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ARTICLE

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Effect of caffeine and cannabidiol (CBD) co-administration on Δ9-tetrahydrocannabinol (Δ9-THC) subjective effects, performance impairment, and pharmacokinetics

Justin C. Strickland[1]✉, Hayleigh E. Tilton[1], Noah M. Patton[1], Ryan Vandrey[1], C. Austin Zamarripa[1], Tory R. Spindle[1], Dustin C. Lee[1], Cecilia L. Bergeria[1], David Wolinsky[1], Jost Klawitter[2], Cristina Sempio[2], Jorge Campos-Palomino[2], Uwe Christians[2], Matthew T. Feldner[3], Jessica G. Irons[4] and Marcel O. Bonn-Miller[5]

Cannabis products premixed with caffeine are increasingly present in the United States marketplace. Despite emergence of this product class, no human laboratory data have directly evaluated the isolated impact of caffeine on Δ9-tetrahydrocannabinol (Δ9-THC) effects as well as additional impacts of other common co-administered cannabinoids. This double-blind, randomized, placebo-controlled, within-subject crossover study evaluated potential pharmacodynamic and pharmacokinetic interactions between/among Δ9-THC, caffeine, and cannabidiol (CBD). Participants ($N = 20$; 10 men/10 women) completed outpatient laboratory sessions in which oral Δ9-THC (7.5 mg cumulative), caffeine (180 mg cumulative), and/or CBD (105 mg cumulative) were co-administered in a cumulative dosing design. Primary outcomes included subjective effects indicative of abuse liability (e.g., drug high), performance effects that underlie safety risk (e.g., simulated driving), and plasma cannabinoid/caffeine concentrations. Caffeine co-administration produced minimal changes in Δ9-THC-induced subjective effects, performance, or metabolism, although signals for perceived driving impairment were observed. In contrast, CBD, when co-administered with Δ9-THC and caffeine increased outcomes associated with abuse liability (e.g., drug high, $p = 0.002$) and performance impairment versus Δ9-THC alone. CBD also increased plasma Δ9-THC ($p = 0.004$) and 11-OH-Δ9-THC ($p < 0.001$) concentrations compared with dose conditions without CBD co-administration. These data provide the first direct assessment of the pharmacodynamic and pharmacokinetic effects of Δ9-THC and caffeine when co-administered in humans. The robust alteration of Δ9-THC-induced effects and Δ9-THC pharmacokinetics by CBD further emphasizes the importance of considering full cannabinoid profiles. Broadly, these data highlight the importance of considering drug combinations and interactions in future cannabis regulatory decision-making.

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INTRODUCTION

Legislative actions have enabled legal access to cannabis products for adults in every state in the United States (US) either through adult-use, medical, and/or commercial (hemp-derived products legal under the 2018 Farm Bill) markets. Understanding how phytocannabinoids (i.e., naturally occurring chemical constituents of the cannabis plant) interact with each other, as well as with other commonly used drugs, is essential for understanding the net public health risks and benefits of cannabis and cannabinoid use.

One combination increasingly present in commercial products is cannabis and caffeine co-formulations. Surveillance of commercial marketplaces indicates numerous caffeine products that co-contain Δ9-THC and/or cannabidiol (CBD) which are sometimes marketed as non-alcohol alternatives and advertised for their effects on subjective energy [1]. These co-formulated products are often oral beverages suggesting that use may occur over a longer duration rather than in a single bolus use typical of other edible products (see example retail products in Supplemental Materials). Despite these marketing claims and the presence of these products in the marketplace, limited controlled laboratory research has evaluated the interactive pharmacodynamic and pharmacokinetic effects of cannabinoids and caffeine.

Preclinical work has demonstrated that caffeine can exacerbate Δ9-THC-induced decreases in working memory performance in rodents [2]. Caffeine is an adenosine A_2 antagonist and selective adenosine A_2 antagonists have also been shown to produce biphasic effects on cannabis self-administration in squirrel monkeys with selective downward shifts in Δ9-THC self-administration dose-response curves with low A_2 antagonist doses, but leftward shifts at high A_2 antagonist doses [3]. Striatal adenosine A_2 receptors can also interact with CB_1 receptors to influence signaling as well as to form heteromeric complexes that may underly these behavioral effects [4–7].

Few controlled human laboratory studies have evaluated the interaction of cannabis constituents and caffeine. One Phase I study evaluated caffeine (200 mg) pharmacokinetics prior to and after 26

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [2]iC42 Clinical Research and Development, Department of Anesthesiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [3]Arkansas Clinic for Stress & Anxiety, Fayetteville, AR, USA. [4]Department of Psychology, James Madison University, Harrisonburg, VA, USA. [5]Charlotte's Web, Louisville, CO, USA. ✉email: jstric14@jhmi.edu

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days of repeated daily administration of high doses of purified CBD (500 mg ascending to 1,500 mg/day) [8]. Relative to baseline, steady-state CBD dosing produced a 15% increase in peak concentration (C_{max}) of caffeine and increase from 1.5 to 3 hours for the time to peak caffeine concentration (t_{max}). Another study found that acute CBD pretreatment (25–240 mg) did not alter the pharmacodynamic effects of caffeine (200 mg) when tested in a remote data collection setting under blinded conditions [9].

In the only study to evaluate directly the interaction of caffeine and Δ9-THC or Δ9-THC+CBD administration, an oral cytochrome P450 (CYP) probe drug cocktail that included 100 mg of caffeine as well as varying doses of omeprazole, losartan, dextromethorphan, and midazolam was administered alone or in combination with Δ9-THC (20 mg) or Δ9-THC and a high dose of CBD (640 mg) [10, 11]. Participants reported greater subjective drug effects and drug-induced impairment in the Δ9-THC+CBD+CYP cocktail condition relative to Δ9-THC+CYP cocktail or CYP cocktail alone. CBD also increased plasma C_{max} for Δ9-THC, its active metabolite 11-OH-Δ9-THC, and its inactive metabolite Δ9-THC-COOH which may be attributable to pharmacokinetic interactions (e.g., increases in the oral bioavailability of Δ9-THC through inhibition of the efflux transporter p-glycoprotein in the intestine [12, 13]; possible CYP-mediated metabolic interactions). In contrast, CBD produced only a modest increase in caffeine area under the plasma curve (AUC), and no change in C_{max}. These findings collectively suggest potential pharmacodynamic and pharmacokinetic interactions involving Δ9-THC, CBD, and caffeine that may impact drug-induced impairment and risk for misuse.

This double-blind, randomized, placebo-controlled, within-subject crossover study was designed to build upon extant findings to evaluate interactions between and/or among Δ9-THC, CBD, and caffeine at doses representative of commercial availability using a comprehensive battery of pharmacodynamic and pharmacokinetic assessments. Participants completed experimental sessions during which Δ9-THC, caffeine, and CBD were co-administered in a cumulative dosing design. Primary outcomes included subjective effects indicative of abuse liability (e.g., drug high), performance effects that underlie safety risk (e.g., simulated driving), and plasma cannabinoid concentrations. This battery was selected to inform potential basic behavioral and biological mechanisms that may underlie the net health impact of this emerging drug combination.

