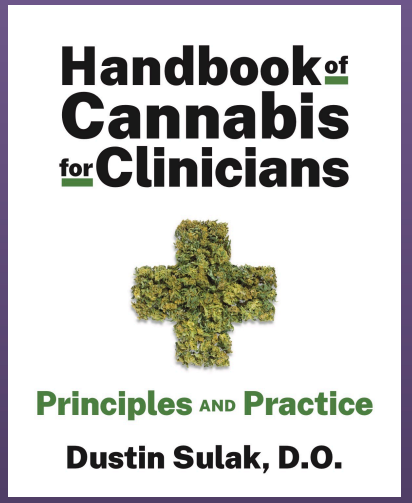
Cannabis Dosing Distilled

Dustin Sulak, D.O.

The 15th National Clinical Conference on Cannabis Therapeutics

Introduction: Dustin Sulak DO

- General practitioner with 11 years clinical experience treating with cannabis.
- Medical director of clinics that have seen >18,000 cannabis-using patients, currently following ~8,000 patients.
- Author and educator



Disclosure

- Healer: equity owner and employee
  - patient education, cannabis and hemp products, industry training, consulting, extraction/formulation
- Forian: former paid scientific advisor
- Society of Cannabis Clinicians: unpaid member of board of directors
- Author of "Handbook of Cannabis for Clinicians: Principles and Practice" published by Norton Professional

Overview

- Wide safe and effective dosing range
- Non-linear dose-response relationships
- Therapeutic window
- THC vs THC/CBD vs CBD
- Dosing for cannabis naïve
- Non-impairing strategies and psychoactive benefits
- Dosing for experienced users
- Dose layering

Goals of Treatment

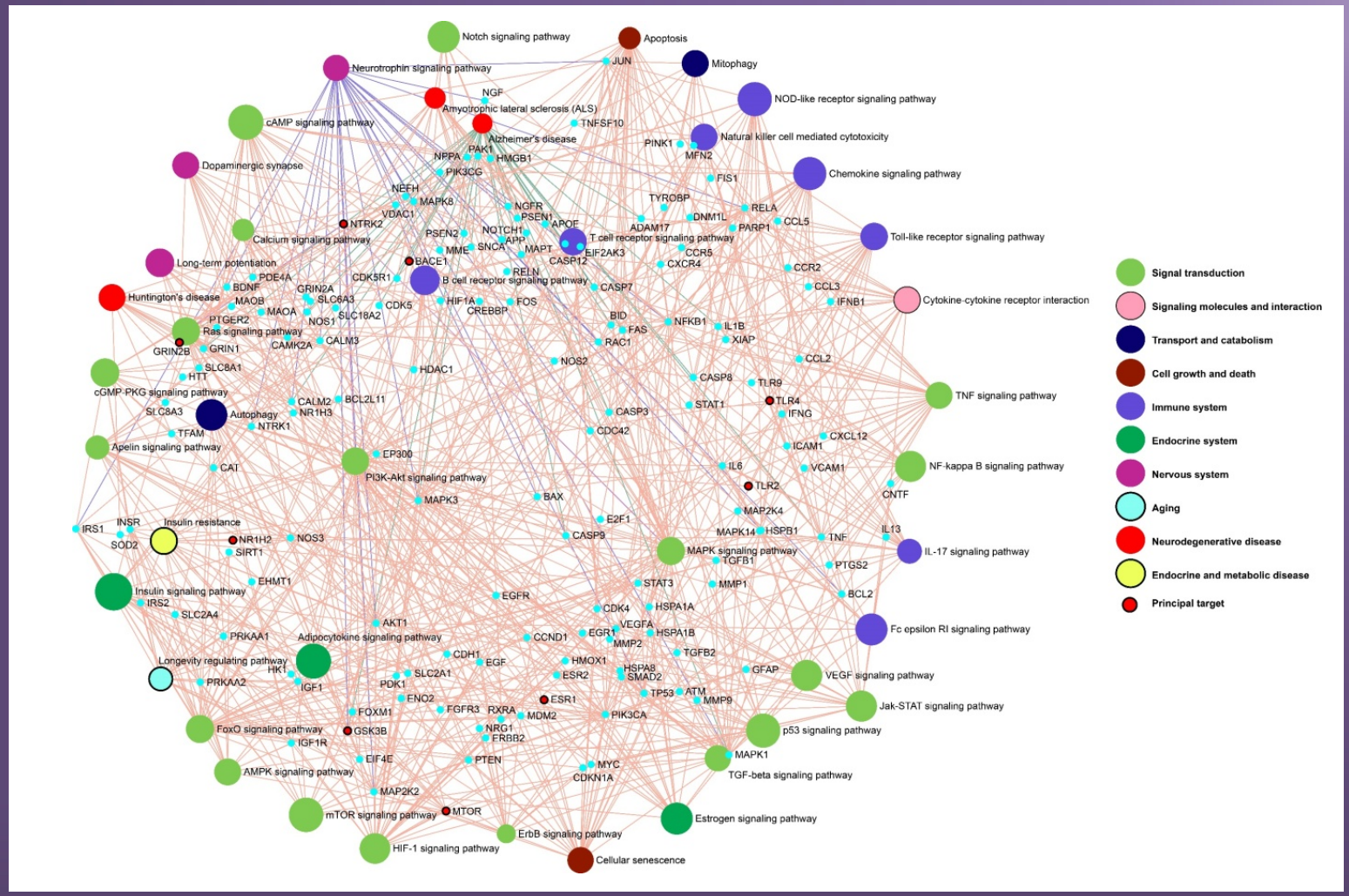
- Improve function and QOL
  - Individually defined goals
- Reduce symptoms
- Improve safety and tolerability of other treatments
- Substitution for more dangerous treatment

Cannabinoid Medicine

- Multi-compound, multi-target medicines
- Interface with the ECS, a homeostatic regulatory system and related targets

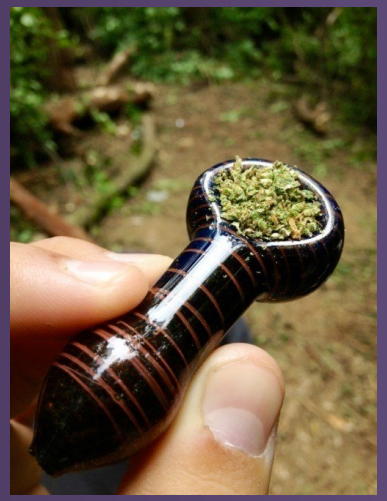
- Treat the patient, not the diagnosis!
- Address barriers to healing (sleep, activity, social and spiritual connection)

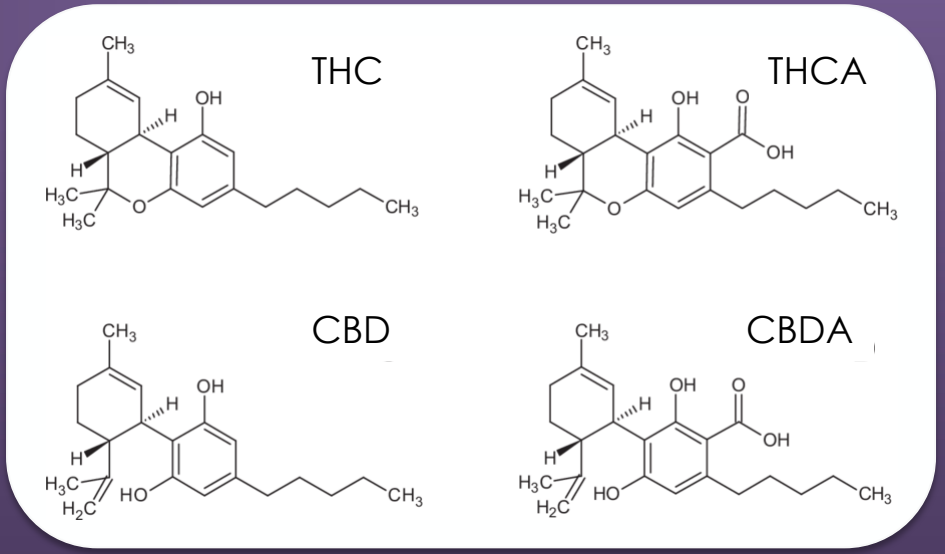
Network Visualization of the Interactions of Curcumin with Alzheimer's Disease



Hannan, Md Abdul, et al. "Mechanistic insights into the curcumin-mediated neuroprotection in Alzheimer's disease: an integrated System Pharmacology and Molecular Simulation Study." (2020).

Cannabis Dosing Nomenclature





Dosing By The Milligram

Oral dosing range effective in my practice:

