a crossover study of 28 patients receiving active (2-8% THC) vs placebo (0% THC) cigarettes 4x/d for 5 days



DDS pain severity scores (mean, 95% CI) for participants in the cannabis (CNB) and placebo (PCB) arms before study treatment (W/I), during each of the 2 treatment weeks (1, 2) and during the Washout (W/O) between treatment weeks.

Source: Ellis, et al. *Neuropsychopharmacology* 2009 Feb;34(3):672-80.

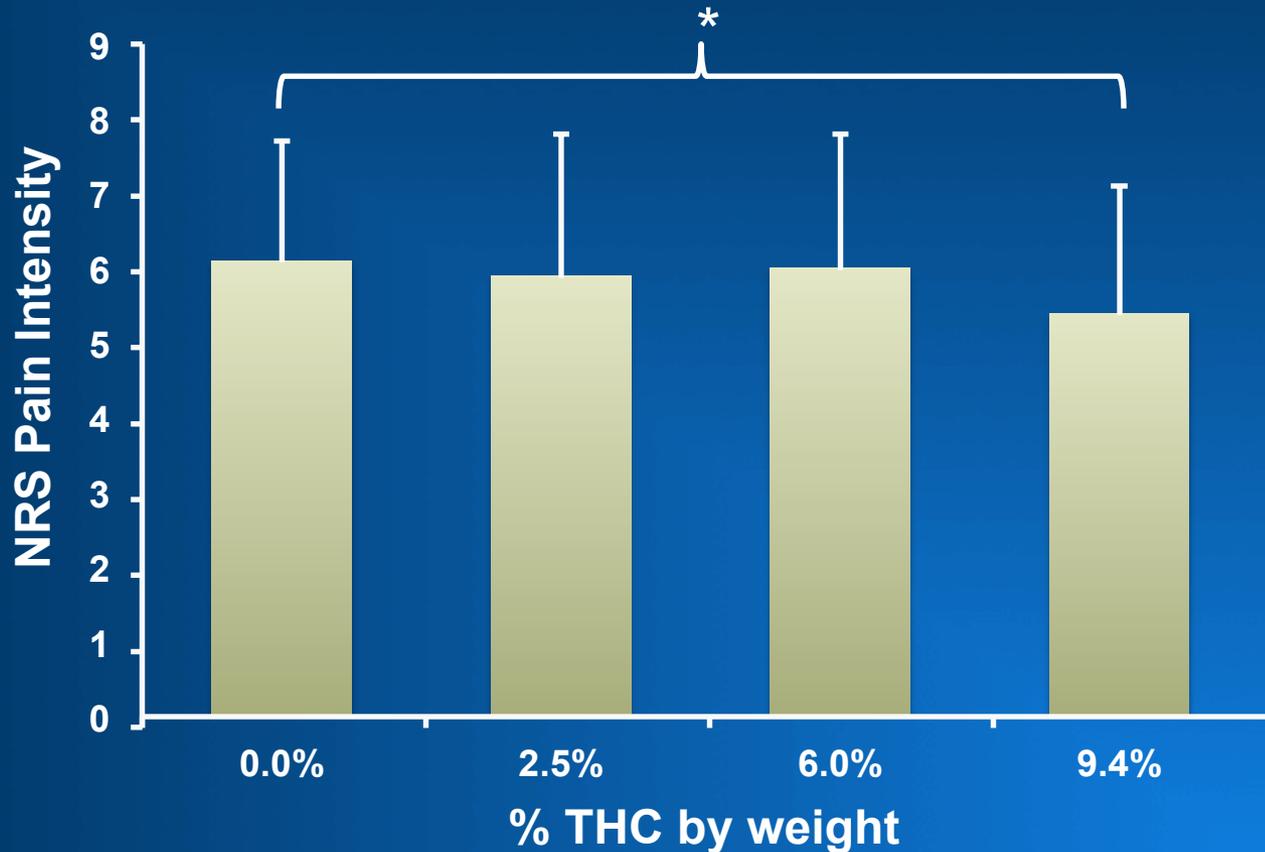
CMCR Study: Wilsey, et al: Cannabis Diminishes Mixed Etiology Neuropathic Pain



Placebo controlled randomized crossover of 33 patients receiving 0%, 3.5% or 7% THC containing cigarettes. VAS = Visual Analog Scale

Source: Wilsey, et al. 2008. *Journal of Pain*, 9 (6); 506-521.

Ware, et al. McGill Study: Higher Concentration THC improves post surgical/traumatic neuropathic pain



*p < 0.05

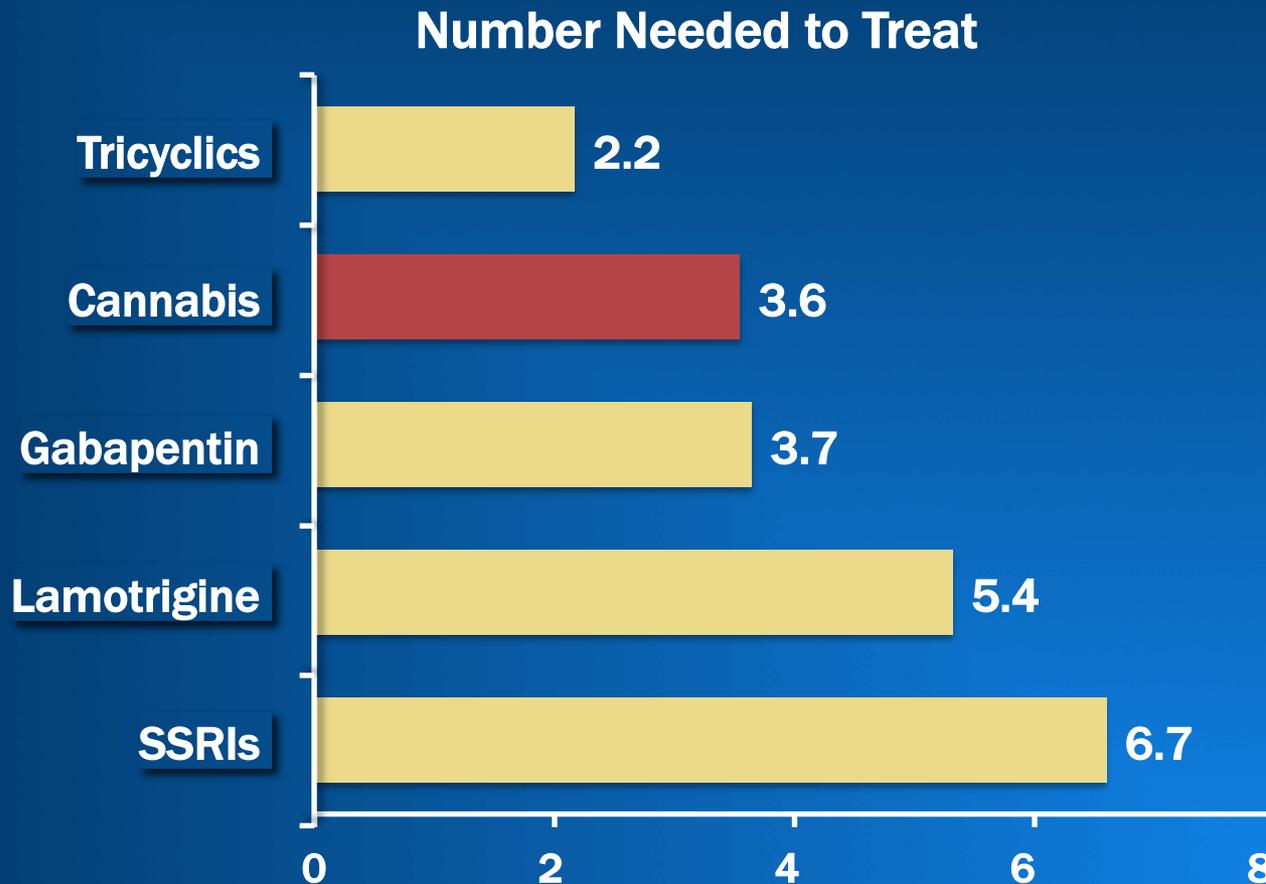
Randomized placebo controlled crossover study of 23 patients receiving 0%, 2.5%, 6% or 9.4% THC containing cannabis 3x/d for 5 d. *Source: Ware, et al. 2010. CMAJ. 2010 Oct 5;182(14):E694-701.*

