University of California, San Diego

Center for Medicinal Cannabis Research

Established 2000 (California SB 847)

Igor Grant, MD, Director

Co-Directors

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

Investigators

Kristin Cadenhead, MD; Ron Ellis, MD, PhD; Robert Fitzgerald, PhD; Emily Gray, MD; David Grelotti, MD; Brook Henry, PhD; Walter Kaye, MD; Alysson Muotri, PhD; Fatah Nahab, MD; William Perry, PhD; Nathaniel Schuster, MD; Gabriel Silva, PhD; Ji Sun, PharmD; Doris Trauner, MD; Mark Wallace, MD; Jared Young, PhD

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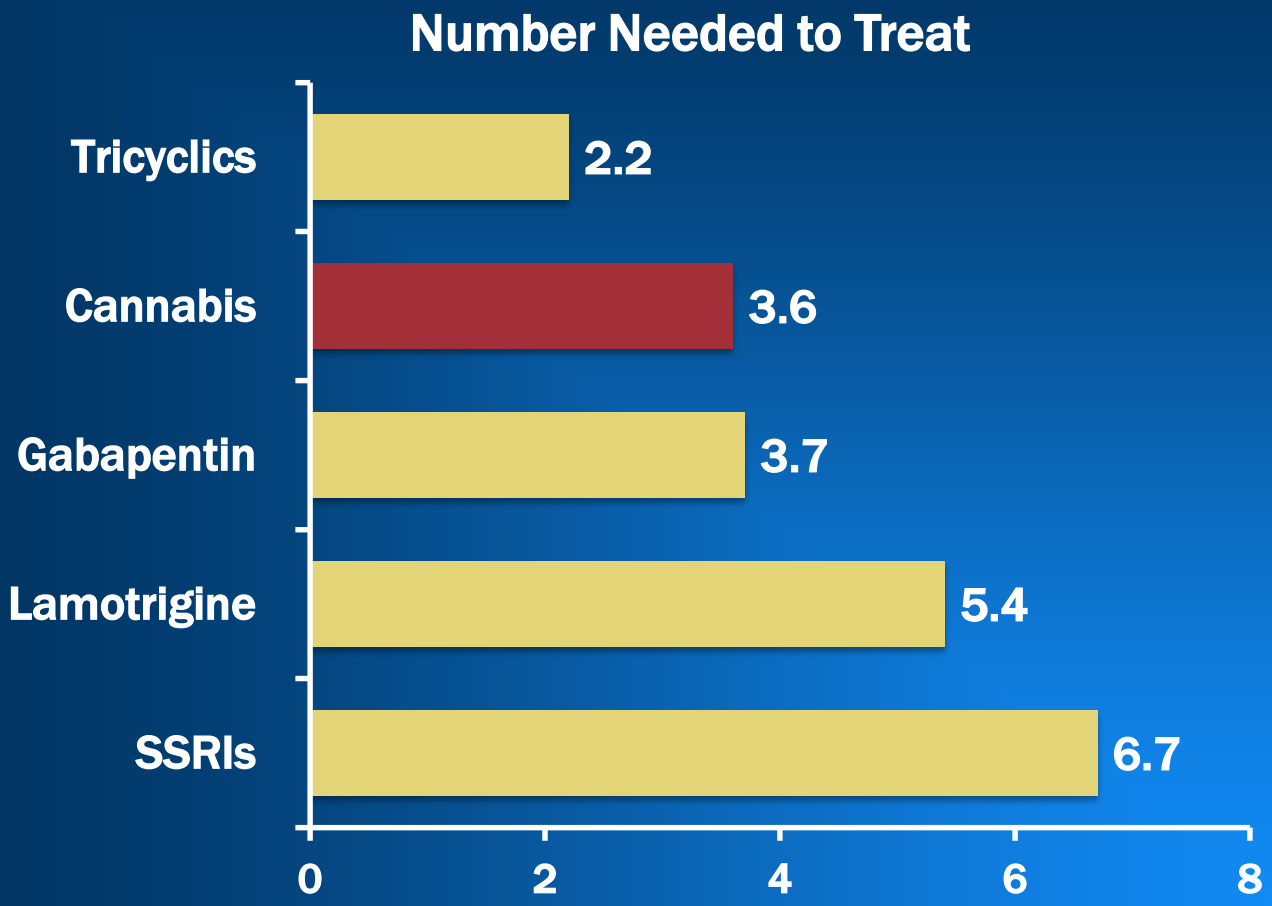
FDA Briefing
CMCR Main Points