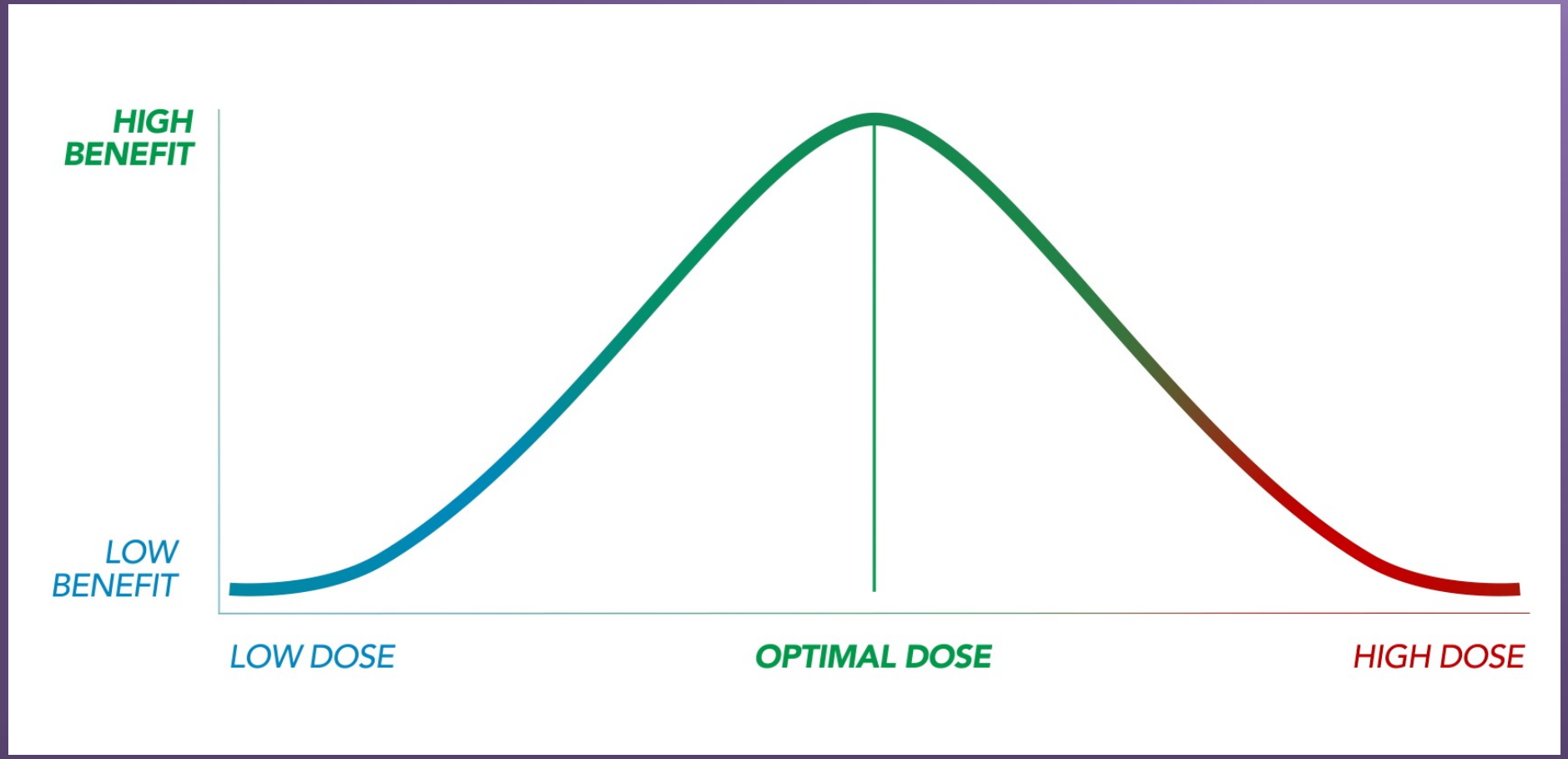
0.01mg/kg/day – 50mg/kg/day

(e.g. 1mg – 3,500mg daily for 70kg adult)

Monkeys treated with oral THC at 9,000mg/kg single dose and 250mg/kg for 28 days survived

(Thompson et al., 1973; Thompson et al., 1974)

Biphasic Dose-Response



Multiphasic Dose-Response

Example: THC & locomotor activity in rats

Sañudo-Peña et al, 2000

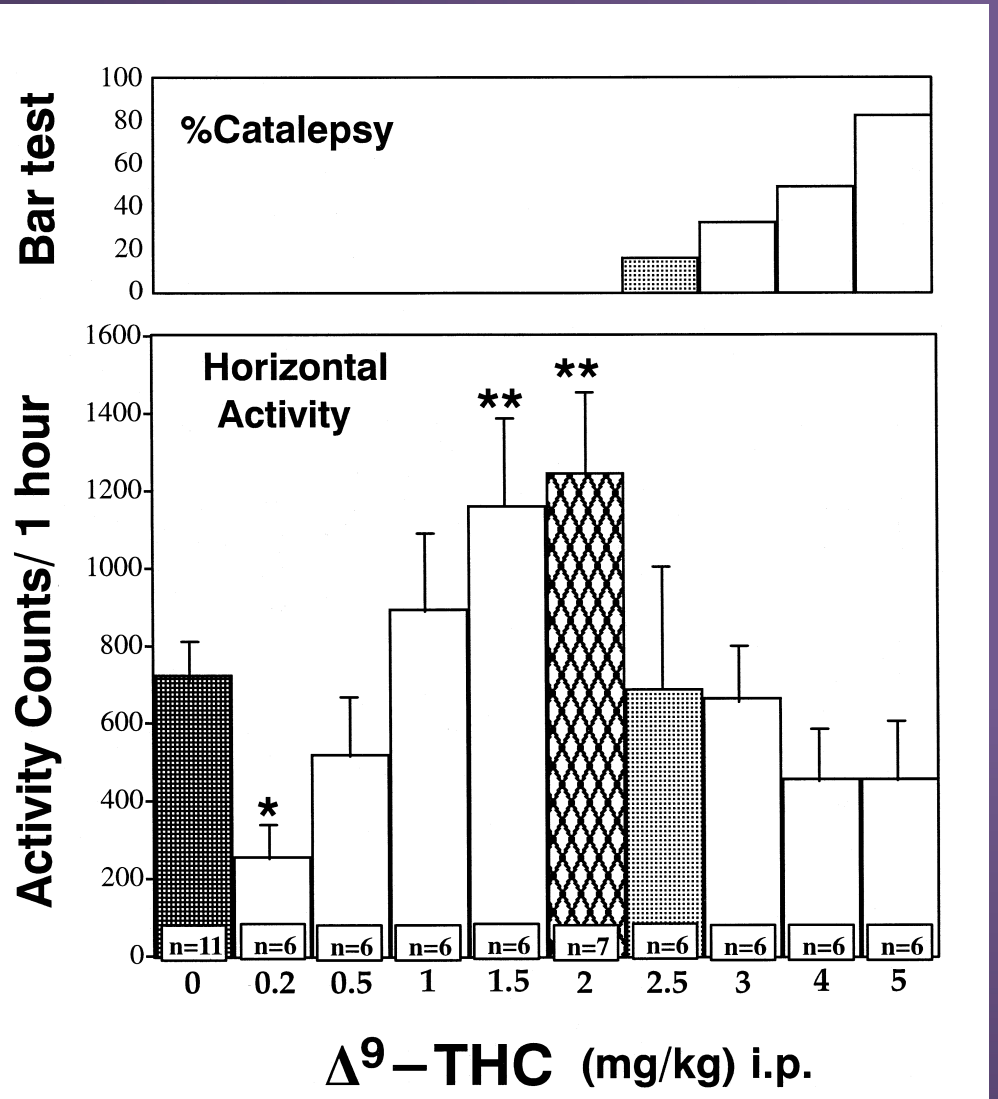


Fig. 1. Dose-curve of systemic administration of Δ^9-tetrahydrocannabinol effects on horizontal activity in rats. There is an increase in activity with relatively low doses (1–2 mg/kg) of the cannabinoid receptor agonist.

Ultra low dose THC in mice: 0.002 mg/kg

- Induced long-lasting activation of protective signaling molecules in the brain, including CREB and BDNF. (Fishbein et al., 2008)
- Reduced damage and preserved cardiac function when administered 2h before myocardial infarction. (Waldman et al., 2013)
- Reduced apoptotic, oxidative, and inflammatory injury in mice with hepatic ischemia/reperfusion. (Hochhauser et al., 2015)

Nabiximols for Opioid-Treated Cancer Patients With Poorly Controlled Chronic Pain

Randomized, placebo-controlled, graded-dose trial, n=263, 9 weeks.

(Portenoy et al, 2012)

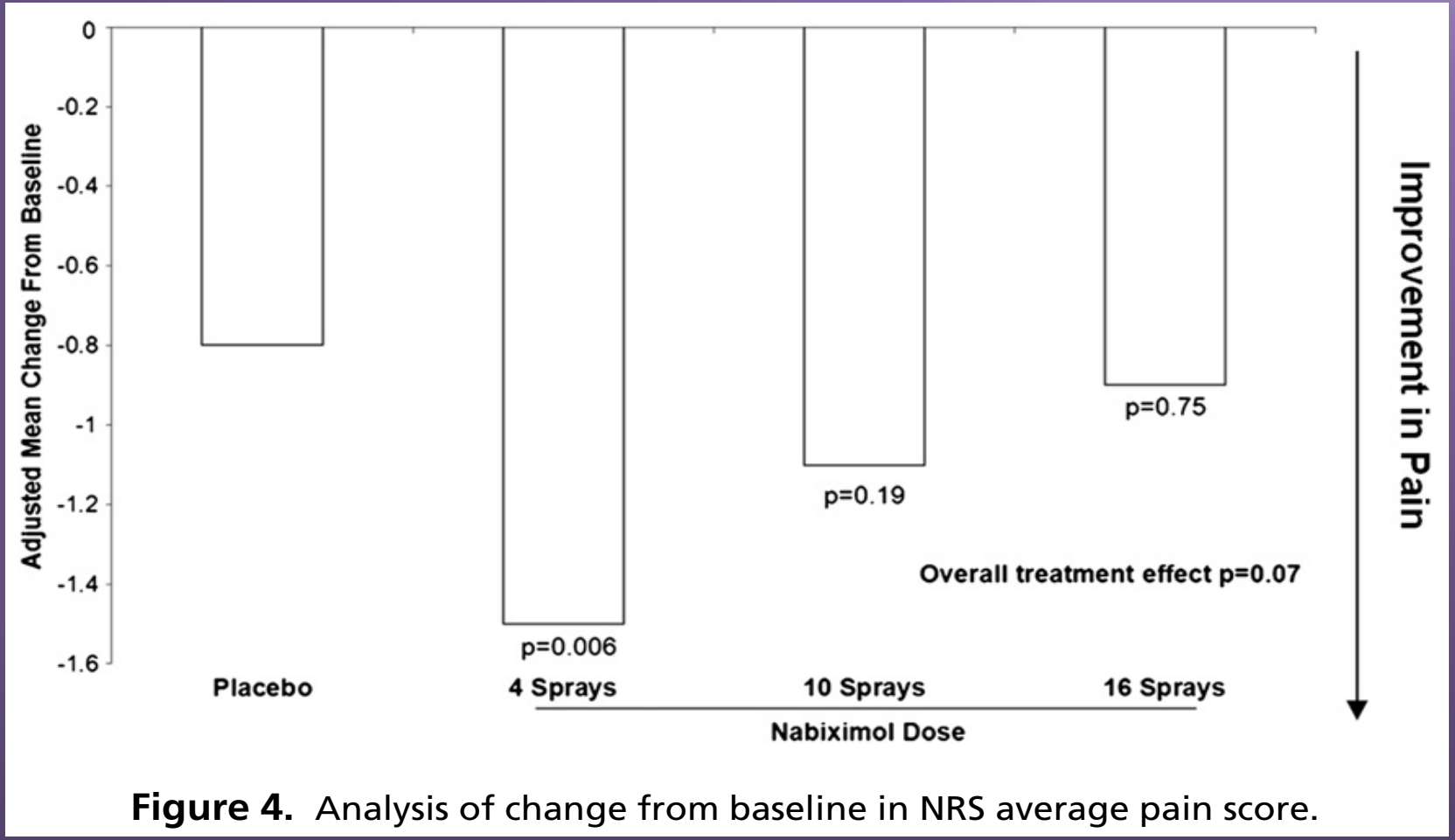


Figure 4. Analysis of change from baseline in NRS average pain score.

