Medicinal Cannabis

Medical Board of California

April 20, 2018

Igor Grant, M.D.,

Director

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

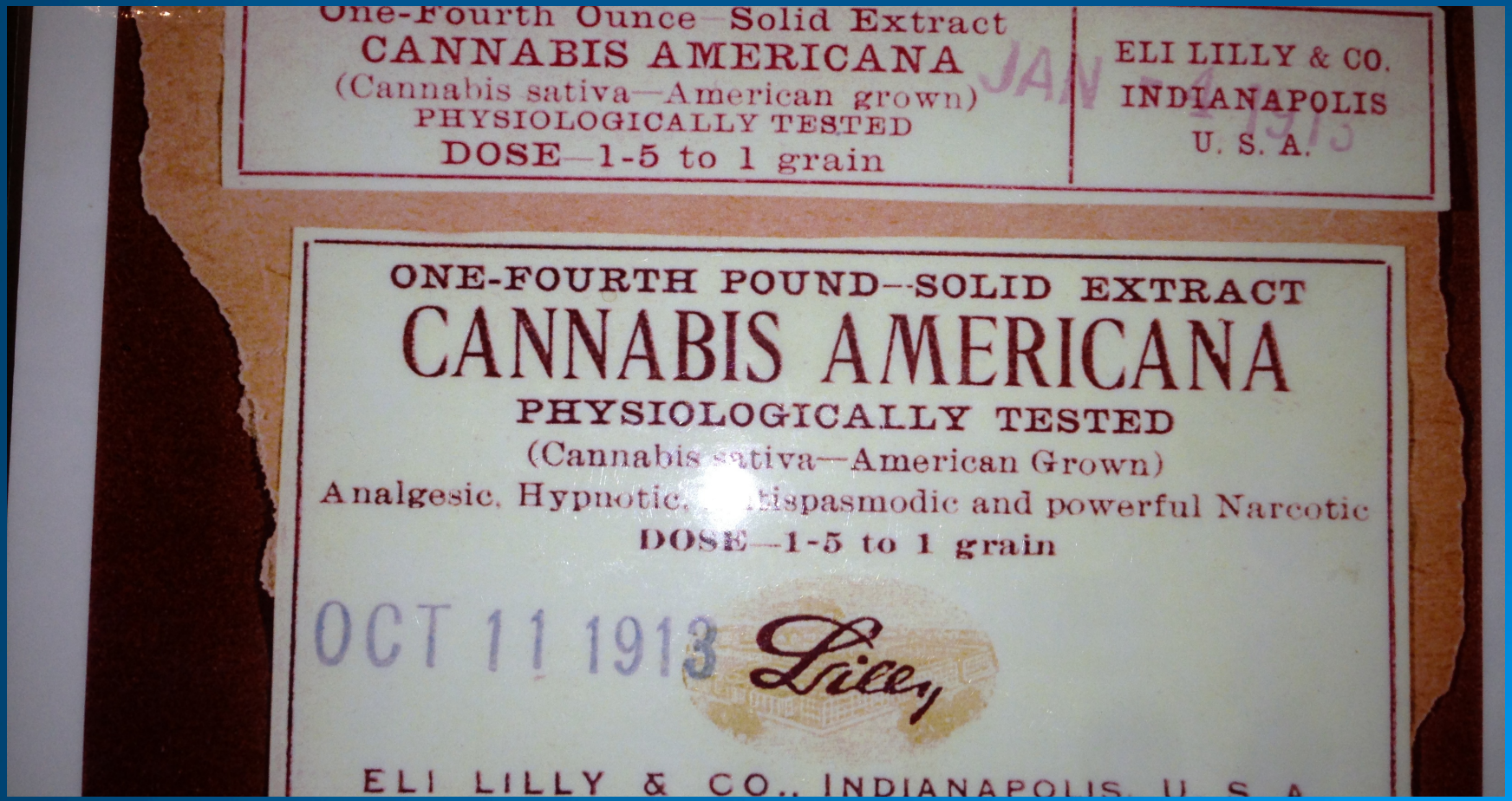
Cannabis and its derivatives

Marijuana

Hashish

Courtesy D. Piomelli, UCI

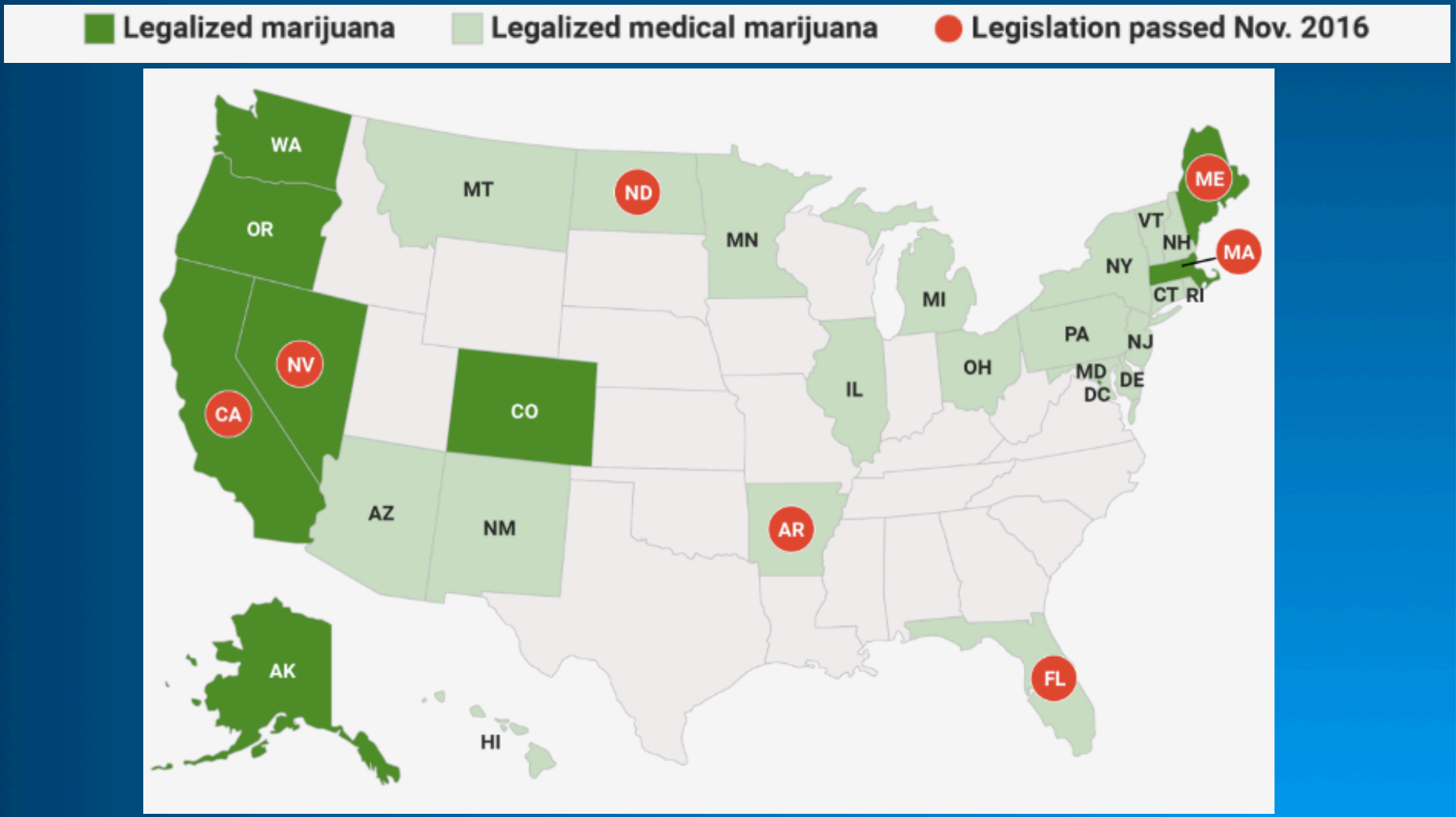
Cannabis: not a new medicine



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)