- Evidence that some cannabinoids have medicinal value
  - » THC for pain, muscle spasticity, nausea, appetite stimulation
  - » Cannabidiol for epilepsy, possibly psychosis, anxiety, anti-inflammatory
- Present research is limited by the availability of many products, modes of administration, lack of access to “real world” products
- Barriers to advancing medical cannabis science are present at many Federal levels
- Specific changes would facilitate research on the impact of cannabis and cannabinoids on health; not addressing barriers is a public health issue as we get progressively behind the curve in terms of real world public use

Completed CMCR Clinical Studies

SITE	DISORDER	DESIGN	N	DOSE (% THC)	Result
UCSD Mark Wallace	Healthy Volunteers (Experimentally-Induced Pain)	Crossover RCT	15	0%, 2%, 4%, 8%	+
UCSD Mark Wallace	Diabetic Neuropathy Smoked Cannabis	Crossover RCT	17	0%, 2%, 4%, 7%	+
UCSD Ronald Ellis	HIV Neuropathy Smoked Cannabis	Crossover RCT	28	0%, 1-8%	+
UCSD J. Corey-Bloom	MS Spasticity Smoked Cannabis	Crossover RCT	30	0%, 4%	+
UCSF Donald Abrams	HIV Neuropathy, Smoked Cannabis	Parallel Groups RCT	50	0%, 3.5%	+
UCSF Donald Abrams	Volcano Vaporizer	Comparison with Smoked Cigarettes		1.7%, 3.4%, 6.8%	+
UCD Barth Wilsey	Neuropathic Pain, Smoked Cigarettes	Crossover RCT	33	0%, 3.5%, 7%	+
UCD Barth Wilsey	Neuropathic Pain, Vaporized Cannabis	Crossover RCT	39	0%, 1.29%, 3.53% (Vaporized)	+

Common Analgesics for Neuropathic Pain



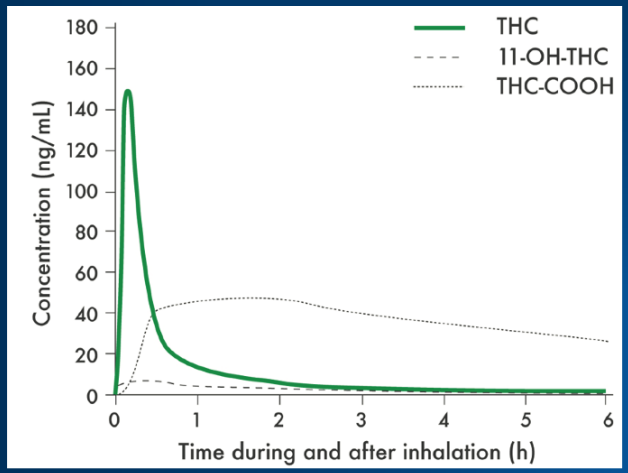
*Number Needed to Treat to to achieve a 30% reduction in pain.