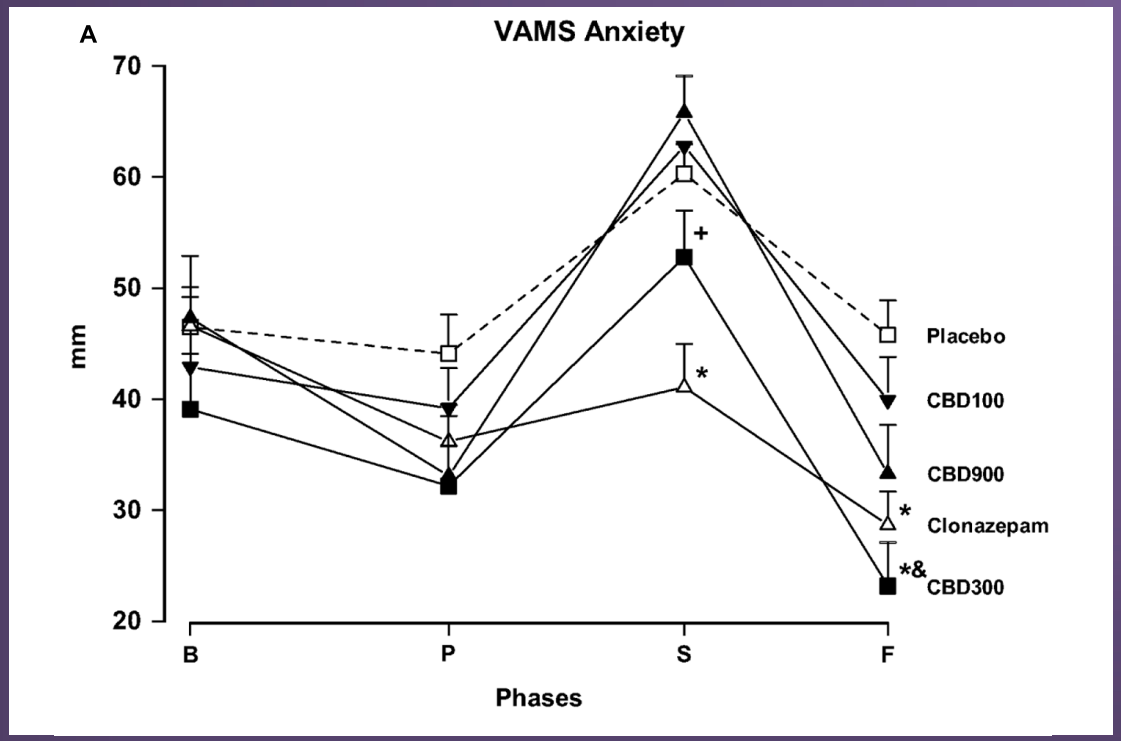
20.8mg 52mg 83.2mg

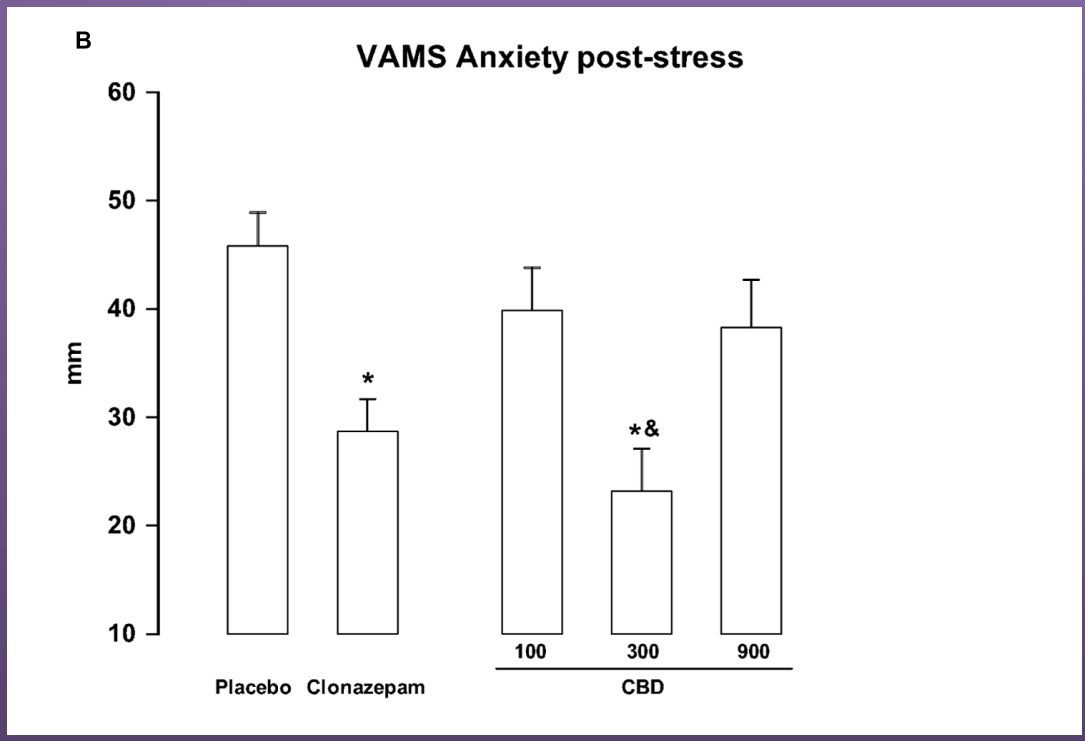
frontiers in Pharmacology

ORIGINAL RESEARCH
published: 11 May 2017
doi: 10.3389/fphar.2017.00259

Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol during Public Speaking in Real Life

Antonio W. Zuardi[1,2], Natália P. Rodrigues[1], Angélica L. Silva[1], Sandra A. Bernardo[1], Jaime E. C. Hallak[1,2], Francisco S. Guimarães[2,3] and José A. S. Crippa[1,2]*





Bidirectional Effects

The same medicine can cause opposite responses in different individuals.

- Anxious subjects tended to become less anxious. More euphoric, non-anxious individuals tended to become somewhat more anxious. (Abel, 1971)
- Sedation vs stimulation
- Appetite stimulant vs suppressant

Bidirectional Effects

- The same medicine can cause opposite responses in the same individual:
  - Different doses (Hollister, 1986)
  - Different settings – stress environments can precipitate adverse emotional responses (Gregg et al, 1976)
- Different cannabis cultivars or cannabinoid ratios can cause opposite responses in the same individual

Widening of THC's Therapeutic Window

- Cannabis-naïve patients demonstrate more frequent adverse effects (Hall et al. 2003)
- Regular users demonstrate less psychotomimetic, perceptual altering, amnestic, and endocrine effects. (D'Souza et al., 2008)

- THC can widen its own therapeutic window
  - Heterogeneous tolerance-building to various effects. (reviewed in Pertwee, 2004)
  - Therapeutic effects may be more resistant to tolerance development than side effects. (De Vry et al., 2004)

THC vs THC/CBD

- 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing
- Patients were randomized to THC:CBD extract (n=60), THC extract (n=58), or placebo (n=59).

Each pump:

- 2.7 mg THC + 2.5 mg CBD.
- 2.7 mg THC

Johnson et al., 2010

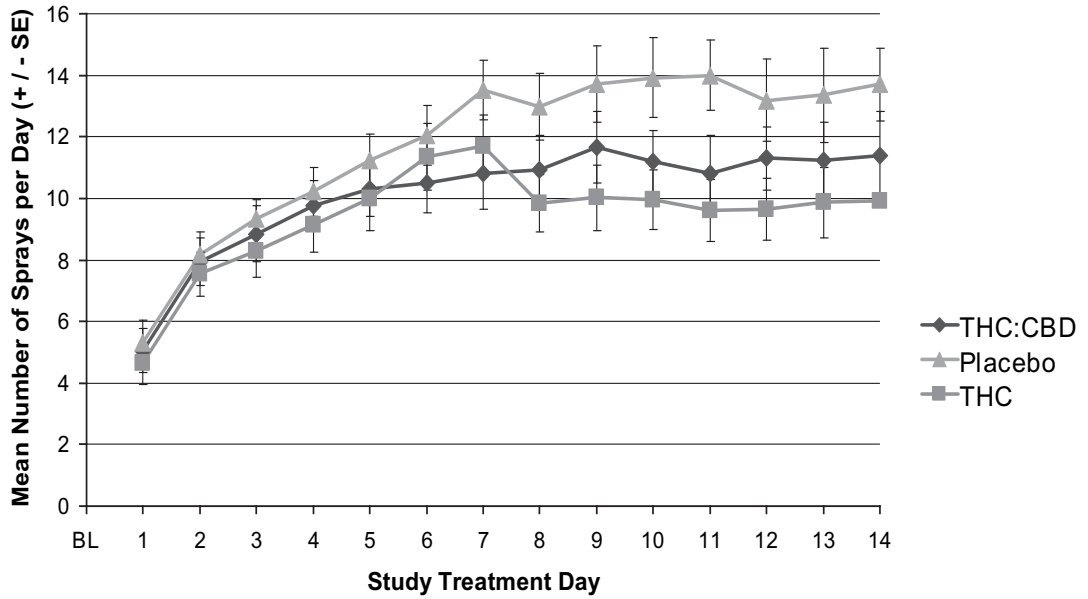


Fig. 2. Exposure to study medication—mean number of sprays per day. SE = standard error.