States With Medical Marijuana Laws; States Where Cannabis is Legal

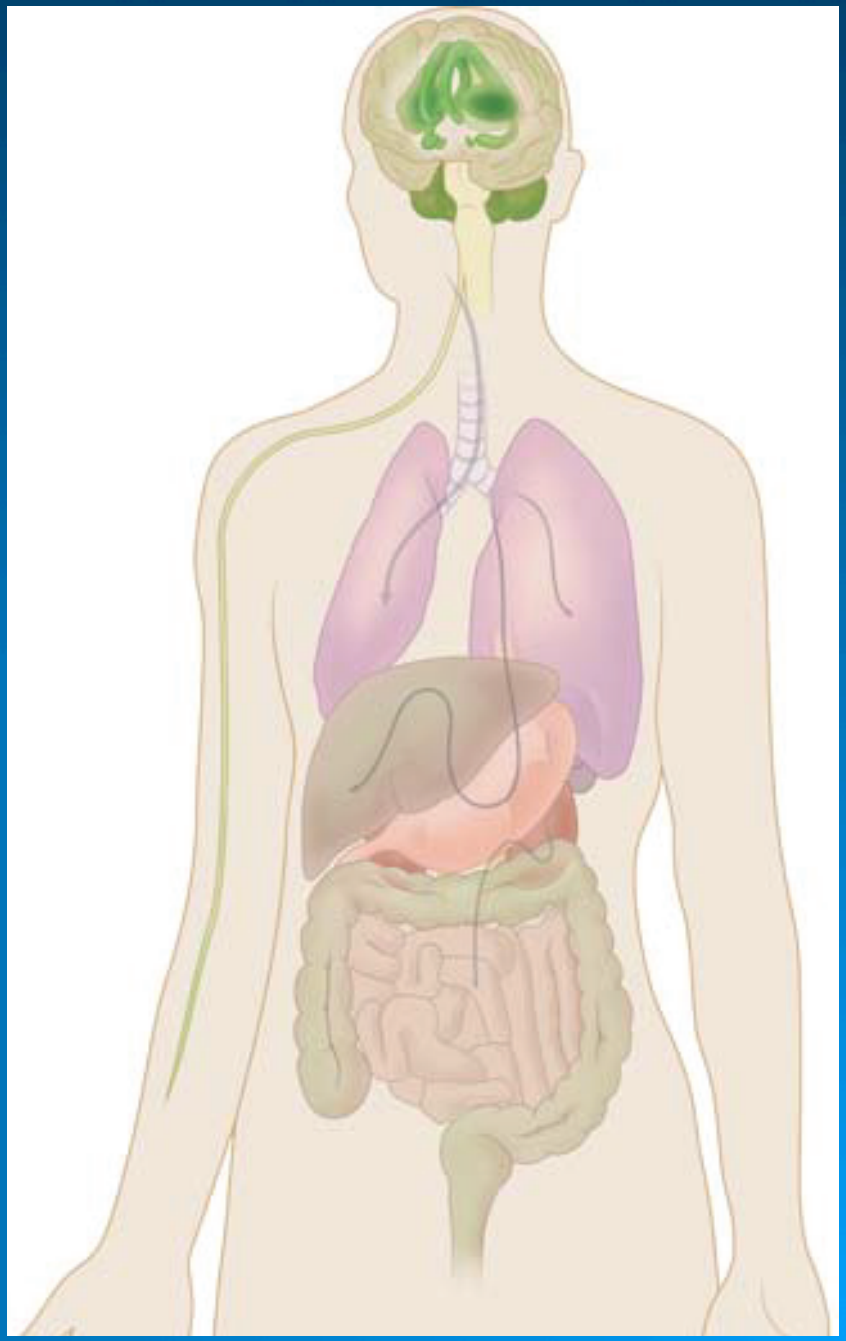


Sources: Politico; Reuters. Courtesy Ziva Cooper; **Picture:** Business Insider

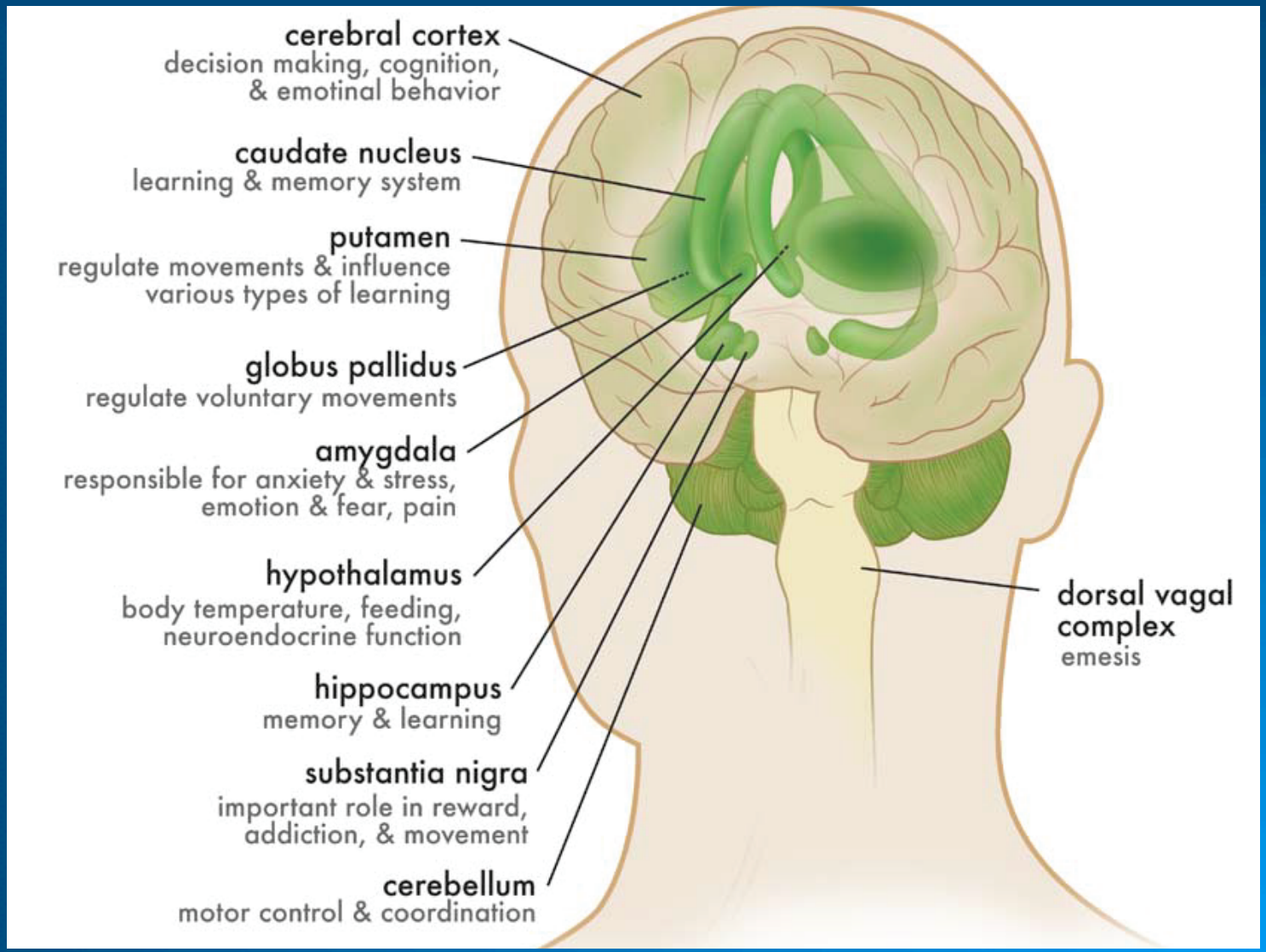
Distribution of CB1 Receptors

Green shading indicates distribution of cannabinoid receptors in the body

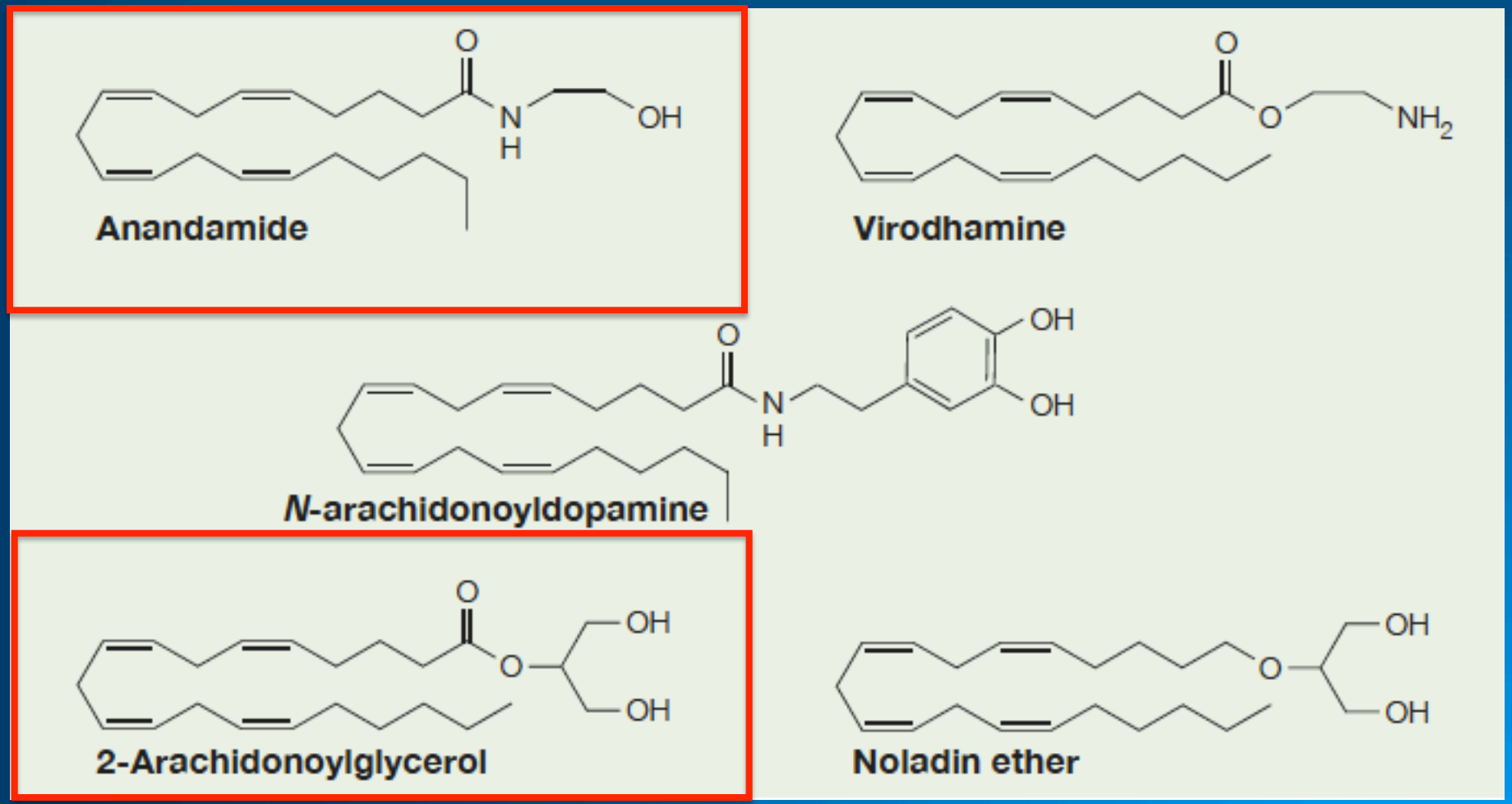
- CNS
- Intestine
- Liver



Distribution of CB1 Receptors



