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Controlled Vaporized Cannabis, With and Without Alcohol: Subjective Effects and Oral Fluid-Blood Cannabinoid Relationships

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Abstract

Background and Aims—Vaporized cannabis and concurrent cannabis and alcohol intake are commonplace. We evaluated cannabis' subjective effects, with and without alcohol, relative to blood and oral fluid (OF, advantageous for cannabis exposure screening) cannabinoid concentrations and OF/blood and OF/plasma vaporized-cannabinoid relationships.

Methods—Healthy adult occasional-to-moderate cannabis smokers received vaporized placebo or active cannabis (2.9% and 6.7% Δ^9-tetrahydrocannabinol, THC) with or without oral low-dose alcohol (~0.065g/210L peak breath alcohol concentration [BrAC]) in a within-subjects design. Blood and OF were collected up to 8.3h post-dose and subjective effects measured at matched time points with visual-analogue scales and 5-point Likert scales. Linear mixed models evaluated subjective effects by THC concentration, BrAC, and interactions. Effects by time point were evaluated by dose-wise analysis of variance (ANOVA). OF versus blood or plasma cannabinoid ratios and correlations were evaluated in paired-positive specimens.

Results—Nineteen participants (13 men) completed the study. Blood THC concentration or BrAC significantly associated with subjective effects including "high," while OF contamination prevented significant OF concentration associations <1.4h post-dose. Subjective effects persisted through 3.3–4.3h, with alcohol potentiating cannabis effects' duration. Effect-versus-THC concentration and effect-versus-alcohol concentration hystereses were counterclockwise and clockwise, respectively. OF/blood and OF/plasma THC significantly correlated (all Spearman r≥0.71), but variability was high.

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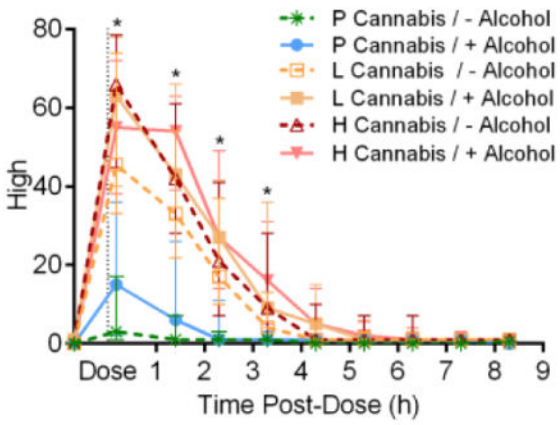
Conclusions—Vaporized cannabis subjective effects were similar to those previously reported after smoking, with duration extended by concurrent alcohol. Cannabis intake was identified by OF testing, but OF concentration variability limited interpretation. Blood THC concentrations were more consistent across subjects and more accurate at predicting cannabis' subjective effects.

Graphical abstract



Vaporized cannabis' subjective effects are comprehensively characterized, with and without alcohol, and cannabinoid blood and oral fluid relationships evaluated. Oral fluid significantly correlated with blood, plasma, and subjective effects, with high intersubject variability. Vaporized cannabis produced similar subjective effects to smoked, but alcohol extended cannabis' effects duration.

Keywords

Cannabis; Alcohol; Subjective; Blood; Oral Fluid

Introduction

Twenty-three US states and the District of Columbia legalized medical marijuana[1], with Colorado, Washington, Oregon, and Alaska decriminalizing recreational cannabis. Smoking, the most common administration route[2], is disadvantageous as pharmacotherapy, delivering hazardous pyrolytic byproducts[3]. Volatilizing cannabinoids at sub-combustion temperatures (vaporizing) should provide similar subjective effects[4–6], with decreased pyrolytic byproducts[7–8] leading to decreased reports of respiratory symptoms[9]. However, limited clinical data are available on vaporized cannabis. As cannabis vaporization prevalence increases, it is important for clinical and forensic purposes to fully characterize subjective effects, blood and oral fluid (OF) disposition, and their relationships.

Cannabis is the most common illicit drug identified in driving under the influence (DUI) cases[10]. States with legalized medical or recreational cannabis had increased DUI-cannabis (DUIC) cases[11–12], with enforcement complicated by changing cannabis laws. Blood Δ^9-tetrahydrocannabinol (THC) and its non-psychoactive metabolite (11-nor-9-carboxy-THC, THCCOOH) concentrations may provide information regarding time since last intake and

cannabis consumption frequency[13–14]. However, blood collection is invasive and may be delayed 90min-4h after a DUI event[15–16]. OF, a valuable alternative sampling matrix, is non-invasively collected, more difficult to adulterate than urine, and provides information about recent intake[17–19]. Some jurisdictions already adopted OF-specific legislation for DUIC[20–22]. However, OF correlation with cannabis effects or blood concentrations is not fully understood, limiting interpretation, and thus requires evaluation. Additionally, cannabis and alcohol are often identified together in DUI cases[10], making understanding their combined effects critical for forensic interpretation.

In this vaporized cannabis and oral alcohol controlled administration study, we evaluated subjective effects and OF and blood/plasma cannabinoid concentration relationships, with and without low-dose alcohol.

Methods

This protocol was approved by the University of Iowa Institutional Review Board. The study was performed at the University of Iowa Hospitals and Clinics Clinical Research Unit (UIHC-CRU) and National Advanced Driving Simulator (NADS).

Participants

Participants were recruited from the NADS subject database and provided written informed consent for the study. Inclusion criteria were ages 21–55 years; self-reported average cannabis consumption ≥1x/3months but ≤3days/week over the past 3months (Cannabis Use Disorders Identification Test [CUDIT][23]); self-reported “light” or “moderate” alcohol consumption according to a Quantity-Frequency-Variability (QFV) scale[24]; or if “heavy”, not more than 3–4 servings in a typical drinking occasion. Exclusion criteria included past or current clinically significant medical illness; history of clinically significant adverse event associated with cannabis or alcohol intoxication; ≥450mL blood donation in 2weeks preceding drug administration; pregnant or nursing; interest in drug abuse treatment within past 60days; and currently taking drugs contraindicated with cannabis or alcohol or known to impact driving.

Study Design

Participants entered the clinical research unit 10–16h before dosing to preclude intoxication. Participants drank 90% grain alcohol (to ~0.065% peak breath alcohol concentration [BrAC][25]) mixed with juice or placebo-alcohol (juice with alcohol-swabbed rim, topped with 1mL alcohol to mimic taste and odor) *ad libitum* over 10min; then inhaled 500mg placebo (0.008±0.002% THC), low (2.9±0.14% THC, ~14.5mg)-, or high (6.7±0.05% THC, ~33.5mg)-dose vaporized ground bulk cannabis (210°C, Volcano® Medic, Storz & Bickel, Tuttlingen, Germany) *ad libitum* over 10min. Cannabis was obtained from NIDA Chemistry and Physiological Systems Research Branch. Participants received all six alcohol/cannabis combinations in randomized order, one combination per session, separated by ≥1week.