THC vs THC/CBD

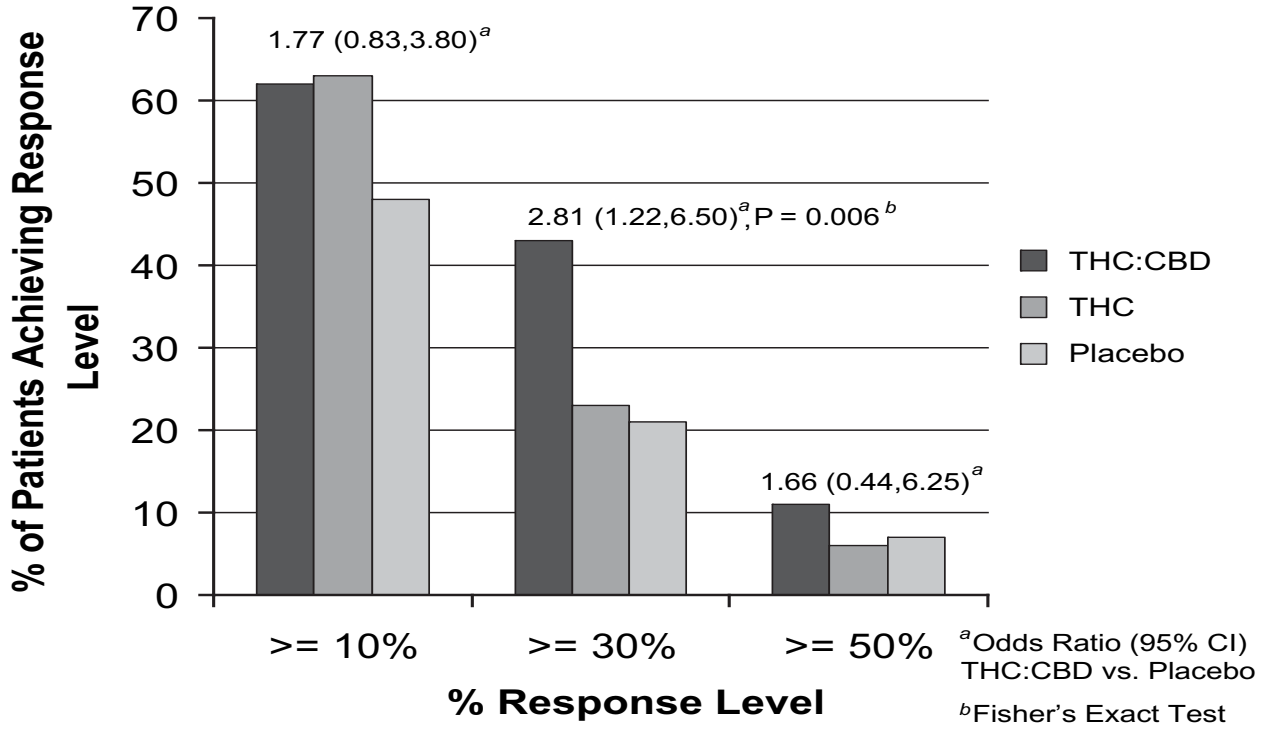


Fig. 3. Pain 0—10 Numerical Rating Scale scores: responder analysis (ITT analysis). [a]Odds ratio (95% CI) THC:CBD vs. placebo; [b]Fisher's exact test.

Table 4

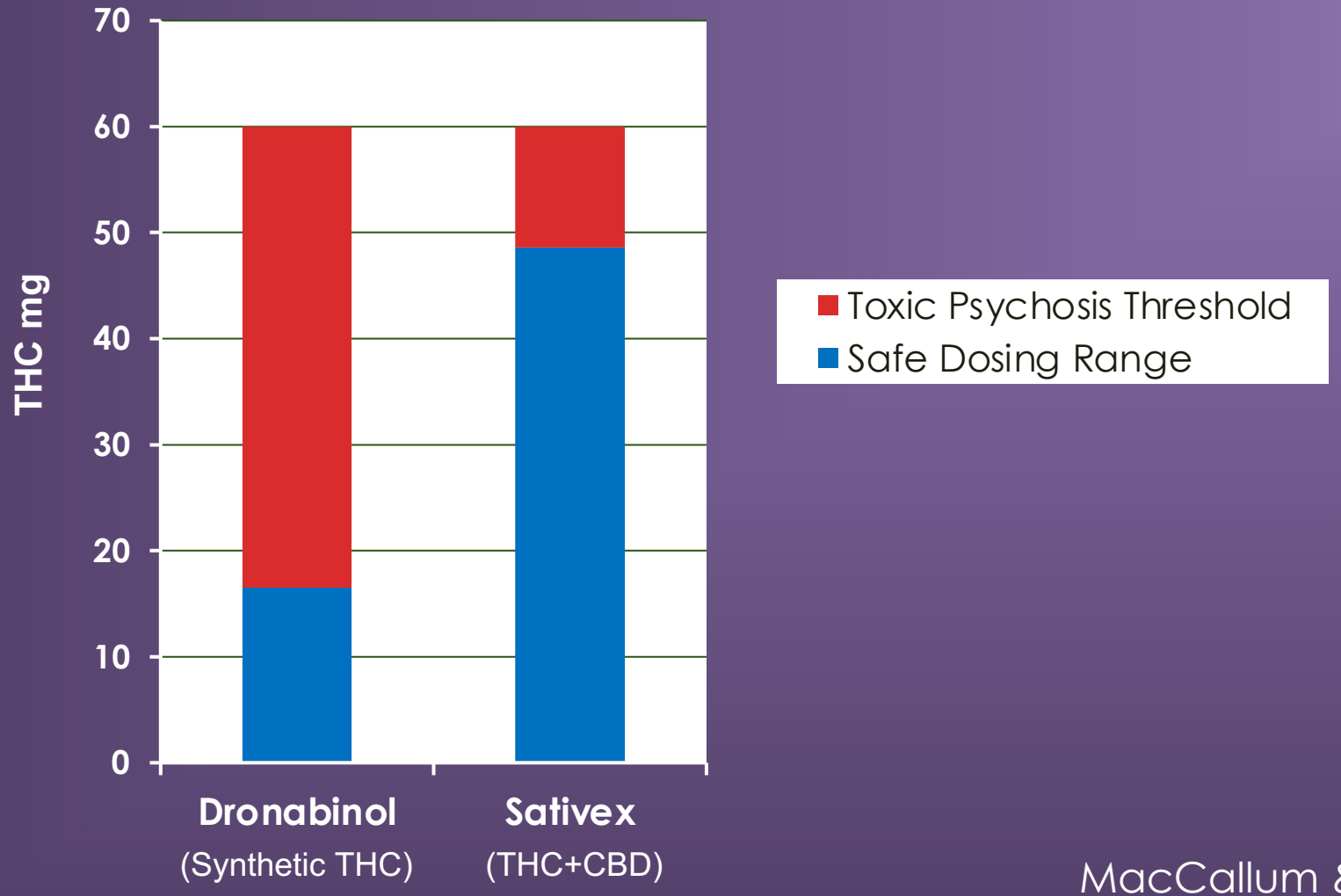
Most Common Treatment-Related Adverse Events (Reported by Three or More Patients)

Description of Event	THC:CBD, *n* (%)	THC extract, *n* (%)	Placebo, *n* (%)
Somnolence	8 (13)	8 (14)	6 (10)
Dizziness	7 (12)	7 (12)	3 (5)
Confusion	4 (7)	1 (2)	1 (2)
Nausea	6 (10)	4 (7)	4 (7)
Vomiting	3 (5)	4 (7)	2 (3)
Raised gamma GT	2 (3)	5 (9)	1 (2)
Hypercalcemia	0	0	3 (5)
Hypotension	3 (5)	0	0

GT = gamma glutamyl transferase.

Johnson et al., 2010

Adverse Effects: THC vs. THC+CBD



MacCallum & Russo, 2018

CBD Dosing Adjustments

Total Milligrams:

THC < THC+CBD < CBD

low doses
awakening

CBD

high doses
sedating?

Many people can feel 5mg

Some conditions respond to 100-500 mg per dose!

PAIN
The Journal of the International Association for the Study of Pain

An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia

van de Donk, Tine, MD[1]; Niesters, Marieke, MD PhD[1]; Kowal, Mikael A., PhD[2]; Olofsen, Erik, PhD[1]; Dahan, Albert, MD PhD[1]; van Velzen, Monique, PhD[1]

PAIN: December 20, 2018 - Volume Articles in Press - Issue - p
doi: 10.1097/j.pain.0000000000001464

- Double blind, placebo-controlled, 4-way crossover study, n=20 female
- Single dose of vapor (Valcano) in each condition, at least 2 weeks in between each session. Full content of bag was inhaled.
  1. 22% THC: used 100 mg that contained 22.4 mg THC and less than 1 mg CBD.
  2. 6.3% THC and 8% CBD: used 200 mg that contained 13.4 mg THC and 17.8 mg CBD.
  3. 9% CBD and less than 1% THC: used 200 mg that contained 18.4 mg CBD and less than 1 mg THC.
  4. Placebo cannabis

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CBD inhalation increased THC plasma concentrations but diminished THC-induced analgesic effects, indicative of a synergistic pharmacokinetic but antagonistic pharmacodynamic interactions of THC and CBD.

Are CBD-dominant preparations enough?

Staci A. Gruber - HIGH ANXIETY? EXAMINING THE IMPACT OF FOUR WEEKS OF TREATMENT WITH A NOVEL HIGH CANNABIDIOL PRODUCT

- "Full spectrum" CBD custom made from NIDA source
- 10mg of tincture TID
- ~80% reduction in anxiety after 4 weeks (open label)
- Significant improvements in depression and mood
- significant improvements in many cognitive domains
  - except some detriment in learning (very small)
- longitudinal study showed improvements exceed baseline at 6 months
- significant improvements in sleep and on several quality of life measures
- no adverse events reported

Journal of Diabetes & Metabolism
ISSN: 2155-6156
OPEN ACCESS Freely available online
Research Article

The Effects of Cannabidiol-Based Sublingual Tablets on Diabetic Neuropathic Pain

Debra Kimless, Matthew K. Caloura*, Ara Kirakosyan, Stephen Goldner

Pure Green Pharmaceuticals, West Bloomfield, 48323, USA

- N= 31 subjects with diabetic peripheral neuropathy
  - 18 female, age 23-73
- 3-week open-label trial
- Water-soluble, sublingual, 20 mg CBD tablet 3x daily, 6 hours apart (morning, afternoon, and evening) for 21 days

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Results

- No adverse events
- All subjects experienced a significant reduction in overall pain
- 1/3 of subjects reported a response within 24 hours of taking the first dose
- 2/3 observed a noticeable change after an average 7 days
- All 23 subjects taking pain medications requested to reduce or stop their prescription but were advised against it.