MATERIALS AND METHODS

Participants

Participants ($N = 20$ [10 female/10 male]; $Age_{mean} = 33$, $Age_{range} = 20$-52; $BMI_{mean} = 25.6$, $BMI_{range} = 20.4$–31.5) were healthy adults reporting recent infrequent cannabis use. Participants included 12 identifying as non-Hispanic White, 5 as non-Hispanic African American, 1 identifying as Hispanic White, 1 identifying as Hispanic multi-racial, and 1 as Hispanic with no identified race. No participants reported current tobacco cigarette use. Primary inclusion criteria were aged 18–55, lifetime cannabis and caffeine use, no self-reported past month cannabis use and a urine specimen negative for cannabis use, no self-reported drug use other than alcohol and nicotine and a negative urine drug test for common illicit drugs, and no mental health or physical health condition contraindicated for drug exposure or that would interfere with data collection (see Supplemental Materials for detailed criteria). Eligibility criteria were evaluated in a screening session including an in-person physical exam with clinical chemistry, hematology, serology, and serum pregnancy test (see Supplementary Fig. 1 for CONSORT). Informed consent was obtained for all participants, the protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board, and registered in clinicaltrials.gov (NCT05478863).

General procedures and drugs

Participants completed a screening and four experimental sessions as a part of this double-blind, randomized, placebo-controlled, within-subject crossover study. Sessions were separated by at least one week to ensure sufficient washout. On session days, participants arrived and completed baseline physiological, subjective, and performance assessments. Observed urine toxicology was conducted to verify no other drug use occurred between sessions. Participants were also asked to refrain from caffeine use the morning of experimental sessions. The four experimental conditions included orally administered 1) placebo, 2) Δ9-THC only, 3) Δ9-THC and caffeine, or 4) Δ9-THC, caffeine, and CBD. Doses were 2.5 mg Δ9-THC (commercially purchased dronabinol), 60 mg caffeine (isolated bulk powder encapsulated), and 35 mg CBD (commercial product in Medium-Chain Triglycerides [MCT] oil) with matched backfilled capsules or MCT oil vehicle administered as placebo conditions. Independent laboratory testing verified that CBD did not contain detectable Δ9-THC or Δ9-tetrahydrocannabinolic acid (THCA). Each session consisted of three drug exposures of the assigned dose condition separated by 60 min (0, 1, and 2 h) to model estimated real world use of caffeine and cannabis products (i.e., use over a longer duration that is likely with beverage products and is better modeled by the cumulative dosing procedure rather than a single bolus use typical of other edible products). Cumulative doses were therefore 7.5 mg Δ9-THC, 180 mg caffeine, and 105 mg CBD. Participants received a standardized snack (e.g., toast with jam) ~10 min prior to each dosing and a caffeine-free lunch between 4 and 5 h post dosing. Following initial oral dosing, participants completed physiological, subjective, and performance assessments at specified intervals (see Measures for specific timepoints for each measure) for 8 h. Participants were discharged at 8 h after initial drug administration following a sobriety and safety assessment.

Measures

Subjective, physiological, and performance effects. A subjective battery was administered that included a Drug Effect Questionnaire (DEQ), Visual Analog Mood Scale (VAMS), Mood Rating Scale (MRS), Self-Assessment Manikin (SAM), and State Trait Inventory-State Form (STAI-S). This analysis focuses on unipolar VAS ratings from the DEQ commonly used in FDA Human Abuse Potential assessment [14] and the total anxiety score from the STAI-S [15]. Vital signs (i.e., heart rate, systolic blood pressure, and diastolic blood pressure) were measured in a seated position. Psychomotor function was measured using the forward and backward digit span task [16], digit symbol substitution task [17], and the DRiving Under the Influence of Drugs (DRUID)® application (Impairment Science Inc., Cambridge, MA) [18]. The DRUID requires users to perform four 30 to 45 s tasks (total time is 2.5 min) which measuring reaction time, decision making, hand-eye coordination, time estimation, balance, and/or divided attention. Scores on each of the four tasks are integrated to yield a global DRUID impairment score. Subjective, physiological, and performance measures were collected at baseline and 0.5, 1.5, 2.5, 3, 4, 5, 6, and 8 h after first drug exposure.

Driving performance. Driving performance was measured using the STISIM Drive® M4000-R Console system [19]. The system includes a fully interactive virtual reality driving simulator software suite that offers the driver a 135-degree field-of-view. Participants completed simulated drives that assessed key aspects of driving that are most affected by acute drug impairment: divided attention, vigilance, lane position, maintenance of speed, adherence to traffic laws, maintaining appropriate distance to other cars, response to unexpected stimuli, and avoidance of collisions. Programmed driving simulations incorporating all these features were conducted during each session, with each simulation lasting ~25 min [20]. Participants completed a distinct version of the same driving performance was assessed using a single Global Drive Score (GDS) simulation in each session to minimize learning effects (as described in ref. [20], the drives differed based on the order with which tasks were completed and the specific accident avoidance stimuli encountered but all drives included the same elements to allow for comparisons across conditions). Overall driving performance was assessed using a single GDS calculated for each condition. GDS was derived by comparing participants' primary and secondary outcome measures for each condition to the group's aggregated placebo session results. Specifically, z-scores were computed for each condition using the mean and standard deviation of all outcome measures relative to placebo session data across all participants [20]. Higher GDS indicate poorer driving performance. All driving simulations were completed at the 3-h time point (i.e., 3 h after first dose administration; 1 h after final dose). Participants completed a training drive during screening to acclimate to the driving simulator.

Table 1. Maximum change from baseline for pharmacodynamic subjective effects.

