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Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration

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ABSTRACT

Background: Although smoking is the most common cannabis administration route, vaporization and consumption of cannabis edibles are common. Few studies directly compare cannabis' subjective and physiological effects following multiple administration routes.

Methods: Subjective and physiological effects, and expired carbon monoxide (CO) were evaluated in frequent and occasional cannabis users following placebo (0.001% Δ^9-tetrahydrocannabinol [THC]), smoked, vaporized, and oral cannabis (6.9% THC, ~54 mg).

Results: Participants' subjective ratings were significantly elevated compared to placebo after smoking and vaporization, while only occasional smokers' ratings were significantly elevated compared to placebo after oral dosing. Frequent smokers' maximum ratings were significantly different between inhaled and oral routes, while no differences in occasional smokers' maximum ratings between active routes were observed. Additionally, heart rate increases above baseline 0.5 h after smoking (mean 12.2 bpm) and vaporization (10.7 bpm), and at 1.5 h (13.0 bpm) and 3 h (10.2 bpm) after oral dosing were significantly greater than changes after placebo, with no differences between frequent and occasional smokers. Finally, smoking produced significantly increased expired CO concentrations 0.25–6 h post-dose compared to vaporization.

Conclusions: All participants had significant elevations in subjective effects after smoking and vaporization, but only occasional smokers after oral cannabis, indicating partial tolerance to subjective effects with frequent exposure. There were no differences in occasional smokers' maximum subjective ratings across the three active administration routes. Vaporized cannabis is an attractive alternative for medicinal administrations over smoking or oral routes; effects occur quickly and doses can be titrated with minimal CO exposure. These results have strong implications for safety and abuse liability assessments.

1. Introduction

While smoking is the most common cannabis administration route, vaporization and consumption of cannabis edibles are common. In a survey of U.S. adults aged ≥18 years who had ever consumed cannabis, 29.8% reported consuming cannabis via "edibles or drinks", and 9.9% by "vaporizer or other electronic device" (Schauer et al., 2016). Additionally, 22.4% and 18.8% reported ever utilizing 2 and ≥3 ways to administer cannabis, respectively, indicating the importance of characterizing cannabis' effects after multiple administration routes.

Desired subjective effects are achieved after consumption of cannabis-containing foodstuffs. After five experienced cannabis smokers (all with 10 years use history) ingested brownies containing the equivalent of zero, one (~22.4 mg THC), and two (~44.8 mg THC) 2.8% THC cigarettes, significantly greater ratings on Feel Drug and Liking scales after the two-cigarette dose were observed compared to the one-cigarette dose (Cone et al., 1988); onset of effects was slow and variable, with peak responses occurring 2.5–3.5 post-dose.

Comparisons of subjective and physiological effects following smoked and oral cannabis were previously conducted. Following THC

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administrations via intravenous (5 mg THC injected over 2 min), smoked (19 mg THC), and oral (20 mg THC) routes, similar ratings of "high" were observed following all administrations, despite lower plasma THC concentrations after oral dosing, in participants with varied cannabis use histories (Ohlsson et al., 1980). In another investigation, active smoked (18.4–32.4 mg THC) cannabis or oral encapsulated (2.5–10 mg) THC produced significant increases in overall drug effect, peak high, and drug liking compared to placebo in participants that self-administered cannabis 1–3x/week (Chait and Zacny, 1992); ratings between smoked and oral routes were similar, but were not directly compared. Smoked and oral cannabis each significantly increased heart rate compared to placebo, with mean increases 18 and 8–9 bpm, respectively, relative to placebo (Chait and Zacny, 1992). Similarly, active oral and smoked cannabis (8.4–16.9 mg THC for both) produced significant increases in ratings for drug "feel", "high", and "want" compared to placebos, but effects following smoking were larger in participants that administered cannabis or hashish at least once in the prior 2 months (Wachtel et al., 2002); however, as with the previous study, ratings after oral and smoked routes were not directly compared. Another study administered either oral (20 mg THC 4x/daily) or smoked THC (3.1% THC, cigarette weights not provided) four times daily for 3 consecutive days to participants that averaged smoking 6.3 ± 5.6 cannabis cigarettes/day and ratings for "high", "mellow", and "good drug effect" following smoking were significantly greater than after oral administration (Hart et al., 2002); the authors concluded, though, that although subjective effects were slightly more pronounced after smoking for some measures, smoked and oral routes produced similar effects.

Smoked cannabis exposes users to harmful combustion by-products, including carbon monoxide (CO) (Hazekamp et al., 2006). CO is not released during edible consumption. However, the low bioavailability and slow, erratic absorption produced by oral cannabis (Ohlsson et al., 1980) suggests an alternative administration route could be useful for medicinal purposes. One such alternate route is vaporization. In a pilot study comparing smoked and vaporized cannabis in participants that smoked 3–10 cannabis cigarettes in the prior 30 days, plasma THC area under the curve (AUC) up to 6 h post-dose and ratings of "high" were not significantly different between smoking and vaporization at any dose, while exhaled CO concentrations were significantly greater following smoking at all cannabis potencies (Abrams et al., 2007).

The effectiveness of vaporized low (2.9% THC) and high (6.7% THC) cannabis doses in producing increased subjective ratings was demonstrated in occasional-to-moderate cannabis smokers (Hartman et al., 2016); blood THC concentrations were significantly associated with participants' ratings of "anxious", "good drug effect", "high", "restless", "stimulated", and "stoned", with subjective effects persisting for 3.3–4.3 h post-dose. We also previously characterized cannabinoid blood pharmacokinetics following smoked, vaporized, and oral cannabis administrations (Newmeyer et al., 2016); frequent smokers' maximum THC concentrations (C_{max}) were significantly greater after smoking compared to vaporization, whereas occasional smokers' THC C_{max} were not different between the inhaled routes. In all participants, inhaled cannabis produced significantly greater THC C_{max} than oral cannabis. Additionally, frequent smokers' observed *and* baseline-adjusted THC C_{max} after smoking and vaporization were significantly greater than THC C_{max} in occasional smokers.

There are few studies directly comparing subjective and physiological effects, and expired CO concentrations following multiple cannabis administration routes, and none investigated differences between frequent and occasional cannabis smokers. We present a novel, placebo-controlled investigation in which subjective and objective effects were evaluated following controlled smoked, vaporized, and oral cannabis administrations to frequent and occasional cannabis smokers with a within-subject study design.