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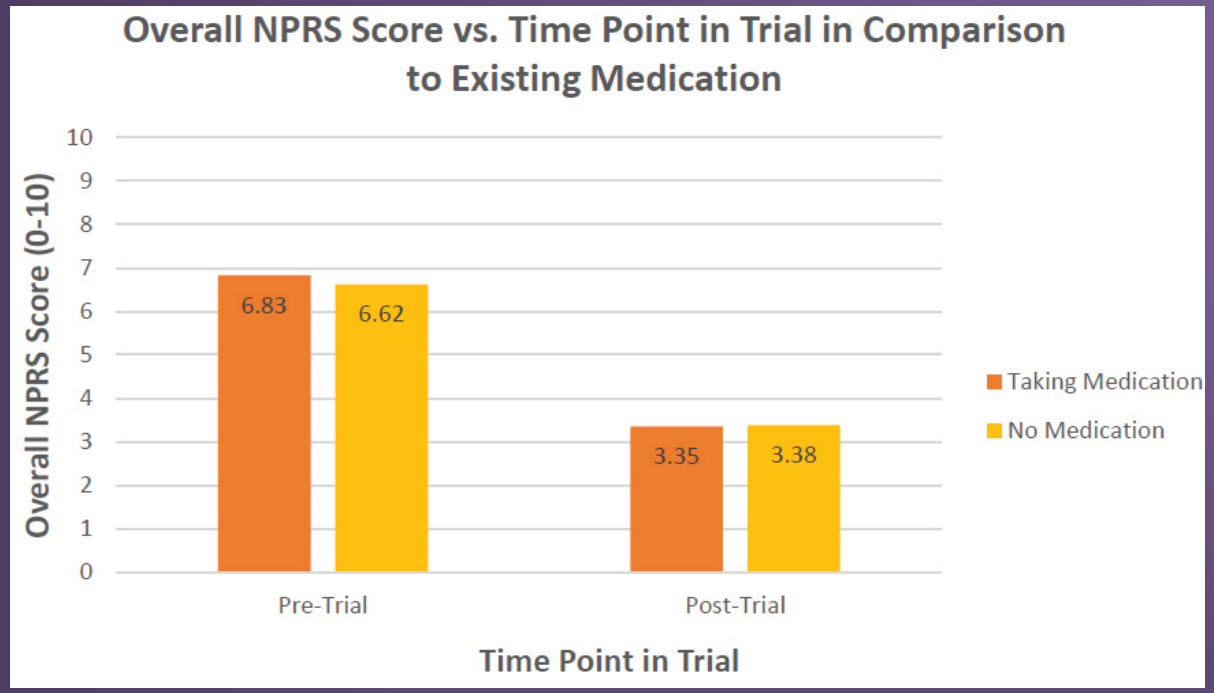

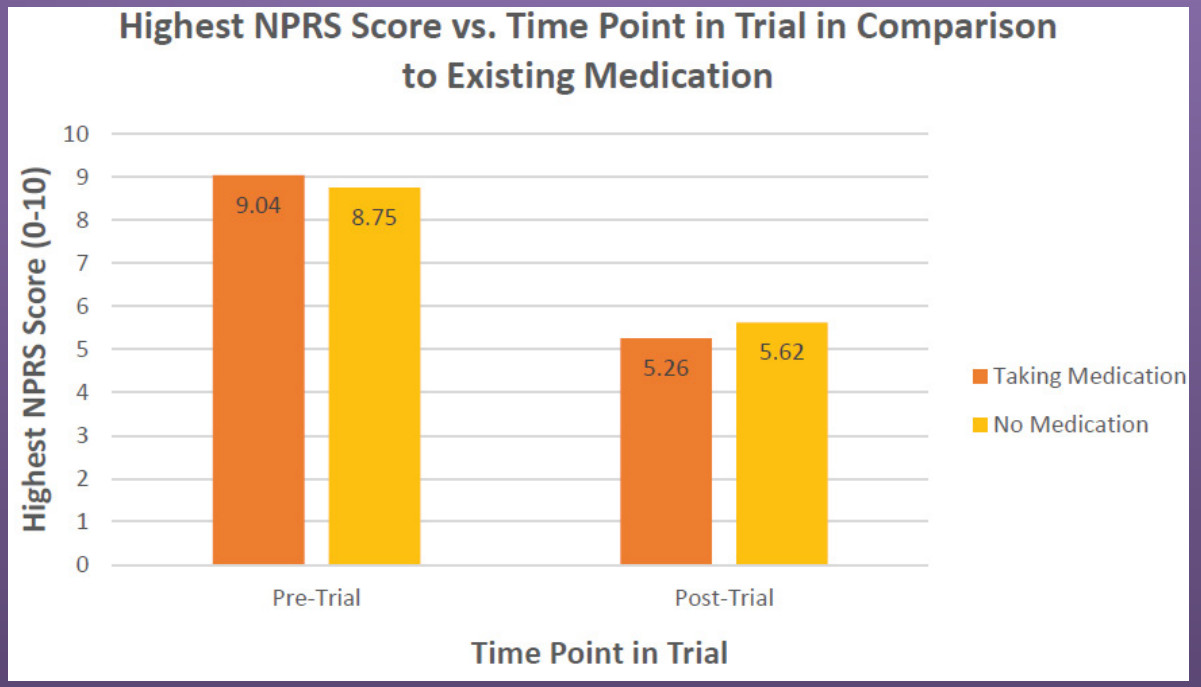

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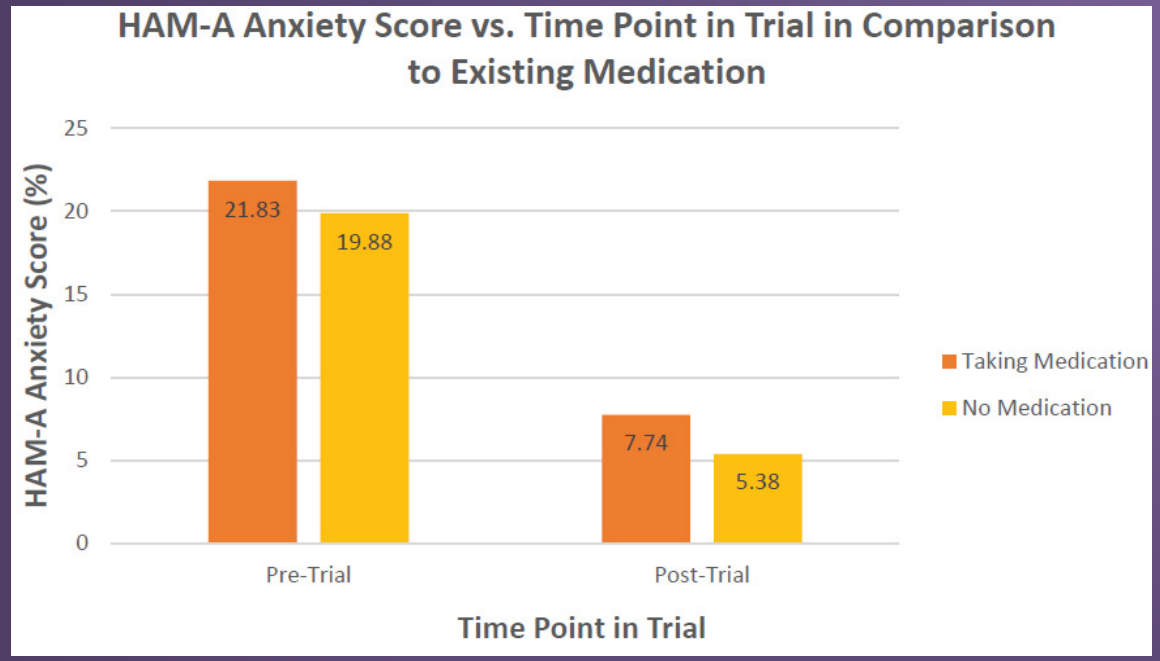
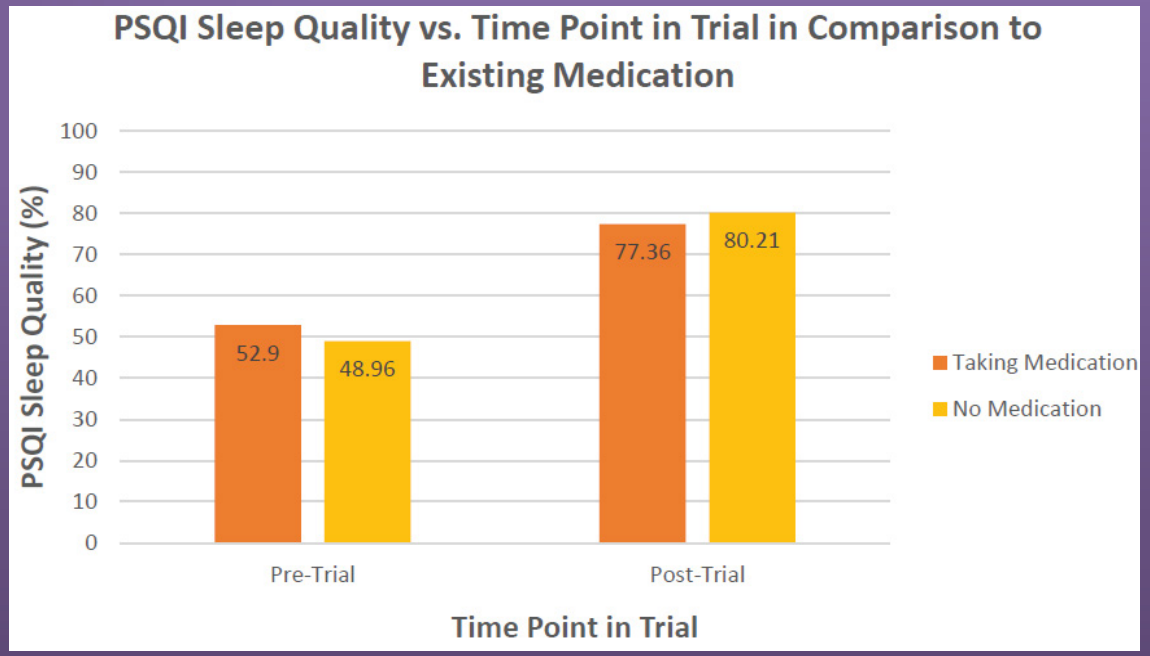
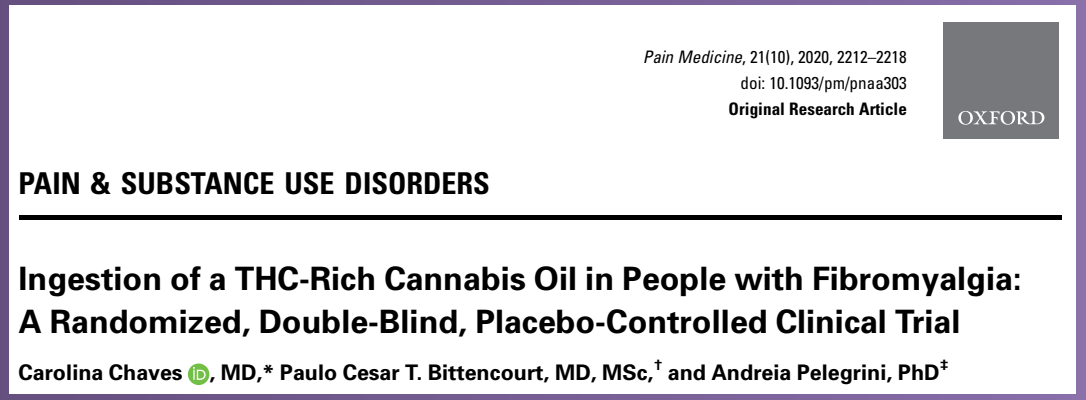




