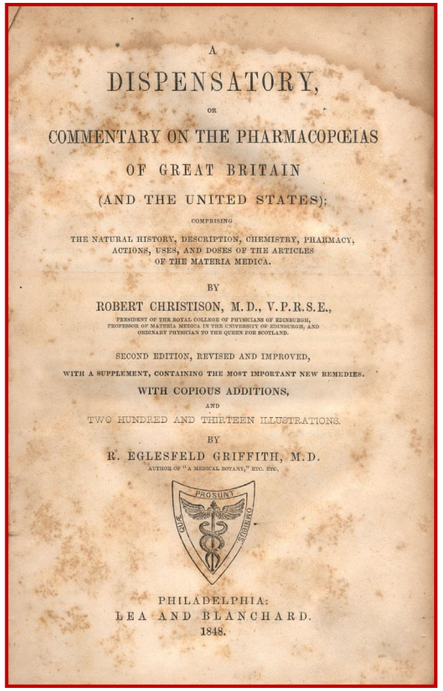
UCI University of California, Irvine

Cannabinoids in the treatment of pain

Daniele Piomelli, PhD
University of California, Irvine

Is cannabis a safe and effective analgesic?

An old question



A

DISPENSATORY,

OR

COMMENTARY ON THE PHARMACOPŒIAS

OF GREAT BRITAIN

(AND THE UNITED STATES);

COMPRISING

THE NATURAL HISTORY, DESCRIPTION, CHEMISTRY, PHARMACY, ACTIONS, USES, AND DOSES OF THE ARTICLES OF THE MATERIA MEDICA.

BY

ROBERT CHRISTISON, M.D., V.P.R.S.E.,

PRESIDENT OF THE ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, PROFESSOR OF MATERIA MEDICA IN THE UNIVERSITY OF EDINBURGH, AND ORDINARY PHYSICIAN TO THE QUEEN FOR SCOTLAND.

SECOND EDITION, REVISED AND IMPROVED,

WITH A SUPPLEMENT, CONTAINING THE MOST IMPORTANT NEW REMEDIES.

WITH COPIOUS ADDITIONS,

AND

TWO HUNDRED AND THIRTEEN ILLUSTRATIONS.

BY

R. EGLESFELD GRIFFITH, M.D.

AUTHOR OF "A MEDICAL BOTANY," ETC. ETC.

PHILADELPHIA:
LEA AND BLANCHARD.
1848.

On trying Dr. Robertson's extracts once for toothache, I found that about 4 grains taken at 3 AM caused in an hour **cessation of pain**, **a pleasant numbness in the limbs**, **giddiness**, a **rapid succession of unassociated ideas** and **impossibility to follow a train of thoughts**, **frequent intervals in sleep**, **and slight increase in the force of the pulse**.

Robert Christison
Commentary on the Pharmacopoeias of Great Britain and the United States, 1848

A strong preclinical rationale

2021 PAIN®

Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies

David P. Finn[a,*], Simon Haroutounian[b], Andrea G. Hohmann[c], Elliot Krane[d], Nadia Soliman[e], Andrew S.C. Rice[e]

Abstract

This narrative review represents an output from the International Association for the Study of Pain's global task force on the use of cannabis, cannabinoids, and cannabis-based medicines for pain management, informed by our companion systematic review and meta-analysis of preclinical studies in this area. Our aims in this review are (1) to describe the value of studying cannabinoids and endogenous cannabinoid (endocannabinoid) system modulators in preclinical/animal models of pain; (2) to discuss both pain-related efficacy and additional pain-relevant effects (adverse and beneficial) of cannabinoids and endocannabinoid system modulators as they pertain to animal models of pathological or injury-related persistent pain; and (3) to identify important directions for future research. In service of these goals, this review (1) provides an overview of the endocannabinoid system and the pharmacology of cannabinoids and endocannabinoid system modulators, with specific relevance to animal models of pathological or injury-related persistent pain; (2) describes pharmacokinetics of cannabinoids in rodents and humans; and (3) highlights differences and discrepancies between preclinical and clinical studies in this area. Preclinical (rodent) models have advanced our understanding of the underlying sites and mechanisms of action of cannabinoids and the endocannabinoid system in suppressing nociceptive signaling and behaviors. We conclude that substantial evidence from animal models supports the contention that cannabinoids and endocannabinoid system modulators hold considerable promise for analgesic drug development, although the challenge of translating this knowledge into clinically useful medicines is not to be underestimated.

Keywords: Cannabinoid$_1$ (CB_1) receptor, Cannabinoid$_2$ (CB_2) receptor, Endocannabinoid, Chronic pain, Neuropathic pain, Inflammatory pain, Nociception, Rats, Mice, Behavior

Initial clinical results

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

D.I. Abrams, MD; C.A. Jay, MD; S.B. Shade, MPH; H. Vizoso, RN; H. Reda, BA; S. Press, BS; M.E. Kelly, MPH; M.C. Rowbotham, MD; and K.L. Petersen, MD

Neurology, February 13, 2007

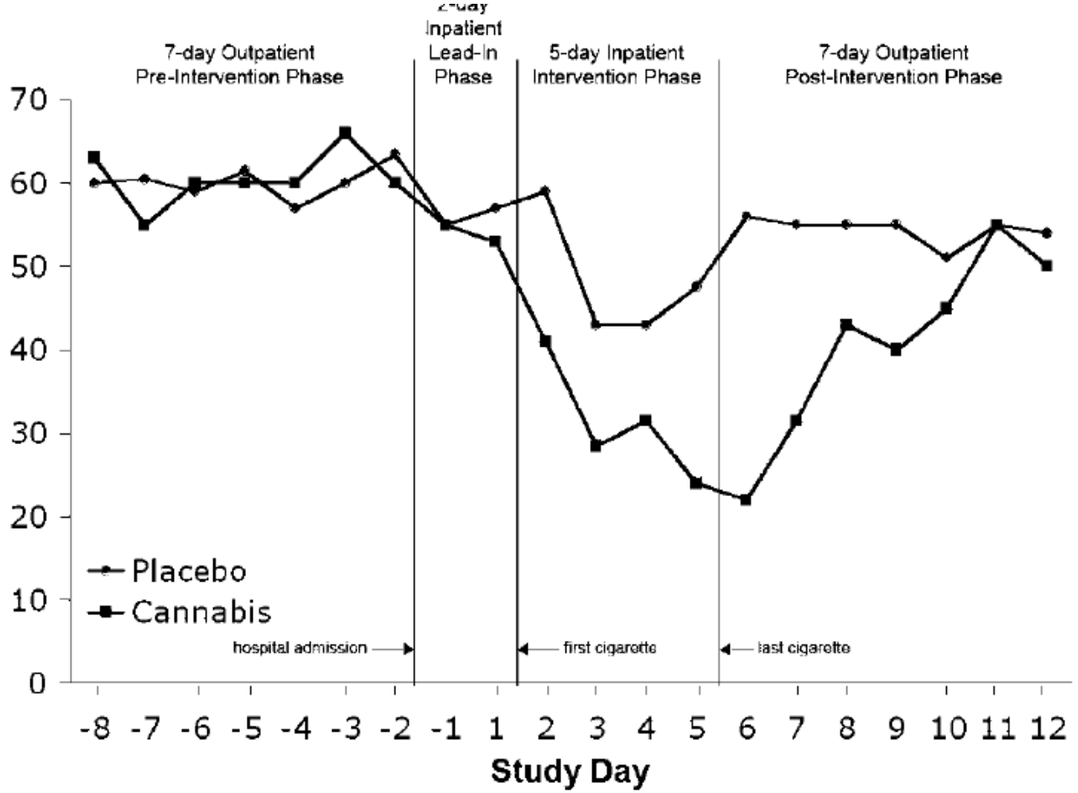


Figure 3. Time course of the intensity of chronic neuropathic pain as rated on the daily diary VAS at 8 AM for the previous 24-hour period. Each point represents the group median. Study admission was at noon on study day –2, the first cigarette was smoked at 2 PM on study day 1, and the last cigarette was smoked at 2 PM on study day 5.

