Marijuana as Medicine: Can we see past the smoke?

August 6, 2016

Igor Grant, M.D.,

Director

University of California, San Diego | Center for Medicinal Cannabis Research

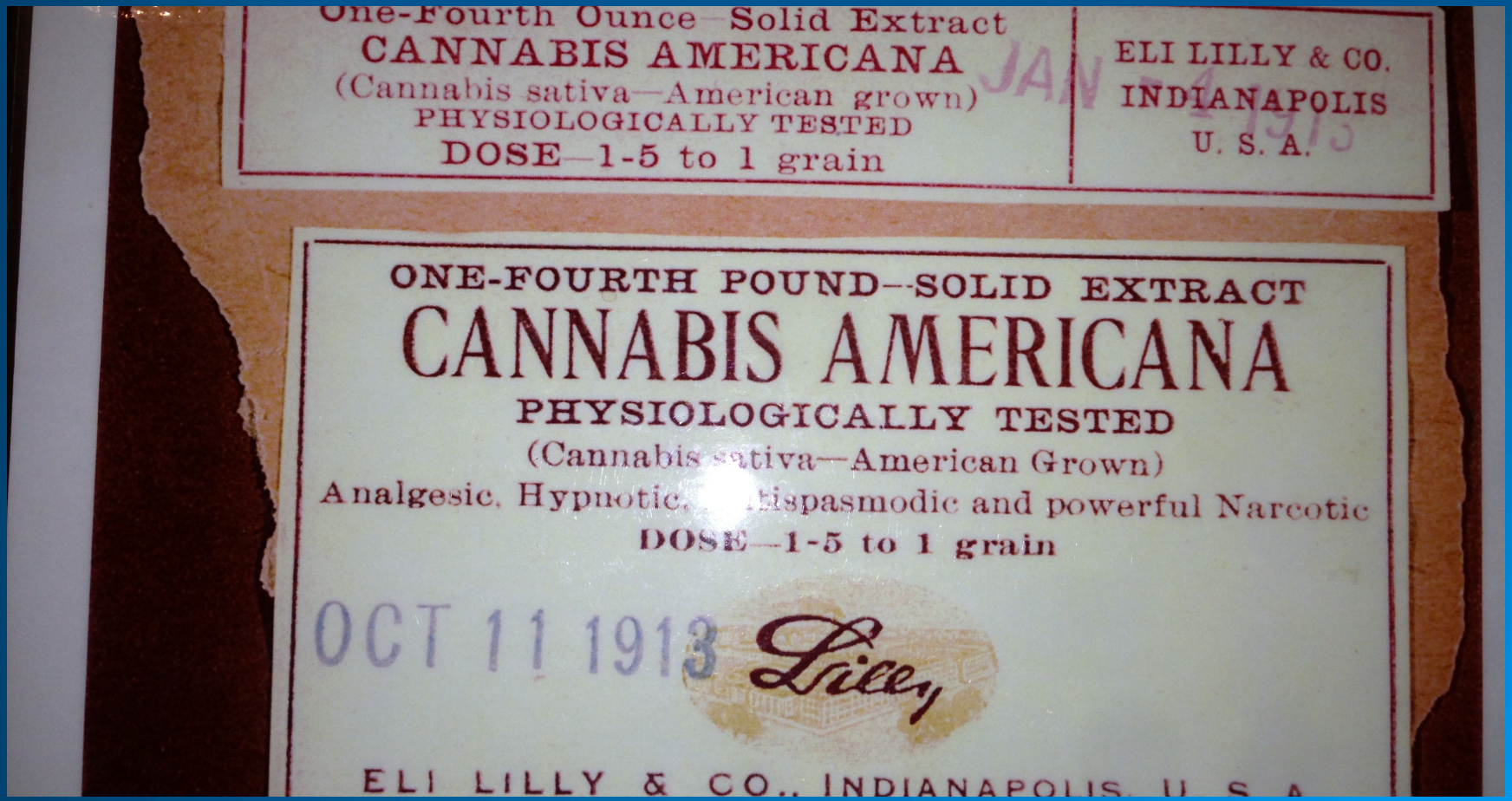
Cannabis and its derivatives

Marijuana

Hashish

Courtesy D. Piomelli, UCI

Cannabis: not a new medicine



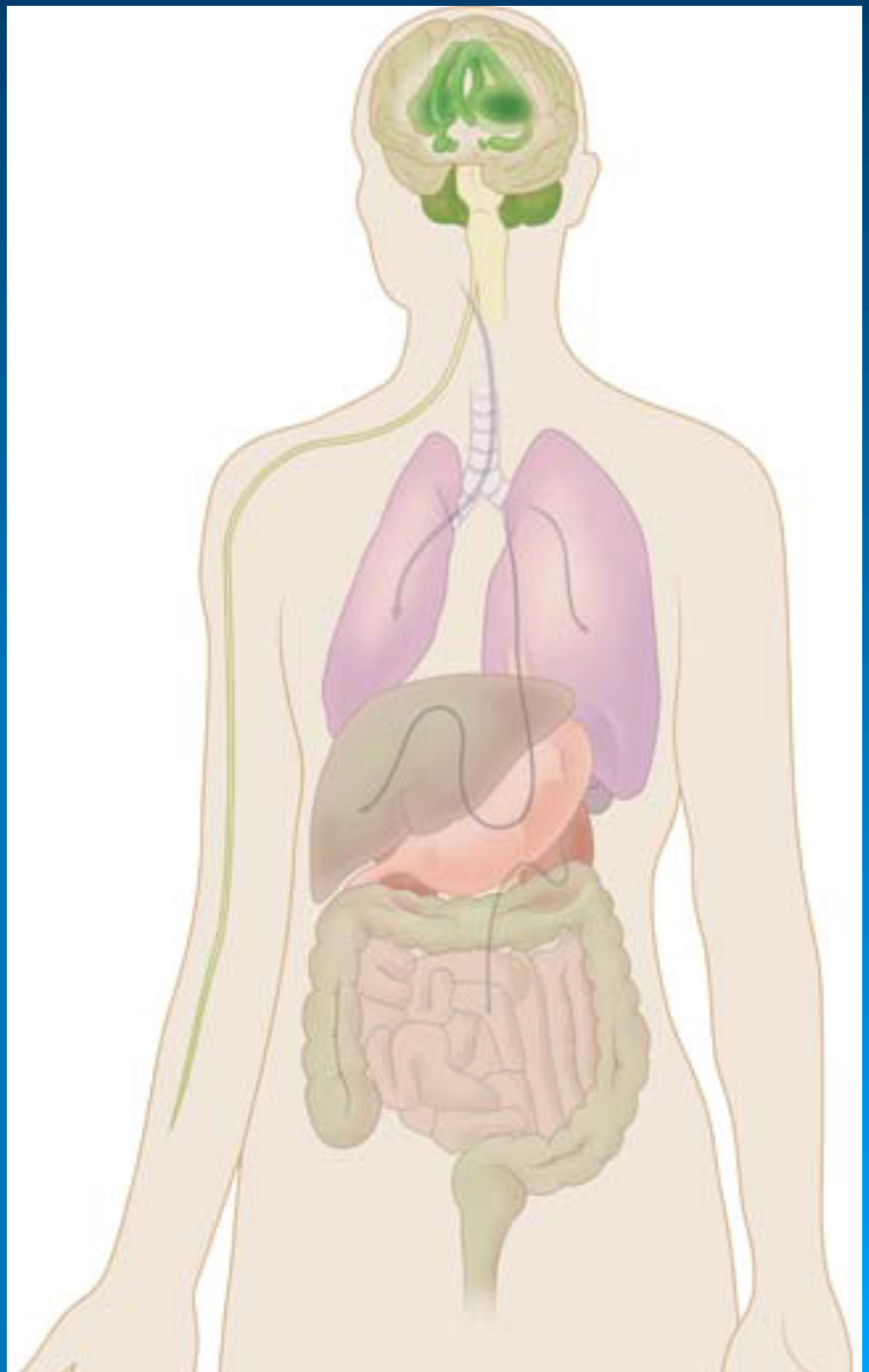
Main Events that Reawakened Interest in Medicinal Cannabis in the 1990s

- **Persistent anecdotal reports of benefits**
- **Political shifts favoring medicinal access (in USA 23 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)