2. Materials and methods

2.1. Participants

Adults 18–50 years old provided written, informed consent to participate in this National Institute on Drug Abuse (NIDA) Institutional Review Board-, Food and Drug Administration-, and Drug Enforcement Administration-approved study (Newmeyer et al., 2016; Swortwood et al., 2016). Inclusion criteria were average self-reported cannabis intake frequency ≥2x/month but < 3x/week (occasional smokers), or ≥5x/week (frequent smokers) for the previous three months, and a positive urine cannabinoid screen (frequent smokers only). All participants underwent extensive medical and psychological evaluations prior to study inclusion.

2.2. Study design

This was a randomized, double-blind, placebo-controlled, crossover, double-dummy study. Participants entered the secure research unit ~19 h before dosing to preclude acute intoxication. Cannabis cigarettes were supplied from the NIDA Research Technology Branch. Active (0.734 ± 0.05 g) and placebo (0.713 ± 0.05 g) cigarettes contained 6.9 ± 0.95% (~50.6 mg) and 0.001 ± 0.000% THC, respectively. Throughout 4 dosing sessions, participants were administered one active or placebo cannabis-containing brownie followed by one active or placebo cigarette or one active or placebo vaporized ground cannabis dose (210° C, Volcano® Medic, Storz and Bickel). Sessions with active cannabis smoking or vaporization included placebo oral doses. The active oral dosing session included either placebo smoked or vaporized cannabis, randomly assigned per participant. The double placebo session contained placebo oral dosing and either placebo smoked or vaporized cannabis, whichever was not administered in the active oral dosing session; therefore, smoked and vaporized cannabis were administered in 2 sessions each (one active and one placebo). An unblinded pharmacist arranged the dosing schedule and prepared and delivered doses to preserve staff blinding. Only one active dose was administered per session. Dosing sessions were conducted under controlled conditions (participants resided on a closed residential unit and were dosed with a known potency of THC and under staff observation); participants consumed the oral, smoked, or vaporized dose *ad libitum* over 10 min. Frequent smokers remained on the unit 72 h post-dose and left the unit for ≥72 h between sessions to minimize withdrawal symptoms. Occasional smokers remained on the unit 54 h post-dose, but could stay or leave between sessions if dosing was no more frequent than self-reported intake.

Oral cannabis doses were prepared per Duncan Hines® Double Fudge cake-like brownie instructions. The contents of an active or placebo cigarette were ground, baked for 30 min at 121° C in aluminum foil, and mixed into equal portions of batter in a muffin tin. Following baking, individual doses were stored frozen, but allowed to thaw refrigerated overnight before dosing.

Participants were permitted to smoke tobacco cigarettes during breaks in study procedures.

2.3. Subjective measures

Visual-analog scales (VAS, 100 mm anchored by "Not at All" and "Most Ever") were presented at baseline (-1.5 h) and 0.25, 0.50, 1.5, 2.5, 3.5, and 5 h after smoking/inhalation initiation; participants marked their rating for "Good Drug Effect", "High", "Stoned", "Stimulated", "Sedated", "Anxious", "Depressed", "Irritable", "Restless", "Craving for Marijuana", "Angry/Aggressive", "Short of Breath", "Hungry", "Willing to Drive − Nonemergency", and "Willing to Drive − Emergency". VAS for "Anxious", "Depressed", "Irritable", "Restless", "Craving for Marijuana", and "Angry/Aggressive" were also presented at 24 and 48 h for all participants and at 72 h for frequent

Table 1
Demographic data and cannabis smoking histories for 11 frequent and 9 occasional smokers.

Participant	Sex	Age (years)	Race and Ethnicity[a]	BMI (kg/m^2)	Age at first use[b]	Lifetime Years Smoked[b]	Cannabis Intake Frequency[b]	Time between last use and admission[c]	Number of days used in last 14[c]	Average joint equivalents per smoking occasion[c]
Frequent Smokers										
A	M	21	AA	26.5	16	5	Daily	17.2 h	14	5
B	M	22	AA	31.0	15	7	Daily	19.3 h	10	4
C	M	19	AA	19.8	13	6	Daily	18.7 h	14	4
D	F	23	AA	31.9	13	10	Daily	7.9 h	14	10
E	M	38	AA	32.2	12	26	Daily	2.4 h	14	15
F	F	29	AA	31.0	11	18	Daily	1.9 h	14	20
G	M	38	AA	22.0	16	22	Daily	2.1 h	14	7
H	M	34	AA	23.0	14	20	5x/week	239.7 h[d]	2[d]	2[d]
I	M	21	AA	25.0	11	10	Daily	0.7 h	14	5
J	M	25	AA	19.0	13	12	5x/week	5.8 h	14	2
K	M	31	AA	16.8	15	16	2–3x/week[e]	5.1 h[e]	4[e]	2.5[e]
Mean		27.4		25.3	13.5*	13.9		8.4 h	13.6*	8.0*
SD		6.9		5.6	1.8	6.9		7.8 h	1.3	6.0
Median		25.3		25.0	13.0	12.3		5.8 h	14.0	5.0
Occasional Smokers										
L	M	24	AA	36.3	17	7	2x/month	1.4 days	3	2
M	M	21	AA	23.0	13	8	2x/week	0.7 days	4	2
N	M	25	W	24.2	21	4	2x/week	13.0 days	1	3
O	M	40	W	28.3	18	22	2x/week	30.7 days	0	2
P	F	46	AA	31.0	26	20	2x/week	0.4 days	4	4
Q	M	33	AA	30.7	16	17	2x/month	22.8 days	0	3
R	F	22	W	22.0	16	6	2x/week	1.7 days	4	1
S	F	22	W	23.0	14	8	2x/week	1.1 days	10	2
T	M	31	W	21.7	22	9	1–2x/week	1.8 days	2	2
Mean		29.4		26.7	18.1*	11.3		8.2 days	3.1*	2.3*
SD		8.6		5.1	4.2	6.3		11.4 days	3.1	0.9
Median		24.9		24.2	17.0	8.5		1.7 days	3.0	2.0

[a] AA, African American; W, white.
[b] Data collected during screening.
[c] Data collected on admission to Session 1. For "joint equivalents", 1 blunt was defined as equal to 3 joints. An "occasion" is any day a participant smokes.
[d] Self-reported data on admission inconsistent with data received at screening. Data excluded from statistics.
[e] Self-reported data inconsistent with biological sample concentrations. Data excluded from statistics.
* Significant difference between groups ($p < 0.05$).

smokers only to assess potential withdrawal. Blood specimens were collected at the same time points for modelling subjective ratings to cannabinoid concentrations.