Experimental human studies

Full length article

Sex-dependent effects of cannabis-induced analgesia

Ziva D. Cooper*, Margaret Haney

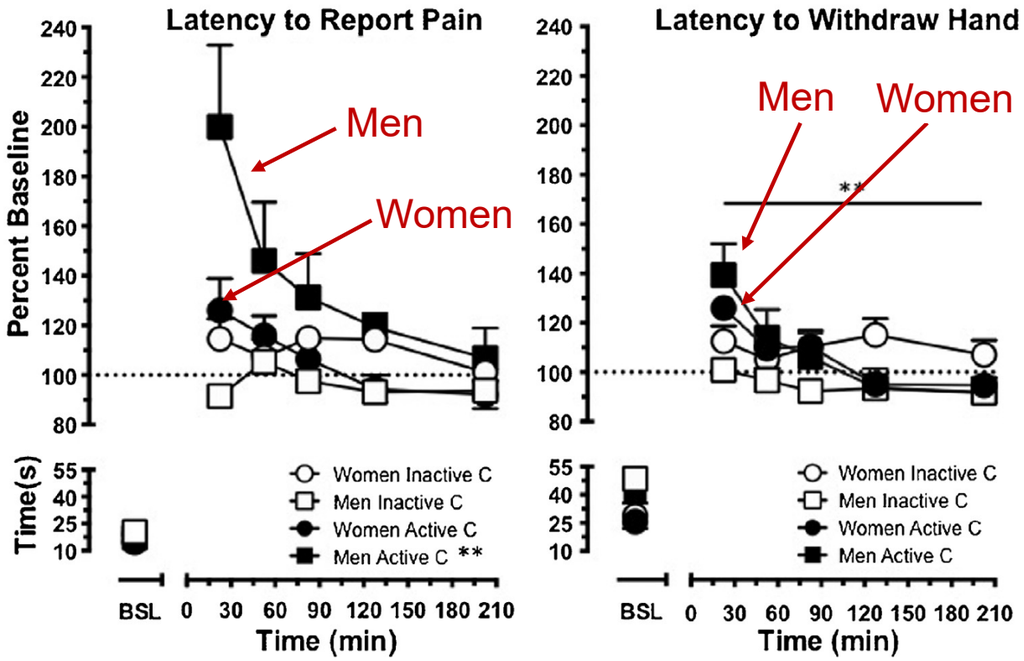
Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA

Drug and Alcohol Dependence 167 (2016) 112–120

Cold pressure test on human volunteers in a laboratory setting. Active cannabis (3.5-5.6%THC). Male (N = 21) and female (N = 21) participants.

Pain sensitivity

Pain tolerance



Both animal and human data support the notion that cannabis alleviates certain kinds of pain.

Reviewing the evidence

2017

CONCLUSION 4-1 There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

What next?

How do we address the causal nature of the link between cannabis and analgesia? Is cannabis both safe and effective as an analgesic?

With appropriately powered placebo-controlled RCTs of chronic pain in adults.

Preclinical studies and n = 1 human trials can aid in the selection of one or more suitable chronic pain condition(s).

A game-changing trial

nature medicine

Article

https://doi.org/10.1038/s41591-025-03977-0

Full-spectrum extract from *Cannabis sativa* DKJ127 for chronic low back pain: a phase 3 randomized placebo-controlled trial

Matthias Karst[1], Winfried Meissner[2], Sabine Sator[3], Jens Keßler[4], Volker Schoder[5] & Winfried Häuser[6,7]

December 2025

Multicenter, double-blind, randomized, placebo-controlled

820 adults with CLBP
(394 received VER-01; 426 received placebo)

Treatment phases:

- **Phase A:** 12-week double-blind placebo-controlled treatment (primary efficacy evaluation).
- **Phase B:** 6-month open-label extension.
- **Phase C:** 6-month continuation; Phase D: randomized withdrawal

Dosing

Dose unit:

- **THC:** 2.5 mg
- **CBG (cannabigerol):** 0.1 mg
- **CBD (cannabidiol):** 0.02 mg

Dosing Regimen:

•Started at **1 dose unit** (2.5 mg THC) each evening and titrated upward.

•Dose was increased every ~3 days based on tolerance and symptom relief.

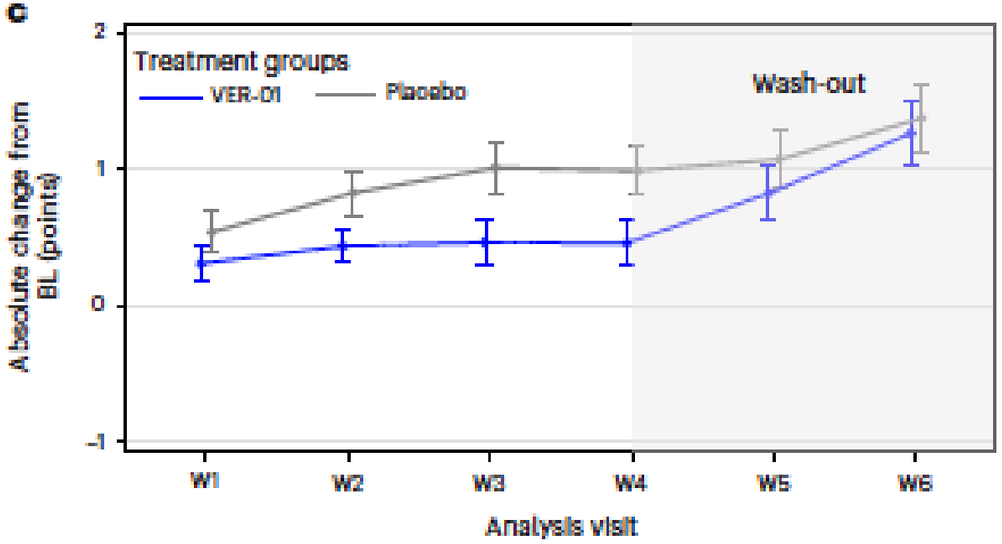
•**Maximum single dose:** 8 dose units (~20 mg THC) daily.

•**Maximum daily dose:** capped at **13 dose units** (~32.5 mg THC) per day.

•Mean dose reached during the study
was roughly **7.6 dose units/day (~19 mg THC)** on average.