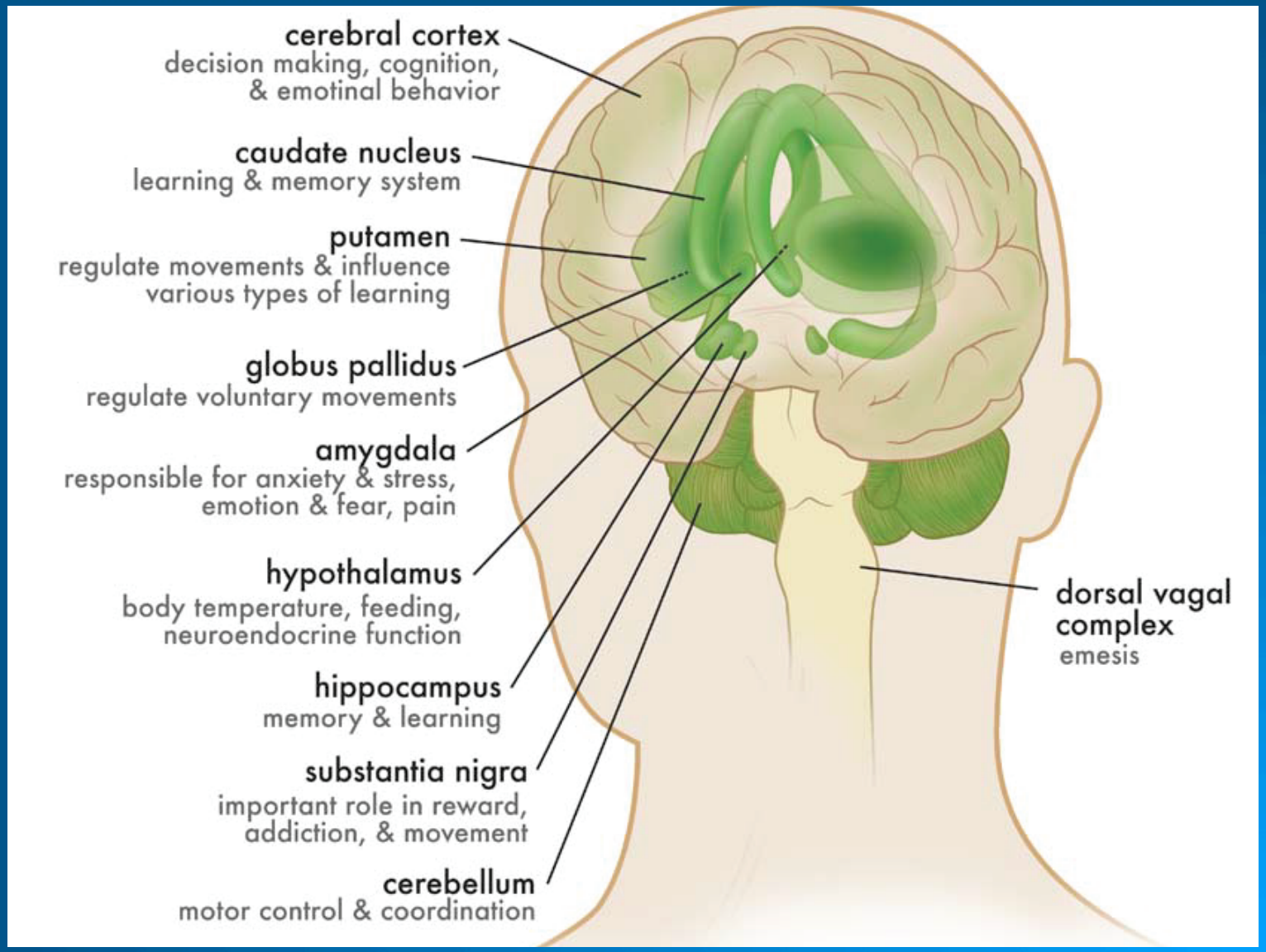
Distribution of CB1 Receptors

Green shading indicates distribution of cannabinoid receptors in the body

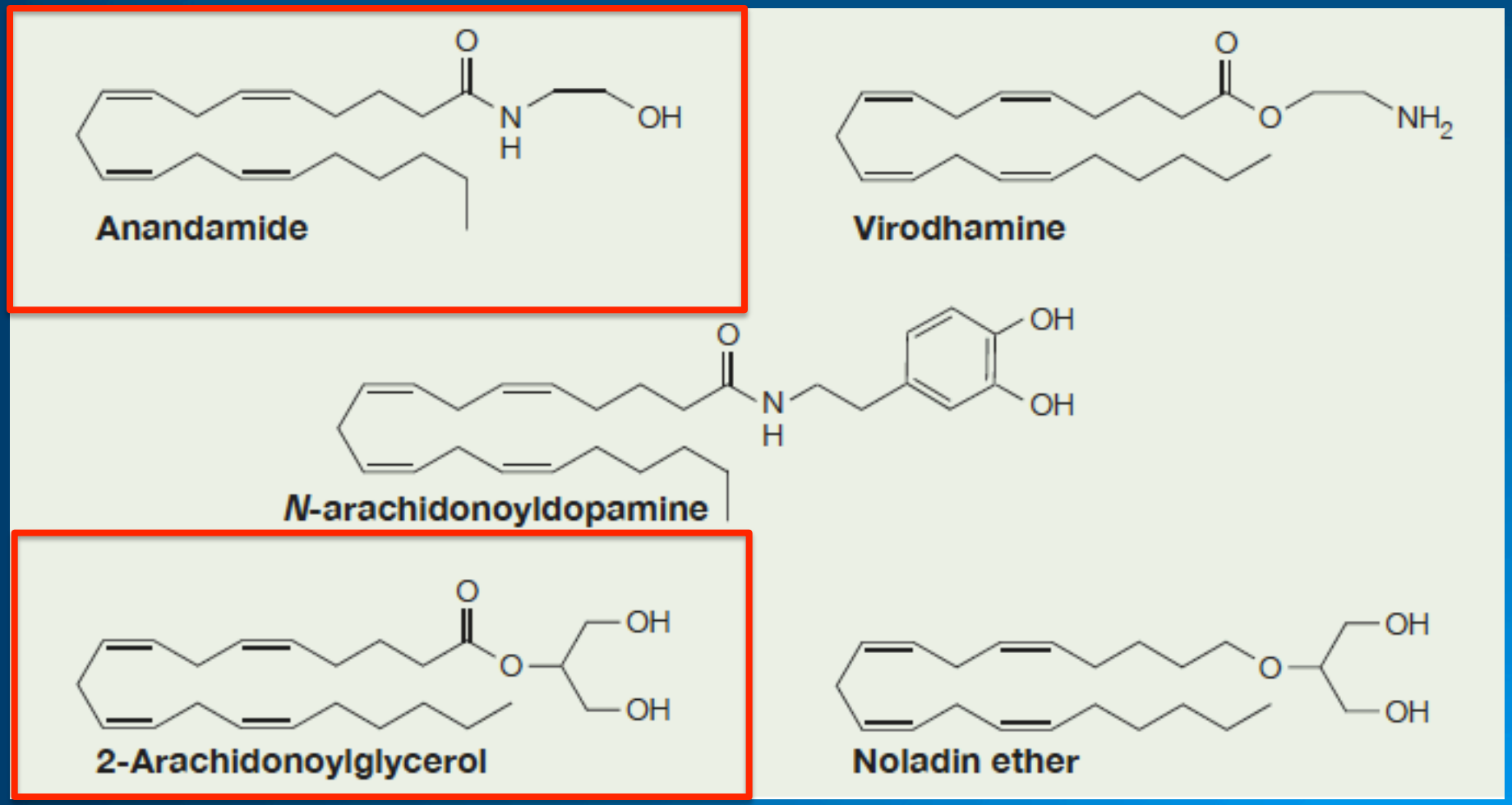
- CNS
- Intestine
- Liver



Distribution of CB1 Receptors



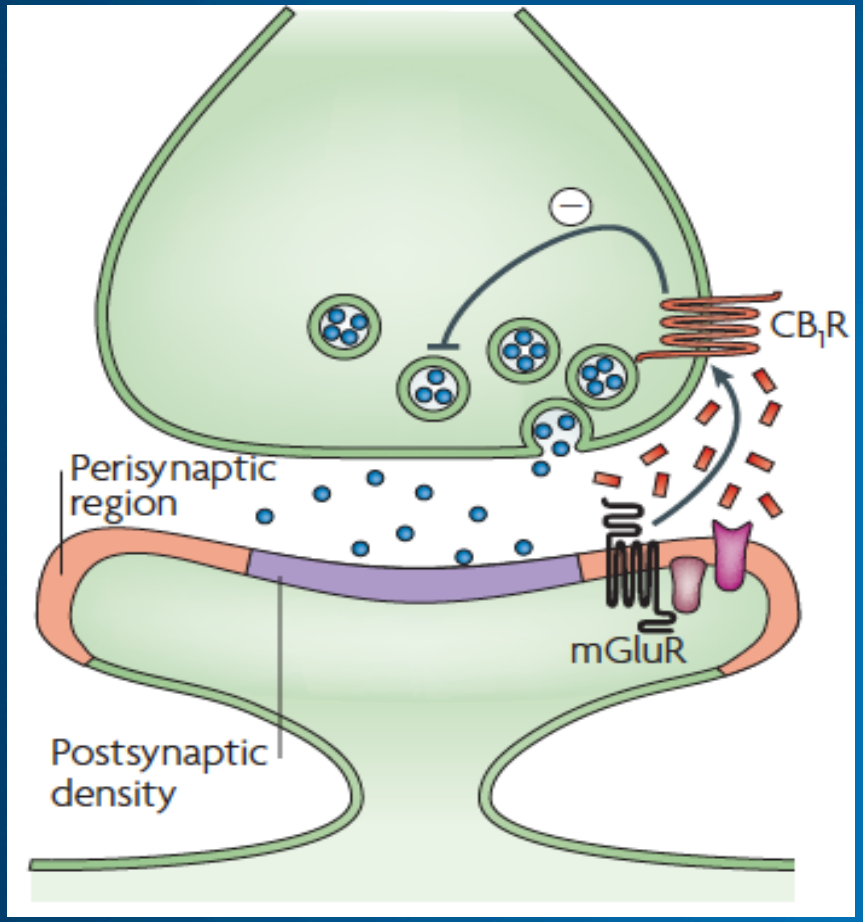
The endogenous cannabinoids

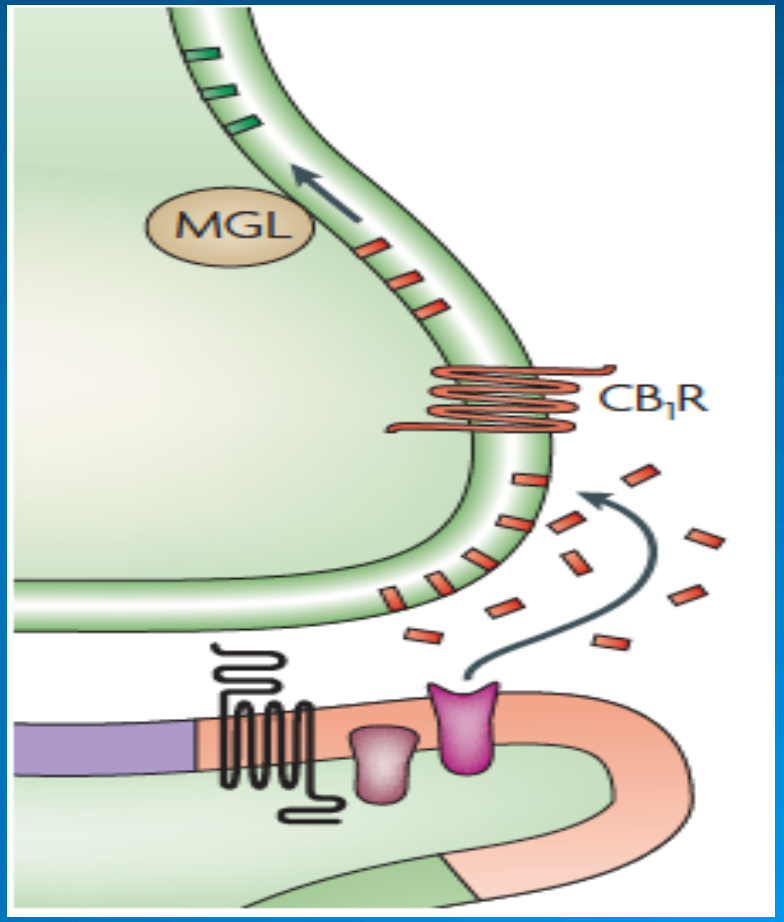


Piomelli, *Nature Rev. Neurosci.*, 2003

"Circuit Breaker" Function of CB Receptors

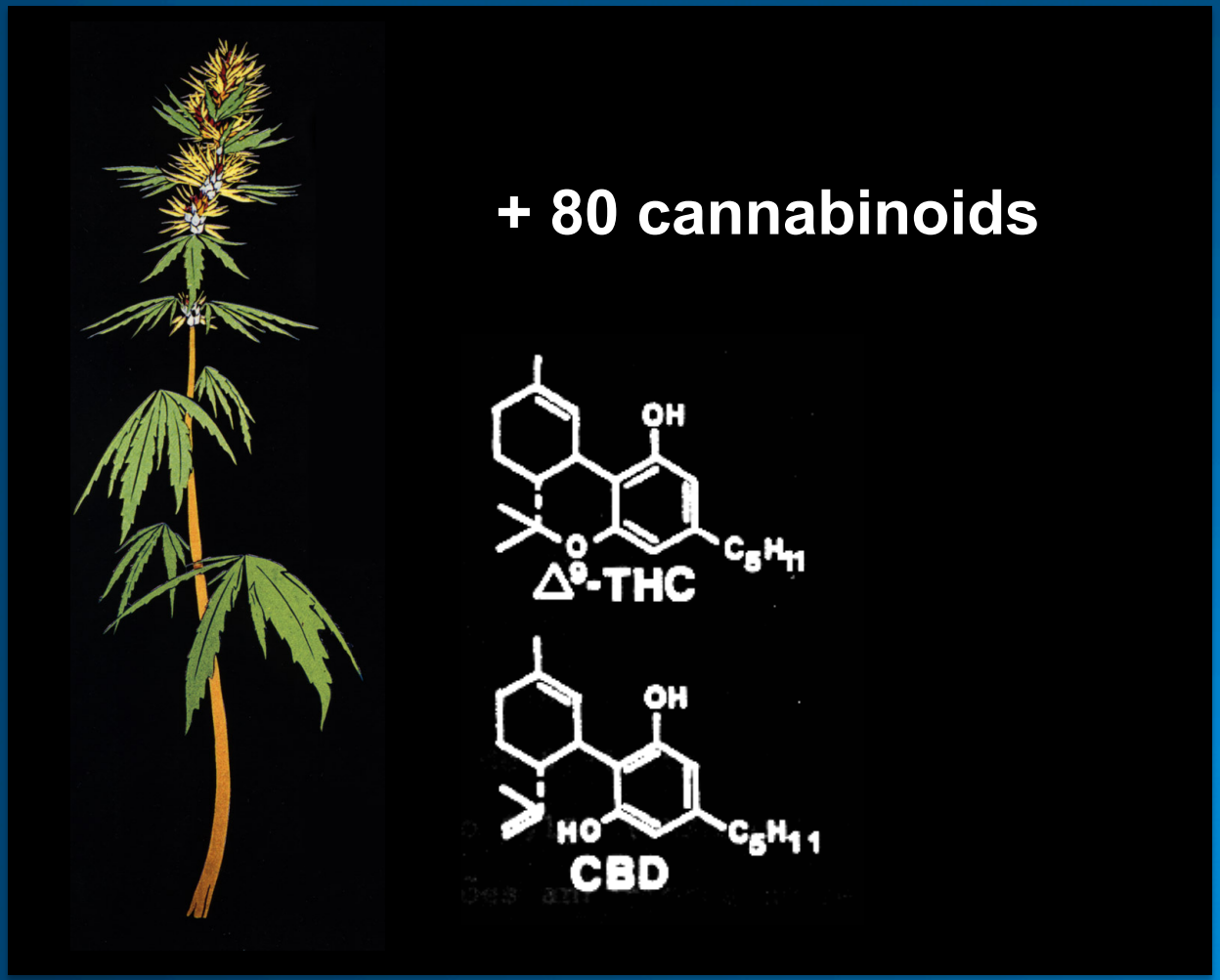
Neurotransmitter (eg., glutamate) action on post synaptic cells triggers them to release endocannabinoids (EC) that act on presynaptic CB receptors to regulate neurotransmission. The EC are then inactivated by FAAH or MGL*





