Cannabidiol Increases Psychotropic Effects and Plasma Concentrations of Δ^9-Tetrahydrocannabinol Without Improving Its Analgesic Properties

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Cannabidiol (CBD), the main non-intoxicating compound in cannabis, has been hypothesized to reduce the adverse effects of Δ^9-tetrahydrocannabinol (THC), the main psychoactive and analgesic component of cannabis. This clinical trial investigated the hypothesis that CBD counteracts the adverse effects of THC and thereby potentially improves the tolerability of cannabis as an analgesic. A randomized, double-blind, placebo-controlled, five-way cross-over trial was performed in 37 healthy volunteers. On each visit, a double-placebo, THC 9 mg with placebo CBD, or THC 9 mg with 10, 30, or 450 mg CBD was administered orally. Psychoactive and analgesic effects were quantified using standardized test batteries. Pharmacokinetic sampling was performed. Data were analyzed using mixed-effects model. Co-administration of 450 mg CBD did not reduce, but instead significantly increased subjective, psychomotor, cognitive, and autonomous effects of THC (e.g., VAS "Feeling High" by 60.5% (95% CI: 12.7%, 128.5%, $P < 0.01$)), whereas THC effects with 10 and 30 mg CBD were not significantly different from THC alone. CBD did not significantly enhance THC analgesia at any dose level. Administration of 450 mg CBD significantly increased AUC_{last} of THC (AUC_{last} ratio: 2.18, 95% CI: 1.54, 3.08, $P < 0.0001$) and 11-OH-THC (AUC_{last} ratio: 6.24, 95% CI: 4.27, 9.12, $P < 0.0001$) compared with THC alone, and 30 mg CBD significantly increased AUC_{last} of 11-OH-THC (AUC_{last} ratio: 1.89, 95% CI: 1.30, 2.77, $P = 0.0013$), and of THC (AUC_{last} ratio: 1.44, 95% CI: 1.01, 2.04, $P = 0.0446$). Present findings do not support the use of CBD to reduce adverse effects of oral THC or enhance THC analgesia.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Cannabis and cannabis products are used as an analgesic for chronic neuropathic pain. Cannabidiol (CBD), a non-intoxicating constituent of cannabis, is hypothesized to attenuate the effects of Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent. However, this effect is not found consistently and its mechanism and the required CBD dose remain unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The modulation of acute subjective, cognitive, psychomotor, autonomous, and analgesic effects of THC by three dose levels of CBD was investigated in healthy volunteers and compared with placebo.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study found no evidence of CBD reducing adverse THC effects. On the contrary, THC effects were significantly increased by 450 mg of CBD, which was most likely explained by CBD inhibiting cytochrome P450-mediated metabolism of THC. Evidence of a pharmacokinetic interaction between CBD and THC was found at both 30 and 450 mg CBD dose levels. CBD did not enhance THC analgesia at any dose level.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These results provide evidence against the hypothesis that CBD attenuates THC effects, highlight the potential for drug interactions even at low doses of CBD, and add to the understanding of THC analgesia.

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Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive component of cannabis plants. Its effects are mediated by partial agonism of the cannabinoid receptor 1 (CB_1) and include feeling high, altered perception, and an elevated heart rate. THC shows promise as an analgesic in patients with chronic neuropathic pain,[1,2] although its effectiveness is limited to an undefined subgroup of patients, and its therapeutic potential is further limited by adverse effects that are typically of a psychotropic nature, including intoxication, cognitive, and psychomotor impairment, anxiety, delusions, and hallucinations.[3,4]

Cannabidiol (CBD), the main non-intoxicating compound in cannabis, has been hypothesized to reduce the adverse effects of THC.[5–7] The purported superior tolerability of CBD-rich cannabis has been the subject of numerous scientific publications[5,8,9] and is routinely referenced in popular and commercial publications.[10] The complex pharmacology of CBD includes multiple pathways, which could plausibly contribute to such an effect. For instance, CBD is a negative allosteric modulator (NAM) of the CB_1 receptor,[11] potentially diminishing any CB_1-mediated THC effects. Additionally, CBD acts as an agonist at the serotonin 5-HT_{1a} receptor with potential for anxiolytic properties[12] and as a partial agonist at the dopamine D_{2High} receptors with a suggested potential for antipsychotic action.[13] Furthermore, CBD potentially possesses analgesic effects via its activity at the $TRPV_1$ and 5-HT_{1a} receptors.[14]

The results of clinical research to date are conflicting. Studies have shown CBD to inhibit THC-elicited paranoid and psychotic symptoms and memory impairment,[15] reduce anxiety,[16] and produce a lower degree of subjective intoxication[17,18] compared with THC alone. However, in other clinical trials, CBD failed to attenuate THC-induced anxiety,[4] subjective intoxication and cognitive task performance[19] as well as acute psychotic and memory-impairing effects of THC.[20]

Drug doses, THC:CBD ratios, and routes of administration varied throughout the studies, further complicating the interpretation of the results. Consequently, there is no consensus on what effects of THC are attenuated by CBD, if any, at which doses or dose ratios, and if different routes of administration alter this.

The goal of this study was to assess whether co-administration of CBD could reduce the adverse effects of THC while not compromising, or potentially even enhancing its analgesic properties. Effects of THC alone were therefore compared with the combination of THC with three doses of CBD, controlled with a placebo and a THC + placebo treatment arm. Subjective, cognitive, and psychomotor effects were measured using a validated CNS test battery,[21] and the analgesic effects using a validated pain test battery.[22]

METHODS

Participants and study design

The study was a double-blind, randomized, double-dummy placebo-controlled, five-way cross-over study in which the effects of THC + placebo were compared with the effects of THC in combination with three doses of CBD and double-placebo. The study was conducted at the Center for Human Drug Research in Leiden, the Netherlands. The study was approved by the Medical Ethics Committee of Stichting Beoordeling Ethiek Biomedisch Onderzoek (Assen, the Netherlands) and was conducted according to the Dutch Act on Medical Research Involving Human Participants (WMO) and in compliance with all International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. This study was registered prospectively with the Netherlands National Trial Register (NTR) under registration number: NL9543.

Each participant provided written informed consent before any screening procedures were performed. All participants were healthy male and female volunteers aged 18–45 years with a body mass index of 18–30 kg/m^2. The participants underwent a full medical screening, including medical history anamnesis, a physical examination, blood chemistry and hematology, urinalysis, and an electrocardiogram (ECG) to assess eligibility. Participants with a clinically significant known medical condition, particularly any psychotic disorder or existing condition affecting cold or pain sensitivity, were excluded. All included participants were cannabis users for at least 1 year prior to screening, with cannabis use not exceeding once per month on average in the 6 months prior to study participation. The participants refrained from cannabis use from at least 3 weeks prior to the first dosing day until the end of the study. Any participant who was a regular user of any illicit drugs other than the casual use of cannabis, or had a history of drug abuse or a positive drug screen at screening, was excluded. Any nutrients known to modulate CYP enzyme activity (e.g., grapefruit or Seville orange-containing products or quinine-containing drinks (tonic water or bitter lemon)) were not permitted from 3 days before each study visit until discharge from the research unit. Smoking and the use of xanthine-containing products were not allowed during dosing days. The full list of inclusion and exclusion criteria is provided in the **Supplementary Materials**.

All females of childbearing potential and all males were required to practice effective contraception during the study and to continue contraception for at least 90 days after the last dosing (detailed contraception requirements provided in the **Supplementary Materials**). Urine pregnancy testing was conducted in female participants on each study day prior to dosing.

Study drugs

On each visit, participants received single doses of one of the five oral treatments: double-placebo, THC 9 mg with placebo, or THC 9 mg with either CBD 10 mg, CBD 30 mg or CBD 450 mg. The doses were chosen based on concentration–effect relationship and receptor occupancy data for three potential mechanistic pathways through which we hypothesized that CBD could attenuate THC effects: (i) negative allosteric modulation of the CB_1 receptor, (ii) partial agonism of the 5-HT_{1a} receptor, and (iii) partial agonism of the $D2_{High}$ receptor (full dose rationale is provided in the **Supplementary Materials**). CBD (or placebo) was always administered 30 minutes prior to THC (or placebo) in order to align the expected T_{max} of the two compounds. The washout period between study visits was at least 14 days.

THC was administered in oral tablets containing 1.5 mg THC (Namisol®) and CBD in oral tablets containing 20 mg or 150 mg CBD (Arvisol®); 20 mg CBD tablets were halved for the 10 mg CBD treatment. Both formulations, as well as matching placebo, were manufactured by Echo Pharmaceuticals. Namisol® had been previously administered in multiple studies in healthy volunteers and patient populations[23,24] and Arvisol® in healthy volunteers only (unpublished). Active and placebo tablets contained an identical amount of excipients. The drug substance in both Namisol® and Arvisol® was botanically derived. Release specifications for impurities are provided in the **Supplementary Materials**.