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

- **Number-Needed-to-Treat (NNT) = $1 / (\text{Proportion improved in experimental condition} - \text{Proportion improved on placebo})$**
- **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**

$$\text{NNT} = 1 / .30 = 3.3$$

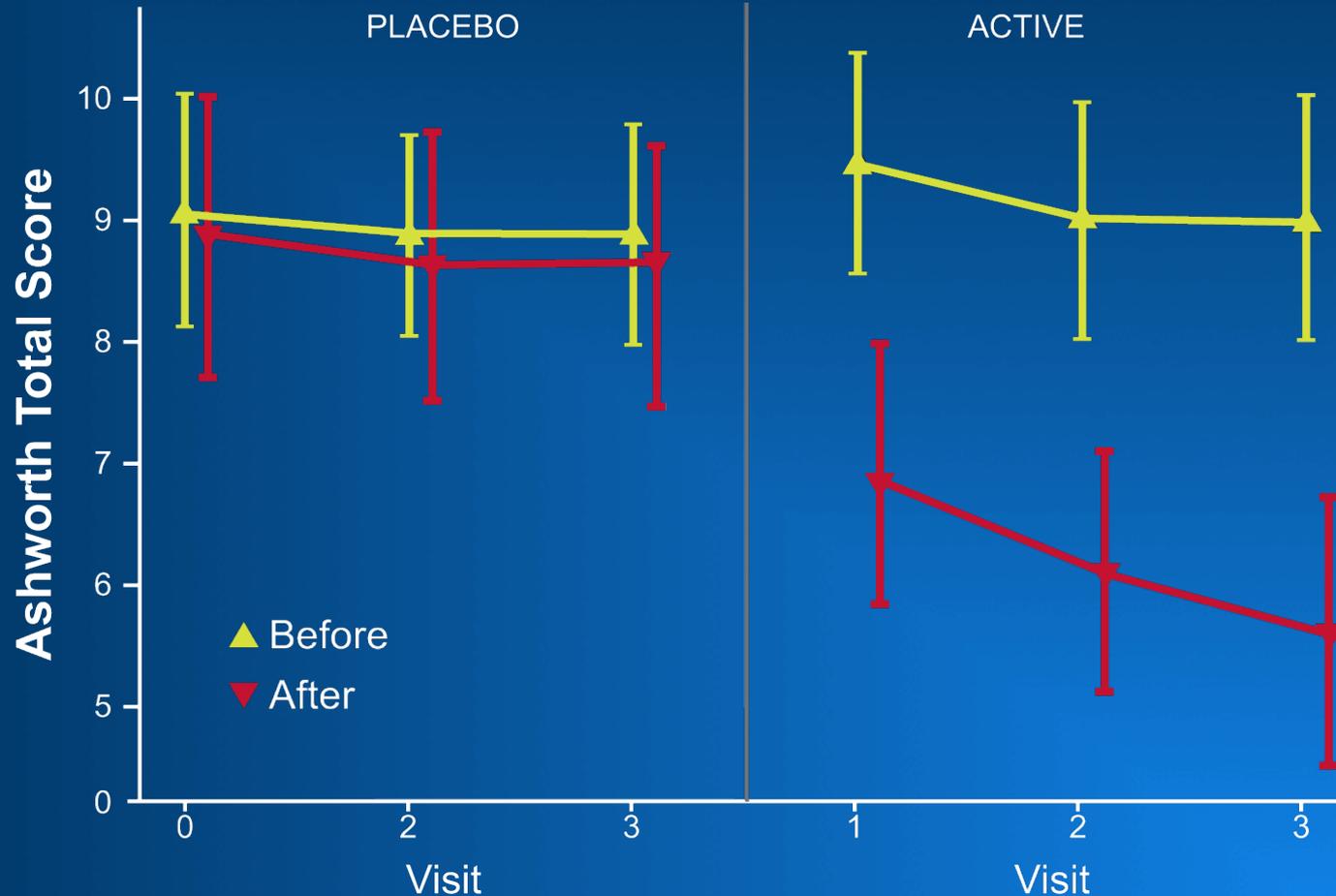
Common Analgesics for Neuropathic Pain



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

CMCR Study by Corey Bloom et al:

Cannabis improves MS spasticity in brief placebo controlled randomized study of 30 patients receiving 0% or 4% THC (1x/d x 3 d)



Ashworth spasticity scores before and after active and placebo cannabis administration. Active treatment reduced Ashworth Total Scores by an average of 2.7 points more than placebo ($p < 0.0001$).

Source: Corey-Bloom, et al. (2012) CMAJ 184(10); 1143-1150.

Summary of CMCR Studies on Smoked Cannabis

- Data from CMCR placebo controlled, limited scale studies of smoked cannabis indicate positive response in patients with neuropathic pain (3 studies) as well as reduced pain in a neuropathic pain model of nonpatients (1 study) , with effect sizes similar to other agents
- One CMCR study also found smoked cannabis reduced spasticity in MS patients
- Side effects were generally mild, with commonest being subjective high, fatigue, and tachycardia
- Neurocognitive testing revealed small reversible decrements during active treatment; comparable to effects of benzodiazepines, and antispasm, antiepileptic drugs for neuropathic pain and spasm
- Other side effects were sedation, dizziness, cough, throat irritation; all reversible and none necessitating discontinuation

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

Alternative Delivery Systems: “Volcano”

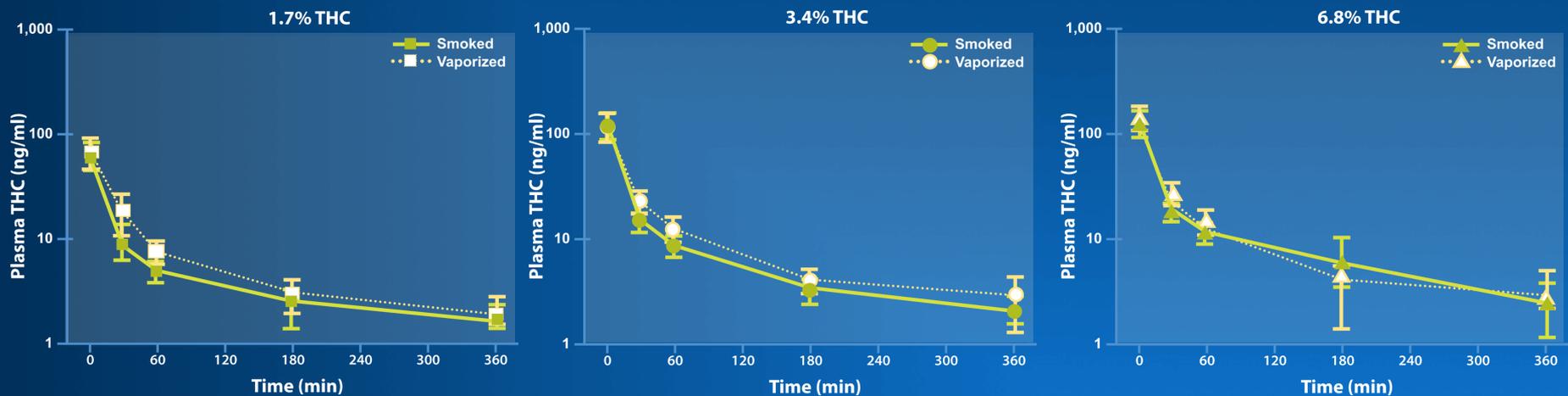
- Cannabis heated to 180 °C
- Below the point of combustion (230 °C)
- Releases cannabinoids as vapor into balloon
- Inhaled via mouthpiece attached to balloon