Efficacy

Primary endpoints phases A and B



Secondary endpoints phase A

Table 2 | Secondary endpoints of phase A

Parameters	VER-01 (*n*=390)	Placebo (*n*=425)	Difference between VER-01 and placebo	Odds ratio (95% CI)	*P* value
≥30% pain responder at week 15 (%)	54.1	39.5	14.6	1.7 (1.22–2.26)	<0.001[c]
≥50% pain responder at week 15 (%)	32.2	22.8	9.4	1.6 (1.11–2.22)	0.010[c]
Cumulative dose (ibuprofen tablets) of rescue medication (s.d.)	10.5 (14.2)	18.3 (53.8)	−7.8	–	<0.001[d]
Cumulative dose (ibuprofen in g) of rescue medication (s.d.)	8.4 (11.4)	14.6 (43.1)	−6.2	–	<0.001[d]
Mean CFB to week 15 in NRS sleep quality (s.d.)	−2.2 (2.2)	−1.5 (2.0)	−0.7	–	<0.001[e]
MOS-SS—mean CFB to visit A6 in sleep problems index I (s.d.)	6.5 (9.1)	4.1 (8.8)	2.4	–	<0.001[e]
MOS-SS—mean CFB to visit A6 in sleep problems index II (s.d.)	6.8 (8.9)	4.5 (8.3)	2.3	–	0.001[e]
RMDQ total score—mean CFB to visit A6	−3.1 (4.0)	−2.0 (4.1)	−1.1	–	<0.001[e]
≥30% RMDQ responder at visit A6 (%)	51.7	42.2	9.5	1.5 (1.06–2.01)	<0.001[f]
PGIC—participants with improvement of symptoms[a] at visit A6 (%)	45.1	23.4	21.7	–	<0.001[c]
SF-36—mean CFB to visit A6 for physical component summary (s.d.)	5.9 (6.8)	3.7 (7.0)	2.1	–	<0.001[e]
SF-36—participants with improvement in quality of life[b] at visit A6 (%)	46.1	31.2	14.9	–	<0.001[c]

What next?

How do we address the causal nature of the link between cannabis and analgesia? Is cannabis both safe and effective as an analgesic?

Additional studies are needed in other pain conditions.

Preclinical studies can aid in the selection of such conditions.

Sickle cell disease: a genetic disorder with a pain phenotype

SCD is an inherited hemoglobinopathy caused by a single point mutation in the β-globin gene, producing hemoglobin S (HbS).

Under low oxygen tension, HbS polymerizes, deforming red blood cells into rigid “sickles.”

Sickled cells obstruct microvasculature,
promoting ischemia, inflammation, and tissue injury.

Sickle cell disease: a genetic disorder with a pain phenotype

These vaso-occlusive events define the clinical course of SCD and cause pain.

Pain in SCD spans a continuum from recurrent acute crises to chronic, persistent pain with neuropathic features.

As survival improves, pain has emerged
not as an episodic complication,
but as a lifelong disease dimension.

Sickle cell disease: a genetic disorder with a pain phenotype

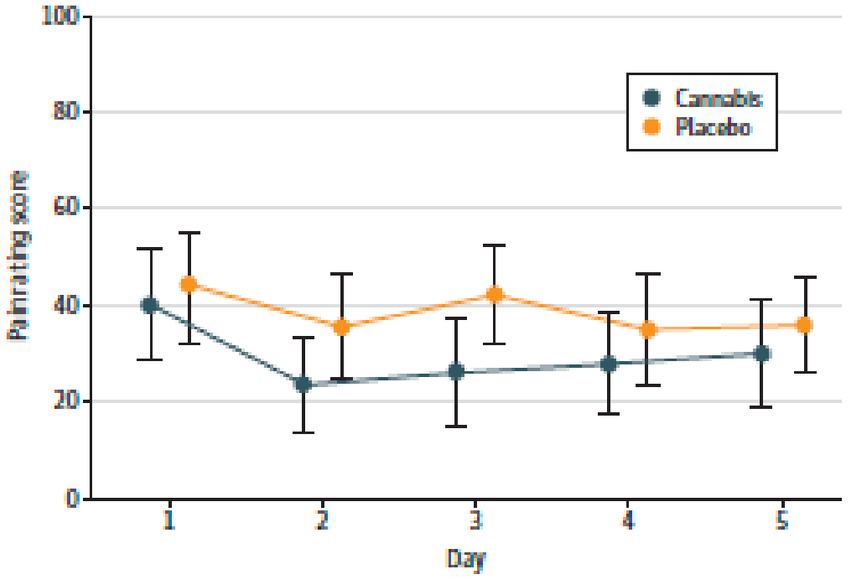
JAMA Network | Open

Original Investigation | Hematology

Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease A Randomized Clinical Trial

Donald I. Abrams, MD; Paul Couey, BA; Niharika Dixit, MD; Varun Sagi, BAS; Ward Hagar, MD; Elliott Vichinsky, MD; Mary Ellen Kelly, MPH; John E. Connett, PhD; Kalpna Gupta, PhD

Vaporized cannabis (4.4% THC, 4.9% CBD)
23 participants, 5 days



Analgesic effects of THC in a humanized mouse model of SCD

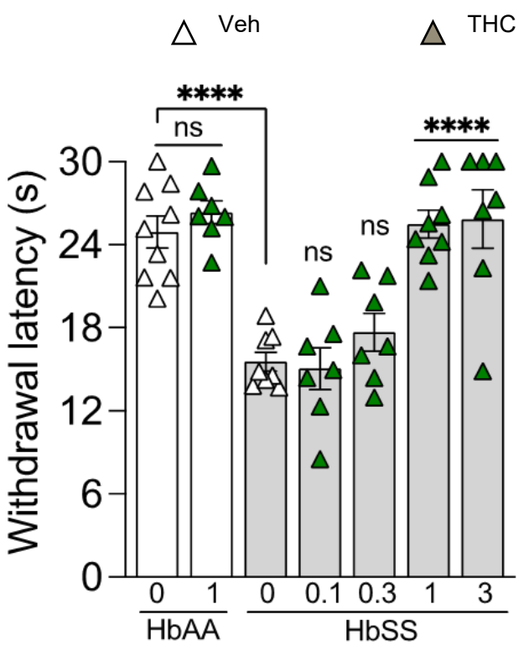
Mabou Tagne A, Fotio Y, Gupta K, Piomelli D.

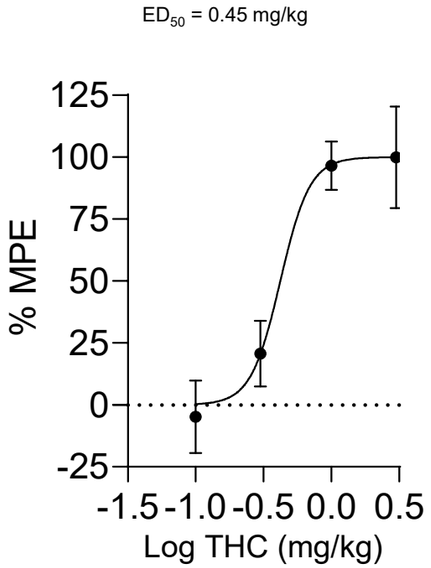
Δ^9-Tetrahydrocannabinol Alleviates Hyperalgesia in a Humanized Mouse Model of Sickle Cell Disease.

