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A within-subject cross-over trial comparing the acute effects of oral delta-8-tetrahydrocannabinol and delta-9-tetrahydrocannabinol in healthy adults

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ABSTRACT

Background: Oral products containing Δ8-tetrahydrocannabinol (Δ8-THC), a chemical isomer of the primary psychoactive consistent of cannabis, Δ9-tetrahydrocannabinol (Δ9-THC), have increased in popularity in recent years. The behavioral effects and pharmacokinetics of oral Δ8-THC remain poorly characterized.

Methods: Nineteen healthy adults with no past-month cannabinoid exposure completed five randomized outpatient sessions in a within-subjects, double-blind, crossover design. Participants ingested a brownie containing Δ8-THC (10, 20, 40 mg), Δ9-THC (20 mg), or placebo. Measures included whole blood cannabinoid concentrations, subjective drug effects, cognitive/psychomotor performance, and vital signs.

Results: Whole blood cannabinoid concentrations peaked between 2 and 4 h post-dose in a dose-orderly manner. The psychoactive 11-OH metabolite of Δ8-THC was markedly lower than that of Δ9-THC at the same dose. Δ8-THC produced dose-dependent subjective effects across multiple domains, differing from placebo. Compared to 20 mg Δ9-THC, 20 mg Δ8-THC resulted in significantly lower ratings of "feel drug effect," negative subjective effects, cognitive/psychomotor impairment, and heart rate increases. No pharmacodynamic differences were observed between 40 mg Δ8-THC and 20 mg Δ9-THC. Both 20 mg and 40 mg Δ8-THC produced comparable positive subjective effects (e.g., drug liking) to 20 mg Δ9-THC, suggesting similar misuse potential.

Conclusion: Δ8-THC demonstrated dose-dependent psychoactive effects qualitatively similar to Δ9-THC but with reduced potency, possibly due to lower biotransformation to its 11-OH metabolite. Importantly, higher doses of Δ8-THC offset reduced potency, as 40 mg Δ8-THC and 20 mg Δ9-THC produced similar effects; this is noteworthy considering people who consume cannabis products generally perceive Δ8-THC as less harmful or intoxicating than Δ9-THC. These findings inform regulatory decisions and public education, though further research on emergent cannabinoids is needed.

1. Introduction

In 2018, the U.S. Congress passed the Agricultural Improvement Act (or, the "Farm Bill"), which removed hemp and its derivatives (defined as cannabis containing ≤0.3 % Δ9-tetrahydrocannabinol, Δ9-THC) from the list of controlled substances (US, 2018). This legislation led to widespread availability of novel hemp-derived cannabinoid products, even in states where cannabis remains illegal (Babalonis et al., 2021). In particular, cannabinoid products featuring Δ8-tetrahydrocannabinol (Δ8-THC) as the primary active ingredient have gained in popularity (Babalonis et al., 2021; Livingston et al., 2022). Notably, Δ8-THC use is increasing among both adolescent and adult populations (Harlow et al., 2024; Livingston et al., 2022; Livne et al., 2022). For example, a 2023 national survey of 12th-grade students found that 11.4 % had used

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Δ8-THC in the past year (Harlow et al., 2024). The primary reasons for its use include therapeutic purposes (e.g., pain relief, insomnia, and depression), recreational use, and the perceived legal advantages over Δ9-THC products (Bergeria et al., 2023; Livne et al., 2022; Pellicane et al., 2024).

Δ8-THC is a phytocannabinoid and a double-bonded isomer of Δ9-THC (Abdel-Kader et al., 2024). Although it is naturally present in small quantities in hemp and cannabis plants, Δ8-THC can be easily synthesized through nonenzymatic isomerization of Δ9-THC or the cyclization of cannabidiol (CBD) (Abdel-Kader et al., 2024; Mechoulam et al., 1967). Pharmacologically, Δ8-THC acts as a partial agonist at cannabinoid type 1 (CB_1) receptors, similar to Δ9-THC, and consequently produces psychoactive effects akin to those of Δ9-THC (Tagen and Klumpers, 2022).

Among Δ8-THC-containing products available for retail purchase, oral products (or "edibles") are among the most popular (Bergeria et al., 2023; Livne et al., 2022). These products come in a wide range of formulations, including beverages, gummies, baked goods, capsules, and tinctures (Livne et al., 2022). Similar to traditional Δ9-THC-containing edibles (Vandrey et al., 2015), Δ8-THC products are often inaccurately labeled for Δ8-THC doses (Kaczor et al., 2024) and can cause unwanted negative effects (e.g., cognitive impairment, panicked reaction) (Leas et al., 2024). Moreover, a significant portion of emergency room visits related to Δ8-THC involve over-intoxication from edibles (Bradley et al., 2023; Miller et al., 2023; Zitek et al., 2024). Despite the increased availability and rate of use, there is limited controlled clinical research on the behavioral pharmacology of Δ8-THC.

To date, only six clinical studies have characterized the acute pharmacodynamic effects of Δ8-THC (Abrahamov et al., 1995; Gong et al., 1984; Hollister, 1974; Hollister and Gillespie, 1973; Karniol and Carlini, 1973; Levander et al., 1974), with three of these directly comparing its effects to Δ9-THC (Gong et al., 1984; Hollister and Gillespie, 1973; Karniol and Carlini, 1973). In these Δ8-THC/Δ9-THC comparison studies, which were all conducted over 50 years ago, healthy adults received multiple doses of Δ8-THC and Δ9-THC via oral, intravenous, or inhalation (smoking) routes and physiological responses and subjective experiences were assessed (Gong et al., 1984; Hollister and Gillespie, 1973; Karniol and Carlini, 1973). Generally, Δ8-THC produced effects comparable to Δ9-THC, albeit with approximately half the potency of Δ9-THC (Gong et al., 1984; Hollister and Gillespie, 1973; Karniol and Carlini, 1973). For example, one study found that 20 mg oral Δ9-THC produced stronger subjective effects than an equivalent oral dose of Δ8-THC (3.5 vs. 2.2 on a 0–10 visual analog scale), while 40 mg Δ8-THC produced comparable subjective effects to 20 mg Δ9-THC (Hollister and Gillespie, 1973). However, these early studies were limited in several ways, including small sample sizes (n = 4–6), inclusion of only male participants, and a lack of modern pharmacodynamic assessments (including tests of cognitive/psychomotor impairment). Further, prior studies did not evaluate Δ8-THC/Δ9-THC pharmacokinetics, which may be useful for understanding the pharmacodynamic differences observed between these two cannabinoids.