Is it the CBD?



Pain Medicine, 21(10), 2020, 2212–2218
doi: 10.1093/pm/pnaa303
Original Research Article

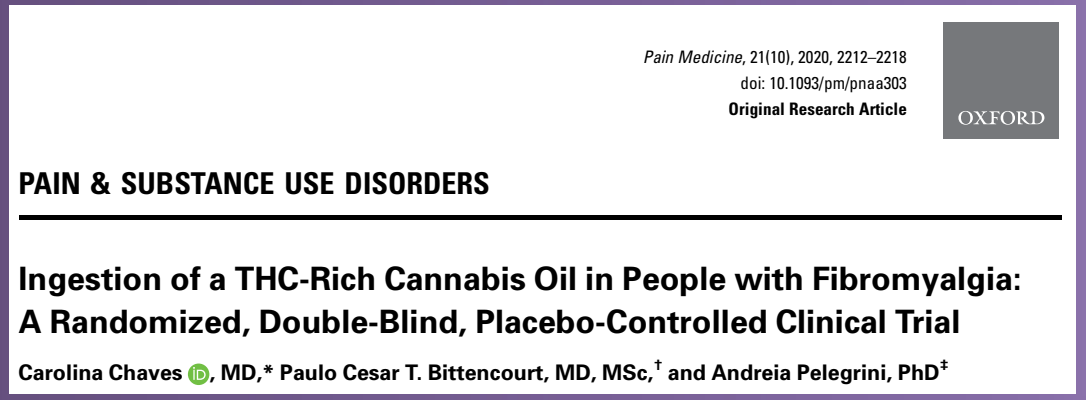
OXFORD

PAIN & SUBSTANCE USE DISORDERS

Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Carolina Chaves, MD,* Paulo Cesar T. Bittencourt, MD, MSc,† and Andreia Pelegrini, PhD‡

- Double-blind, randomized, placebo-controlled clinical trial, 8 weeks
- 17 women (mean age was 51.9) with fibromyalgia, residents of a neighborhood with a low socioeconomic profile and a high incidence of violence in the city of Florianopolis, Brazil.
- THC-rich cannabis oil (THC 24.44 mg/mL + CBD 0.51 mg/mL) made from White Widow



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- The initial dose in both groups was one drop (~1.2 mg of THC and 0.02mg of CBD)
- Mean daily dose at post-intervention evaluation was 3.6 drops of cannabis oil (~4.4 mg of THC and 0.08 mg of CBD) and 4.3 drops of olive oil in the placebo group.

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Table 2. Comparison of FIQ mean scores pre- and postintervention in both groups

	Cannabis			Placebo		
Study Variable	Pre $\bar{x}$ (sd)	Post $\bar{x}$ (sd)	*P* Value	Pre $\bar{x}$ (sd)	Post $\bar{x}$ (sd)	*P* Value
FIQ (0–100)	75.50 (12, 93)	30.50 (16, 18)	<0.001	70.22 (11, 18)	61.22 (17, 30)	0.070
Physical function (0–10)	6.37 (1.88)	5.83 (2.02)	0.109	4.03 (2.08)	4.07 (2.25)	0.495
Feel good (0–10)	9.47 (1.06)	1.72 (0.64)	0.039	9.68 (0.95)	7.50 (2.93)	0.104
Work missed (0–10)	5.10 (3.86)	2.38 (1.65)	0.317	7.14 (4.95)	6.57 (3.29)	0.317
Job ability (0–10)	7.13 (2.90)	4.29 (1.70)	0.093	7.89 (2.15)	7.89 (1.36)	0.831
Pain (0–10)	8.25 (1.98)	3.72 (2.49)	0.011	8.67 (2.96)	7.67 (1.87)	0.235
Fatigue (0–10)	8.00 (2.07)	4.00 (2.08)	0.027	7.33 (3.39)	6.11 (3.37)	0.112
Morning tiredness (0–10)	7.88 (2.42)	4.50 (1.91)	0.257	8.33(2.06)	7.67(3.16)	0.465
Stiffness (0–10)	7.75 (2.05)	3.33 (3.21)	0.285	6.11 (2.84)	5.00 (3.91)	0.512
Anxiety (0–10)	8.38 (1.69)	7.00 (2.91)	0.135	8.00 (2.00)	7.00 (2.87)	0.397
Depression (0–10)	7.50 (2.45)	5.80 (3.11)	0.465	7.78 (2.49)	4.67 (3.84)	0.027

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- Participants were not instructed to reduce other medications, yet 3 patients spontaneously reduced antidepressants and 1 reduced benzodiazepine
- Reports of improved well-being, more energy for activities of daily living, subjectively reduced intensity and frequency of “pain attacks”

Many other cannabinoids and classes of compounds

Dosing: New to Cannabis

1. Start sub-therapeutic.
2. Increase to minimal noticeable dose for 3 days.
3. Increase to effective therapeutic dose on day 4.

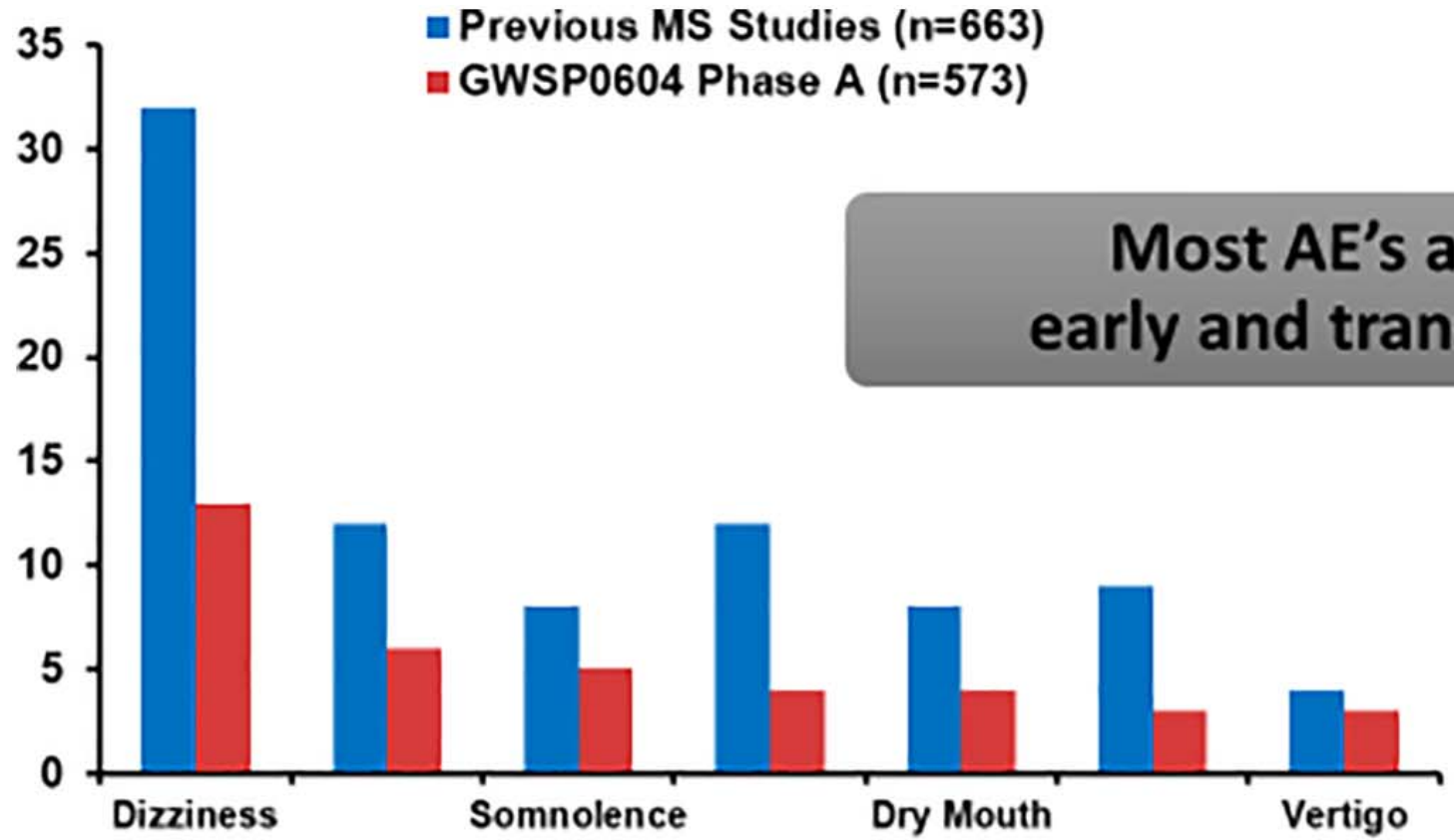
New User Dosing Tips

- Starting dose:
  - Tincture or oil 1-2mg 3x daily
  - Vapor 1-2 puffs 3x daily
- Choose initial THC:CBD ratio based on symptoms and goals, adjust later.
  - 1:1 is broadly effective and well-tolerated.
- Track and document response
- First therapeutic goal = restorative sleep