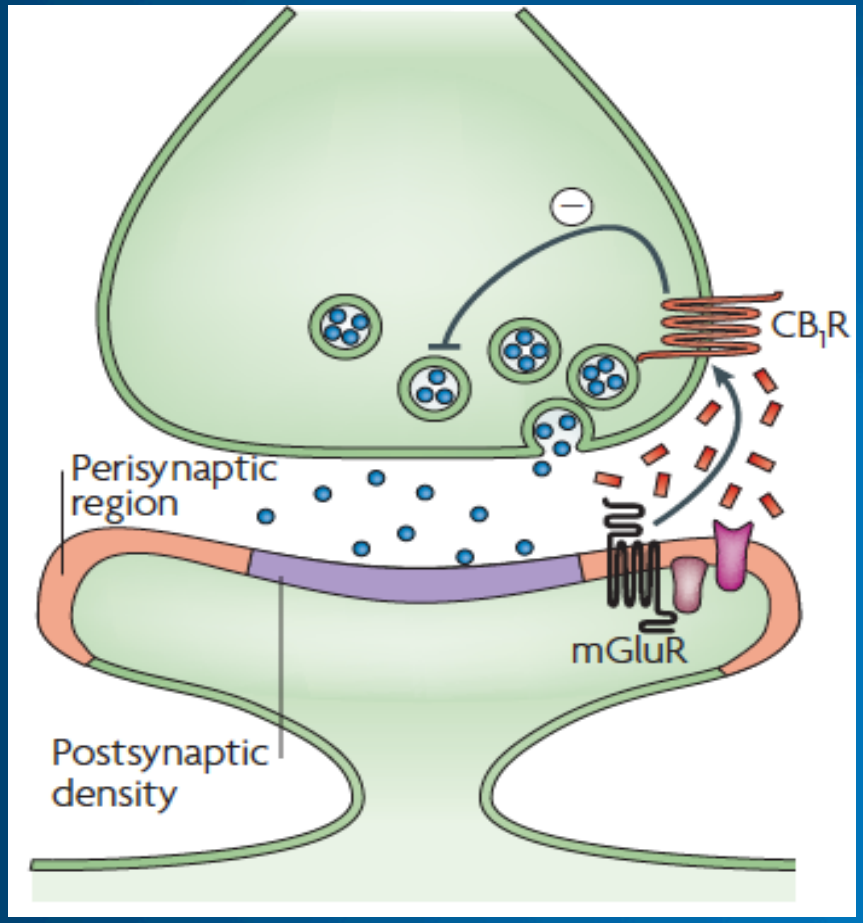
The endogenous cannabinoids

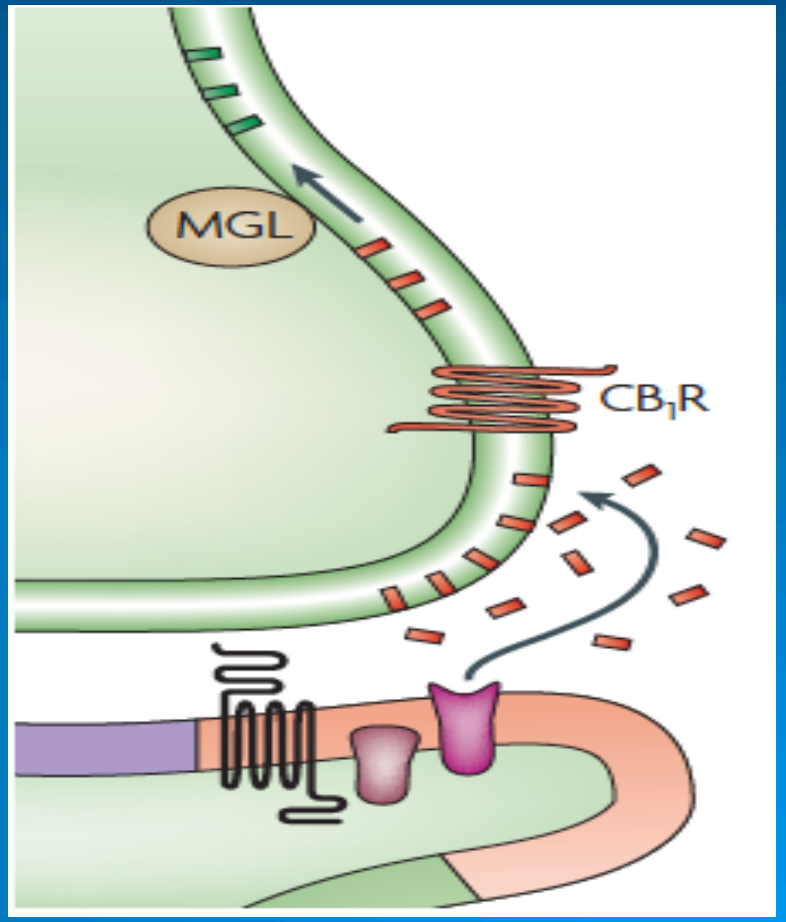


Piomelli, *Nature Rev. Neurosci.*, 2003

"Circuit Breaker" Function of CB Receptors

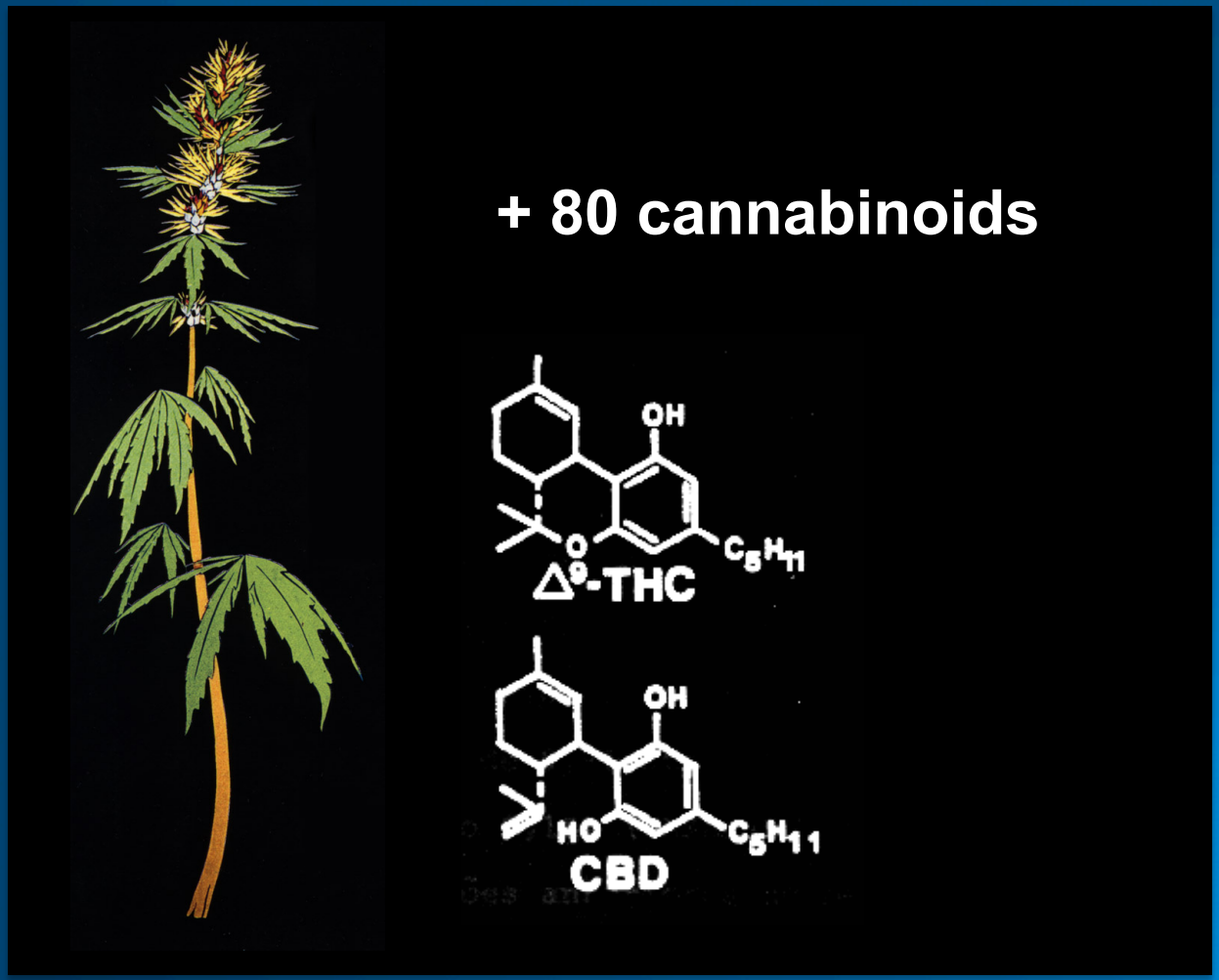
Neurotransmitter (eg., glutamate) action on post synaptic cells triggers them to release endocannabinoids (EC) that act on presynaptic CB receptors to regulate neurotransmission. The EC are then inactivated by FAAH or MGL*