The primary goal of this study was to compare the acute effects of Δ8-THC and Δ9-THC when administered orally to healthy adults who infrequently use cannabis. This study is one of two concurrently conducted experiments; the other evaluated vaporized Δ8-THC and Δ9-THC and is reported separately. This study extends previous human laboratory research by including a comprehensive pharmacodynamic and pharmacokinetic assessment battery. Based on earlier clinical findings, we hypothesized that Δ9-THC would produce stronger pharmacodynamic effects than equivalent doses of Δ8-THC due to its higher potency.

2. Methods

2.1. Participants

Participants were recruited via media advertisements and word-of-mouth communication. Participants were required to be 18–45 years old, in good general health (e.g., based on a physical examination, vital signs, and routine blood testing), test negative for recent use of cannabis, alcohol, and other drugs with misuse potential at screening and before each session, not be pregnant or breast feeding, and report using cannabis in the prior 2 years, but not within the past 30 days. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB00321661) and the Food and Drug Administration (IND #161,681), pre-registered on ClinicalTrials.gov (NCT05287256), and conducted in accordance with the Declaration of Helsinki.

2.2. Study design and procedures

This within-subjects, double-blind crossover study was conducted at the Johns Hopkins Behavioral Pharmacology Research Unit. Participants completed five outpatient experimental sessions (in randomized order) during which they orally self-administered either: placebo, 10 mg, 20 mg, or 40 mg Δ8-THC, or 20 mg Δ9-THC. Sessions were completed at least one week apart.

At the beginning of each experimental session, participants ate a standardized low-fat breakfast (e.g., toast and jam), had an intravenous catheter placed into a forearm vein to enable repeated blood collections, and completed baseline assessments (see 2.4 Outcome Measures). Next, participants orally ingested a brownie containing the assigned study dose. After drug administration, participants completed study assessments and had blood samples drawn at designated timepoints for 8 h post-dosing (see below).

2.3. Study drugs

Synthetic Δ8-THC (>99 % purity) was obtained from ElSohly Laboratories Inc. (Oxford, Mississippi) and synthetic Δ9-THC (>99 % purity) was obtained from THC-Pharm GmbH (Frankfurt, Germany). Prior to each experimental session, a pharmacist applied a precise amount of Δ8-THC, Δ9-THC, or nothing (for Placebo administration) to a brownie mix (Betty Crocker Fudge Brownie Mix), and baked the brownies per the manufacturer's instructions; additional drug preparation details are described elsewhere (Sholler et al., 2022; Spindle et al., 2021; Vandrey et al., 2017; Zamarripa et al., 2023).

2.4. Outcome measures

2.4.1. Blood specimens

Whole blood specimens were collected and stored at −80 °C until being shipped frozen on dry ice for quantitative analysis by Clinical Reference Laboratory (Lenexa, Kansas). Concentrations of Δ9-THC, Δ8-THC, and metabolites of each (11-OH-Δ9-THC, Δ9-THC-COOH, 11-OH-Δ8-THC, and Δ8-THC-COOH) were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS) (see Beals et al., 2023) for description of analytical methods). The limit of quantitation was 0.5 and the upper limit of linearity was 200 ng/mL. Pharmacokinetic outcomes included maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration curve (AUC), and the ratio of parent compounds (e.g., Δ8-THC) to metabolites (e.g., 11-OH-Δ8-THC, and Δ8-THC-COOH) using AUC values. Blood biospecimens were collected at baseline and at the following timepoints: 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after drug administration.

2.4.2. Subjective drug effects

Subjective drug effects were assessed with the Drug Effect Questionnaire (DEQ) (Spindle et al., 2018; Elder et al., 2025). DEQ items were presented individually on a 100 mm visual analog scale with the horizontal line anchored from 0 (not at all) to 100 (extremely). Individual items assessed the overall magnitude of effects (e.g., "feel drug effect"), positive effects (e.g., drug "liking"), negative/adverse effects (e.

g., "unpleasant"), perceived degree of impairment (e.g., "confidence to drive"), and other common effects of cannabis/THC exposure. Subjective drug effects were measured at baseline and at the following timepoints: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h after drug administration.

2.4.3. Cognitive and psychomotor performance

Cognitive/psychomotor performance was evaluated using four tasks shown to be sensitive to acute effects of cannabis/THC and described in detail elsewhere (Spindle et al., 2018, 2021). The tasks assessed psychomotor performance (Digit Symbol Substitution Task, DSST), working memory (Paced Serial Addition Task, PASAT), divided attention (Divided Attention Task, DAT), and global impairment using a tablet-based application (Driving Under the Influence of Drugs, DRUID App®) that includes four brief tasks assessing balance, divided attention,

