Cooper Ziva (Orcid ID: 0000-0001-8001-2332)

RUNNING TITLE: ANALGESIC EFFECTS OF CANNABIDIOL

TITLE: The dose-dependent analgesic effects, abuse liability, safety and tolerability of oral cannabidiol in healthy humans

RUNNING TITLE: ANALGESIC EFFECTS OF CANNABIDIOL

AUTHORS: Caroline A. Arout,[1] Margaret Haney,[1] Evan S Herrmann,[2] Gillinder Bedi,[3] Ziva D. Cooper[4,5]

[1]Division on Substance Use Disorders, New York Psychiatric Institute and Department of Psychiatry, Columbia University Irving Medical Center, New York, NY USA
[2] Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse
[3] Centre for Youth Mental Health, The University of Melbourne and Substance Use Research Group, Orygen, Melbourne, Australia
[4] University of California, Los Angeles Cannabis Research Initiative, Jane & Terry Semel Institute for Neuroscience & Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine. Los Angeles, CA, USA
[5] Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

CORRESPONDING AUTHOR:

ZIVA D COOPER, PH.D.
UCLA Cannabis Research Initiative
Semel Institute for Neuroscience and Human Behavior,
Department of Psychiatry and Biobehavioral Science,
760 Westwood Plaza, 37-418
Los Angeles, CA 90095
Email: zcooper@mednet.ucla.edu

DATA AVAILABILITY STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING STATEMENT: This investigator-initiated study was funded by Insys Therapeutics.

CONFLICT OF INTEREST DISCLOSURE: This investigator-initiated study was funded by Insys Therapeutics. The authors have no other competing interests in relation to the work described. In the past three years, ZDC has served as a consultant to the following companies: GB Sciences and Beckley Canopy Therapeutics and has served on the scientific advisory board of FSD Pharma and has received honoraria from Canopy Growth. In the past three years, MH has served on the scientific advisory board for Pleo Pharma.

ETHICS APPROVAL STATEMENT: Procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov under the identifier NCT02751359.

PRINCIPAL INVESTIGATOR STATEMENT

The authors confirm that the PI for this paper is Ziva D Cooper and that she had direct clinical responsibility for patients in tandem with study physicians.

WORD COUNT ABSTRACT: 243

WORD COUNT TEXT: 3505

Figures: 3

Tables: 3

What is already known about this subject:

- Preclinical studies demonstrate that cannabidiol (CBD) elicits an antinociceptive response in animal models of neuropathic pain.
- Pain is one of the primary reasons for self-reported CBD use.
- Because of CBD's non-intoxicating properties, low abuse liability and lack of effects on cognitive endpoints in various populations CBD holds promise as a potential therapeutic option for pain relief

What this study adds:

- This is the first study to assess the dose-dependent analgesic effects of CBD (200-800 mg, oral) compared to placebo in tandem with subjective drug effects and cardiovascular endpoints.
- CBD failed to elicit reliable analgesia in an experimental pain model.
- CBD produced modest effects on mood and subjective drug effects associated with abuse liability.

ABSTRACT

Aims. Preclinical studies demonstrate that cannabidiol (CBD) elicits an antinociceptive response in animal models of neuropathic pain; in humans, limited data are available to support such analgesic effects. Few studies have examined CBD's analgesic effects when administered without other compounds, and little is known regarding dose-dependent effects in non-cannabis users.

Methods. This double-blind, placebo-controlled, within-subject outpatient clinical laboratory study sought to determine the analgesic effects, abuse liability, safety and tolerability of acute CBD (0, 200, 400, and 800 mg PO) in healthy non-cannabis using volunteers (N=17; 8 men, 9 women). Outcomes included experimental pain threshold and pain tolerance using the Cold Pressor Test (CPT), subjective ratings of CPT 'Painfulness' and 'Bothersomeness,' subjective ratings of abuse liability and mood, and cardiovascular measures, which were assessed at baseline and several time points after drug administration. Data analyses included repeated measures analysis of variance (ANOVA) with planned comparisons.

Results. CBD failed to consistently affect pain threshold and tolerance in the CPT relative to placebo. All doses of CBD increased ratings of 'Painfulness' compared to placebo ($p < 0.01$). Further, CBD had dose-dependent, modest effects on mood and subjective drug effects associated with abuse liability. Oral CBD was safe and well tolerated, producing small decreases in blood pressure ($p < 0.01$).

Conclusion. CBD did not elicit consistent dose-dependent analgesia and in fact increased pain on some measures. Future studies exploring CBD-induced pain relief should consider using a more extensive pain assessment paradigm in different participant populations.

Keywords: Cannabidiol, Cannabinoids, Analgesia, Pain, Abuse liability

INTRODUCTION

Clinical studies suggest that the combination of delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, and cannabidiol (CBD), a non-intoxicating constituent of cannabis, reduces pain in patient populations (i.e., [1, 2]). However, medicinal cannabis patients are increasingly seeking products high in CBD and low in THC as a pain management strategy (particularly when they first begin using medicinal cannabis), despite a lack of rigorously controlled research to support this cannabinoid's analgesic efficacy when used in isolation [3]. When administered without THC, acute CBD dosing reduces resting blood pressure and heart rate [4], and it blunts stress-induced increases in these measures when administered chronically [5, 6]. Because of its favorable effects on cardiovascular measures under stress, its non-intoxicating properties, low abuse liability signal in current cannabis smokers (i. e., [7, 8]) and lack of effects on cognitive endpoints in various populations (i. e., [9-11]), CBD holds promise as a potential therapeutic option for pain relief.

Numerous studies in laboratory animals provide convincing data supporting CBD's potential therapeutic benefits for treatment of chronic pain. Although the compound does not reliably elicit antinociceptive effects in animal models of acute pain, it shows a positive signal in neuropathic pain models, [12-14]. This effect is mediated by CBD's complex pharmacology, including action at the non-cannabinoid receptors, TRPV1, GPR55, 5-HT_{1a}, and adenosine A_{2A} [14-16] to decrease inflammation [17]. Preclinically, *repeated* CBD administration reduces circulating levels of pro-inflammatory cytokines known to influence inflammatory pain, including interleukin (IL)-1β, IL10, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, with most of these studies showing corresponding decreases in measures of inflammatory pain [18, 19]. As many people report using CBD for pain relief [20-23], elucidating its effects on pain is a public health necessity.