STORZ & BICKEL GMBH & CO. KG



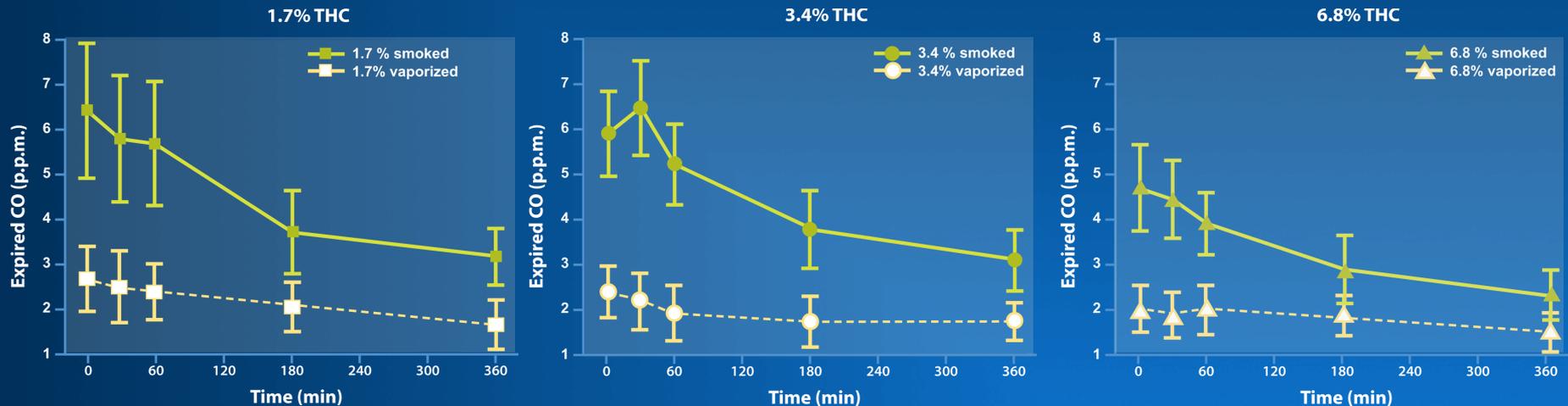
Vaporized administration yields plasma THC concentrations comparable to smoking



Plasma THC using vaporizer and smoked cannabis by THC strength (mean and 90% CI).

Source: Abrams, et al. 2007. Clin Pharmacol Ther.

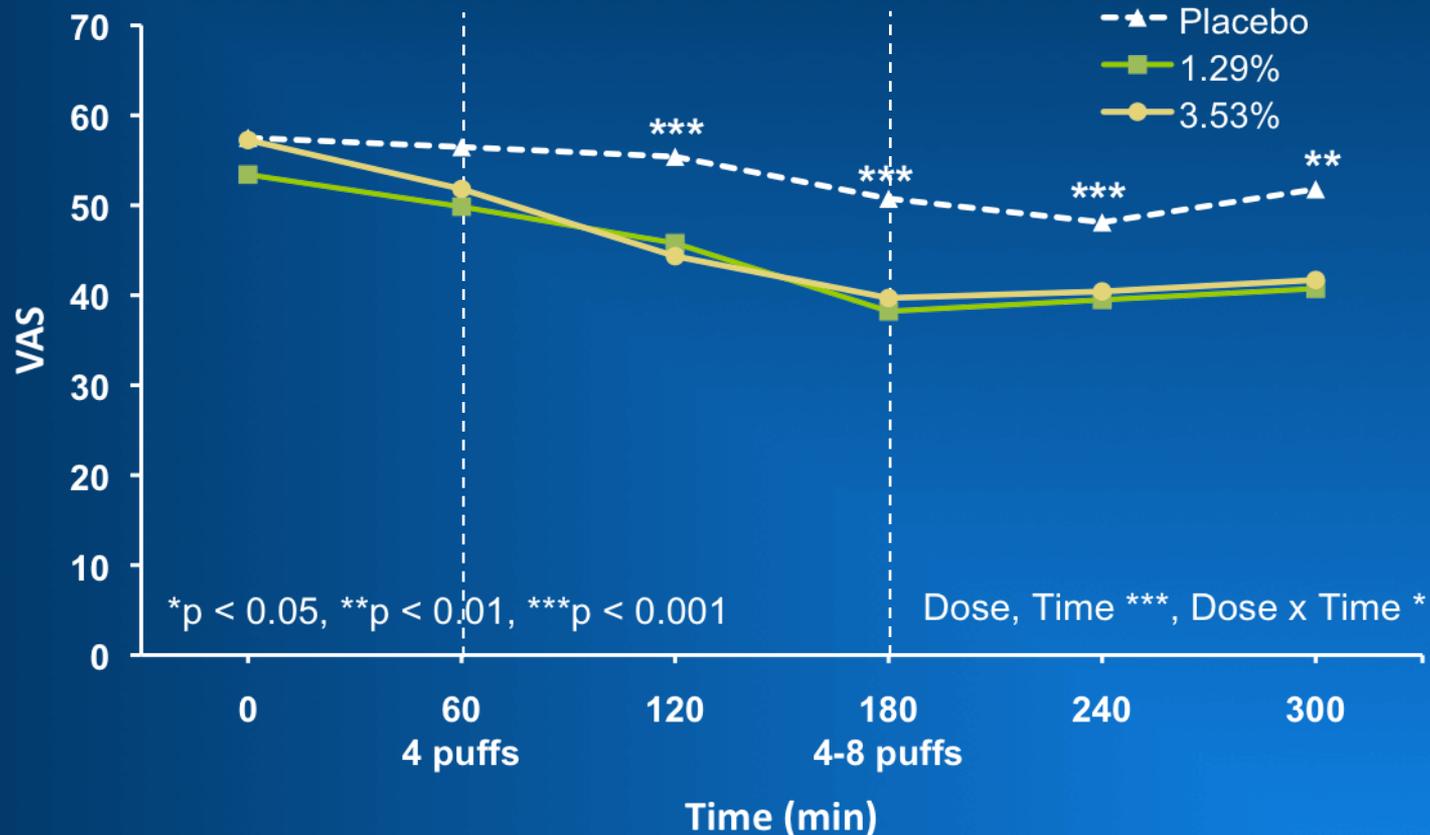
Vaporized administration produces less CO than smoking cannabis



Expired CO at each time point for each mode of administration and THC strength (mean and 95% CI).

Source: Abrams, et al. 2007. Clin Pharmacol Ther.