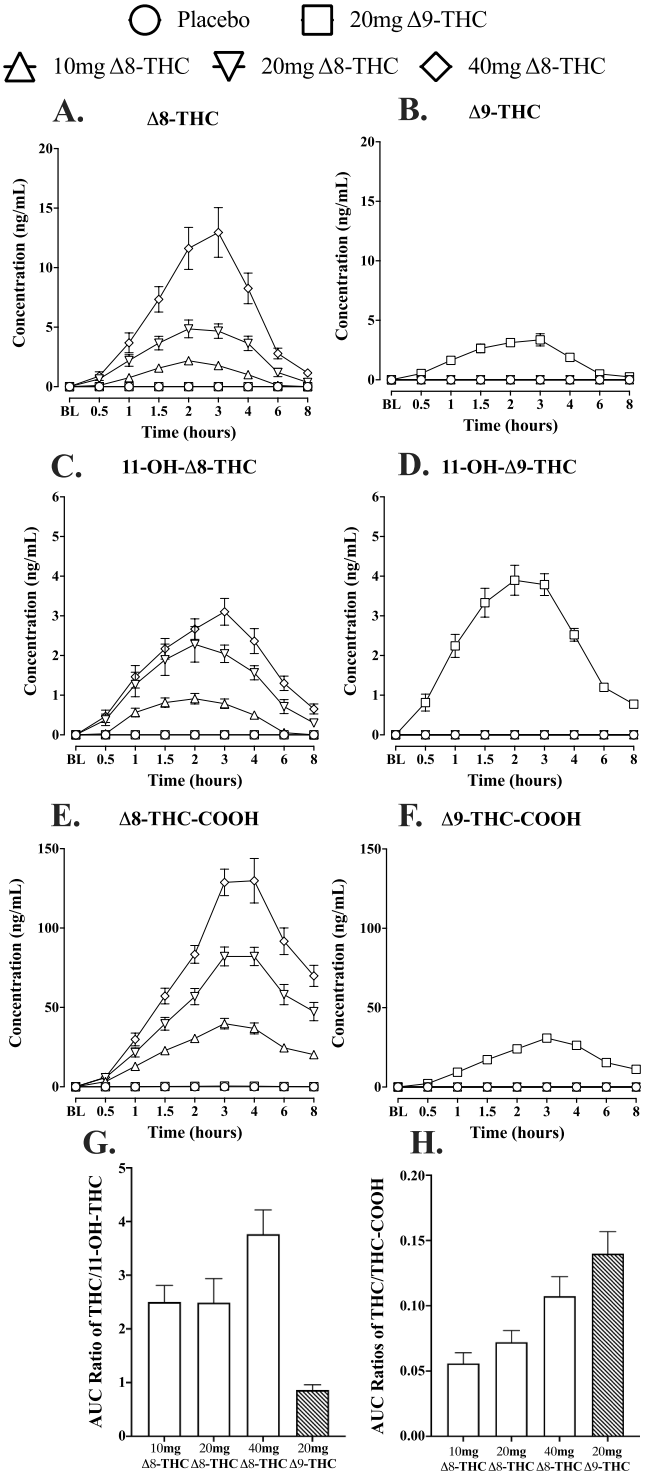


Fig. 1. Mean whole blood concentration vs. time profiles for A) Δ8-THC, B) Δ9-THC, C) 11-OH-Δ8-THC, D) 11-OH-Δ9-THC, E) Δ8-THC-COOH, and F) Δ9-THC-COOH. Horizontal axes are not accurate time scales and represent the time points at which subjective drug effects were assessed. D) and E) depict area under-the-curve ratios of 11-OH-Δ9-THC:Δ9-THC and Δ9-THC-COOH:Δ9-THC, respectively. Black and white stripped bars are presented to help distinguish between Δ8-THC and Δ9-THC conditions. Error bars indicate SEMs.

Table 1
Maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), and ranges for cannabis analytes in whole blood following acute drug administration.

	Δ8-THC			
	Cmax (ng/mL + Range)	Tmax (h + Range)	AUC (Range)	Parent drug to drug metabolite ratio (SD)
10mg Δ8-THC	2.5 (0.8–5.8)	2.4 (1.5–4.0)	10.7 (3.1–27.1)	NA
20mg Δ8-THC	5.9 (1.5–12.2)	2.6 (1.0–4.0)	28.4 (6.9–82.9)	NA
40mg Δ8-THC	15.1 (3.5–45.2)	2.8 (2.0–4.0)	62.1 (13.6–143.8)	NA
20mg Δ9-THC	ND	ND	ND	NA
	11-OH-Δ8-THC			Ratio of Δ8-THC:11-OH-Δ8-THC
10mg Δ8-THC	1 (0.0–2)	33.7 (14.7)	5.4 (0.0–12.3)	2.5 (1.9)
20mg Δ8-THC	2.6 (0.7–7.5)	28.2 (14.9)	14.2 (4.9–41.5)	2.5 (1.3)
40mg Δ8-THC	3.3 (1.1–6.5)	29.7 (13.8)	17.9 (6.9–36.9)	3.8 (2.0)
20mg Δ9-THC	ND	ND	ND	ND
	Δ8-THC-COOH			Ratio of Δ8-THC:Δ8-THC-COOH
10mg Δ8-THC	43 (23.8–78.6)	2.2 (0.7)	209.4 (79–343.7)	0.06 (0.04)
20mg Δ8-THC	92.1 (61–135.2)	2.6 (1.1)	407.0 (177.2–640.2)	0.07 (0.04)
40mg Δ8-THC	142.6 (94.2–243.8)	1.9 (0.8)	600.4 (301.1–974.1)	0.11 (0.06)
20mg Δ9-THC	0.5 (0–1.9)	ND	1.8 (0.0–8.2)	ND
	Δ9-THC			
10mg Δ8-THC	ND	NA	ND	NA
20mg Δ8-THC	ND	NA	ND	NA
40mg Δ8-THC	ND	NA	ND	NA
20mg Δ9-THC	4.2 (1.5–8.9)	NA	19.3 (9.1–34.9)	NA
	11-OH-Δ9-THC			Ratio of Δ9-THC:11-OH-Δ9-THC
10mg Δ8-THC	ND	ND	ND	ND
20mg Δ8-THC	ND	ND	ND	ND
40mg Δ8-THC	ND	ND	ND	ND
20mg Δ9-THC	4.4 (2.6–7.6)	18.5 (9.5)	25 (12.3–43.4)	0.9 (0.4)
	Δ9-THC-COOH			Ratio of Δ9-THC:Δ9-THC-COOH
10mg Δ8-THC	ND	ND	ND	ND
20mg Δ8-THC	ND	ND	ND	ND
40mg Δ8-THC	ND	ND	ND	ND
20mg Δ9-THC	32.9 (16.6–51.4)	5.4 (2.9)	156.3 (58.9–249.5)	0.2 (0.1)