2.4. Physiological measures

Heart rate, systolic/diastolic blood pressure, and respiration rate were measured at baseline (−0.67 h) and 0.50, 1.5, and 3 h after smoking/inhalation initiation while participants were seated. Blood specimens were collected at the same time points for modelling physiologic responses to cannabinoid concentrations.

2.5. Expired CO

Expired CO was measured with a BreathCO monitor (Vitalograph®, Lenexa, KS, USA) at baseline (−0.42 h) and 0.25, 1.5, 2, 3, 4, 5, 6, and 7 h after smoking/inhalation initiation. Participants were instructed to take two deep breaths, then inhale deeply a third time and hold for 10 s before exhaling completely into the monitor.

2.6. Data analysis

Differences in demographic data between smoking groups (i.e., between frequent and occasional smokers) were evaluated with *t*-tests (SPSS® version 20 for Windows, IMB, Armonk, NY). When analyzing differences in VAS ratings and physiological measures after active dosing sessions compared to placebo (double-dummy oral and inhaled session) across the entire time course, data from oral and inhaled routes were analyzed separately due to differences in cannabinoid blood pharmacokinetics (Newmeyer et al., 2016). In these analyses, differences were evaluated with repeated-measures ANOVA. For analyses comparing placebo, smoking, and vaporization, planned Helmert contrasts were considered only if a significant overall effect was observed; contrast 1 compared the placebo dose to the combined inhaled doses, contrast 2 compared smoking and vaporization. If a significant interaction was observed, pairwise comparisons were conducted − comparing each session pairwise at each time point − with a Bonferroni correction. Differences in participants' maximum VAS ratings and baseline-adjusted physiological measures after each session were analyzed via repeated-measures ANOVA with all sessions included. For significant overall effects, planned Helmert contrasts were: 1, comparing placebo to active doses; 2, comparing the oral route to inhaled routes; 3, comparing smoking to vaporization. For all ANOVA analyses, the Greenhous-Geisser correction was utilized for sphericity violations, and analyses were re-run with frequent and occasional smokers separated if a significant smoking group effect was observed. Additionally, ratings for "Craving for Marijuana", "Willing to Drive − Nonemergency", and "Willing to Drive − Emergency", and all physiological measures were evaluated as baseline-adjusted values due to variable, non-zero baseline values across dosing sessions. VAS for "Anxious", "Depressed", "Irritable", "Restless", "Craving for Marijuana", and "Angry/Aggressive" were evaluated with smoking groups separated *a priori* due to differences in time courses. For VAS items and physiological measures that demonstrated significant differences between active and placebo doses, blood cannabinoid concentrations were modeled to the data via linear mixed models (LMM); baseline data were excluded and data from inhaled and oral routes were analyzed separately. Blood cannabinoid concentrations, time, and smoking group were included as fixed or random effects to find the best fitting model. If a significant smoking group effect was observed, separate models

were built for frequent and occasional smokers. Additionally, participants' subjective ratings were plotted against blood cannabinoid concentrations to identify if the concentration-effect curve displayed a counterclockwise hysteresis (a delay between peak effects and peak blood concentrations). Finally, differences in participants' expired CO concentrations between active smoked and active vaporized sessions were evaluated with repeated-measures ANOVA as described above; data were analyzed as change from baseline. Participants that smoked nicotine cigarettes while on the unit were excluded from this analysis to remove confounding CO concentrations, resulting in 5 frequent and 6 occasional smokers for the analysis. In all analyses, statistical significance was attributed to a $p < 0.05$.

3. Results

3.1. Participants

Table 1 summarizes 11 frequent and 9 occasional cannabis smokers' demographic information (ages 19–46 y, 75% male, 75% African American). Participant K was originally recruited as an occasional cannabis smoker, but reclassified as a frequent smoker because baseline and post-dose THC and metabolite concentrations were consistent with published frequent smoker data (Desrosiers et al., 2014; Schwope et al., 2011); all other participants' cannabinoid pharmacokinetics were consistent with self-report. Participant H reported last use ~10 days prior to session 1 admission, despite self-reporting smoking 5x/week during screening; reported histories on subsequent sessions were consistent with screening. Occasional smokers began smoking at a significantly older age, smoked on a significantly fewer number of days out of the previous 14, and smoked significantly less per smoking occasion (any day smoking occurred). Mean (range) days discharged between sessions was 15 (0–75) days for frequent smokers and 8.4 (0–43) days for occasional smokers; frequent smokers' range includes 0 days because participant K was originally recruited as an occasional smoker.

3.2. Subjective measures

Ratings for "Sedated", "Anxious", "Depressed", "Irritable", "Restless", "Angry/Aggressive", "Short of Breath", and "Hungry" showed no significant effects (data not shown).

3.2.1. Duration of effects

Ratings for "Good Drug Effect", "High", "Stoned", and "Stimulated" after smoking, vaporization, and placebo sessions are shown in Fig. 1. Ratings on all four measures were significantly greater after smoking and vaporization than after placebo at the first post-dose time point (0.25 h); ratings remained significantly elevated after smoking up to 1.5–3.5 h post-dose while ratings remained significantly elevated after vaporization up to 0.25–1.5 h post-dose, depending on the VAS item. No significant differences in ratings between smoking and vaporizations were observed at any time point.

A significant effect between frequent and occasional smokers (smoking group effect) was observed for ratings of "Good Drug Effect", "High", and "Stoned" when comparing oral and placebo doses; Fig. 2 shows each smoking groups' ratings for these items. No significant effects were observed for frequent smokers' ratings on these items after oral dosing compared to placebo. Occasional smokers' ratings for "Good Drug Effect" and "High" were significantly greater following oral dosing compared to placebo 1.5–3.5 and 0.5–3.5 h post-dose, respectively; only an overall dose effect was observed for occasional smokers' ratings of "Stoned". Ratings for "Stimulated" (not shown) showed an overall dose effect with no significant smoking group effect.