Fasting was required for at least 4 hours prior to every scheduled visit. Shortly after arrival, participants received a semi-standardized light breakfast (contents described in **Supplementary Materials**). Participants remained fasted for at least 2 hours before, and 1.5 hours after study drug administration (water was allowed as required).

Pharmacodynamic assessments

Assessments were performed in "test-blocks," where for each nominal timepoint (e.g., 1 hour post-dose), vital signs were measured 2 minutes prior to the timepoint, blood sampling for hormones and pharmacokinetics was performed exactly on the timepoint, and subjective, psychomotor, and cognitive tests were performed thereafter, with the analgesic tests performed last. Such a "test-block" ended approximately 45 minutes after the nominal timepoint. Measurements were performed at approximately the same clock time during each visit to account for circadian effects. Within 3 weeks prior to the first study visit, participants had a training session to get acquainted with the pharmacodynamic tests and to minimize learning effects. Brief descriptions of each pharmacodynamic assessment are provided below; detailed descriptions can be found in the **Supplementary Materials**.

Subjective effects. Visual Analogue Scales (VAS) according to Bond and Lader were used for assessment of study participant's subjective state.[25] Three main factors, namely, "alertness," "mood" and "calmness," were calculated from 16 bipolar horizontal scales ranging from 0 to 100, where values of 0 and 100 represented opposing subjective states and a value of 50 represented the neutral state.[26] Subjective psychedelic effects including VAS 'Feeling High' were evaluated using the 13-item VAS 'Bowdle' with unipolar scales ranging from 0 to 100.[27] The VAS scales were performed twice pre-dose and at 1, 2, 3, 4, and 6 hours post-dose. The state-trait anxiety inventory was used to quantify present feelings of anxiety or tension and was performed twice pre-dose and 1, 2, 4, and 6 hours post-dose.[28] Once pre-dose and 6 hours post-dose, participants completed the brief symptom inventory (BSI), which is a self-assessment instrument to measure psychopathology in adults across nine different dimensions: general somatic symptoms, cognitive symptoms, interpersonal sensitivity, depressed mood, anxiety, hostility, phobic anxiety, paranoid thoughts, and psychoticism.

Psychomotor and cognitive effects. A selection of tests from the validated NeuroCart® CNS test battery was performed pre-dose and at 1, 2, 3, 4, and 6 hours post-dose for assessment of THC effects on psychomotor function and cognition. The body sway task measures postural stability.[29] The adaptive tracking test is used to evaluate visuomotor coordination and vigilance.[21] The Stroop task is used to assess attention, perception, and inhibition. Two parameters were derived from the Stroop task: Stroop 1 relates to reaction time and Stroop 2 relates to the number of correct responses. The simple reaction time (SRT) task is designed to measure the attention and speed of information processing of the participant.

Autonomous effects. Measurements of autonomous effects were performed pre-dose (twice for heart rate and once for cortisol and prolactin) and 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose. Heart rate measurements were performed using Dash 3000, Dash 4000, Dynamap 400, or Dynamap ProCare 400 automated devices after 5 minutes in the supine position. Serum prolactin levels were determined as a potential marker of antipsychotic effects of CBD, as antipsychotic drugs consistently increase prolactin levels due to their antidopaminergic properties[30] and CBD has been hypothesized to have potential antipsychotic properties due to its partial agonism of the D_{2High} receptor.[13,31] Serum cortisol levels have been shown to increase after administration of THC compared with placebo in previous research.[32]

Analgesic effects. During each treatment period, a validated battery of pain tests, the PainCart®, was performed twice pre-dose and at 1, 2, 3, and 6 hours after dosing, consisting of a heat pain test, a pressure pain test, an electrical pain test, and the cold pressor pain test.[33,34] For all tests (except heat pain) participants were given an electronic visual analogue scale (eVAS) slider to hold, with which they could indicate their current perceived pain intensity. The eVAS had a range of 0–100, with 0 defined as "no pain," sliding > 0 defined the pain detection threshold (PDT), and 100 defined the pain tolerance threshold (PTT; "worst pain tolerable"). When PTT was reached, the test automatically stopped and immediately relieved participants of their pain. Following the test, the participant was asked to rate the pain experienced during the test using the short form of the McGill pain questionnaire (SF-MPQ), a questionnaire that evaluates the affective and sensory components of pain with four-point Likert-type scales. The SF-MPQ also evaluated the peak pain intensity of the test just performed using a five-point Likert-type scale (SF-MPQ PPI), as well as using a visual analogue scale (SF-MPQ VAS).

The capsaicin 1% solution model was included as a model for thermal and mechanical allodynia by selectively sensitizing the $TRPV_1$ channel.[33,34] A 3 × 3 cm surface on the dominant volar forearm was used for the application of the 1% capsaicin solution. The nondominant volar forearm served as a control (not treated with capsaicin). The size of the area of secondary mechanical allodynia around the 3 × 3 cm area where capsaicin was applied was assessed using Von Frey filaments. The heat pain test was performed on capsaicin-treated skin as well as the untreated skin.

Pharmacokinetic assessments

Venous blood samples were taken pre-dose and between 0.5, 1, 2, 3, 4, 6, and 8 hours following THC dosing. Approximately 2 mL of blood per sample was collected via a venous catheter in an antecubital vein. Plasma THC and its metabolites 11-OH-THC, 11-COOH-THC, and CBD and its metabolites 6α-OH-CBD, 6β-OH-CBD, 7-OH-CBD, 7-CBD-COOH, and 2'-CBD-Glucuronide concentrations were measured using a validated LC–MS/MS method.[35] The lower limits of quantification (LLOQs), as well as reference material sources and analytical run acceptance criteria, are provided in the **Supplementary Materials**.

R 3.6.1 for Windows (R Foundation for Statistical Computing/R Development Core Team, Vienna, Austria, 2019) was used to calculate pharmacokinetic parameters. When an actual sampling time differed from the protocol time by more than 10% and at least 5 minutes, the concentration was excluded from the descriptive statistics, but not from the non-compartmental analysis. For the calculation of PK parameters, concentration values below the LLOQ (BLQ) were replaced by 0, except when such values could be interpolated from two neighboring concentration values. Metabolite-to-parent ratios (MPRs) were calculated for 11-OH-THC with respect to THC and for 11-COOH-THC with respect to 11-OH-THC using AUC_{last} estimates.

Sample size, randomization, and blinding

VAS "Feeling High" was used for the sample size calculation as this assessment has been shown sensitive to the effects of THC in previous studies, data from which were used to determine variability.[22,23] A sample size of 24 was calculated to have 81.5% power to detect a reduction of 25% of the VAS "Feeling High," assuming a CV% of 50% (conservative estimate) and using a one-sample *t*-test with a 0.05-sided significance level, presuming a log-normal distribution. To properly balance the cross-over study with five treatment arms, a sample size of $n = 30$ (15 males and 15 females) was chosen. Additional details regarding the sample size are provided in the **Supplementary Materials**.

Study staff and subjects remained blinded until the database lock. The balanced Williams design randomization code was generated using SAS version 9.4 by a study-independent statistician. 10 sequences were randomized in 3 blocks of 10, with 10 females in one block, 10 males in the second block, and 5 males and 5 females in the third block. Blinded study staff assigned the randomization numbers to the participants sequentially after medical screening.

Statistical analysis

To establish whether significant treatment effects could be detected, the repeatedly measured pharmacodynamic (PD) parameters were analyzed with a mixed-effects model with fixed factors treatment, period, time and treatment by time, random factors participant, participant

by treatment, and participant by time and the average baseline value as covariate. Single measured PD data were compared with a mixed-effects model with fixed factors treatment, period, as random factors participant, and the baseline value as a covariate. PK parameters were compared with a mixed-effects model with treatment and period as fixed factors and subject as random factors on log-transformed data. Post-dose measurements that were performed outside a 10% time window around the scheduled protocol time were excluded from the analysis. The general treatment effect and specific contrasts were reported with the estimated difference and the 95% confidence interval, the least square mean estimates, and the *P*-value. Graphs of the least square mean estimates over time by treatment were presented with 95% confidence intervals as error bars. All calculations were performed using SAS for Windows V9.4 (SAS Institute, Cary, NC, USA). No adjustments for multiple comparisons were employed in accordance with the exploratory nature of this study.[36]

RESULTS

Participants and demographics

The clinical phase of the trial ran from July 2021 to May 2022. A total of 108 participants were screened and 37 participants were enrolled in the study and dosed at least once. **Table S1** contains a summary of the baseline demographics. Of the 37 dosed participants, 8 withdrew from the study and 3 were excluded prior to completion; 26 participants (15 males and 11 females) completed the trial per protocol. Further details are contained in the study flow diagram (**Figure S2**).

Pharmacodynamic outcomes

Pharmacodynamic measurements of all participants (completers and drop-outs) were analyzed. No measurements fell outside the 10% time window around the planned timepoints and had to be excluded from the analysis.