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

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

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

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

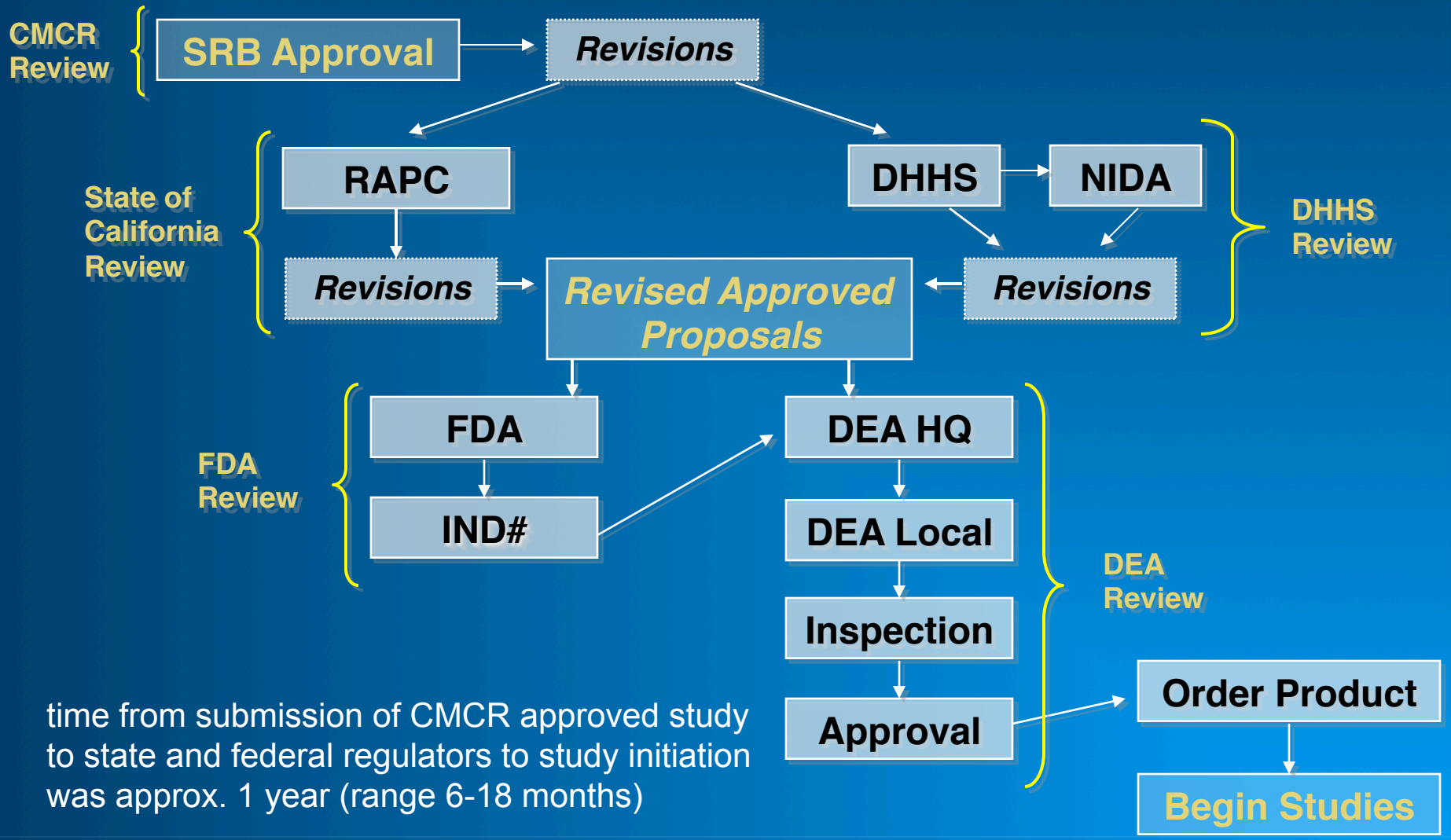
Barth Wilsey, MD, Ron Ellis, MD, PhD, Mark Wallace, MD, Robert Fitzgerald, PhD, Investigators; Ben Gouaux and Jennifer Marquie Beck, Senior Staff

www.cmcr.ucsd.edu

California Events Leading To CMCR

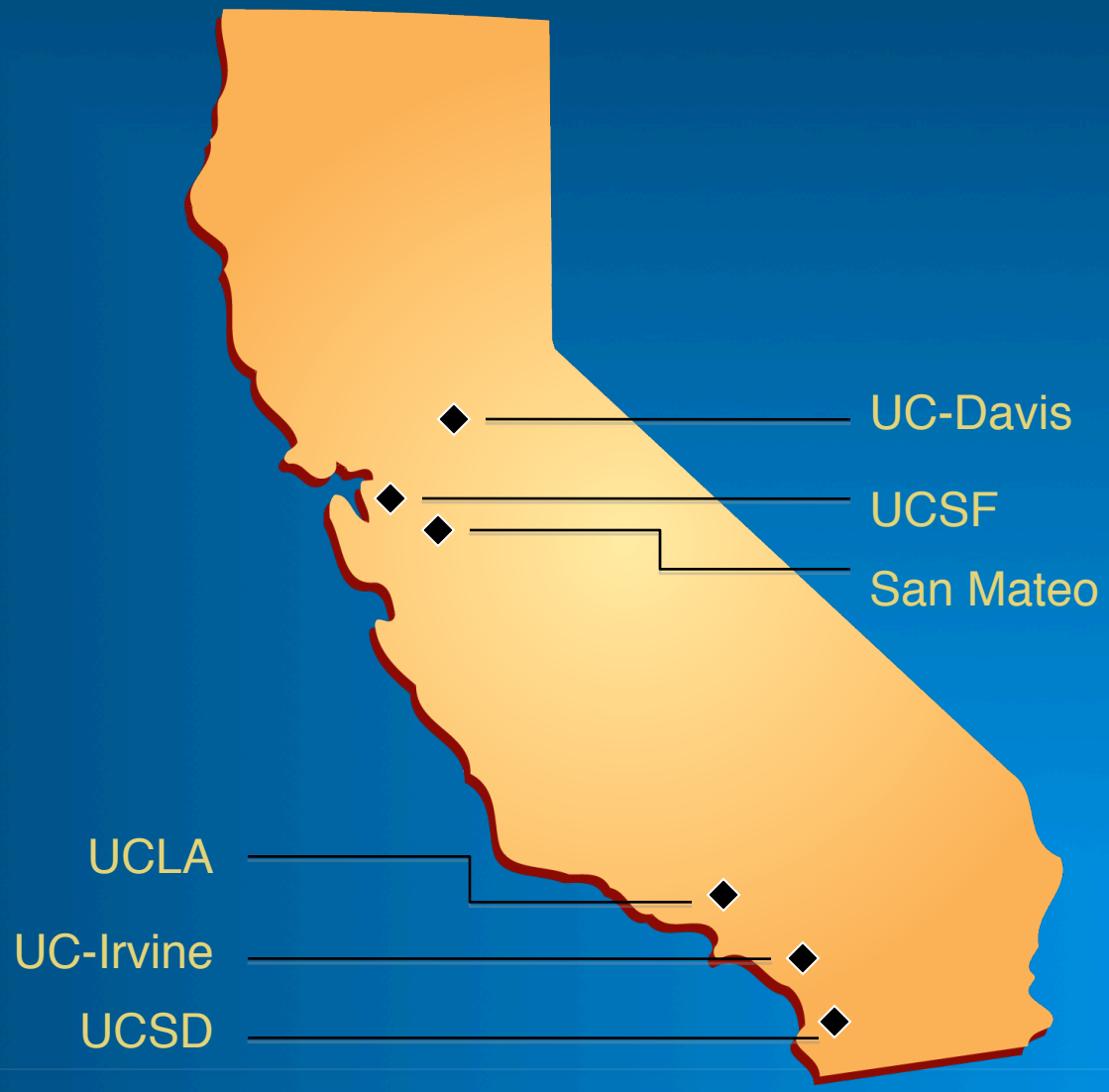
November 1996:	**California Prop 215 passes: Compassionate Use Act**
September 1999:	**Medical Marijuana Research Act of 1999, authored by Senator John Vasconcellos.**
August 2000:	**Center for Medicinal Cannabis Research established at the University of California.**
September 2003:	**Amendment to Medical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

CMCR Regulatory Pathway



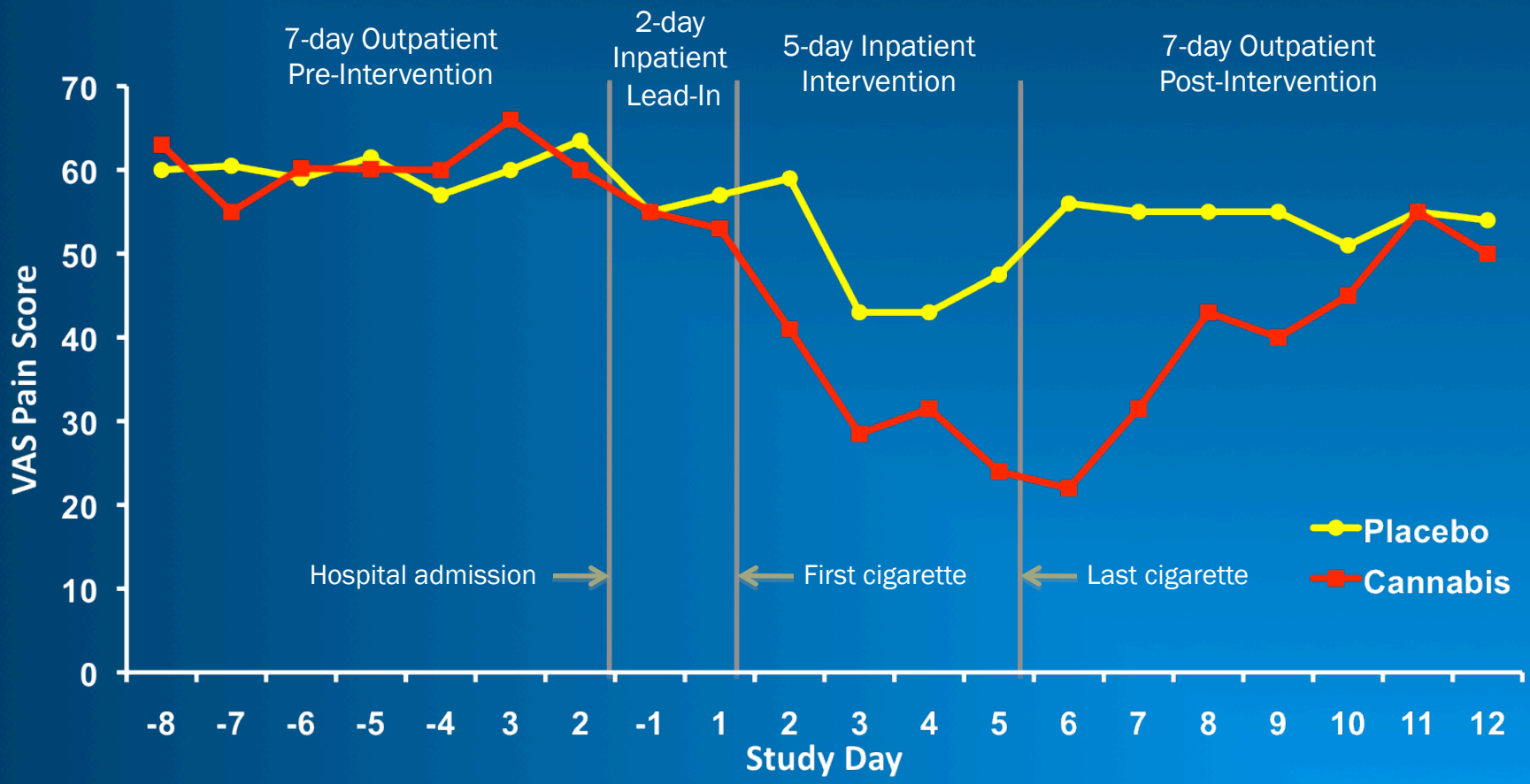
time from submission of CMCR approved study to state and federal regulators to study initiation was approx. 1 year (range 6-18 months)