Nabiximols Titration Schedule

Day	**Number of sprays in the morning**	**Number of sprays in the evening**	(Total number of sprays per day)
1	**0**	**1**	1
2	**0**	**1**	1
3	**0**	**2**	2
4	**0**	**2**	2
5	**1**	**2**	3
6	**1**	**3**	4
7	**1**	**4**	5
8	**2**	**4**	6
9	**2**	**5**	7
10	**3**	**5**	8
11	**3**	**6**	9
12	**4**	**6**	10
13	**4**	**7**	11
14	**5**	**7**	12

Each spray = 2.5mg CBD + 2.7mg THC



Most AE's are early and transient

Improved safety profile as result of modified 'lower and slower' dose titration regimen

MacCallum and Russo, 2018

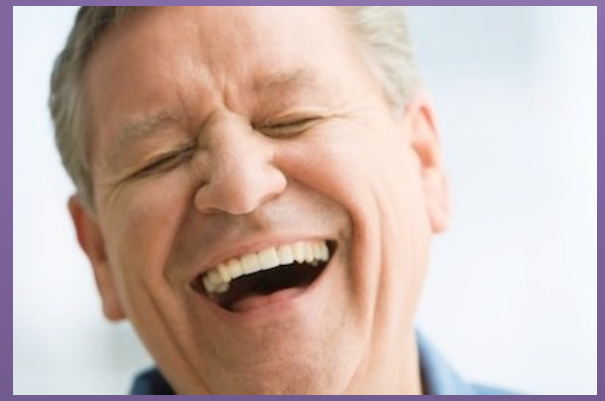
Non-Psychoactive Strategies

- Low dose THC after widening therapeutic window
- CBD:THC ratio > 3:1
- Acidic (raw) cannabinoids
- Topical delivery

Psychoactive Benefits?

Psychoactive Benefits: Euphoria

- Positive Mood
- Relaxation
- Laughter, Socializing
- Time Distortion
- Intensification of Ordinary Experiences
  - Eating, listening to music, watching films, sex, etc.



Cannabis Consciousness

- Increased self-awareness
- Sense of connection to the universe
- View oneself from a different vantage point
- Fosters acceptance
- Helps users find creative solutions
- Promotes mental/emotional/physical flexibility, capacity to change

Unbundling of Chronic Pain Perception and Behavior

Pain bundle

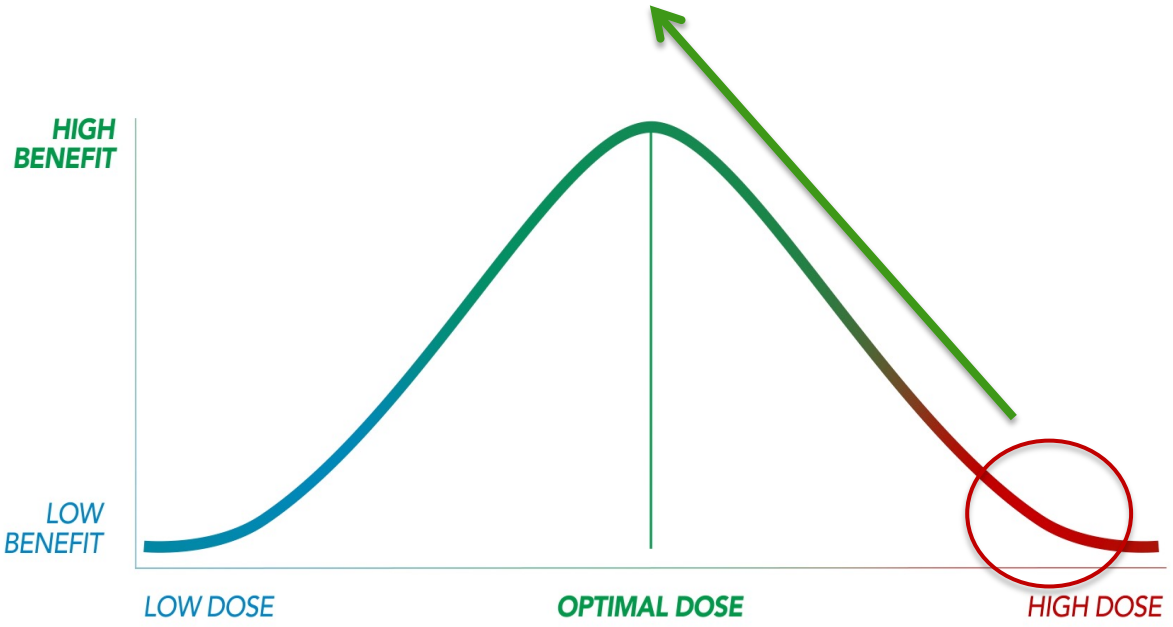
- Nociceptive sensation
- Categorization
- Assignment of meaning
- Attentional fixation, exaggeration of aversiveness
- Anxiety about ongoing future pain
- Pain-related behavior and consequences
  - Decreased activity
  - Facial and vocal expressions of pain and irritability, others' reactions
  - Absenteeism from work, disability
  - Social isolation
- **Lack of recognition and ability to modulate these distinct components of the illness**

Cannabis

Pain unbundling

- Nociceptive sensation sometimes less intense, but usually different in quality
- Categorization of the sensation as an ongoing part of life, increased acceptance, ↓ judgment
- More neutral assignment of meaning, e.g. viewing the pain as a companion or teacher
- Decreased attention on pain, often described as less bothersome, with increased attention on other perceptions including natural rewards
- ↓ Anxiety about future symptoms
- ↓ Pain-related behaviors, ↑ supportive social interactions
- ↓ Overall experience of suffering
- Increased recognition and ability to intentionally modulate these distinct components of the illness

Dosing: Experienced User



1. Sensitization Protocol: 6 days
2. Try switching from inhalation to oromucosal delivery
3. Mitigate side effects and enhance benefits – adjust strain or CBD:THC ratio

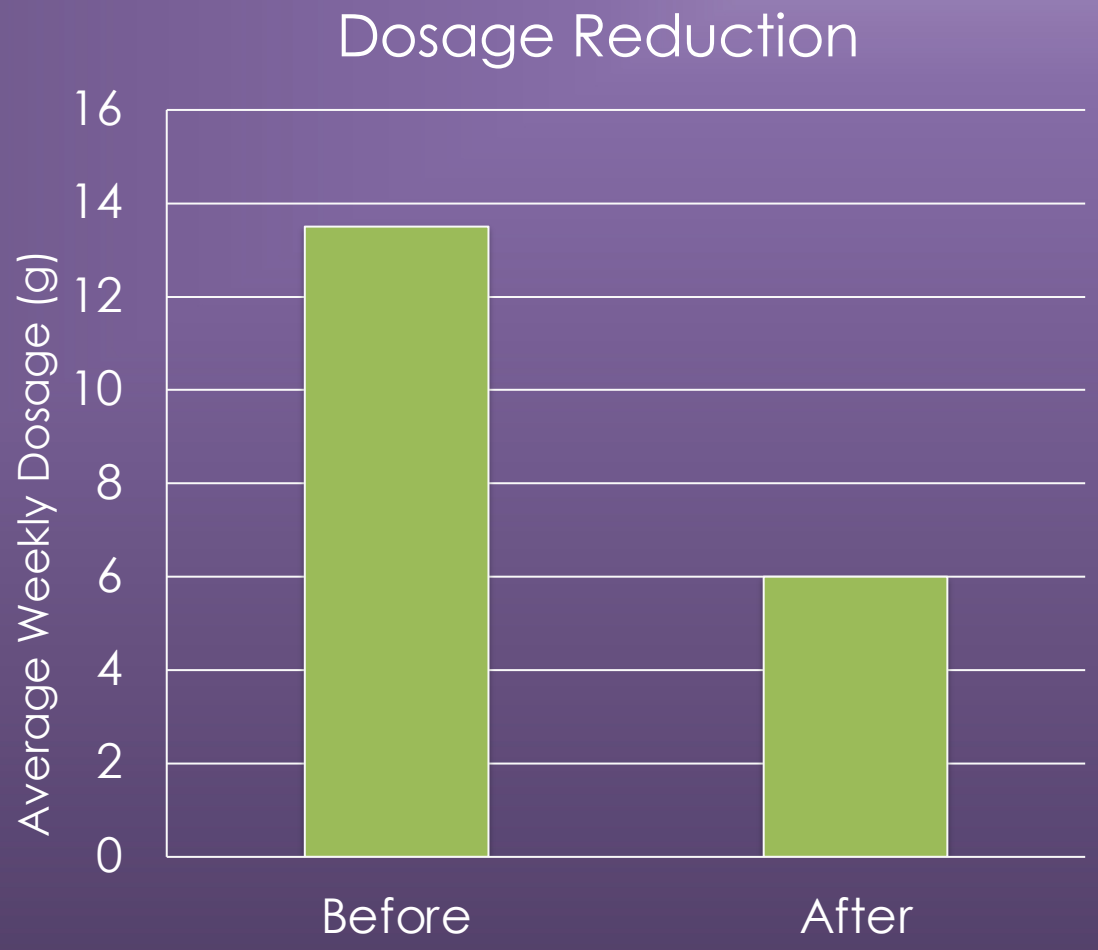
Dosage Recommendations: Experienced Users