Subjective effects. Statistics of the subjective effects are summarized in **Table 1**. VAS 'Alertness' was significantly reduced by THC with 450 mg CBD compared with THC alone (**Figure 1**). VAS "Mood" was not significantly affected by any treatment. VAS "Calmness" did not differ significantly between THC alone and any combination of THC and CBD. VAS "Feeling High," VAS "Internal perception" and VAS "External perception" were significantly increased by THC with 450 mg CBD compared with THC alone. State anxiety did not differ significantly between THC alone and any combination of THC and CBD (**Figure 1**). THC with 450 mg CBD significantly increased the BSI total score compared with THC alone. The statistics of the BSI subscales are provided in the **Table S3**.

Psychomotor and cognitive effects. Statistics of the psychomotor and cognitive effects are summarized in **Table 1**. Postural stability was significantly impaired by THC with 450 mg CBD compared with THC alone (**Figure 1**). Adaptive tracking performance did not differ significantly between THC alone and any combination of THC and CBD (**Figure 1**). Scores on the Stroop task (both Stroop 1 and Stroop 2 parameters) were not significantly affected by any treatment. Reaction time was significantly increased by THC with 450 mg CBD compared with THC alone (**Figure 1**).

Autonomous effects. Statistics of the autonomous effects are summarized in **Table 1**. Heart rate was significantly increased by THC with 450 mg CBD compared with THC alone (**Figure 2**). Serum cortisol and prolactin concentrations did not differ significantly between THC alone and any combination of THC and CBD (**Figure 2**).

Analgesic effects. Statistics of the SF-MPQ VAS scores, PTTs, and the area of secondary allodynia are summarized in **Table 2**, statistics of the SF-MPQ affective, sensory, and PPI scores in **Table S4**, and statistics of the PDTs in **Table S5**.

The area of secondary allodynia was significantly reduced by THC alone compared with placebo. Area of secondary allodynia was not significantly reduced by any CBD-containing treatment compared with placebo, and was significantly increased by THC with 30 mg CBD, compared with THC alone (**Figure 3**). The SF-MPQ VAS was significantly reduced by all THC-containing treatments compared with placebo following the electrical pain, pressure pain, cold pain, and heat pain (on capsaicin-treated skin) tests, except THC alone on pressure pain and THC with 10 mg CBD on cold pain (**Figure 3**). SF-MPQ VAS following the heat pain test on control skin was significantly reduced by THC alone compared with placebo (**Figure 3**). SF-MPQ affective and sensory scores were not significantly reduced compared with placebo by any treatment, except for the THC with 30 mg CBD following the electrical pain test (**Table S4**).

SF-MPQ PPI scores were significantly reduced compared with placebo by some, but not all THC-containing treatments following the electrical pain, cold pain and heat pain (on capsaicin-treated skin) tests (**Table S4**).

PDTs for electrical pain, pressure pain, cold pain, or heat pain (capsaicin-treated skin and control skin) were not increased significantly by any of the study treatments (**Table S5**). PTTs for electrical pain, pressure pain, or cold pain were not increased significantly by any of the study treatments. Conversely, the electrical PTT was significantly reduced by all combinations of THC and CBD compared with placebo. The pressure PTT was reduced significantly by THC alone, as well as THC with 30 and 450 mg CBD compared with placebo, and further reduced significantly by THC with 450 mg CBD compared with THC alone (**Figure 3**). The cold PTT was significantly reduced by THC with 10 mg CBD and THC with 450 mg CBD both compared with placebo and compared with THC alone (**Figure 3**).

Pharmacokinetics

Pharmacokinetic parameters of THC, 11-OH-THC, 11-COOH-THC, and CBD are summarized in **Tables S6–S9**, concentration–time profiles are displayed in **Figure 4** (linear *y*-axis), as well as **Figures S10–S13** (logarithmic *y*-axis) and statistical comparisons of PK parameters between treatments are provided in **Table 3**. Administration of 450 mg CBD significantly increased the AUC_{last} of THC, 11-OH-THC, and 11-COOH-THC, as well as the C_{max} of 11-OH-THC and 11-COOH-THC, and significantly increased the metabolite-to-parent ratio for both THC metabolites, when

Table 1 Overall treatment effects on subjective, psychomotor, cognitive, and autonomous outcome measures (estimated means, estimated mean difference, 95% CI, *P*-value)

Measurement	Treatment	*N*	LSM	Estimated difference vs. placebo (95% CI), *P*-value	Estimated difference vs. THC 9 mg (95% CI), *P*-value
Subjective effects					
VAS Alertness (mm)	Placebo	32	51.0	–	–
	THC 9 mg	27	45.4	**−5.7 (−8.2, −3.1), *P*<0.0001**	–
	THC+CBD 10 mg	32	45.1	**−5.9 (−8.4, −3.4), *P*<0.0001**	−0.2 (−2.8, 2.3), *P*=0.86
	THC+CBD 30 mg	30	43.0	**−8.0 (−10.5, −5.6), *P*<0.0001**	−2.4 (−5.0, 0.2), *P*=0.067
	THC+CBD 450 mg	30	41.6	**−9.5 (−11.9, −7.0), *P*<0.0001**	**−3.8 (−6.4, −1.2), *P*<0.01**
VAS Mood (mm)	Placebo	32	53.7	–	–
	THC 9 mg	27	53.6	−0.2 (−2.5, 2.2), *P*=0.88	–
	THC+CBD 10 mg	32	52.9	−0.9 (−3.2, 1.4), *P*=0.45	−0.7 (−3.1, 1.7), *P*=0.56
	THC+CBD 30 mg	30	53.5	−0.2 (−2.5, 2.1), *P*=0.87	−0.0 (−2.4, 2.4), *P*=0.98
	THC+CBD 450 mg	30	52.5	−1.2 (−3.6, 1.1), *P*=0.29	−1.1 (−3.5, 1.3), *P*=0.38
VAS Calmness (mm)	Placebo	32	53.8	–	–
	THC 9 mg	27	56.7	**2.8 (0.1, 5.6), *P*=0.045**	–
	THC+CBD 10 mg	32	57.1	**3.2 (0.5, 5.9), *P*=0.02**	0.4 (−2.4, 3.2), *P*=0.79
	THC+CBD 30 mg	30	59.1	**5.2 (2.5, 8.0), *P*<0.001**	2.4 (−0.4, 5.2), *P*=0.098
	THC+CBD 450 mg	30	57.2	**3.4 (0.6, 6.1), *P*=0.02**	0.5 (−2.3, 3.4), *P*=0.71
VAS Feeling High (mm+2)	Placebo	32	2.6	–	–
	THC 9 mg	27	11.0	**321.7% (199.2%, 494.3%), *P*<0.0001**	–
	THC+CBD 10 mg	32	10.2	**291.7% (180.6%, 446.8%), *P*<0.0001**	−7.1% (−34.4%, 31.6%), *P*=0.68
	THC+CBD 30 mg	30	14.6	**459.3% (298.5%, 684.9%), *P*<0.0001**	32.6% (−6.7%, 88.5%), *P*=0.11
	THC+CBD 450 mg	30	17.7	**576.8% (382.0%, 850.3%), *P*<0.0001**	**60.5% (12.7%, 128.5%), *P*<0.01**
VAS Internal Perception (Log(mm+2))	Placebo	32	0.34	–	–
	THC 9 mg	27	0.42	**0.08 (0.0004, 0.16), *P*=0.049**	–
	THC+CBD 10 mg	32	0.39	0.05 (−0.03, 0.13), *P*=0.20	−0.03 (−0.11, 0.05), *P*=0.47
	THC+CBD 30 mg	30	0.42	0.08 (−0.003, 0.15), *P*=0.058	−0.003 (−0.08, 0.08), *P*=0.94
	THC+CBD 450 mg	30	0.52	**0.18 (0.11, 0.26), *P*<0.0001**	**0.11 (0.02, 0.19), *P*=0.01**
VAS External perception (Log(mm+2))	Placebo	32	0.33	–	–
	THC 9 mg	27	0.58	**0.25 (0.15, 0.35), *P*<0.0001**	–
	THC+CBD 10 mg	32	0.55	**0.22 (0.12, 0.31), *P*<0.0001**	−0.03 (−0.13, 0.07), *P*=0.54
	THC+CBD 30 mg	30	0.64	**0.31 (0.21, 0.41), *P*<0.0001**	0.06 (−0.04, 0.16), *P*=0.26
	THC+CBD 450 mg	30	0.74	**0.40 (0.31, 0.50), *P*<0.0001**	**0.15 (0.05, 0.26), *P*<0.01**
STAI	Placebo	32	27.1	–	–
	THC 9 mg	27	29.8	**10.1% (4.1%, 16.3%), *P*<0.001**	–
	THC+CBD 10 mg	32	29.7	**9.7% (3.9%, 15.7%), *P*=0.001**	−0.4% (−5.8%, 5.4%), *P*=0.90
	THC+CBD 30 mg	30	29.8	**10.2% (4.3%, 16.4%), *P*<0.001**	0.1% (−5.4%, 6.0%), *P*=0.96
	THC+CBD 450 mg	30	30.6	**13.2% (7.1%, 19.5%), *P*<0.0001**	2.8% (−2.9%, 8.8%), *P*=0.34
BSI total	Placebo	32	1.8	–	–
	THC 9 mg	27	8.5	**6.8 (2.0, 11.5), *P*<0.01**	–
	THC+CBD 10 mg	32	8.1	**6.3 (1.7, 10.9), *P*<0.01**	−0.5 (−5.2, 4.3), *P*=0.84
	THC+CBD 30 mg	30	12.1	**10.3 (5.6, 15.1), *P*<0.0001**	3.6 (−1.3, 8.4), *P*=0.15
	THC+CBD 450 mg	30	16.1	**14.3 (9.6, 19.1), *P*<0.0001**	**7.6 (2.7, 12.5), *P*<0.01**

