

Medicinal Cannabis

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July 12, 2012



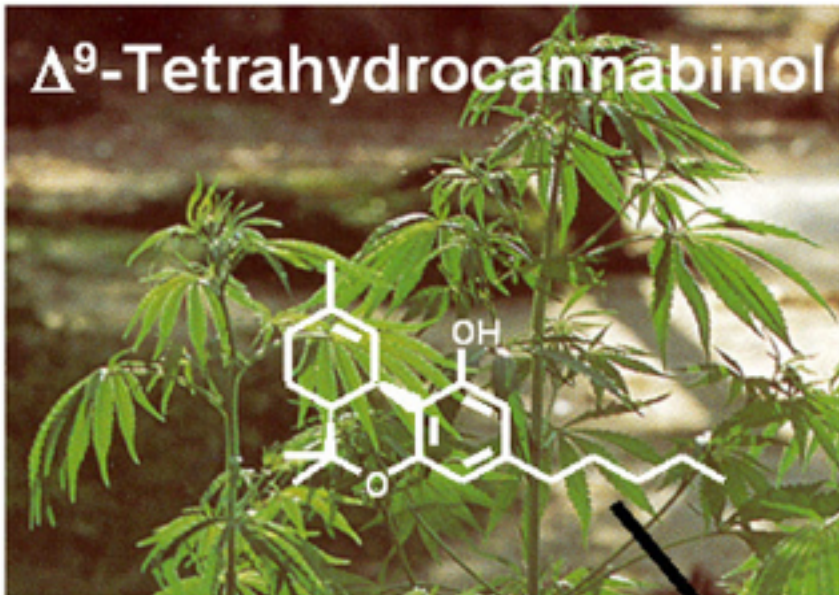
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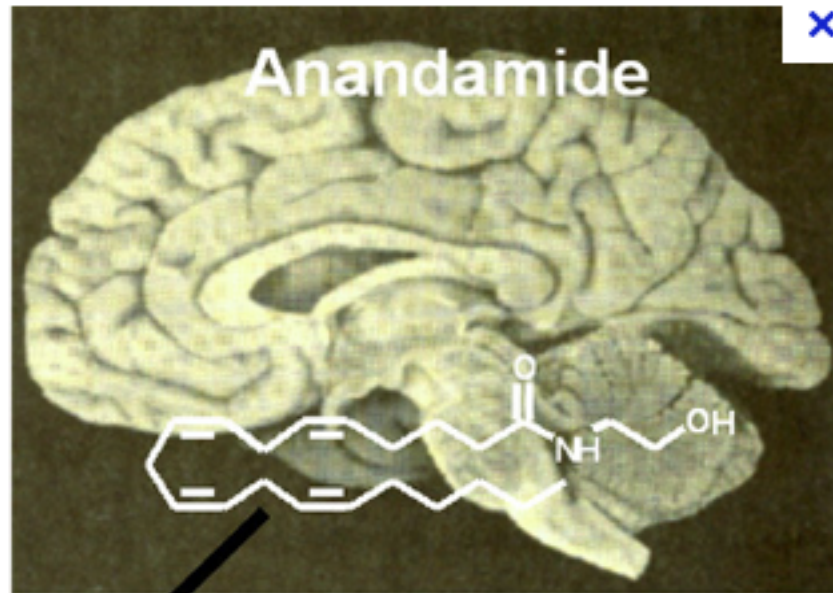
Main Events that Reawakened Interest in Medicinal Cannabis in the 1990s

- **Persistent anecdotal reports of benefits**
- **Political shifts in states favoring medicinal access (15 states now provide for some measure of access)**
- **Discovery of the endocannabinoid system**
 - » CB1 and CB2 receptors
 - » Anandamide, 2-arachidonoylglycerol (2-AG) 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)

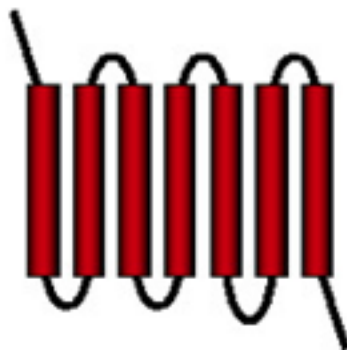
Δ^9 -Tetrahydrocannabinol



Anandamide



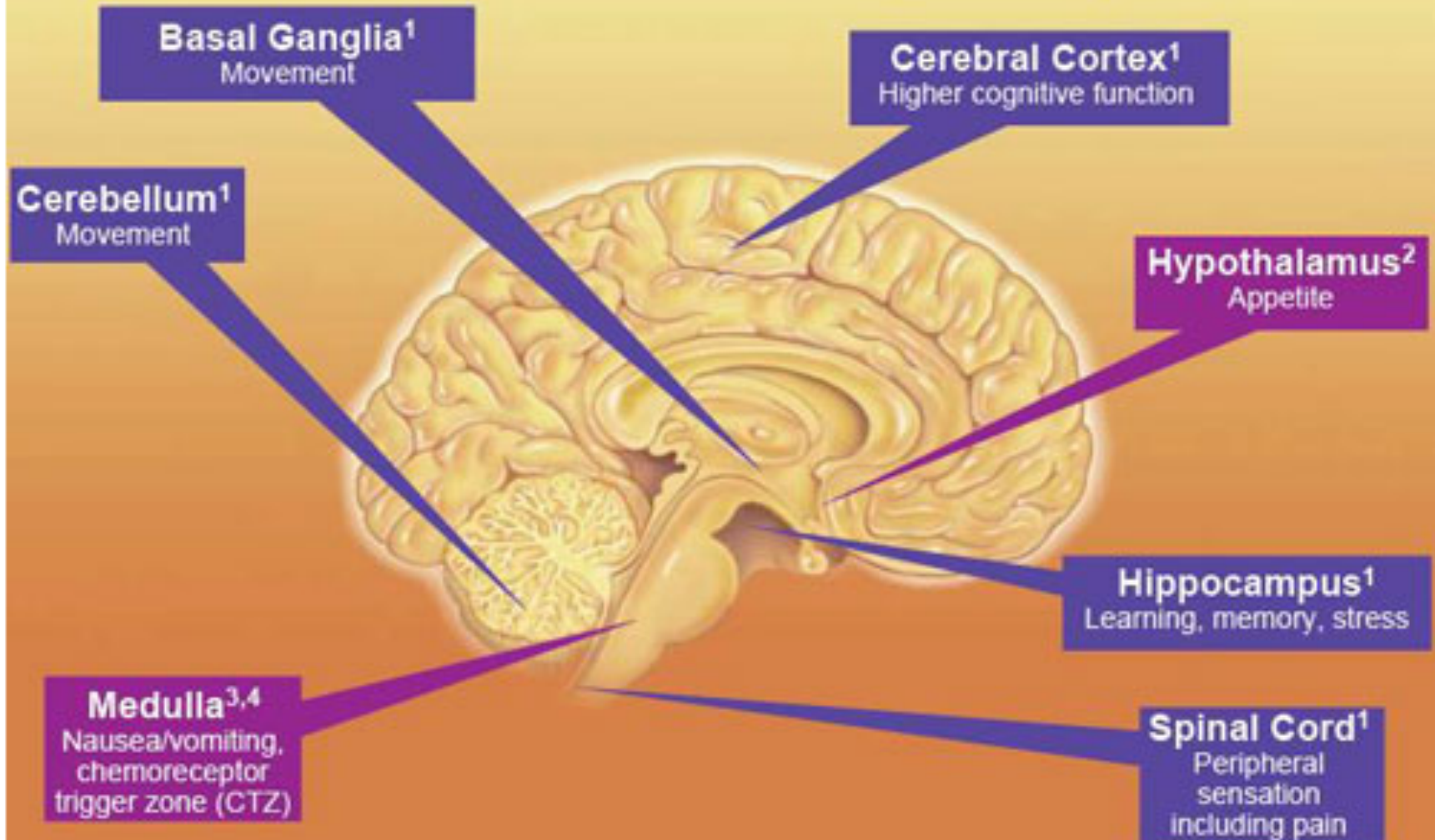
Cannabinoid Receptor



Distribution of 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

Concentrations of CB₁ receptors



1. Joy JE, et al, eds. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:33-81. 2. Martin BR, et al. *J Support Oncol*. 2004;2(4):305-316. 3. Grotenhermen F. *Curr Drug Targets CNS Neurol Disord*. 2005;4(5):507-530. 4. Navari RM, et al. *Expert Opin Emerg Drugs*. 2006;11(1):137-151.

Potential Uses: 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.

3-Stage Research Vision

- **STAGE I: Smoked Cannabis**

Conduct well-designed, rigorously controlled clinical trials of smoked cannabis. Marijuana cigarettes are provided by NIDA.

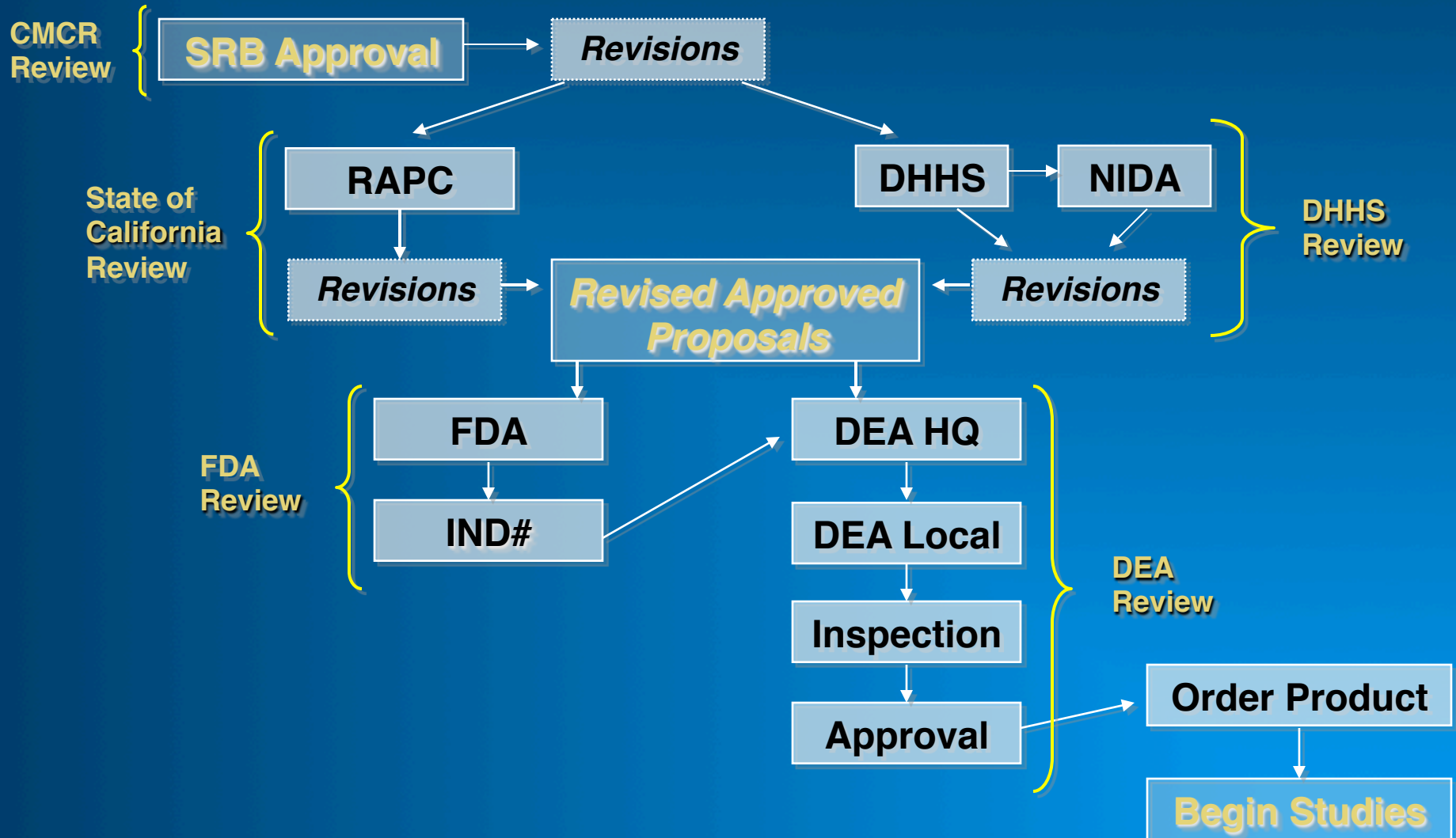
- **STAGE II: Non-Smoked Delivery Methods**

Explore the safety and effectiveness of non-smoked forms of medicinal cannabis, such as sprays, patches, oral forms, or suppositories.