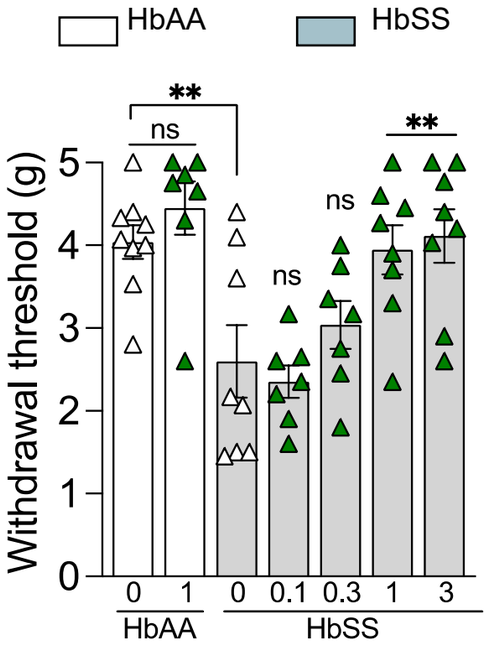
J Pharmacol Exp Ther. **2024**

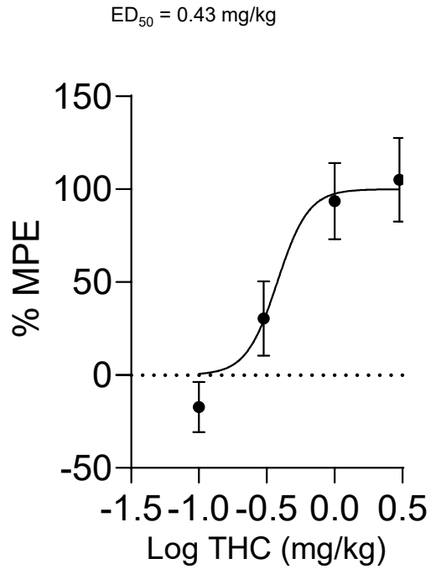
Supported by a CMCR grant

Acute THC attenuates SCD pain: dose response

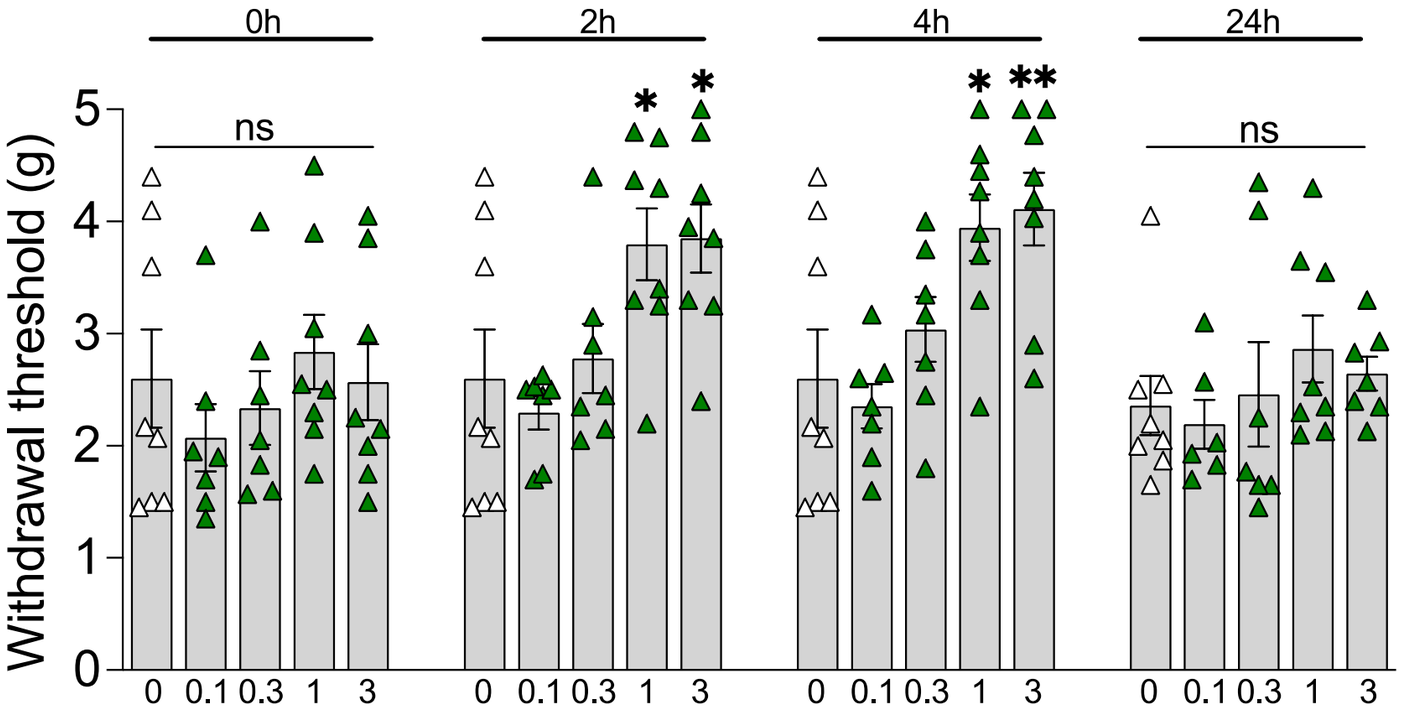






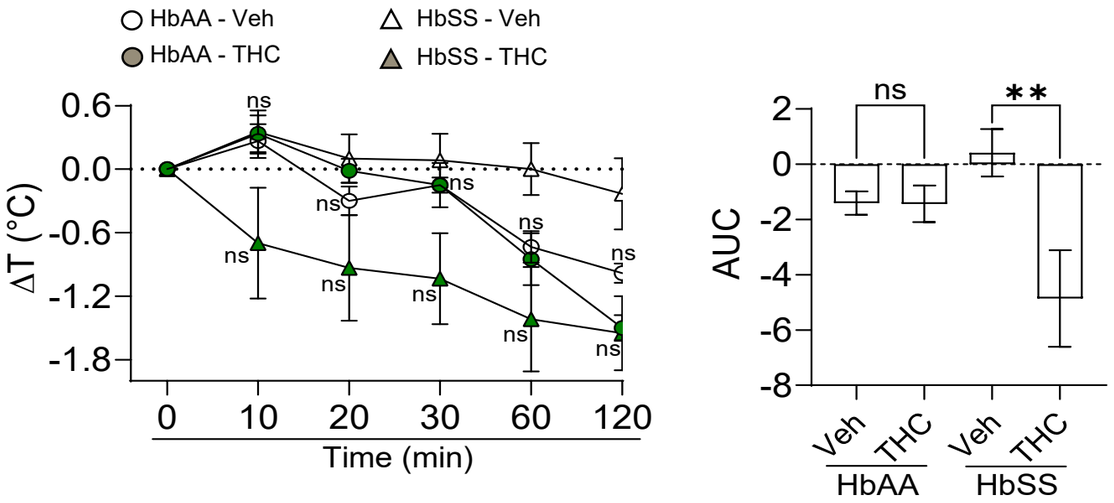


Acute THC attenuates SCD pain: time-course

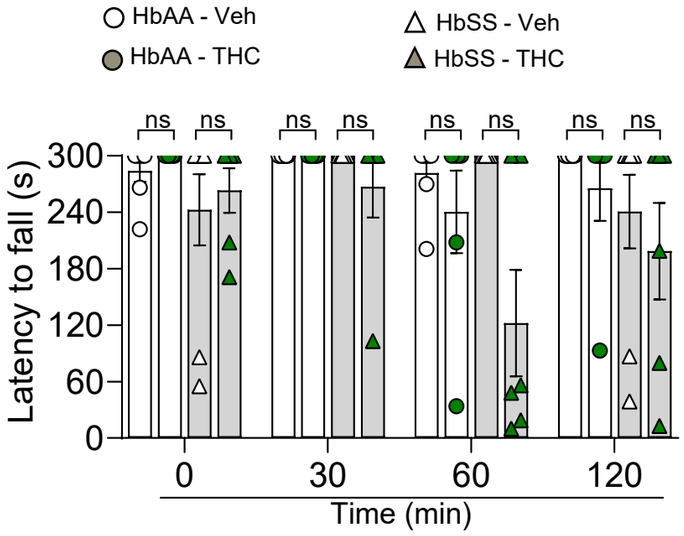


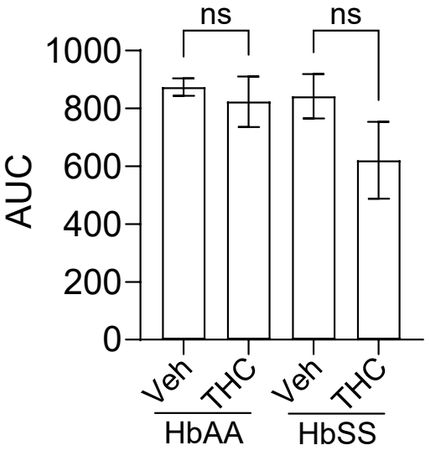