Measure	Placebo	Δ9-THC	Δ9-THC+Caffeine	Δ9-THC+Caffeine+CBD	*p*
Drug effect	14.8 (21.4)	**39.3 (26.4)**	**47.0 (25.9)**	***60.1 (28.9)***	<0.001
Unpleasant	5.2 (20.1)	10.3 (17.7)	15.2 (21.4)	18.5 (25)	0.140
Pleasant	17.7 (28.2)	**46.7 (32)**	**51.6 (29.8)**	**56.2 (30.5)**	<0.001
Like drug	15.1 (23.3)	**45.3 (30.8)**	**52.3 (30)**	**50.5 (34.3)**	<0.001
High	7.4 (11.4)	**38.3 (25.5)**	**41.1 (28.7)**	***57.7 (24.9)***	<0.001
Sick	1.1 (2.4)	5.3 (11)	7.2 (12.7)	10.3 (20.9)	0.072
Heart racing	0.6 (2.1)	6.4 (9.9)	**9.4 (13.1)**	***14.5 (17.7)***	0.002
Anxious	0.1 (0.2)	**6.4 (12.9)**	**10.9 (16.8)**	**9.9 (14.3)**	0.015
Relaxed	9.4 (16.5)	23.9 (28.4)	20.3 (26.5)	18.8 (26.4)	0.172
Paranoid	0.5 (2)	6 (14.1)	6.6 (16)	10.9 (19.9)	0.106
Sleepy	23.9 (29)	38.5 (31.4)	29.1 (30.6)	39.1 (27.2)	0.088
Alert	9 (25.2)	−1.6 (17.3)	5.3 (23.3)	7.7 (25.3)	0.442
Irritable	1 (5.9)	4.5 (12.3)	4.4 (10.3)	3.6 (8.8)	0.389
Vigorous/motivated	2.8 (18.7)	4.6 (22.5)	11 (24.3)	13.9 (24.2)	0.361
Restless	2.8 (11.9)	9.7 (16.3)	13.3 (20.9)	**20.2 (20.6)**	0.007
Hungry/munchies	4.5 (20)	**33.7 (32.2)**	22.4 (31)	**30.0 (36.7)**	0.005
Mouth dry	4.3 (11.1)	**19.2 (21.8)**	15.5 (15.7)	***34.7 (27.3)***	<0.001
Eyes dry/irritated	3.5 (10.1)	9.7 (17.6)	5.8 (17)	**14 (17.2)**	0.038
Memory trouble	3.4 (10.4)	**11.3 (14)**	**12.9 (17.2)**	***19.9 (22.9)***	<0.001
Irritated throat	2.7 (9.9)	6.6 (14)	4.1 (6.5)	12.4 (23.3)	0.108
Difficulty with tasks	4.3 (13.5)	**16 (15.6)**	**18.1 (21.3)**	***29.3 (21.6)***	<0.001
Happy	5.7 (13.3)	11.6 (21.4)	14.6 (23.1)	17.5 (23.2)	0.224
Sad	2.6 (8.6)	3.3 (9.6)	4.8 (14.6)	6 (12.7)	0.707
Confidence to drive	−22.1 (29.3)	**−58.2 (37.9)**	**−47.9 (41.8)**	**−63.7 (33.1)**	<0.001
Willingness to drive	−25.6 (35.8)	**−69.7 (37.1)**	**−52.8 (43.8)**	***−76.7 (35)***	<0.001
STAI (State)	2.6 (3.9)	**7.9 (8.2)**	**8.1 (5)**	**9.1 (9.9)**	0.023

Values are Mean (SD) peak change from baseline. Values for Confidence to Drive and Willingness to Drive are maximum decrease. Values for all measures but STAI are measured on a 0–100 visual analog scale. *p* values are for the main effect of dose. Post-hoc tests were conducted for significant main effects using a false discovery rate correction.
Bold values are significantly different from placebo.
Italicized values are significantly different from Δ9-THC only.
Underline values are significantly different from Δ9-THC + Caffeine.
STAI State-Trait Anxiety Inventory.

Pharmacokinetic collection. Serial blood sampling occurred at baseline, 1, 2, 3, 4, 5, 6, and 8 h post initial drug administration. Blood was collected via an indwelling intravenous catheter inserted prior to the start of their session. Samples were collected into 6-mL ethylenediaminetetraacetic acid-containing vacutainer tubes and spun at 1228 × *g* at 4 °C for 10 min to obtain plasma. Plasma samples were stored at −80 °C and shipped frozen on dry ice to the University of Colorado for analysis. Concentrations of 17 cannabinoids including Δ9-THC and metabolites (11-OH-Δ9-THC, and Δ9-THC-COOH), CBD and metabolites (7-OH-CBD and 7-COOH-CBD), and minor cannabinoids (CBC, CBN, CBG, THCV, and CBDV) as well as caffeine and metabolites (theobromine, paraxanthine, and theophylline) were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Primary analyses were conducted on Δ9-THC and metabolites. Limits of quantitation were 0.39, 1.56, and 0.78 ng/ml for Δ9-THC, 11-OH-Δ9-THC, and Δ9-THC-COOH, respectively [21]. Outcomes included maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and area under the plasma concentration vs time curve (AUC). Participants were required to opt-in to the pharmacokinetic component as well as have adequate venous access for serial collection. Pharmacokinetic data were collected and analyzed from 8 participants (4 male/4 female).

Data analysis

Maximum change from baseline for subjective, physiological, and performance effects were compared by dose condition using linear mixed effect models with dose condition as a fixed effect and a random intercept to account for the repeated within-person measurement. Significant omnibus effects of dose were followed by pairwise comparisons using a false discovery rate correction with the Benjamini-Hochberg method [22]. Pharmacokinetic data (i.e., C_{max}, T_{max}, and AUC) were estimated using a non-compartment model and were compared using the same method as the pharmacodynamic outcomes. Sensitivity analyses evaluating the impact of caffeine intake and between-session variability in caffeine use did not alter results (Supplemental Materials). Exploratory analyses by participant sex are also included in the Supplemental Materials. All analyses were conducted using *R* Statistical Language with two-tailed tests and family wise error rate of 0.05.

RESULTS

Subjective effects and abuse liability

Descriptive statistics and inferential test statistics for main effects of Dose for subjective effect measures are summarized in Table 1 with timecourse and peak effects for representative measures included in Fig. 1. Significant main effects of Dose were observed for 11 items on the Drug Effect Questionnaire (Drug Effect, Pleasant Effect, Like Drug, High, Heart Racing, Anxious, Restless, Hungry/Munchies, Mouth Dry, Eyes Dry/Irritated, Memory Troubles, and Difficulty with Tasks; p values < 0.038). Post-hoc tests indicated that ratings for the Δ9-THC+Caffeine+CBD combination condition were significantly higher than all other dose conditions