OF was collected with Quantisal™ collection devices (Immunalysis, Pomona, CA) −0.8, 0.17, 1.4, 2.3, 3.3, 4.3, 5.3, 6.3, 7.3, and 8.3h after start of cannabis dosing[26]. Devices were placed under the tongue until indicators turned blue (collecting 1.0±0.1mL OF) or for 10min

maximum, and placed into the stabilizing buffer. OF was stored in Nunc® cryotubes (Thomas Scientific, Swedesboro, NJ) at 4°C for analysis within a month[27]. Oral intake was prohibited 10min prior to OF collection. Blood was collected via indwelling peripheral venous catheter into grey-top potassium oxalate/sodium fluoride Vacutainer® tubes (BD, Franklin Lakes, NY) concurrently with OF (except 4.3 and 5.3h due to blood volume limits), with a second sample centrifuged at 1600×g, 15min. Blood and plasma were stored at −20°C in 3.6mL Nunc cryotubes, and analyzed within 3months[28]. BrAC was measured by Alco-Sensor® IV (Intoximeters, St. Louis, MO), a portable breath alcohol testing device, at the same times as OF and additionally at 0.42h post-dose. It reports alcohol in g/210L breath (limit of quantification [LOQ] 0.006g/210L), equivalent to approximate blood alcohol concentration (BAC) in g/dL.

Subjective effects were measured at the same times as OF collection by 100mm visual-analogue scales (VAS; “high”, “good drug effect”, “stimulated”, “stoned”, “anxious”, “sedated”, and “restless”) anchored by “Not At All”-”Most Ever”; and 5-point (“none”, “slight”, “mild”, “moderate”, “severe”) Likert scales (“difficulty concentrating”, “altered sense of time”, “slowed or slurred speech”, “body feels sluggish/heavy”, “feel hungry”, “feel thirsty”, “shakiness/tremulousness”, “nausea”, “headache”, “palpitations”, “upset stomach”, “dizzy”, and “dry mouth or throat”).

Specimen Analysis

OF was quantified for THC, THCCOOH, cannabidiol (CBD), and cannabinol (CBN) by two-dimensional gas chromatography-mass spectrometry[29], modified by adding 0.4mL hexane to solid-phase extraction columns before loading the initial elution solvent. THC, THCCOOH, CBD and CBN linear ranges were 0.5–50μg/L, 15–500ng/L, 1–50μg/L and 1–50μg/L, respectively. Inter- and intra-assay imprecision were ≤12.3%; analytical bias, ≤14.4% (n=21). For concentrations >upper limit of quantification (LOQ), OF was diluted with drug-free Quantisal buffer. Blood and plasma cannabinoids were quantified by liquid chromatography-tandem mass spectrometry (LCMSMS)[30]. Briefly, 0.5mL blood or plasma was protein-precipitated with ice-cold acetonitrile, supernatants diluted and solid-phase extracted with Bond-Elut Plexa cartridges (Agilent Technologies, Santa Clara, CA). THC, THCCOOH, CBD, and CBN linear ranges were 1–100μg/L. Inter-assay (n=30) analytical bias and imprecision were ≤9.3% and ≤10.0%.

Data Analysis

VAS and Likert results were assessed via linear mixed models in SPSS® version 19 for Windows (IBM, Armonk, NY). Initial data review and analyses indicated insufficiently different low-versus-high cannabis-dose THC concentrations; consequently, mixed-model analyses utilized blood THC and BrAC concentrations (continuous variables), producing the best-fit models. THC, BrAC, time, THC*BrAC, time*THC, time*BrAC, and time*THC*BrAC were evaluated as fixed effects; subject*THC and intercepts as random effects (heterogeneous (1) autoregressive). Two-tailed $p<0.05$ indicated significance. The same analyses were conducted with OF THC concentrations, including and excluding t=0.17h. For analytical purposes, concentrations <lower LOQ were set to 0, VAS responses were converted to percentages (0–100), and Likert responses to 5-point numerical scales

(0≡"None"−4≡"Severe"). Likert linear mixed models for "feel hungry" and "feel thirsty" were only evaluated through 3.3h due to lunch. Friedman's [factorial] repeated measures analysis of variance (ANOVA, factors: cannabis, alcohol; cannabis*alcohol interaction term, pairwise post-hoc comparisons) evaluated within-subject dose differences by time point. The Greenhouse-Geisser correction was utilized for sphericity violations (Mauchly's test). For time point analyses, the conservative Bonferroni correction was utilized for multiple comparisons ($p<0.005$ significance level), and Bonferroni post-hoc testing for subjective effects differences from baseline by dosing condition at each time point. OF versus blood and plasma correlations and regression comparisons were performed with GraphPad Prism®6 (La Jolla, CA). OF/blood and OF/plasma cannabinoid ratios were calculated when quantifiable data were available for both. Dose and baseline differences were calculated via ANOVA.

Results

Participants

Nineteen cannabis smokers (13 men, ages 21–37 years, 74% white) reported cannabis consumption ≥2x/month (but ≤3days/week), and last use within a week prior to admission (Table 1). One participant (13) self-reported last intake 4months ago, despite reporting overall average consumption ≥1x/3months.

Subjective effects

Table 2 presents linear mixed models subjective effects by THC and alcohol concentrations. The overall equation tested is represented by

$$\begin{aligned}[\text{Subjective Effect Result}] = \text{Intercept} &+ b_{\text{Blood THC}} * [\text{THC}]_{\text{blood}} \\ &+ b_{\text{BrAC}} * \text{BrAC} \\ &+ b_{\text{Time}} * \text{post-dose time} \\ &+ b_{\text{THC*BrAC}} * [\text{THC}]_{\text{blood}} * \text{BrAC} \\ &+ b_{\text{Time*THC}} * \text{post-dose time} * [\text{THC}]_{\text{blood}} \\ &+ b_{\text{Time*BrAC}} * \text{post-dose time} * \text{BrAC} \\ &+ b_{\text{Time*THC*BrAC}} * \text{post-dose time} * [\text{THC}]_{\text{blood}} * \text{BrAC}\end{aligned}$$

. Non-significant effects ($p>0.05$) were not included in the final model. In these models, b is the coefficient estimate for each contributing factor (negative or positive b indicates parameter decreases or increases effect, respectively). It represents a scaling factor by which each tested effect (e.g., blood THC, BrAC) can be multiplied to produce the best overall model for our data, thereby describing the contribution of each effect to the final model. Non-significant effects were not included in models (b=0). Blood THC was positively associated with "high", "good drug effect", "stimulated", "stoned", "anxious", and "restless" (Table 2, Figure 1, Supplemental Figure 1), and feelings of altered time, "slowed/slurred speech", "dizziness", and "dry mouth/throat" (Table 2, Supplemental Figure 2). BrAC was positively associated with "high", "good drug effect", and "stimulated" and "difficulty concentrating", "slowed/slurred speech", and "body feels sluggish/heavy". Most models contained negative time terms, indicating effects generally were highest immediately post-dose, decreasing over time. Significant negative THC*BrAC interactions were observed for "high", "good drug effect",