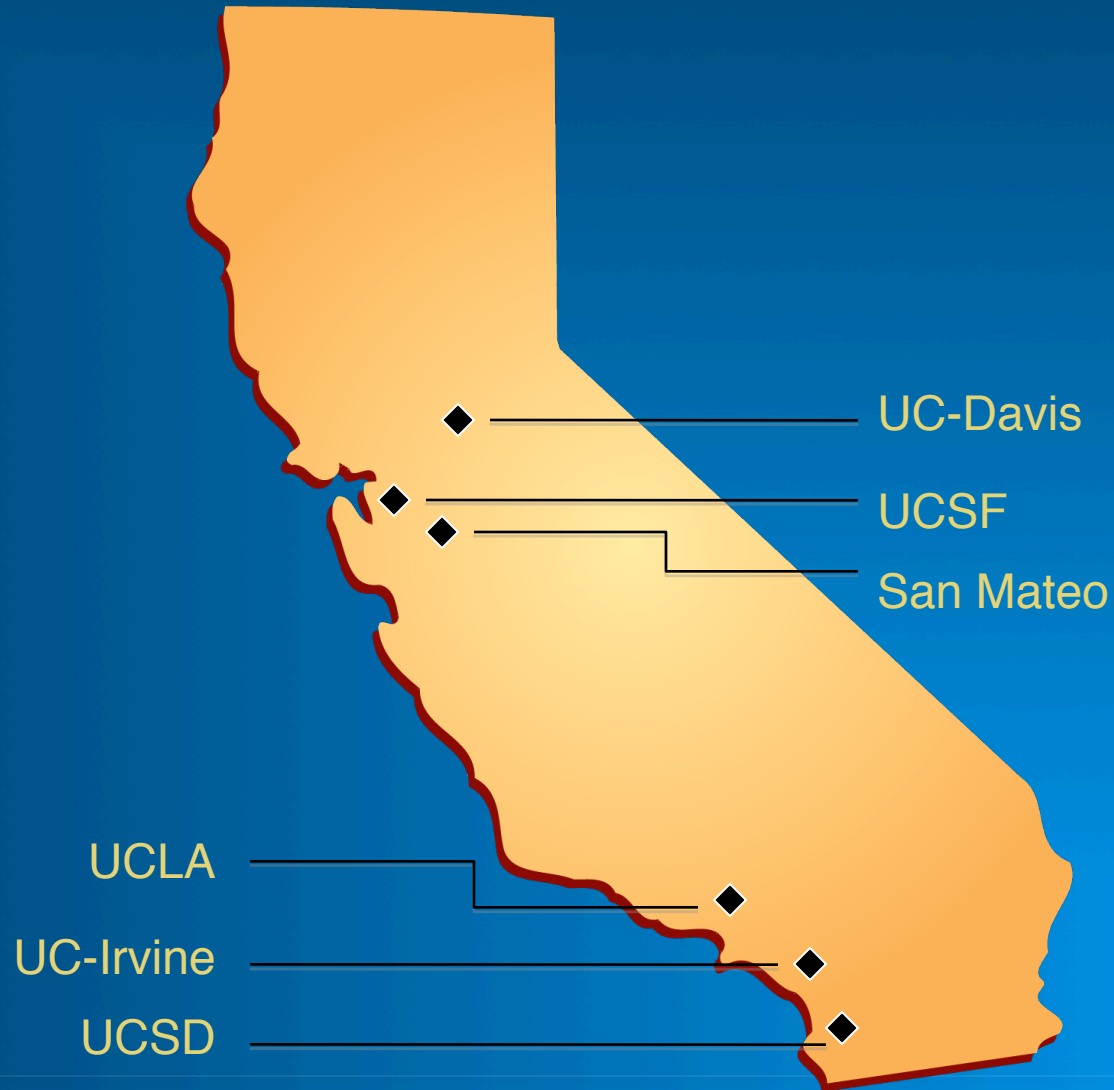
- **STAGE III: Molecules to Target Cannabinoid System**

Provide clinical testing of specific molecules to activate, modulate, or deactivate the body's in-built cannabinoid system.

CMCR Regulatory Pathway



Study Locations



CMCR Clinical Studies completed (1 more finalizing)

SITE	DISORDER	DESIGN	N	DOSE (% THC)
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%

RCT – Randomized controlled trial

Analgesic Efficacy of Smoked Cannabis

Mark Wallace, MD, Gery Schulteis, PhD,
J. Hampton Atkinson, MD, Tanya Wolfson, MA,
Deborah Lazzaretto, MS, Heather Bentley, CCRA,
Ben Gouaux, BA, Ian Abramson, PhD

Study Design

Study Design	Placebo-Controlled, randomized, crossover study
Enrollment	15 subjects
Population	Healthy volunteers
Pain Model	Experimental
Dose protocol	1 session per day
Dose(s)	0%, 2%, 4%, 8%

Methods

- **Baseline**
 - » Neurosensory exam on volar aspect of right forearm
 - » Neurocognitive exam
- **Cannabis Exposure (placebo, 2%, 4%, 7% THC by weight)**
 - » **5 minutes post exposure:**
 1. Blood sample for THC level, repeat baseline measurements, Subjective Highness Score
 - » **2. Capsaicin injection volar aspect of right forearm**
 - Pain score and McGill questionnaire at the time of injection
 - Every 2.5 minutes for 10 minutes: pain scores, HR, BP, RR
 - 10 minutes post injection: area of hyperalgesia mapped
 - 40 minutes post injection: blood sample, repeat baseline measurements, subjective highness score
- **After completing the 40 minute period testing, a second capsaicin injection performed on the volar aspect of the left forearm and testing described for the right arm repeated**

Intradermal Capsaicin

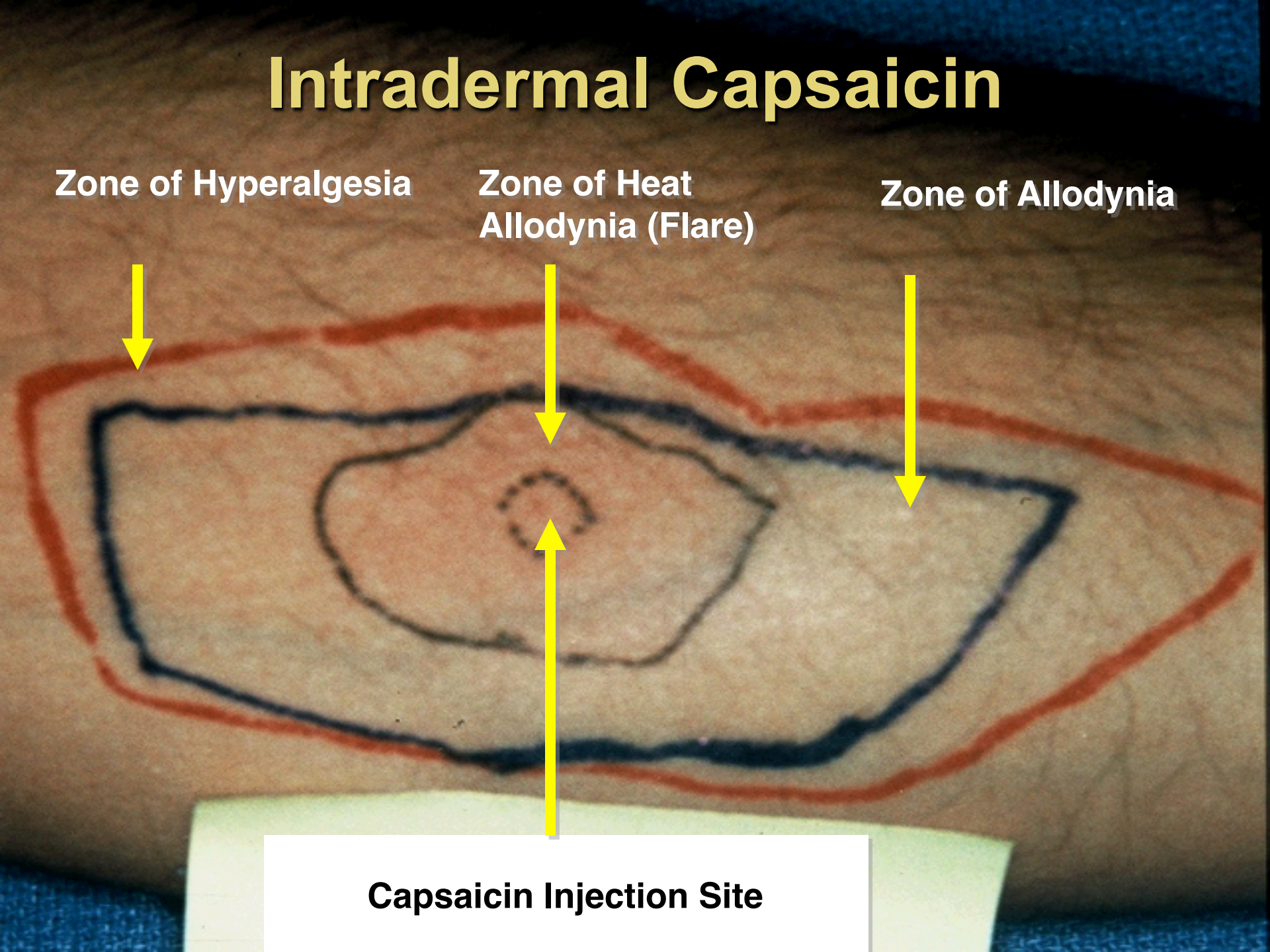
Zone of Hyperalgesia

Zone of Heat
Allodynia (Flare)

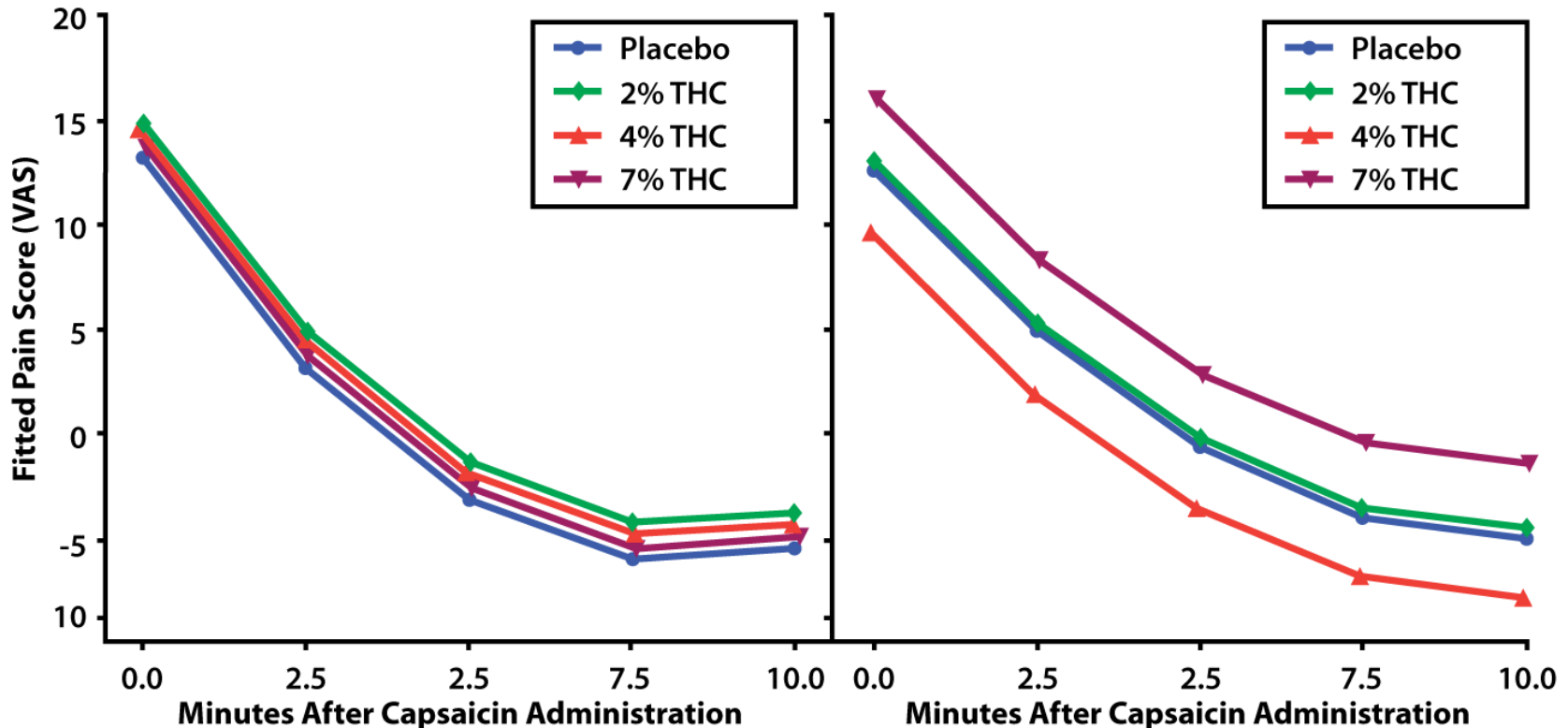
Zone of Allodynia



Capsaicin Injection Site



Experimental Pain



The effects of smoked cannabis on pain induced by the injection of capsaicin 20 minutes (early) and 55 minutes (late) after cannabis administration. Results are presented using the fitted data of the VAS pain intensity scores.