Mean baseline-adjusted ratings for "Willingness to Drive" in either nonemergency or emergency situations showed no significant effects

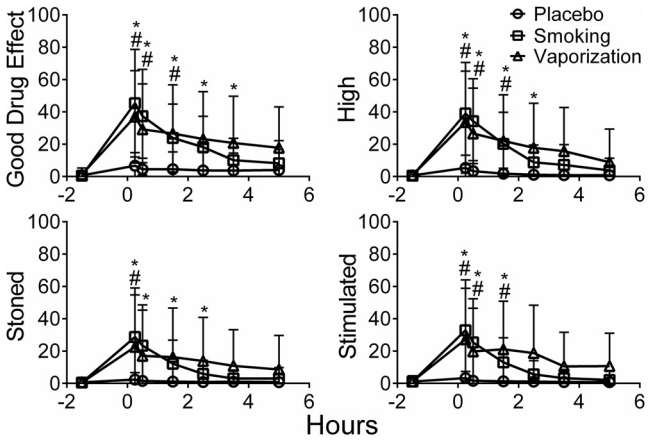

Fig. 1. Mean (± SD) subjective ratings for 11 frequent and 9 occasional smokers following placebo (0.001 ± 0.000% Δ^9-tetrahydrocannabinol [THC]) and smoked and vaporized (6.9 ± 0.95% [~50.6 mg] THC) cannabis. Data from all participants presented together because no significant smoking group effect was observed. * = significant difference between smoked and placebo doses, # = significant difference between vaporized and placebo doses.

when comparing among inhaled and placebo doses. When comparing oral and placebo doses, a significant smoking group effect was observed. Frequent smokers' "Willingness to Drive – Nonemergency" ratings were not significantly different between doses; occasional smokers, though, were less willing to drive from 1.5–3.5 h after oral dosing compared to placebo. Similarly, for "Willingness to Drive – Emergency", occasional smokers were less willing to drive at 1.5 and 3.5 h after oral dosing compared to placebo; however, an overall dose effect was observed for frequent smokers.

Mean baseline-adjusted ratings for "Craving for Marijuana" showed no significant effects when comparing oral dosing to placebo. Occasional smokers' ratings were not significantly different after inhaled and placebo cannabis. However, frequent smokers craved cannabis significantly less after smoking compared to placebo from 0.25–5 h after smoking initiation, whereas they craved cannabis significantly less only at 0.5 h after vaporization; additionally, ratings after smoking were significantly less than those after vaporization from 0.5-1.5 h after inhalation initiation.

3.2.2. Peak effects

Differences in maximum ratings among sessions were only observed for ratings of "Good Drug Effect", "High", "Stoned", and "Stimulated" (Table 2). Significant smoking group effects were observed for maximum "Good Drug Effect" and "Stoned" ratings. For both items, frequent smokers' maximum ratings were significantly greater following active cannabis compared to placebo, and maximum ratings after inhaled cannabis were significantly greater than after oral cannabis with no difference between smoking and vaporization. In contrast, occasional smokers' maximum ratings were significantly greater following active cannabis compared to placebo, but maximum ratings were not different between the three active routes. No significant smoking group effect was observed for maximum ratings of "High" or "Stimulated"; active cannabis produced significantly greater maximum ratings compared to placebo for both items.

3.2.3. Relationship to blood cannabinoid concentrations

Fig. 3 depicts mean blood concentration-effect curves for "Good Drug Effect", "High", "Stoned", and "Stimulated". Following smoking and vaporization, counter-clockwise hysteresis was observed for both frequent and occasional smokers, with occasional smokers' curves shifted to the left, indicating lower blood cannabinoid concentrations. However, ratings for frequent and occasional smokers were comparable despite differences in blood cannabinoid concentrations. Ratings fol-

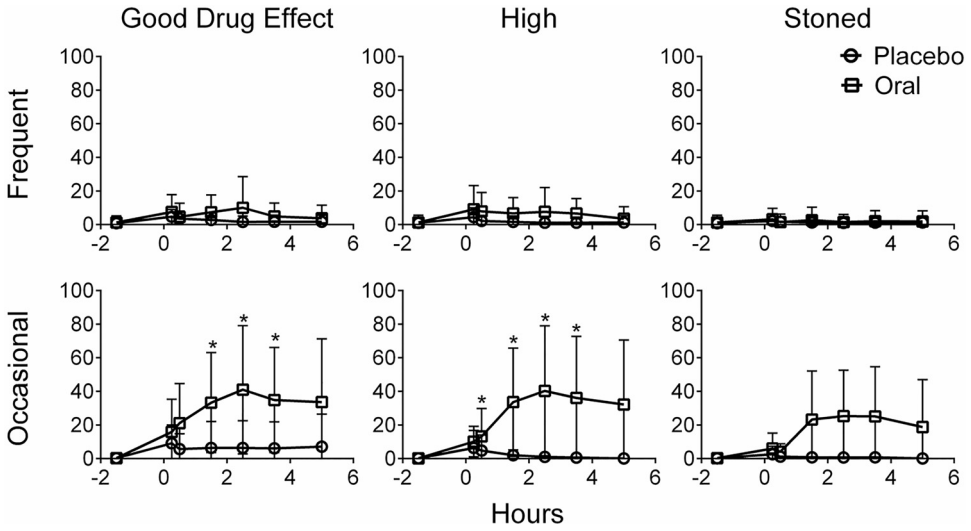

Fig. 2. Mean (± SD) subjective ratings for 11 frequent and 9 occasional smokers following placebo (0.001 ± 0.000% Δ^9-tetrahydrocannabinol [THC]) and oral (6.9 ± 0.95% [~50.6 mg] THC) cannabis. * = significant difference between oral and placebo doses.

lowing oral dosing were plotted against either THC or 11-OH-THC concentrations. Hysteresis was not observed in either case after oral dosing. Despite blood concentrations being lower in occasional as compared to frequent cannabis users, their subjective ratings after oral dosing were larger than those for frequent smokers'.