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



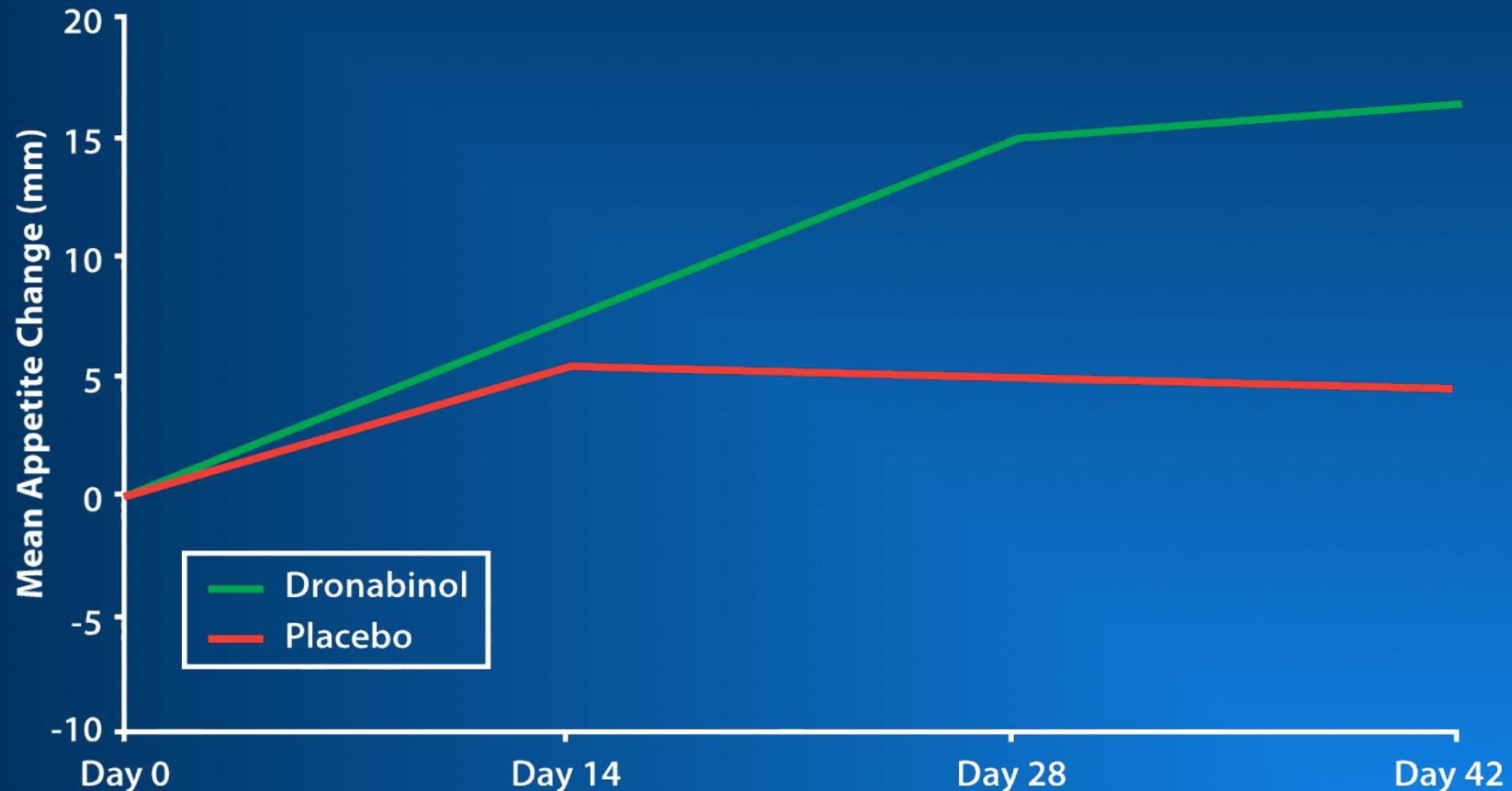
Placebo controlled randomized crossover study of 39 patients with neuropathic pain of mixed etiology treated 2x/d. THC conc. = 0%; 1.3%; 3.5%

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

Other current or potential cannabinoid modulators

- **Agonists**
 - » THC/CBD plant extract, eg., Nabiximols)
 - » Synthetic THC analogs (Dronabinol; Nabilone; selective CB1 or CB2 agonists)
- **Antagonists, partial agonists**
 - » (Rimonabant, Taranabant, etc)
- **Modifiers of endocannabinoid metabolism**
 - » Fatty Acid Amide Hydrolase (FAAH) inhibitors; possibly monoglyceride lipase (MGL) inhibitors

Dronabinol for Appetite Stimulation

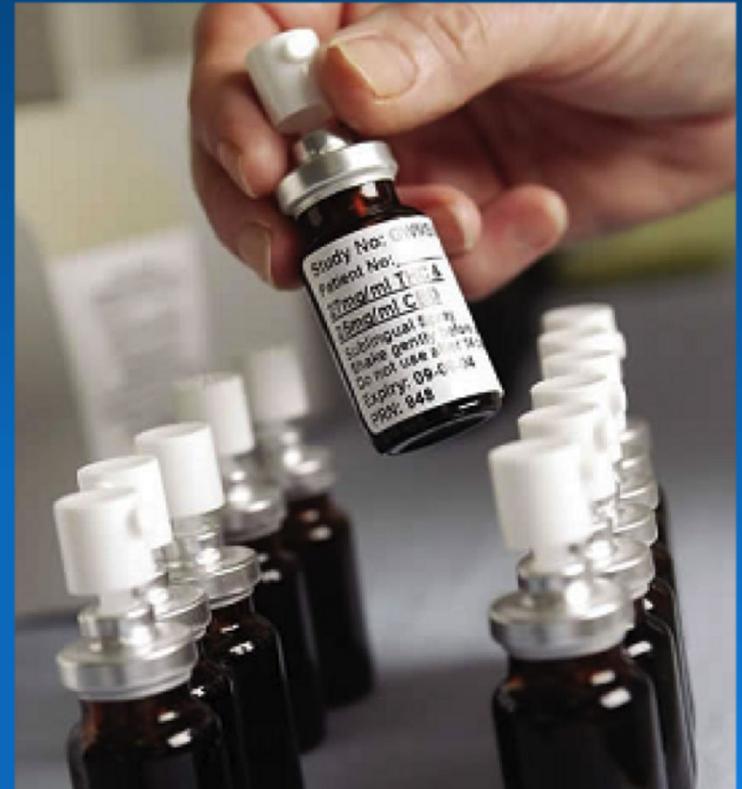


Mean change in appetite from baseline, evaluable patients.

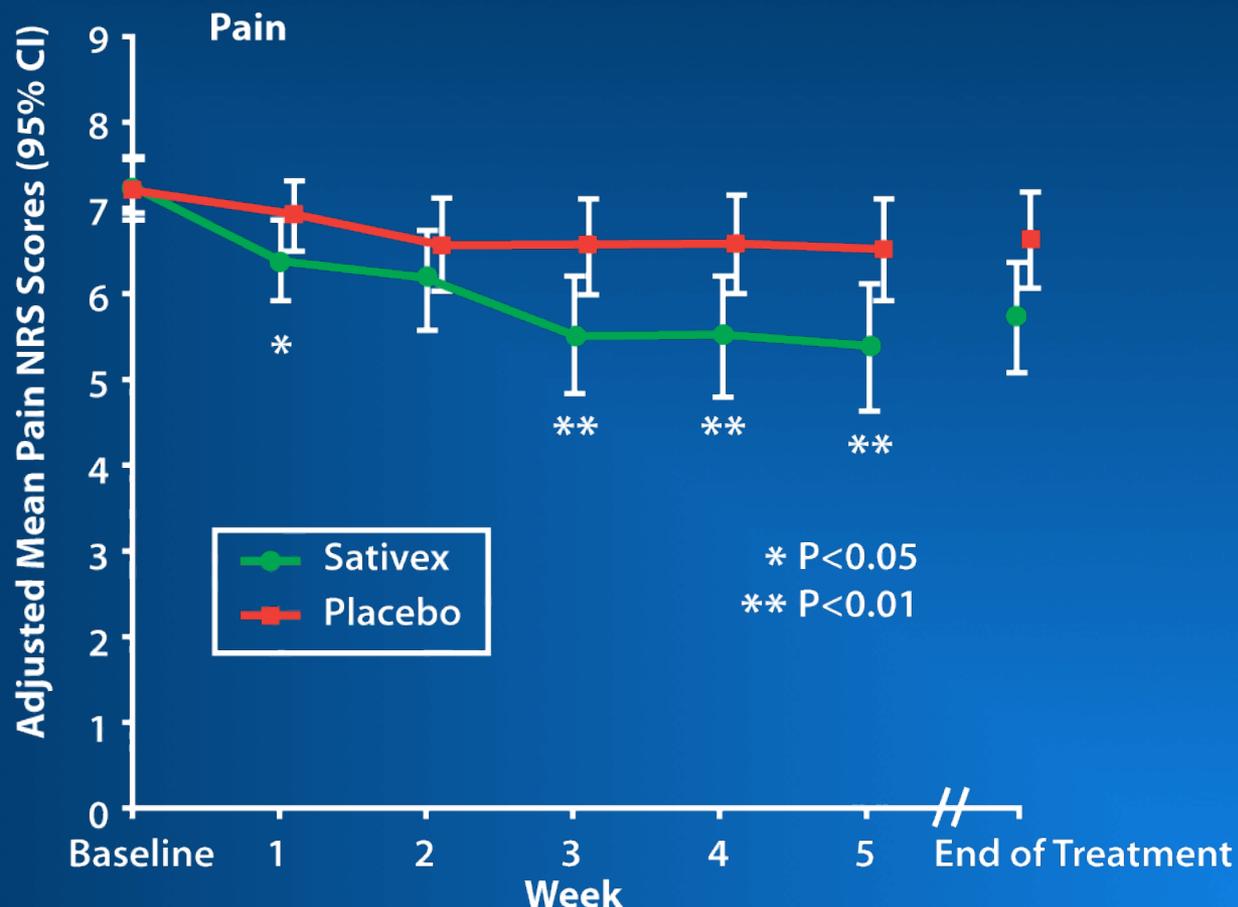
Source: Beal, et al. (1995). *Journal of Pain and Symptom Management*. 10;2. 89-97.