Source: Wallace, et al. 2007. *Anesthesiology*. 107(5):785-796,

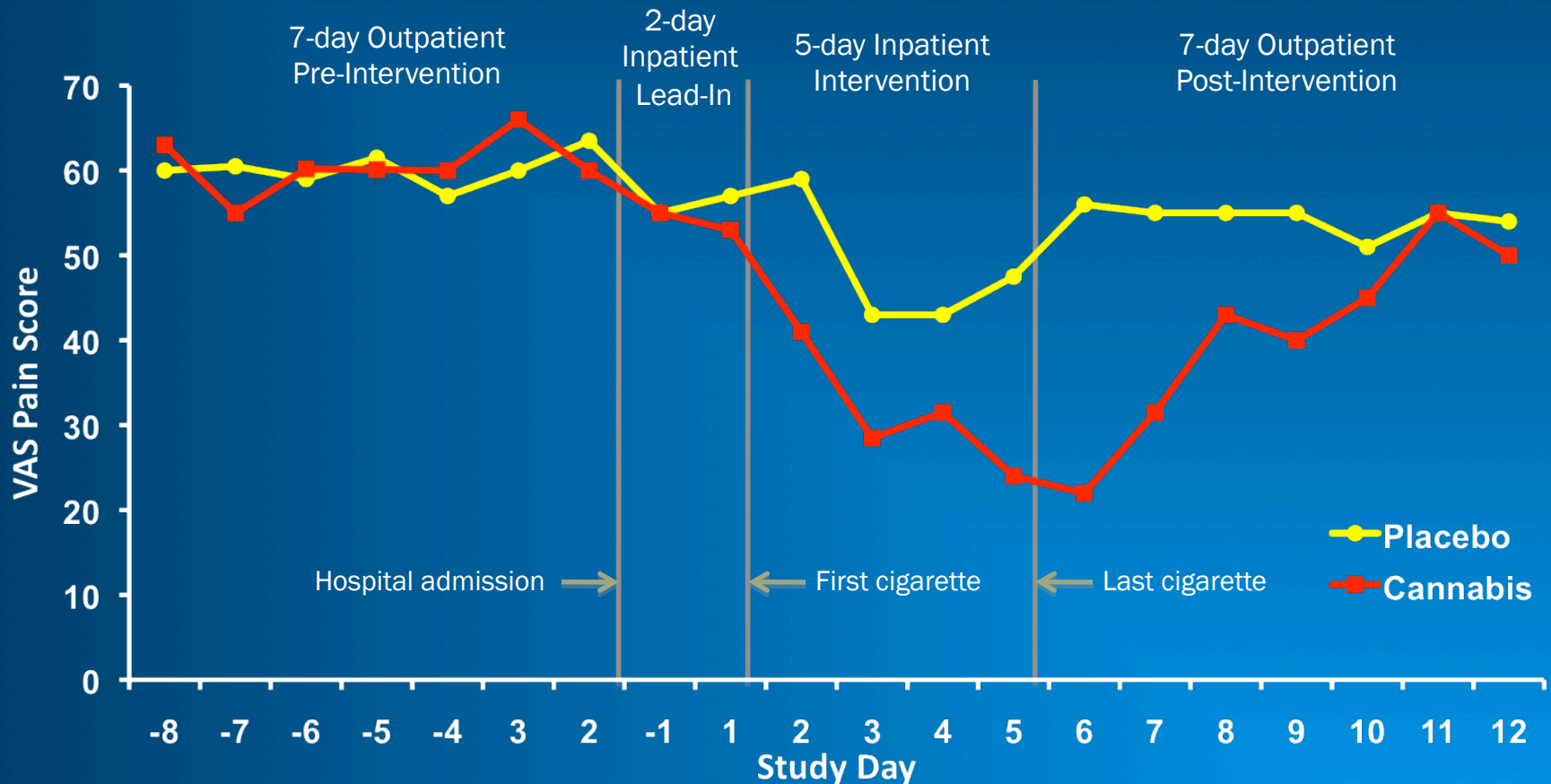
The Effects of Smoked Marijuana on Chronic Neuropathic and Experimentally- induced Pain in Patients With HIV Peripheral Neuropathy – A Feasibility Study

Donald I Abrams, MD, Cheryl Jay, MD,
Starley Shade, MPH, Hector Vizoso, RN,
Haatem Reda, BA, Mary-Ellen Kelly, MPH, Michael C
Rowbotham, MD, Karin L Petersen, MD

Study Design

Study Design	Placebo-Controlled, randomized, parallel groups study
Enrollment	50 subjects
Population	HIV+
Pain Model	Peripheral Neuropathy
Dose protocol	3 sessions per day, 5 days
Dose(s)	0%, 4%

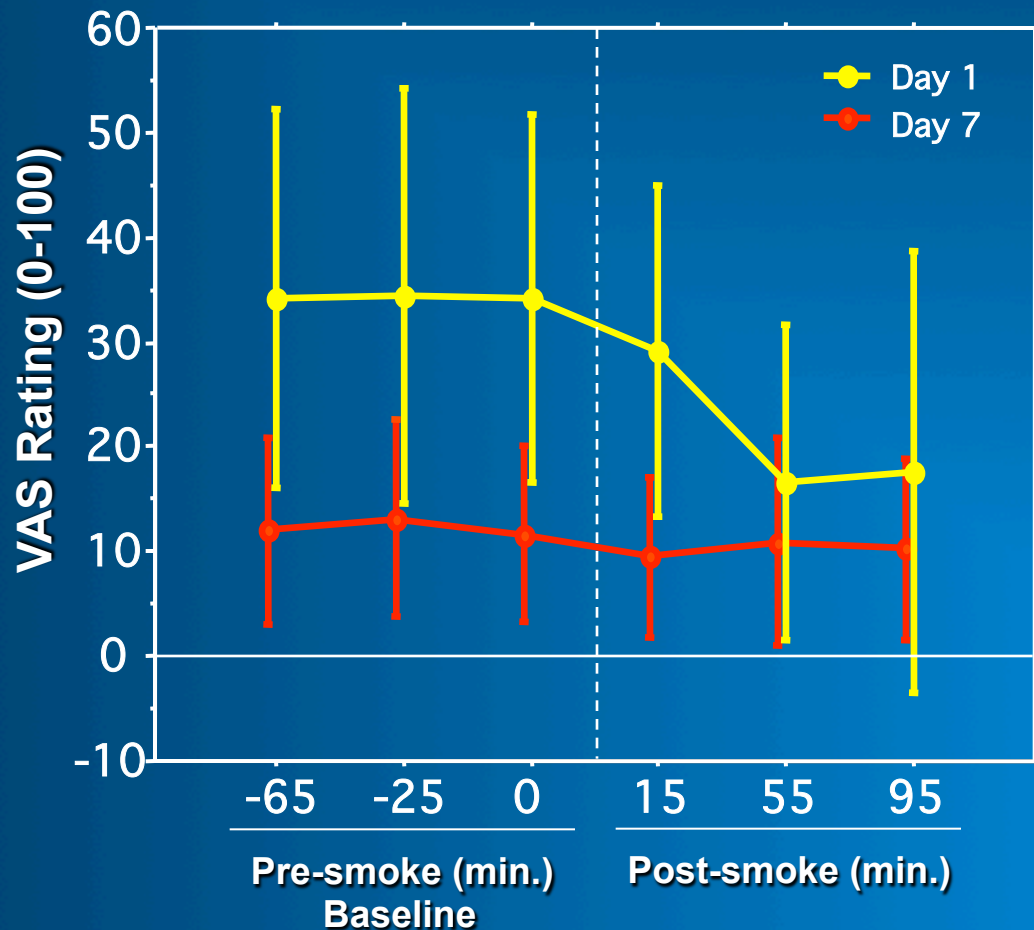
HIV-Neuropathic Pain



Intensity of neuropathic pain as rated on the daily diary VAS at 8 a.m. for the previous 24 hour period. Each point represents the group median.

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

Acute Effect of Marijuana on Neuropathy Pain



→ 13 of 16 patients experienced $\geq 30\%$ reduction in pain after smoking

Error bars = ± 1 Std Dev

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

Short-term, Placebo-controlled Trial of Medicinal Cannabis for Painful HIV Neuropathy

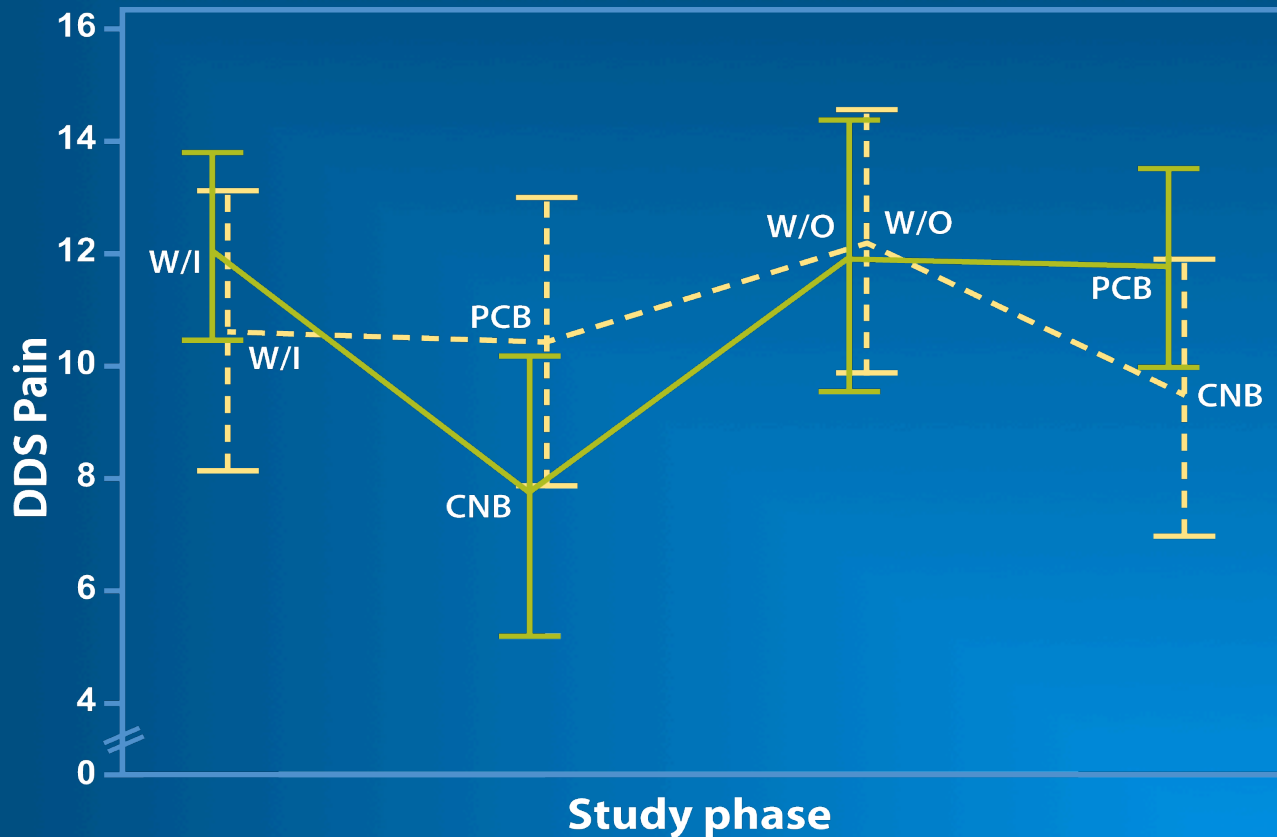
Ron Ellis, MD, PhD, Will Toperoff, RN,
Florin Vaida, PhD, Geoffrey van den Brande, RN, James Gonzales, PharmD,
Ben Gouaux, BA, Heather Bentley, CCRA, J. Hampton Atkinson, MD

Neuropsychopharmacology. 2009 Feb;34(3):672-80. Epub 2008 Aug 6

Study Design

Study Design	Placebo-Controlled, randomized, crossover study
Enrollment	28 subjects
Population	HIV+
Pain Model	Peripheral Neuropathy
Dose protocol	4 sessions per day, 5 days
Dose(s)	0%, 1-8% Dose Titration on Day 1 (begins at 4% or placebo)