We are aware of only five human studies to date that have rigorously examined the analgesic effects of CBD administered alone or with low concentrations of THC, the results of which are mixed, and none have examined the CBD's dose-dependent effects. Wade et al. (2003) demonstrated analgesia from CBD extract doses of up to 120 mg/day relative to placebo over a two-week period in 24 patients with various types of chronic pain including multiple sclerosis-associated pain, spinal cord injury, brachial plexus damage, and limb amputation due to neurofibromatosis [24]. Notcutt et al. (2004) also investigated the utility of the same CBD extract (2.5 mg sublingual spray) for chronic pain; CBD's effects were similar to placebo, and thus was reported to have little impact on chronic pain symptoms when compared to a THC extract [25]. Recent data from De Vita et al. (2021) reported that an acutely administered dose of CBD isolate oil solution (50 mg administered sublingually via a dropper) did not reduce experimental heat pain threshold, tolerance, or intensity in healthy volunteers [26]. A fourth study investigated acutely vaporized high-CBD cannabis flower that contained < 1 mg of THC in 20 women with fibromyalgia, which ultimately did not provide clinical pain relief when compared to placebo [27]. Finally, a recently published investigation by Schneider et al. (2021) reported no effect of 800 mg oral CBD (oil-based) on experimental intradermal electrical stimulation [28]. To date, no placebo-controlled studies have assessed the dose-dependent effects of CBD alone on pain. Further, none have assessed CBD's effects on pain response in tandem with measures of abuse liability, the latter being a critical endpoint when considering its clinical utility.

This within-subject, randomized, placebo-controlled, double-blind study sought to determine oral CBD's dose-dependent analgesic, abuse-related, and cardiovascular effects, and safety and tolerability in healthy humans. Acute effects of 0, 200, 400, and 800 mg oral CBD were assessed in healthy volunteers in four experimental sessions. CBD's analgesic effects were measured using the Cold Pressor Test (CPT), an experimental pain paradigm that has predictive validity for the clinical efficacy of prescribed non-cannabinoid

pain medications including opioids [29-31], gabapentin [32], and lamotrigine [33], as well as oral THC [34] and smoked cannabis with THC [35]. Enrolling healthy volunteers without pain and using an elicited pain test such as the CPT provides robust experimental control and removes two confounding variables that interfere with detecting the potential analgesic effects of test medications when studying a pain population: fluctuations in baseline pain sensitivity across the study, and current use of analgesics that potentially interact with the test medication.

METHODS AND MATERIALS

Participants. Volunteers for this study were 21-50 years of age and were assessed for basic inclusion/exclusion criteria during an initial telephone screen to ensure initial eligibility. Those who met these criteria were then invited to the laboratory for further screening, where they provided a medical history, including details on their past and current drug use, and underwent a psychiatric and medical evaluation. Eligible participants could not be using illicit substances including cannabis, as determined by urine toxicology and self-report, and were healthy as determined by a physical examination, electrocardiogram, and urine and blood chemistries. Pregnant or nursing females were excluded from participation. Volunteers were also excluded if they endorsed current pain, regularly used over the counter or prescription medications with the exception of oral contraceptives, used any illicit drugs or had problematic alcohol consumption as assessed by the Short Michigan Alcohol Screening Test and clinical interview. Those meeting Diagnostic and Statistical Manual (of Mental Disorders), fourth edition revised criteria for current major Axis I psychopathology requiring medical intervention were also excluded. Another exclusion criterion was the ability to withstand the CPT for the maximum 3 minutes during the training session (in order to avoid a ceiling effect). Participants were told that the purpose of the study was to examine the effects of an experimental drug on a human laboratory model of pain, and that during each session they would be administered an oral

solution that contained one of three different active doses of CBD or placebo. Participants were admitted into the study after providing written informed consent. Procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute, were in accordance with the Declaration of Helsinki, and the study was registered on ClinicalTrials.gov under the identifier NCT02751359.

Design and procedures. Following screening, volunteers participated in a training session during which they were familiarized with computerized tasks, the CPT, and study procedures; no medication was given during these training sessions. The experimental portion of the study comprised four 8-hour outpatient sessions over four weeks at the New York State Psychiatric Institute. Sessions began at approximately 9 AM. They were separated by at least five days to prevent potential medication carryover effects. During each session, participants were administered the study drug or placebo. A within-subject design was used in which all participants received all four dose conditions in randomized order. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Experimental sessions. Upon arrival at the laboratory, breath alcohol levels were assessed, and urine toxicology screens confirmed no recent use of illicit drugs. Participants were asked not to use any over-the-counter analgesics (i.e. ibuprofen, acetaminophen) for at least 24 h prior to each session (confirmed via Timeline Follow Back assessment) and to eat before coming to the laboratory. They were served the same standard breakfast before each session to control for possible effects of GI content on drug pharmacokinetics.

Before CBD or placebo was administered, participants completed a baseline pain assessment (CPT threshold, CPT tolerance, and subjective ratings of 'Painfulness' and 'Bothersomeness'). Heart rate and blood pressure were measured using a Sentry II vital signs monitor (Model 6100: NBS Medical Services, Costa Mesa CA). After drug administration, heart rate, blood pressure, pain (CPT and pain ratings), and subjective drug effects were assessed several times throughout the session (**Table 1**). At the end of each session, participants were given subway fare and left the laboratory after passing field sobriety tasks and verbally agreeing not to drive for the remainder of the day in case of any residual effects of the study medication.

Pain Assessment. Pain responses were measured at baseline, and 60, 120, 180, 240, 300, and 360 minutes after CBD administration (**Table 1**). Timing of the pain assessments was based on earlier reports of oral CBD's pharmacokinetics [8].

Cold Pressor Test. Two water coolers were fitted with a wire cradle and an aquarium pump for water circulation. One cooler was filled with warm water (37ºC) and the other was filled with cold water (4ºC) [34]. Each CPT began with an immersion of the left hand into the warm-water bath for three minutes to standardize skin temperature, prior to submersion into the cold-water bath. Participants were told to report the first painful sensation after the cold-water immersion, and this latency (in seconds) was recorded as "pain threshold". They were also asked to tolerate the immersion as long as possible before withdrawing their hand, and this latency (in seconds) was recorded as "pain tolerance". Research staff administering the CPT were of the same sex as each study participant [36], and a 3-minute maximum was implemented for pain tolerance to avoid tissue damage.

Pain Intensity and Bothersomeness Scales (PIB). Immediately after removing the hand from the cold water, participants rated pain intensity and bothersomeness of the cold-water stimulus on a scale from 0 to 10, 0 being “not painful/bothersome at all’ and 10 being “most painful/bothersome feeling imaginable.”