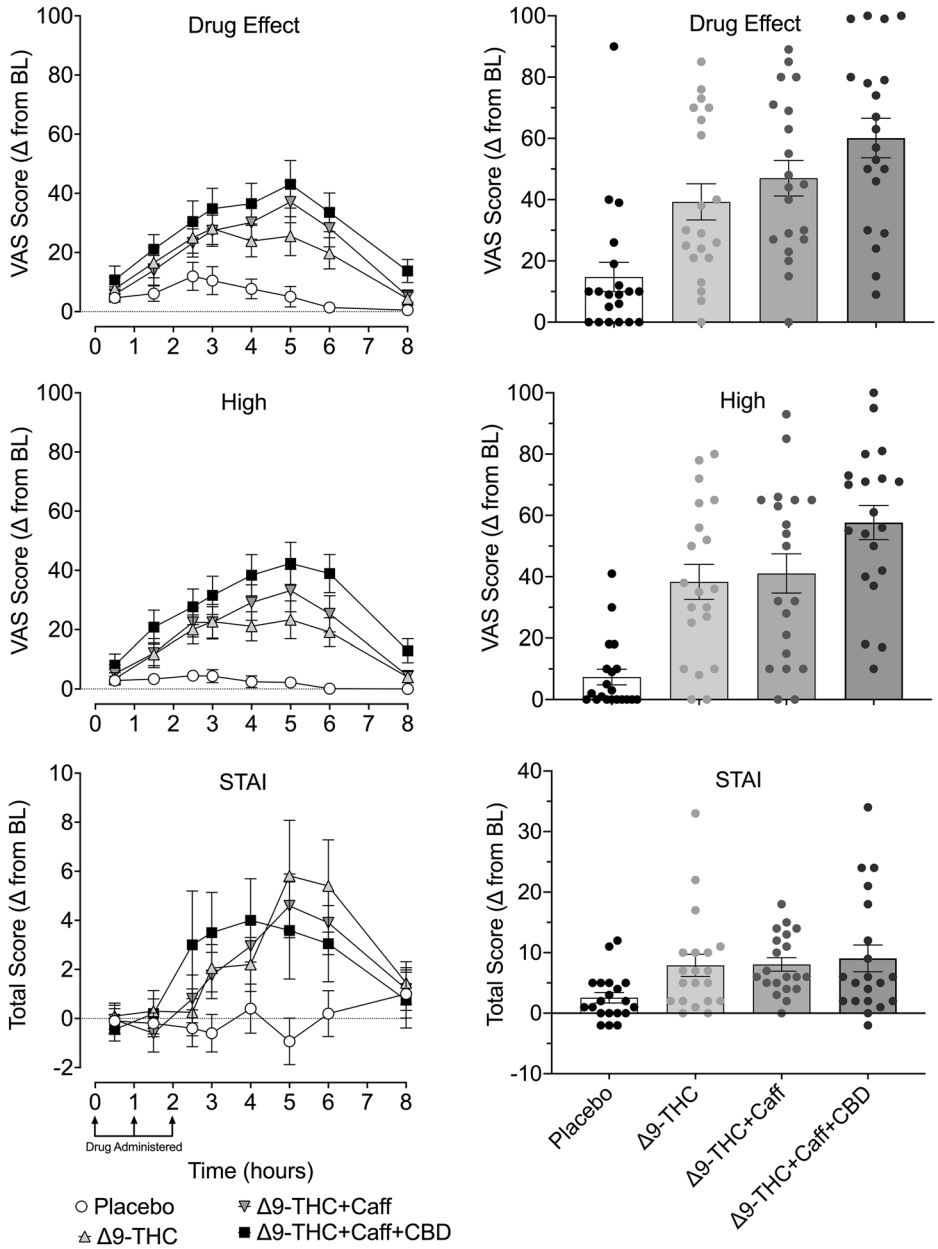

Fig. 1 Timecourse and peak effects for subjective effects. Presented are timecourse (left panels) and peak effect (right panels) data for prototypic subjective effects. Data are presented as mean with standard error of the mean. Individual subject data are included in peak effect panels.

for four items (High, Memory Troubles, Difficulty Concentrating, and Dry Mouth $p_{corrected}$ values <0.048) and significantly higher than Δ9-THC and placebo for ratings of Heart Racing ($p_{corrected} = 0.042$). There was also a significant main effect of Dose on the STAI reflecting higher anxiety in all three active drug conditions relative to placebo ($p = 0.023$).

Physiological effects

Supplementary Fig. 2 includes timecourse and peak effect data for heart rate and blood pressure readings. A main effect of dose was observed for heart rate ($p = 0.045$) and systolic blood pressure ($p = 0.017$). Pairwise comparisons for heart rate indicated that the Δ9-THC+Caffeine+CBD combination condition was the only condition with significantly elevated peak heart rate relative to placebo ($p_{corrected} = 0.035$). Pairwise comparisons for systolic blood pressure indicated that the Δ9-THC-Caffeine combination condition had significantly elevated peak systolic blood pressure relative to placebo ($p_{corrected} = 0.019$) and Δ9-THC alone ($p_{corrected} = 0.019$).

Performance effects

No main effects for the DSST ($p = 0.53$), forward digit span ($p = 0.99$), and backward digit span ($p = 0.09$) emerged. A significant main effect of dose was observed for DRUID performance ($p = 0.003$; Fig. 2). Pairwise comparisons for the DRUID indicated that the Δ9-THC+Caffeine+CBD dose combination was associated with significantly worse performance on the DRUID relative to placebo ($p_{corrected} = 0.001$). Significant main effects were also observed for subjective confidence to drive ($p < 0.001$) and willingness to drive ($p < 0.001$) (Table 1 and Fig. 2) such that confidence and willingness to drive decreased for all active dose conditions relative to placebo; the maximum decrease in the Δ9-THC+Caffeine+CBD combination condition was greater