* 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

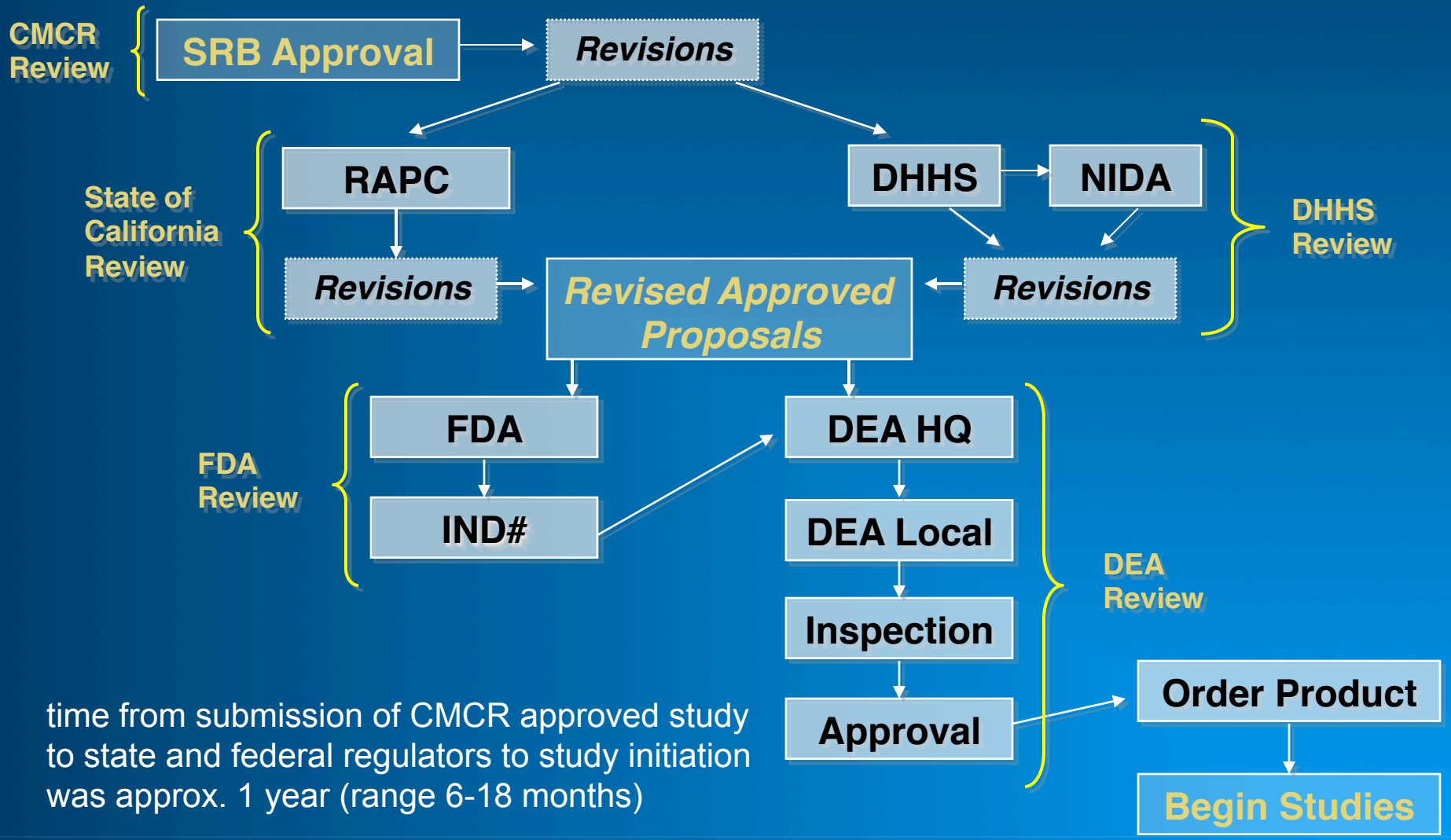
Barth Wilsey, MD, Ron Ellis, MD, PhD, Mark Wallace, MD, Robert Fitzgerald, PhD, Investigators; Ben Gouaux and Jennifer Marquie Beck, Senior Staff

www.cmcr.ucsd.edu

California Events Leading To CMCR

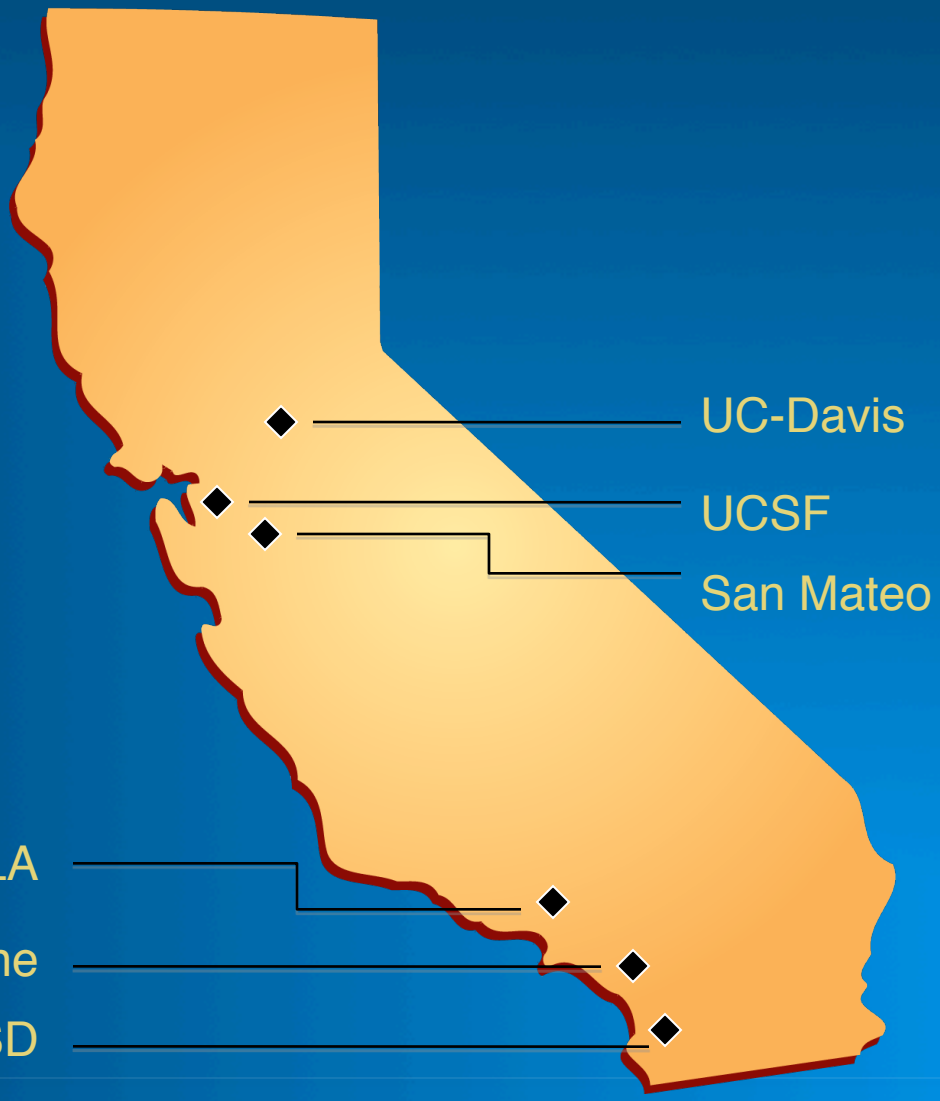
November 1996:	**California Prop 215 passes: Compassionate Use Act**
September 1999:	**Medical Marijuana Research Act of 1999, authored by Senator John Vasconcellos (SB 847).**
August 2000:	**Center for Medicinal Cannabis Research established at the University of California.**
September 2003:	**Amendment to Medical Marijuana Research Act of 1999, sunset restrictions removed. (SB 295)**