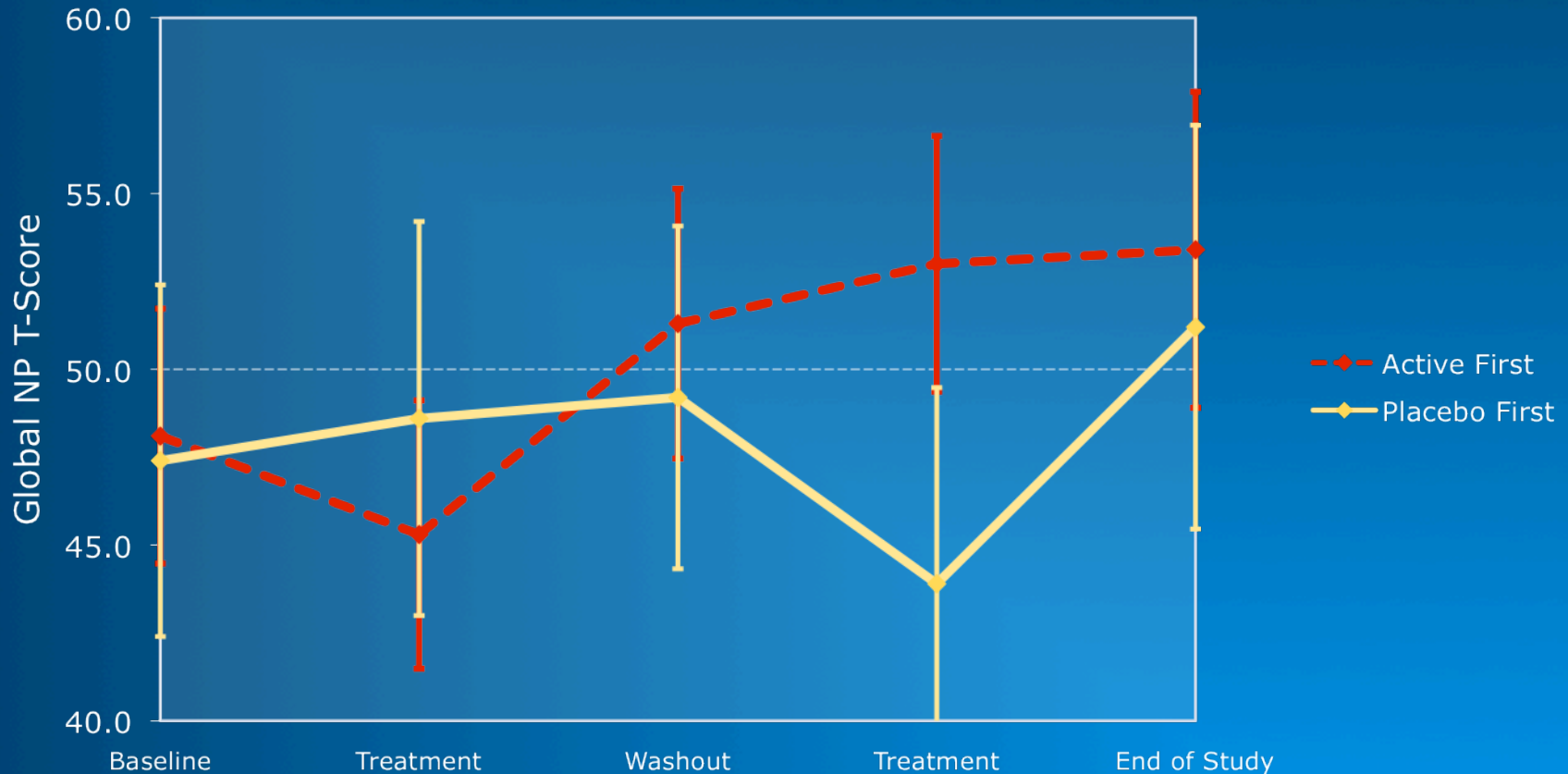
Reduction in HIV-Neuropathic Pain



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.

Neurocognitive Effects after 3 Days of Daily Cannabis Administration to Neuropathy Patients



Neuropsychological t-scores after active and placebo cannabis administration. Active cannabis reduced the NP T score by a median of 7.3 points (IQR = -10.6, - 2.6), $p < 0.001$. Treatment = third day; washout = 2 wk after last treatment

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

A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain

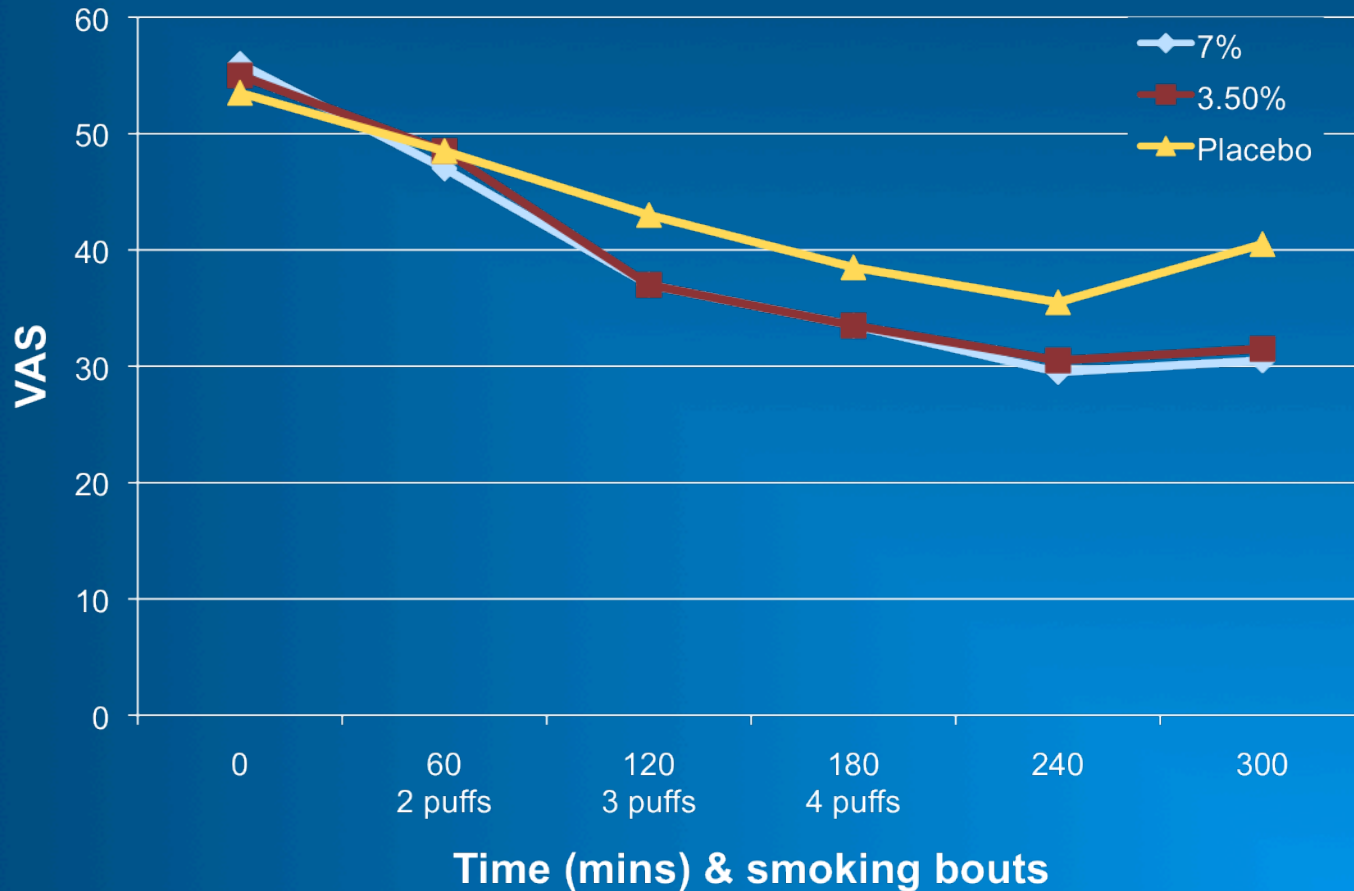
Barth Wilsey, MD, Thomas Marcotte, PhD,
Alexander Tsodikov, PhD, Jeanna Millman, BS,
Heather Bentley, CCRA, Ben Gouaux, BA,
Scott Fishman, MD

Journal of Pain, 9 (6); 506-521

Study Design

Study Design	Placebo-Controlled, randomized, crossover study
Enrollment	33 subjects
Population	Mixed Neuropathy
Pain Model	Neuropathic Pain
Dose protocol	3 session cumulative dosing per day
Dose(s)	0%, 3.5%, 7%

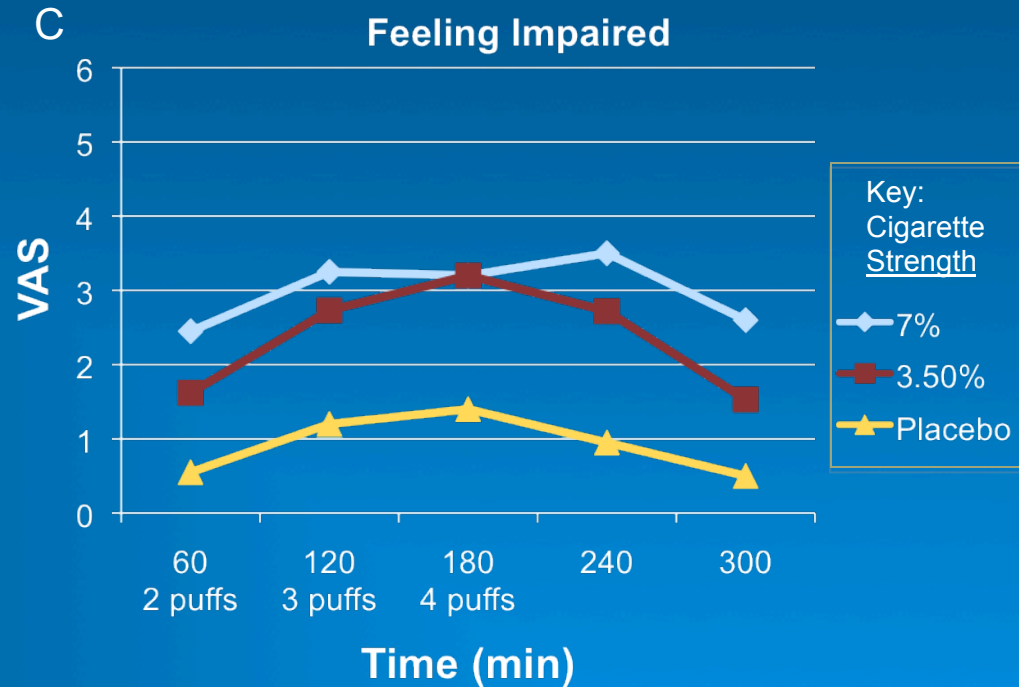
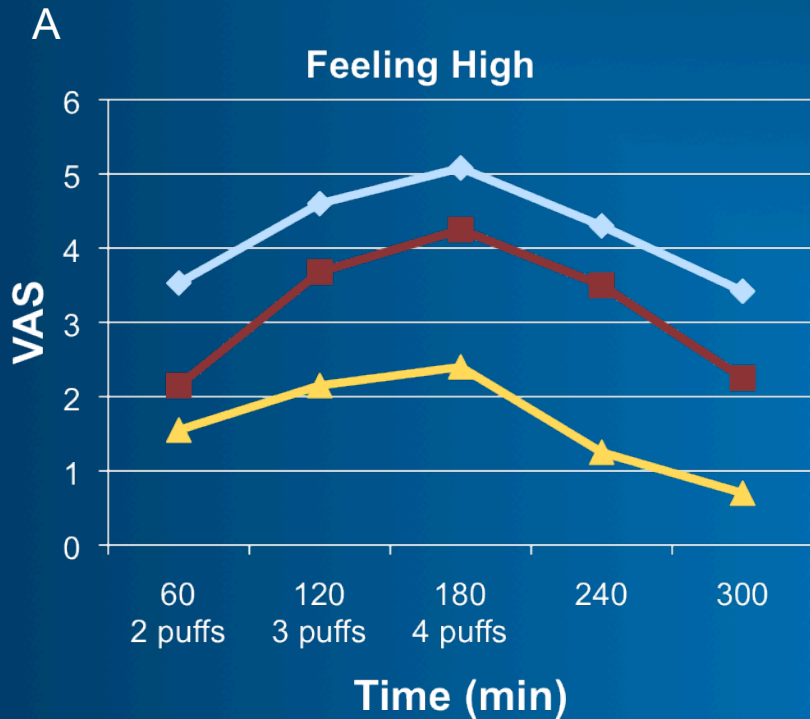
Neuropathic Pain



Mean visual analog scale (VAS) pain intensity scores before and after cannabis administration.

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

Psychoactive Effects



Mean visual analog scale (VAS) pain intensity scores before and after cannabis administration.