"stoned", "stimulated", "anxious", and "slowed/slurred speech", but the first three contained additional significant positive *time**THC*BrAC interactions. Supplemental Table 1 provides model results where subject covariance parameters could not be calculated (thus resultant model is less certain). Models produced from OF THC were different than for blood (Supplemental Tables 2–3). For multiple subjective effects, significant main effects for blood THC were not detected in OF when the time course included <1.4h; but "high", "good drug effect", "anxious", "stimulated", "stoned", "altered sense of time", "feel thirsty", and "dry mouth/throat" had significant main OF effects for models that only included times ≥1.4h, after oromucosal contamination cleared. For "anxious" and "sedated", significant (but small) OF THC*time effects were present but blood THC*time effects were not significant. Several models ("good drug effect", "high", "stimulated", "stoned", "difficulty concentrating", "altered sense of time", "body feels sluggish/heavy", "feel thirsty", "dry mouth/throat") had significant THC*time interactions common to blood and OF.

All active-drug interventions were positively associated with subjective "good drug effect" 0.17 and 1.4h post-dose relative to baseline (time-point analyses, Supplemental Figure 1). Although alcohol only displayed a significant main dose effect at 0.17h, significant increases from baseline persisted 3.3 and 4.3h with combined cannabis and alcohol. Both low (2.9%-THC) and high (6.7%-THC) cannabis doses were positively associated with "high", "good drug effect", "stimulated", and "stoned" over the first 3.3h (Figure 1 and Supplemental Figure 1). Significant alcohol-dose effects were detected 0.17h after cannabis dosing initiation (0.24h after drinking initiation) for "good drug effect" and "stimulated". We observed only two significant low-versus-high cannabis differences by time point: "stoned" 1.4h post-dose and "anxious" 0.17h post-dose. Significant cannabis effects on "sedated" occurred at time points 2.3–4.3h post-dose. Cannabis also affected "altered sense of time" (1.7–2.3h), "feel thirsty" (0.17–2.3h), and "dry mouth/throat" (0.17–3.3h) (Supplemental Figure 2). Subjective effects versus blood and OF THC concentrations displayed counterclockwise hysteresis; whereas subjective effects versus BrAC showed clockwise hysteresis (Figure 2, Supplemental Figure 3).

OF/Blood and OF/Plasma

OF/blood and OF/plasma ratios showed large variability. Median [range] paired-positive OF/blood ratios were 9.4 [0.3–887, N=413] THC and 3.7 [0.6–20.9]ng/μg, N=339] THCCOOH (Supplemental Table 4). Median [range] OF/plasma ratios were 7.3 [0.2–585, N=455] THC and 2.4 [0.4–13.3]ng/μg, N=341] THCCOOH. Paired-positive CBD and CBN specimens occurred only 0.17h post-dose (9–12 pairs) and showed high variability. OF THC concentration significantly correlated ($p<0.001$) with blood THC concentration (Figure 3, Spearman r [95%CI]=0.7469 [0.6574–0.8156] and 0.8057 [0.7339–0.8598] for low- and high-dose cannabis *without* alcohol, r=0.7321 [0.6389–0.8042] and 0.8447 [0.7858–0.8884] for cannabis *with* alcohol) and with plasma THC (Spearman r≥0.7066 in either matrix for every dose) (Supplemental Table 5). Alcohol presence did not significantly affect ratios. Due to high variability, the only significant dose effect by time point was an overall cannabis effect on OF/plasma 8.3h post-dose (Figure 4). Ratio differences between time points could not be statistically evaluated because ratio variability was high with few paired-positives (Figure 4, Supplemental Table 4).

Discussion

Blood THC concentration after vaporization was significantly and positively associated with subjective effects (Table 2), while there generally was no significant differentiation between effects of low (2.9% THC) and high (6.7% THC) dose cannabis. This is consistent with pharmacokinetic results from these participants[26, 31], and supports previous findings that THC concentrations are a better predictor of subjective effects than cannabis dose[32]. Observed effect sizes (represented by coefficient b) for most Likert measures generally were much lower than VAS for the same factors, possibly because of the shorter Likert measurement scale. Blood THC concentration was not significantly associated with "sedated" in the overall linear mixed model, although time point dose-wise ANOVA showed significant increases over 1.4–4.4h (Supplemental Figure 1). This may result from higher variability and less-consistent results throughout the time course, or possibly other study procedures (e.g., simulated driving). "High", "good drug effect", and "stimulated" are likely desirable effects for recreational intake, whereas "anxious" and "restless" are likely undesirable. "Stoned" and "sedated" could be either, but would be undesirable for pharmacotherapy. Vaporized cannabis significantly increased these measures immediately post-dose, lasting 3.3 or 4.3h. "Anxious" showed significant cannabis-dose effects through 1.4h. Undesirable effects including "feel thirsty" and "dry mouth/throat" increased for the first 3.3h post-cannabis. "Difficulty concentrating" and "altered sense of time" produced mixed effects over 2.3h. Only time significantly increased "feel hungry" in the hours prior to lunch, unexpectedly with no significant THC effect. Another study found cannabis significantly increased "feel hungry" relative to baseline on a 5-point Likert scale after smoking a 6.8% THC cigarette[33]; however, as there was no placebo, possibly the observed effect was due to time since last eating.

There is growing interest in correlating cannabis' subjective effects directly to OF THC concentrations, due to OF advantages as a sampling matrix[17–19]. However, our results indicate caution in interpreting effects from OF concentrations. Unlike blood models, OF regression models (full time course, Supplemental Table 3) had low b-values even when main effects or interactions were statistically significant, probably due to high inter-individual variability in OF THC concentrations and a time course influenced by OF oral contamination rather than systemic cannabinoid concentrations[17–18]. THC concentrations after active doses ranged from 22.7–66,200μg/L[26]. OF THC b-values represented concentration coefficients, so b in the thousandths (order of magnitude) would indicate clinically significant effects for OF THC>1000μg/L. Considering only times ≥1.4h post-dose (Supplemental Table 2) produced models with more robust significant OF main effects, as initial OF contamination decreased. However, active-dose OF THC concentrations still ranged ~1000-fold, 3.0–3940μg/L at 1.4h and 1.6–1541μg/L at 2.3h. The ≥1000-fold concentration differences impose challenges to reliably assess effects based on OF; blood THC at 0.17, 1.4, and 2.4h ranged only 11.4–210μg/L, 0–18.4μg/L, and 0–9.6μg/L, respectively. Additionally, this may account for the high variability of OF/blood and OF/plasma THC ratios (Figure 4), although the influence of OF contamination should be greatest immediately post-inhalation. In other words, OF did not closely track blood or plasma THC changes during this 8.3h time course. Overall, OF THC concentrations were