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)



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

Nabiximols (Sativex[®]) for MS Spasticity

■ Design & Methods:

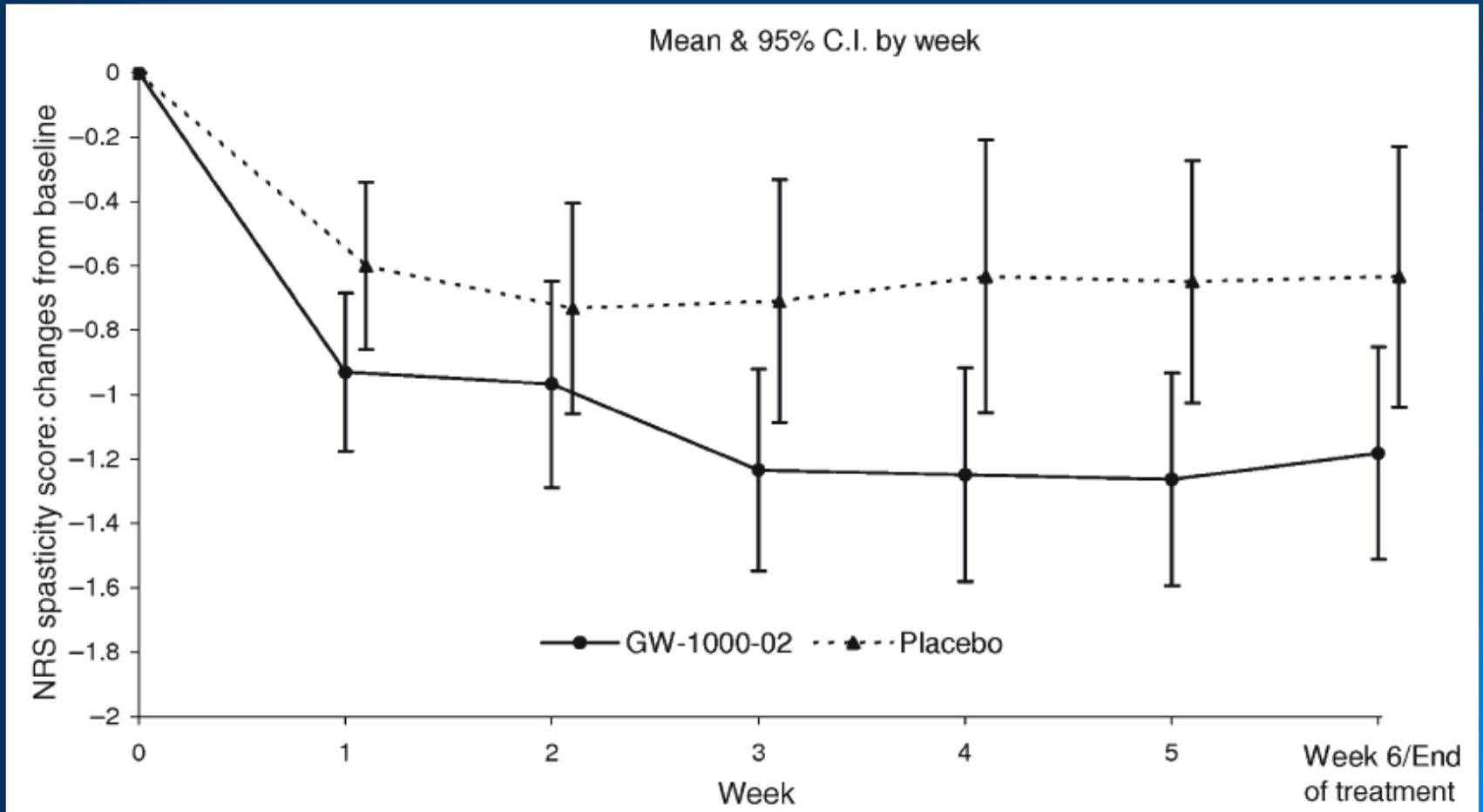
- » Multi-center, randomized, double-blind, parallel group study
- » Adults with stable multiple sclerosis for >3 mos who have not responded positively to spasticity treatment
- » Active oralmucosal spray (Sativex, GW Pharmaceuticals) vs. placebo for 6 weeks for treatment of spasticity

Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis

C. Collin^a, P. Davies^b, I. K. Mutiboko^c, S. Ratcliffe^d for the Sativex Spasticity in MS Study Group*

^aDepartment of Neurorehabilitation, Royal Berkshire and Battle NHS Trust, Reading, UK; ^bDepartment of Neurology, Northampton General Hospital, Northampton, UK; ^cTrial-Link Ltd, Bexhill-on-Sea, UK; and ^dBarts Pain Research Group, Barts and The London NHS Trust, London, UK

Nabiximols (Sativex[®]) for MS Spasticity



Source: Collin, et al. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. 2007. *European Journal of Neurology*. 14:290-296.

Cannabidiol - CBD

- Natural component of the Cannabis plant
- Constitutes up to 40% of marijuana extracts
- Devoid of typical psychological effects of THC
- Evidence for:
 - » Anti-inflammatory
 - » Analgesia
 - » Anti-nausea
 - » Hypnotic and sedative
 - » **Antipsychotic**
 - » Anticonvulsive
 - » Neuro-protective
 - » **Anxiolytic**
 - » Others
- Antagonism of the Δ^9 -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

Cannabidiol: Animal Models of Anxiety

STUDY	MODEL	ANXIOLYTIC EFFECT
Animal		
Silveira Filho and Tufik (1981)	Conflict test	-
Zuardi and Karniol (1983)	Conditioned emotional response paradigm	+
Onaivi et al. (1990)	Elevated plus maze test	+
Guimarães et al. (1990)	Elevated plus maze test	+
Moreira and Guimarães (2006)	Vogel conflict test	+
Resstel et al. (2006)	Contextual conditioned fear	+
Campos and Guimarães (2008)	Elevated plus maze test and the Vogel conflict test	+
Bitencourt, Pamplona, Takahashi, (2008)	Conditioning context	+
Campos and Guimarães (2009)	Elevated plus maze test	+
Resstel et al. (2009)	Restraint stress	+
Soares et al. (2010)	Elevated T maze	+
Lemos, Resstel and Guimarães (2010)	Contextual conditioning fear	+
Casarotto et al. (2010)	Marble-burying test	+
Gomes, Resstel and Guimarães (2011)	Vogel conflict test	+
Deiana et al. (2012)	Marble-burying test	+
Uribe-Mariño et al. (2012)	Prey vs predator paradigm	+
Campos et al. (submitted)	Elevated T maze	+