(Continued)

Table 1 (Continued)

Measurement	Treatment	*N*	LSM	Estimated difference vs. placebo (95% CI), *P*-value	Estimated difference vs. THC 9 mg (95% CI), *P*-value
Psychomotor and cognitive effects					
Body Sway (mm)	Placebo	32	243.2	–	–
	THC 9 mg	27	322.1	**32.5% (16.1%, 51.1%) *P*<0.0001**	–
	THC+CBD 10 mg	32	323.5	**33.0% (17.1%, 51.1%), *P*<0.0001**	0.4% (–12.1%, 14.7%), *P*=0.95
	THC+CBD 30 mg	30	365.8	**50.4% (32.2%, 71.1%), *P*<0.0001**	13.6% (–0.7%, 29.9%), *P*=0.06
	THC+CBD 450 mg	30	396.3	**62.9% (43.1%, 85.5%), *P*<0.0001**	**23.0% (7.4%, 40.9%), *P*<0.01**
Adaptive tracking (%)	Placebo	32	31.7	–	–
	THC 9 mg	27	29.3	**–2.5 (–3.9, –1.0), *P*<0.01**	–
	THC+CBD 10 mg	32	29.4	**–2.3 (–3.7, –0.8), *P*<0.01**	0.2 (–1.3, 1.7), *P*=0.81
	THC+CBD 30 mg	30	28.6	**–3.1 (–4.6, –1.7), *P*<0.0001**	–0.7 (–2.2, 0.8), *P*=0.38
	THC+CBD 450 mg	30	27.8	**–3.9 (–5.4, –2.5), *P*<0.0001**	–1.5 (–3.0, 0.04), *P*=0.06
Stroop 1 (ms)	Placebo	32	84.9	–	–
	THC 9 mg	27	92.7	7.8 (–13.7, 29.2), *P*=0.47	–
	THC+CBD 10 mg	32	93.5	8.6 (–12.2, 29.4), *P*=0.42	0.8 (–20.8, 22.5), *P*=0.94
	THC+CBD 30 mg	30	81.8	–3.2 (–24.1, 17.7), *P*=0.76	–10.9 (–32.6, 10.7), *P*=0.32
	THC+CBD 450 mg	30	91.3	6.4 (–14.6, 27.3), *P*=0.55	–1.4 (–23.2, 20.4), *P*=0.90
Stroop 2	Placebo	32	0.3	–	–
	THC 9 mg	27	0.4	0.1 (–0.2, 0.4), *P*=0.40	–
	THC+CBD 10 mg	32	0.2	–0.1 (–0.4, 0.2), *P*=0.44	–0.3 (–0.6, 0.1), *P*=0.12
	THC+CBD 30 mg	30	0.2	–0.1 (–0.4, 0.2), *P*=0.56	–0.2 (–0.5, 0.1), *P*=0.17
	THC+CBD 450 mg	30	0.2	–0.1 (–0.4, 0.3), *P*=0.67	–0.2 (–0.5, 0.1), *P*=0.23
Simple Reaction Time Test (ms)	Placebo	32	237.4	–	–
	THC 9 mg	27	248.9	**4.9% (0.2%, 9.7%), *P*=0.04**	–
	THC+CBD 10 mg	32	247.3	4.2% (–0.3%, 8.8%), *P*=0.07	–0.6% (–5.1% 4.0%), *P*=0.78
	THC+CBD 30 mg	30	255.1	**7.5% (2.8%, 12.3%), *P*<0.01**	2.5% (–2.1% 7.3%), *P*=0.29
	THC+CBD 450 mg	30	262.2	**10.5% (5.6%, 15.5%), *P*<0.0001**	**5.3% (0.6% 10.3%), *P*=0.03**
Autonomous effects					
Heart rate (bpm)	Placebo	32	60.2	–	–
	THC 9 mg	27	66.0	**5.8 (3.4, 8.3), *P*<0.0001**	–
	THC+CBD 10 mg	32	64.9	**4.7 (2.3, 7.1), *P*<0.001**	–1.1 (–3.6, 1.4), *P*=0.37
	THC+CBD 30 mg	30	67.7	**7.5 (5.1, 10.0), *P*<0.0001**	1.7 (–0.8, 4.2), *P*=0.18
	THC+CBD 450 mg	30	70.8	**10.0 (7.6, 12.5), *P*<0.0001**	**4.2 (1.7, 6.8), *P*=0.001**
Cortisol (nmol/L)	Placebo	32	168.3	–	–
	THC 9 mg	27	205.4	**22.0% (7.8%, 38.2%), *P*=0.002**	–
	THC+CBD 10 mg	32	200.0	**18.8% (5.2%, 34.1%), *P*=0.006**	–2.7% (–14.1%, 10.3%), *P*=0.67
	THC+CBD 30 mg	30	206.5	**22.7% (8.6%, 38.6%), *P*=0.001**	0.5% (–11.4%, 14.0%), *P*=0.93
	THC+CBD 450 mg	30	229.9	**36.6% (20.8%, 54.3%), *P*<0.0001**	11.9% (–1.5%, 27.1%), *P*=0.08
Prolactin (μg/L)	Placebo	32	10.4	–	–
	THC 9 mg	27	9.0	**–13.7% (–22.9%, –3.6%), *P*=0.01**	–
	THC+CBD 10 mg	32	9.3	**–10.6% (–19.8%, –0.2%), *P*<0.05**	3.7% (–7.5%, 16.2%), *P*=0.53
	THC+CBD 30 mg	30	8.9	**–14.5% (–23.4%, –4.5%), *P*<0.01**	–0.9% (–11.6%, 11.1%), *P*=0.88
	THC+CBD 450 mg	30	8.8	**–15.4% (–24.3%, –5.6%), *P*<0.01**	–2.0% (–12.6%, 9.9%), *P*=0.73

The figures in bold indicate statistical significance. bpm, beat per minute; BSI, brief symptom inventory; CBD, cannabidiol; CI, confidence interval; LSM, least square mean; N, number; STAI, state–trait anxiety inventory; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

compared with THC alone. Administration of CBD 30 mg significantly increased the AUC_{last} of THC, 11-OH-THC, and 11-COOH-THC, the C_{max} of 11-OH-THC and 11-COOH-THC, and significantly changed the metabolite-to-parent ratio for 11-COOH-THC compared with administration of THC alone. The 10 mg CBD dose did not significantly