not reliable indices of blood and plasma THC concentration, accounting for the former's weak association with subjective effects. The relationship between subjective effects and blood or OF THC concentration showed counterclockwise hysteresis (Figure 2), consistent with previous findings[33]. During cannabis inhalation, maximum blood and OF THC concentrations (C_{max}) occurred immediately prior to last inhalation, then decreased rapidly[34], while peak subjective effects occur over the first 2h[32, 35–37]. Subjective effects are related to brain THC concentration, with THC equilibration time in brain accounting for the lag between blood THC C_{max} and maximum subjective effects[38]. Blood THC rapidly decreases during distribution to highly-perfused and adipose tissues[39], producing maximum subjective effects after blood t_{max}, explaining the counterclockwise hysteresis. In contrast, alcohol's slower absorption and later C_{max}[26] led to observed clockwise hysteresis. Clockwise hysteresis may be caused by tachyphylaxis (acute tolerance to an effect happening within a single dose time course, possibly due to receptor down-regulation) or feedback regulation[40].

BrAC was significantly associated, albeit not robustly, with "good drug effect", "high", and "stimulated". The THC*BrAC interaction was less-than-additive (i.e., significant negative interaction term), suggesting that THC+BrAC effects were less than the sum of each individual substance effect (i.e., partial mitigation of simple main effects). However, models for several subjective effects ("high", "good drug effect", "stoned") included positive *time**THC*BrAC interaction terms that yielded overall approximately-additive THC+BrAC effects immediately post-dose and more-than-additive (synergistic) effects as time progressed, prolonging subjective effects. Significant increases from baseline persisting in these effects longer in cannabis-alcohol combinations (extending effects beyond those of either drug alone) corroborate this finding (Figure 1, Supplemental Figure 1).

Alcohol-alone produced hystereses shifted lower than curves for cannabis+alcohol combinations (Figure 2), indicating that participants experienced more effects after alcohol combined with active cannabis compared to alcohol-alone. Low- and high-dose cannabis combined with alcohol produced superimposed curves for "high", "good drug effect", "stimulated", and "stoned", suggesting no dose differential in cannabis effects when combined with alcohol, although individual variability was high (e.g., Supplemental Figure 4 subjective "high" (N=19)). A previous study found similar variability in individual hysteresis curves[33], albeit with just one dosing condition. Only high-THC cannabis combined with alcohol produced substantially higher blood THC C_{max}. This possibly resulted from increased THC-absorption rates during inhalation (due to alcohol-induced increased cardiac output[41] and pulmonary capillary flow) or less-careful cannabis self-titration during alcohol intoxication.

Vaporized cannabis produced subjective effects and time courses similar to smoking, consistent with prior findings[33, 35]. Few studies examined combined cannabis-alcohol subjective effects[32, 42–44], and none as comprehensively as reported herein. In one study, mean subjective "high" post-cannabis intake did not significantly increase with prior alcohol relative to without[42]. Although alcohol-only increased subjective *cannabis-specific* "high" (corroborating our findings (Figure 1)), overall, participants correctly distinguished cannabis' from ethanol's "high". Participants who drank alcohol before cannabis smoking

also were aware of this distinction[32]: subjective “drunkenness” was dominant *before* smoking, subjective [cannabis] “high” thereafter. Alcohol pretreatment significantly decreased latency to smoked-cannabis effects and increased euphoria duration[44]. In the current study, subjective effects significantly >baseline persisted longer post-cannabis dosing *with* alcohol than post-cannabis dosing *without* alcohol (“high”, “good drug effect”, “stimulated”, “stoned”, “sedated”, “difficulty concentrating”, “dry mouth/throat”).

Prior studies directly compared THC and THCCOOH relationships between OF and blood[45–46] or OF and plasma/serum[19, 47–51]. However, few included concurrent alcohol administration[49], and none provided within-subject blood *and* plasma data. Plasma is more commonly used for clinical and pharmacokinetic purposes, but blood is more common in forensic settings. A forensic OF-blood THC linear regression study in suspected drugged drivers had negligible (albeit statistically significant) correlation (R^2=0.030)[46], likely caused by high variability in time since last intake and unknown food or drink ingestion. Our controlled-administration fits were stronger for all doses (Supplemental Table 3), and we observed higher correlations (Spearman r=0.7321–0.8447 among all active-cannabis conditions). However, consistent with prior research, we observed high variability in OF/blood and OF/plasma ratios (Figure 4), particularly for THC. Recently reported OF/serum THC ratios showed similar ranges[49], reiterating that OF/blood or OF/serum ratios are too variable to predict one concentration from the other[51–52]. Recently, 44 [95%CI 27–90]μg/L OF THC produced the same cannabis driving prevalence as 1μg/L blood THC[53], but as we showed, there is too much variability to predict blood or oral fluid THC from the other matrix concentration. OF retains its value in identifying recent cannabis exposure[46], but is more limited in predicting cannabis effects. There were no significant alcohol effects on OF/blood or OF/plasma THC (consistent with other findings[49]).

Our study found narrower OF/blood and OF/plasma THCCOOH ratio ranges because THCCOOH enters OF from systemic circulation rather than oromucosal contamination. THCCOOH was not always detected in OF in this occasional-to-moderate-smokers cohort and, when present, was in low ng/L concentrations. OF THCCOOH distinguishes passive environmental smoke exposure from cannabis intake[54] [although chronic passive exposure was not studied][26]. Alcohol did not affect OF/blood or OF/plasma THCCOOH. THCCOOH is non-psychoactive and cannot be related to subjective effects. Its value remains as a cannabis use marker. Although OF CBD and CBN persisted for hours due to oral contamination[26], they were not present in blood and plasma after 0.42h. When present, these markers help identify recent intake, but are more likely to be detected in OF than blood in forensic settings, where blood collection lag times often exceed detection windows[15–16].

Study strengths and limitations

This is the most comprehensive evaluation of which we are aware of vaporized cannabis subjective effects time courses, with and without alcohol. We observed significant cannabis subjective effects for most measures through 3.3 or 4.3h. Our robust within-subjects design, evaluation of multiple subjective effects utilizing two different types of measurement scales, and concentration-based linear mixed models approach provided in-depth analyses of cannabis, alcohol, and interaction effects over time, also comparing blood and OF

concentrations. Study limitations include lack of an explicit “bad drug effect” measure, although we did measure potential negative side effects (“anxious”, “difficulty concentrating”, “body feels sluggish/heavy”), and exclusion of frequent cannabis users (>3x/week) as participants. The latter may limit the external validity of our findings, as a prior study found different subjective effects patterns in frequent versus occasional cannabis smokers[45]. To our knowledge, only one other study compared OF/serum THC concentrations after controlled vaporized cannabis in frequent smokers[19]. Authors found similar broad variability in OF/serum THC, but did not report OF/serum THCCOOH ratios.