CMCR Regulatory Pathway

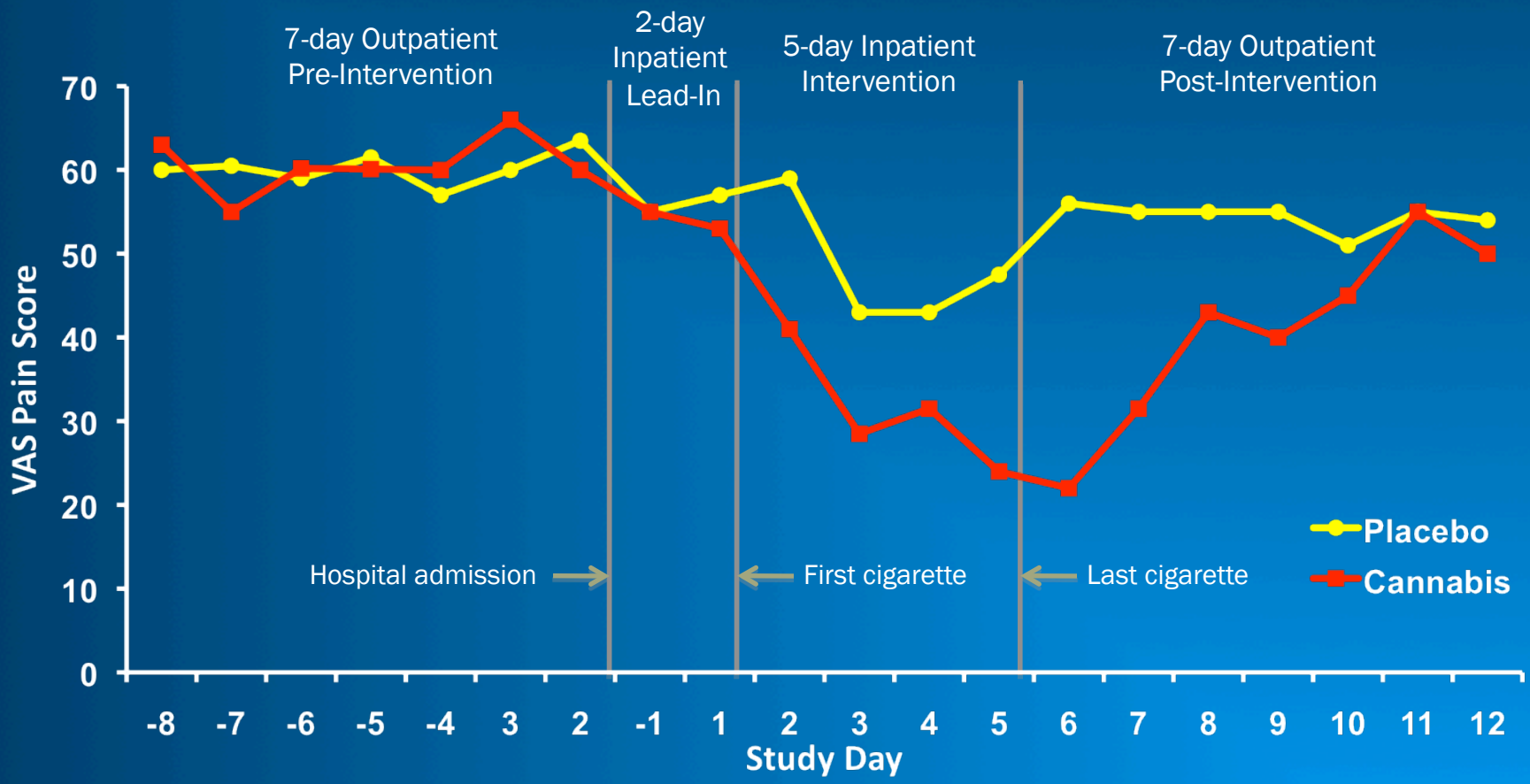


time from submission of CMCR approved study to state and federal regulators to study initiation was approx. 1 year (range 6-18 months)

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%	+

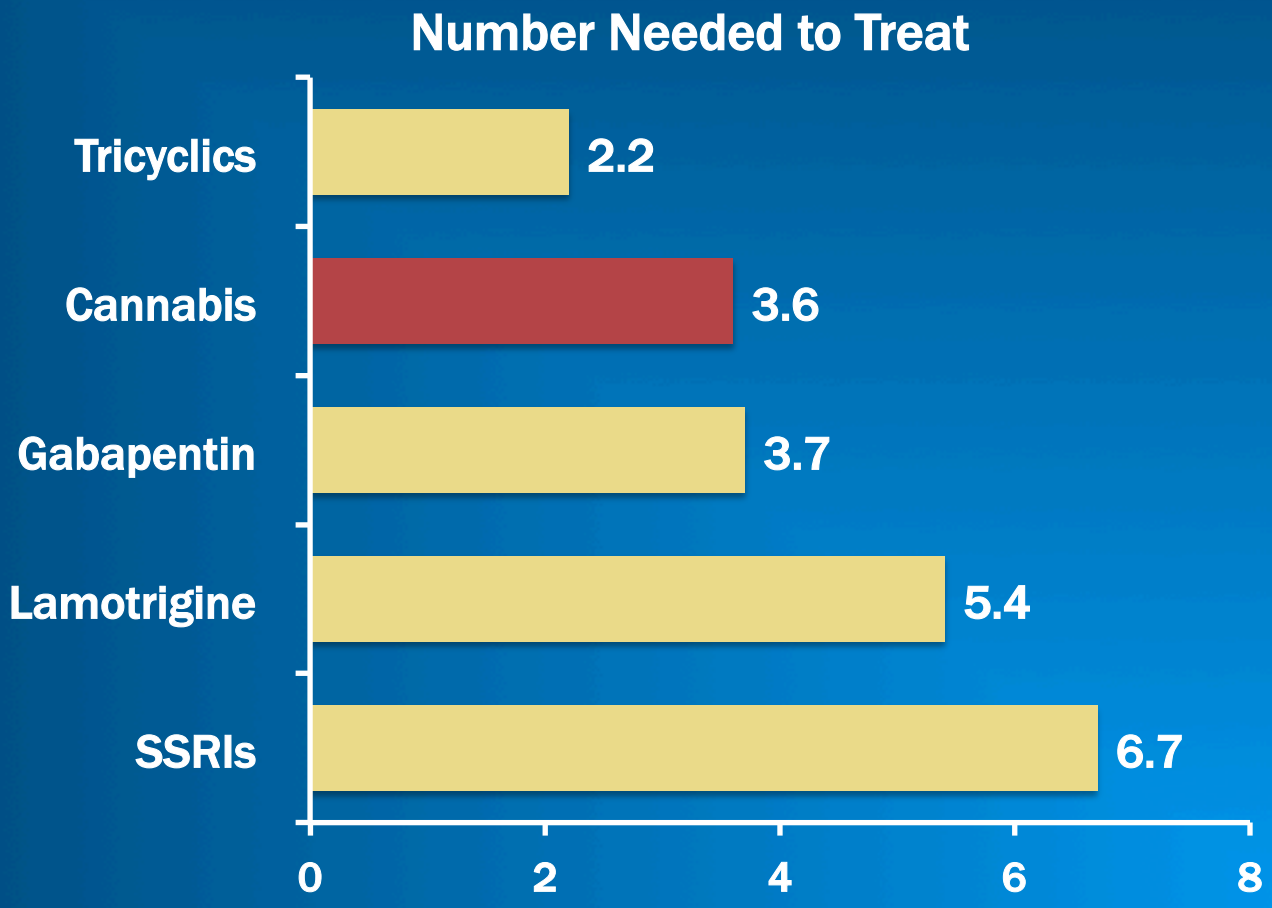
How effective is cannabis relative to other pain medications? Number-Needed-to-Treat

- 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.

Summary of CMCR Studies on Smoked Cannabis

- Data from CMCR placebo controlled, limited scale studies of smoked cannabis indicate positive response in neuropathic pain 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

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

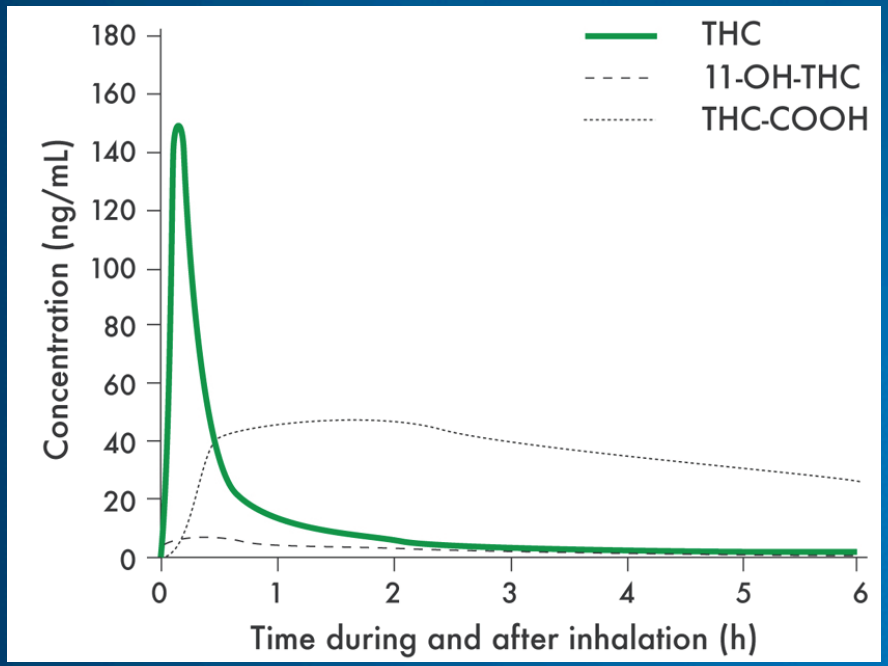
Ref: The Health Effects of Cannabis and Cannabinoids. Washington (DC): National Academies Press (US); 2017 Jan.

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

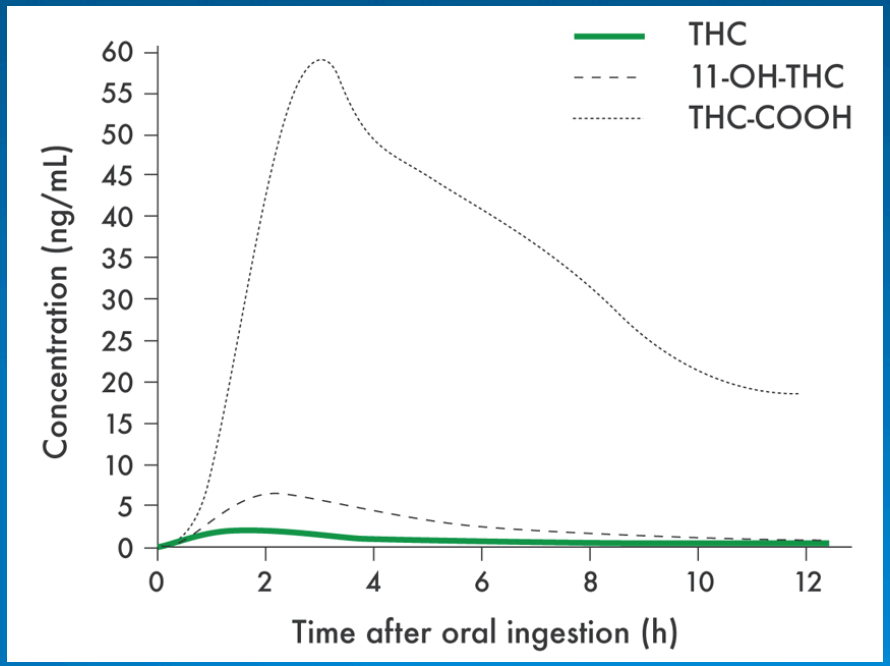
- Safety of combustible material in clinical setting
- Second hand smoke as an irritant, possibly health hazard
- Efficiency and tolerability in smoking naïve
- Availability of cigarettes with standardized dose
- Conflict with anti drug laws
- Possibility of misuse and diversion
- Difficulty in conducting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

Plasma THC Levels – Smoked vs. Oral

inhaled cannabis ~34mg THC



15mg oral THC (dronabinol)



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.