Subjective Drug Effects. Ratings of subjective drug effects were measured repeatedly on a visual analog scale (VAS) of 0 mm = no effect to 100 mm = maximum possible effect (**Table 1**).

Drug Rating Form (DRF): Subjective drug-related effects were assessed using a 5-item VAS asking participants to rate the strength of the drug effect, good effect, bad effect, drug liking, and willingness to take the drug again. This drug-effect questionnaire was modified from cannabis drug-effect questionnaires used previously in our laboratory [34].

Subjective Effect-Visual Analog Scale (SE-VAS). Participants were asked to rate their mood and physical symptoms on a modified 44-item VAS intended to measure affective and physical subjective drug effects (see [37] for description of the original 50-question version).

Drugs. Placebo or active CBD (0, 200, 400, or 800 mg (+)-CBD isomer), provided by Insys Therapeutics, Inc., was administered orally in liquid solution form. The New York State Psychiatric Institute pharmacy prepared each dose for each session to maintain the investigator blind.

Adverse effects. Participants were asked to report any unusual symptoms during the course of each session. At the beginning of each session, participants were also asked about any adverse effects experienced since the previous session. Finally, during the study debriefing (after the fourth session),

participants were asked to reflect on each session and if they experienced any sensations or symptoms that were out of the ordinary.

Data Analysis. Repeated measures analysis of variance (ANOVA) with planned comparisons were used to assess CBD's dose-related effects on measures of pain and subjective drug effects associated with abuse liability. For each participant under each dose condition, pain threshold and tolerance were calculated as the difference from baseline CPT (pre-drug administration) values. Subjective pain ratings (Pain Intensity and Bothersomeness Scales) were also measured as a function of change from the baseline response. Post-drug administration cardiovascular endpoints taken independent of the CPT were also subtracted from the baseline (pre-drug administration) values. To assess the cardiovascular response to the cold pressor test, heart rate and blood pressure values from before cold-water immersion (baseline) was subtracted from these values after the cold-water immersion. Impact of drug administration on CPT induced changes in heart rate and blood pressure were determined by calculating the difference from the baseline CPT cardiovascular response. Changes in scores from each of the three active CBD dose strengths were compared to placebo (i. e., 0 mg vs 200 mg; 0 mg vs 400 mg; 0 mg vs 800 mg) for each of the measures specified above. Results were considered statistically significant when *p* values were equal to or less than 0.01 using Huynh-Feldt corrections (SuperANOVA, Abacus Concepts, Inc., Berkley, CA).

RESULTS

Demographic Characteristics. Seventeen participants completed the study; Table 2 portrays the demographic characteristics. One additional volunteer enrolled but did not complete the study due to lost contact.

Analgesic Effects. *CPT: Pain Threshold and Tolerance.* Figure 1A portrays average pain threshold (latency to first report pain) and pain tolerance (latency to withdraw the hand from cold water) as a function of CBD dose. The low CBD dose (200 mg) increased pain threshold compared to placebo ($F(1,96) = 125.3$, $p < 0.0001$), whereas the high CBD dose decreased pain tolerance relative to placebo ($F(1,96) = 28.5$, $p < 0.01$). The 400 mg dose did increase pain tolerance, but not significantly compared to placebo.

Pain Ratings. Figure 1B illustrates average change in subjective ratings of CPT "Painfulness" and "Bothersomeness" as a function of CBD dose. CBD did not impact ratings of "Bothersomeness", whereas ratings of "Painfulness" were higher after CBD administration compared to placebo (200 mg CBD = $F(1,96) = 34.3$, $p < 0.0001$; 400 mg = $F(1,96) = 13.2$, $p < 0.01$; 800 mg CBD = $F(1,96) = 30.3$, $p < 0.0001$). Notably, three male participants exhibited hand withdrawal latencies (pain tolerance) under placebo conditions up to three times greater than their baseline (pre-placebo administration) pain responses.

Subjective drug effects. Figure 2 illustrates representative subjective drug effects as measured by the DRF (Panel A) and the Subjective Effect-VAS (Panel B). Average session drug effect ratings for 'Good drug effect' were lower under 200 mg CBD compared to placebo ($F(1,192) = 30.4$, $p < 0.001$); 'Bad drug effect' ratings were higher after 400 mg CBD administration ($F(1,192) = 48.2$, $p < 0.01$). Decreased ratings for 'Drug liking' were observed under 800 mg of CBD compared to placebo ($F(1,192) = 24.7$, $p < 0.01$, data not shown). Despite these reduced ratings associated with abuse liability for CBD, 400 mg increased ratings of 'Take again' ($F(1,192) = 66.0$, $p < 0.0001$) and 'Good drug effect' ($F(1,192) = 47.1$, $p < 0.001$) relative to placebo.

Average session subjective effect ratings depicted in Figure 2B show that 800 mg CBD decreased ratings of 'Stimulated' ($F(1,192) = 21.4$, $p < 0.01$) compared to placebo. This dose of CBD also decreased ratings of 'Intoxicated' ($F(1,192)=21.7$, $p < 0.01$; data not shown).

Cardiovascular effects. Change in heart rate and blood pressure as a function of CBD dose during the session and in response to the CPT is depicted in Figure 3. CBD decreased systolic (200 mg CBD = $F(1,128) = 16.9$, $p < 0.001$; 400 mg CBD = $F(1,128) = 9.8$, $p < 0.01$) and diastolic blood pressure (400 mg CBD = $F(1,128) = 19.5$, $p < 0.001$) but did not affect heart rate relative to placebo (Panel 3A). CBD (200 mg and 800 mg) decreased systolic blood pressure responses to CPT compared to placebo (200 mg CBD = $F(1,96) = 39.1$, $p < 0.0001$; 800 mg CBD = $F(1,96) = 21.7$, $p < 0.0001$) and increased heart rate CPT responses (200 mg CBD = $F(1,96) = 26.4$, $p < 0.0001$; 400 mg = $F(1,96) = 16.8$, $p < 0.001$; 800 mg CBD = $F(1,96) = 18.3$, $p < 0.0001$), with no effect on diastolic BP responses to the CPT.

Adverse effects. Table 3 portrays participant-reported adverse effects according to CBD dose as reported on the day of the session, retrospectively at the following session, or during the debriefing at the end of the study. The most common symptoms reported were lethargy (reported during or after 47% of the sessions) and gastrointestinal discomfort (reported during or after 18% of the sessions); these symptoms were not dependent on CBD dose. No participants discontinued the study because of adverse medication effects.