Acute THC attenuates SCD pain: side effects

Decreased body temperature



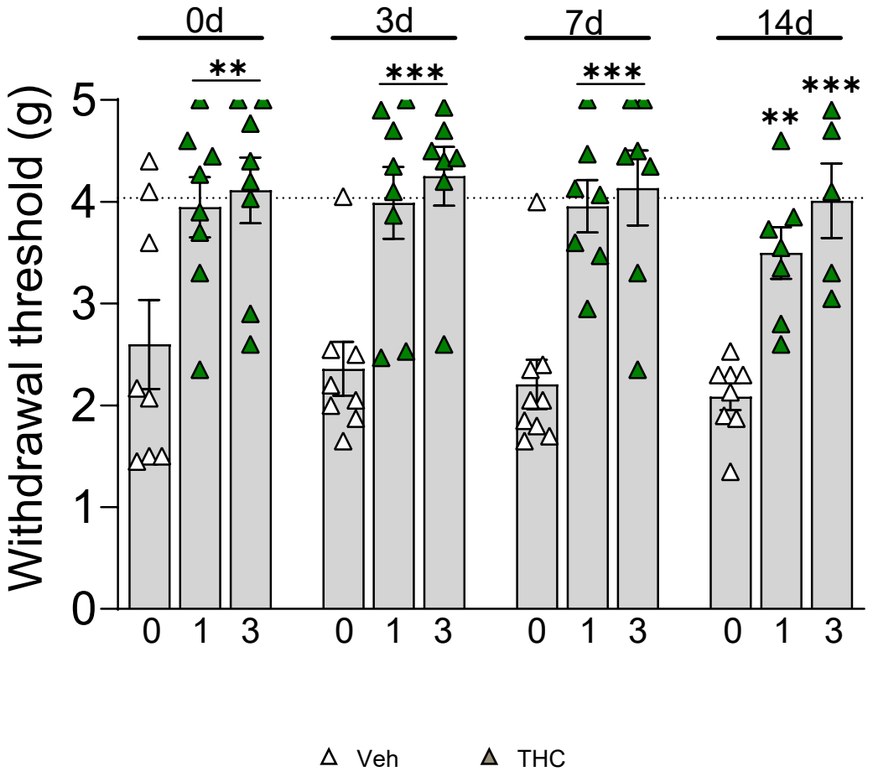
No effect on motor coordination



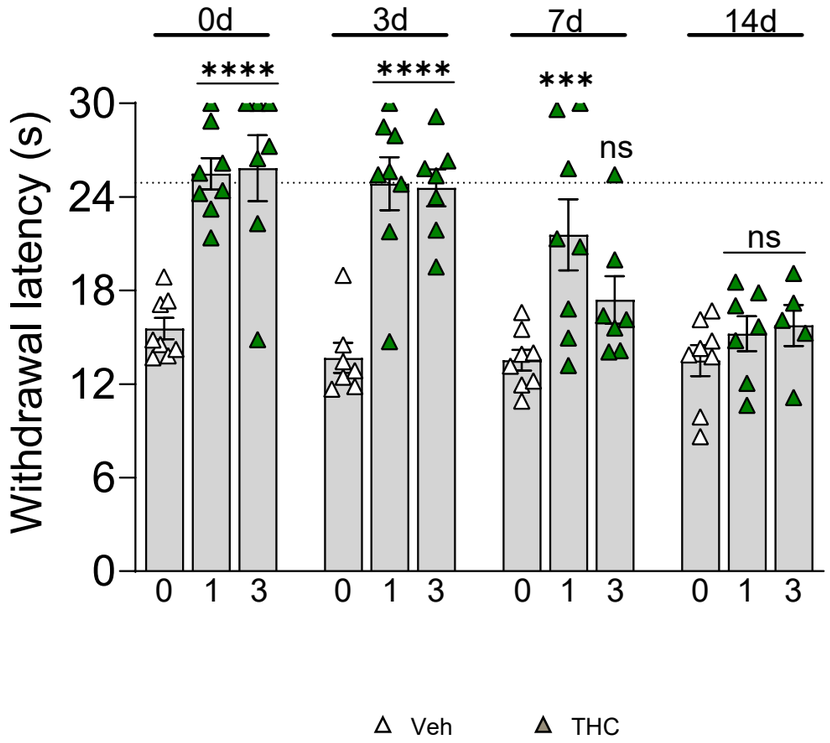


Subacute THC attenuates SCD pain, but causes modality-specific tolerance

Mechanical allodynia



Cold hyperalgesia



Analgesic effects of THC plus CBD in a humanized mouse model of SCD

Mabou Tagne A, Ajegbe O, Al-Masri S. Gupta K, Piomelli D.