Table 3 summarizes linear mixed modeling results relating blood cannabinoid concentrations and time to participants' subjective ratings. Following inhaled administrations, blood THC concentrations were positively related to ratings of "Good Drug Effect", "High", "Stoned", and "Stimulated", and inversely related to "Craving for Marijuana"; time was inversely associated with ratings of "Good Drug Effect", "High", "Stoned", and "Stimulated". Following oral administration in occasional smokers, THC and 11-OH-THC were related to feelings of "Good Drug Effect", and only THC was related to feelings of "High". Time was never a significant covariate following oral administration.

3.3. Physiological measures

No significant effects of route of administration, time, or smoking history on systolic/diastolic blood pressure or respiration rate were observed. For heart rate, a significant dose*time interaction was observed for inhaled doses compared to placebo and oral dosing compared to placebo, with no significant smoking group effect. Post-hoc pairwise comparisons revealed mean (S.E.) increases in heart rate above baseline at 0.5 h after initiation of smoking and vaporization were 12.2 (3.3) and 10.7 (3.0) bpm greater, respectively, than changes observed after placebo; heart rate increases above baseline at 1.5 and 3 h after oral administration were 13.0 (2.3) and 10.2 (2.6) bpm greater, respectively, than changes observed after placebo. Mean (SD) maximum heart rate increases compared to baseline were 2.7 (8.9), 11.9 (10.2), 11.7 (7.3), and 12.0 (6.9) bpm after placebo, smoking, vaporization, and oral administrations respectively; post-hoc contrasts revealed active cannabis produced significant heart rate increases compared to placebo, but increases were not significantly different among active routes.

Table 4 summarizes linear mixed modeling results relating blood THC concentrations and heart rate following inhaled and oral doses. Significant smoking group effects were observed for inhaled and oral routes, so separate models were built. Following inhaled cannabis, increasing blood THC concentrations were associated with heart rate increases in both frequent (b = 0.655, 95% CI 0.442–0.867) and occasional (b = 2.627, 1.859–3.369) smokers, but after oral administration, THC was only associated with occasional smokers' heart rate (b = 1.884, 1.019–2.749).

Table 2
Mean (SD) maximum ratings following administration of placebo, oral, smoked, and vaporized cannabis (6.9% THC [~50.6 mg]) to 11 frequent and 9 occasional cannabis smokers. Repeated-measures ANOVA F-statistic and p-value for overall effect, and planned Helmert contrasts are presented (contrast 1 evaluated the difference between the variance from placebo and the combined variance from active doses, contrast 2 evaluated the difference between the variance from the oral route and the combined variance from the smoking and vaporization routes, and contrast 3 evaluated the difference between variances from the smoking and vaporization routes). Separate data are presented for frequent and occasional smokers' ratings of "Good Drug Effect" and "Stoned" due to significant group effects. Bolded p-values denote significance.

	Placebo	Oral	Smoking	Vaporization	Overall F	Overall p	Placebo vs Active		Oral vs Inhaled		Smoking vs Vaporization	
							F	p	F	p	F	p
Good Drug Effect – Frequent	5.9 (4.9)	13.8 (18.3)	40.8 (32.3)	30.9 (29.9)	7.165	**0.001**	11.769	**0.006**	8.575	**0.015**	1.394	0.265
Good Drug Effect – Occasional	11.9 (17.5)	49.0 (35.1)	53.3 (34.0)	54.0 (30.9)	7.037	**0.001**	17.018	**0.003**	0.225	0.648	0.006	0.941
Stoned – Frequent	2.8 (5.1)	3.6 (7.6)	24.8 (26.1)	15.4 (28.8)	4.077	**0.034**	5.895	**0.036**	5.458	**0.042**	1.487	0.251
Stoned – Occasional	3.0 (5.0)	38.8 (32.5)	38.9 (35.6)	35.1 (36.8)	6.021	**0.003**	13.056	**0.007**	0.036	0.854	0.300	0.599
High	5.9 (8.0)	28.2 (32.2)	43.2 (30.2)	36.9 (32.5)	12.757	< **0.001**	37.816	< **0.001**	2.918	0.105	0.883	0.360
Stimulated	3.6 (4.5)	19.4 (28.7)	34.0 (31.8)	30.6 (33.8)	9.322	< **0.001**	19.279	< **0.001**	4.717	**0.043**	0.313	0.583