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

Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial

Mark A. Ware, MBBS, Tongtong Wang, PhD,
Stan Shapiro, PhD, Ann Robinson, RN,
Thierry Ducruet, MSc, Thao Huynh, MD,
Ann Gamsa, PhD, Gary J. Bennet, PhD,
Jean-Paul Collet, MD, PhD

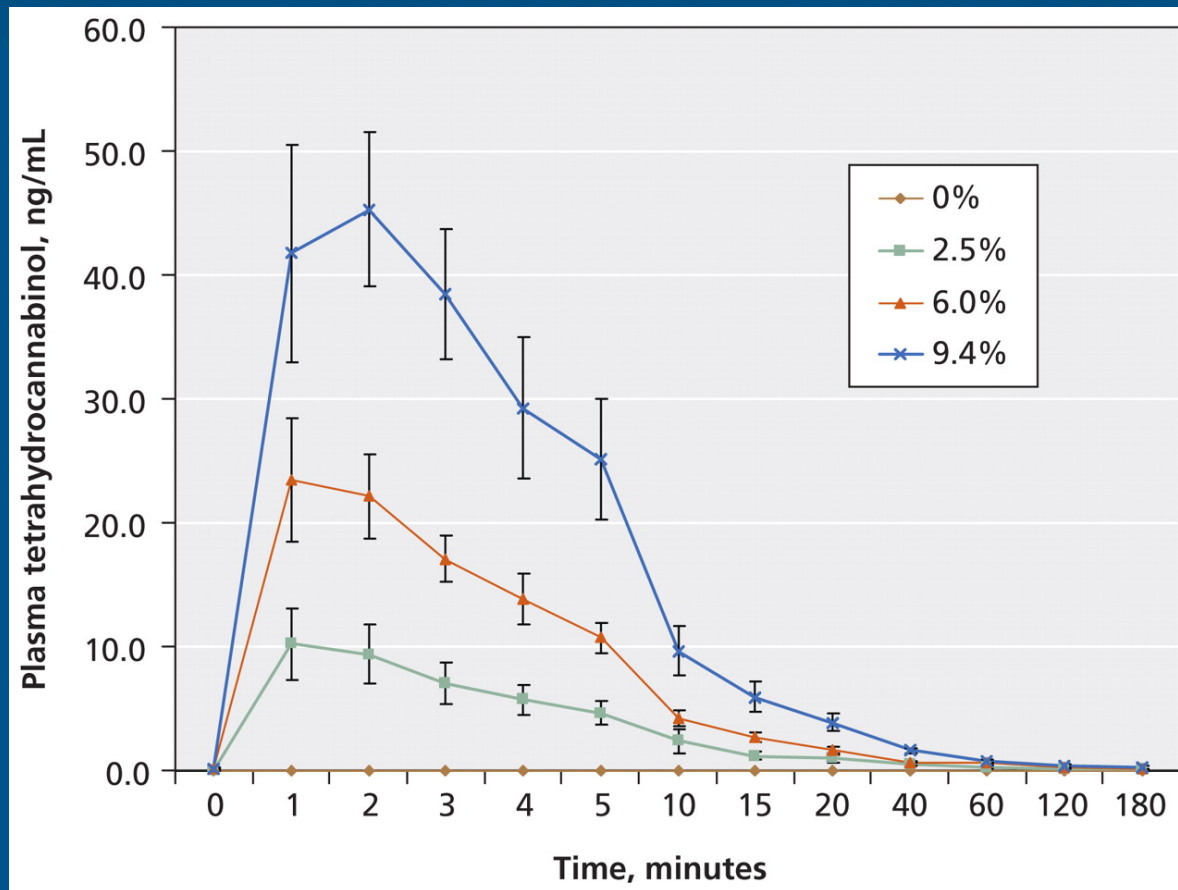
Study Design

Study Design	Placebo-Controlled, randomized, crossover study
Enrollment	23 subjects
Population	Post-traumatic or postsurgical pain
Pain Model	Neuropathic pain
Dose protocol	25mg dose 3x daily for 5 days
Dose(s)	0%, 2.5%, 6%, 9.4%

Methods

- **Baseline**
 - » Average weekly pain score >4/10
 - » Duration of pain at least 3 months
 - » Stable analgesic regime
- **Treatment Schedule**
 - » 5 day treatment phase
 - 25mg cannabis or placebo smoked 3x daily
 - » 9 day washout phase
- **Primary Outcome Measure**
 - » Reduction in average daily pain intensity on 11-point numeric rating scale
- **Secondary Outcome Measures**
 - » Improvement in pain quality, sleep, mood, and quality of life

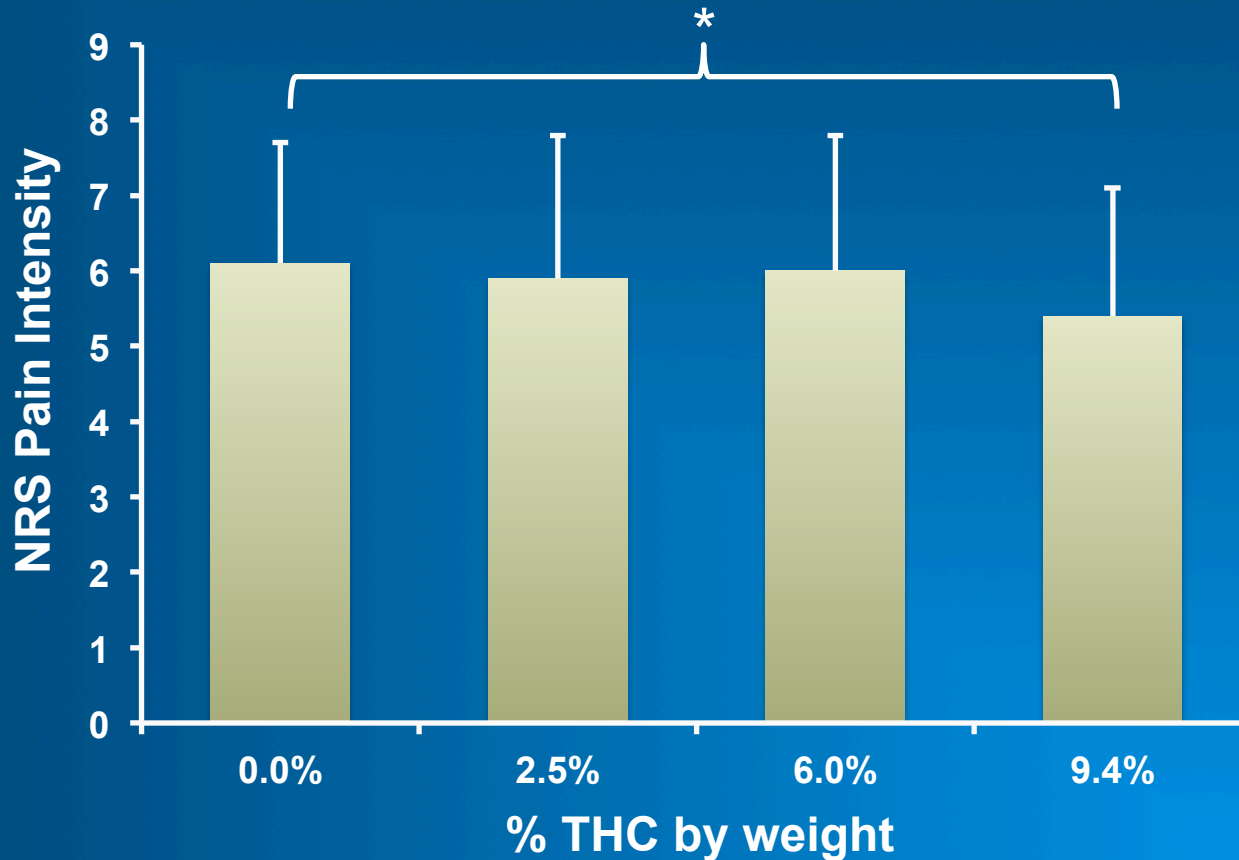
Plasma THC Levels



Levels of tetrahydrocannabinol (THC) in plasma after inhalation of a single dose. Data are presented as means and standard deviations.

Source: Ware, et al. 2010. CMAJ. 2010 Oct 5;182(14):E694-701

Pain Intensity Scores



*p < 0.05

A significant reduction in average daily pain intensity was found between 9.4% THC and placebo (p < 0.05). Error bars represent SD.

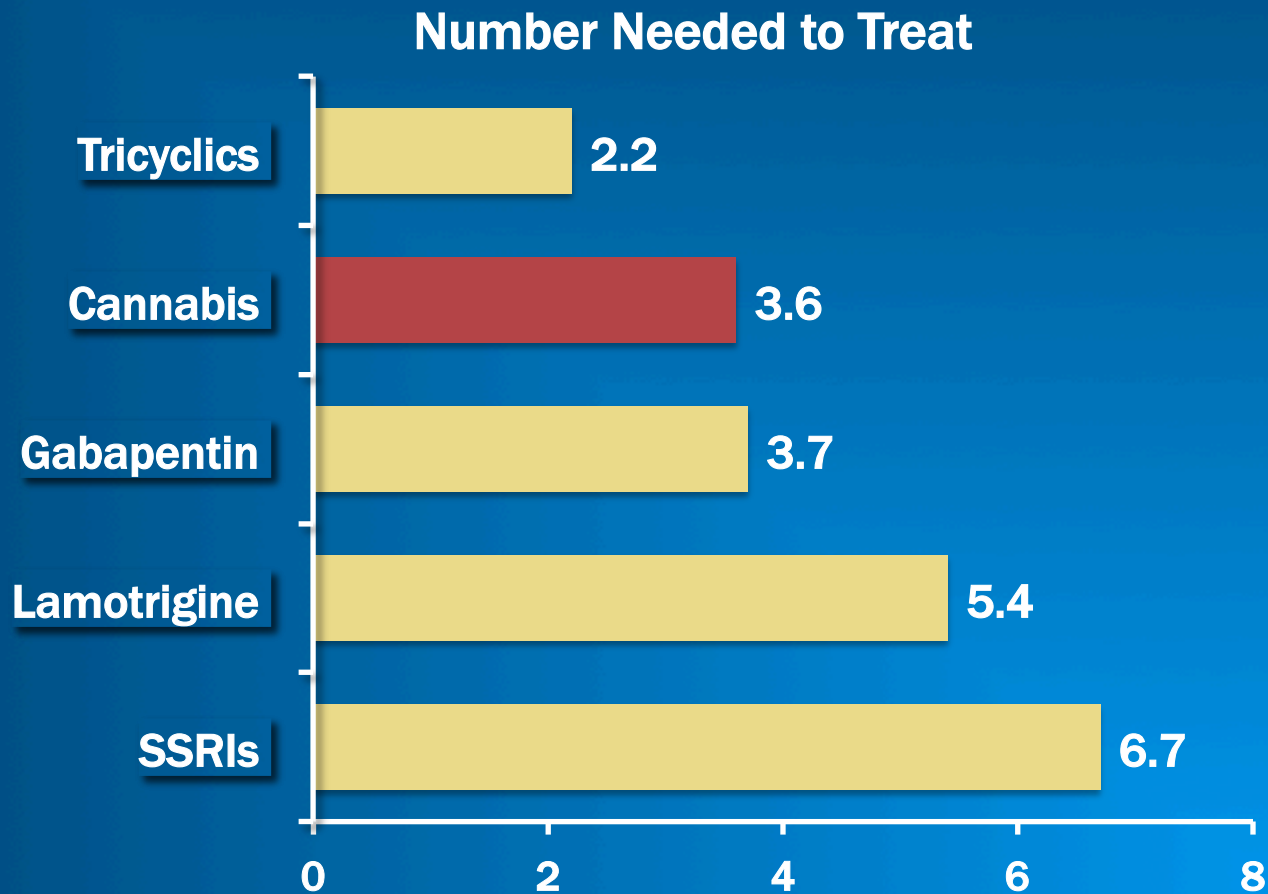
Source: Ware, et al. 2010. CMAJ. 2010 Oct 5;182(14):E694-701.

How effective is cannabis relative to other 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.*

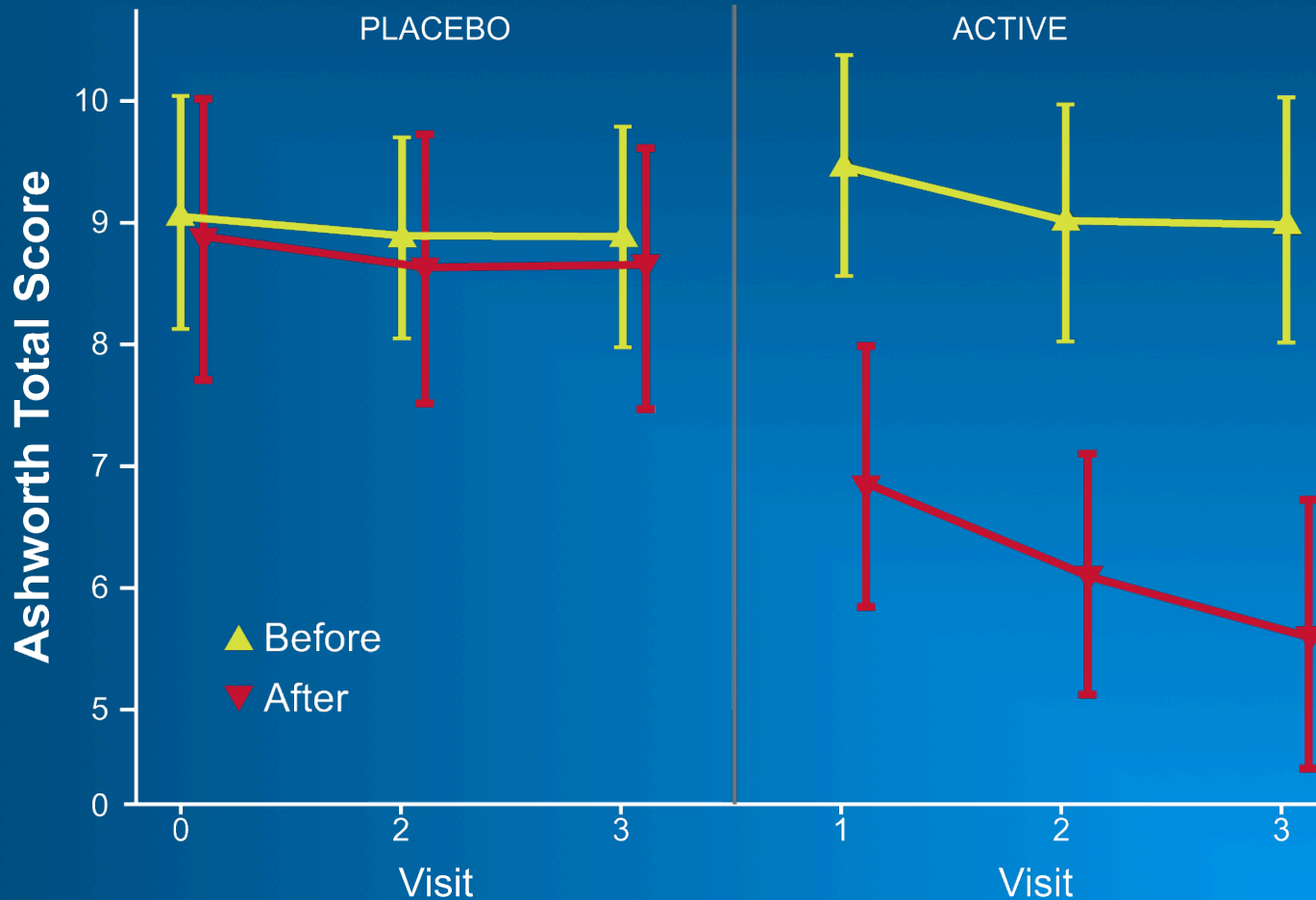
Short-Term Effects of Medicinal Cannabis on Spasticity in Multiple Sclerosis