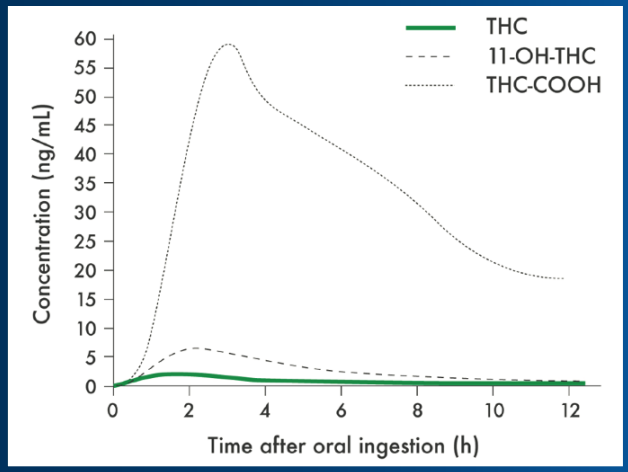
Current CMCR Cannabinoid Studies

PI	CONDITION	SPONSOR	DESIGN	N	T
Barth Wilsey Thomas Marcotte	Low Back Pain	NIH	Parallel Groups RCT	120	Vaporized CBD/THC Oral Dronabinol Oral / Vaporized Placebo
Doris Trauner	Severe Autism	Wholistic Foundation	Crossover RCT	30	Oral CBD Oral Placebo
Fatta Nahab	Essential Tremor	Essential Tremor Foundation Tilray Pharmaceuticals	Crossover RCT	16	Oral CBD/THC Oral Placebo
Kristin Cadenhead	Early Psychosis	Krupp Family Foundation	Crossover RCT	78	Oral CBD Oral Placebo
William Perry Jared Young	Bipolar Disorder Healthy Volunteers	NIH	Parallel Groups RCT	144	Oral CBD Oral THC Oral Placebo
Brook Henry	HIV Sensory Neuropathy	NIH	Within Subjects Crossover	100	Vaporized CBD/THC Vaporized Placebo
Thomas Marcotte	Driving Impairment	State of California	Parallel Groups RCT	180	Smoked THC Smoked Placebo

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

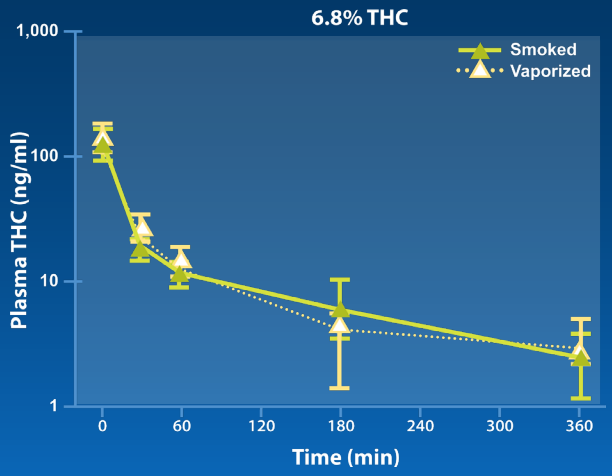
Inhaled vs. Edible

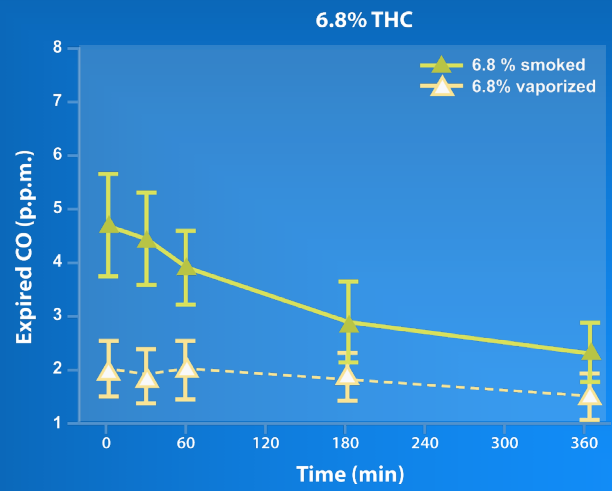




Grotenhermen, et al. 2003. Clin Pharmacokinet 2003; 42 (4): 327-360.