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
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%	+

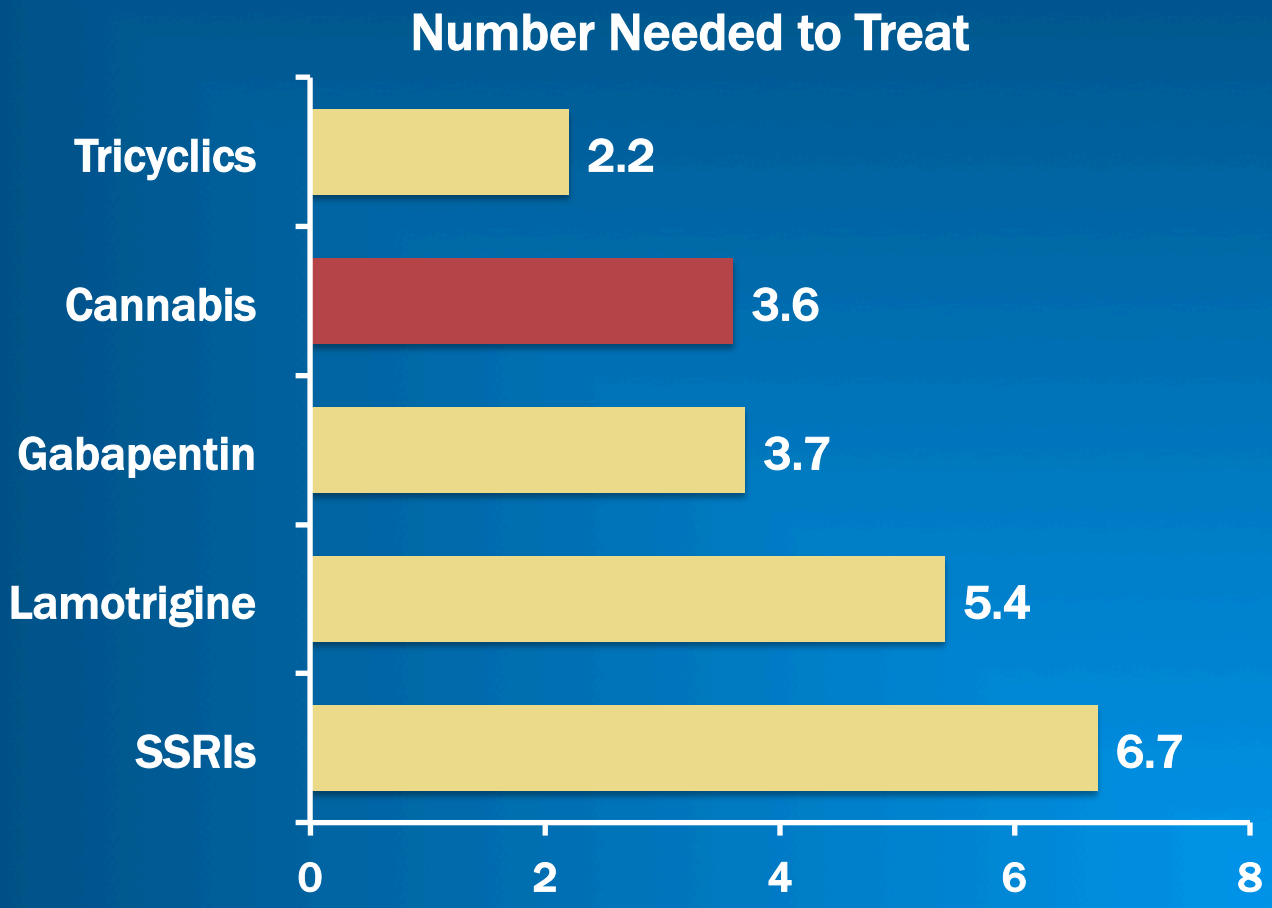
How effective is cannabis relative to other pain medications? Number-Needed-to-Treat

- 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

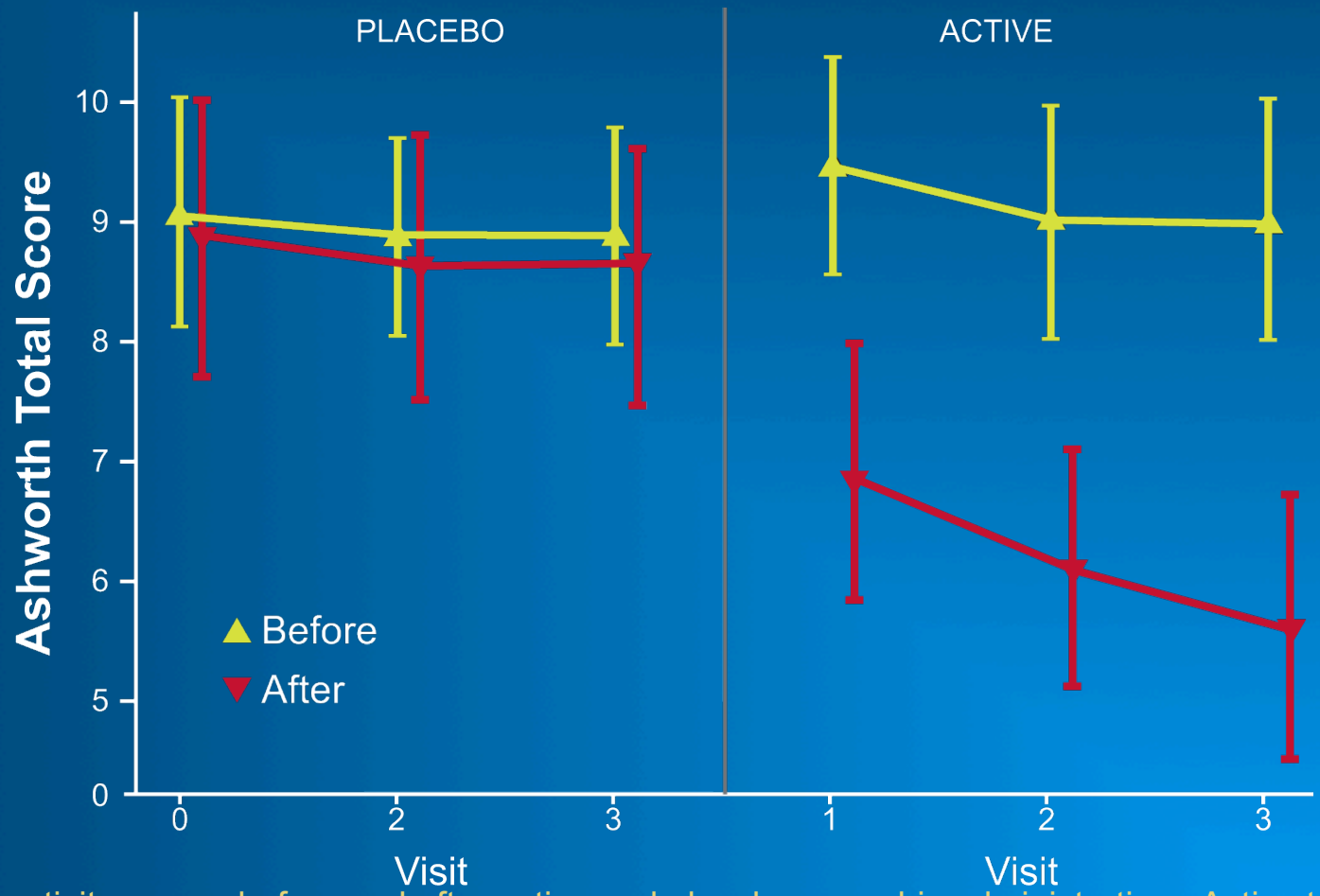
Common Analgesics for Neuropathic Pain



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

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

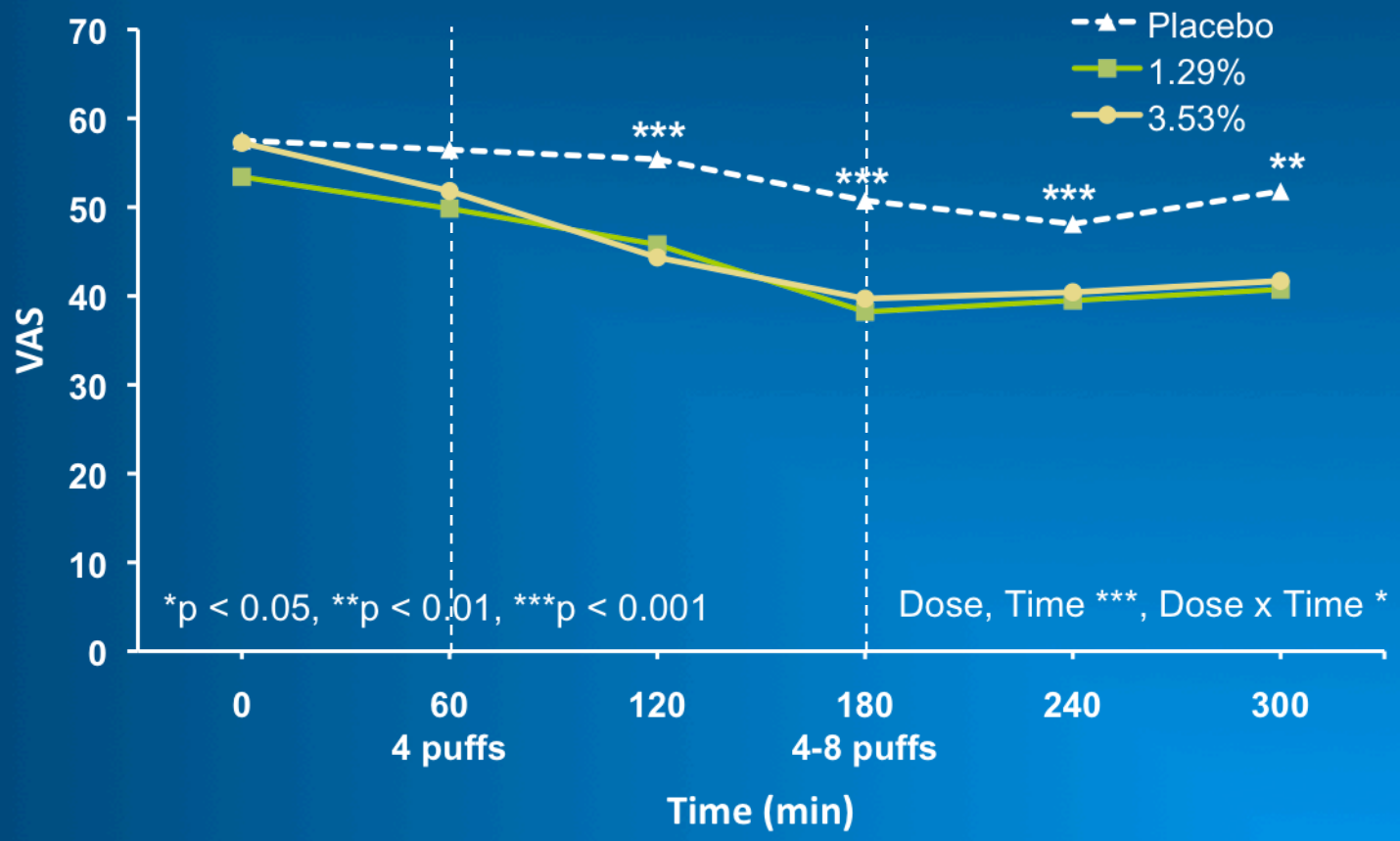
- Safety of combustible material in clinical setting
- Second hand smoke as an irritant, possibly health hazard
- Efficiency and tolerability in smoking naïve
- Availability of cigarettes with standardized dose
- Conflict with anti drug laws
- Possibility of misuse and diversion
- Difficulty in conducting 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

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.