- Sensitization Protocol: 6 days
  - Experienced users who inhale >1/8 oz per week or equivalent
  - Patients who have built cannabis tolerance
  - Patients who seem out of balance in their relationship with cannabis
- Results
  - Decreased consumption
  - Improved benefits, less side effects (especially fatigue)
  - Save $$$
  - Improved self-awareness

Cannabinoid Sensitization Protocol

- 6-day specific protocol to reduce dose with equivalent or improved efficacy
- 90% of participants decrease dosage
- Average dosage decrease: 56%

Data from patient email survey n=48



American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER
The Journal of Pain, Vol 00, No 00 (), 2019: pp 1–11
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Cannabis Use Preferences and Decision-making Among a Cross-sectional Cohort of Medical Cannabis Patients with Chronic Pain

Kevin F. Boehnke,* J. Ryan Scott,* Evangelos Litinas,† Suzanne Sisley,‡ Daniel J. Clauw,* Jenna Goesling,* and David A. Williams*

- How do patients use cannabis to treat pain?
- Online survey of adults (≥18 years old) who use cannabis medically for chronic pain in states with legal medical or recreational cannabis.
- N=1,321 participants (59% female)

Administration routes

- 93.4% used 2 or more
- 72.5% used 3 or more
- Female, medical-only, and novice users
  - less likely to smoke or vaporize
  - more likely to rank edibles, tinctures, and topicals as a first-choice administration route

Delivery Methods

Delivery Methods: Inhalation

Delivery Methods: Oromucosal and Enteral

Delivery Methods: Topical, Transdermal, Rectal

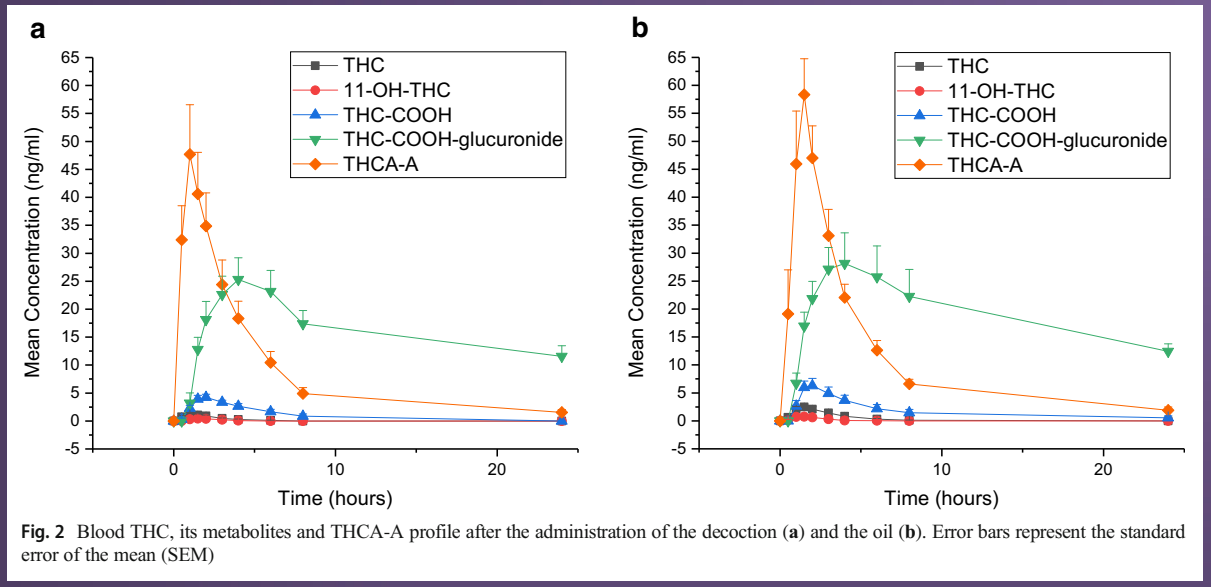


Fig. 2 Blood THC, its metabolites and THCA-A profile after the administration of the decoction (**a**) and the oil (**b**). Error bars represent the standard error of the mean (SEM)

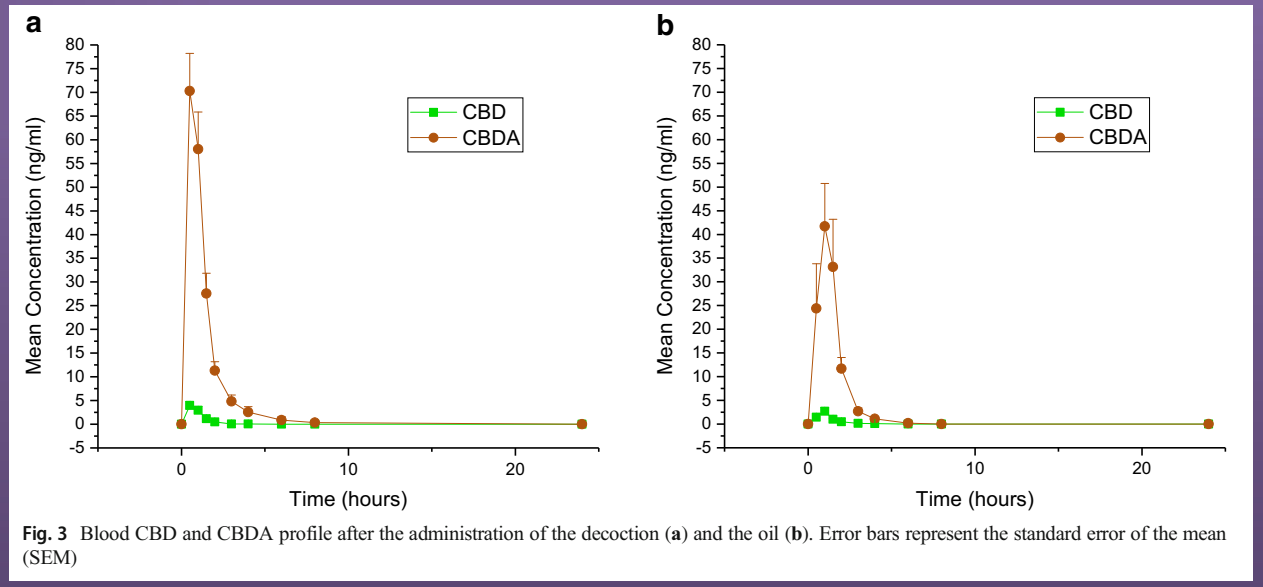


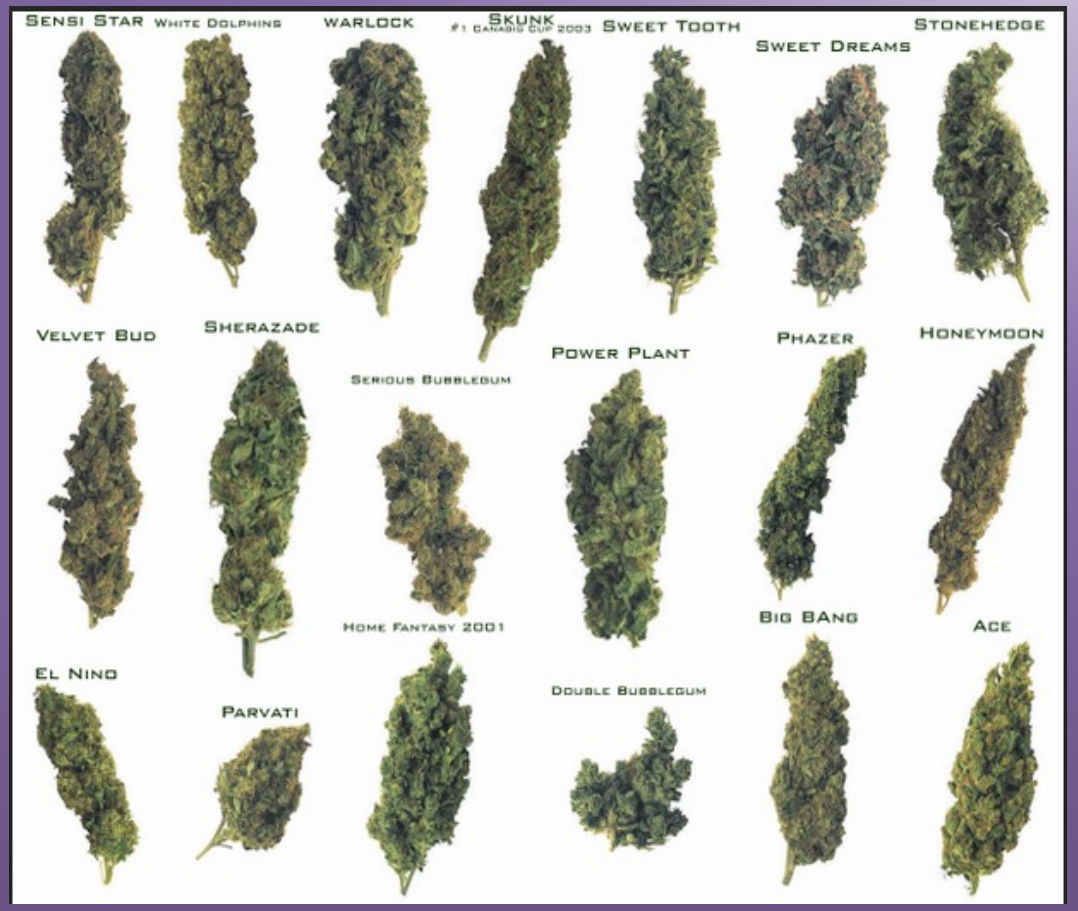
Fig. 3 Blood CBD and CBDA profile after the administration of the decoction (**a**) and the oil (**b**). Error bars represent the standard error of the mean (SEM)

Pellesi et al., 2018

Chemovars (strains)

Common terms (usually inaccurate):

- Sativa
  - Taller plant
  - More energetic, "cerebral" effects
  - "High"
- Indica
  - Shorter, easier for indoor growing
  - More relaxing, "body" effects
  - "Stoned"
- Most are a hybrid, each has a unique content of therapeutic compounds.
- Growing conditions can impact effects



What's important?

- CBD vs THC
- Stimulating vs Sedating
- Patient-specific response

Thank you!

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www.healer.com