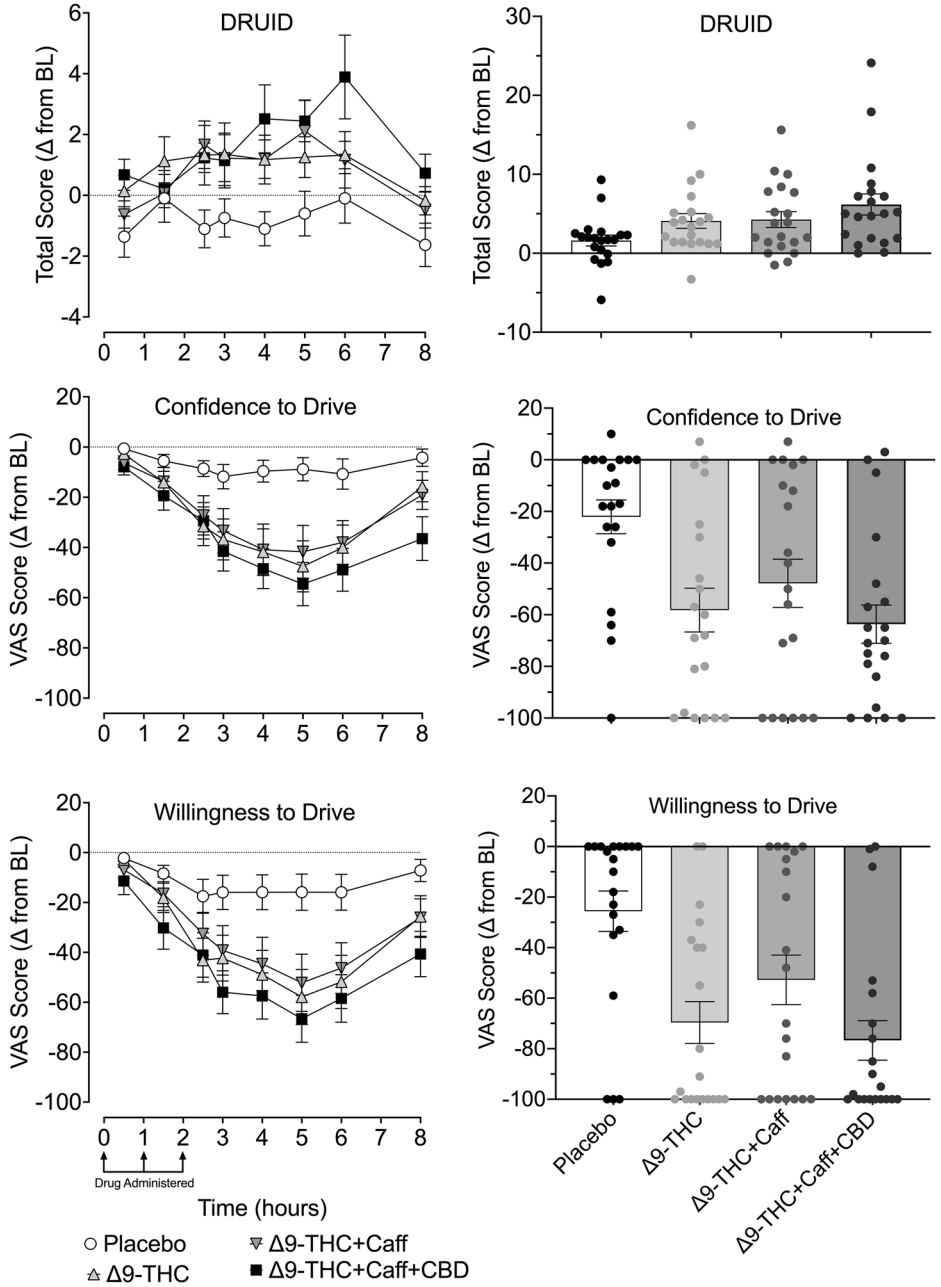

Fig. 2 Timecourse and peak effects for performance effects. Presented are timecourse (left panels) and peak effect (right panels) data for prototypic performance effects. Data are presented as mean with standard error of the mean. Individual subject data are included in peak effect panels.

than the Δ9-THC-Caffeine condition. No main effect of dose on the Global Drive Score (GDS) for simulated driving ability emerged ($p = 0.29$; Supplementary Fig. 3).

Pharmacokinetics

Table 2 includes a summary of pharmacokinetic outcomes for Δ9-THC, CBD, and caffeine parent compounds and metabolites and Fig. 3 includes timecourse and C_{max} values for Δ9-THC and metabolites. For C_{max} values, significant main effects of Dose were observed for the metabolites 11-OH-Δ9-THC ($p = 0.001$) and Δ9-THC-COOH ($p = 0.002$), but not the parent compound Δ9-THC ($p = 0.13$). C_{max} values for 11-OH-Δ9-THC and Δ9-THC-COOH were both elevated after Δ9-THC+Caffeine+CBD administration relative to Δ9-THC alone and Δ9-THC+Caffeine ($p_{corrected}$ values <0.006) with no differences between Δ9-THC alone and Δ9-THC+Caffeine ($p_{corrected} > 0.41$). No significant differences were observed in t_{max} for Δ9-THC, 11-OH-Δ9-THC, or Δ9-THC-COOH ($p > 0.44$). Significant main effects of Dose were observed for Δ9-THC ($p = 0.003$), 11-OH-Δ9-THC ($p < 0.001$), and Δ9-THC-COOH ($p < 0.001$) AUC values. AUC values for Δ9-THC, 11-OH-Δ9-THC, and Δ9-THC-COOH were elevated for Δ9-THC+Caffeine+CBD relative to Δ9-THC alone and Δ9-THC+Caffeine ($p_{corrected}$ values <0.009) with no differences between Δ9-THC alone and Δ9-THC+Caffeine ($p_{corrected} > 0.50$). No significant effects were observed for pharmacokinetic outcomes for caffeine and metabolites (see Supplementary Fig. 4).

DISCUSSION

This study evaluated the effect of combinations of commercially relevant doses of Δ9-THC, CBD, and caffeine on key pharmacodynamic

Table 2. Pharmacokinetic outcomes for Δ9-THC, CBD, and caffeine parent compound and metabolites.

	Δ9-THC		
	Cmax (ng/mL) (Range)	**Tmax (h) (Range)**	**AUC (Range)**
Placebo	ND	ND	ND
Δ9-THC	2.1 (0.7–6.2)	4.6 (3–6)	4.6 (2.4–10.3)
Δ9-THC+Caffeine	2.6 (1–5.6)	5.1 (2–8)	5.1 (1.7–8.9)
Δ9-THC+Caffeine+CBD	3.1 (1.8–6.2)	4.5 (2–6)	7.4 (3.8–11.3)
	11-OH-Δ9-THC		
Placebo	ND	ND	ND
Δ9-THC	2.4 (0–4.2)	4.6 (2–8)	7.1 (0–13.5)
Δ9-THC+Caffeine	2.9 (0–6.2)	5.0 (3–8)	6.9 (0–13.4)
Δ9-THC+Caffeine+CBD	5.6 (3.1–12.3)	5.0 (4–6)	16.3 (6.4–25.2)
	Δ9-THC-COOH		
Placebo	ND	ND	ND
Δ9-THC	18.5 (6.1–35.3)	4.8 (3–8)	63.8 (21.1–122.7)
Δ9-THC+Caffeine	22.5 (9.1–44.4)	5.0 (4–8)	68.4 (25.9–142.2)
Δ9-THC+Caffeine+CBD	38.5 (12.4–91.6)	5.1 (4–6)	114.2 (29.6–200.7)
	Caffeine		
Placebo	637.9 (152.9–1149.9)	Baseline Only	2834.8 (703.8–5169.9)
Δ9-THC	737.5 (48.8–1840.9)	Baseline Only	3291.2 (171.8–8251.5)
Δ9-THC+Caffeine	3983.3 (2403.1–5823.8)	3.2 (3–4)	18625.1 (10790.7–29470.8)
Δ9-THC+Caffeine+CBD	4323.7 (2881.3–6206.5)	3.1 (3–4)	20664.5 (13484.2–31282.1)
	Theobromine		
Placebo	856.6 (172.7–2707.8)	3.5 (1–6)	4251.6 (934.2–13909.7)
Δ9-THC	1127.0 (108.4–2082.8)	1.5 (1–2)	5527.1 (647.9–10354.6)
Δ9-THC+Caffeine	842.8 (377.8–1567.7)	5.5 (1–8)	4285.9 (1661.1–8556)
Δ9-THC+Caffeine+CBD	677.7 (206.5–1989.3)	5.8 (2–8)	3881.4 (760.5–11281.2)
	Paraxanthine		
Placebo	980.7 (187.3–1747.9)	Baseline Only	4719.6 (923.4–8744.7)
Δ9-THC	1025.3 (142.2–2199.7)	1.0 (1–1)	4766.4 (525.1–10196.3)
Δ9-THC+Caffeine	1639.6 (1131.2–2491.3)	6.2 (4–8)	8508.7 (5680.3–15262)
Δ9-THC+Caffeine+CBD	1891.3 (1131.4–2876.8)	5.8 (4–8)	10310.7 (3890–17646.3)
	Theophylline		
Placebo	247.4 (63.4–409.3)	Baseline Only	1282.8 (334.4–2183.9)
Δ9-THC	269.2 (43.3–552.9)	1.0 (1–1)	1362.6 (173.4–2742.6)
Δ9-THC+Caffeine	370.7 (213.3–598.8)	6.0 (4–8)	2031.9 (1018.7–3777.5)
Δ9-THC+Caffeine+CBD	440.0 (226.4–685.5)	5.9 (4–8)	2408.9 (786.2–4257.6)