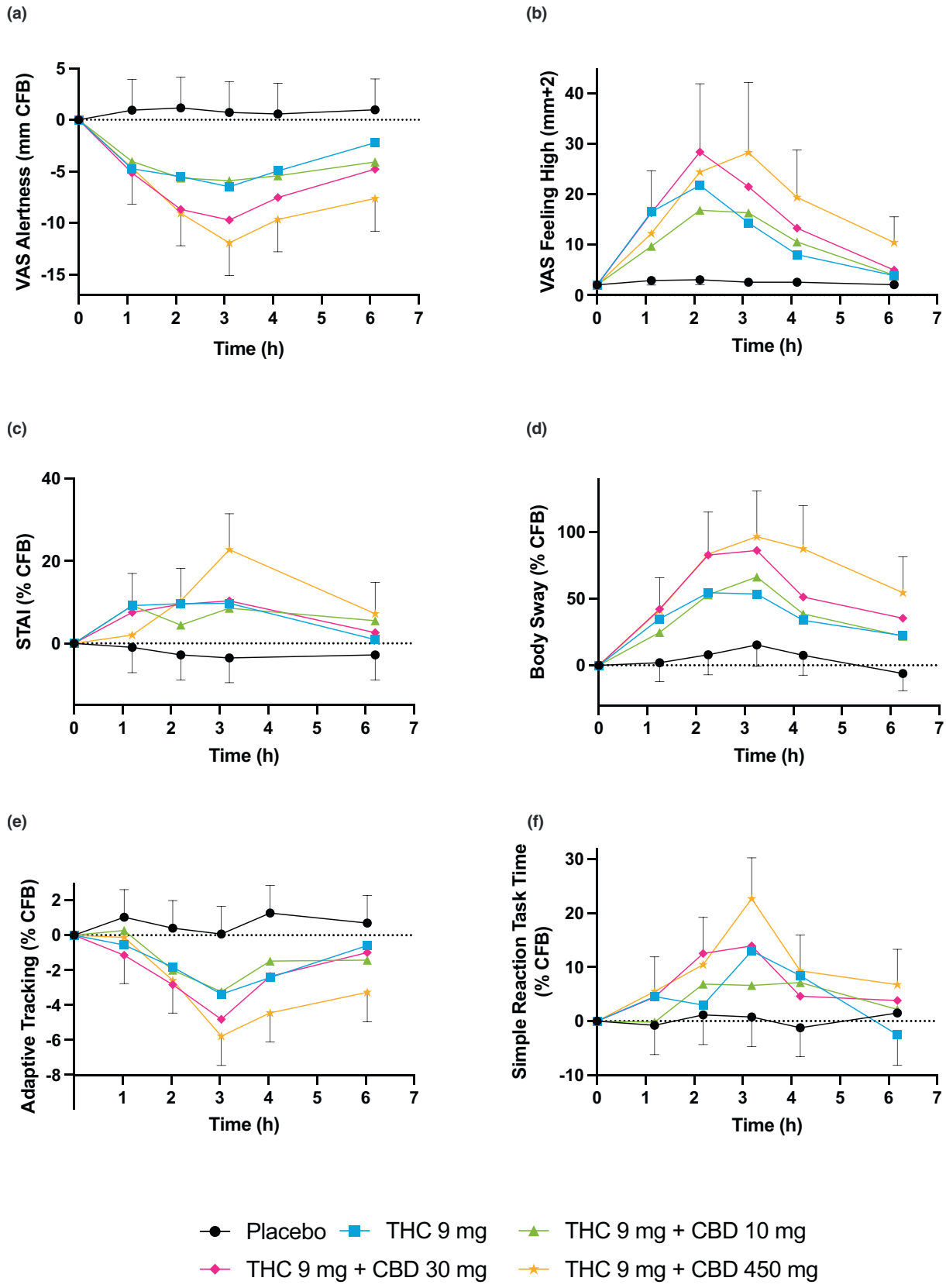

Figure 1 Least square means of (**a**) VAS Alertness (displayed as mm change from baseline, (**b**) VAS Feeling High (absolute values in mm+2), (**c**) State–Trait Anxiety Inventory state scores, (**d**) postural stability, (**e**) Adaptive Tracking performance, and (**f**) reaction time in the Simple Reaction Time Task displayed as % change from baseline. Means are displayed with 95% confidence intervals (for the treatments with the highest and lowest means only; confidence intervals for other treatments omitted for visual clarity).

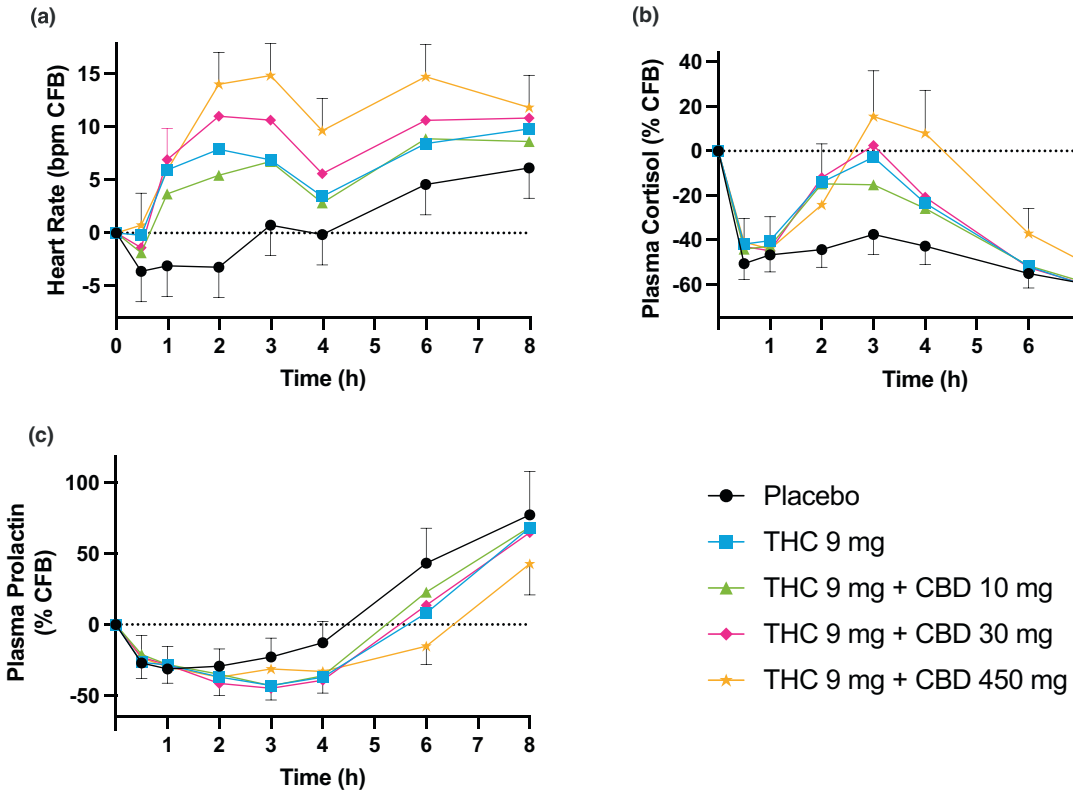

Figure 2 Least square means of the autonomous outcome measures. (**a**) Heart Rate, displayed as beats per minute change from baseline with 95% confidence intervals, (**b**) Plasma Cortisol concentrations, and (**c**) Plasma Prolactin concentrations, displayed as % change from baseline with 95% confidence intervals (for the treatments with the highest and lowest means only; confidence intervals for other treatments omitted for visual clarity).

change any pharmacokinetic parameters compared with THC alone. The pharmacokinetic parameters and concentration–time profiles of CBD metabolites are displayed in **Tables/Figures S14–S26**. The number and percentage of BLQ samples per analyte are provided in **Table S27**.

DISCUSSION

In this study, in contrast to what is commonly hypothesized in (popular) literature, CBD did not reduce the adverse effects of THC, and CBD did not enhance the analgesic properties of THC. While the lower doses of 10 and 30 mg of CBD did not significantly influence the subjective (including anxiety), psychomotor, cognitive, or autonomous effects of 9 mg THC, the high dose of 450 mg CBD significantly increased THC effects on most measures. The enhanced THC effects were accompanied, and most plausibly explained by significantly elevated plasma concentrations of THC and its psychoactive metabolite 11-OH-THC.

A cytochrome P450-mediated drug–drug interaction with CBD as the perpetrator drug and THC as the victim drug appears the most likely explanation for the pharmacokinetic findings of this study. CBD has been shown to inhibit CYP3A4-, CYP2C9-, CYP2CB6-, and CYP2C19-mediated metabolism *in vitro* and[37–40] in humans,[41] and CYP2C9 is the major enzyme responsible for metabolism of THC.[42] The significant changes in THC metabolite-to-parent ratios observed in this study support the presence of a cytochrome P450-mediated drug–drug interaction. Furthermore, pharmacokinetic interactions have been reported in two recent clinical trials, where CBD was co-administered with THC[43] or with a cytochrome P450 drug cocktail.[41]

Previous studies reporting pharmacokinetic interactions with CBD either administered 640 mg CBD[41,43] or took place in the context of treatment of rare epilepsy syndromes, where daily doses up to 50 mg/kg were administered.[44–46] Most patient populations or recreational cannabis users are unlikely to use CBD in such high doses. However, our results show that pharmacokinetic drug interactions could be caused by CBD doses as low as 30 mg, which are easily available to consumers in the United States as CBD-containing gummies, oils and tinctures, and other oral formulations referred to as edibles. In fact, some online retailers of such products recommend a starting dose of 20–30 mg CBD,[47] potentially putting consumers at risk for drug interactions. Theoretically, recreational cannabis use could similarly result in sufficient CBD intake to influence CYP450 metabolism, although the risk would depend on the CBD content of the cannabis variety, and the amount of cannabis consumed, both of which are highly variable.

