Early Observations from a Controlled Study Examining the Analgesic and Subjective Effects of the Terpene *ß*-Caryophyllene Alone and in Combination with Δ-9-THC

Stephanie Lake[1,2] and Ziva Cooper[1,2,3]

Background

- The *Cannabis sativa* plant contains >500 chemical compounds, including >100 identified terpenes
- Beta-Caryophyllene (BCP) is one of the most abundant terpenes found in cannabis[1]
- In preclinical studies, BCP reduces pain, and does not appear to have rewarding effects[2,3]
- Effects of BCP alone and in combination with cannabis' main analgesic and intoxicating component (D9-THC) in humans have not been investigated
- **We are testing the analgesic and subjective effects of BCP alone and in combination with THC in healthy volunteers**

Methods

- **Design:**
  - Within-subject, double-blinded, placebo-controlled study design
  - Nine dosing conditions in randomized order
- **Doses:**
  - THC (Dronabinol): 0 mg, 5mg, 15mg
  - BCP: 0 mg, 0.5 mg, 7.5 mg
  - Vaporized using Volcano (Storz and Bickel)
  - This presentation will focus on the higher dose (7.5 mg) of BCP
- **Outcomes:**
  - Analgesic: Cold Pressor Test (pain threshold), Subjective pain ratings (McGill Pain Questionnaire, bothersomeness of stimulus)
  - Subjective: Visual Analog Scales to assess intoxication, strength of drug effect, drug liking
  - Measured 1x pre- and 6x post-drug administration; peak change from baseline calculated for each outcome

Session	1	2	3	4	5	6	7	8	9
THC (mg)	0	5	15	0	0	5	5	15	15
BCP (mg)	0	0	0	0.5	7.5	0.5	7.5	0.5	7.5

Above: Example of dosing order for a participant

Right: Preparation of the study drug

Results

Demographics (n = 6)

Sex (Male / Female)	2/4
Ethnicity (H/NH)	1/5
Race (B/W/M)	2/2/2
Mean Age (Years ± SD)	29 ± 9
Days/Wk smoke cannabis	4.6 ± 2.2
Cannabis /day (g)	1.0 ± 0.6
~THC Exposure / day (mg)	244 ± 168

Analgesic

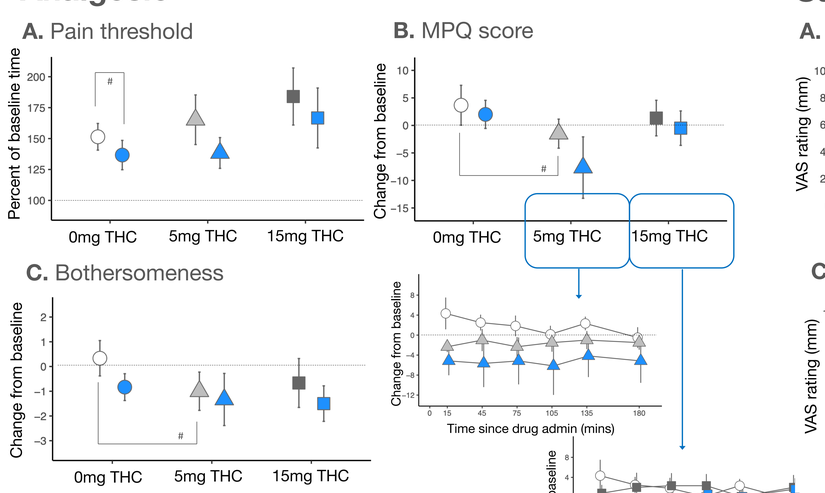

Figure 1. Analgesic Endpoints. A. Peak % of baseline pain threshold; B. Peak change from baseline in McGill Pain Questionnaire (MPQ) score with time-course examples; C. Peak change from baseline in bothersomeness. Mean and standard error plotted for each; pairwise comparisons conducted for BCP vs. THC within 0, 5, and 15 mg groups (#p<0.10 shown above) and for all active THC+/-BCP vs. placebo (#p<0.10 shown below)