Studies on medicinal cannabis effects: Whiting et al (2015) meta-analysis

# RCTs		# Reports	# Patients
28	Chronic Pain	63	2454
28	Nausea and vomiting due to chemotherapy	37	1772
14	Spasticity due to multiple sclerosis/ paraplegia	33	2280
4	HIV/AIDS	4	255
2	Sleep Disorder	5	54
2	Psychosis	9	91
2	Tourette syndrome	7	36
1	Anxiety disorder	1	24
1	Glaucoma	1	6
0	Depression		

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA.* 313:2456-2473, 2015

Meta-Analysis

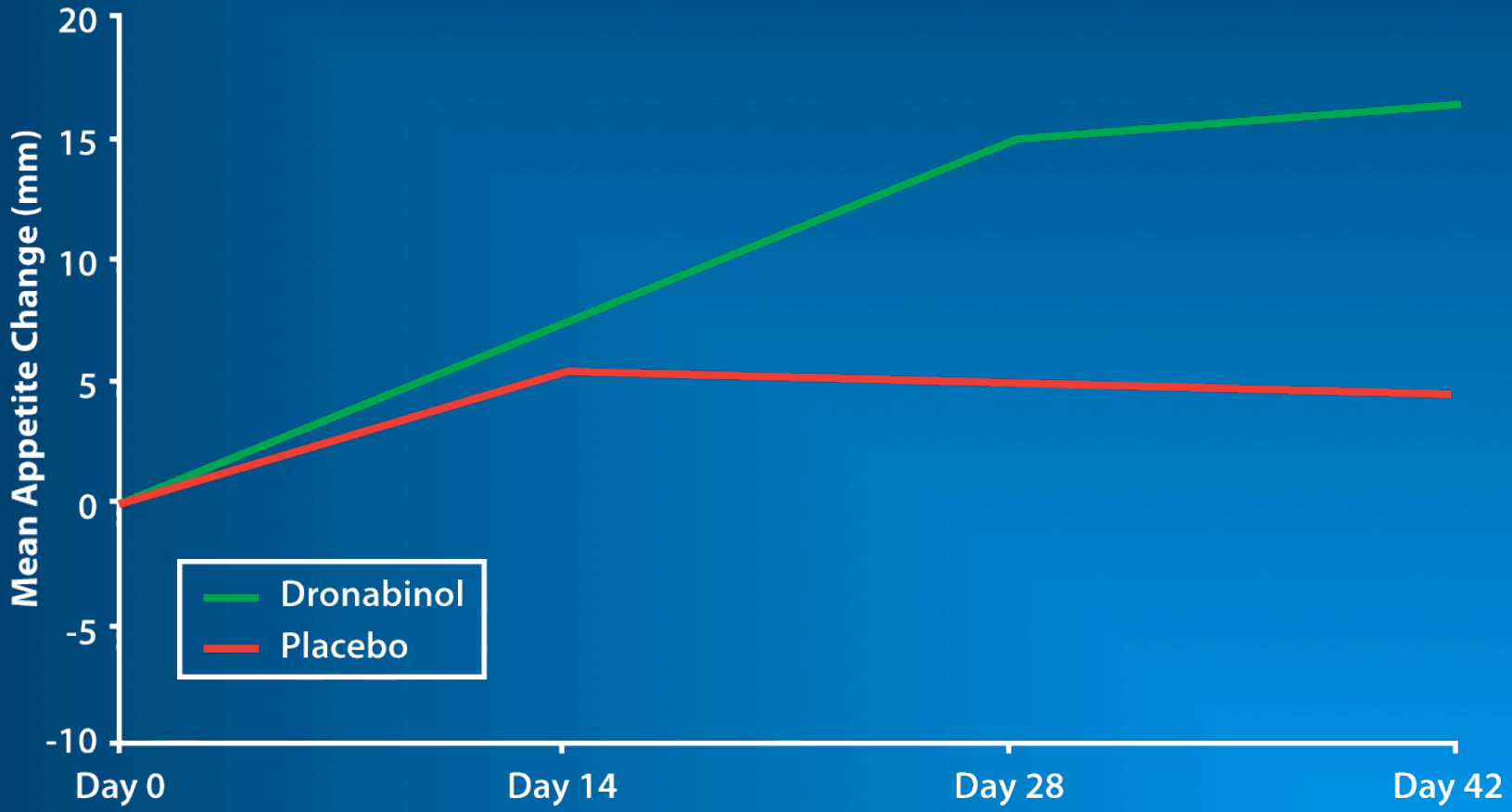
- moderate-quality evidence to support the use of cannabinoids in:
  - » chronic pain
  - » spasticity
- low-quality evidence suggesting that cannabinoids were associated with improvements in:
  - » nausea and vomiting due to chemotherapy
  - » weight gain in HIV infection
  - » sleep disorders
  - » Tourette syndrome

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA.* 313:2456-2473, 2015

Other current or potential cannabinoid modulators

- Agonists
  - » THC/CBD plant extract, eg., Nabiximols)
  - » Synthetic THC (Dronabinol [Marinol] & analogs]: Nabilone [Cesamet]; 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)

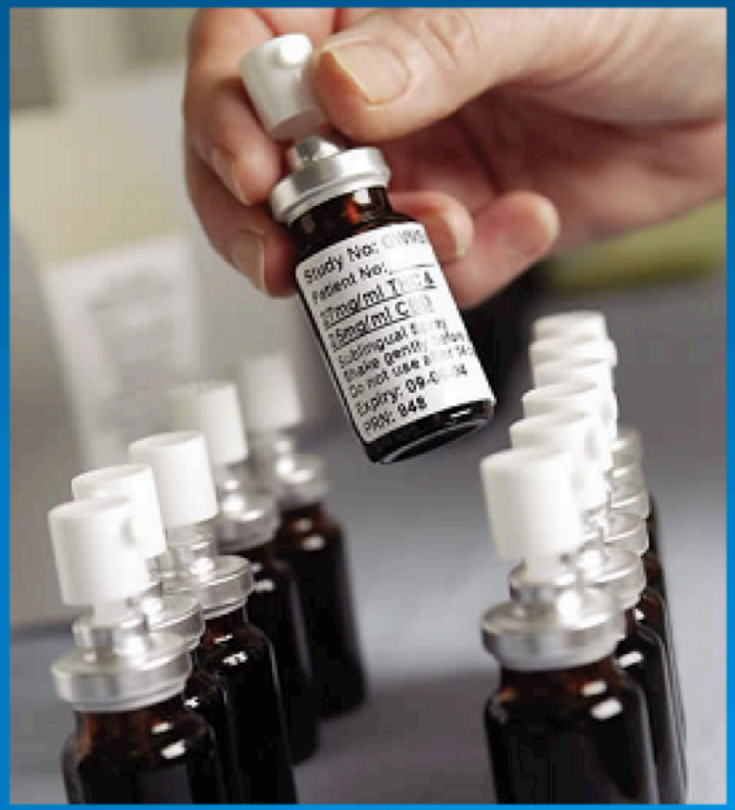
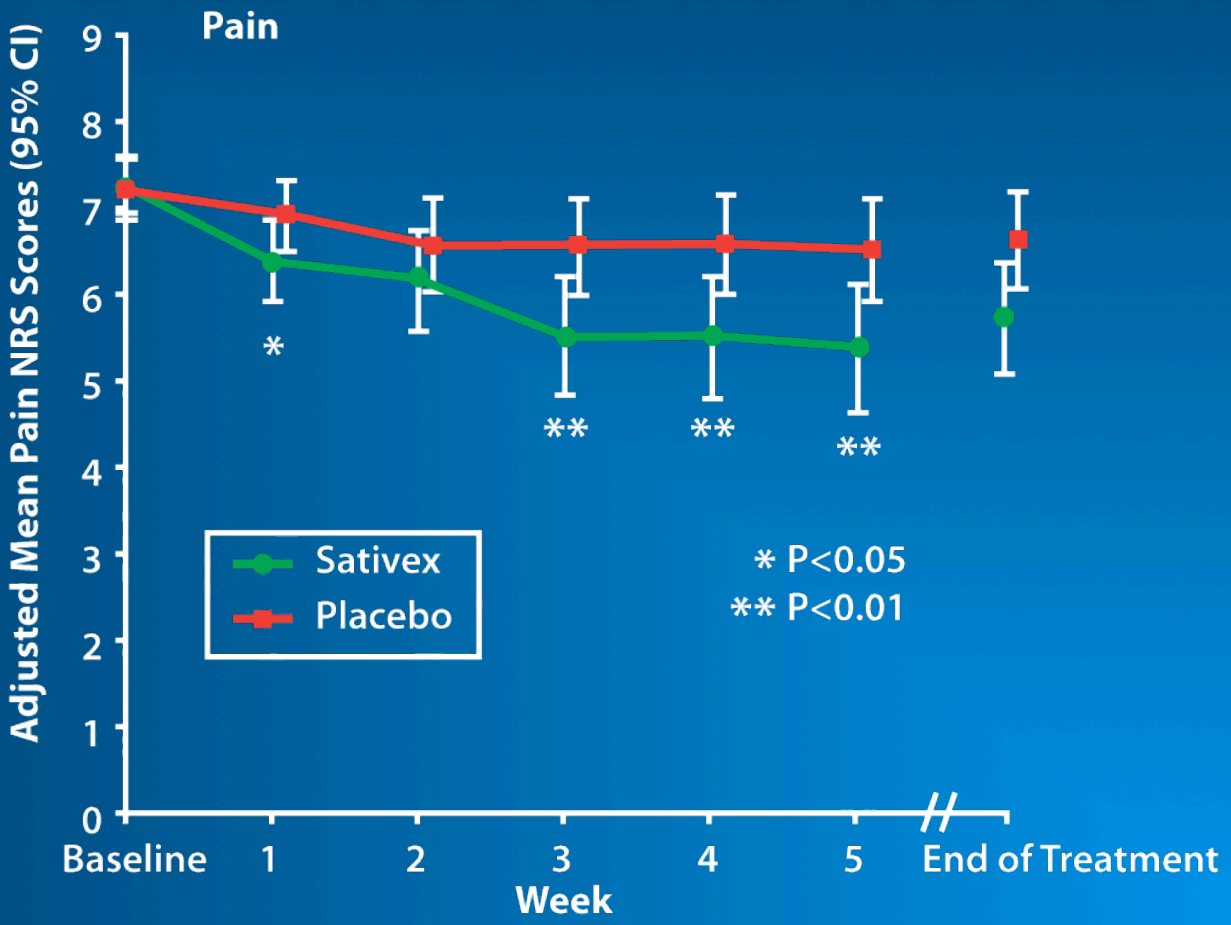


Image courtesy G. Guy, GW Pharmaceuticals

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

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 ∆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: Human Models of Anxiety

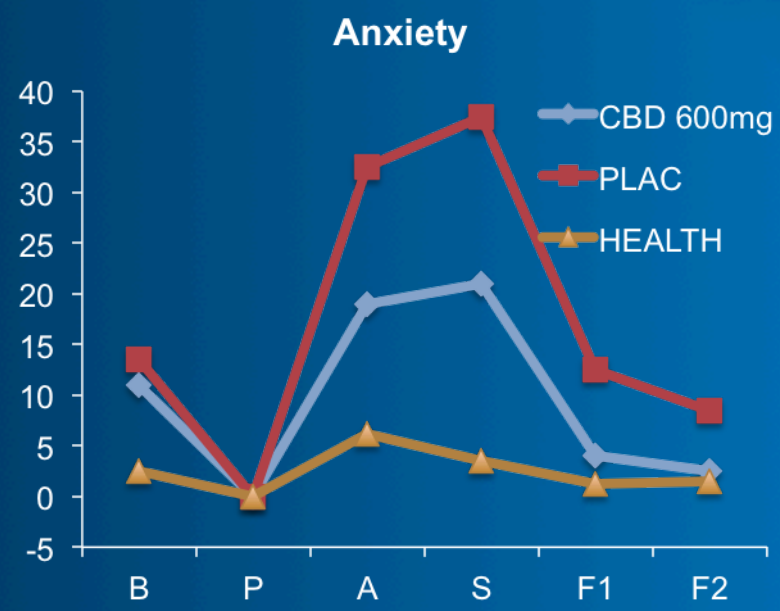
STUDY	MODEL	ANXIOLYTIC EFFECT
Humans		
Zuardi et al. (1982)	Decreased STAI scores elevation induced by THC (healthy volunteers)	+
Zuardi et al. (1993)	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	+
Crippa et al. (2004)	Decreased VAS factor anxiety scores before SPECT 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)	+