Devices for Marijuana Vaporization

E-cigarettes

Volcano®

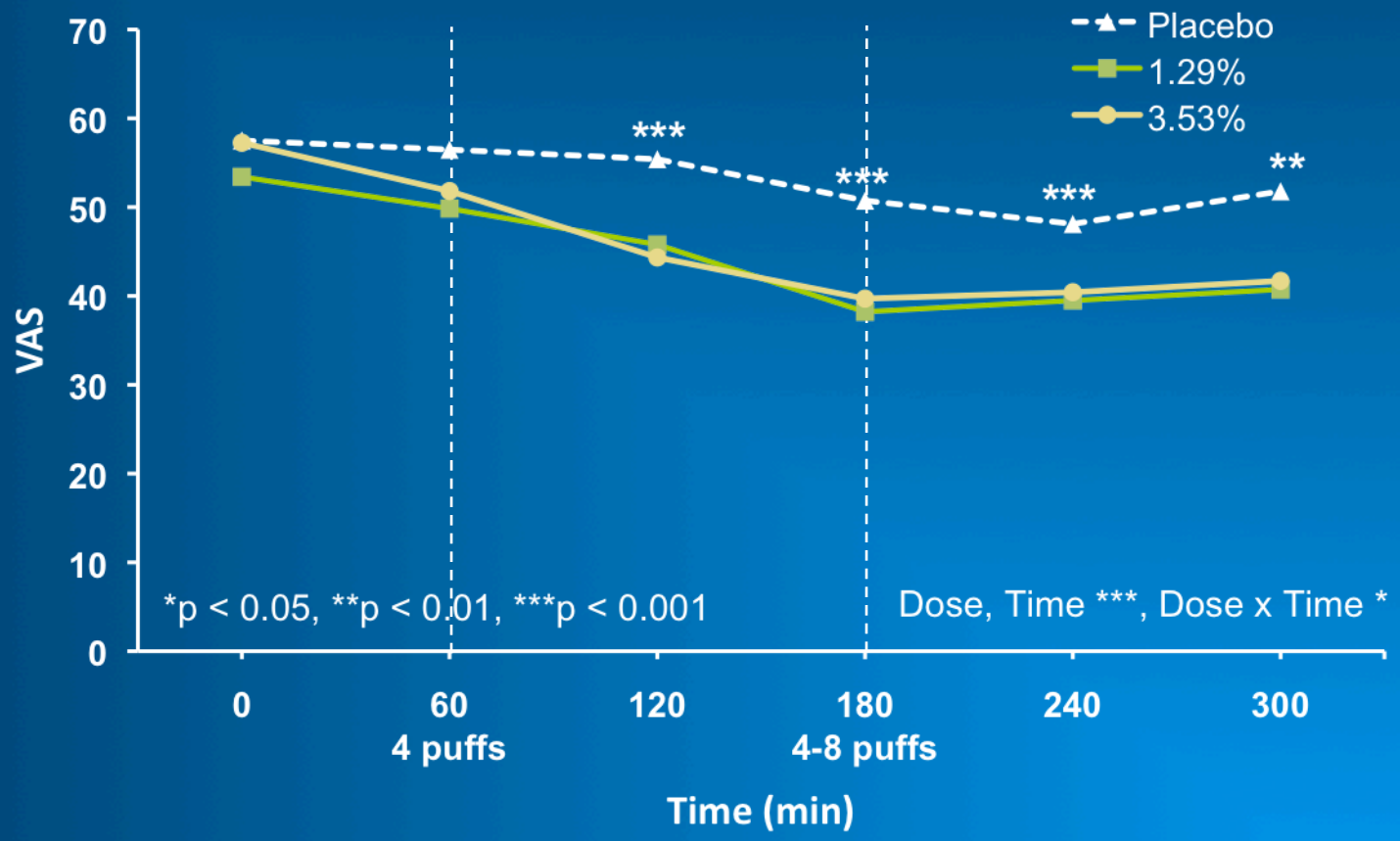
Courtesy David Gorelick, MD

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)

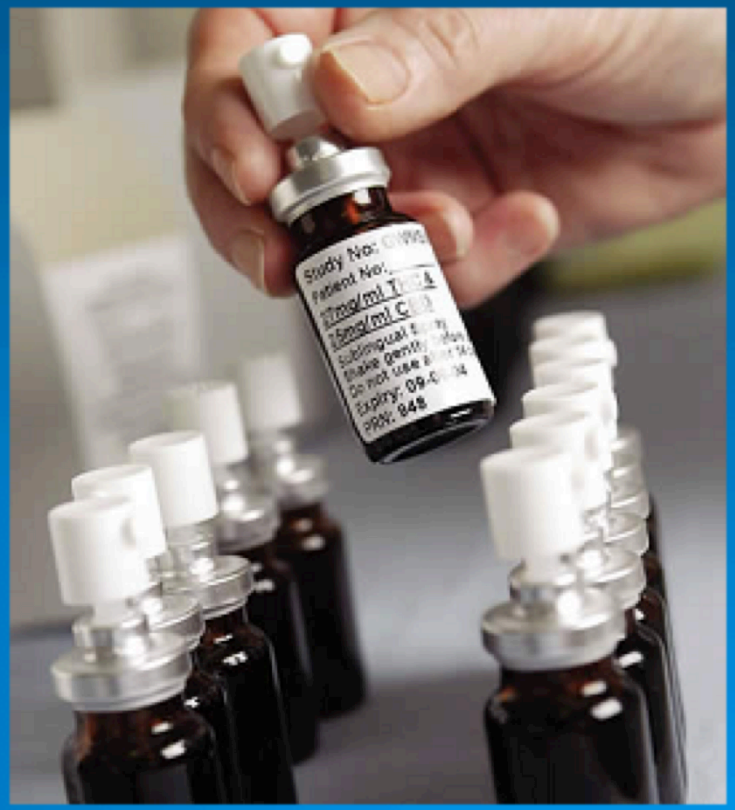
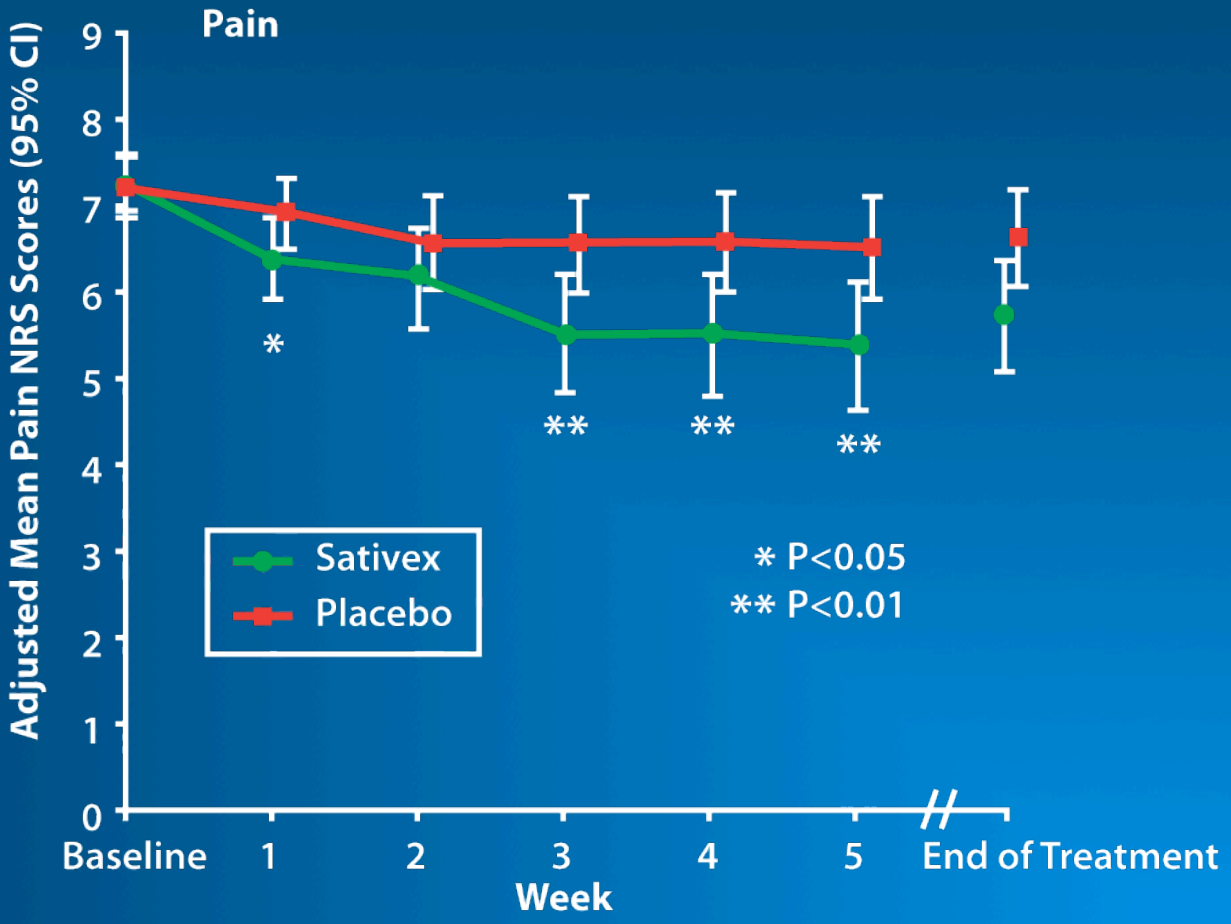