Note: ND = Not Detected; THC = Tetrahydrocannabinol. a indicates a significant difference from 20mg Δ8-THC; b indicates a significant difference from 40mg Δ8-THC.

reaction time, and higher order cognition. The standard DRUID app was used for this study, and lasted approximately 2.5 min (Spindle et al., 2021). Participants received training on these tasks to establish a stable baseline and minimize practice effects during sessions. Cognitive/psychomotor assessments were measured at baseline and at the following timepoints: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h after drug administration.

2.4.4. Vital signs

Heart rate (HR) systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in the seated position using an automated monitor. Vital signs were collected at baseline and at the following timepoints: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h after drug administration.

2.5. Data presentation and analysis

Demographic characteristics and pharmacokinetic outcomes are presented using descriptive statistics. Subjective, cognitive, and vital signs data were analyzed using two-way repeated measures analysis of variance (ANOVAs), with time (11 levels) and dose condition (5 levels) serving as the two factors. Separate ANOVAs were used to analyze each individual outcome and all raw data were converted to change-from-baseline values prior to analysis. In addition, three sets of planned comparisons were performed using peak change-from-baseline scores to compare: 1) each condition to placebo, 2) each Δ8-THC condition to the Δ9-THC condition, and 3) all Δ8-THC conditions. Bonferroni tests of multiple comparisons were used for planned comparisons to control the family-wise error rate. For all analyses, statistical significance was defined as a p value of less than 0.05. Analyses were conducted using GraphPad Prism, Version 10 (La Jolla, CA).

3. Results

Thirty-nine volunteers signed informed consent. Participants consented to possibly participate in either the oral dose study (this study), the vaporized dose study (referenced above), or both studies sequentially. Of the 39 participants consented, four participated in the vaporized dose study only, 12 were deemed ineligible at screening, 4 were lost-to-follow-up prior to the start of the study, and 19 (12 biological men and 7 biological women) were randomized and completed this

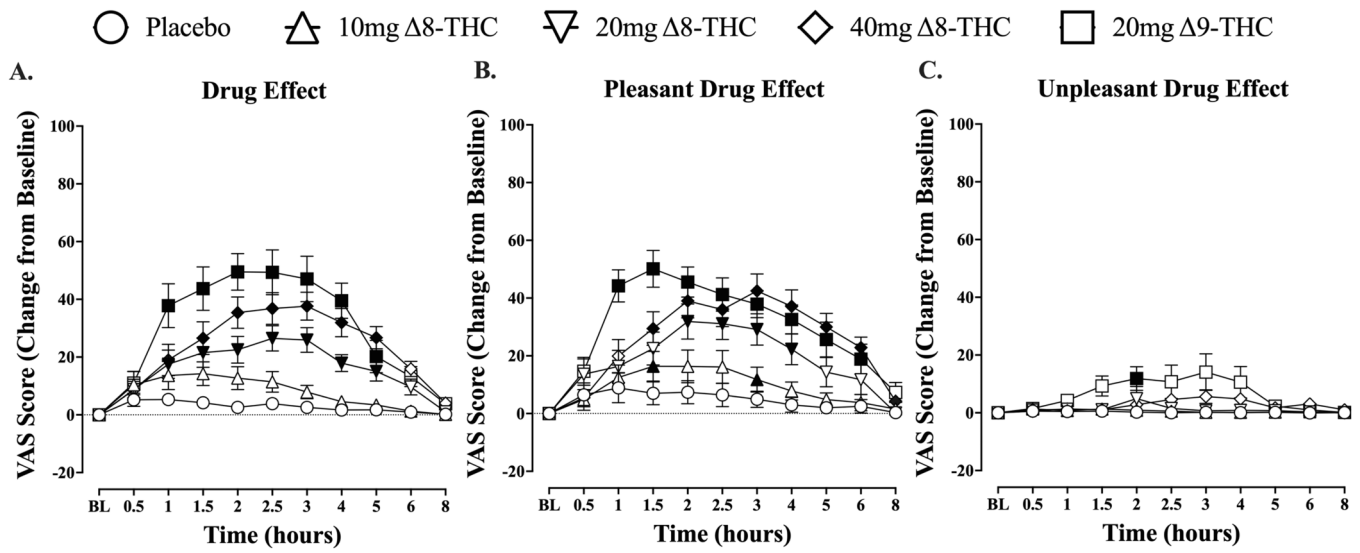


Fig. 2. Change from baseline mean ratings for the visual analog scale (VAS) items A) drug effect, B) pleasant drug effect, and C) unpleasant drug effect from the drug effect questionnaire displayed over time. Scores ranged from 0 (not at all) to 100 (extremely). Error bars indicate SEMs. Horizontal axes are not accurate time scales and represent the time points at which subjective drug effects were assessed. Filled symbols indicate a significant difference from placebo.

study. Their mean (SD) age, weight, and BMI was 28 (6) years, 79 (14) kg, and 26 (3) kg/m^2, respectively. Self-reported race and ethnicity for study completers were as follows: 9 white and non-Hispanic, 2 white and Hispanic, 4 black and non-Hispanic, and 2 Asian and non-Hispanic, 2 other/not listed. On average, 67 days had passed (SD [range], 30 [30–101] days) since participants' last self-reported cannabis use at the time of study entry (Supplemental Table 1).