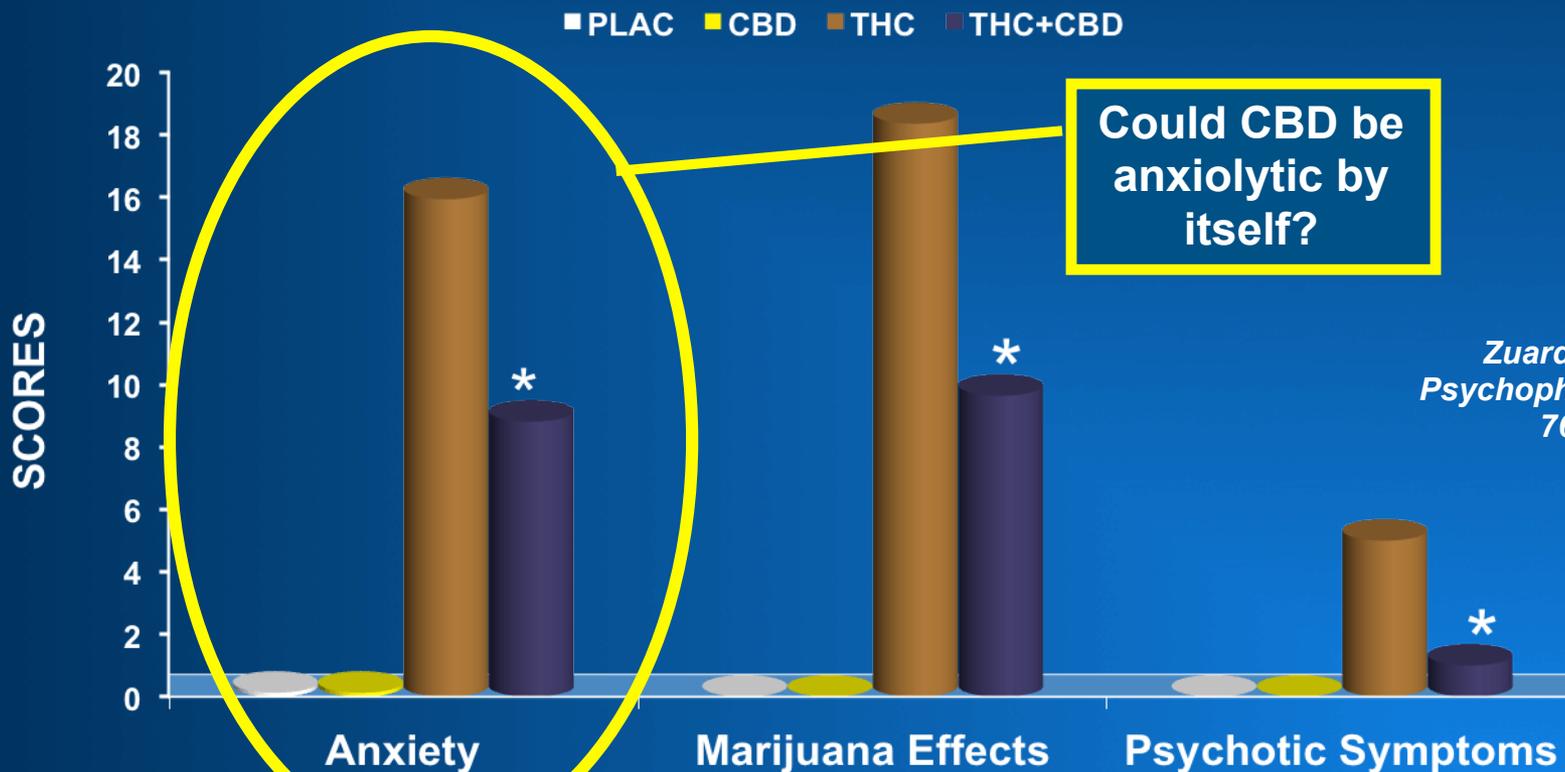
Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

Cannabidiol: Human Models of Anxiety

STUDY	MODEL	ANXIOLYTIC EFFECT
Humans		
Zuardi et al. (1982)	Decreased STAI scores elevation induced by THC (healthy volunteers)	+
Zuardi et al. (1993)	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	+
Crippa et al. (2004)	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	+
Fusar-Poli et al. (2009)	Decreased skin conductance fluctuation in task with fearful face during an fMRI procedure (healthy volunteers)	+
Crippa et al. (2011)	Decreased VAS factor anxiety scores before SPECT procedure (Social Phobic patients)	+
Bergamaschi et al. (2011)	Decreased VAS factor anxiety scores after public speaking (Social Phobic patients)	+

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

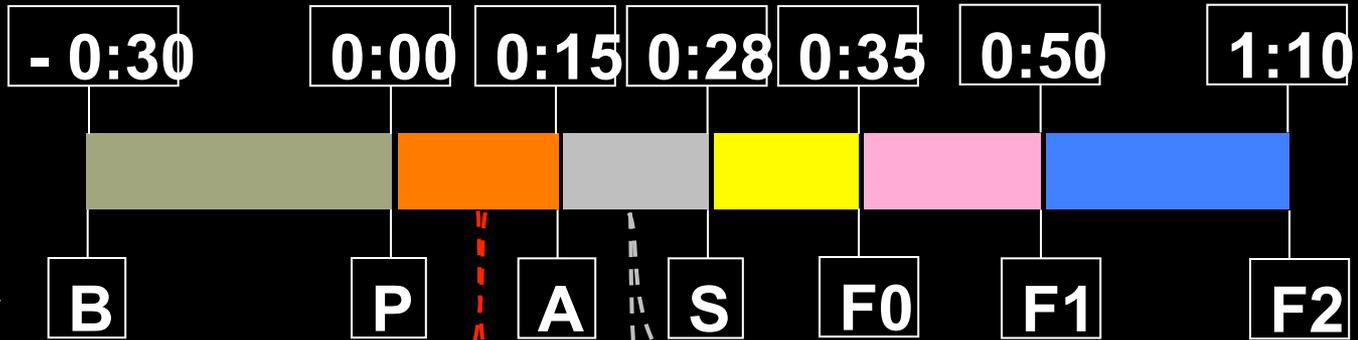
Interaction THC x CBD Healthy Volunteers



Zuardi et al, 1982 ,
Psychopharmacology,
76 (3):245-250.

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

The Simulated Public Speaking Test



Phases

- B: baseline
- P: pre-stress
- A: anticipatory
- S: performance
- F: post-stress



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

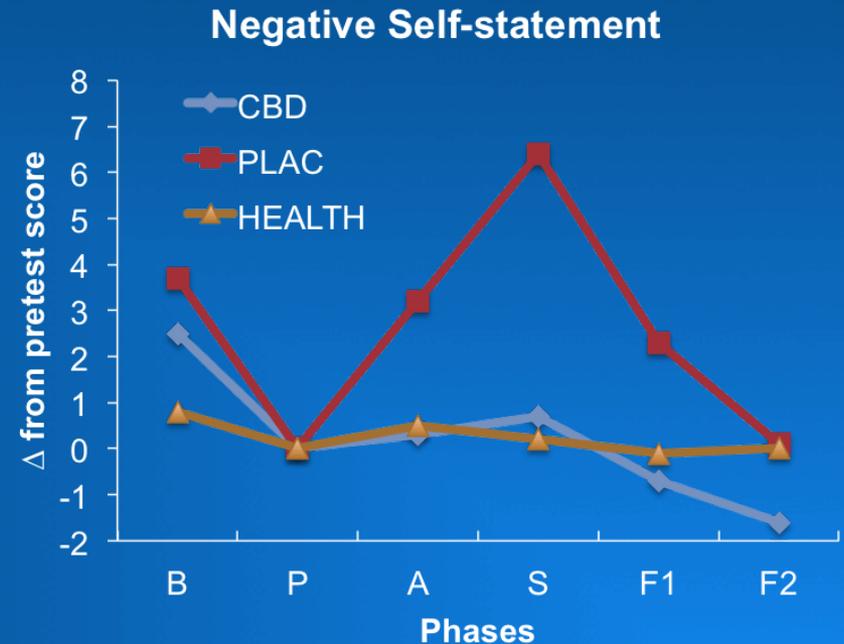
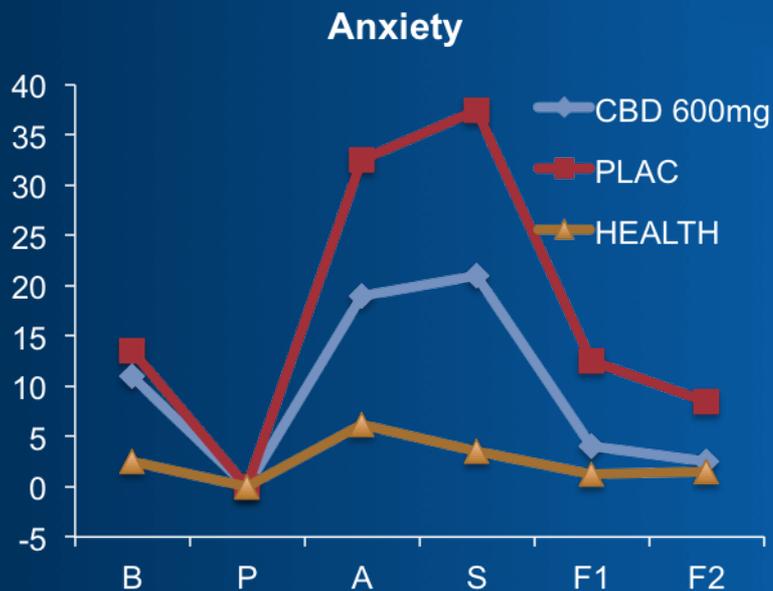
Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Neuropsychopharmacology (2011), 1–8