DISCUSSION

Preclinical studies support the potential clinical utility of CBD for chronic pain including chemotherapy-induced neuropathy and inflammatory pain [13-15]. While isolated CBD has been suggested to provide pain relief in case reports [38], the five studies investigating this effect under rigorous double-blind procedures [24-

28] have shown conflicting results (see Introduction). While these studies were largely negative, it is notable that each utilized a single dose of CBD and different pain assessments (clinical pain visual analogue scales, experimental heat or electrical pain). Our study sought to examine the dose-dependent analgesic effects of an oral formulation of CBD, as well as its positive subjective effects associated with abuse liability, cardiovascular endpoints, and safety and tolerability in a healthy control population. In support of previous literature [4], we found that CBD lowered blood pressure but had no impact on heart rate, and it was well-tolerated with minimal side effects and abuse-related subjective effects. However, we did not find acutely administered CBD to have any consistent impact on analgesia, as measured by the Cold Pressor Test.

The current results add to other reports pointing to CBD's safety and tolerability in people who use cannabis, people who do not use cannabis, and patient populations [7, 8, 39-41]. In agreement with Notcutt et al. (2004) and Schneider et al. (2021), the current findings do not support analgesic effects of CBD on experimentally-induced pain [25, 28]. The inconsistent effects seen here were similar to other studies pointing to an inverted-U shape dose-response curve of CBD on other constructs, including anxiety [42]. Furthermore, all doses increased subjective ratings of the painfulness of the CPT stimulus compared to placebo.

CBD's lack of analgesic effects in the current study may be due to a variety of factors. Previous studies in our labortory with oral CBD reported that T_{max} for plasma CBD is 3 hours after administration [8]. As such, the study was designed to capture peak plasma levels with pain assessments spanning 1 – 6 hours after administration and to yield effects that varied across timecourse. However, we did not capture reliable analgesic effects across the session or as a function of time despite our outcomes being collected during peak plasma levels of CBD,. Therefore, we consider the current results to be an indication that CBD, when

acutely administered prior to a nociceptive stimulus in healthy volunteers, does not have an analgesic effect. Based on preclinical findings, it is possible that CBD's pain-relieving effects are only elicited and detectable if administered chronically over an extended period (i.e., a month), and in a clinical pain population. This notion is consistent with a lack of effect on other experimental pain paradigms, such as the heat pain threshold and tolerance model used in De Vita et al. (2021) and the noxious electrical stimulation paradigm used in Schneider et al. (2021) [26, 28]. For instance, in preclinical models, CBD demonstrated efficacy when administered daily to rodents exposed to a chronic pathological state like chemotherapy-induced neuropathy [12-14] or arthritis [15]. The effects of CBD in chronic pain models speak to the potential of CBD to relieve chronic, inflammatory pain by targeting a multitude of systems that are activated during *chronic* disease states such as pro-inflammatory biomarkers [15] and TRPV1 pathways [43, 44]. This is unlike preclinical and human laboratory evidence demonstrating the analgesic effects of CB1 receptor agonists like THC, where substantial literature supports analgesic effects after an acute dose in a range of acute, experimental pain models as well as chronic pain states [34, 45-49]. Given the previous literature and in conjunction with our findings, a logical next step would be to conduct a study in which patients with clinical pain syndromes, perhaps those inflammatory in nature, are given CBD over time and a multitude of assessments are conducted for comparative purposes. This might include several, a combination of different modalities that model neuropathic pain conditions (Cold Pressor Test, Quantitative Sensory Testing) as well as clinical pain outcomes (the Brief Pain Inventory). Such a study would provide the opportunity to determine if our suspicions are correct; that repeatedly administered CBD in a clinical population is required to detect a reliable, robust analgesic effect.

A primary limitation of the study, which hindered the ability to adequately assess the analgesic effects of CBD, is the failure of the CPT to produce a reliable pain response as depicted by an increase in pain

tolerance and decrease in subjective ratings of painfulness after placebo was administered compared to baseline values. We and others have successfully used the CPT in healthy [29, 31, 50] and drug-using [32, 34, 35] populations to determine the analgesic effects of a several drug classes. The current procedures controlled for the time of day that the CPT was administered and matched the sex of the participant to the experimenter, two variables that can potentially impact pain responses in the CPT [36, 51]. As such, it is difficult to determine why the CPT data were inconsistent under the placebo condition; these findings could be due to the robust response exhibited by the three male participants under placebo conditions, which skewed the data to show a strong placebo response. Although the within-subject design of the study enhances statistical power to detect differences between placebo and active CBD doses, increasing the sample size in future studies could be useful in determining if the modest effects observed among in the current study are reliable. Finally, it is notable that the isomer present in the synthetic CBD used in this study ((+)-CBD) is different than what is naturally occurring in the plant ((-)-CBD), each of which differentially binds the cannabinoid receptor 1- and 2- subtypes [52]; this may underlie differing effects of synthetic vs. natural forms of CBD, the latter of which has little to no affinity for the CB-1 receptors.

CONCLUSION

Considering preclinical studies that have shown promise for CBD analgesia in chronic pain conditions, to our knowledge, the current study is the first to assess isolated CBD's dose-dependendent analgesic effectiveness using an experimental pain model that has demonstrated predictive validity for pain medications. While CBD was safe and well-tolerated, we found no acute effects on experimental pain. CBD use over time in a chronic pain patient population may be more likely produce effective analgesia than acute dosing in a non-pain population.

Conflict of Interest

This investigator-initiated study was funded by Insys Therapeutics. The authors have no other competing interests in relation to the work described. In the past three years, ZDC has served as a consultant to the following companies: GB Sciences and Beckley Canopy Therapeutics and has served on the scientific advisory board of FSD Pharma and has received honoraria from Canopy Growth. In the past three years, MH has served on the scientific advisory board for Pleo Pharma.

Author Contributions

ZDC led study conceptualization, design, initiation, and study implementation with review from MH. ZDC led the data analysis and management of manuscript submission. CAA led the drafting of the manuscript and ZDC, MH, ESH and GB managed study procedures. All authors contributed to the review and interpretation of data and manuscript review.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 [53, 54].