Image courtesy G. Guy, GW Pharmaceuticals

Nabiximols (Sativex®) for Neuropathic Pain



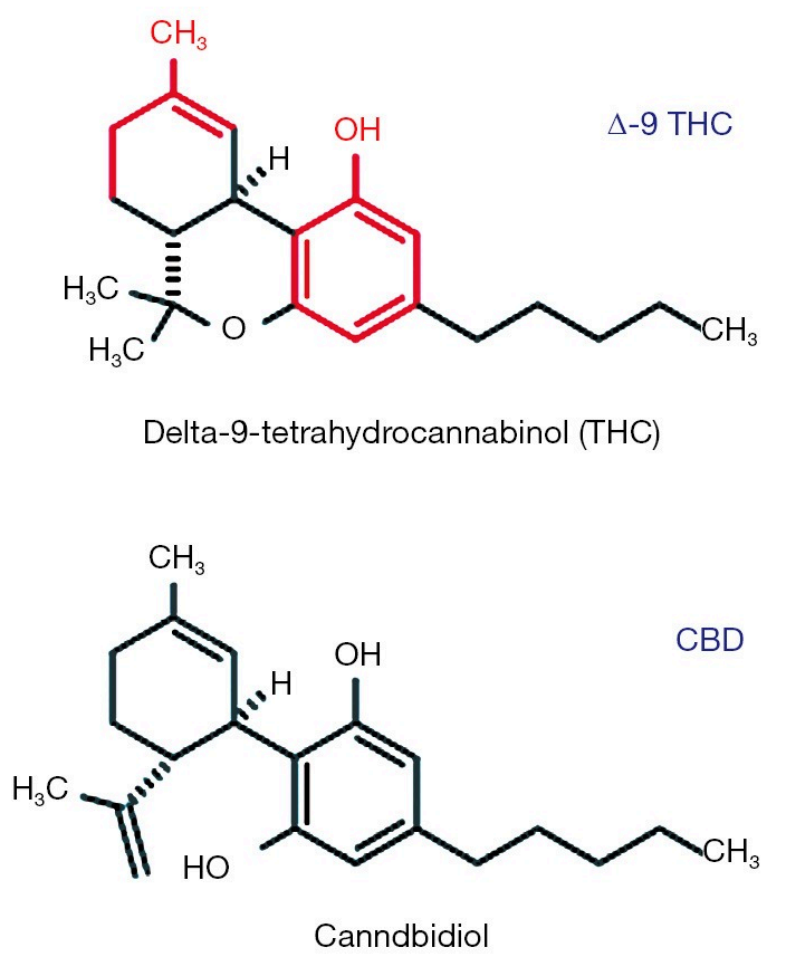
Reduction of global neuropathic pain NRS scores in the two groups during the trial. Weekly mean pain scores were obtained from pain diaries.

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

Current or potential cannabinoid modulators that may be administered orally

- Agonists
  - » Cannabis itself
  - » 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

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

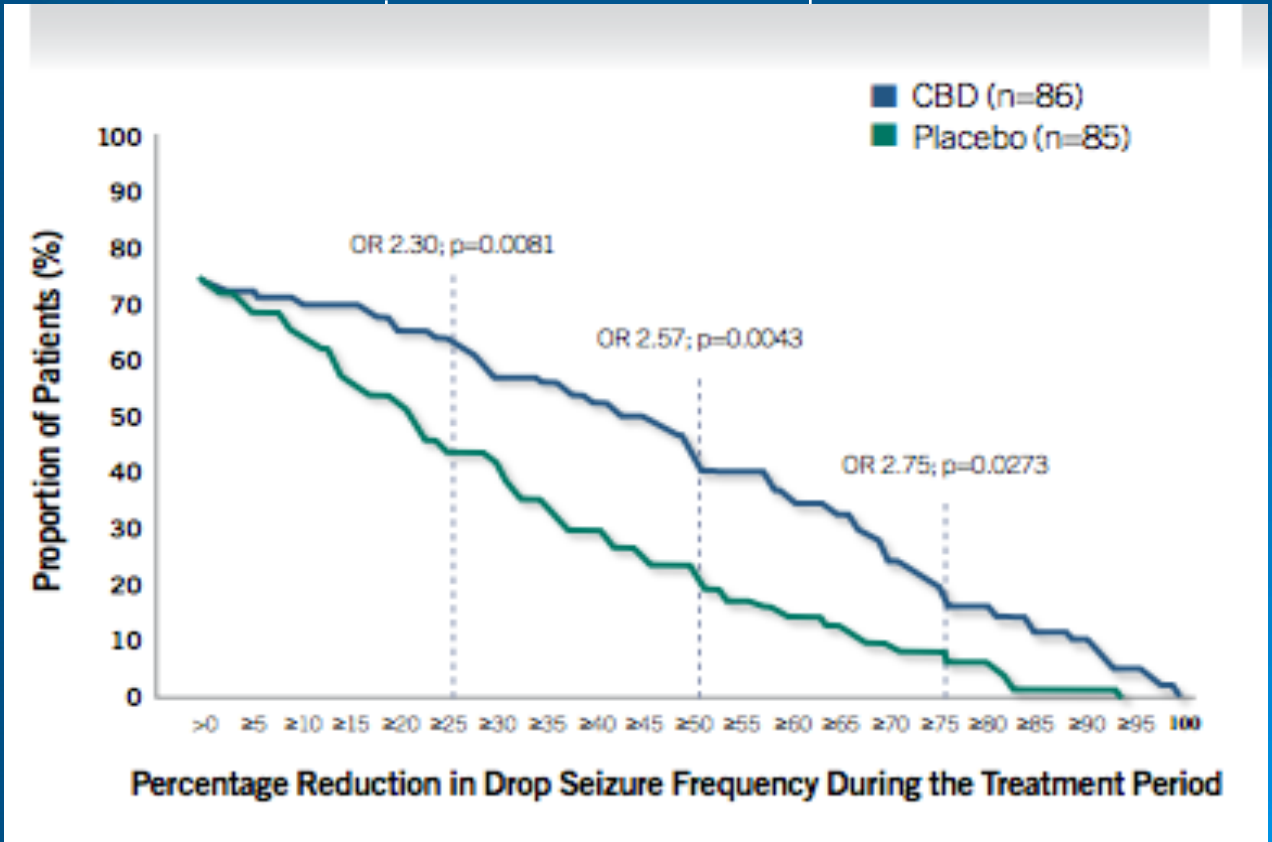
Cannabidiol: Seizure Reduction in Epilepsy

STUDY	MODEL	EFFECT
Human Devinsky et al., 2015	N=137 children Dravet or Lennox Gastaud. Epidiolex, a CBD extract	+
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. **Devinsky O, Marsh E, Friedman D, et al Lancet Neurol. 2015;4422(15):1–9**

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

Proportion of patients achieving 50% or greater reduction in episodes

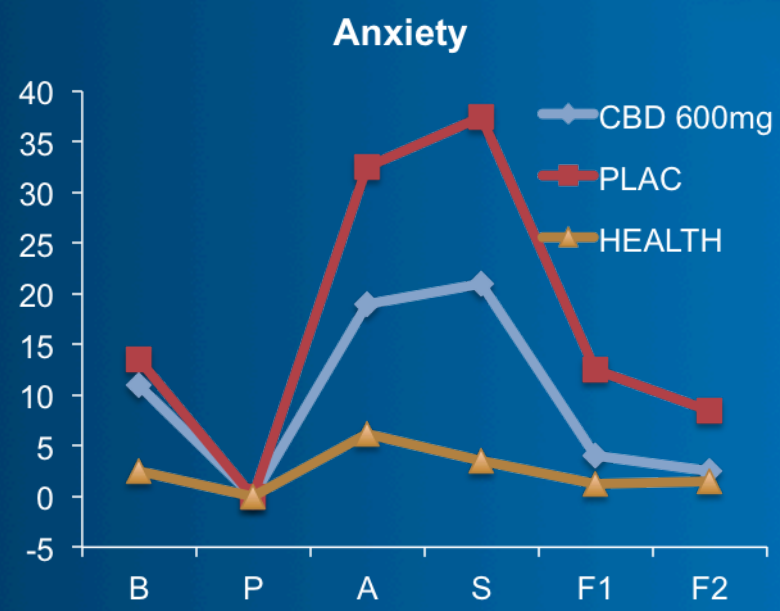


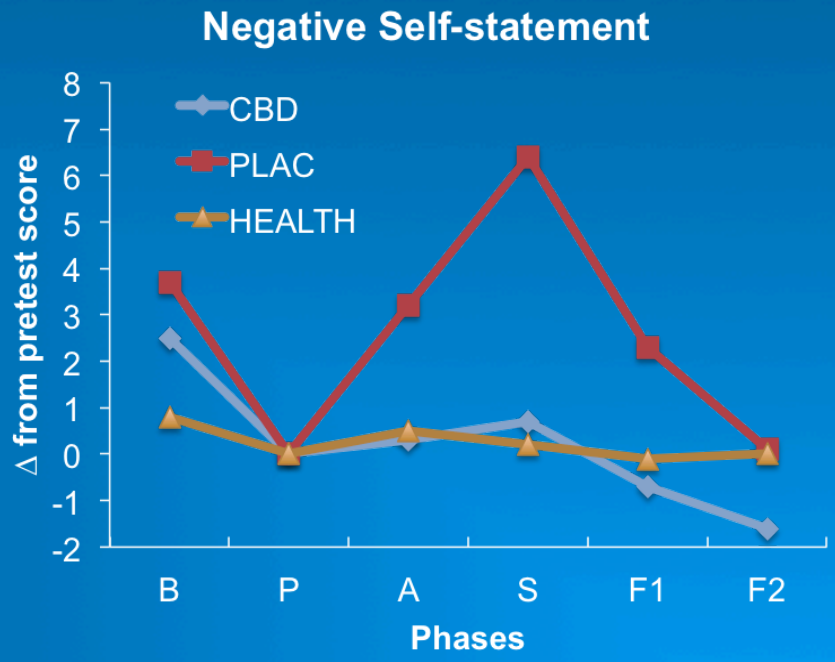
- Thiele.AE et al. The American Epilepsy Society Annual Meeting; Houston, TX; December 2–6, 2016.