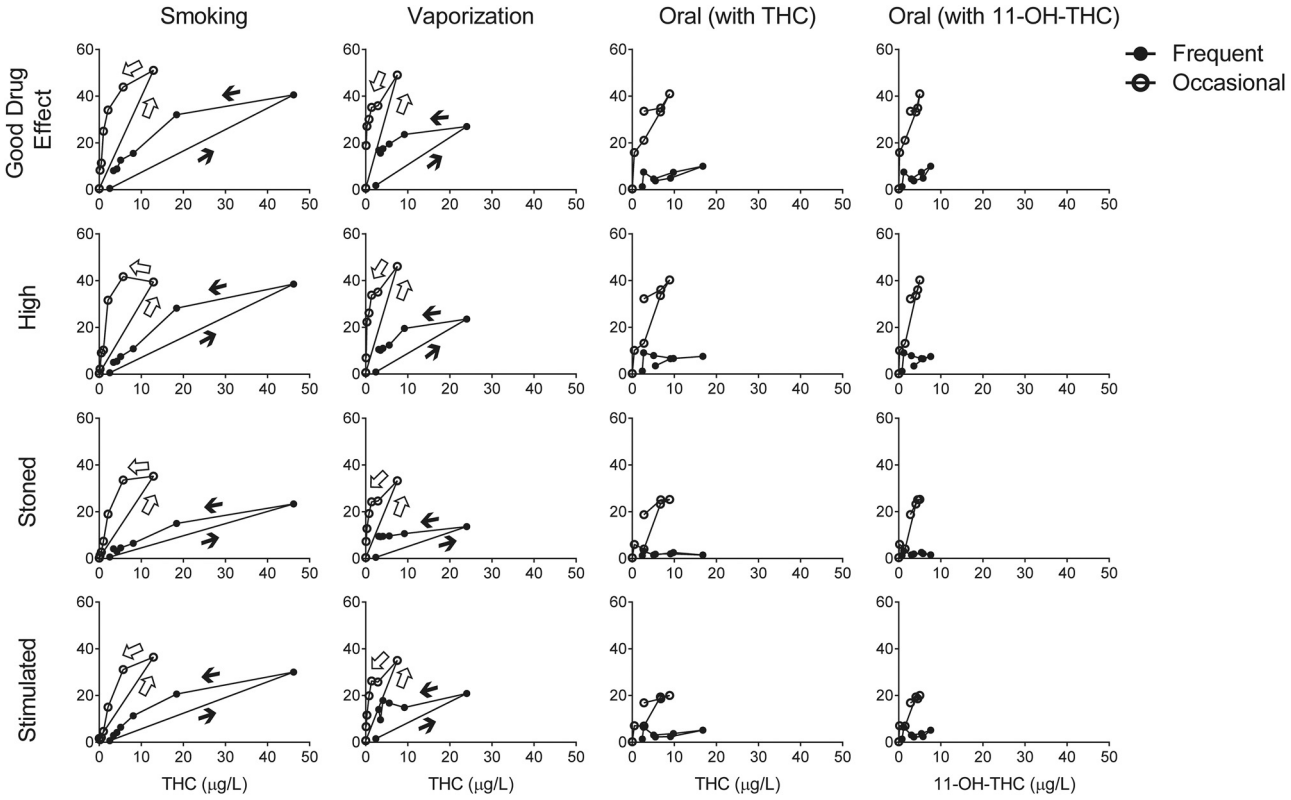

Fig. 3. Mean VAS score as a function of Δ^9-tetrahydrocannabinal (THC) or 11-hydroxy-THC (11-OH-THC, oral route only) in 11 frequent and 9 occasional smokers following smoked, vaporized, and oral (6.9 ± 0.95% [~50.6 mg] THC) cannabis. Arrows represent hysteresis progression over time.

3.4. Expired CO

Fig. 4 shows baseline-adjusted expired CO concentrations after smoking and vaporization. No significant smoking group effect was observed. Smoking produced significantly greater increases in expired CO concentrations compared to vaporization from 0.25–6 h post-dose.

4. Discussion

We sought to characterize and compare subjective and objective effects after smoked, vaporized, and oral cannabis in frequent and occasional cannabis smokers. Comparisons of subjective effects following controlled smoked and oral (Chait and Zacny, 1992; Hart et al., 2002; Ohlsson et al., 1980; Wachtel et al., 2002) or smoked and vaporized (Abrams et al., 2007) cannabis were previously performed. The only difference between smoking and vaporization observed here was in frequent smokers' ratings of "Craving for Marijuana" with lower ratings 0.5–1.5 h post-dose after smoking, consistent with frequent smokers achieving significantly higher blood THC concentrations after smoking compared to vaporization (Newmeyer et al., 2016). Smoking group differences were observed in maximum "Good Drug Effect" and "Stoned" ratings, with significantly higher ratings after inhaled routes compared to the oral route in frequent smokers. This is likely due to significantly greater blood THC concentrations following inhaled compared to oral cannabis (Newmeyer et al., 2016) due to degradative loss of THC in the acidic stomach environment, and to first-pass metabolism after oral dosing since frequent users cannot titrate (altering achieved blood THC concentrations to reach desired subjective effects) their oral dose as they can when smoking cannabis. The subjective effects reported by occasional smokers at low THC concentrations after oral administration were not reported by frequent users at similar concentrations, most likely attributed to development of partial tolerance (Figs. 2 and 3).

In contrast to frequent smokers, occasional smokers' maximum VAS ratings were not significantly different among the three active routes. This was evident in concentration-effect curves in which occasional smokers' peak ratings after inhaled administrations were approximately equal to those achieved after oral administration (Fig. 3). This observation is similar to another investigation among participants with varied cannabis use histories in which similar ratings of "high" were observed following intravenous, smoked, and oral routes, despite lower plasma THC concentrations after oral administration (Ohlsson et al., 1980). Significantly greater blood 11-OH-THC concentrations were observed after oral compared to inhaled cannabis for occasional smokers in the present study (Newmeyer et al., 2016); this was not observed in frequent smokers. 11-OH-THC is an equipotent psychoactive metabolite (Hollister, 1974; Lemberger et al., 1973) and may contribute to occasional smokers' subjective ratings. This is an important consideration as recreational cannabis legalization and ingestion of cannabis-containing edibles increases (Schauer et al., 2016).

Counter-clockwise hysteresis following smoking and vaporization was observed, in agreement with previous investigations (Barnett et al., 1982; Chiang and Barnett, 1984; Cocchetto et al., 1981; Cone and Huestis, 1993; Desrosiers et al., 2015; Hartman et al., 2016; Schwope et al., 2012). Peak subjective effects lag behind rapid increases in blood THC concentrations following inhalation due to longer THC equilibration time in the brain (Chiang and Barnett, 1984). After oral administration, hysteresis was not observed in frequent or occasional smokers when ratings were plotted against either blood THC or 11-OH-THC concentrations. This is likely because of the slow absorption and first-pass metabolism that occurs with oral administration, narrowing the lag time between peak subjective effects and peak blood concentrations. Concentration-effect curves also demonstrate that for inhaled routes, frequent and occasional smokers' ratings were similar despite significantly greater observed *and* baseline-adjusted blood THC concentrations in frequent smokers (Newmeyer et al., 2016), also demonstrating partial tolerance to subjective effects in frequent smokers.

Increased THC concentrations were significantly related to in-

Table 3
Effects of blood Δ^9-tetrahydrocannabinol (THC),11-hydroxy-THC (11-OH-THC) concentrations, and time on subjective ratings from 11 frequent and 9 occasional smokers following administration of smoked and vaporized (inhaled routes) and oral cannabis (6.9% THC [~50.6 mg]).