REFERENCES

1. Langford, R., J. Mares, A. Novotna, M. Vachova, I. Novakova, W. Notcutt, and S. Ratcliffe, *A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis.* Journal of neurology, 2013. **260**(4): p. 984-997.
2. Portenoy, R.K., E.D. Ganae-Motan, S. Allende, R. Yanagihara, L. Shaiova, S. Weinstein, R. McQuade, S. Wright, and M.T. Fallon, *Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial.* The Journal of Pain, 2012. **13**(5): p. 438-449.
3. Boehnke, K.F., J.R. Scott, E. Litinas, S. Sisley, D.J. Clauw, J. Goesling, and D.A. Williams, *Cannabis Use Preferences and Decision-making Among a Cross-sectional Cohort of Medical Cannabis Patients with Chronic Pain.* J Pain, 2019. **20**(11): p. 1362-1372.
4. Jadoon, K.A., G.D. Tan, and S.E. O'Sullivan, *A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study.* JCI insight, 2017. **2**(12).
5. Sultan, S.R., S.A. Millar, T.J. England, and S.E. O'Sullivan, *A systematic review and meta-analysis of the haemodynamic effects of cannabidiol.* Frontiers in pharmacology, 2017. **8**: p. 81.
6. Sultan, S.R., S.E. O'Sullivan, and T.J. England, *The effects of acute and sustained cannabidiol dosing for seven days on the haemodynamics in healthy men: A randomised controlled trial.* British Journal of Clinical Pharmacology, 2020. **86**(6): p. 1125-1138.
7. Babalonis, S., M. Haney, R.J. Malcolm, M.R. Lofwall, V.R. Votaw, S. Sparenborg, and S.L. Walsh, *Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers.* Drug and alcohol dependence, 2017. **172**: p. 9-13.
8. Haney, M., R.J. Malcolm, S. Babalonis, P.A. Nuzzo, Z.D. Cooper, G. Bedi, K.M. Gray, A. McRae-Clark, M.R. Lofwall, and S. Sparenborg, *Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis.* Neuropsychopharmacology, 2016. **41**(8): p. 1974-1982.
9. Belgrave, B., K. Bird, G. Chesher, D. Jackson, K. Lubble, G. Starmer, and R. Teo, *The effect of cannabidiol, alone and in combination with ethanol, on human performance.* Psychopharmacology, 1979. **64**(2): p. 243-246.

10. Boggs, D.L., T. Surti, A. Gupta, S. Gupta, M. Niciu, B. Pittman, A.M.S. Martin, H. Thurnauer, A. Davies, and D.C. D'Souza, *The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial.* Psychopharmacology, 2018. **235**(7): p. 1923-1932.
11. Solowij, N., S.J. Broyd, C. Beale, J.-A. Prick, L.-m. Greenwood, H. Van Hell, C. Suo, P. Galettis, N. Pai, and S. Fu, *Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: a pragmatic open-label clinical trial.* Cannabis and Cannabinoid Research, 2018. **3**(1): p. 21-34.
12. King, K.M., A.M. Myers, A.J. Soroka-Monzo, R.F. Tuma, R.J. Tallarida, E.A. Walker, and S.J. Ward, *Single and combined effects of Δ9-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain.* British journal of pharmacology, 2017. **174**(17): p. 2832-2841.
13. Ward, S.J., M.D. Ramirez, H. Neelakantan, and E.A. Walker, *Cannabidiol prevents the development of cold and mechanical allodynia in paclitaxel-treated female C57Bl6 mice.* Anesthesia and analgesia, 2011. **113**(4): p. 947.
14. Ward, S.J., S.D. McAllister, R. Kawamura, R. Murase, H. Neelakantan, and E.A. Walker, *Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT1A receptors without diminishing nervous system function or chemotherapy efficacy.* British journal of pharmacology, 2014. **171**(3): p. 636-645.
15. Hammell, D., L. Zhang, F. Ma, S. Abshire, S. McIlwrath, A. Stinchcomb, and K. Westlund, *Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis.* European Journal of Pain, 2016. **20**(6): p. 936-948.
16. Harris, H.M., K.J. Sufka, W. Gul, and M.A. ElSohly, *Effects of delta-9-tetrahydrocannabinol and cannabidiol on cisplatin-induced neuropathy in mice.* Planta medica, 2016. **82**(13): p. 1169-1172.
17. De Gregorio, D., R.J. McLaughlin, L. Posa, R. Ochoa-Sanchez, J. Enns, M. Lopez-Canul, M. Aboud, S. Maione, S. Comai, and G. Gobbi, *Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain.* Pain, 2019. **160**(1): p. 136.
18. Britch, S., A. Goodman, J. Wiley, A. Pondelick, and R. Craft, *Antinociceptive and Immune Effects of Delta-9-tetrahydrocannabinol or Cannabidiol in Male Versus Female Rats with Persistent Inflammatory Pain.* Journal of Pharmacology and Experimental Therapeutics, 2020.
19. Burstein, S.H. and R.B. Zurier, *Cannabinoids, endocannabinoids, and related analogs in inflammation.* The AAPS journal, 2009. **11**(1): p. 109.
20. Capano, A., R. Weaver, and E. Burkman, *Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study.* Postgraduate Medicine, 2020. **132**(1): p. 56-61.
21. Corroon, J. and J.A. Phillips, *A cross-sectional study of cannabidiol users.* Cannabis and cannabinoid research, 2018. **3**(1): p. 152-161.
22. MacCallum, C.A. and E.B. Russo, *Practical considerations in medical cannabis administration and dosing.* European journal of internal medicine, 2018. **49**: p. 12-19.
23. Sexton, M., C. Cuttler, J.S. Finnell, and L.K. Mischley, *A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy.* Cannabis and cannabinoid research, 2016. **1**(1): p. 131-138.