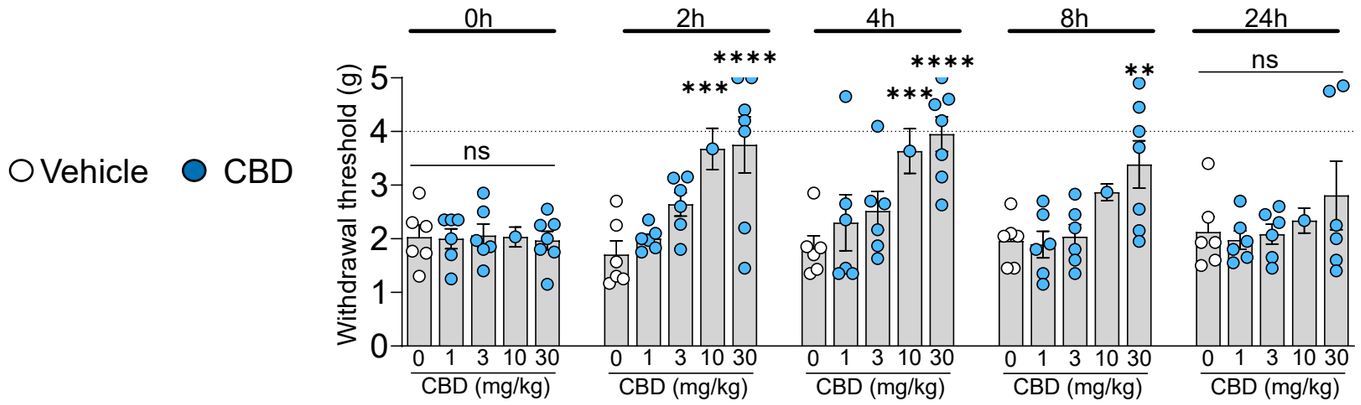
Δ^9-Tetrahydrocannabinol and Cannabidiol Synergistically Alleviate Hyperalgesia in a Humanized Mouse Model of Sickle Cell Disease.