Baseline Only values that had their highest concentrations at baseline in all participants and were unaffected by drug administration, *ND* Not Detected.

and pharmacokinetic outcomes underlying misuse potential and performance effects. Caffeine co-administration produced minimal changes in the pharmacodynamic and pharmacokinetic effects of Δ9-THC. CBD, when co-administered with Δ9-THC and caffeine, enhanced subjective measures related to abuse liability (e.g., drug high) and drug-induced impairment. Although these findings should be interpreted with caution given the smaller sample size of the pharmacokinetic sample, CBD co-administration produced increases in the systemic exposure (AUC) of Δ9-THC and its active metabolite 11-OH-Δ9-THC. These data provide the first direct assessment of the pharmacodynamic and pharmacokinetic effects of Δ9-THC and caffeine when co-administered in humans and further inform the interaction of constituent cannabinoids with each other and common drug products.

To date, only one study has evaluated Δ9-THC and caffeine in a human laboratory setting, doing so in the context of a CYP cocktail involving other psychoactive substances and without evaluating Δ9-THC and caffeine when administered alone [11]. Here we found that caffeine co-administered with Δ9-THC did not produce significant changes in subjective drug effects or performance effects relative to Δ9-THC administered alone, although it did partly mitigate the orexigenic effect of Δ9-THC (Table 1). This is partly inconsistent with a prior preclinical report showing that caffeine enhanced Δ9-THC-induced memory impairment, although that effect was selective to the highest caffeine dose tested (10 mg/kg IP) in that study [2]. We also did not observe robust changes in Δ9-THC pharmacokinetics with the addition of caffeine. These findings collectively suggest that caffeine administered in doses representative of common retail cannabis and caffeine products does not markedly alter the pharmacodynamic or pharmacokinetic effects of Δ9-THC.

In contrast, CBD significantly altered Δ9-THC-induced subjective effects and impairment compared to Δ9-THC administered in isolation and in combination with caffeine. These findings are

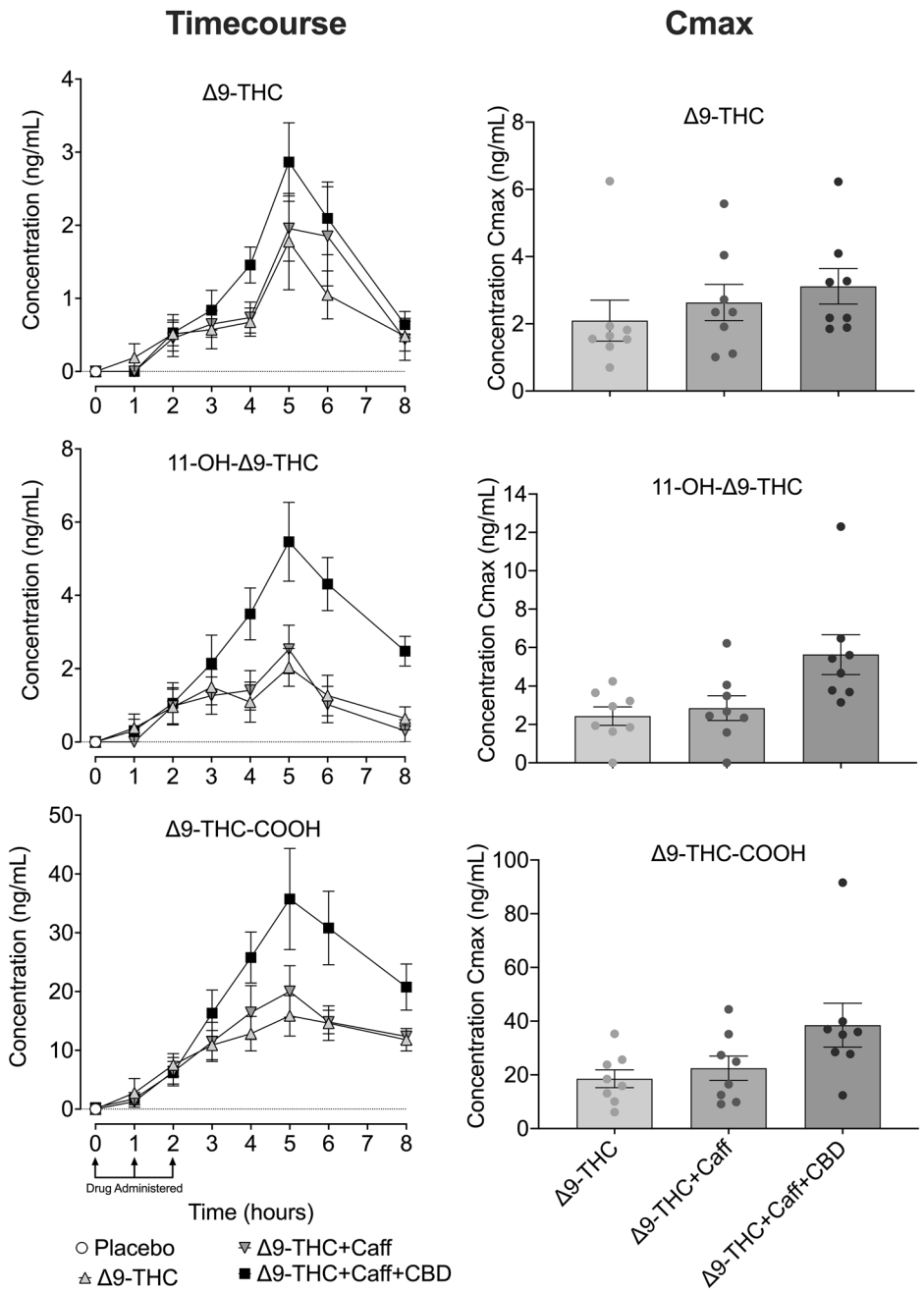

Fig. 3 Timecourse and peak effects (Cmax) for plasma Δ9-THC and metabolites. Presented are timecourse (left panels) and peak effect (right panels) data for Δ9-THC and its metabolites. Data are presented as mean with standard error of the mean. Individual subject data are included in peak effect panels.