Conclusion

We delineated subjective psychological effects of inhaled THC, with and without oral alcohol, concomitantly comparing blood and plasma to OF cannabinoid concentrations during the treatment period. Vaporized cannabis produced a notable “high” and other subjective effects through 4.3h post-dose, similar to the effect of smoked cannabis. Alcohol prolonged the duration of cannabis’ effects. Subjective effect-versus-cannabinoid concentration curves displayed counterclockwise hysteresis, but subjective effect-versus-alcohol concentration produced clockwise hysteresis possibly due to slower alcohol absorption. We observed robust OF/blood and OF/plasma correlations, but high OF cannabinoid variability challenged reliable cannabis-effects predictions. Although OF retains strong cannabis exposure screening validity, blood THC demonstrated considerably more consistent results for predicting intoxicating effects of cannabis inhalation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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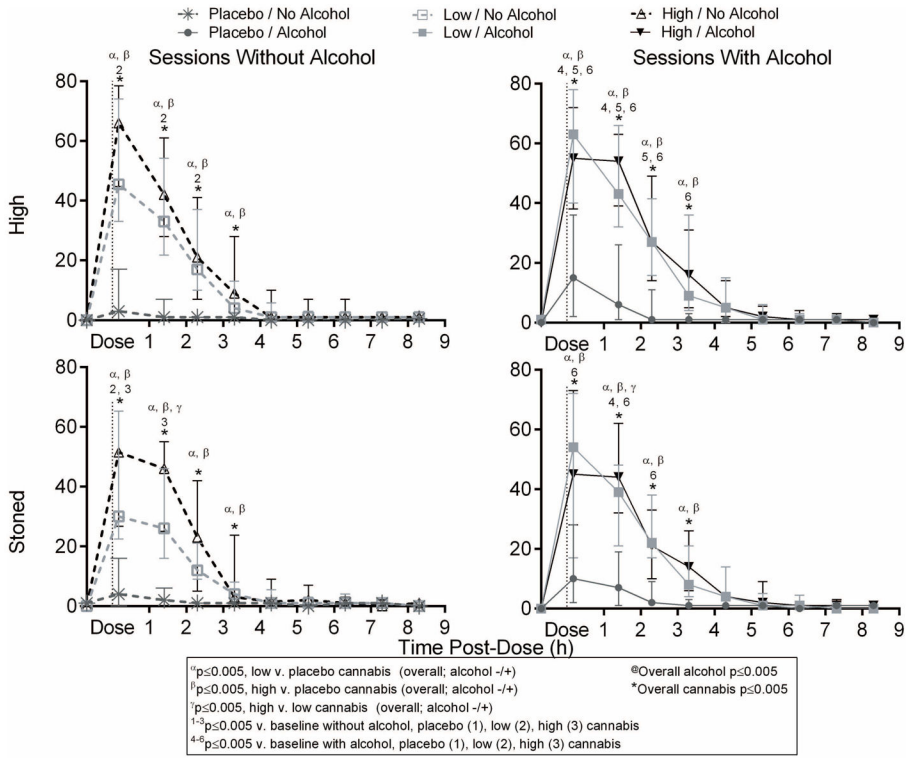

Figure 1.

Median [interquartile range] “high” and “stoned” visual-analogue scales (VAS) results versus time in 19 participants after low (2.9% THC) and high (6.7% THC) vaporized cannabis doses with and without low-dose oral alcohol. All VAS were out of 100.

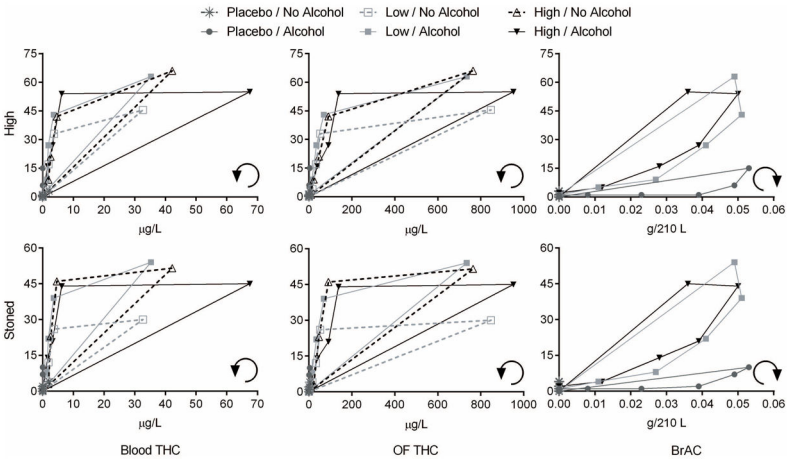

Figure 2.

Median “high” and “stoned” visual-analogue scales (VAS) results versus median blood Δ^9-tetrahydrocannabinol (THC) concentrations, oral fluid (OF) THC, and breath alcohol concentration (BrAC) in 19 participants after placebo, low (2.9% THC) and high (6.7% THC) vaporized cannabis doses with and without low-dose oral alcohol. Counterclockwise and clockwise arrows represent hysteresis curve progressions over time.

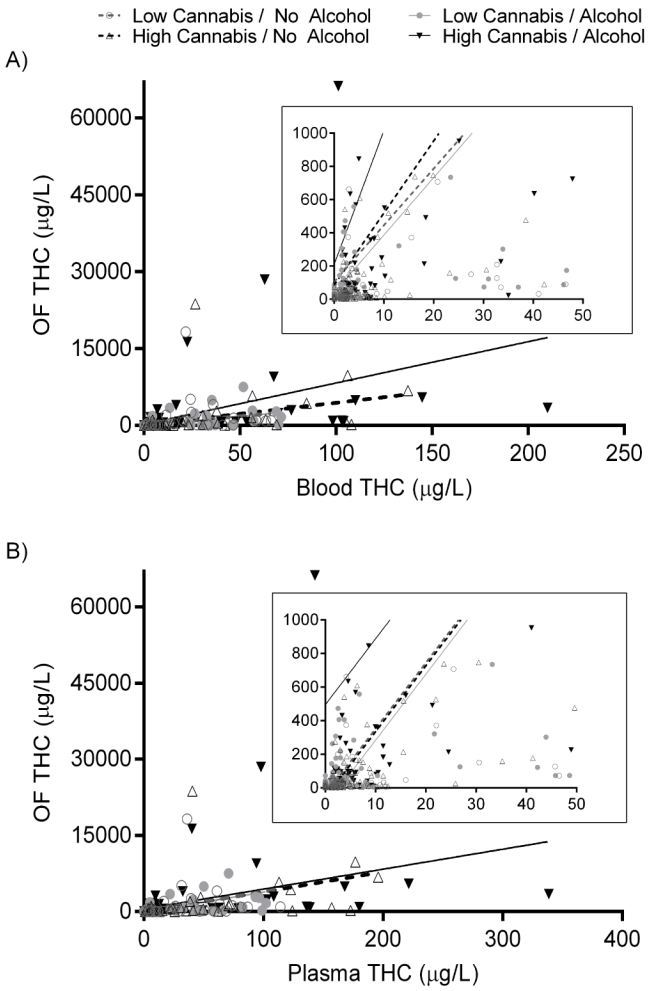

Figure 3.