Six adverse events (AEs) were reported during the study, all of which were of mild or moderate severity. One participant experienced discomfort with the intravenous catheter, two participants reported nausea and dizziness after receiving 20 mg Δ9-THC, one reported lightheadedness and dizziness after 10 mg Δ8-THC, and one reported dizziness and headache after placebo administration. All AEs were transient, resolved without medical intervention, and did not lead to any participant withdrawing from the study.

3.1. Whole blood pharmacokinetics

Fig. 1A-F displays whole blood concentrations of Δ8-THC, Δ9-THC, and the respective metabolites of each over time and Table 1 shows data for C_{max}, T_{max}, AUC, and parent drug to metabolite ratios (Fig. 1G and H). Notably, Δ9-THC and its metabolites were not detected in Δ8-THC conditions, Δ8-THC and its metabolites were not detected in the Δ9-THC condition, and no cannabinoids were detected in the placebo condition. Peak concentrations of both parent compounds and their metabolites occurred between 2- and 4-h post-drug administration, and decreased steadily over the remaining 4 h of the session. C_{max} and AUC for Δ8-THC and its metabolites generally increased in a dose-orderly fashion. The ratio of Δ8-THC:11-OH-Δ8-THC was higher in all Δ8-THC conditions than the ratio of Δ9-THC:11-OH-Δ9-THC in the Δ9-THC condition. Conversely, the ratio of Δ8-THC:Δ8-THCCOOH was lower in all Δ8-THC conditions than the ratio of Δ9-THC:Δ9-THCCOOH in the Δ9-THC condition.

3.2. Subjective drug effects

Fig. 2A-C illustrates data for three DEQ items, "drug effect," "unpleasant," and "pleasant", measured over time. ANOVA results for all pharmacodynamic outcomes are provided in Supplemental Table 2, while planned comparison results are summarized in Table 2. Significant main effects of dose, time, and/or dose × time interactions were observed for 19 individual items (see Supplemental Table 2). Planned comparisons revealed that subjective ratings of overall drug effect, misuse liability, and common interoceptive drug effects associated with acute cannabis exposure were higher after both 40mg Δ8-THC and 20mg Δ9-THC compared with placebo. At the same 20mg dose, Δ9-THC produced significantly higher subjective ratings for "drug effect," "high," "anxious/nervous," and "dry mouth" compared with Δ8-THC. There were no significant differences observed between 40mg Δ8-THC and 20mg Δ9-THC or between 10mg Δ8-THC and placebo.

3.3. Cognitive and psychomotor performance

Main effects of time were observed for the DSST, PASAT, and DRUID application, and main effects of condition were observed for the DAT and DRUID application (Fig. 3; Supplemental Table 2); there were no condition x time interactions observed on cognitive/psychomotor outcomes. Planned comparisons revealed that 40mg Δ8-THC and 20mg Δ9-THC, but not 10mg or 20mg Δ8-THC, decreased the number of correct responses on the DSST relative to placebo. Only the 20mg Δ9-THC dose condition increased global impairment scores on the DRUID application compared with placebo. Dose-orderly decrements in performance on the PASAT and DAT were observed, but these were not significantly different from placebo.

3.4. Vital signs

A main effect of time and a condition x time interaction was observed for HR, and a main effect of time was observed for Diastolic BP. Planned comparisons revealed that HR increased significantly in the 40mg Δ8-THC and 20mg Δ9-THC conditions relative to placebo and 20mg Δ9-THC increased HR more than both the 10mg and 20mg Δ8-THC doses (Table 2).

4. Discussion

The widespread popularity of oral Δ8-THC products following the passage of the "Farm Bill" underscores the critical need for controlled research characterizing the acute effects of Δ8-THC. The present human laboratory study addressed this gap by comparing the acute effects of orally administered Δ8-THC and Δ9-THC in healthy adults who were infrequent cannabis users. Overall, ingestion of Δ8-THC produced dose-

Table 2
Mean (SD) peak change from baseline values for pharmacodynamic measures.