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Mateus M Bergamaschi^{1,2,3}, Regina Helena Costa Queiroz^{2,3}, Marcos Hortes Nisihara Chagas^{1,3}, Danielle Chaves Gomes de Oliveira^{1,3}, Bruno Spinosa De Martinis^{3,4}, Flávio Kapczinski^{3,5}, João Quevedo^{3,6}, Rafael Roesler^{3,7}, Nadja Schröder^{3,8}, Antonio E Nardi^{3,9}, Rocio Martín-Santos^{3,10}, Jaime Eduardo Cecílio Hallak^{1,3}, Antonio Waldo Zuardi^{1,3} and José Alexandre S Crippa^{*1,3}



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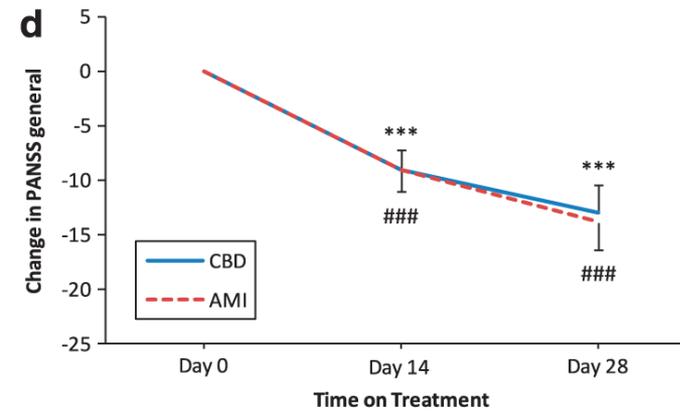
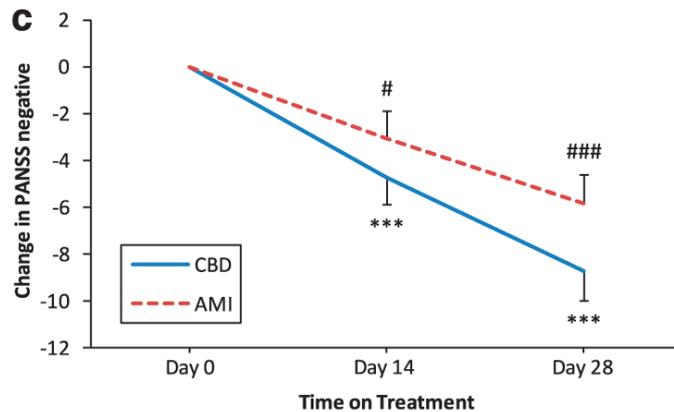
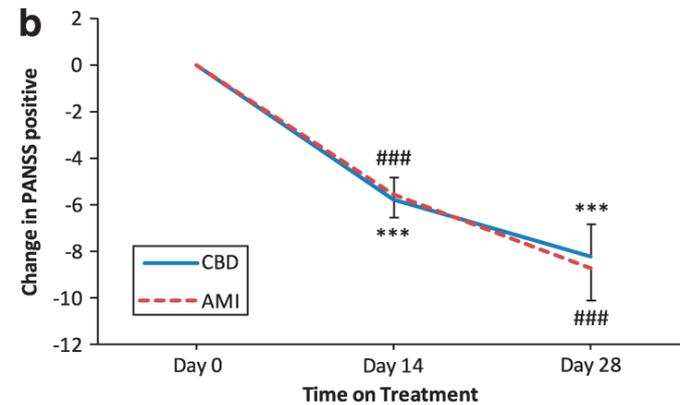
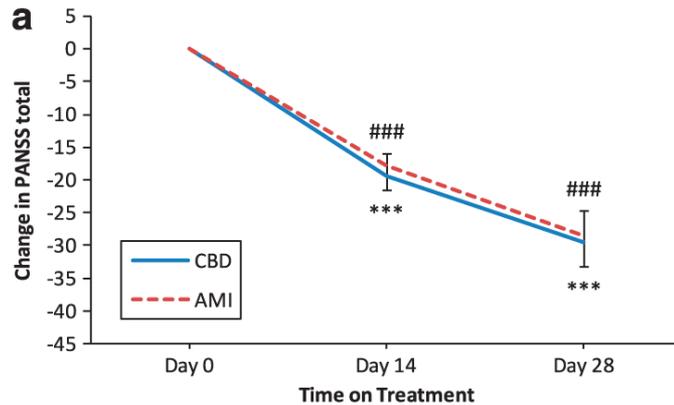
Role for cannabinoids in schizophrenia treatment?

Some evidence for cannabinoid involvement

- Heavy MJ use associated with increased risk of psychosis in some studies; THC itself can produce acute psychosis
- PCP administration (animal model of psychosis) associated with regional brain increase in 2 AG
- Human PET studies show increase in CB1 binding in various brain regions in untreated schizophrenia
- Serum/CSF anandamide increased during onset of psychotic symptoms, but not in heavy MJ users
- Higher CSF anandamide associated with less likely transition to psychosis in “high risk” cases
- In psychosis cases treated with cannabidiol, improvement in negative symptoms associated with greater CSF anandamide rise

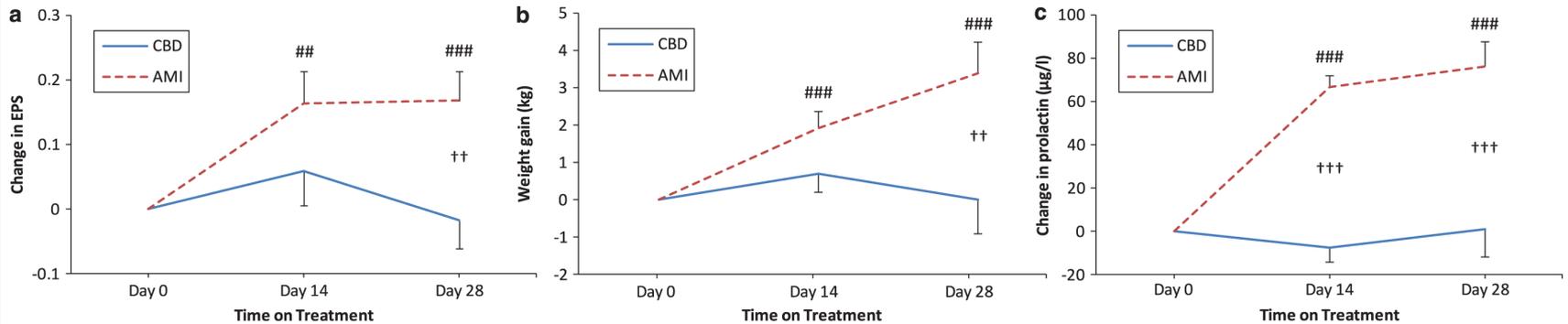
Cannabidiol improves positive and negative symptoms of schizophrenia:

(42 cases randomized to receive 800 mg/d cannabidiol or amisulpride)