24. Wade, D.T., P. Robson, H. House, P. Makela, and J. Aram, *A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms.* Clinical rehabilitation, 2003. **17**(1): p. 21-29.
25. Notcutt, W., M. Price, R. Miller, S. Newport, C. Phillips, S. Simmons, and C. Sansom, *Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies.* Anaesthesia, 2004. **59**(5): p. 440-452.
26. De Vita, M.J., S.A. Maisto, C.E. Gilmour, L. McGuire, E. Tarvin, and D. Moskal, *The effects of cannabidiol and analgesic expectancies on experimental pain reactivity in healthy adults: A balanced placebo design trial.* Experimental and Clinical Psychopharmacology, 2021: p. No Pagination Specified-No Pagination Specified.
27. van de Donk, T., M. Niesters, M.A. Kowal, E. Olofsen, A. Dahan, and M. van Velzen, *An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia.* Pain, 2019. **160**(4): p. 860-869.
28. Schneider, T., L. Zurbriggen, M. Dieterle, E. Mauermann, P. Frei, K. Mercer-Chalmers-Bender, and W. Ruppen, *Pain response to cannabidiol in induced acute nociceptive pain, allodynia and hyperalgesia by using a model mimicking acute pain in healthy adults in a randomized trial (CANAB I).* PAIN, 9000. **Articles in Press**.
29. Conley, K.M., A.Y. Toledano, J.L. Apfelbaum, and J.P. Zacny, *Modulating effects of a cold water stimulus on opioid effects in volunteers.* Psychopharmacology, 1997. **131**(4): p. 313-320.
30. Kowalczyk, W.J., S.M. Evans, A.M. Bisaga, M.A. Sullivan, and S.D. Comer, *Sex differences and hormonal influences on response to cold pressor pain in humans.* The Journal of Pain, 2006. **7**(3): p. 151-160.
31. Zacny, J.P., D.W. Coalson, C.J. Young, J.M. Klafta, J.L. Lichtor, G. Rupani, P. Thapar, and J.L. Apfelbaum, *Propofol at conscious sedation doses produces mild analgesia to cold pressor-induced pain in healthy volunteers.* Journal of clinical anesthesia, 1996. **8**(6): p. 469-474.
32. Compton, P., P. Kehoe, K. Sinha, M.A. Torrington, and W. Ling, *Gabapentin improves cold-pressor pain responses in methadone-maintained patients.* Drug and alcohol dependence, 2010. **109**(1): p. 213-219.
33. Webb, J. and F. Kamali, *Analgesic effects of lamotrigine and phenytoin on cold-induced pain: a crossover placebo-controlled study in healthy volunteers.* Pain, 1998. **76**(3): p. 357-363.
34. Cooper, Z.D., S.D. Comer, and M. Haney, *Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers.* Neuropsychopharmacology, 2013. **38**(10): p. 1984.
35. Cooper, Z.D., G. Bedi, D. Ramesh, R. Balter, S.D. Comer, and M. Haney, *Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability.* Neuropsychopharmacology, 2018.
36. Fillingim, R.B., C.D. King, M.C. Ribeiro-Dasilva, B. Rahim-Williams, and J.L. Riley III, *Sex, gender, and pain: a review of recent clinical and experimental findings.* The journal of pain, 2009. **10**(5): p. 447-485.
37. Haney, M., A.S. Ward, S.D. Comer, R.W. Foltin, and M.W. Fischman, *Abstinence symptoms following smoked marijuana in humans.* Psychopharmacology (Berl), 1999. **141**(4): p. 395-404.
38. Chelliah, M.P., Z. Zinn, P. Khuu, and J.M. Teng, *Self-initiated use of topical cannabidiol oil for epidermolysis bullosa.* Pediatric Dermatology, 2018. **35**(4): p. e224-e227.

39. Arndt, D.L. and H. de Wit, *Cannabidiol does not dampen responses to emotional stimuli in healthy adults.* Cannabis and cannabinoid research, 2017. **2**(1): p. 105-113.
40. Linares, I.M., F.S. Guimaraes, A. Eckeli, A. Crippa, A.W. Zuardi, J.D. Souza, J.E. Hallak, and J.A. Crippa, *No acute effects of cannabidiol on the sleep-wake cycle of healthy subjects: a randomized, double-blind, placebo-controlled, crossover study.* Frontiers in pharmacology, 2018. **9**: p. 315.
41. Naftali, T., R. Mechulam, A. Marii, G. Gabay, A. Stein, M. Bronshtain, I. Laish, F. Benjaminov, and F.M. Konikoff, *Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial.* Digestive diseases and sciences, 2017. **62**(6): p. 1615-1620.
42. Zuardi, A.W., N.P. Rodrigues, A.L. Silva, S.A. Bernardo, J.E. Hallak, F.S. Guimarães, and J.A. Crippa, *Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life.* Frontiers in pharmacology, 2017. **8**: p. 259.
43. de Almeida, D.L. and L.A. Devi, *Diversity of molecular targets and signaling pathways for CBD.* Pharmacology research & perspectives, 2020. **8**(6): p. e00682.
44. Costa, B., G. Giagnoni, C. Franke, A.E. Trovato, and M. Colleoni, *Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation.* British journal of pharmacology, 2004. **143**(2): p. 247-250.
45. Cox, M.L. and S.P. Welch, *The antinociceptive effect of Delta9-tetrahydrocannabinol in the arthritic rat.* European journal of pharmacology, 2004. **493**(1-3): p. 65-74.
46. Mao, J., D. Price, J. Lu, L. Keniston, and D. Mayer, *Two distinctive antinociceptive systems in rats with pathological pain.* Neuroscience letters, 2000. **280**(1): p. 13-16.
47. Smith, F.L., D. Cichewicz, Z.L. Martin, and S.P. Welch, *The enhancement of morphine antinociception in mice by Δ9-tetrahydrocannabinol.* Pharmacology Biochemistry and Behavior, 1998. **60**(2): p. 559-566.
48. Tseng, A.H. and R.M. Craft, *Sex differences in antinociceptive and motoric effects of cannabinoids.* European journal of pharmacology, 2001. **430**(1): p. 41-47.
49. Varvel, S., J. Wiley, R. Yang, D. Bridgen, K. Long, A. Lichtman, and B. Martin, *Interactions between THC and cannabidiol in mouse models of cannabinoid activity.* Psychopharmacology, 2006. **186**(2): p. 226-234.
50. Cooper, Z.D., M.A. Sullivan, S.K. Vosburg, J.M. Manubay, M. Haney, R.W. Foltin, S.M. Evans, W.J. Kowalczyk, P.A. Saccone, and S.D. Comer, *Effects of repeated oxycodone administration on its analgesic and subjective effects in normal, healthy volunteers.* Behavioural pharmacology, 2012. **23**(3): p. 271.
51. van Eekelen, A.P., G.A. Kerkhof, and J.G. van Amsterdam, *Circadian variation in cortisol reactivity to an acute stressor.* Chronobiology international, 2003. **20**(5): p. 863-878.
52. Wheless, J.W., D. Dlugos, I. Miller, D.A. Oh, N. Parikh, S. Phillips, J.B. Renfroe, C.M. Roberts, I. Saeed, and S.P. Sparagana, *Pharmacokinetics and tolerability of multiple doses of pharmaceutical-grade synthetic cannabidiol in pediatric patients with treatment-resistant epilepsy.* CNS drugs, 2019. **33**(6): p. 593-604.
53. Alexander, S.P., A. Christopoulos, A.P. Davenport, E. Kelly, A. Mathie, J.A. Peters, E.L. Veale, J.F. Armstrong, E. Faccenda, and S.D. Harding, *The Concise Guide to PHARMACOLOGY 2019/20: G protein-coupled receptors.* British journal of pharmacology, 2019. **176**: p. S21-S141.