	b	SE	df	t	p-value	95% Confidence Interval for *b*	
						Lower bound	Upper Bound
Good Drug Effect							
Inhaled Routes							
Intercept	30.353	4.667	33.936	6.504	< **0.001**	20.869	39.838
THC	0.735	0.296	13.872	2.482	**0.027**	0.099	1.370
Time	−3.767	0.675	213.482	−5.579	< **0.001**	−5.098	−2.436
Subject variance in intercepts	193.570	118.466			0.102	58.331	642.362
Subject variance in THC concentrations	1.092	0.567			0.054	0.394	3.023
AR1 rho	0.705	0.074			< **0.001**	0.529	0.823
Oral route (Occasional only)							
Intercept	9.161	3.881	12.701	2.361	**0.035**	0.756	17.566
THC	0.914	0.279	10.849	3.272	**0.008**	0.298	1.529
11-OH-THC	4.480	0.510	9.219	8.782	< **0.001**	3.330	5.629
THC*11-OH-THC	−0.210	0.023	9.550	−9.074	< **0.001**	−0.262	−0.158
High							
Inhaled Routes							
Intercept	18.853	4.482	26.870	4.206	< **0.001**	9.655	28.052
THC	1.075	0.457	17.222	2.350	**0.031**	0.111	2.039
Time	−4.461	0.566	127.223	−7.877	< **0.001**	−5.582	−3.341
Time*THC	0.835	0.233	194.254	3.583	< **0.001**	0.375	1.295
Subject variance in intercepts	322.414	108.589			**0.003**	166.621	623.875
Subject variance in THC concentrations	3.468	1.344			**0.010**	1.623	7.411
AR1 rho	−0.435	0.067			< **0.001**	−0.558	−0.294
Oral Route (Occasional only)							
Intercept	5.623	2.045	9.201	2.750	**0.022**	1.013	10.233
THC	0.429	0.189	11.159	2.263	**0.045**	0.013	0.845
Stoned							
Inhaled Routes							
Intercept	9.535	3.787	25.041	2.518	**0.019**	1.736	17.334
THC	0.980	0.450	18.380	2.176	**0.043**	0.035	1.925
Time	−2.401	0.398	144.721	−6.031	< **0.001**	−3.188	−1.614
Time*THC	0.713	0.172	188.959	4.134	< **0.001**	0.373	1.053
Subject variance in intercepts	246.130	80.585			**0.002**	129.561	467.579
Subject variance in THC concentrations	3.594	1.280			**0.005**	1.788	7.225
AR1 rho	−0.589	0.056			< **0.001**	−0.688	−0.470
Stimulated							
Inhaled Routes							
Intercept	17.271	3.833	38.268	4.506	< **0.001**	9.514	25.028
THC	0.903	0.363	16.117	2.486	**0.024**	0.133	1.673
Time	−2.474	0.609	211.683	−4.062	< **0.001**	−3.675	−1.274
Subject variance in intercepts	110.194	77.059			0.153	27.984	433.914
Subject variance in THC concentrations	1.980	0.854			**0.020**	0.850	4.612
AR1 rho	0.684	0.076			< **0.001**	0.509	0.806
Craving for Marijuana							
Inhaled Routes (Frequent only)							
Intercept	32.967	6.787	11.260	4.857	< **0.001**	18.070	47.864
THC	−0.283	0.082	126.534	−3.433	**0.001**	−0.445	−0.120
Subject variance in intercepts	450.353	213.732			**0.035**	177.658	1141.623
AR1 rho	0.489	0.091			< **0.001**	0.291	0.646

Dosing session and time were set as within-subject repeated measures. Models for inhaled routes were built with an autoregressive (AR(1)) covariance structure, and models for the oral route were built with an unstructured covariance structure. Abbreviations: *b*, model parameter (coefficient); SE, standard error; df, degrees of freedom; t, t-statistic. Only significant terms were included in the final model.

creased subjective ratings following inhaled administrations. Although ratings for "Stoned" and "Stimulated" showed significant overall dosing session effects between oral and placebo cannabis, blood cannabinoid concentrations were not significantly related to ratings for these items after oral administration in any model, possibly because ratings were the lowest (mean 0.3–25.3 for "Stoned" and 0.2–20.0 for "Stimulated") among the subjective effects that showed significant effects after oral administration (0.3–41.0 for "Good Drug Effect" and 0.2–40.3 for "High"). Both THC and 11-OH-THC were significantly related to occasional smokers' "Good Drug Effect" ratings. In contrast, only THC concentrations were significantly related to occasional smokers' "High" ratings after oral administration. Intravenous 11-OH-THC administration was frequently referred to as a "rush" among some participants (Hollister, 1974). It is possible 11-OH-THC produces specific subjective effects, such that concentrations are related to certain effects and not others. Additional investigations in which THC and 11-OH-THC are administered separately while monitoring multiple subjective effects are needed to properly evaluate this hypothesis.

In other comparisons of smoked and oral cannabis, increases in heart rate were 0–80 (measured as early as 3 min post-dose) and 4–68 bpm (significant increases compared to placebo) among participants with varied cannabis use histories (Ohlsson et al., 1980), and 18 and 8–9 bpm among participants that administered cannabis 1–3x/week (Chait and Zacny, 1992), respectively. Additionally, following vaporized THC, average increase was 19 bpm (95% CI 13.2–25.5, measured immediately after dosing completion), with no changes in

Table 4
Effects of blood Δ^9-tetrahydrocannabinol (THC) concentrations on heart rate in 11 frequent and 9 occasional smokers following administration of smoked and vaporized (inhaled routes) and oral cannabis (6.9% THC [~50.6 mg]).

	b	SE	df	t	p-value	95% Confidence Interval for *b*	
						Lower bound	Upper Bound
Inhaled Routes							
Frequent smokers							
Intercept	66.494	2.052	18.933	32.405	< **0.001**	62.198	70.791
THC	0.655	0.106	45.025	6.195	< **0.001**	0.442	0.867
AR1 rho	0.611	0.010			< **0.001**	0.379	0.771
Occasional smokers							
Intercept	71.727	2.795	13.075	25.659	< **0.001**	65.691	77.762
THC	2.627	0.379	37.464	6.924	< **0.001**	1.859	3.369
AR1 rho	0.648	0.102			< **0.001**	0.404	0.805
Oral Route							
Frequent smokers							
Intercept	66.657	3.035	20.306	21.965	< **0.001**	60.333	72.982
THC	0.379	0.299	28.614	1.268	0.215	−0.233	0.991
AR1 rho	0.671	0.127			< **0.001**	0.344	0.853
Occasional smokers							
Intercept	69.691	1.980	19.372	35.205	< **0.001**	65.553	73.829
THC	1.884	0.422	26.952	4.469	< **0.001**	1.019	2.749
AR1 rho	0.119	0.206			0.564	−0.282	0.485

Dosing session and time were set as within-subject repeated measures. Abbreviations: *b*, model parameter (coefficient); SE, standard error; df, degrees of freedom; t, t-statistic. Only significant terms were included in the final model.