Although the simplest and most obvious explanation for our study results is a PK interaction between oral CBD and THC in the absence of a PD interaction, the study design cannot conclusively rule out the presence of a PD interaction that is distinct from the PK interaction. Such hypothetical PD interaction could either be negative, meaning CBD *reduced* THC effects (as was

Table 2 Overall treatment effects on analgesic outcome measures (estimated means, estimated mean difference, 95% CI, *P*-value)

Measurement	Treatment	*N*	LSM	Estimated difference vs. placebo (95% CI), *P*-value	Estimated difference vs. THC 9 mg (95% CI), *P*-value
Area of Secondary Allodynia					
Area of Secondary Allodynia (mm^2)	Placebo	32	745.6	–	–
	THC 9 mg	27	587.6	**−158.0 (−313.0, −3.1), *P*=0.046**	–
	THC+CBD 10 mg	32	647.6	−98.1 (−245.1, 49.0), *P*=0.19	60.0 (−94.6, 214.5), *P*=0.44
	THC+CBD 30 mg	30	747.1	1.4 (−148.7, 151.6), *P*=0.98	**159.5 (3.2, 315.7) *P*=0.046**
	THC+CBD 450 mg	30	695.6	−50.1 (−201.2, 101.1), *P*=0.51	108.0 (−49.9, 265.9), *P*=0.18
SF-MPQ peak pain intensity VAS scores					
SF-MPQ VAS Electrical Pain (mm)	Placebo	32	47.2	–	–
	THC 9 mg	27	42.9	**−4.34 (−7.30, −1.37), *P*<0.01**	–
	THC+CBD 10 mg	32	42.8	**−4.37 (−7.27, −1.47), *P*<0.01**	−0.03 (−3.03, 2.97), *P*=0.99
	THC+CBD 30 mg	30	42.7	**−4.50 (−7.43, −1.57), *P*<0.01**	−0.16 (−3.18, 2.86), *P*=0.92
	THC+CBD 450 mg	30	42.6	**−4.61 (−7.56, −1.65), *P*<0.01**	−0.27 (−3.32, 2.78), *P*=0.86
SF-MPQ VAS Pressure Pain (mm)	Placebo	32	40.1	–	–
	THC 9 mg	27	37.3	−2.9 (−6.1, 0.4), *P*=0.09	–
	THC+CBD 10 mg	32	36.5	**−3.6 (−6.8, −0.3), *P*=0.03**	−0.7 (−4.0, 2.6), *P*=0.66
	THC+CBD 30 mg	30	36.2	**−3.9 (−7.1, −0.7), *P*=0.02**	−1.0 (−4.3, 2.3), *P*=0.54
	THC+CBD 450 mg	30	36.1	**−4.0 (−7.2, −0.7), *P*=0.02**	−1.1 (−4.5, 2.2), *P*=0.50
SF-MPQ VAS Cold Pain (mm)	Placebo	32	49.6	–	–
	THC 9 mg	27	45.7	**−3.9 (−7.1, −0.7), *P*=0.02**	–
	THC+CBD 10 mg	32	46.5	−3.1 (−6.2, 0.03), *P*=0.052	0.8 (−2.4, 4.0), *P*=0.62
	THC+CBD 30 mg	30	45.6	**−4.0 (−7.1, −0.8), *P*=0.01**	−0.1 (−3.3, 3.1), *P*=0.96
	THC+CBD 450 mg	30	45.4	**−4.2 (−7.3, −1.0), *P*=0.01**	−0.3 (−3.6, 3.0), *P*=0.86
SF-MPQ VAS Heat Pain (capsaicin skin) (mm)	Placebo	32	35.6	–	–
	THC 9 mg	27	30.6	**−5.0 (−8.5–1.6), *P*<0.01**	–
	THC+CBD 10 mg	32	31.1	**−4.5 (−7.9, −1.2), *P*<0.01**	0.5 (−3.0, 4.0), *P*=0.78
	THC+CBD 30 mg	30	31.0	**−4.6 (−8.0, −1.2), *P*<0.01**	0.4 (−3.1, 3.9), *P*=0.83
	THC+CBD 450 mg	30	31.7	**−3.9 (−7.4, −0.5), *P*=0.03**	1.1 (−2.4, 4.6), *P*=0.54
SF-MPQ VAS Heat Pain (control skin) (mm)	Placebo	32	24.5	–	–
	THC 9 mg	27	21.5	**−2.9 (−5.8, −0.1), *P*=0.04**	–
	THC+CBD 10 mg	32	23.3	−1.2 (−3.9, 1.6), *P*=0.41	1.8 (−1.0, 4.6), *P*=0.21
	THC+CBD 30 mg	30	23.6	−0.9 (−3.7, 1.8), *P*=0.51	2.0 (−0.8, 4.9), *P*=0.16
	THC+CBD 450 mg	30	24.2	−0.3 (−3.1, 2.5), *P*=0.85	2.7 (−0.2, 5.6), *P*=0.07
Pain Tolerance Thresholds					
Electrical Stair Pain Tolerance Threshold (mA)	Placebo	32	17.2	–	–
	THC 9 mg	27	16.2	−5.4% (−12.8%, 2.5%), *P*=0.17	–
	THC+CBD 10 mg	32	15.8	**−7.9% (−14.8%, −0.4%), *P*=0.04**	−2.6% (−10.2%, 5.7%), *P*=0.53
	THC+CBD 30 mg	30	15.5	**−9.5% (−16.3%, −2.1%), *P*=0.01**	−4.3% (−11.8%, 3.9%), *P*=0.29
	THC+CBD 450 mg	30	15.2	**−11.7% (−18.5%, −4.3%), *P*<0.01**	−6.6% (−14.0%, 1.5%), *P*=0.11
Pressure Pain Tolerance Threshold (kPa)	Placebo	32	42.3	–	–
	THC 9 mg	27	38.6	**−3.7 (−6.6, −0.8), *P*=0.01**	–
	THC+CBD 10 mg	32	39.8	−2.4 (−5.2, 0.3), *P*=0.08	1.3 (−1.6, 4.2), *P*=0.39
	THC+CBD 30 mg	30	38.9	**−3.4 (−6.2, −0.6), *P*=0.02**	0.3 (−2.6, 3.2), *P*=0.83
	THC+CBD 450 mg	30	34.7	**−7.6 (−10.4, −4.8), *P*<0.0001**	**−3.9 (−6.9, −0.9), *P*=0.01**

(Continued)

Table 2 (Continued)

Measurement	Treatment	*N*	LSM	Estimated difference vs. placebo (95% CI), *P*-value	Estimated difference vs. THC 9 mg (95% CI), *P*-value
Cold Pain Tolerance Threshold (s)	Placebo	32	16.5	–	–
	THC 9 mg	27	16.3	−0.8% (−8.4%, 7.5%), *P*=0.85	–
	THC+CBD 10 mg	32	15.1	**−8.5% (−15.3%, −1.1%), *P*=0.03**	**−7.8% (−14.9%, −0.0%), *P*<0.05**
	THC+CBD 30 mg	30	16.5	0.3% (−7.3%, 8.4%), *P*=0.95	1.0% (−6.8%, 9.6%), *P*=0.80
	THC+CBD 450 mg	30	14.9	**−9.2% (−16.1%, −1.8%), *P*=0.02**	**−8.5% (−15.7%, −0.7%), *P*=0.03**

The figures in bold indicate statistical significance. CBD, cannabidiol; CI, confidence interval; LSM, least square mean; *N*, number; SF-MPQ, Short-Form McGill Pain Questionnaire; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

hypothesized prior to the study) or positive, meaning CBD *increased* THC effects. Both cases contradict the use of CBD to attenuate THC effects. If the negative interaction was present, then its magnitude must have been relatively small, as it was clearly overshadowed by the increased psychotropic effects of increased THC and metabolite exposures. If the positive interaction was present, then the THC effects would be in effect enhanced by *both* PK and PD interactions. What is certain then, is that CBD is not useful for attenuation of adverse THC effects when administered orally.

It is possible that the findings of this study are specific to the oral administration route, and findings in studies with other administration routes differ.[9,48] To our knowledge, studies with inhaled