Subjective

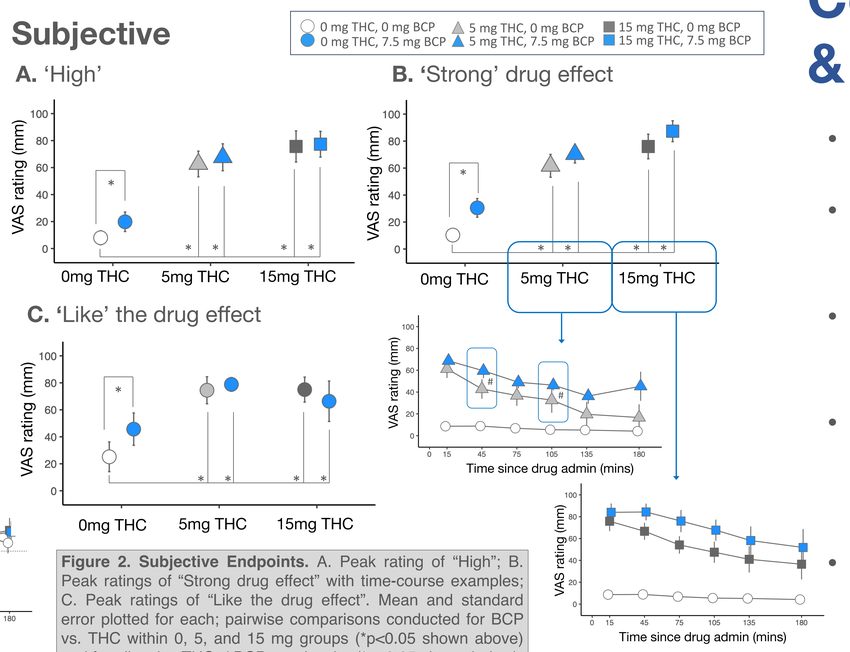

Figure 2. Subjective Endpoints. A. Peak rating of "High"; B. Peak ratings of "Strong drug effect" with time-course examples; C. Peak ratings of "Like the drug effect". Mean and standard error plotted for each; pairwise comparisons conducted for BCP vs. THC within 0, 5, and 15 mg groups (*p<0.05 shown above) and for all active THC+/-BCP vs. placebo (*p<0.05 shown below)

Conclusion & Future Directions

- These are preliminary data from 6 study completers; more data incoming
- BCP alone and in combination with THC ***may*** reduce pain threshold yet reduce subjective ratings of pain
- BCP alone elicits slight feelings of intoxication, greater perceived drug strength, greater drug liking
- When combined with THC, BCP ***may*** increase perceived strength of effect, drug liking (low THC dose), and reduce drug liking (high THC dose)
- Next steps: complete study, pharmacokinetic analysis, second terpene (myrcene)

1. UCLA Center for Cannabis and Cannabinoids, Jane and Terry Semel Institute for Neuroscience and Human Behavior, UCLA; 2. Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, UCLA; Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, UCLA

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References: 1. Smith C, J. , Vergara D, Keegan B, et al. The phytochemical diversity of commercial cannabis in the United States. bioRxiv. 2021; 2. Schwarz AM, Keresztes A, Bui T, et al. Terpenes from Cannabis sativa induce antinociception in mouse chronic neuropathic pain via activation of spinal cord adenosine A (2A) receptors. bioRxiv. 2023; 3. Mlost J, Kac P, Kędziora M, et al. Antinociceptive and chondroprotective effects of prolonged β-caryophyllene treatment in the animal model of osteoarthritis: Focus on tolerance development. Neuropharmacology. 2022;204:108908.

UCLA Center for Cannabis and Cannabinoids

David Geffen School of Medicine

SEMEL INSTITUTE UCLA