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]





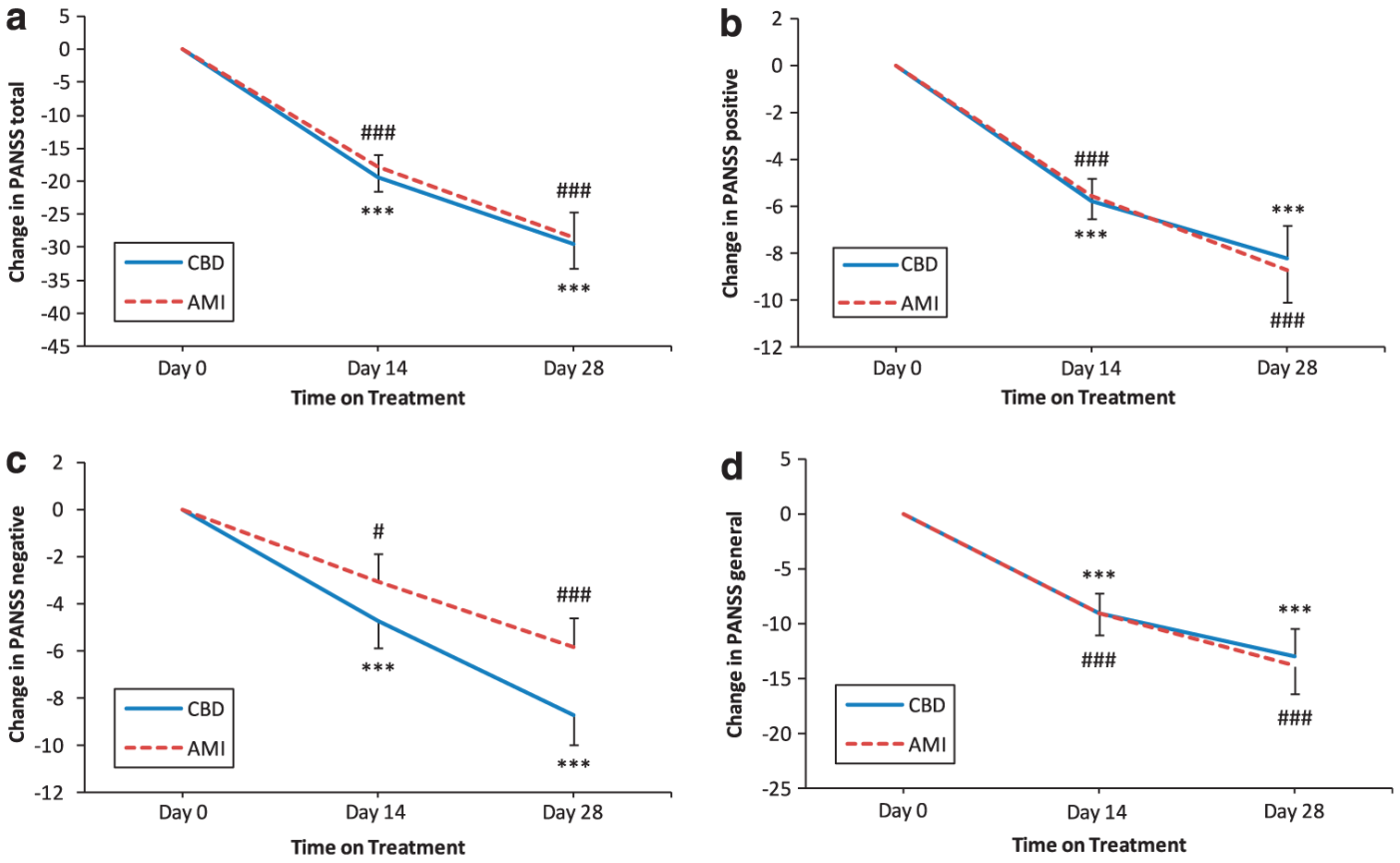
Slide information courtesy of Dr. José Alexandre de Souza Crippa, Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Brazil

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

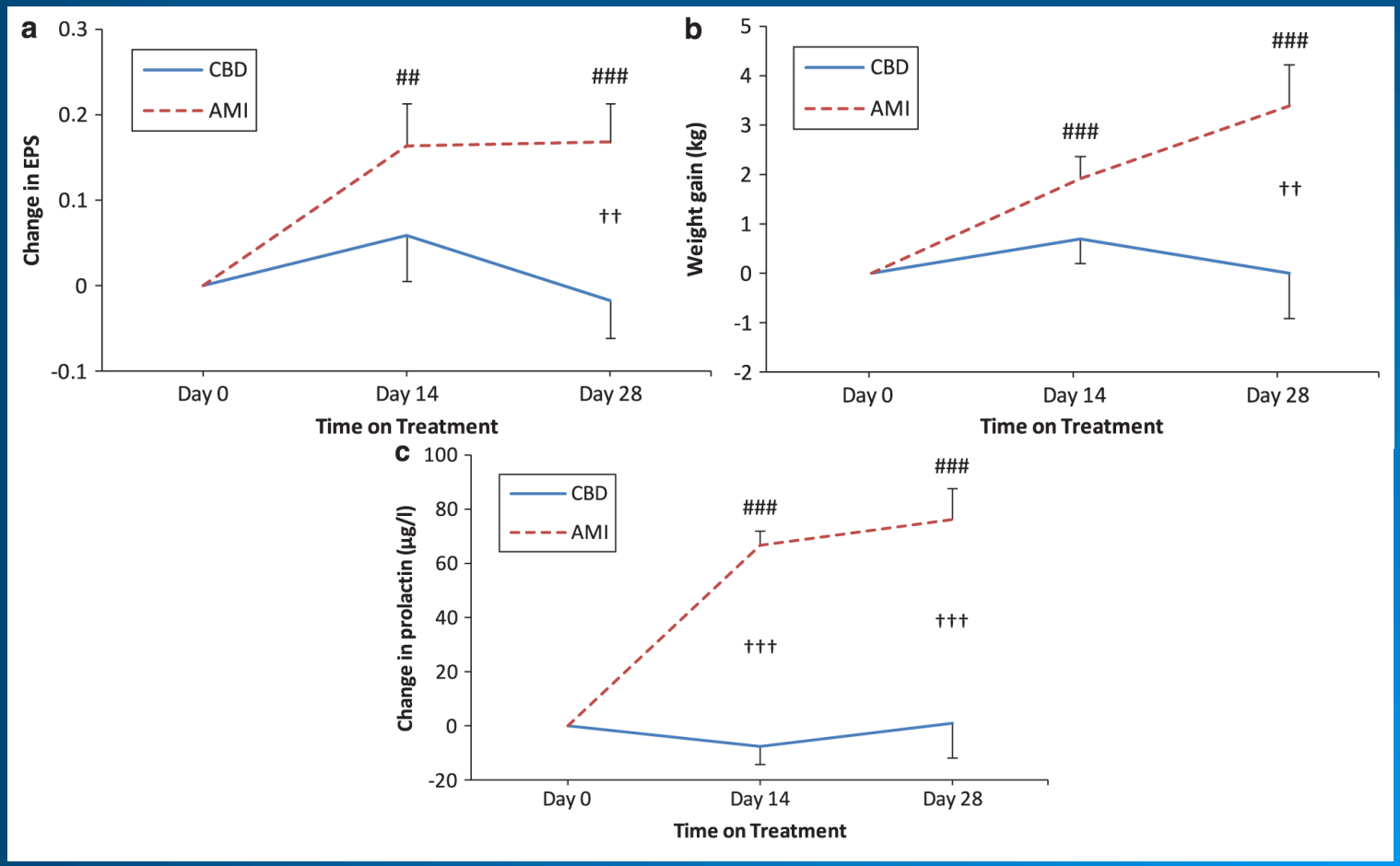
Cannabidiol improves positive and negative symptoms of schizophrenia:

(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.

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
- Possible efficacy in sleep disorders treatment
- Synthetic THC-like molecules efficacious in appetite stimulation and control of nausea
- Potential 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
- Cannabidiol showing initial promise in treatment of anxiety, psychosis, and intractable epilepsy (eg., Dravet; Lennox Gastaud Syndromes: FDA panel recommends Epidiolex approval 4/19/18)
- FAAH inhibitors promising in animal models of chronic pain
- Anti-inflammatory actions of cannabinoids deserve further exploration

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

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
  - » Only 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

How do we move forward? In most countries, including the USA, it isn't that easy

- We need to separate out discourse on medicinal cannabis from that of broader social policy on recreational use [as we have done with other abusable drugs]
- We need both proof of principle and larger scale clinical trials on cannabis, administered via several routes, and specific constituents, plus their combinations. Consider effects of age, sex, comorbidities, other medications
- Tax dollars collected from cannabis sales can support such studies, which should also focus on longer term benefits, toxicity, and broader social effects.
- In the USA and other jurisdictions regulatory authorities need to "re-schedule" cannabis away from the most restrictive designation, recognizing that harm potential is modest, and there are medical benefits. This will facilitate medical research. Example: CBD, which is non psychoactive, is still Schedule 1 and practically unavailable for broader medical research
- In the USA the Federal Government needs to empower States to license producers for medical research to make available a diversity of products in a timely manner.
- If cannabis is to be used as a medicine, it needs to be capable of physician 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].

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

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

www.cmcr.ucsd.edu