In preparation

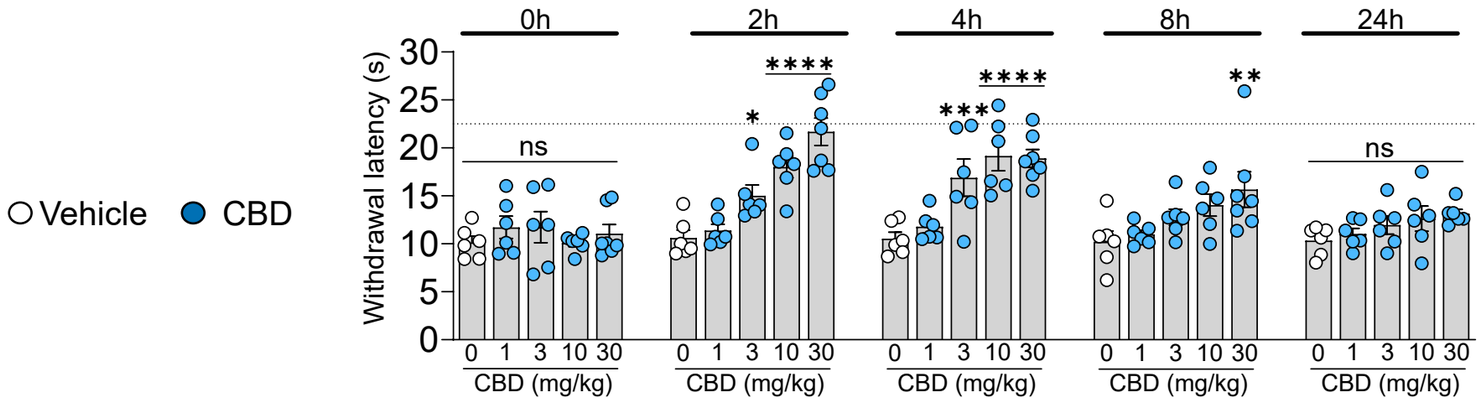
Supported by a CMCR grant

Acute CBD attenuates SCD pain

Mechanical allodynia

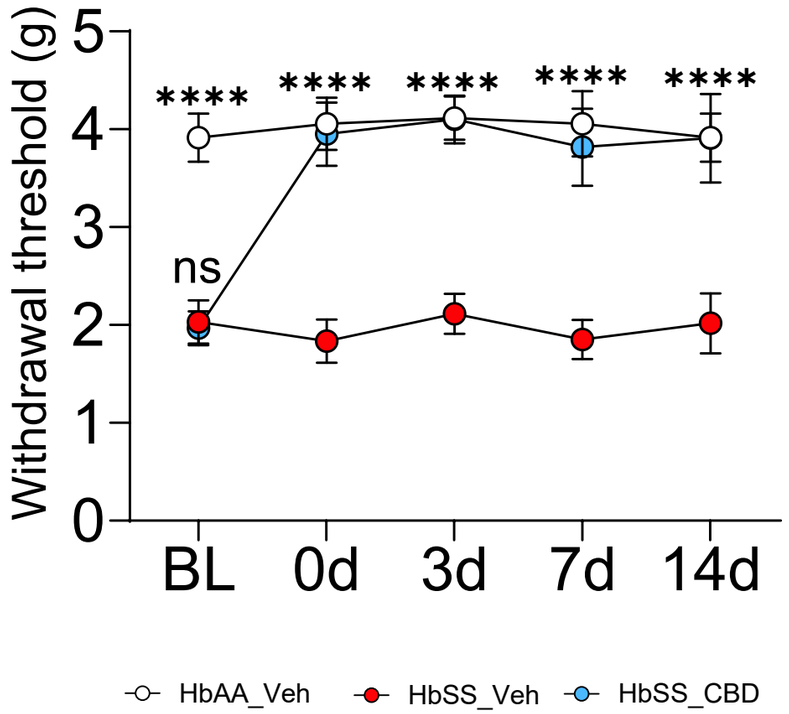


Cold hyperalgesia

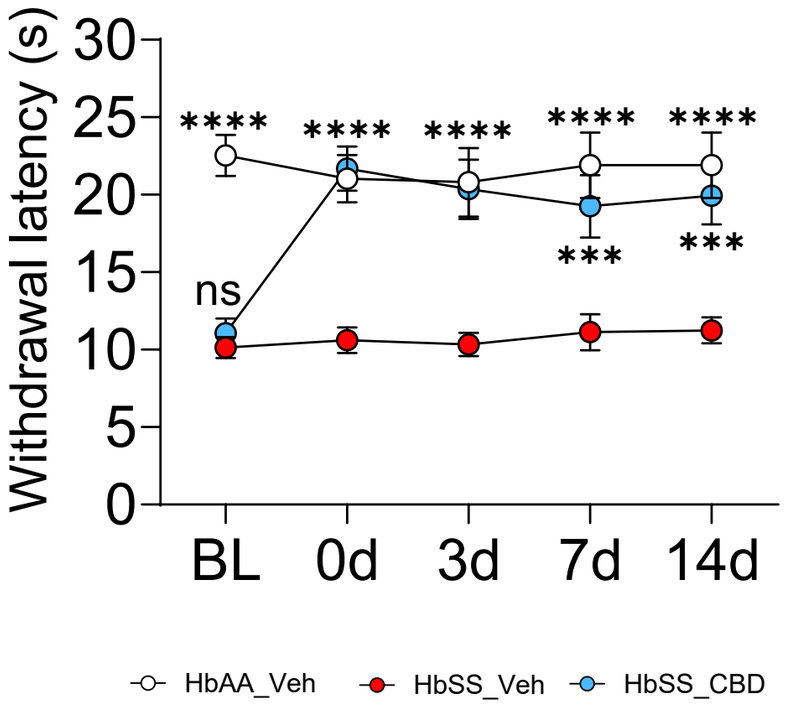


Subacute CBD attenuates SCD pain without causing tolerance

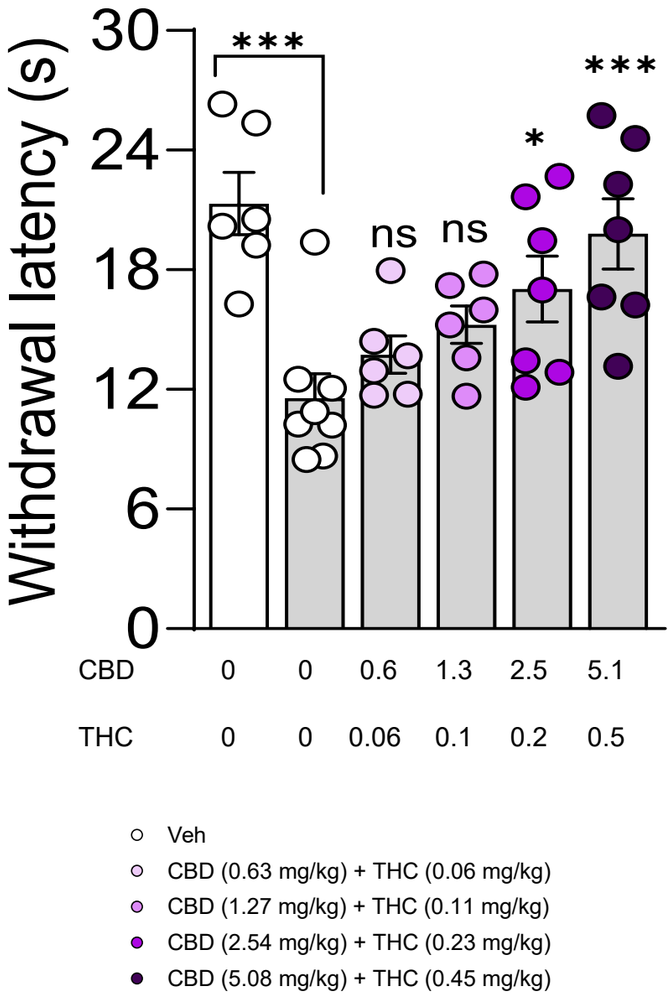
Mechanical allodynia

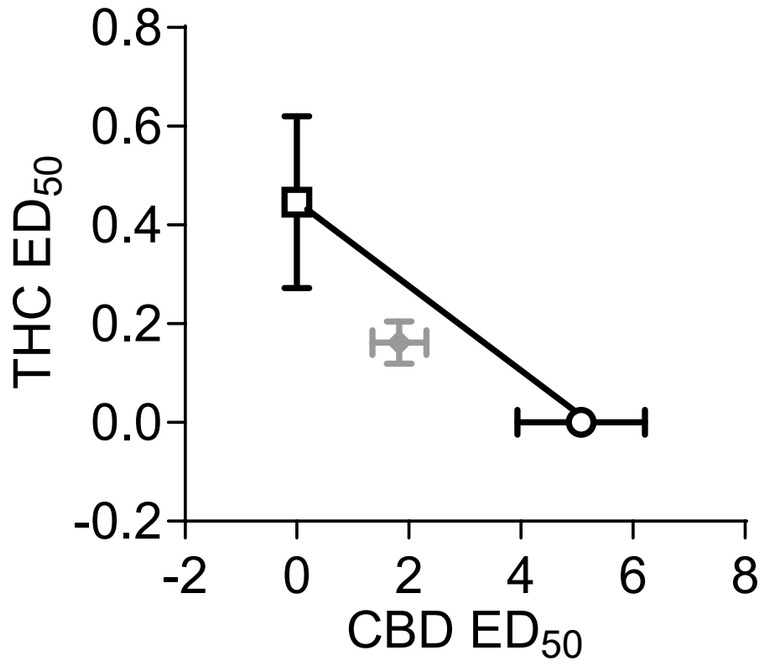


Cold hyperalgesia



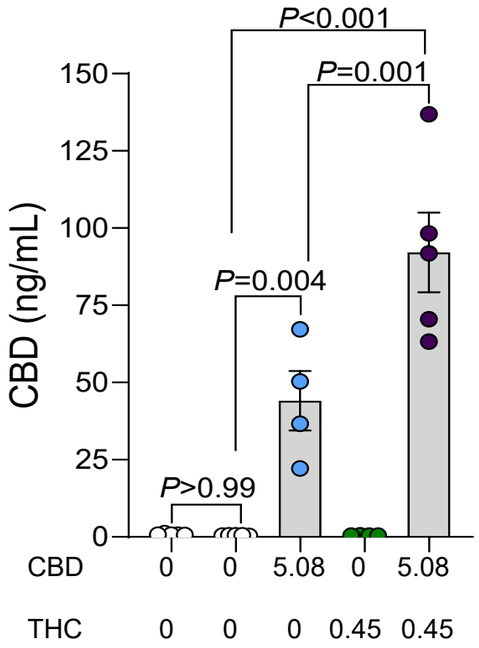
Synergistic interaction of THC and CBD

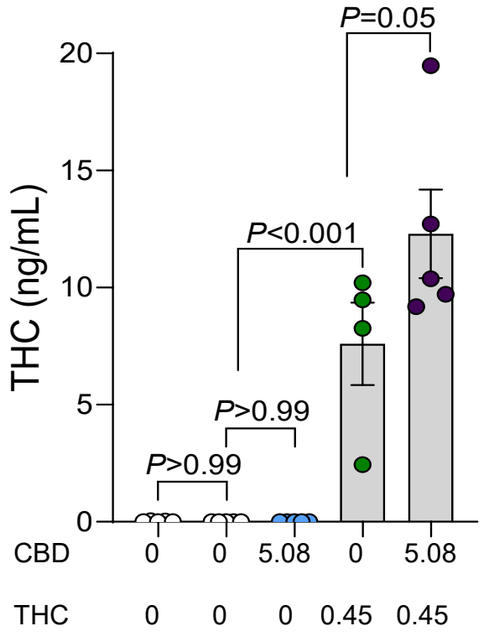




Synergistic interaction of THC and CBD: Pharmacokinetic component

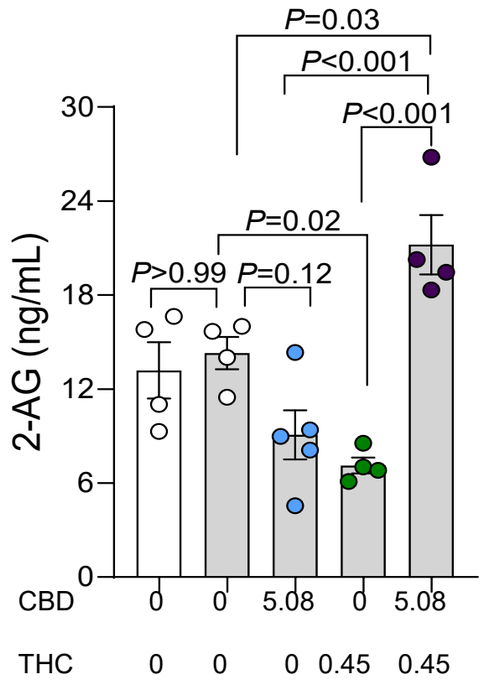
Co-administration enhances systemic exposure to both compounds