54. Alexander, S.P., D. Fabbro, E. Kelly, A. Mathie, J.A. Peters, E.L. Veale, J.F. Armstrong, E. Faccenda, S.D. Harding, and A.J. Pawson, *The concise guide to pharmacology 2019/20: catalytic receptors.* British Journal of Pharmacology, 2019. **176**: p. S247-S296.

TABLES

Table 1. Session Schedule

Time (min)	Event
- 60	Urine toxicology, Breathalyzer, Carbon monoxide, Adverse effects form, Breakfast
- 30	BP/HR, Pain assessments
0	Drug Administration
30	Drug rating form, SE-VAS, BP/HR
60	Drug rating form, SE-VAS, Pain assessments
90	Drug rating form, SE-VAS, BP/HR
120	Drug rating form, SE-VAS, Pain assessments
150	Drug rating form, SE-VAS, BP/HR
180	Drug rating form, SE-VAS, Pain assessments
210	Drug rating form, SE-VAS, BP/HR, Lunch
240	Drug rating form, SE-VAS, Pain assessments
270	Drug rating form, SE-VAS, BP/HR
300	Drug rating form, SE-VAS, Pain assessments
330	Drug rating form, SE-VAS, BP/HR
360	Drug rating form, SE-VAS, Pain assessments
375	BP/HR, Discharge

Timing of session events relative to cannabidiol administration. Sessions began at approximately 9 AM. *Pain assessments* = Cold Pressor Test and Painful and Bothersome Rating Forms. *BP/HR* = Blood pressure and heart rate readings. *SE-VAS* = Subjective Effects Visual Analog Scale

Table 2. Demographic Characteristics of Study Participants.

Demographics (N = 17)	
Age (years)	32 ± 8
Sex (Men / Women)	8 / 9
Race (B / W / A / M)	8 / 2 / 4 / 3
Daily Nicotine Smokers	0%
Weekly Alcohol Drinkers	47%
Drinking occasions/week	2.0 ± 0.9

Note: Data are presented as means (± SD) or as percent.
Race is indicated as Black (B), White (W), Asian (A)
and Mixed or other (M).

Table 3. Adverse effects as a function of cannabidiol dose

	Total # of Participants Reporting Symptom				% of Total N			
Cannabidiol (mg)	**0**	**200**	**400**	**800**	**0**	**200**	**400**	**800**
Lethargy	5	5	5	5	29%	29%	29%	29%
Stomach upset (gas, cramps)	1	1	4	4	6%	6%	24%	24%
Subtle mood change	1	0	0	0	6%	0%	0%	0%
Frequent urination	0	0	1	0	0%	0%	6%	0%
Wooziness	0	0	1	1	0%	0%	6%	6%

FIGURE LEGENDS

Figure 1. **A.** Cold Pressor Task pain threshold and tolerance as calculated by average post administration change from baseline latency (seconds) to report pain and withdraw the hand (respectively) from cold water. Data are presented as means +/- SEM according to cannabidiol dose. **B.** Subjective pain ratings of Painfulness and Bothersomeness as calculated by average change across the session from baseline (possible range, -10 – 10). Data are presented as means +/- SEM according to cannabidiol dose. Significant differences between placebo and an active dose are indicated by * for pain threshold and 'painful' ratings, and # for pain tolerance. One symbol (i.e., *) indicates statistical significance < 0.01; two symbols (i.e., **) indicates < 0.001.

Figure 2. A. Average drug effect ratings for 'Take again,' 'Good drug effect' and 'Bad drug effect' across the session (post-baseline). Data are presented as means +/- SEM according to cannabidiol dose. Significant differences between placebo and an active dose are indicated by * for 'Take again', # for 'Good drug effect' and ‡ for 'Bad drug effect'. **B.** Average subjective effect ratings for 'Stimulated', 'Alert' and 'Tired' across the session (post-baseline). Data are presented as means +/- SEM according to cannabidiol dose. Significant differences between placebo and an active dose are indicated by * for 'Stimulated. For both Figure 2A and 2B, one symbol (i.e., *) indicates statistical significance < 0.01; two symbols (i.e., **) indicates < 0.001, three symbols (i.e., ***) indicates < 0.0001.

Figure 3. A. Average change from baseline in cardiovascular effects as a function of cannabidiol dose. **B.** Average change in cardiovascular effects in response to the CPT across the session, as a function of cannabidiol dose. Data are presented as means +/- SEM according to cannabidiol dose. Significant differences between placebo and an active dose are indicated by * for diastolic blood pressure, # for systolic blood pressure and ‡ for heart rate. For both Figure 3A and 3B, one symbol (i.e., *) indicates statistical significance < 0.01; two symbols (i.e., **) indicates < 0.001, three symbols (i.e., ***) indicates < 0.0001.