Oral fluid (OF) Δ^9-tetrahydrocannabinol (THC) concentrations versus blood (A) and plasma (B) THC, and least-squares linear regressions from 19 participants after low (2.9% THC) and high (6.7% THC) vaporized cannabis doses with and without low-dose oral alcohol. Insets illustrate (zoom) densest regions; note graph scales. OF significantly correlated ($p<0.001$) with blood and plasma (Spearman $r\geq0.7066$ in either matrix for every dose). See Supplemental Table 5 for regression equations and comparisons.

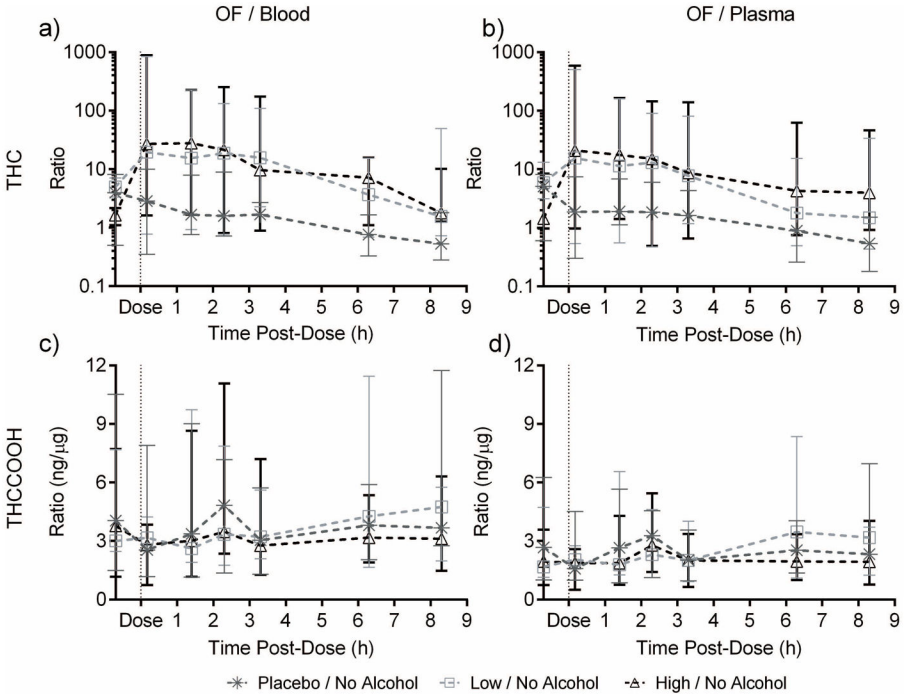

Figure 4.

Median [range] oral fluid (OF)/blood and OF/plasma Δ^9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-THC (THCCOOH) ratios over time in paired-positive specimens from 19 participants after low (2.9% THC) and high (6.7% THC) vaporized cannabis doses.

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Table 1

Self-reported demographic characteristics and recent cannabis and alcohol consumption history of 19 healthy adult occasional-to-moderate cannabis smokers

Participant	Sex	Age (years)	Race and ethnicity	BMI (kg/m^2)	Alcohol intake frequency	Typical drinks per occasion	Cannabis intake frequency	Hours "stoned" on typical cannabis occasion[a]	Time since last cannabis consumed (days)	Amount last consumed[b] (joint or joint equivalent)
1	M	23.7	W	24.3	2–3x/wk	2–4	2–4x/m	1–2	1	1
2	F	28.4	AA	23.8	≥4x/wk	2–4	2–4x/m	3–4	14	1
3	M	21.9	W	24.7	2–3x/wk	5–6	2–4x/m	1–2	6	1
4	M	37.8	W	26.1	2–3x/wk	2–4	2–3x/wk	1–2	3	2.5
5	M	26.6	W	21.6	≤1x/m	2–4	≤1x/m	1–2	11	3.5
6	F	26.3	W	20.0	2–3x/wk	2–4	2–3x/wk	3–4	1	0.25
7	M	25.8	W	40.6	2–4x/m	2–4	2–3x/wk	1–2	0.3	0.5
8	M	26.1	H	31.5	2–4x/m	1–2	2–3x/wk	1–2	3	1
9	M	23.2	W	19.5	2–3x/wk	2–4	2–3x/wk	3–4	2	1
10	M	23.1	W	23.9	2–4x/m	2–4	≤1x/m	1–2	2	0.25
11	M	32.3	O, H	28.9	2–3x/wk	2–4	2–3x/wk	1–2	4	1
12	F	23.4	W	23.3	2–3x/wk	2–4	2–4x/m	3–4	4	1
13	F	30.3	AA	24.1	2–3x/wk	2–4	≤1x/m	<1	120	1
14	M	24.6	W	23.3	2–3x/wk	2–4	2–4x/m	1–2	7	0.8
15	M	21.8	W	32.7	≤1x/m	1–2	2–4x/m	1–2	7	0.13
16	F	21.7	AA, W	23.0	2–4x/m	1–2	2–3x/wk	1–2	1.1	1.5
17	M	28.7	W	18.3	2–3x/wk	2–4	≤1x/m	3–4	45	0.5
18	M	28.1	W	48.3	2–4x/m	2–4	2–4x/m	3–4	5	1
19	F	22.9	W	21.6	2–4x/m	5–6	2–3x/wk	3–4	1	1
Median		25.8		23.9					4.0	1.0
Mean		26.1		26.3					12.5	1.0
StDev		4.1		7.5					27.9	0.8

[a]'Hours "stoned" ' wording originates from Cannabis Use Disorders Identification Test, source of self-reported cannabis frequency data

[b] Cannabis amount last consumed is based on empirically-normalized joint consumption, to account for various administration routes and self-reported "sharing" between multiple individuals

Abbreviations: W, White; AA, African American; H, Hispanic or Latino; As, Asian; O, Other; AI, American Indian/Native American; StDev, standard deviation

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Table 2

Overall effect of blood Δ^9-tetrahydrocannabinol (THC) concentration (μg/L), breath alcohol concentration (BrAC, g/210L), time, and interactions (THC*BrAC, time*THC, time*BrAC, time*THC*BrAC) on Visual analogue (VAS) or Likert scales subjective effects in 19 occasional-to-moderate cannabis smokers following controlled vaporized cannabis administration with and without oral alcohol.