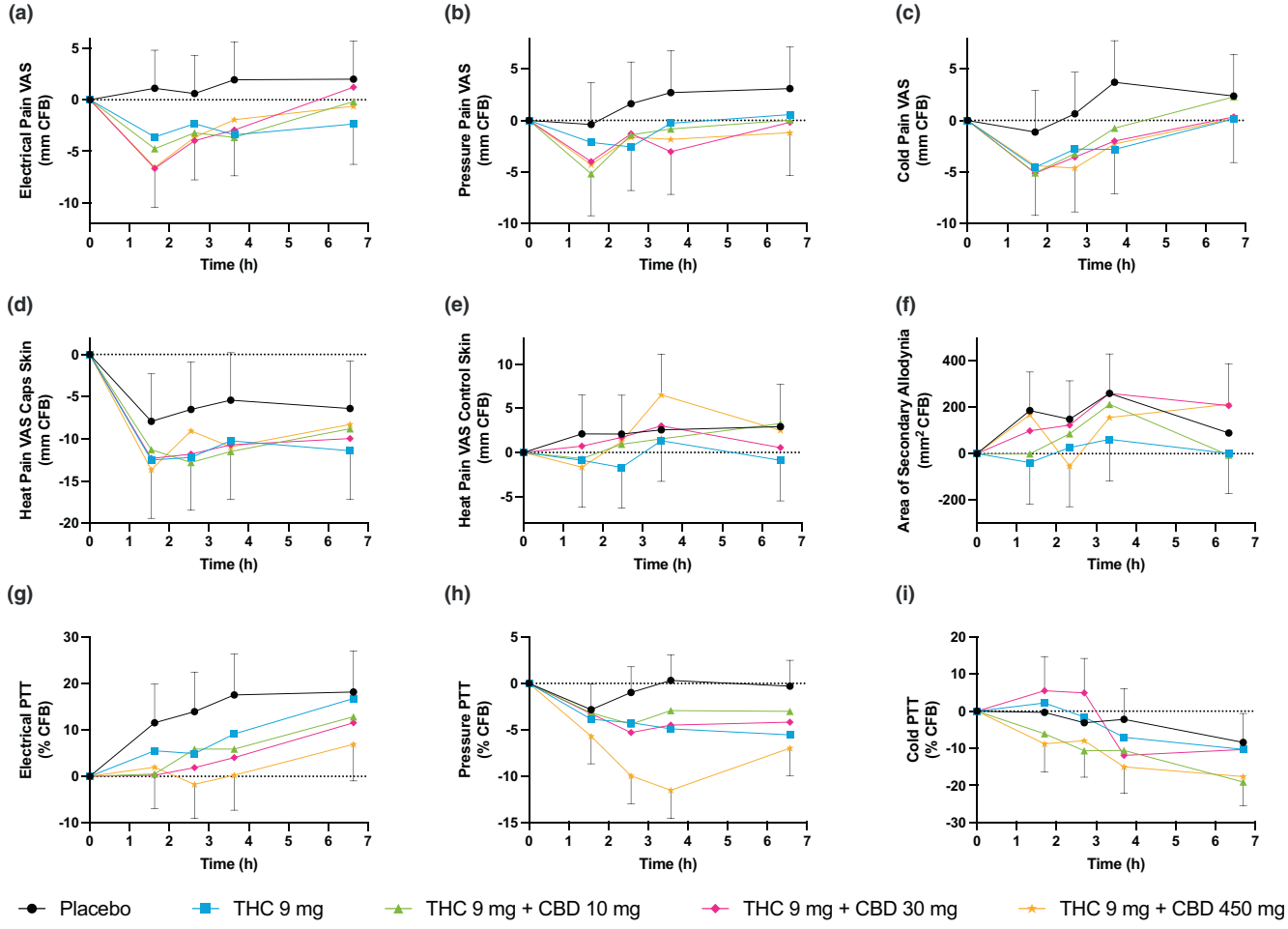

Figure 3 Least square means of selected measurements of the nociceptive test battery. Short-Form McGill Pain Questionnaire (**a**) VAS Electrical Pain, (**b**) VAS Pressure Pain, (**c**) VAS Cold Pain, (**d**) VAS Heat Pain on capsaicin-treated skin, and (**e**) VAS Heat Pain on control skin, displayed as mm change from baseline with 95% confidence intervals. (**f**) Area of Secondary Allodynia, displayed as mm^2 change from baseline with 95% confidence intervals. (**g**) Electrical Pain Tolerance Threshold, (**h**) Pressure Pain Tolerance Threshold, (**i**) Cold Pain Tolerance Threshold, displayed as % change from baseline with 95% confidence intervals (for the treatments with the highest and lowest means only; confidence intervals for other treatments omitted for visual clarity).

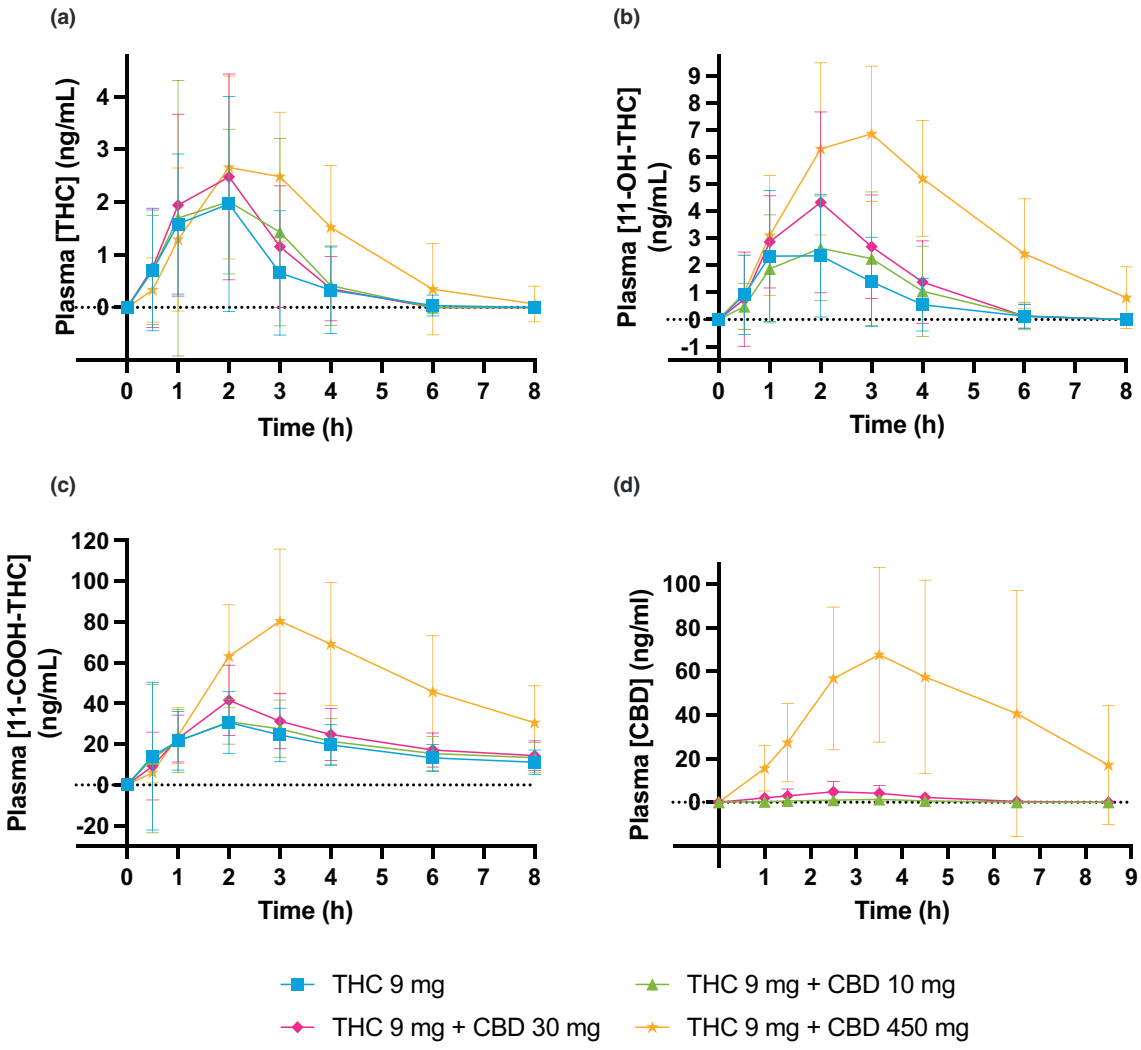

Figure 4 Concentration–time profiles of (**a**) THC, (**b**) 11-OH-THC, (**c**) 11-COOH-THC, and (**d**) CBD following oral administration, displayed as means with standard deviation.

cannabinoids have not reported PK interactions between CBD and THC, nor increases in THC effects when co-administered with CBD. Possibly, the difference in findings is due to the substantial formation of the active metabolite 11-OH-THC following oral administration of THC,[49] and further elevation of 11-OH-THC levels via CBD-induced CYP inhibition. In contrast, comparatively little 11-OH-THC is formed following THC inhalation.[50] Nevertheless, similar to oral dosing studies, inhalation studies have not yet produced convincing evidence of CBD attenuating THC effects.[9,48,51] Regardless of the administration route, the hypothesis that CBD attenuates THC effects remains contentious, and our results add to a growing body of evidence against it. Besides, alternative explanations have emerged for the purported superior long-term safety of CBD-rich cannabis. For example, CBD-rich cannabis varieties could cause fewer long-term side effects simply by virtue of containing smaller absolute amounts of THC, rather than due to a pharmacological interaction.[48]

A key strength of this study was the wide, and pharmacologically relevant, dose range of CBD administered. The pharmaceutical drug formulations in this study contained low levels of impurities, minimizing the risk of other cannabis constituents biasing the study results. The extensive set of both subjective and objective validated CNS tests, the use of a validated pain test battery, and a dense PK sampling schedule around the T_{max} resulted in a detailed assessment of oral THC/CBD interaction effects over time, both at the level of PK and PD, and the cross-over design allowed for within-participant comparison of effects.