Jody Corey-Bloom, MD, PhD, Tanya Wolfson, MA, Anthony Gamst, PhD, Sheila Jin, MS, Tom Marcotte, PhD, Heather Bentley, CCRA, Ben Gouaux, BA

Study Design

Study Design	Placebo-Controlled, randomized, crossover study
Enrollment	30 subjects
Population	Multiple Sclerosis
Condition	Spasticity
Dose protocol	1 session per day, 3 days
Dose(s)	0%, 4%

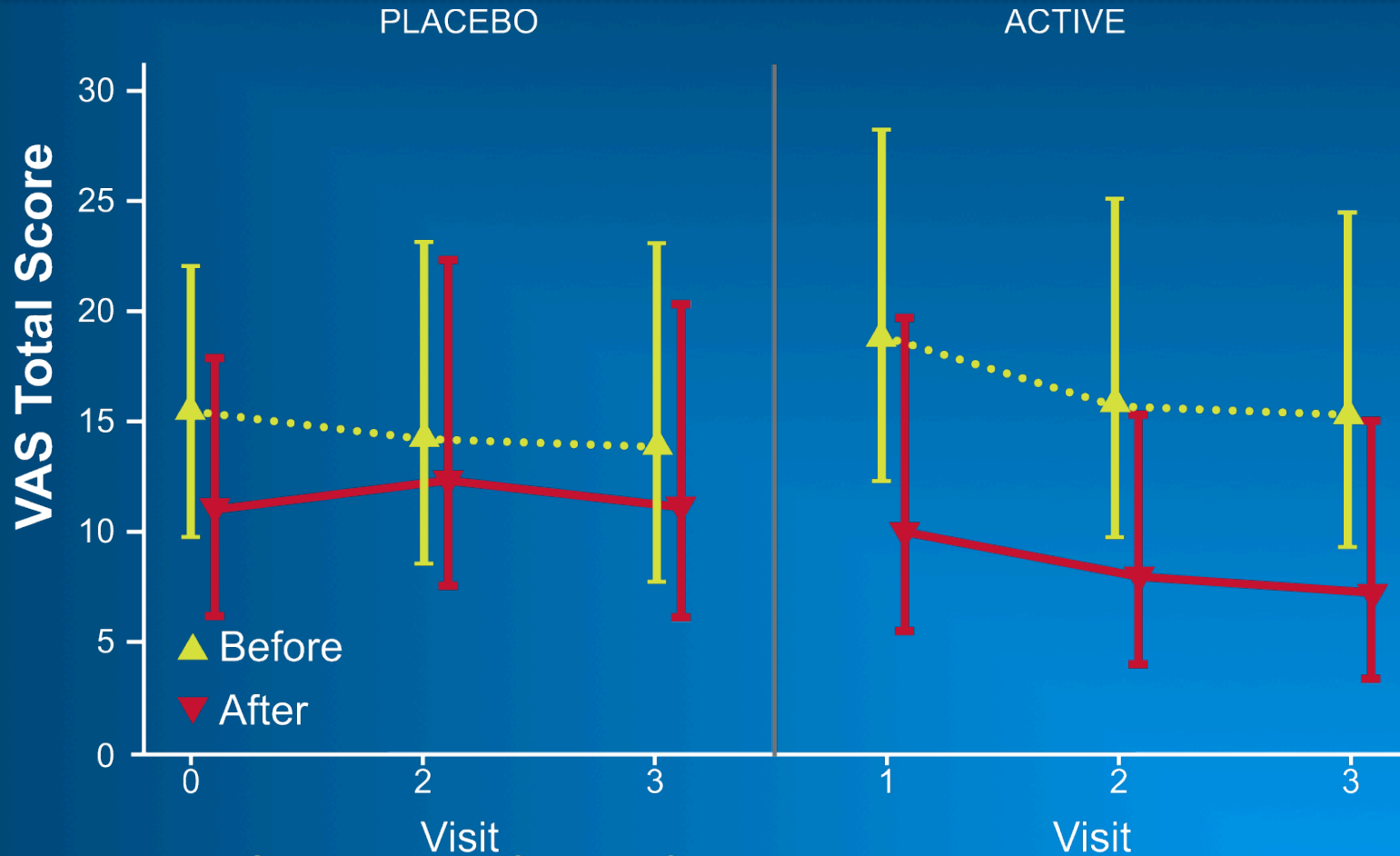
Cannabis for MS Spasticity



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. In preparation.

Cannabis for MS Pain



Visual analog scale (VAS) pain scores before and after active and placebo cannabis administration. Active treatment reduced VAS pain scores by an average of 5.3 points more than placebo ($p < 0.01$).

Source: Corey-Bloom, et al. In preparation.

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

Acute and Short Term Adverse Effects Reported in Clinical Trials Literature

Medical & Neurological

- Dizziness (50%)
- Dry Mouth (25%)
- Fatigue (25%)
- Muscle complaints eg., weakness, myalgia (15%)
- Palpitations (20%)
- Ataxia (10%)
- Syncope (<5%)
- Hypotension (<5%)

Neuropsychiatric

- “High” or Intoxicated (dose dependent)
- Neurocognitive (dose dependent)
 - » processing speed
 - » perceptual (time sense; visual; other senses)
 - » reaction time
 - » attention
 - » recall
- Euphoria (5-25%)
- Anxiety (5-25%)
- Paranoia/Psychosis (< 1%)

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

- » Safety of combustible material in clinical setting
- » Second hand smoke as an irritant
- » 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



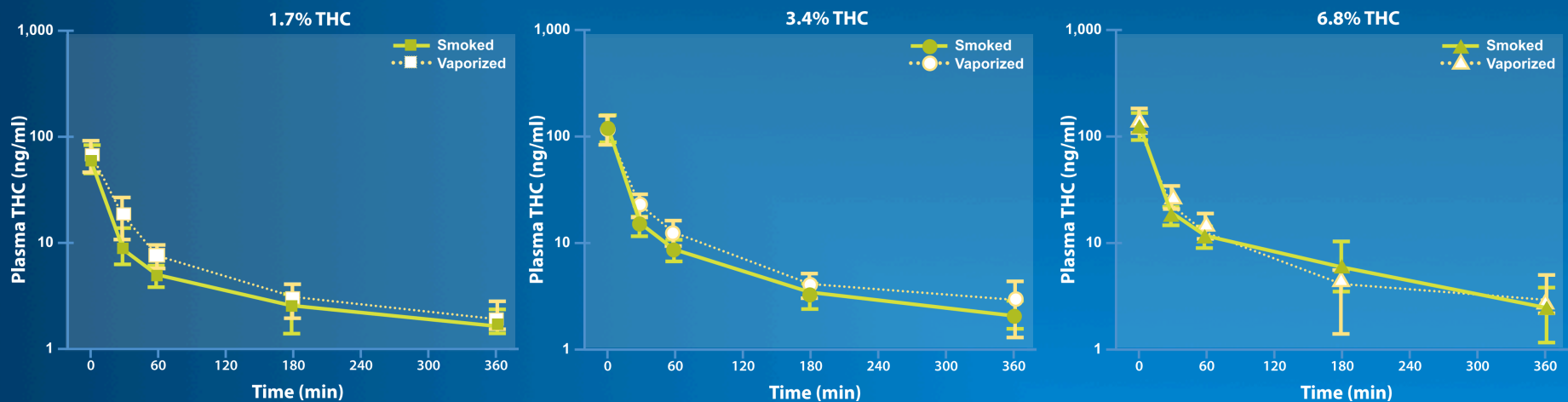
Vaporization as a Smokeless Cannabis Delivery System – A Pilot Study

Donald I Abrams, MD, Hector Vizoso, RN,
Starley Shade, MPH, Cheryl Jay, MD,
Mary-Ellen Kelly, MPH, Neil Benowitz, MD

Study Design: “Volcano”

Study Design	Randomized, crossover study
Enrollment	18 subjects
Population	Healthy volunteers
Dose protocol	1 session per day, 6 days
Dose(s)	1.7%, 3.4%, 6.8%

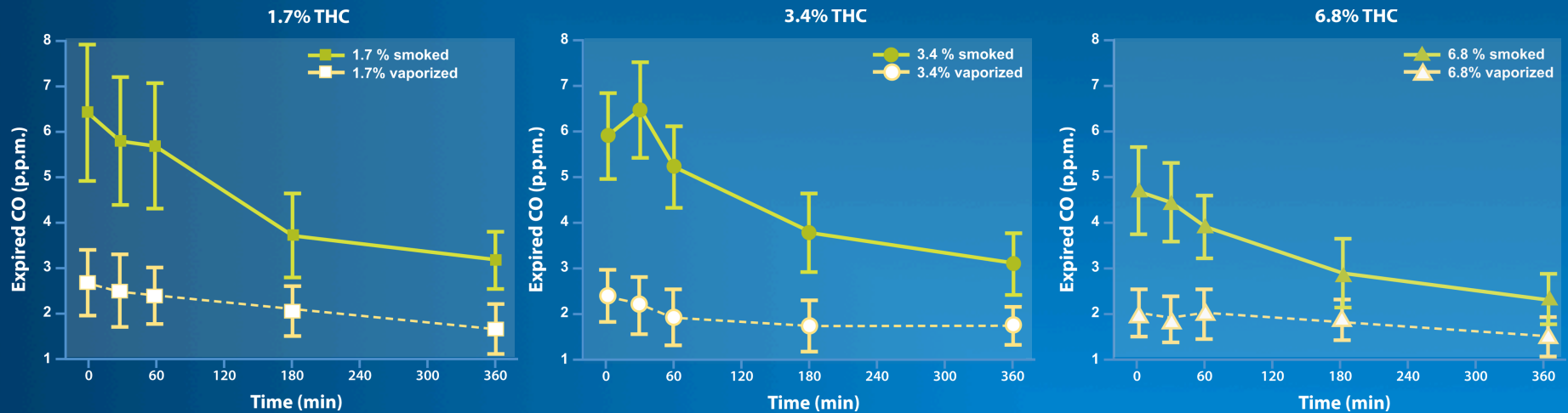
Alternative Delivery Systems: “Volcano”



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

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

Alternative Delivery Systems: “Volcano”



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.