	Placebo		10mg Δ8-THC		20mg Δ8-THC		40mg Δ8-THC		20mg Δ9-THC	
Outcome Measures	**Cmax**	**Tmax**	**Cmax**	**Tmax**	**Cmax**	**Tmax**	**Cmax**	**Tmax**	**Cmax**	**Tmax**
Subjective Drug Effect										
Drug Effect	6.6 (10.9)	1.2 (1.0)	**16.8 (17.2) b,c**	1.6 (0.6)	**34.1 (22.1) b**	2.3 (1.2)	**49.2 (22.4) a**	2.9 (1.2)	**66.6 (26.3) a**	1.9 (0.9)
Unpleasant	1.1 (2.2)	2.1 (2.2)	**2.3 (4.5)b**	1.3 (0.8)	6.9 (17.8)	1.9 (0.7)	9.6 (11.8)	3.5 (1.1)	**20.9 (27.7) a**	2.4 (0.7)
Pleasant	11.2 (25.1)	1.9 (1.1)	**22.6 (27.2) b,c**	2 (1.1)	40.5 (25.7)	2.1 (1.4)	**51 (23.5)a**	2.6 (1.4)	**60 (24.4)a**	2.6 (1.9)
Like Drug Effect	11.4 (22.8)	2.3 (2.1)	**25.4 (28.9) b**	1.7 (0.7)	**43.5 (27.6) a**	2.7 (1.6)	**47.5 (31)a**	2.8 (1.9)	**61.3 (21.2) a**	2.1 (1.6)
High	5.7 (9.4)	1.9 (2.2)	**17.7 (18.4) b,c**	1.6 (0.6)	**33.4 (23.2) b**	2.2 (1.3)	**48.8 (21.4) a**	2.8 (1.2)	**60.1 (28.1) a**	2.1 (1.0)
Sick	1.3 (3.3)	3.3 (3.2)	1.1 (3.1)	1.6 (1.7)	3.5 (10.9)	4.5 (3)	8.8 (16.8)	4 (1.5)	12.9 (24.1)	3.0 (1.3)
Heart Racing	0.6 (1.5)	1.7 (2.0)	**1.6 (6.2)b**	3.7 (2.9)	6.1 (10.2)	1.6 (1.3)	7.3 (9.9)	3.2 (1.8)	**18.5 (20.2) a**	2.7 (2.1)
Anxious/Nervous	1 (2.4)	2.6 (1.9)	4.9 (18.3)	2.2 (1.2)	**0.4 (6.2)b**	2 (1.5)	9.5 (11.8)	3.4 (1.5)	18.0 (25.6)	2.8 (1.3)
Relaxed	−6.6 (35.5)	2.4 (2.1)	10.4 (39.4)	3.8 (2.4)	1.8 (32.4)	3.1 (2.4)	11 (35.6)	3.6 (2.7)	**35.1 (37.4) a**	2.9 (2.1)
Paranoid	0.4 (1.0)	2.1 (1.7)	1.6 (6.4)	4.9 (2.5)	1.9 (4.5)	3.6 (3.2)	8.6 (14.9)	3.6 (1.5)	15.3 (24.6)	2.2 (0.6)
Sleepy/Tired	23.4 (31.0)	3.3 (2.2)	17.3 (43)	3.4 (2.5)	35.1 (33.6)	3 (2.2)	33.8 (39.8)	3.6 (1.9)	50.5 (42.4)	3.6 (2.2)
Alert	−17.1 (33)	3.5 (2.4)	−20.4 (28.7)	3.4 (1.7)	−10.6 (28.4)	3 (1.4)	−10.5 (23.7)	3.3 (2.1)	−2.9 (42.9)	3.1 (2)
Irritable	4.4 (9.9)	2.6 (2.1)	5.7 (18.4)	2.9 (2.9)	1.6 (7.0)	1.8 (1.9)	3.8 (12.5)	2.6 (1.8)	5.4 (15.9)	2.3 (1.4)
Vigorous/Motivated	−1.8 (16.3)	3.2 (2.0)	−6.2 (22.7)	2.5 (2.0)	−4.2 (18.1)	3.7 (2.4)	−5.2 (25.9)	2.2 (1.4)	0.4 (27.7)	3.6 (2.6)
Restless	5.5 (11.3)	4.9 (3.1)	0.1 (5.3)	2.0 (2.0)	11.0 (17.0)	3.2 (1.0)	11.5 (21.8)	2.5 (1.6)	22.7 (27.7)	2.0 (1.0)
Munchies	19.5 (38.2)	3.3 (1.5)	**30.7 (40)b**	2.7 (1.3)	42.9 (38.1)	3.5 (0.8)	53.9 (37.2)	3.6 (1.5)	**50.9 (45.6) a**	3.7 (1.8)
Dry Mouth	6.7 (18.5)	2.5 (2.0)	**13.7 (25.5) b,c**	2.5 (1.5)	**32.4 (24.7) b**	2.8 (1.1)	**55.7 (30.4) a**	3.2 (1.6)	**66.7 (32.7) a**	2.3 (1.0)
Dry/Irritated Eyes	2.2 (6.1)	2.1 (1.9)	**3.2 (10.8)b**	2 (1.1)	12 (18.3)	3.6 (1.9)	**23.6 (20.7) a**	3.2 (1.7)	**36.6 (29.6) a**	2.9 (1.4)
Trouble With Memory	5.2 (17.1)	2.8 (2.3)	7.1 (11.3)	3.3 (1.8)	8.2 (11)	2.8 (1.6)	21.6 (26.6)	3.1 (1.3)	**31.1 (33.3) a**	2.1 (0.8)
Throat Irritated	0.6 (3.4)	3 (2.3)	0.2 (3.0)	3 (1.8)	5.2 (13)	2.7 (0.8)	5 (7.9)	3.1 (1.4)	**14.9 (17)a**	3.0 (1.6)
Difficulty With Routine Tasks	4.9 (10.8)	3.1 (3.1)	**7.7 (12.5)b**	2.5 (1.5)	11.4 (15.5)	2.0 (1.6)	**25.2 (20.3) a**	3 (1.1)	**37.7 (35.3) a**	2.5 (1.1)
Happy	7.5 (16.6)	3.5 (2.5)	2.4 (25.9)	4.1 (2.8)	1.8 (20.4)	5.5 (2.5)	8.1 (27.4)	3 (2.3)	10.6 (31.7)	2.8 (1.9)
Sad	0.6 (4.7)	1.9 (2)	−2.1 (7.8)	3.1 (3.4)	2.6 (17)	2.9 (2.6)	1.1 (10.4)	3 (1.7)	8.3 (26.3)	3.4 (2.3)
Confidence in Driving	−5.2 (25.4)	2.9 (2)	**−22.7 (24.2)b,c**	2.5 (1.6)	−48.7 (27.8)	2.6 (1.3)	**−56.7 (37.6)a**	3 (1.8)	**−65.1 (39.6)a**	2.3 (1.8)
Cognitive Measures										
Divided Attention Task (DAT) Mean Distance from central target	4 (11.7)	3.8 (2.5)	5.3 (21.5)	3.8 (2.4)	6.9 (10.4)	4.5 (2.2)	13.1 (15.7)	4.3 (2.6)	18.5 (24.2)	3.9 (1.6)
Digit Symbol Substitution Task (DSST) Total Correct	−0.6 (11.5)	3.2 (2.4)	**−1.8 (12.6) b,**	2.7 (1.8)	**−4.7 (11.2)b,c**	3.3 (2.2)	**−10.7 (12.9)a**	3.5 (2.1)	**−15.1 (16.6)a**	3.2 (2.2)
Paced Auditory Serial Addition Task (PASAT) Total Correct	−6.3 (8.3)	3.8 (2.8)	**−7.4 (14.7) b**	2.8 (2)	−8.7 (18.1)	3.5 (2.4)	−14.8 (19.8)	4.0 (2.0)	−15.4 (19.3)	3.0 (2.0)
Driving Under the Influence of Drugs (DRUID)	2.4 (6.6)	3.4 (2.6)	4.4 (5.6)	3.9 (2.4)	3.5 (5.1)	3.1 (1.9)	6.4 (7.1)	4.1 (1.9)	**7.4 (7.8)a**	3.5 (1.9)
Vital Signs										
Systolic Blood Pressure	0 (17.9)	2.9 (2.2)	5.5 (19.1)	3.7 (2.6)	−3.2 (14.5)	3.2 (2)	−2.9 (16.8)	3.8 (2.3)	−5.1 (19.7)	4.3 (3.1)
Diastolic Blood Pressure	−4.9 (16)	3.6 (2)	−2 (13.3)	3.6 (2.2)	−5.4 (16)	3.4 (2.4)	−7.2 (14.3)	3.2 (2.6)	−3.3 (14.1)	3.3 (1.7)
Heart Rate	−5.1 (13.3)	3 (1.9)	**0.9 (15.5)b**	2.7 (1.6)	**7.2 (16.6)b**	3.8 (2.7)	**11.2 (16.7) a**	2.9 (2.5)	17.4 (14)a	3.0 (2.6)