consistent with our prior work which demonstrated a significant increases in plasma concentrations of Δ9-THC and its active metabolite 11-OH-Δ9-THC [11]. Data are also consistent with a recent independent study showing that 450 mg of CBD enhanced the subjective effects of Δ9-THC (9 mg oral) as well as increased plasma 11-OH-Δ9-THC concentrations [23]. The current findings extend previous work by showing that similar pharmacokinetic interactions may occur at doses more representative of commercial CBD products (i.e., 35 mg/dose; 105 mg cumulative). It is relevant to note that these differences have not been observed with inhaled routes of administration (e.g., vaporized). For example, a recent study in patients with schizophrenia found that 1000 mg of CBD did not alter plasma concentrations of vaporized Δ9-THC (20–60 mg) or its metabolites [24]. These differences suggest an interaction specific to oral dosing (e.g., increases in the oral bioavailability of Δ9-THC through inhibition of the efflux transporter p-glycoprotein in the intestine [12, 13]).

Meta-analysis of human laboratory data has also shown that CBD, when administered alone, produces minimal acute performance effects (omnibus effect Hedges' $g = 0.12$, primarily subjective sedation) and even smaller effects when considering only objective measures of impairment (Hedges' $g = 0.05$) [25]. Our design did not allow for direct observation of the independent contribution of CBD given the lack of a Δ9-THC and CBD or CBD alone condition. However, these meta-analytic findings reinforce that the effects observed here are not likely attributable to a direct effect of CBD. Instead, pharmacokinetic interactions with Δ9-THC and its active metabolite 11-OH-Δ9-THC

may underlie an enhanced Δ9-THC-induced subjective effect and impairment—a drug-drug interaction also hypothesized to underlie other aversive effects of CBD including CBD-associated hepatotoxicity [26]. Additional studies may benefit from dose-manipulations of CBD and caffeine combinations to further clarify the isolated and interactive effects on pharmacodynamic and pharmacokinetic effects.

From a public health perspective, the emergence of cannabis and caffeine containing products poses regulatory questions similar to those previously presented following the emergence of premixed caffeine-enhanced alcohol beverages (e.g., Four Loko) [27, 28]. We found that caffeine in this dose range and when administered without other common supplements often present in premixed products (e.g., taurine) did not robustly alter Δ9-THC-induced effects. On balance, these findings somewhat lessen emergent concerns regarding the potential risks of premixed cannabis and caffeine products; however, we found no evidence that caffeine could mitigate other Δ9-THC-induced effects typically included in marketing claims. We also observed a trend for less reduction in perceived willingness to drive in the Δ9-THC-Caffeine condition relative to Δ9-THC alone ($p_{corrected} = .07$; $d = 0.62$; Fig. 2 bottom-right panel) despite similarities in objective decreases in performance (peak DRUID score; $p_{corrected} = .89$, $d = 0.05$; Fig. 2 upper-right panel). These findings suggest potentially a greater wiliness to drive in contrast to the similarities in objective driving outcomes which requires closer follow-up investigation. As noted above, the addition of CBD also enhanced Δ9-THC-induced impairment suggesting that products containing CBD may produce functionally greater impact than expected for consumers. Extensions of this work to include broader dose ranges as well as other additives likely for this emergent product class (e.g., B vitamins) are needed.

Other design considerations provide additional directions for future work to inform the basic and applied implications of cannabis and caffeine combinations. We elected to use a cumulative dosing procedure in which participants administered 3 doses over a two-hour period. This design decision while chosen to improve ecological validity based on the expected use profile of beverage products common in the retail market may result in different outcomes than bolus dosing typically used in laboratory settings. We also chose doses in a range representative of many retail products that include Δ9-THC, CBD, and/or caffeine (e.g., 60 mg caffeine is approximately equivalent to a single shot of espresso or small cup of coffee). Products that include higher doses as well as those that are expected to be administered as a bolus dose (e.g., energy shots) mean that these alternative doses and schedules should be evaluated to determine impact on pharmacodynamic and pharmacokinetic outcomes. We also focused on specific drug combinations rather than testing the full factorial of products. This design decision was made to maximize comparisons of interest while minimizing participant burden and carryover effects that can occur with repeated testing. Further expansion to test reciprocal influences at the alternative dose ranges and regimens noted above is also needed.

We also did not closely control caffeine use outside of experimental sessions resulting in variability in use and baseline caffeine levels. Nonetheless, sensitivity analyses did not indicate a substantive influence of caffeine use and supported the fidelity of pre-session caffeine abstinence. The consistency of the observed pharmacokinetic effects (e.g., the increase in AUC values were observed for all 8 participants) helps support the observed findings, however, the sample size was small so these should still be replicated in future studies. Larger pharmacokinetic samples will also allow for analyses of the association of changes in drug concentrations and behavioral effects to further evaluate this hypothesized pharmacokinetic mechanism for the observed behavioral effects. One strength of this study was the use of a simulated driving approach in addition to laboratory assessments of performance; however, this driving assessment was at a timepoint (i.e., 3 hours) that occurred prior to maximum drug effect and plasma concentrations. Evaluation of driving impairment at additional timepoints in future work would further inform real-world risk assessment.

Collectively, these findings contribute to understanding how cannabinoids interact with commonly available drugs to alter pharmacodynamic and pharmacokinetic outcomes. In this first direct evaluation of Δ9-THC and caffeine interactions in human participants, we did not observe marked changes in Δ9-THC-induced effects but did observe signals for possible alterations in perceived impairment that require follow up. In contrast, the robust alteration of Δ9-THC-induced effects and Δ9-THC metabolism by CBD when combined with caffeine emphasizes the importance of considering the full cannabinoid profile and possible impacts on functional dose delivered. More broadly, these data highlight the importance of considering drug combinations in cannabis regulatory decision-making. Development of public health messaging to describe these potential impacts of CBD on Δ9-THC is needed to ensure adequate understanding of risk.

DATA AVAILABILITY

Data and source code for analysis are available upon request.