Alternative Delivery Systems: “Volcano” Summary

- Plasma THC levels were comparable between smoked and vaporized cannabis
- Vaporization resulted in reduction in expired CO levels compared to smoking
- Subjective ratings of “highness” were comparable between groups
- Overall, 14 subjects preferred vaporization, 2 subjects preferred smoking, and 2 subjects expressed no preference

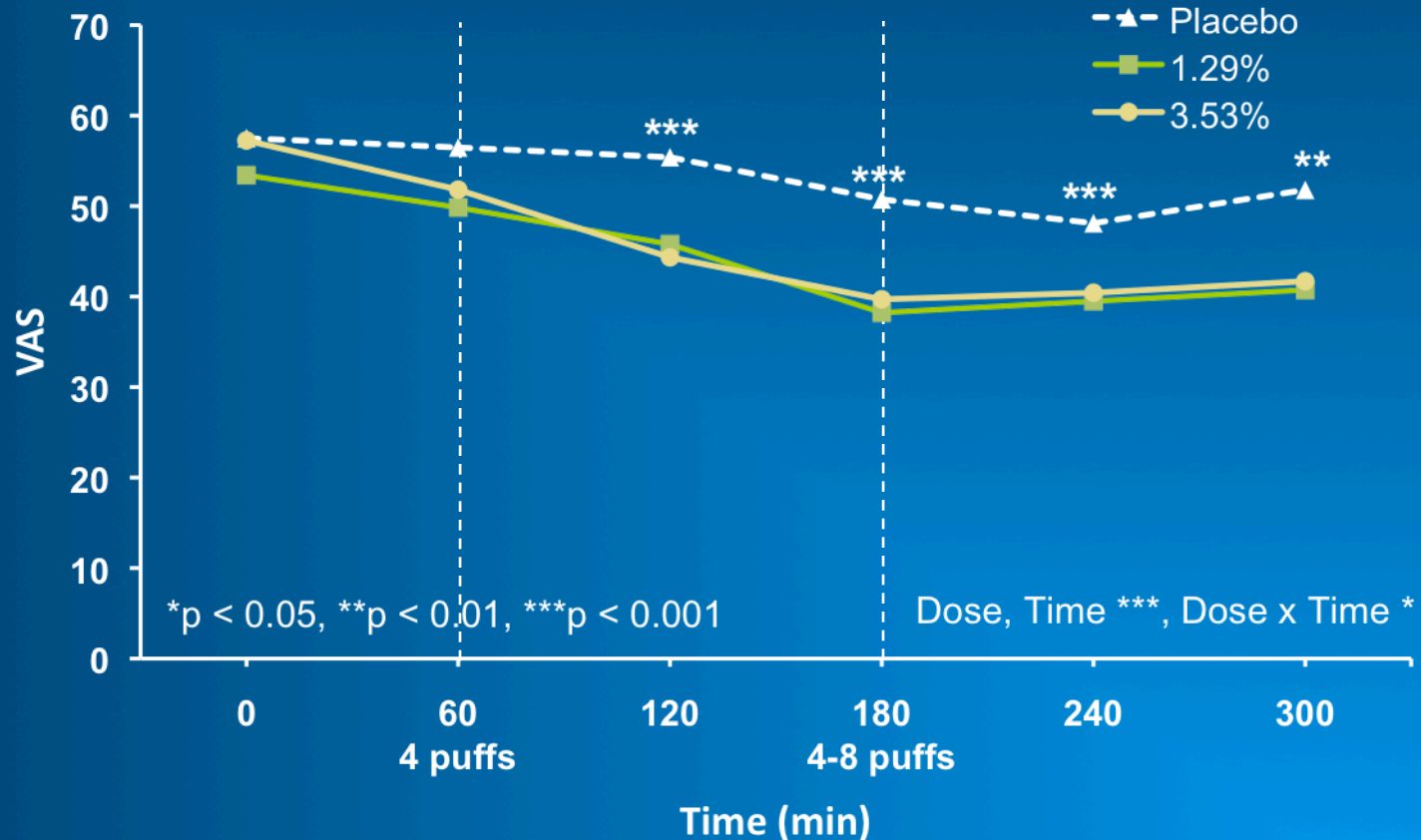
The Analgesic Effect of Vaporized Cannabis on Neuropathic Pain

Barth Wilsey, MD, Thomas Marcotte, PhD,
Reena Deutsch, PhD, Ben Gouaux,
Stacy Sakai, Haylee Donaghe

Study Design

Study Design	Placebo-Controlled, randomized, crossover study
Enrollment	39 subjects
Population	Mixed Neuropathy
Pain Model	Neuropathic Pain
Dose protocol	2 session cumulative dosing per day using volcano vaporizer
Dose(s)	0%, 1.29%, 3.53%

Neuropathic Pain



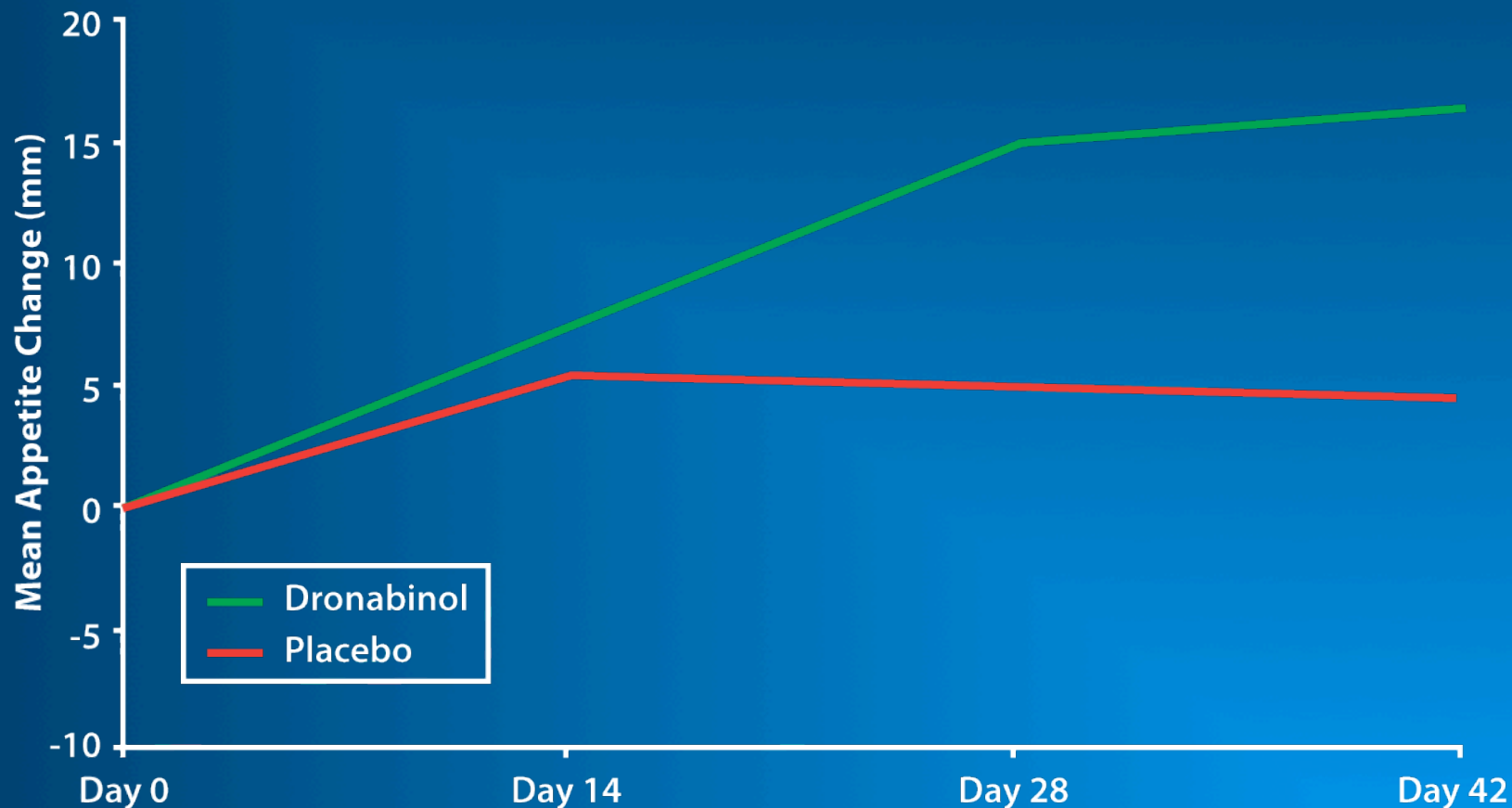
Mean visual analog scale (VAS) pain intensity scores before and after cannabis administration.

Source: Wilsey, et al. In progress..

Other current or potential cannabinoid compounds

- **Dronabinol, Nabilone**
 - » Synthetic THC analogs
- **Nabiximols**
 - » THC/CBD plant extract
- **CT-3 (ajulemic acid)**
 - » CB1 agonist
- **Rimonabant (SR141716A)**
 - » CB1 inverse agonist–withdrawn
- **Taranabant**
 - » CB1 inverse agonist–withdrawn

Dronabinol for Appetite Stimulation



Mean change in appetite from baseline, evaluable patients.

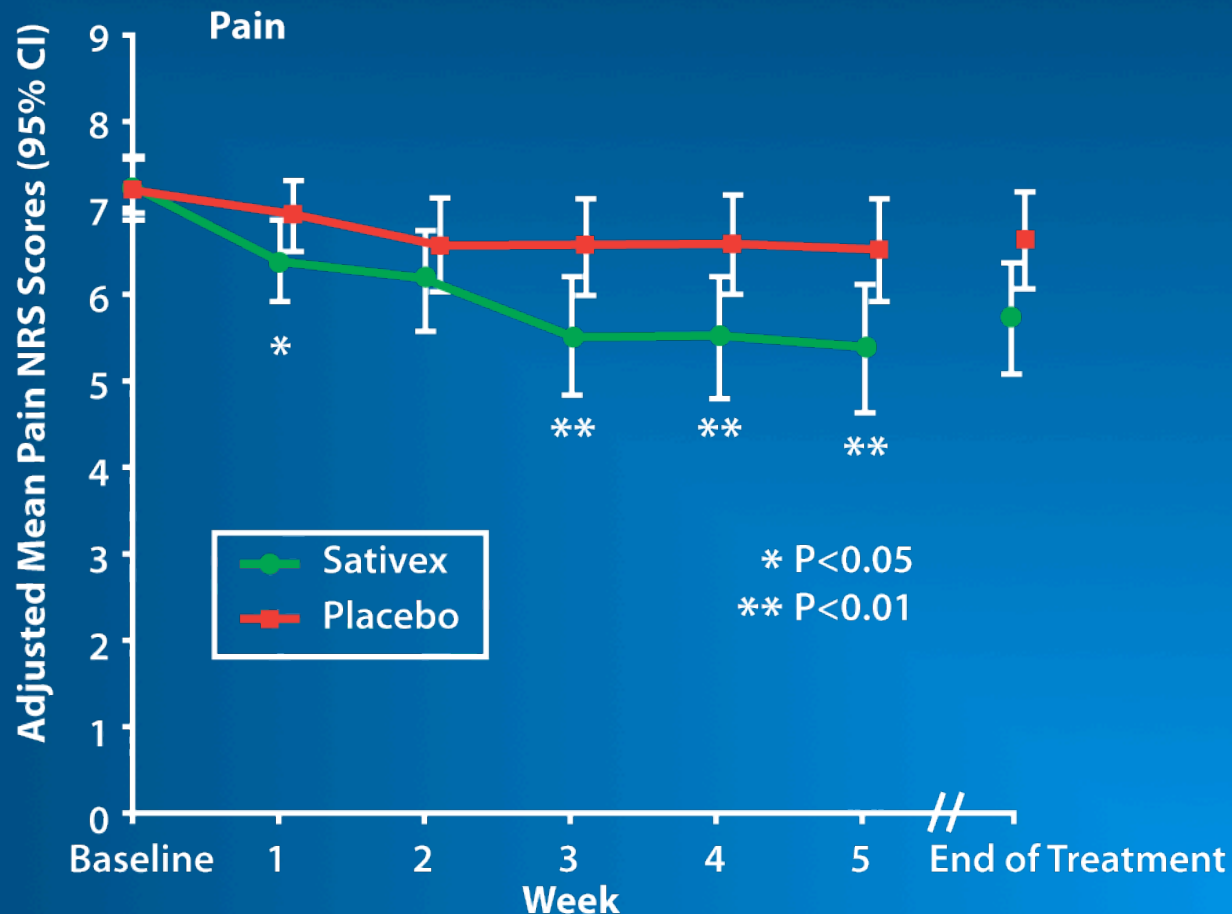
Source: Beal, et al. (1995). *Journal of Pain and Symptom Management*. 10;2. 89-97.