Smoked vs. Vaporized

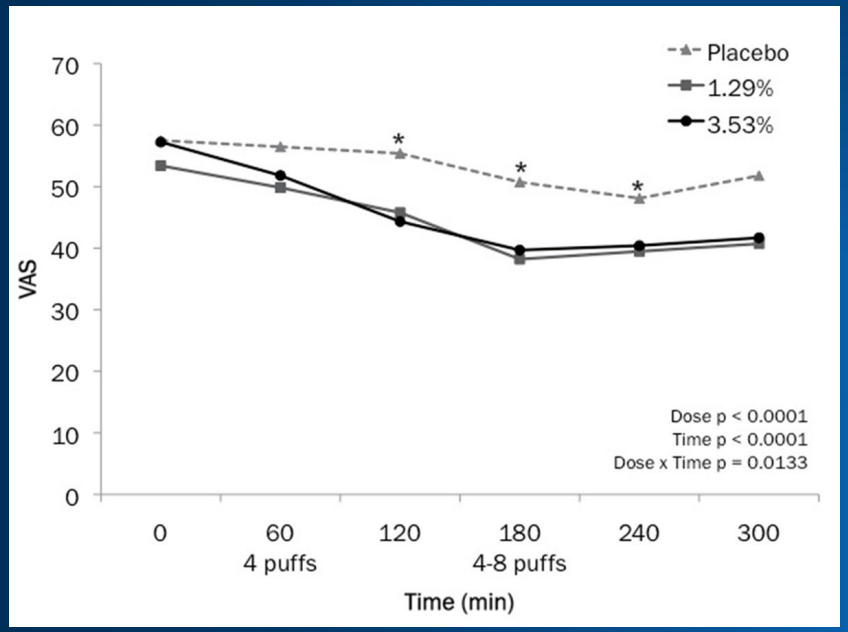




Abrams, et al. 2007. Clin Pharmacol Ther.

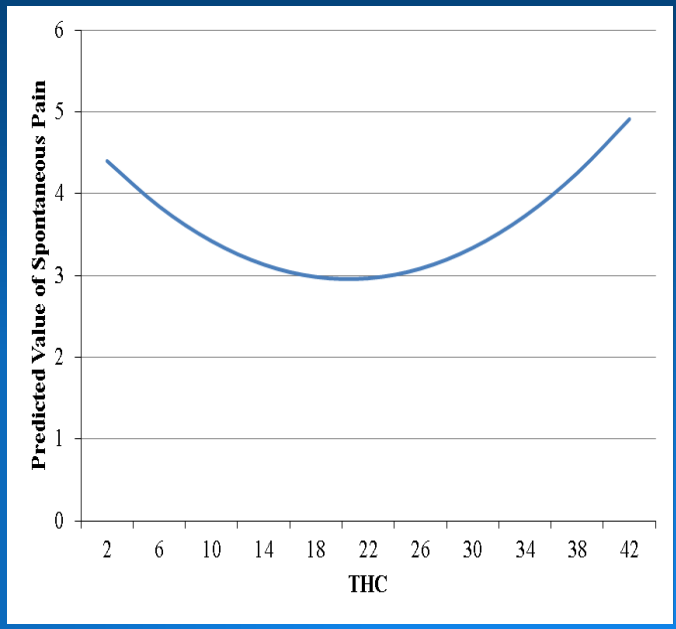
Optimal dosage?: Therapeutic window?

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)

Path Forward

- Important to conduct controlled studies on promising directions that include plant and synthetic cannabinoids, routes of administration, diverse populations, longer term efficacy and toxicity
- Need to get ahead of the curve in regard to products available to public
- This will require flexibility, e.g.,
  - » Permit research exemptions
  - » Not require detailed pharmacology and toxicology for all new cultivars
  - » Allow researchers to work with products in states with robust laws and rigorous potency and contaminant test requirements
    - Can FDA delegate approval of clinical cannabinoid research to State authorities, if there is no interstate issue?
  - » Facilitate importation from CGMP companies
  - » All non-THC cannabinoids should be treated equally and removed from the CSA schedule, e.g., de-scheduling would open up studies on the pharmacological potential of these molecules

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