REFERENCES

1. Business Insider. I tried one of the first caffeinated cannabis drinks, and it gave me a giddy buzz. 2021. https://www.businessinsider.com/i-drank-caffeinated-cannabis-seltzer-was-perfect-for-going-out-2021-8.
2. Panlilio LV, Ferré S, Yasar S, Thorndike EB, Schindler CW, Goldberg SR. Combined effects of THC and caffeine on working memory in rats. Br J Pharm. 2012;165:2529–38.
3. Justinová Z, Ferré S, Redhi GH, Mascia P, Stroik J, Quarta D, et al. Reinforcing and neurochemical effects of cannabinoid CB1 receptor agonists, but not cocaine, are altered by an adenosine A2A receptor antagonist. Addiction Biol. 2011;16:405–15.
4. Ferré S, Lluís C, Justinova Z, Quiroz C, Orru M, Navarro G, et al. Adenosine–cannabinoid receptor interactions. Implications for striatal function. Br J Pharm. 2010;160:443–53.
5. Ferreira S, Gonçalves F, Marques J, Tomé ÂR, Rodrigues R, Nunes-Correia I, et al. Presynaptic adenosine A2A receptors dampen cannabinoid CB 1 receptor-mediated inhibition of corticostriatal glutamatergic transmission. Br J Pharm. 2015;172:1074–86.
6. Tebano MT, Martire A, Popoli P. Adenosine A2A–cannabinoid CB1 receptor interaction: an integrative mechanism in striatal glutamatergic neurotransmission. Brain Res. 2012;1476:108–18.
7. Moreno E, Chiarlone A, Medrano M, Puigdellívol M, Bibic L, Howell LA, et al. Singular location and signaling profile of adenosine A2A-cannabinoid CB1 receptor heteromers in the dorsal striatum. Neuropsychopharmacology. 2018;43:964–77.
8. Thai C, Tayo B, Critchley D. A phase 1 open-label, fixed-sequence pharmacokinetic drug interaction trial to investigate the effect of cannabidiol on the CYP1A2 Probe caffeine in healthy subjects. Clin Pharm Drug Dev. 2021;10:1279–89.
9. Ferretti ML, Gustin ND, Sokol CM, Zamarripa CA, Feldner MT, Bonn-Miller MO, et al. A preliminary investigation of the simultaneous effects of cannabidiol and caffeine. Exp Clin Psychopharmacol. 2024;32:475.
10. Bansal S, Zamarripa CA, Spindle TR, Weerts EM, Thummel KE, Vandrey R, et al. Evaluation of cytochrome P450-mediated cannabinoid-drug interactions in healthy adult participants. Clin Pharm Therapeutics. 2023;114:693–703.
11. Zamarripa CA, Spindle TR, Surujunarain R, Weerts EM, Bansal S, Unadkat JD, et al. Assessment of orally administered Δ9-tetrahydrocannabinol when coadministered with cannabidiol on Δ9-tetrahydrocannabinol pharmacokinetics and pharmacodynamics in healthy adults: a randomized clinical trial. JAMA Netw Open. 2023;6:e2254752–e52.
12. Christians U, Schmitz V, Haschke M. Functional interactions between P-glycoprotein and CYP3A in drug metabolism. Expert Opin drug Metab Toxicol. 2005;1:641–54.
13. Zhu H-J, Wang J-S, Markowitz JS, Donovan JL, Gibson BB, Gefroh HA, et al. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. J Pharm Exp Therapeutics. 2006;317:850–57.

14. Food and Drug Administration. Assessment of Abuse Potential of Drugs. (Food and Drug Administration, 2017).
15. Spielberger, C. D., Gorsuch, R. L. & Lushene, R. E. The State-Trait Anxiety Inventory (Test Manual). Palo Alto, California: Consulting Psychologists Press, 1970.
16. Reynolds CR. Forward and backward memory span should not be combined for clinical analysis. Arch Clin Neuropsychol. 1997;12:29–40.
17. McLeod DR, Griffiths RR, Bigelow GE, Yingling J. An automated version of the digit symbol substitution test. Behav Res Methods Instrum. 1982;14:463–66.
18. Spindle TR, Martin EL, Grabenauer M, Woodward T, Milburn MA, Vandrey R. Assessment of cognitive and psychomotor impairment, subjective effects, and blood THC concentrations following acute administration of oral and vaporized cannabis. J Psychopharmacol. 2021;35:786–803.
19. Mayhew DR, Simpson HM, Wood KM, Lonero L, Clinton KM, Johnson AG. On-road and simulated driving: concurrent and discriminant validation. J Saf Res. 2011;42:267–75.
20. Zamarripa CA, Novak MD, Weerts EM, Vandrey R, Spindle TR. The effects of oral and vaporized cannabis alone, and in combination with alcohol, on driving performance using the STISIM driving simulator: a two-part, double-blind, double-dummy, placebo-controlled, randomized crossover clinical laboratory protocol. Front Pharm. 2022;13:964749.
21. Sempio C, Almaraz-Quinones N, Jackson M, Zhao W, Wang GS, Liu Y, et al. Simultaneous quantification of 17 cannabinoids by LC–MS-MS in human plasma. J Anal Toxicol. 2022;46:383–92.
22. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B. 1995;57:289–300.
23. Gorbenko AA, Heuberger JA, Klumpers LE, de Kam ML, Strugala PK, de Visser SJ, et al. Cannabidiol increases psychotropic effects and plasma concentrations of Δ9-tetrahydrocannabinol without improving its analgesic properties. Clin Pharm Therapeutics. 2024;116:1289–303.
24. Chesney E, Oliver D, Sarma A, Lamper AD, Slimani I, Lloyd M, et al. Does cannabidiol reduce the adverse effects of cannabis in schizophrenia? A randomised, double-blind, cross-over trial. Neuropsychopharmacology. 2025; https://doi.org/10.1038/s41386-025-02175-3. Epub ahead of print.
25. Lo LA, Christiansen AL, Strickland JC, Pistawka CA, Eadie L, Vandrey R, et al. Does acute cannabidiol (CBD) use impair performance? A meta-analysis and comparison with placebo and delta-9-tetrahydrocannabinol (THC). Neuropsychopharmacology. 2024;49:1425–36.
26. Lo LA, Christiansen A, Eadie L, Strickland JC, Kim DD, Boivin M, et al. Cannabidiol-associated hepatotoxicity: a systematic review and meta-analysis. J Intern Med. 2023;293:724–52.
27. Marczinski CA, Fillmore MT. Energy drinks mixed with alcohol: what are the risks?. Nutr Rev. 2014;72:98–107.
28. McKetin R, Coen A, Kaye S. A comprehensive review of the effects of mixing caffeinated energy drinks with alcohol. Drug Alcohol Depend. 2015;151:15–30.

AUTHOR CONTRIBUTIONS

JCS, RV, CAZ, TRS, DL, CLB, MTF, JGI, and MOBM contributed to study design. JCS, HET, NMP, and DW contributed to study oversight and data collection. JK, CS, JCP, and UC contributed to pharmacokinetic analysis. JCS and CAZ contributed to data analysis. JCS drafted the initial manuscript with critical feedback from all authors.

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COMPETING INTERESTS

JCS has received research related funding from Canopy Growth Corporation and DynamiCare Health and consulting fees from Realm of Caring Foundation and Merck Corporation in the past three years. TRS has received research funding from Cultivate Biologics and consulting fees from Canopy Growth in the past three years. MOBM is employed by Charlotte's Web, serves as a board member of DeFloria, and is a past employee of Canopy Growth Corporation. The remaining authors have nothing to disclose.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Justin C. Strickland.