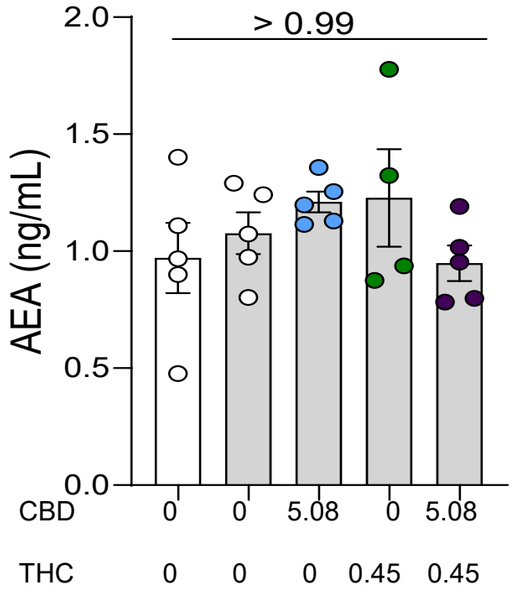




Synergistic interaction of THC and CBD: Pharmacodynamic component

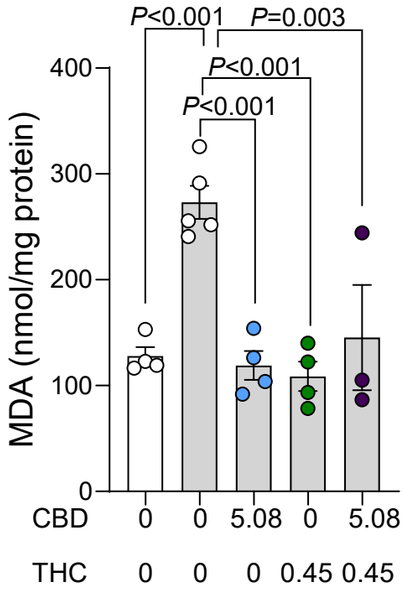
Co-administration increases circulating 2-AG concentrations



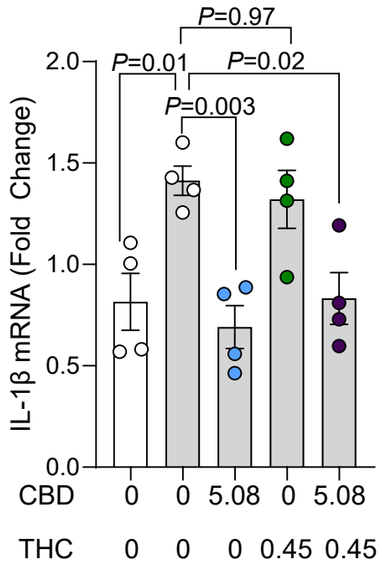


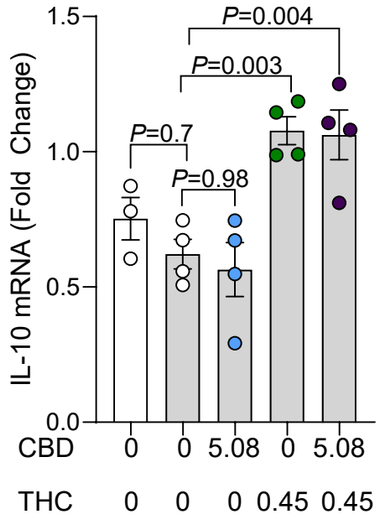
Synergistic interaction of THC and CBD: Reduced spinal-cord oxidative stress

Oxidative stress (L4-L6)

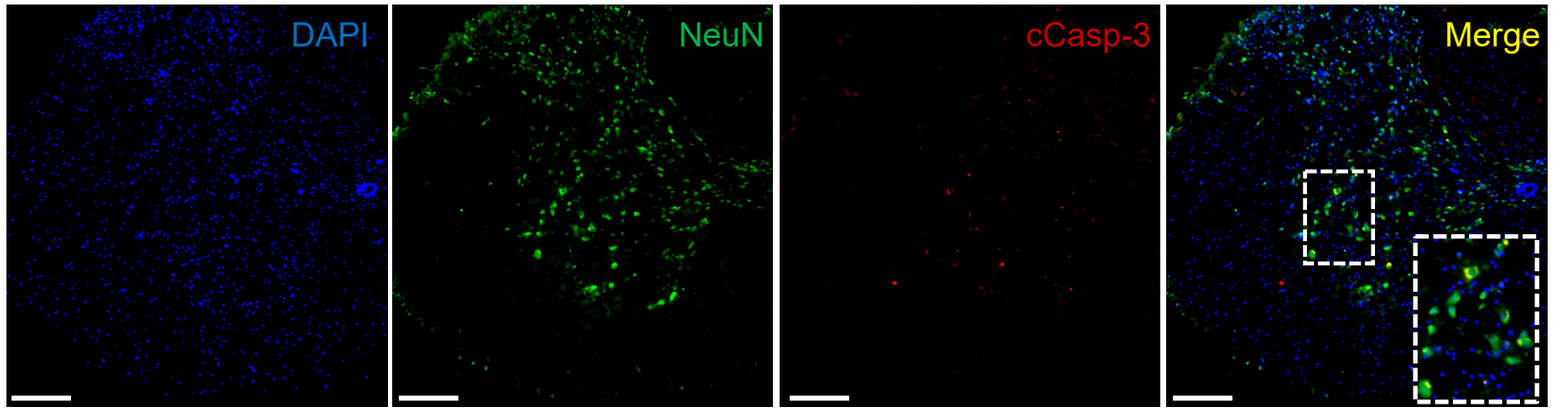


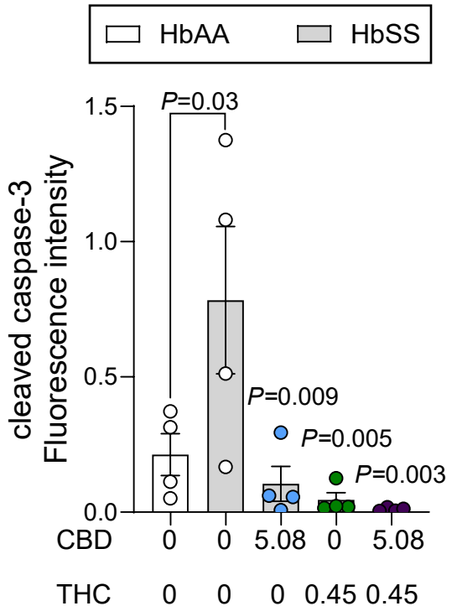
Inflammation (L4-L6)





Synergistic interaction of THC and CBD: Reduced spinal-cord neuron apoptosis





What next?

What is needed is an appropriately designed and powered RCT in SCD.

We also need to continue identify clinical pain conditions that might be amenable to cannabis-based treatment

Thank you!

Questions?