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)



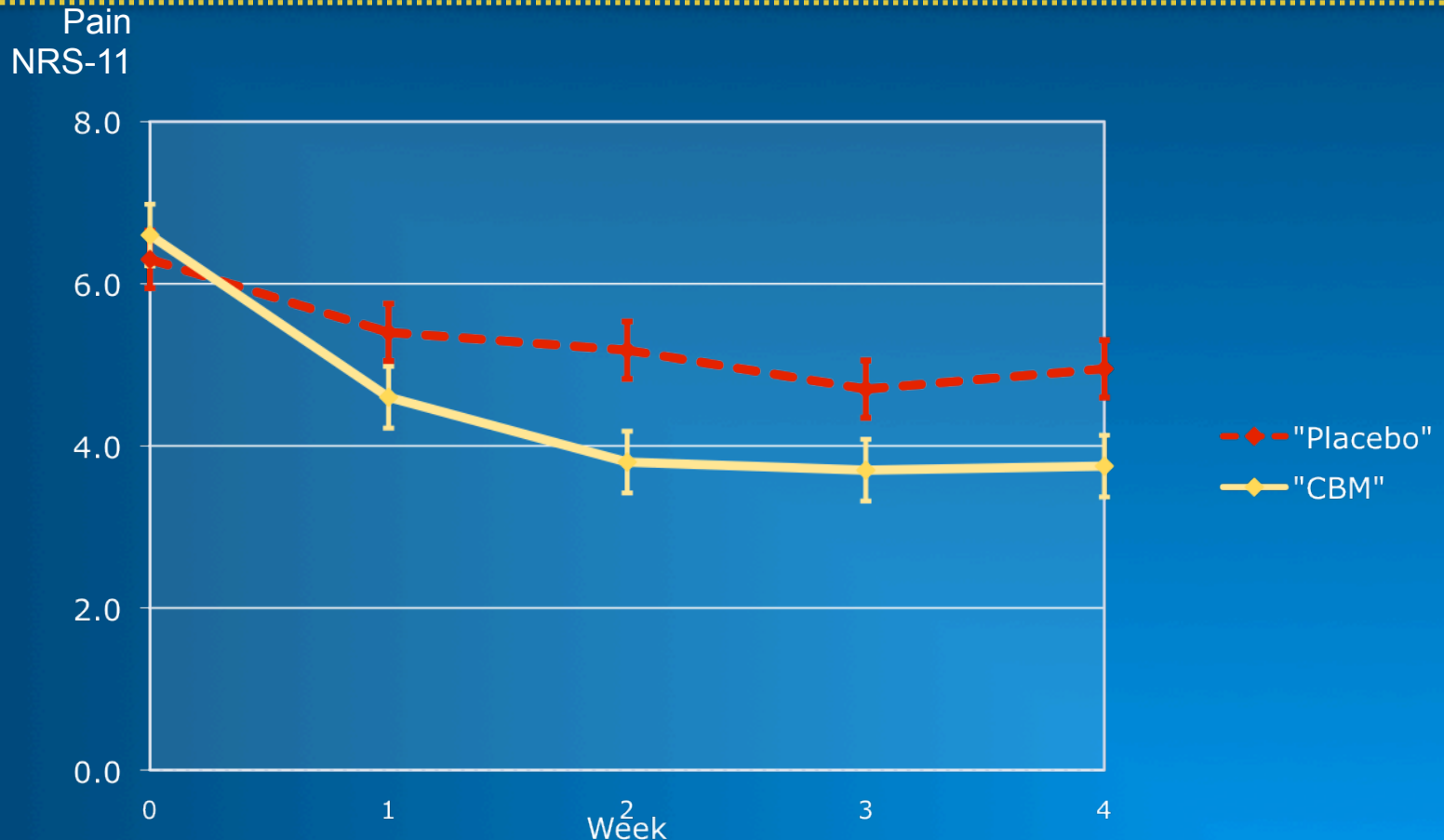
Nabiximols (Sativex®) for Neuropathic Pain



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 Pain



Mean 11-point numerical rating scale (NRS-11) pain scores (\pm SEM) for the cannabis-based medicine (CBM) (n=33) and placebo group (n=32). Week 0 refers to the run-in week. The patients were on test medication in weeks 1 to 4.

Source: Rog, et al. (2005). *Neurology*. 65;812-819.

Nabiximols (Sativex[®]) for MS Spasticity

■ Design & Methods:

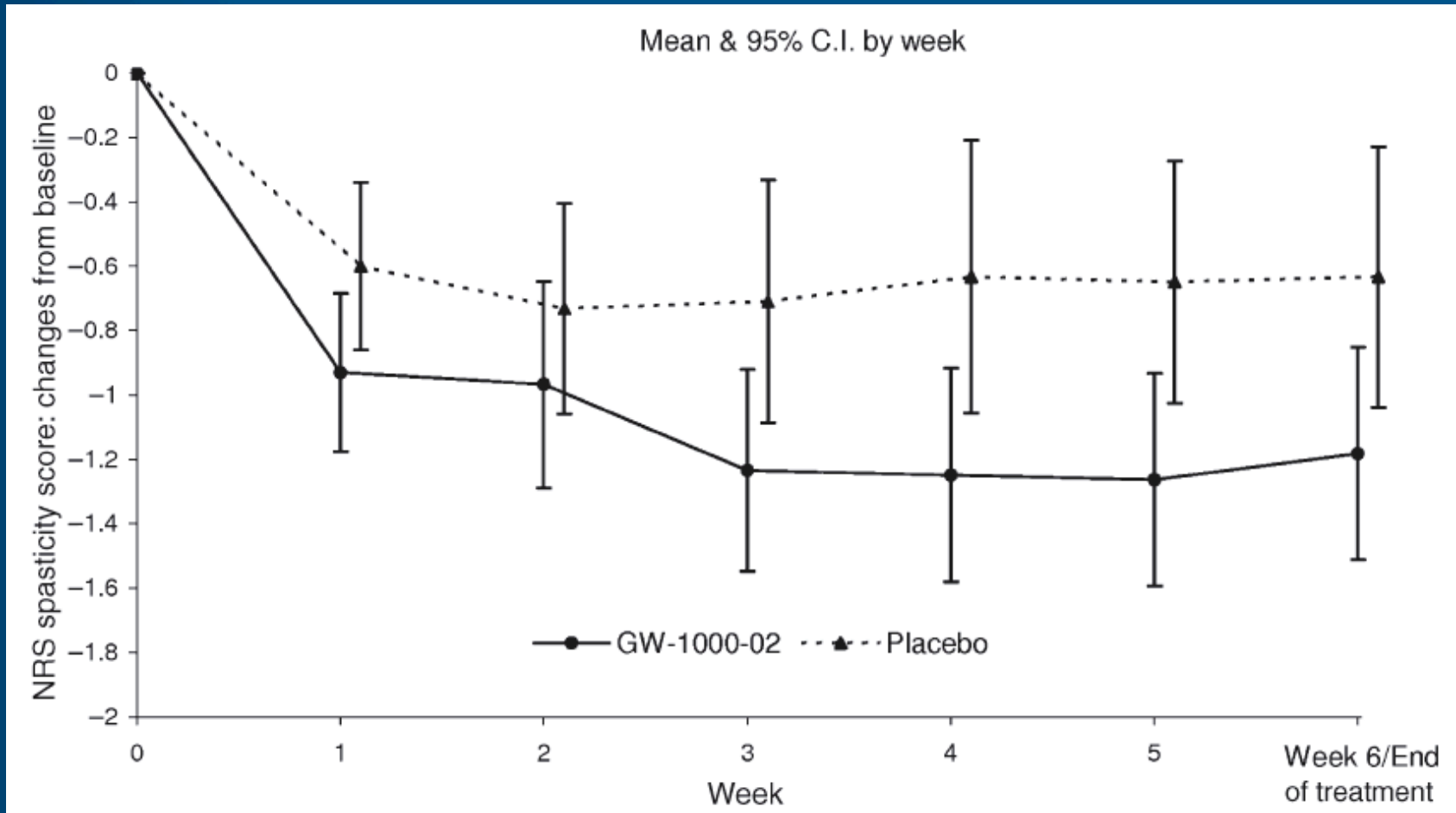
- » Multi-center, randomized, double-blind, parallel group study
- » Adults with stable multiple sclerosis for >3 mos who have not responded positively to spasticity treatment
- » Active oralmucosal spray (Sativex, GW Pharmaceuticals) vs. placebo for 6 weeks for treatment of spasticity

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.

Cannabinoid Agonist CT-3

Analgesic Effect of the Synthetic Cannabinoid CT-3 on Chronic Neuropathic Pain A Randomized Controlled Trial

Matthias Karst, MD, PhD

Kahlid Salim, MS

Sumner Burstein, PhD

Ingomar Conrad, MD

Ludwig Hoy, PhD

Udo Schneider, MD, PhD

Context 1',1'-Dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid (CT-3), a potent analog of THC-11-oic acid, produces marked antiallodynic and analgesic effects in animals without evoking the typical effects described in models of cannabinoids. Therefore, CT-3 may be an effective analgesic for poorly controlled resistant neuropathic pain.

Objective To examine the analgesic efficacy and safety of CT-3 in chronic neuropathic pain in humans.

Design and Setting Randomized, placebo-controlled, double-blind crossover trial

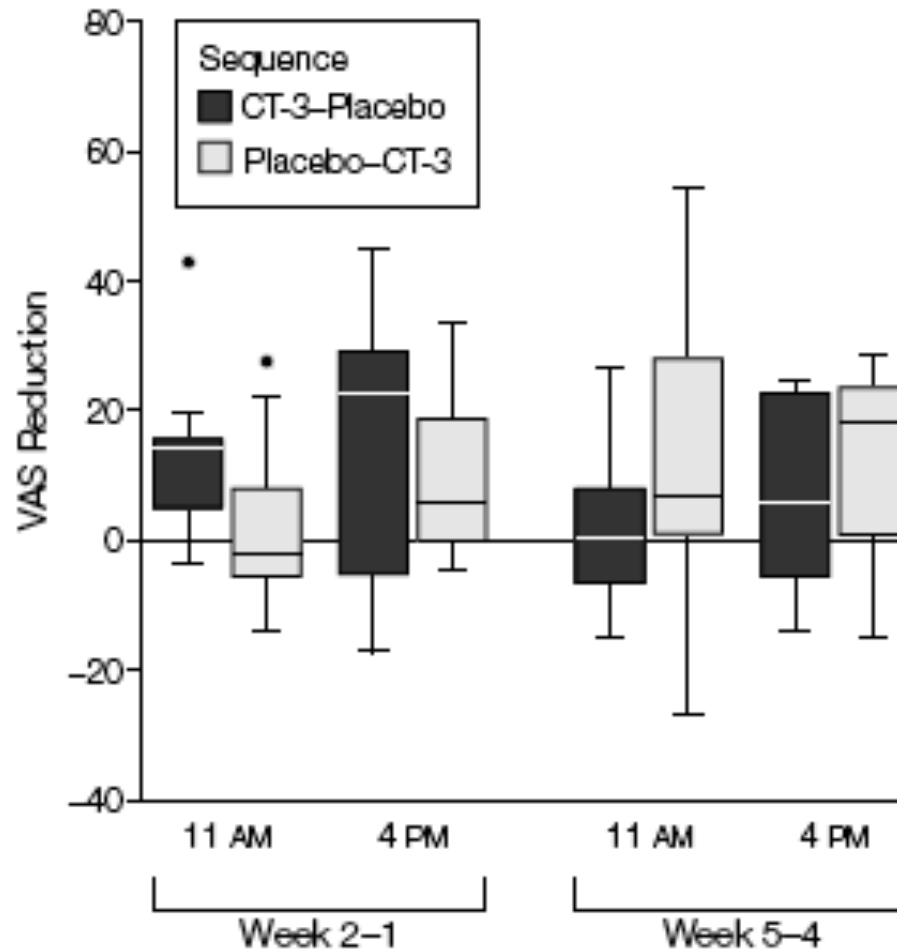
Conclusions In this preliminary study, CT-3 was effective in reducing chronic neuropathic pain compared with placebo. No major adverse effects were observed.

JAMA. 2003;290:1757-1762

www.jama.com

Cannabinoid Agonist CT-3

Effects of CT-3 on reduction in VAS score. The reduction in VAS score was significantly different ($P=.02$) in the 11 AM measurement.



Source: Karst, et al. (2003). JAMA. 290;13. 1757-1762.

Possible Uses of CB Antagonists

- **CB₁ antagonists and appetite suppression**
- **CB₁ antagonists as antipsychotics**
- **CB₁ antagonists and drug abuse treatment**

Challenges In Developing CB Based Pharmaceuticals

- How to separate “undesirable” psychotropic from other effects
- In USA — political climate at federal level has been nonsupportive of medicinal cannabis research
 - » Fear of addiction & diversion discourages full exploration of phytocannabinoids
 - » Concern for lasting toxicity
 - » Resultant perception of poor risk: benefit dampens research & pharma investment in novel molecules
- Endogenous ligands (eg., anandamide) generally not useful - rapidly hydrolyzed

Longer Term Health Consequences of Cannabis: Evidence Unclear (?) for most Major Concerns

Medical

- Respiratory Infection; chronic lung disease?
- Cancers ?
- Myocardial Infarction?
- Teratogenicity?
- Fatal Overdose Not Reported

Neuropsychiatric

- Dependence
- Persisting Neurocognitive impairment?
- Psychotic disorder?
- Neurodevelopmental maturation?

Public Health

- Traffic Accidents
 - Cannabis?
 - Alcohol
 - Cannabis + Alcohol
- Scholastic and occupational difficulties
- “Gateway drug”?

Where Do We Go?

- It is asserted that oral cannabinoids (e.g. dronabinol) are not as effective as smoked marijuana due to:
 - » Markedly different kinetics (eg., poor or variable absorption from gut, first pass metabolism of THC by liver = lower plasma levels)
 - » Less ability to titrate dose
 - » Solution: proper trials comparing modes of administration
- CMCR and other studies point to efficacy of inhaled cannabis in neuropathic pain, perhaps spasticity
 - » Need phase III studies with more diverse, representative patient groups to confirm efficacy and document adverse effects, contraindications
 - » Studies should involve smoked & alternative delivery systems
 - » If efficacy confirmed, need systematic studies of components of efficacy – e.g. THC, CBD & others, alone and in combination

Medicinal Cannabis

Thank you

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