Parameter	b	SE_b	df	t	p[a]	95% Confidence Interval of b	
						Lower Bound	Upper Bound
VAS Anxious							
Intercept	6.777	1.294	47.2	5.2	**<0.001**	4.174	9.380
Blood THC	0.307	0.076	19.8	4.0	**0.001**	0.147	0.466
BrAC			630.5	0.2	0.826		
Time	−0.615	0.156	634.0	−4.0	**<0.001**	−0.921	−0.309
THC*BrAC	−4.204	1.090	639.0	−3.9	**<0.001**	−6.344	−2.065
Time*THC			489.0	1.7	0.085		
Time*BrAC			632.3	0.6	0.525		
Time*THC*BrAC			628.9	1.5	0.125		
Subject Variance in Intercepts (THC)	17.188	6.483			**0.008**	8.206	36.000
Subject variance in Slopes (THC)	0.086	0.035			**0.014**	0.039	0.190
ARH1 rho (slope-intercept covariance)					0.316		
VAS Good Drug Effect							
Intercept	20.542	2.942	27.2	7.0	**<0.001**	14.507	26.578
Blood THC	0.488	0.088	27.2	5.5	**<0.001**	0.307	0.668
BrAC	249.443	46.260	637.8	5.4	**<0.001**	158.603	340.283
Time	−3.150	0.251	643.0	−12.6	**<0.001**	−3.643	−2.658
THC*BrAC	−8.023	1.755	649.1	−4.6	**<0.001**	−11.470	−4.577
Time*THC	0.764	0.105	624.7	7.3	**<0.001**	0.558	0.971
Time*BrAC			640.0	−1.8	0.079		
Time*THC*BrAC	12.821	5.427	632.8	2.4	**0.018**	2.164	23.478
Subject Variance in Intercepts (THC)	126.563	44.553			**0.005**	63.485	252.318
Subject variance in Slopes (THC)	0.085	0.038			**0.024**	0.036	0.203

Parameter	b	SE_b	df	t	p[a]	95% Confidence Interval of b	
						Lower Bound	Upper Bound
ARH1 rho (slope-intercept covariance)	0.276	0.250			0.269	−0.242	0.672
VAS High							
Intercept	21.541	3.016	27.3	7.1	**<0.001**	15.356	27.726
Blood THC	0.552	0.091	24.5	6.1	**<0.001**	0.364	0.740
BrAC	119.404	48.271	639.8	2.5	**0.014**	24.614	214.193
Time	−3.394	0.262	645.9	−13.0	**<0.001**	−3.908	−2.879
THC*BrAC	−7.440	1.823	652.2	−4.1	**<0.001**	−11.020	−3.861
Time*THC	0.829	0.108	558.3	7.7	**<0.001**	0.617	1.042
Time*BrAC			642.5	−0.9	0.375		
Time*THC*BrAC	22.343	5.665	633.4	3.9	**<0.001**	11.220	33.467
Subject Variance in Intercepts (THC)	131.518	46.704			**0.005**	65.570	263.792
Subject variance in Slopes (THC)	0.093	0.043			**0.029**	0.038	0.229
ARH1 rho (slope-intercept covariance)	0.588	0.190			**0.002**	0.105	0.847
VAS Restless							
Intercept	11.466	2.266	36.6	5.1	**<0.001**	6.873	16.059
Blood THC	0.156	0.064	25.4	2.4	**0.022**	0.024	0.288
BrAC			635.9	0.1	0.903		
Time			643.2	−0.2	0.860		
THC*BrAC			648.3	−1.5	0.136		
Time*THC			593.6	0.8	0.436		
Time*BrAC			638.2	−0.1	0.952		
Time*THC*BrAC			623.8	0.8	0.439		
Subject Variance in Intercepts (THC)	63.440	22.696			**0.005**	31.467	127.903
Subject variance in Slopes (THC)					0.146		
ARH1 rho (slope-intercept covariance)					0.549		
VAS Sedated							
Intercept	17.942	2.893	28.9	6.2	**<0.001**	12.023	23.860
Blood THC			15.9	0.2	0.879		

Parameter	b	SE_b	df	t	p[a]	95% Confidence Interval of b	
						Lower Bound	Upper Bound
BrAC			632.9	0.0	0.984		
Time	−1.444	0.253	639.0	−5.7	**<0.001**	−1.942	−0.947
THC*BrAC			647.7	−0.4	0.701		
Time*THC			593.0	1.6	0.119		
Time*BrAC			634.8	1.3	0.186		
Time*THC*BrAC			627.4	0.1	0.941		
Subject Variance in Intercepts (THC)	120.808	41.818			**0.004**	61.298	238.091
Subject variance in Slopes (THC)	0.149	0.074			**0.043**	0.057	0.392
ARH1 rho (slope-intercept covariance)	−0.749	0.118			**<0.001**	−0.905	−0.417
VAS Stimulated							
Intercept	21.682	2.838	27.1	7.6	**<0.001**	15.860	27.503
Blood THC	0.297	0.080	19.2	3.7	**0.001**	0.130	0.464
BrAC	168.759	43.163	633.6	3.9	**<0.001**	84.000	253.518
Time	−2.827	0.232	645.0	−12.2	**<0.001**	−3.284	−2.371
THC*BrAC	−3.620	1.624	652.8	−2.2	**0.026**	−6.809	−0.431
Time*THC	0.568	0.097	611.4	5.8	**<0.001**	0.377	0.759
Time*BrAC	−60.558	23.436	637.7	−2.6	**0.010**	−106.58	−14.536
Time*THC*BrAC			628.8	1.5	0.133		
Subject Variance in Intercepts (THC)	120.357	41.508			**0.004**	61.223	236.608
Subject variance in Slopes (THC)	0.069	0.037			0.060	0.024	0.196
ARH1 rho (slope-intercept covariance)	0.469	0.214			**0.028**	−0.028	0.780
VAS Stoned							
Intercept	19.446	2.790	28.8	7.0	**<0.001**	13.737	25.154
Blood THC	0.398	0.109	18.1	3.7	**0.002**	0.170	0.627
BrAC			630.2	1.2	0.236		
Time	−2.875	0.254	634.7	−11.3	**<0.001**	−3.374	−2.375
THC*BrAC	−5.502	1.780	640.5	−3.1	**0.002**	−8.997	−2.007
Time*THC	0.687	0.107	634.4	6.4	**<0.001**	0.477	0.896