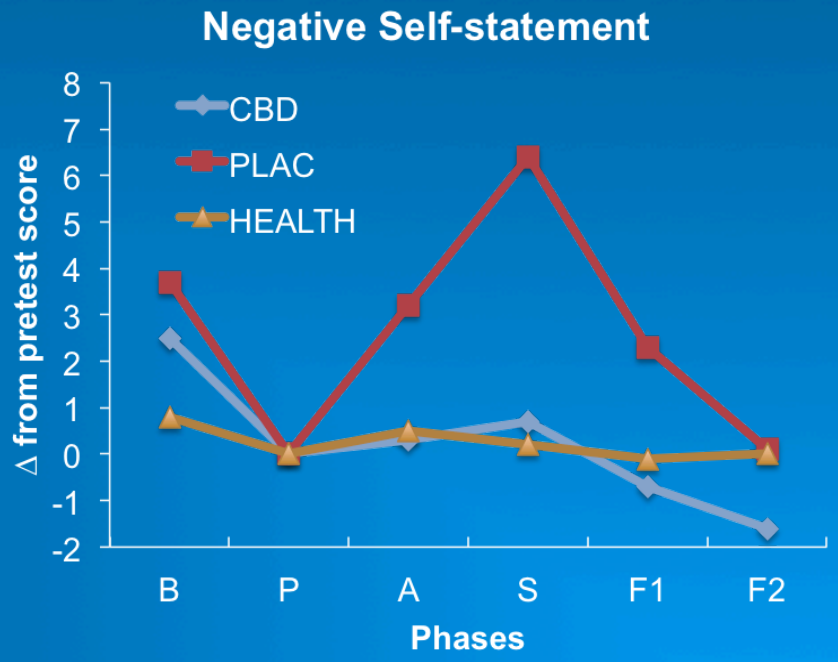
Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

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

Neuropsychopharmacology (2011), 1–8

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]





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: Seizure Reduction in Epilepsy

STUDY	MODEL	EFFECT
Human		
Porter, et al. (2013)	N=19, children with treatment resistant epilepsy, survey results	+
Trembly, et al. (1990)	N=12, 300mg cannabidiol/placebo	-
Ames, et al. (1985)	N=12, uncontrolled seizures, 200-300mg cannabidiol/placebo daily	-
Cunha, et al. (1980)	N=15, temporal lobe epilepsy, 200-300mg cannabidiol/placebo daily	+
Mechoulam, et al. (1978)	N=9, temporal lobe epilepsy, 200mg cannabidiol/placebo	+
Pre-Clinical		
Shirazi-zand, et al (2013)	Pentylenetetrazol, electroshock-induced seizures	+
Jones, et al (2012)	Intraventricular penicillin, pilocarpine-induced seizures	+
Jones, et al (2010)	Pentylenetetrazol-induced seizures, epileptiform activity in hippocampal tissue	+
Consroe, et al (1982)	Bicuculline, picrotoxin, 3-mercaptopropionic acid, pentylenetetrazol, isonicotinic acid hydrazide, electroshock induced seizures	+
Consroe, et al (1982)	Seizures induced by strychnine sulphate	-
Izquierdo, et al (1978)	Convulsant hippocampal discharges	+
Consroe, et al (1977)	Electroshock-induced seizure	+
Turkanis, et al (1974)	Electroshock-induced seizure	+
Carlini, et al (1973)	Leptazol-induced seizures	+

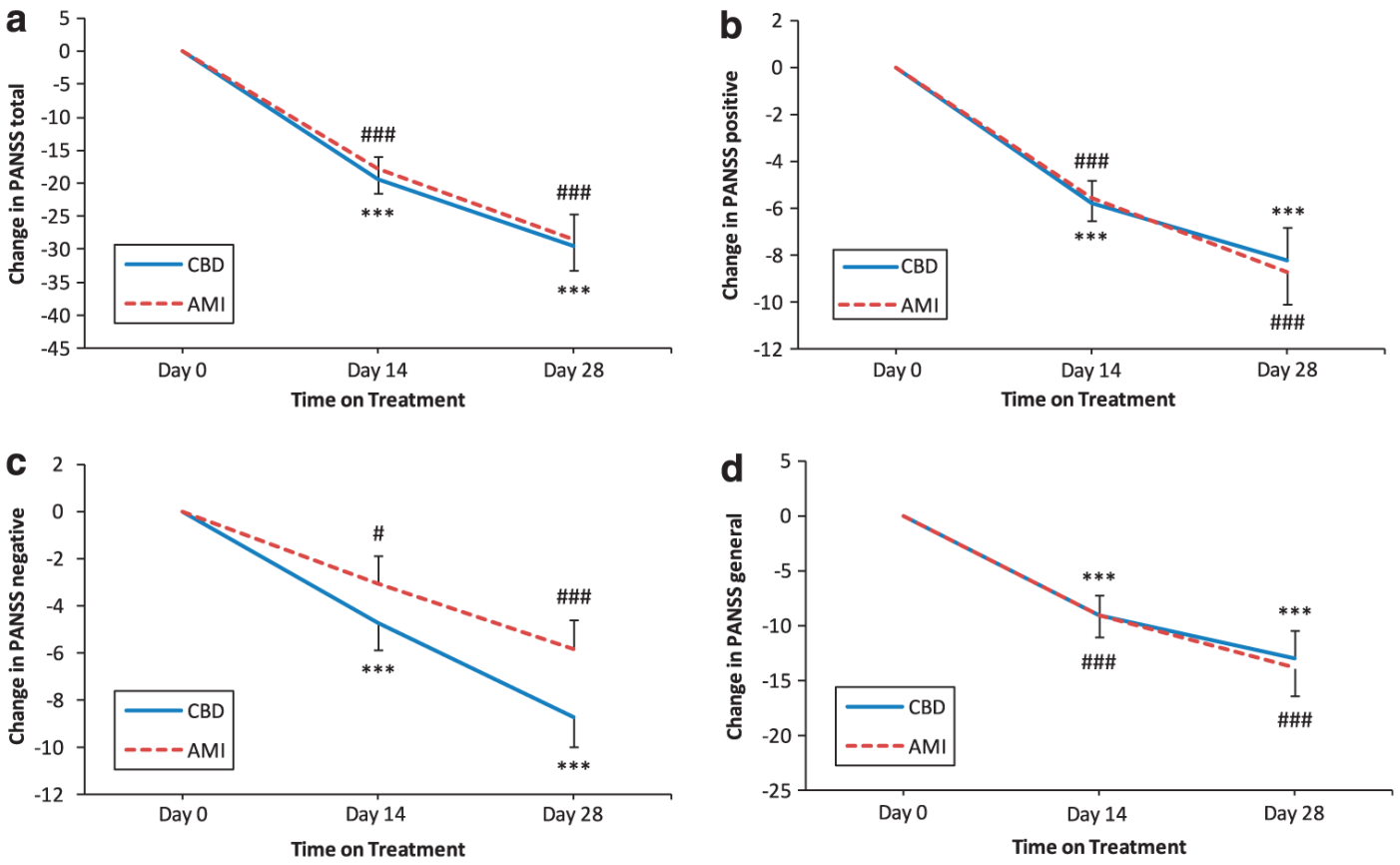
Sources: Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2014 Mar 5;3:CD009270.
Dos Santos RG, et al. Phytocannabinoids and epilepsy. J Clin Pharm Ther. 2015 Apr;40(2):135-43.

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

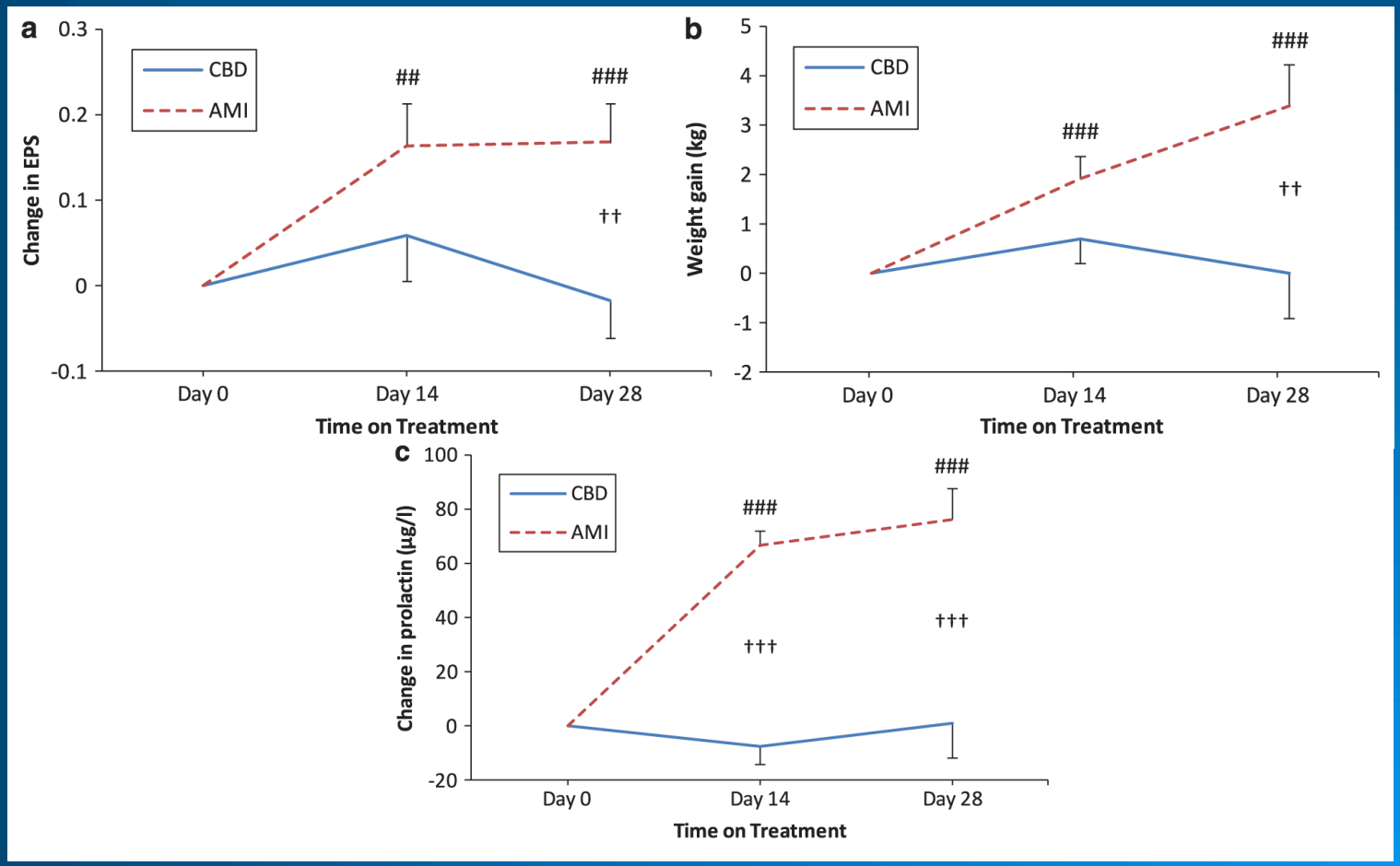
Cannabidiol improves positive and negative symptoms of schizophrenia:

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



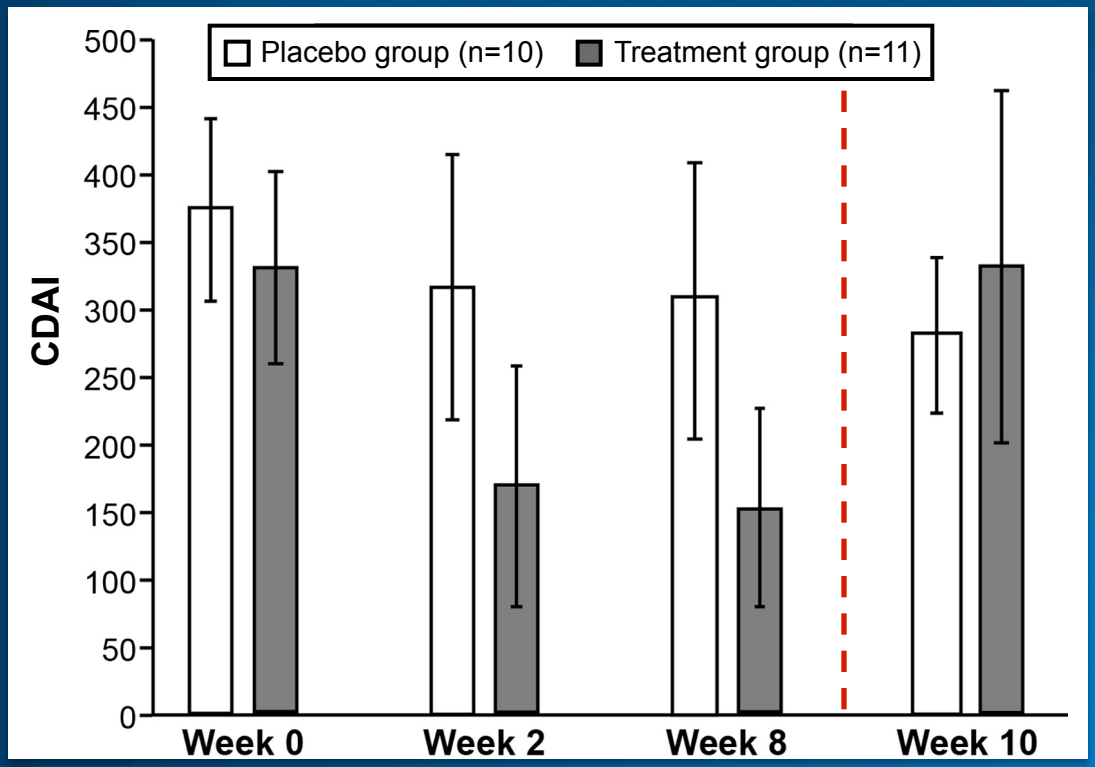
Leweke FM, Transl Psychiatry. 2012 Mar 20;2:e94.

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

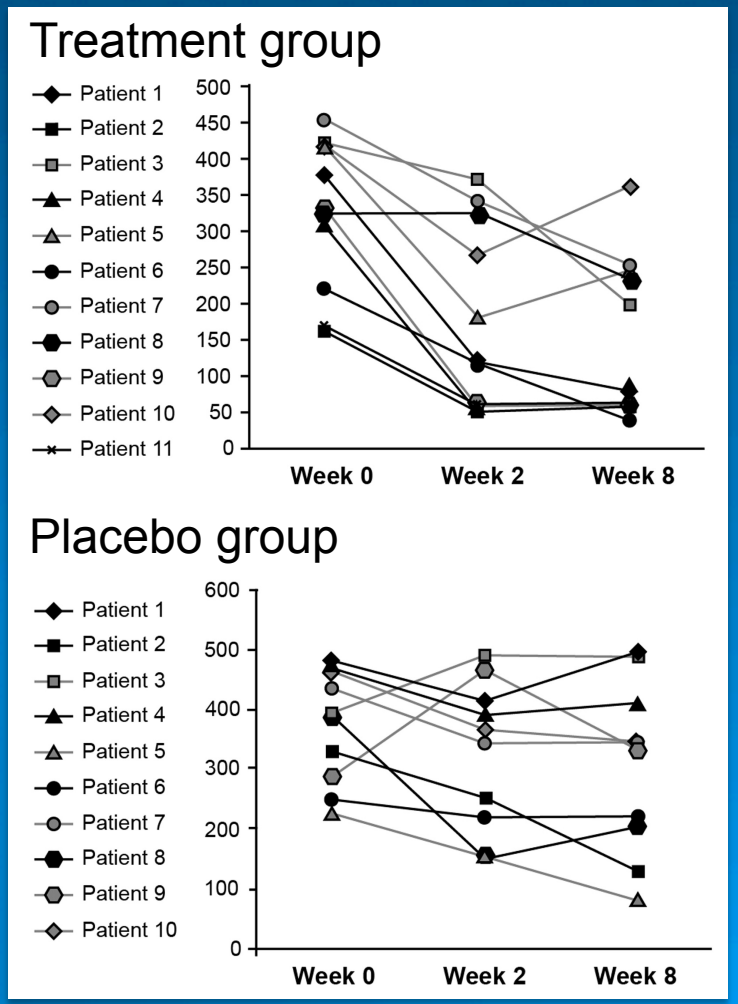


Leweke FM, Transl Psychiatry. 2012 Mar 20;2:e94.

Cannabis Might Induce a Clinical Response in Patients With Crohn's Disease

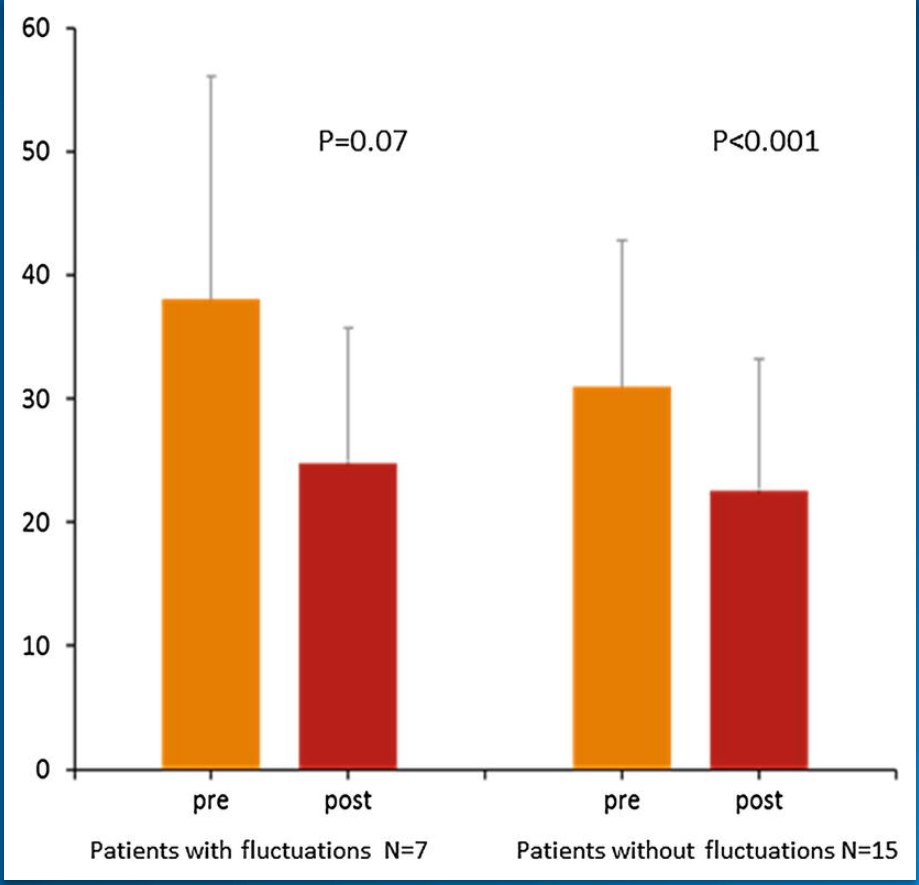


500mg cannabis (23% THC) x2 daily
8 weeks treatment, 2 weeks washout



Source: Naftali T, et al. Clin Gastroenterol Hepatol. 2013 Oct;11(10):1276-1280.e1. doi: 10.1016/j.cgh.2013.04.034. Epub 2013 May 4.

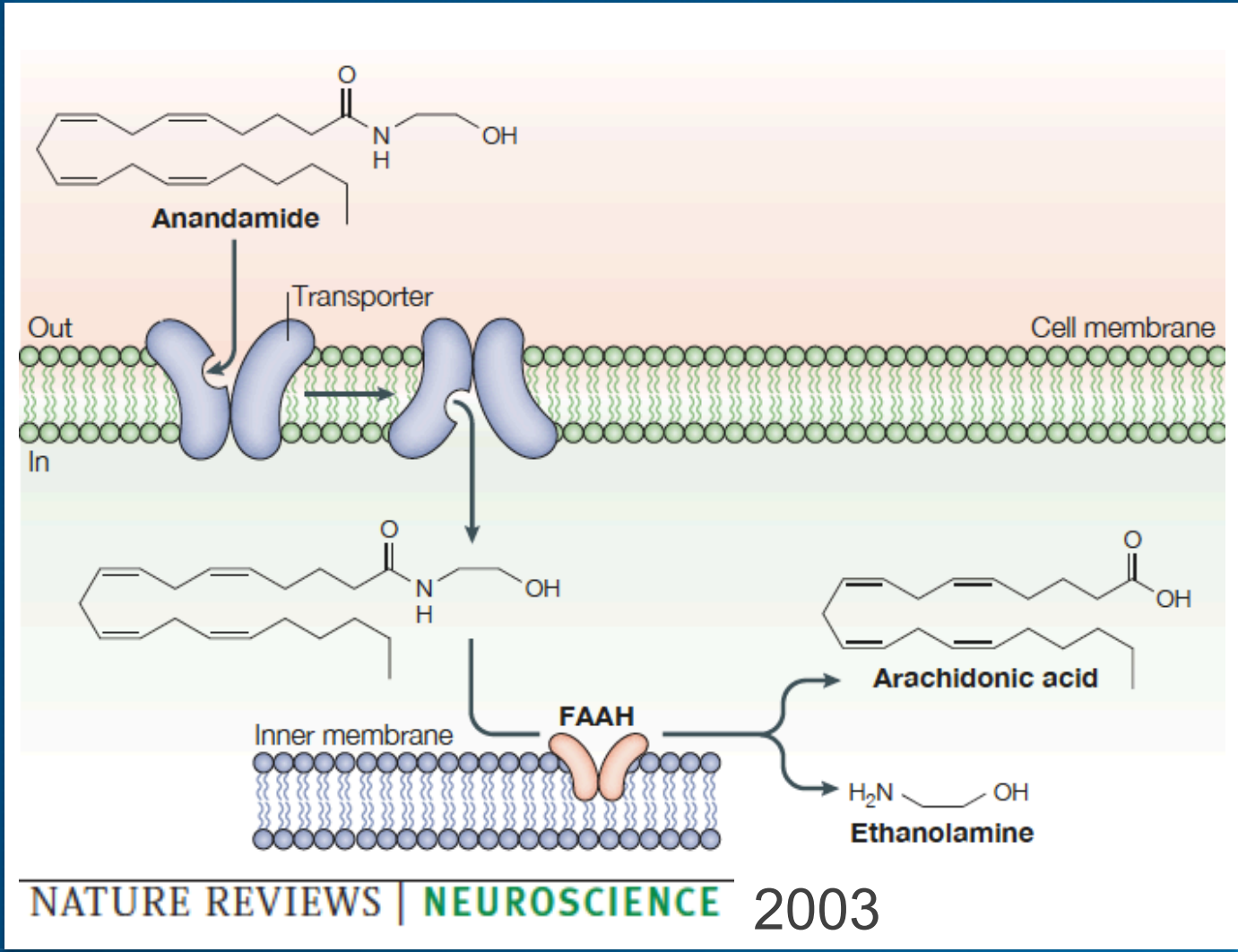
Smoked Cannabis Treatment for Motor and Non–Motor Symptoms of Parkinson Disease



Pre- and Post-treatment motor UPDRS score in 22 patients with and without response fluctuations 30 minutes after smoking 500mg cannabis.