Our study is not without limitations. A larger sample size may have confirmed the presence of increased THC effects at the 30 mg CBD dose level – a possibility which appears plausible due to the confirmed presence of the PK interaction and the consistent, although not statistically significant increases across multiple measures of THC effects at the 30 mg CBD dose level. The administration of CBD 30 minutes prior to THC, while done to align the T_{max} of the study drugs, may have enhanced the PK interaction compared with simultaneous administration, as CYP450 inhibition is a time-dependent process. However, in all likelihood the staggered administration was not a decisive factor in the study outcomes, as simultaneous administration studies have led to similar conclusions.[43] Also, because

Table 3 Overall treatment effects on pharmacokinetic parameters (estimated means, estimated mean ratios, 95% CI, *P*-value)

Parameter	Treatment	*N*	LSM	Estimated LSM ratio vs. THC 9 mg (95% CI), *P*-value
THC				
AUC_{last}	THC 9 mg	25	3.26	–
	THC + CBD 10 mg	30	3.03	0.93 (0.66, 1.32), *P* = 0.6776
	THC + CBD 30 mg	27	4.68	**1.44 (1.01, 2.04), *P* = 0.0446**
	THC + CBD 450 mg	28	7.09	**2.18 (1.54, 3.08), *P* < 0.0001**
C_{max}	THC 9 mg	25	2.63	–
	THC + CBD 10 mg	30	2.50	0.95 (0.76, 1.19), *P* = 0.6526
	THC + CBD 30 mg	27	2.64	1.00 (0.80, 1.26), *P* = 0.9889
	THC + CBD 450 mg	28	3.25	1.23 (0.98, 1.55), *P* = 0.0687
11-OH-THC				
AUC_{last}	THC 9 mg	25	4.00	–
	THC + CBD 10 mg	29	4.27	1.07 (0.73, 1.56), *P* = 0.7324
	THC + CBD 30 mg	28	7.58	**1.89 (1.30, 2.77), *P* = 0.0013**
	THC + CBD 450 mg	28	24.95	**6.24 (4.27, 9.12), *P* < 0.0001**
C_{max}	THC 9 mg	25	3.18	–
	THC + CBD 10 mg	29	3.23	1.02 (0.87, 1.18), *P* = 0.8480
	THC + CBD 30 mg	28	4.64	**1.46 (1.25, 1.70), *P* < 0.0001**
	THC + CBD 450 mg	28	7.52	**2.36 (2.02, 2.75), *P* < 0.0001**
MPR	THC 9 mg	25	1.12	–
	THC + CBD 10 mg	29	1.21	1.08 (0.72, 1.63), *P* = 0.7052
	THC + CBD 30 mg	28	1.67	1.49 (0.99, 2.24), *P* = 0.0575
	THC + CBD 450 mg	28	3.24	**2.88 (1.93, 4.31), *P* < 0.0001**
11-COOH-THC				
AUC_{last}	THC 9 mg	27	127.86	–
	THC + CBD 10 mg	31	142.22	1.11 (1.00, 1.24), *P* = 0.0557
	THC + CBD 30 mg	29	162.69	**1.27 (1.14, 1.42), *P* < 0.0001**
	THC + CBD 450 mg	28	355.41	**2.78 (2.49, 3.10), *P* < 0.0001**
C_{max}	THC 9 mg	27	31.46	–
	THC + CBD 10 mg	31	35.48	1.13 (0.95, 1.33), *P* = 0.1546
	THC + CBD 30 mg	29	38.60	**1.23 (1.04, 1.45), *P* = 0.0172**
	THC + CBD 450 mg	28	80.60	**2.56 (2.17, 3.03), *P* < 0.0001**
MPR	THC 9 mg	27	32.51	–
	THC + CBD 10 mg	31	33.48	1.03 (0.73, 1.45), *P* = 0.8661
	THC + CBD 30 mg	29	19.31	**0.59 (0.42, 0.84), *P* = 0.0038**
	THC + CBD 450 mg	28	13.38	**0.43 (0.30, 0.60), *P* < 0.0001**

The figures in bold indicate statistical significance. AUC_{last}, area under the concentration–time curve from time zero to time of last measurable concentration; CBD, cannabidiol; CI, confidence interval; C_{max}, maximum concentration; LSM, least square mean; MPR, metabolite-to-parent ratio; *N*, number; THC, Δ^9-tetrahydrocannabinol.

CBD is a time-dependent inhibitor of many CYPs,[38,39,41] the interaction may be more profound in chronic administration compared with single doses administered in this study. Another limitation is that no CBD-only cross-over arms were included. This could obscure the distinction between "pure" CBD effects and THC/CBD interaction effects. However, it is highly likely that the observed increase in THC effects is explained by a THC/CBD interaction, rather than the PD effects of CBD alone, since CBD is not known to cause psychotropic effects on its own.[52] Furthermore, a relatively high proportion of the study participants dropped out of the study due to adverse effects or the study being too burdensome, which may have introduced a selection bias toward participants who are less sensitive to adverse effects of THC. The drop-outs were disproportionately female; although sex differences in sensitivity to THC effects have been described previously,[53] more research is needed on the differences in THC effects between sexes.

A substantial proportion of plasma concentration values for THC and 11-OH-THC fell below the limit of quantification in this study. As BLQ values were replaced by "0" when calculating pharmacokinetic parameters, resulting AUC_{last} estimates are likely to be lower than if the bioanalytical method with lower quantification limits had been used. The exact magnitude of this effect is unknown, but we can deduce that it must have differed between the treatments in this study. The underestimation of the AUC_{last} will be greater when THC was administered alone, as this treatment had the lowest THC and metabolite exposures and the highest proportion of BLQ values – and for the opposite reasons, will be smaller when 450 mg CBD was co-administered. Therefore, some degree of overestimation of the point estimate of the AUC_{last}

ratios between treatments will have occurred – although it can be assumed to have been limited. Per definition, plasma concentrations reported as BLQ are relatively low, and therefore would contribute relatively little to the AUC estimate. Most importantly, the presence of a pharmacokinetic drug interaction in this study is not under question. First, a decreasing proportion of BLQ values at an increasing CBD dose is in itself an indication of an increase in concentration and therefore a pharmacokinetic interaction. Second, the drug interaction is also evident from the significant treatment effects on the mean 11-OH-THC C_{max}, a pharmacokinetic parameter which is not meaningfully impacted by varying proportions of BLQ values between treatments.

This is the first study to evaluate the analgesic effects of a wide dose range of CBD when co-administered with THC. We found relatively small, but significant analgesic effects on the peak pain intensity VAS scores of the McGill Pain Questionnaire following the pressure, cold, and electrical pain tests, and after the heat test on capsaicin-sensitized skin, which occurred to a similar extent following all THC-containing treatments, regardless of CBD dose. This points to THC, and not CBD, being the cannabinoid responsible for the analgesia, and to the analgesia not being linearly dependent on plasma THC concentrations, since the magnitude of the analgesia across treatments was similar despite varying THC and 11-OH-THC concentrations. On the other hand, we did not find any analgesic effects on nociceptive thresholds for any treatment regardless of the presence and dose of CBD. In fact, we occasionally found THC-containing treatments had small, but significant *hyperalgesic* effects on cold pressor, pressure, and electrical PTTs. These findings are consistent with previous observations by our group and by others[22,54] that THC can paradoxically decrease nociceptive thresholds.

The absence of THC analgesia on nociceptive thresholds in our study should not be interpreted as contradictory to earlier evidence of efficacy in patient populations.[2] Pain is a complex subjective phenomenon which, in addition to nociception, also involves cognitive and affective components, and in case of neuropathic pain, additional neurological pathology like central sensitization.[55] Therefore, results obtained with evoked pain tests in healthy volunteers do not lend themselves to a straightforward translation to patients. Rather, our findings provide insights into the mechanisms of cannabinoid-induced analgesia. The absence of THC analgesia on nociceptive thresholds, a measure obtained *during* the administration of the painful stimulus, combined with clear analgetic effects when pain scores were measured shortly *after* the stimulus, suggests that THC exerts its analgesic effects at the level of pain experience or pain memory, rather than at the level of nociception. This aligns with previous research suggesting that THC may target preferentially the affective qualities of pain, for example, via dissociative effects resulting from reduced sensory-limbic functional connectivity.[56] Furthermore, we found THC to reduce mechanical allodynia, which is a prominent symptom of many neuropathic pain syndromes.[55] This finding may partially explain how THC exerts its analgesic effects in patients with neuropathic pain.[2]

In conclusion, in this study, CBD did not reduce the (adverse) effects of THC, but rather increased them at higher doses, likely by way of a pronounced pharmacokinetic interaction, while not enhancing the analgesic effects of THC. In a future study, we aim to learn more about the potential phenotypical differences between neuropathic pain patients who respond to cannabinoid-induced analgesia vs. patients for whom cannabinoid-based treatments do not work well.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.A.G., J.A.A.C.H, L.E.K., S.J.V. and G.J.G wrote the manuscript, A.A.G., J.A.A.C.H., L.E.K., G.J.G. designed the research, A.A.G., J.A.A.C.H. and G.J.G. performed the research, M.K. and P.K.S. analyzed the data.

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