Notes: SD = Standard Deviation; a indicates a significant difference from placebo ($p < 0.05$); b indicates a significant difference from D9-THC ($p < 0.05$); c indicates a significant difference from 40mg D8-THC ($p < 0.05$).

dependent increases in subjective, cognitive performance, and physiological outcomes that were qualitatively similar to Δ9-THC. Consistent with prior findings, Δ8-THC exhibited lower potency compared to Δ9-THC at equivalent doses, though this reduced potency was overcome by increasing the Δ8-THC dose (Gong et al., 1984; Hollister and Gillespie, 1973; Karniol and Carlini, 1973). Together, these findings demonstrate that Δ8-THC products have the potential to produce psychoactive and physiological effects that are comparable to Δ9-THC. This is important

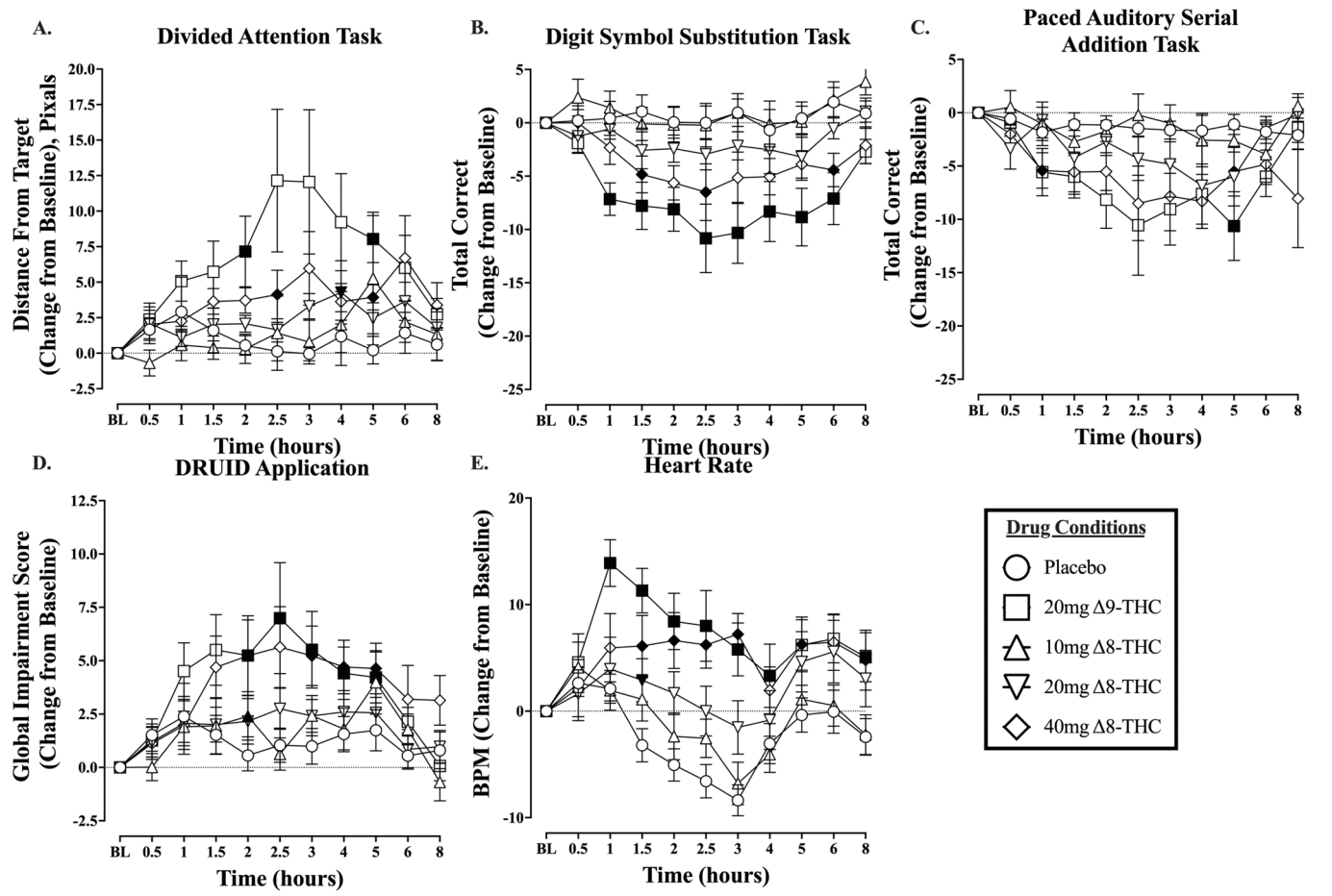


Fig. 3. Change from baseline average total correct on the A) Digit Symbol Substitution Task (DSST) and B) modified Paced Auditory Serial Addition Task (PASAT), the average distance from the central stimulus from the C) Divided Attention Task (DAT), the global impairment score from the D) DRUID application, and the beats per minute (BPM) for E) heart rate. A and B, Lower scores indicate poorer performance relative to baseline. C and D, higher scores indicate poorer performance relative to baseline. Error bars indicate SEMs. Horizontal axes are not accurate time scales and represent the time points at which subjective drug effects were assessed. Filled symbols indicate a significant difference from placebo.