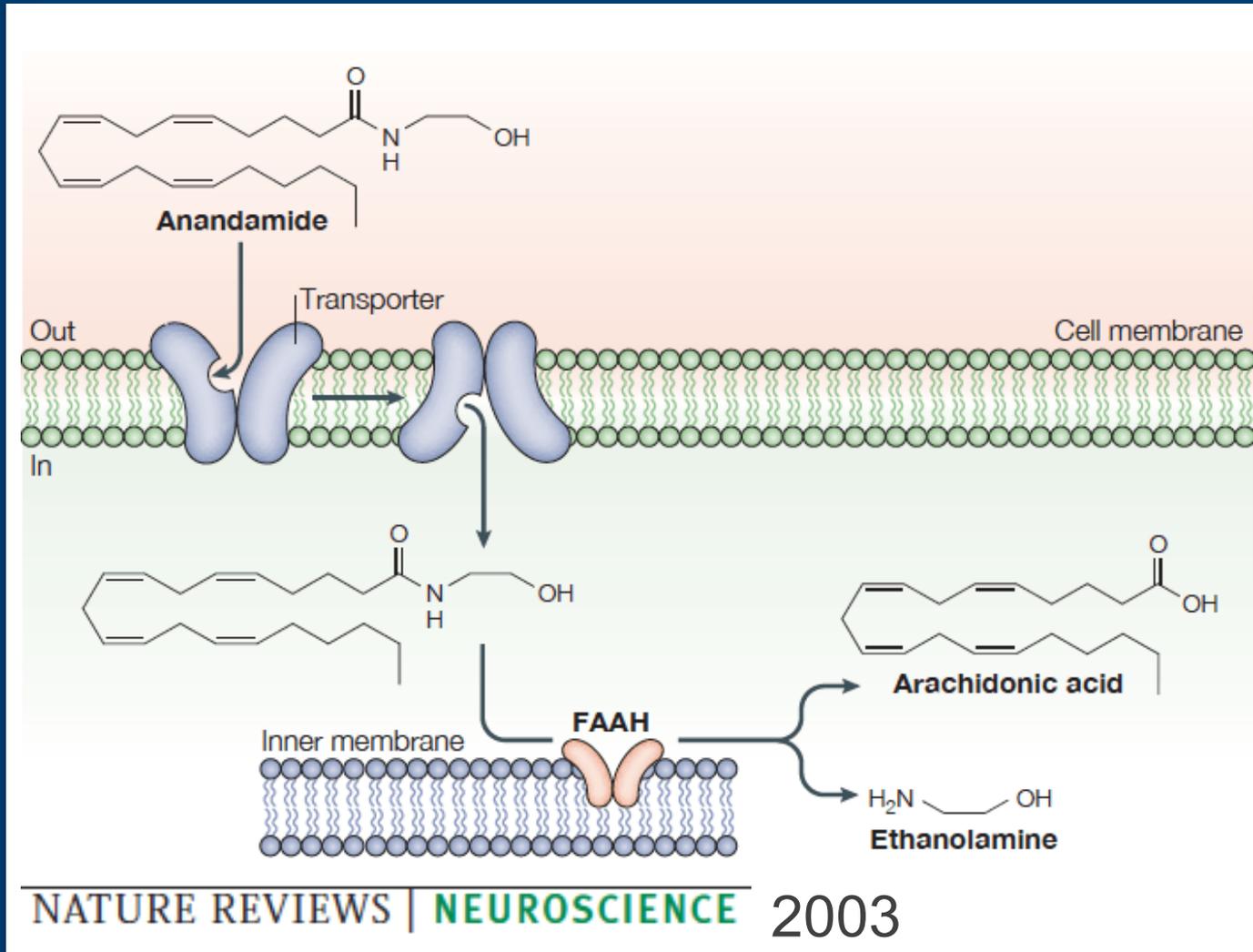
Leweke FM, Transl Psychiatry. 2012 Mar 20;2:e94.

Compared to atypical antipsychotic amisulpiride, cannabidiol does not worsen extrapyramidal symptoms, and is not associated with weight gain or elevated prolactin



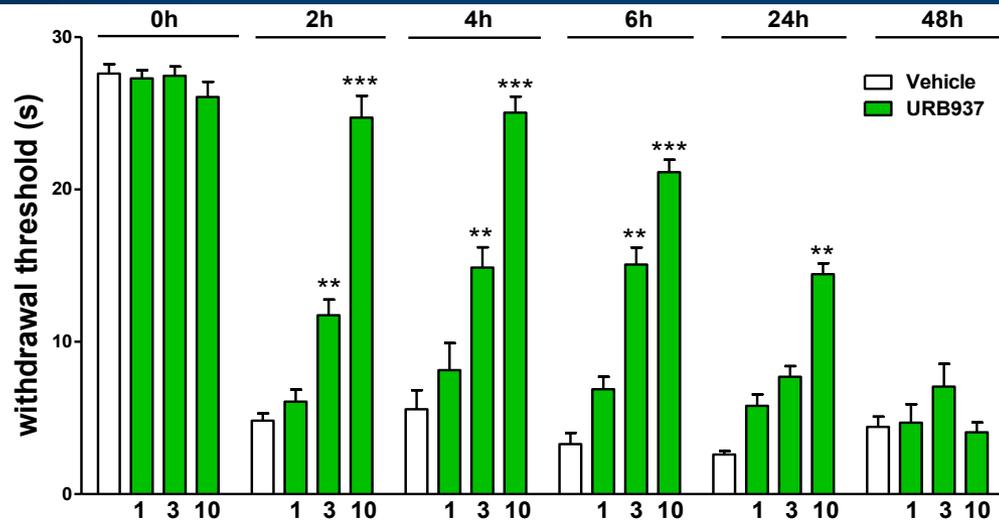
Leweke FM, Transl Psychiatry. 2012 Mar 20;2:e94.

FAAH inhibitors as therapeutic agents?



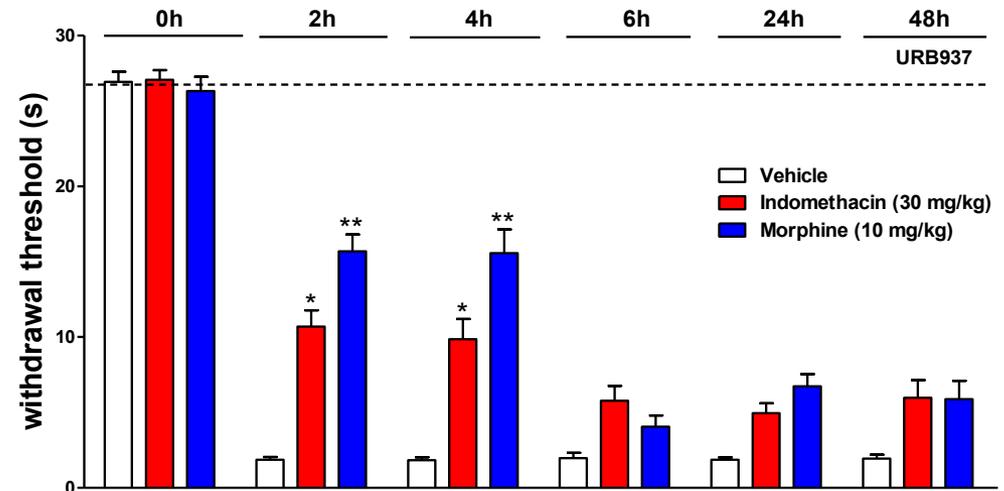
Courtesy
D.Piomelli,
UCI

Peripheral FAAH inhibitor URB937 efficacious in animal model of post-surgical pain



Oral dosing
Strong, prolonged
effect on pain

More effective and long-lasting than NSAIDs (oral) or opiates (ip)



Courtesy D. Piomelli, personal communication

Summary of current status of Medicinal Cannabis/ Cannabinoid Modulators

- Smoked/vaporized cannabis probably efficacious in neuropathic pain of various etiologies, and spasticity from MS
- Cannabis plant extracts containing mix of THC and CBD may also be efficacious in neuropathic pain and MS spasticity
- Synthetic THC-like molecules efficacious in appetite stimulation and control of nausea
- Potential utility of synthetic CB1 agonists not yet established
- CB1 antagonists, partial agonists may be useful in appetite suppression, but adverse psychiatric effects have been problematic
- Cannabidiol showing initial promise in treatment of anxiety and psychosis
- FAAH inhibitors promising in animal models of chronic pain
- Anti-inflammatory actions of cannabinoids deserve further exploration

Medicinal Cannabis

Thank you

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