Parameter	b	SE_b	df	t	p[a]	95% Confidence Interval of b	
						Lower Bound	Upper Bound
Time*BrAC			632.1	−0.7	0.489		
Time*THC*BrAC	19.712	5.496	625.9	3.6	**<0.001**	8.919	30.505
Subject Variance in Intercepts (THC)	109.037	38.954			**0.005**	54.135	219.620
Subject variance in Slopes (THC)	0.159	0.073			**0.030**	0.065	0.392
ARH1 rho (slope-intercept covariance)					0.631		
Likert Difficulty Concentrating							
Intercept	0.554	0.111	27.3	5.0	**<0.001**	0.327	0.781
Blood THC			21.8	1.9	0.077		
BrAC	5.151	1.672	645.3	3.1	**0.002**	1.868	8.434
Time	−0.062	0.009	652.2	−6.9	**<0.001**	−0.080	−0.044
THC*BrAC			657.5	0.4	0.658		
Time*THC	0.012	0.004	441.4	3.2	**0.001**	0.005	0.019
Time*BrAC			648.6	−0.9	0.390		
Time*THC*BrAC			638.0	0.5	0.611		
Subject Variance in Intercepts (THC)	0.183	0.063			**0.004**	0.093	0.358
Subject variance in Slopes (THC)	0.000	0.000			**0.019**	0.000	0.000
ARH1 rho (slope-intercept covariance)	0.787	0.130			**<0.001**	0.373	0.940
Likert Altered Sense of Time							
Intercept	0.406	0.106	29.6	3.8	**0.001**	0.190	0.623
Blood THC	0.010	0.004	18.5	2.6	**0.018**	0.002	0.018
BrAC			652.8	1.2	0.227		
Time	−0.059	0.009	656.0	−6.3	**<0.001**	−0.078	−0.041
THC*BrAC			603.0	−0.2	0.806		
Time*THC	0.013	0.003	83.3	3.7	**<0.001**	0.006	0.020
Time*BrAC			654.0	0.9	0.386		
Time*THC*BrAC			645.5	0.1	0.917		
Subject Variance in Intercepts (THC)	0.159	0.055			**0.004**	0.080	0.314
Subject variance in Slopes (THC)	0.000	0.000			**0.021**	0.000	0.000

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Parameter	b	SE_b	df	t	p[a]	95% Confidence Interval of b	
						Lower Bound	Upper Bound
ARH1 rho (slope-intercept covariance)	0.987	0.047			**<0.001**	−0.807	1.000
Likert Slowed/Slurred Speech							
Intercept	0.163	0.071	32.4	2.3	**0.030**	0.017	0.308
Blood THC	0.008	0.003	20.2	2.7	**0.015**	0.002	0.014
BrAC	3.774	1.280	647.3	2.9	**0.003**	1.261	6.287
Time	−0.028	0.007	652.8	−4.1	**<0.001**	−0.042	−0.015
THC*BrAC	−0.095	0.048	650.5	−2.0	**0.049**	−0.189	−0.001
Time*THC	0.009	0.003	210.0	3.6	**<0.001**	0.004	0.015
Time*BrAC			649.9	0.1	0.903		
Time*THC*BrAC			641.5	1.2	0.228		
Subject Variance in Intercepts (THC)	0.068	0.024			**0.005**	0.034	0.136
Subject variance in Slopes (THC)	0.000	0.000			**0.015**	0.000	0.000
ARH1 rho (slope-intercept covariance)	0.912	0.075			**<0.001**	0.585	0.984
Likert Body Feels Sluggish/Heavy							
Intercept	0.600	0.101	34.5	6.0	**<0.001**	0.396	0.805
Blood THC			28.8	1.6	0.115		
BrAC	4.568	1.936	645.0	2.4	**0.019**	0.767	8.369
Time	−0.066	0.010	651.1	−6.3	**<0.001**	−0.087	−0.046
THC*BrAC			658.3	0.0	0.965		
Time*THC	0.015	0.004	558.1	3.6	**<0.001**	0.007	0.024
Time*BrAC			647.6	0.4	0.691		
Time*THC*BrAC			638.7	0.0	0.993		
Subject Variance in Intercepts (THC)	0.127	0.046			**0.006**	0.062	0.259
Subject variance in Slopes (THC)	0.000	0.000			**0.038**	0.000	0.000
ARH1 rho (slope-intercept covariance)					0.322		
Likert Feel Thirsty							
Intercept	0.728	0.166	64.2	4.4	**<0.001**	0.396	1.059
Blood THC			45.3	−0.1	0.949		

Parameter	b	SE_b	df	t	p[a]	95% Confidence Interval of b	
						Lower Bound	Upper Bound
Time*BrAC			649.1	1.4	0.157		
Time*THC*BrAC	1.308	0.301	626.2	4.3	**<0.001**	0.716	1.900
Subject Variance in Intercepts (THC)	0.211	0.079			**0.007**	0.102	0.438
Subject variance in Slopes (THC)					0.212		
ARH1 rho (slope-intercept covariance)					0.147		

Data from 19 healthy, adult cannabis smokers who participated in all dosing sessions. Subjective effects were measured by 100 mm VAS or 5-point Likert scales with choices 0≡"none", 1≡"slight", 2≡"mild", 3≡"moderate", 4≡"severe" after drinking placebo or active alcohol (calculated to produce approximate peak 0.065% BrAC) and inhaling placebo, 2.9% THC, or 6.7% THC vaporized cannabis (500 mg, Volcano® Medic vaporizer).

Linear mixed model results; b is parameter (coefficient) estimate for each factor (negative b indicates the parameter decreases the subjective effect; positive b indicates the parameter increases the overall effect).

Overall equation:

$$\begin{aligned}[\text{Subjective Effect Result}] = \text{Intercept} &+ b_{\text{Blood THC}} * [\text{THC}]_{\text{blood}} \\ &+ b_{\text{BrAC}} * \text{BrAC} \\ &+ b_{\text{Time}} * \text{post- dose time} \\ &+ b_{\text{THC*BrAC}} * [\text{THC}]_{\text{blood}} * \text{BrAC} \\ &+ b_{\text{Time*THC}} * \text{post- dose time} * [\text{THC}]_{\text{blood}} \\ &+ b_{\text{Time*BrAC}} * \text{post- dose time} * \text{BrAC} \\ &+ b_{\text{Time*THC*BrAC}} * \text{post- dose time} * [\text{THC}]_{\text{blood}} * \text{BrAC}\end{aligned}$$

[a]Values in **bold** are statistically significant (p<0.05); only significant predictors are considered in the final model.

Abbreviations: SE, standard error; df, degrees of freedom; VAS, 100mm visual-analogue scale; Likert, 5-point Likert scale; THC, Δ^9-tetrahydrocannabinol; BrAC, breath alcohol concentration.