considering that hemp-derived Δ8-THC is no longer a controlled substance, is more widely available than Δ9-THC for retail sale in the U.S. and elsewhere due to differences in legal status (Babalonis et al., 2021), and is often perceived as less intoxicating and harmful by people who use cannabis products (Bergeria et al., 2023).

Δ8-THC produced dose-dependent increases on all pharmacodynamic measures, although the potency of Δ8-THC appeared lower compared to Δ9-THC. Specifically, 20 mg Δ8-THC produced significantly lower subjective, cognitive, and physiological effects compared to 20 mg Δ9-THC. These differences in potency to produce the behavioral effects were overcome by increasing dose as evidenced by comparable effects between 40 mg Δ8-THC and 20 mg Δ9-THC. These findings for subjective and physiological effects align with prior research (Gong et al., 1984; Hollister and Gillespie, 1973; Karniol and Carlini, 1973) and extend our understanding to include cognitive/psychomotor effects. Interestingly, while a 20 mg dose of Δ9-THC was associated with negative affect (e.g., anxiety and paranoia) compared to placebo, Δ8-THC did not produce similar effects at any dose tested. These results are consistent with user-reported surveys suggesting that Δ8-THC may elicit fewer negative experiences than Δ9-THC (Bergeria et al., 2023; Kruger and Kruger, 2023; Szczypka et al., 2014). However, Δ8-THC maintained comparable positive subjective effects (e.g., drug liking), indicating Δ8-THC may have comparable misuse potential to Δ9-THC, despite having a lower potency.

This is the first human laboratory study to characterize the whole-blood pharmacokinetics of Δ8-THC and its metabolites in comparison to Δ9-THC. Concentrations of Δ8-THC and its metabolites increased in a dose-dependent manner, and 20 mg doses of Δ8-THC and Δ9-THC elicited similar concentrations of the parent drug. Preclinical evidence suggests that the 11-OH-Δ9-THC metabolite of Δ9-THC produces stronger PD effects than Δ9-THC (Lemberger et al., 1973), and is differentially metabolized compared with Δ8-THC (Erdmann et al., 1976; Just et al., 1975; Watanabe et al., 2007). Consistent with this, the mean blood concentration of 11-OH-Δ8-THC was about half that of 11-OH-Δ9-THC at the same 20 mg dose. Thus, one mechanism for the difference in potency between Δ8-THC and Δ9-THC appears to be related to differential metabolism.

The present study had several limitations. First, it used pure Δ8-THC and Δ9-THC, whereas retail products often contain additional compounds (e.g., cannabidiol [CBD], “minor” cannabinoids like cannabigerol [CBG]) (Kaczor et al., 2024). The use of pure compounds represents a crucial initial step in this line of research, as it is necessary to eliminate confounding variables. Secondly, the study used a single edible formulation (i.e., high-fat brownie), which may limit generality of the findings to other formulations (e.g., beverages, low-fat gummies) that could influence acute effects (Poyatos et al., 2020). Thirdly, the study was not powered to detect sex differences or other participant-level factors, areas highlighted as potentially significant (Zamarripa et al., 2022). Finally, the study excluded individuals who frequently use cannabis or cannabinoid products, meaning the findings may not translate to individuals with tolerance to THC effects (Zamarripa et al., 2022).

In this randomized clinical trial, oral administration of 40 mg Δ8-THC reliably produced Δ9-THC-like subjective drug effects, impairment of cognitive and psychomotor function, and increases to physiological outcomes. In contrast, doses of 10 mg and 20 mg Δ8-THC were well tolerated and did not significantly differ from placebo with the exception of increased drug liking at 20 mg Δ8-THC. Variation in blood concentrations of the 11-OH metabolite was identified as a likely mechanism to explain the difference in potency between the two isomers. With the widespread availability of retail Δ8-THC products as a byproduct of the 2018 "Farm Bill," the findings from the present study underscore the importance of establishing regulatory frameworks that address safety, labeling, and user education related to Δ8-THC products. It also necessitates a reconciliation of differences in regulation between Δ8-THC and Δ9-THC in jurisdictions where there are stark differences in level of control and/or retail access.

CRediT authorship contribution statement

Edward J. Cone: Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Ruth E. Winecker:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Ronald Flegel:** Writing – review & editing, Funding acquisition. **Eugene Hayes:** Writing – review & editing. **Lisa S. Davis:** Writing – review & editing. **David Kuntz:** Writing – review & editing, Methodology, Formal analysis. **Ryan Vandrey:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **C. Austin Zamarripa:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation. **Tory R. Spindle:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Destiny Schriefer:** Writing – original draft, Data curation.

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Declaration of Competing Interest

Dr. Vandrey has been paid as a consultant or scientific advisory board member for Canopy Health Innovations Inc., MyMD Pharmaceuticals, Mira1a Pharmaceuticals, Syqe Medical Ltd., Radicle Science LLC., Jazz Pharmaceuticals, Charlotte's Web, and WebMD outside the submitted work. Dr. Spindle has been a paid consultant for Canopy Health Innovations Inc. and has received funding from Cultivate Biologics for an unrelated study.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112676.

Data availability

The data underlying this article are available in the article and its supplementary materials.

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