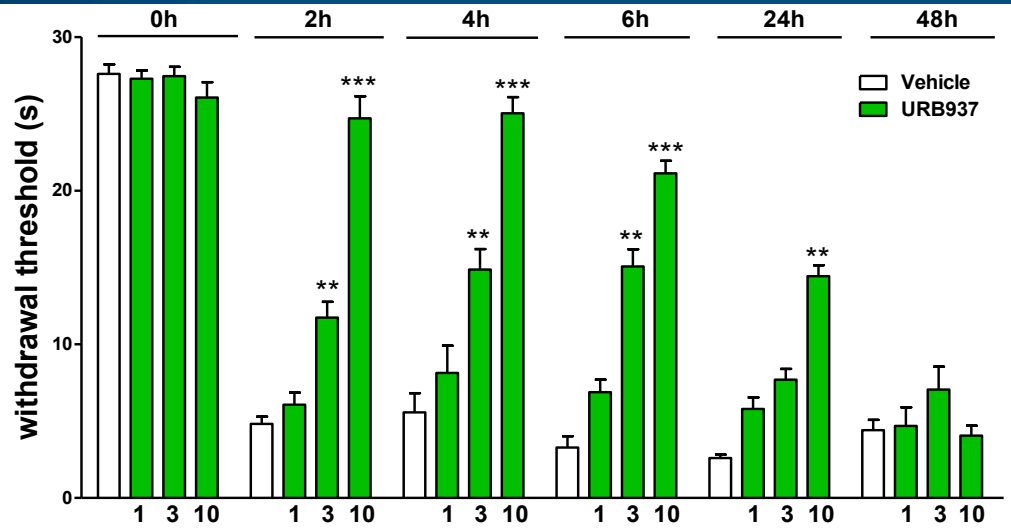
Source: Lotan I, Treves TA, Roditi Y, Djaldetti R. Clin Neuropharmacol. 2014 Mar-Apr;37(2):41-4.

FAAH inhibitors as therapeutic agents?



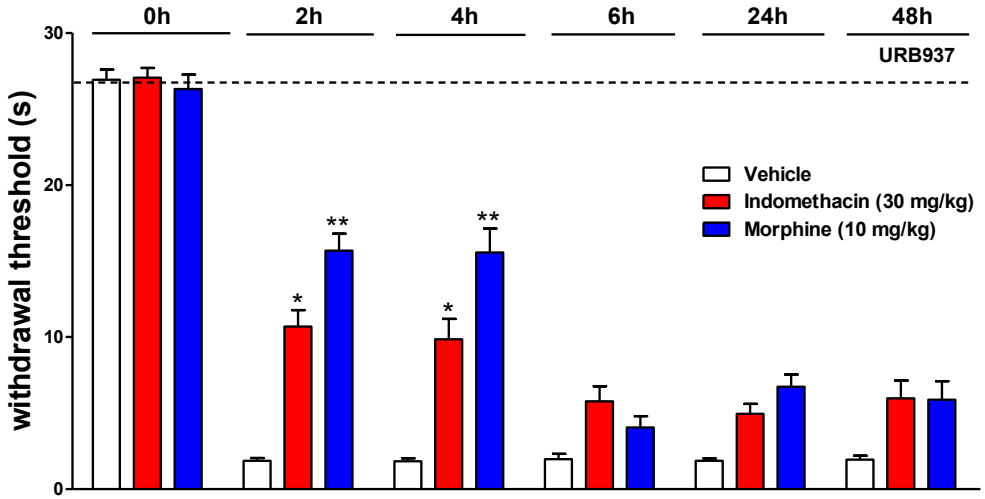
Courtesy D.Piomelli, UCI

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, and extracts containing THC/CBD mix probably efficacious in neuropathic pain and spasticity from MS
- Very early data on possible efficacy of cannabis in Crohn's Disease, Parkinson's. Confirmation needed.
- 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, psychosis, and there are case reports on benefits for intractable epilepsy
- FAAH inhibitors promising in animal models of chronic pain
- Anti-inflammatory actions of cannabinoids deserve further exploration

How do we move forward? Let's clear away the smoke and get past the heat and into the scientific light!

- We need to separate out discourse on medicinal cannabis from that of broader social policy on recreational use [as we have done with other potentially abusable substances]
- We need serious larger scale clinical trials on cannabis, administered via several routes, and specific constituents, plus their combinations.
- Governments are the logical sponsors of such trials, as there is not an immediate incentive for pharma to be involved. Tax dollars collected from cannabis sales can support such studies, which should also focus on longer term benefits, and possible individual toxicity, and broader social harm.
- In the USA and other jurisdictions regulatory authorities need to "re-schedule" cannabis away from the most restrictive schedule, recognizing that harm potential is modest, and there are likely medical benefits. This will facilitate medical research
- If cannabis is to be used as a medicine, it needs to be capable of MD prescription, in accordance with agreed protocols, and subject to availability from trusted sources that confirm potency and purity, and regulated dispensing [eg., pharmacies; regulated dispensaries]

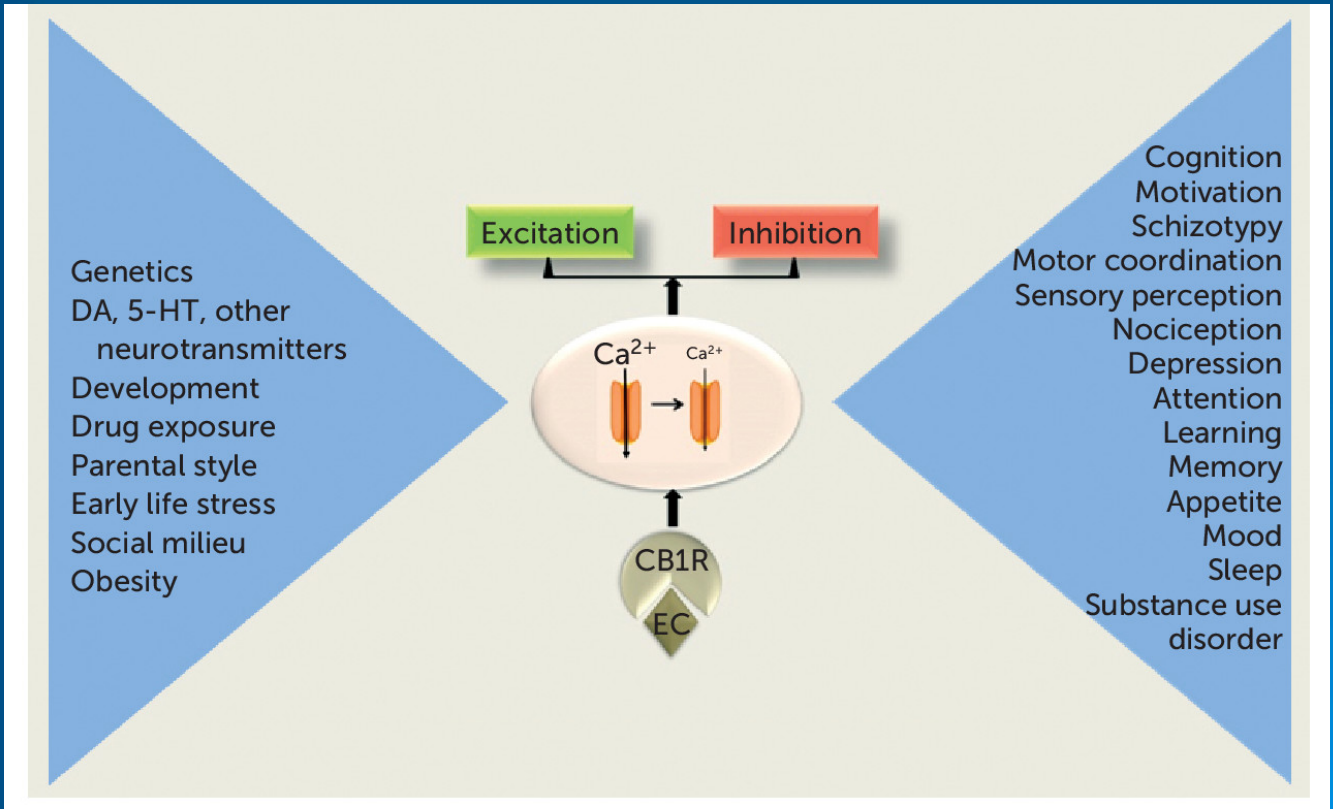
Marijuana as Medicine: Can we see past the smoke?

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

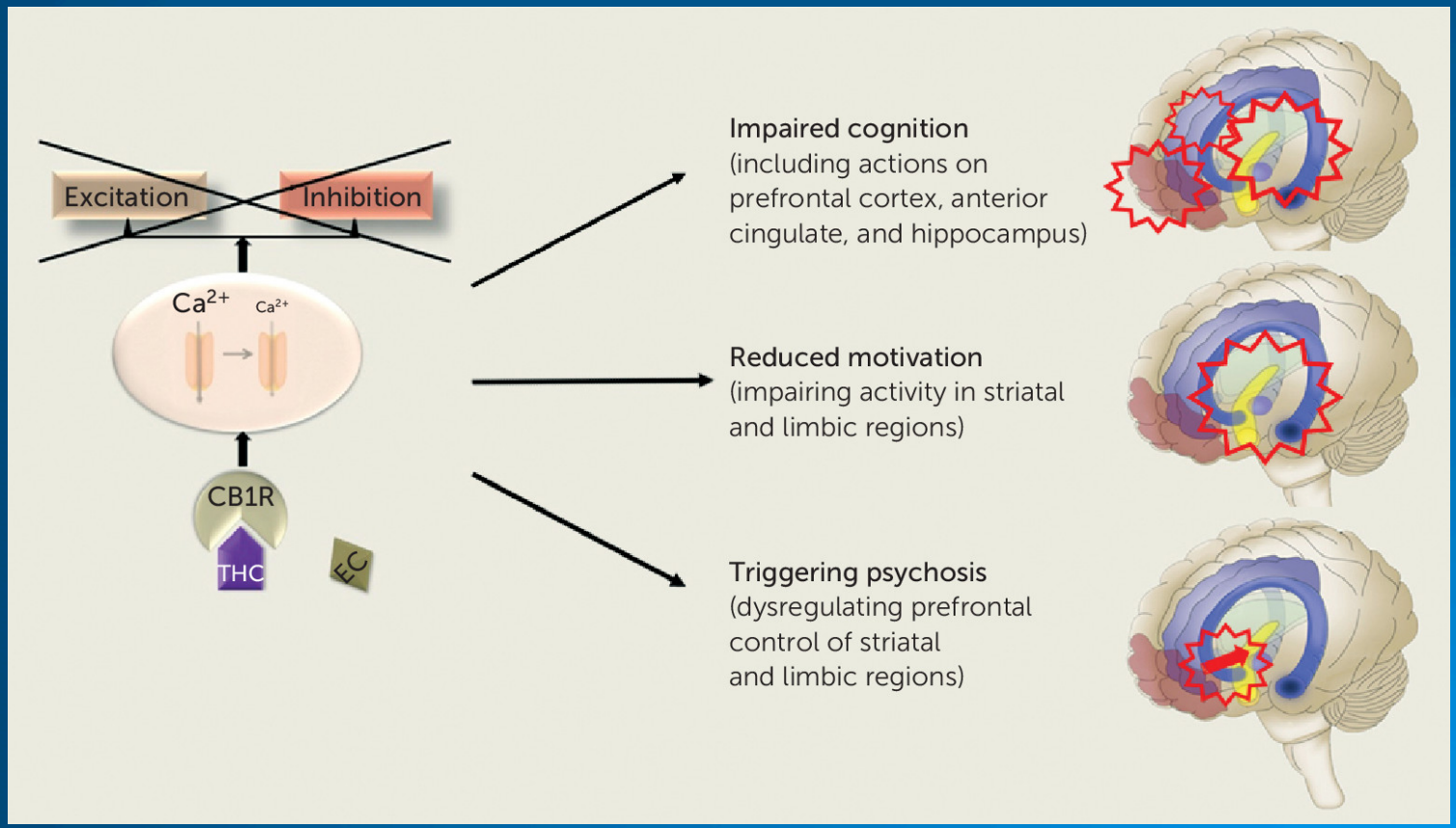
www.cmcr.ucsd.edu

Actions of the Endocannabinoid System



Compton W and Baler R. Am J Psychiatry, 2016, 173:551-553.

Potential effect of exogenous cannabinoids, eg., THC, on endocannabinoid system



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