Figure 1

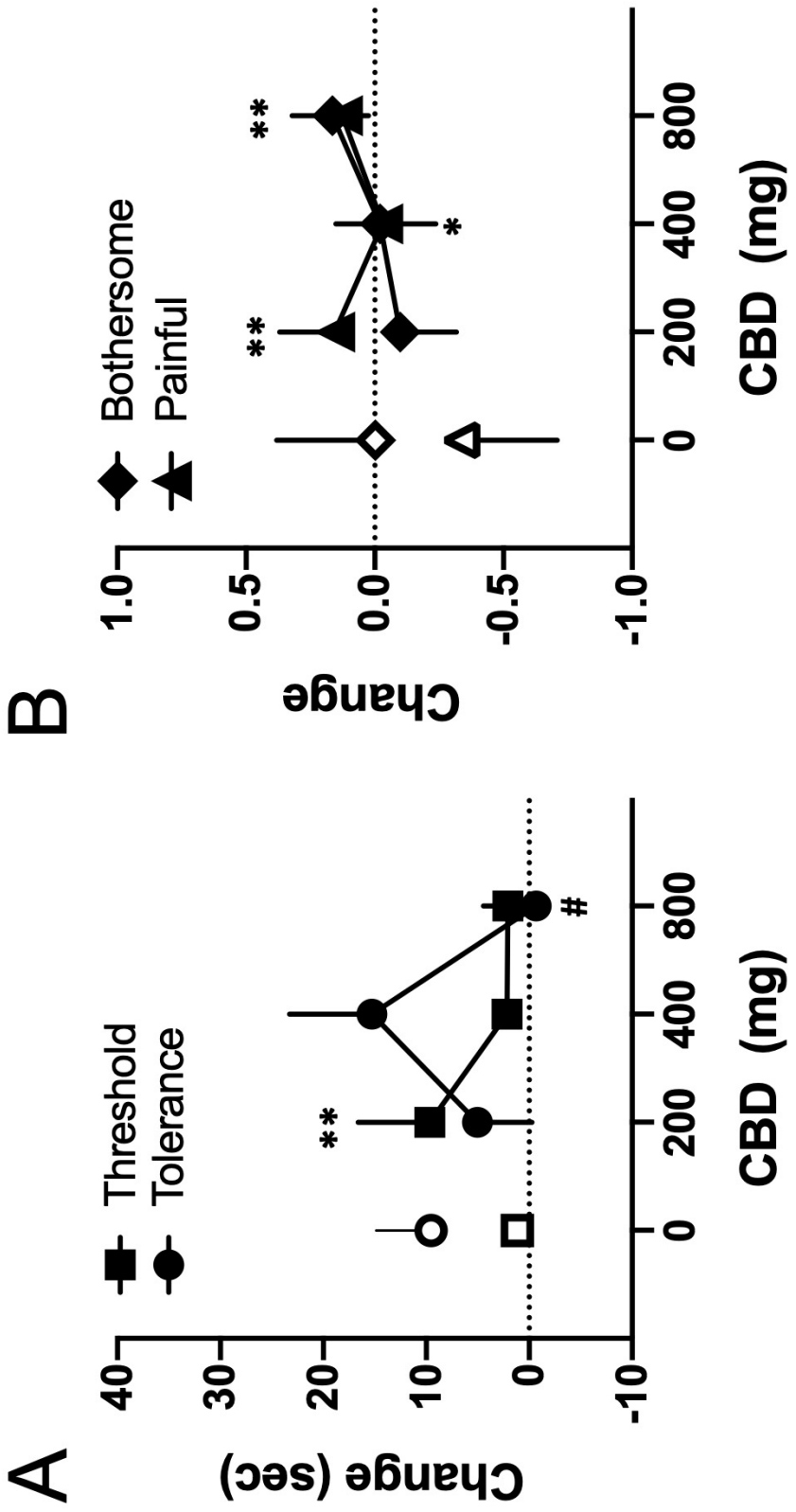

Figure 2

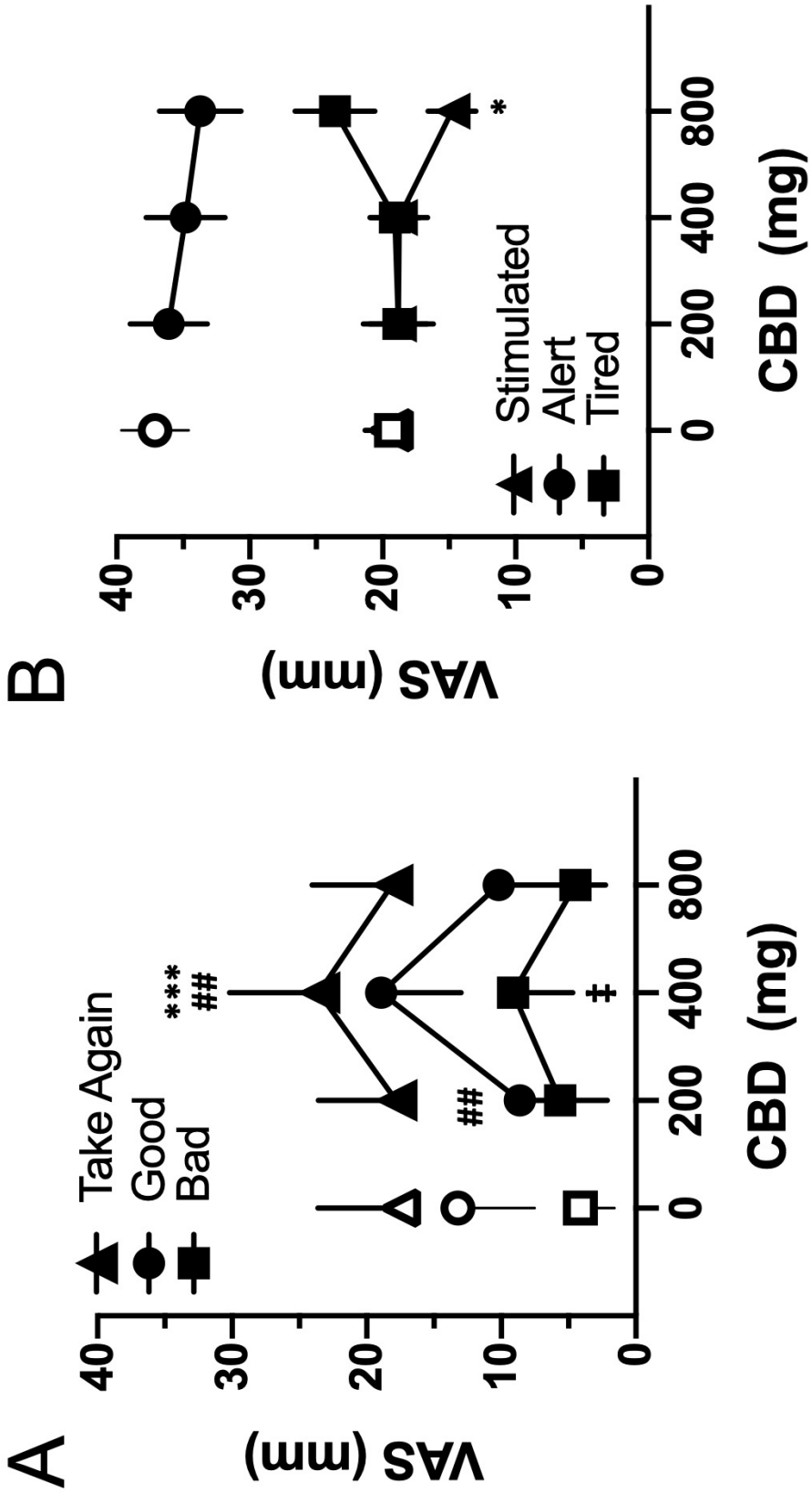

Figure 3