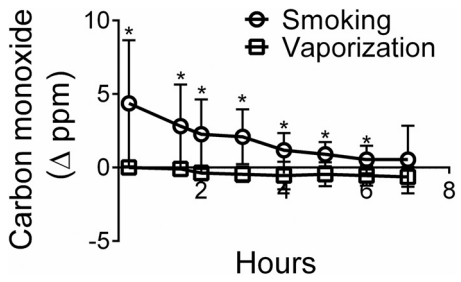

Fig. 4. Mean (± SD) baseline-adjusted expired carbon monoxide concentrations for 11 frequent and 9 occasional smokers following smoked and vaporized (6.9 ± 0.95% [~50.6 mg] Δ^9-tetrahydrocannabinol [THC]) cannabis. Data from all participants presented together because no significant smoking group effect was observed. * = significant difference between smoking and vaporization.

systolic/diastolic blood pressure among participants that smoked no more than once a week (Zuurman et al., 2008). Heart rate increases observed here after smoking and vaporization are smaller than those observed previously (Ohlsson et al., 1980; Zuurman et al., 2008), most likely due to a later first-measurement time (0.5 h post-dose) compared to < 5 min post-dose. Magnitudes of heart rate increases were not different between the three active routes, possibly due to the extra step taken during brownie preparation to maximize conversion of the precursor THC-carboxylic acid A to THC before baking. Smoking converts approximately 70% of the precursor to active THC (Dussey et al., 2005), documented by detection of the precursor in biological specimens following active or passive cannabis exposure (Auwärter et al., 2010; Jung et al., 2007; Moore et al., 2007; Moosmann et al., 2014; Raikos et al., 2014). Given that baking occurs at a lower temperature than smoking, we increased the conversion of the precursor to THC by including an additional step that baked the cannabis for extra time (based on personal communication with Dr. Ryan Vandrey who also conducted an edible cannabis study).

Smoking group differences in heart rate were not observed after any active administration in this cohort. After smoking a 6.8% THC cigarette, heart was elevated only at 0.5 h post-dose in frequent smokers (> 4 days/week) (Schwope et al., 2012). In contrast, though, occasional smokers (< 2x/week) demonstrated significant increases in heart rate from 1 to 3 h after smoking a 6.8% THC cigarette compared to baseline (significant time*group effect), whereas only a time effect was observed at 0.5 h post-dose (Desrosiers et al., 2015). Following six days of increasing oral THC doses (up to 120 mg) tolerance to the tachycardic effect of THC was not observed in nine frequent and four abstaining cannabis smokers (Gorelick et al., 2013); however, the authors note that a previous study showed cardiovascular tolerance that developed after 12 days of 180 mg daily oral THC among participants that smoked ≥2x/week (Jones et al., 1976), indicating that dose and exposure time may be factors in the development of cardiovascular tolerance. None of these investigations included a placebo dose for comparison. THC concentration increases were associated with larger increases in occasional smokers' heart rate than in frequent smokers' after inhaled and oral doses (Table 4), potentially demonstrating partial tolerance to this effect. Frequent smokers' significantly greater THC concentrations compared to occasional smokers after inhaled cannabis due to increased dose titration (Newmeyer et al., 2016) may have produced heart rate increases like those in occasional smokers, eliminating statistical differences between groups when only comparing measured heart rates.

The Institute of Medicine suggested that smoking is an inappropriate route for medical cannabis administration (Institute of Medicine, 1999), with CO among the toxic by-products smokers are exposed to. Elevated CO concentrations were associated with increased risk of ischemic heart disease, atherosclerosis, coronary heart disease, chronic obstructive pulmonary disease, and fetal damage (Frederiksen and Martin, 1979); mean (range) alveolar CO concentrations were 4.9 (2–8) ppm among non-smokers and 34.4 (6–90) ppm among smokers (Frederiksen and Martin, 1979). Cannabis smoking was associated with a nearly 5-fold greater increment in carboxyhemoglobin concentrations compared to tobacco smoking, likely due to significant differences in smoking topography including ~two-thirds larger puff volume, one-third greater inhalation depth, and 4-fold longer breath-hold time (Wu et al., 1988). Our results agree with another study demonstrating significantly decreased expired CO concentrations after vaporization compared to smoking in participants that smoked 3–10 cannabis cigarettes in the prior 30 days (Abrams et al., 2007). Vaporization offers an attractive alternative to inhaled cannabis administration, particularly for medicinal administration, producing similar effects to smoked cannabis while reducing exposure to toxic by-products.

Limitations of this investigation include the small study population (due to prolonged residence on the closed research unit to ensure no access to unauthorized drug self-administration), which may limit the statistical power when performing comparisons between occasional and frequent smoking groups. Additionally, all members of the frequent smoker group were African American, while occasional smokers were African American and White, which may account for some observed differences. The population also was predominantly male; larger male and female cohorts are needed to evaluate sex differences. Generalizability of results may be limited due to the minimal racial and gender diversity in the study population. Finally, subjective results may have been influenced by unrestricted access to tobacco smoking during breaks, although this avoided effects of potential tobacco withdrawal on subjective effects. Strengths of the study include the within-subject design; inclusion of smoked, vaporized, and oral administrations; comparisons of frequent and occasional smokers; conduct of the study on a closed research unit; quantification of blood cannabinoid concentrations and relating pharmacodynamic effects to these concentrations.

We demonstrated smoking and vaporization are effective at producing significant changes in participants' subjective ratings compared to placebo, while oral dosing produced significant increases in subjective ratings in occasional smokers only. These data are indicative of the development of partial tolerance to subjective effects in frequent

smokers. First pass-metabolism (reducing achieved blood THC concentrations) and the inability to titrate an oral dose produced no significant increases in frequent smokers' subjective ratings. We also demonstrated that all active cannabis administrations produced significant increases in heart rate. While smoking group differences were not observed in measured heart rates, blood THC concentrations were associated with greater increases in heart rate in occasional than in frequent smokers, potentially indicating development of partial tolerance in frequent smokers; however, the ability to titrate the inhaled cannabis, leading to significantly greater blood THC concentrations in frequent smokers, may have eliminated statistical differences between smoking groups when only comparing measured heart rates. Finally, expired CO was significantly increased following smoking compared to vaporization. These data highlight the importance of considering dose titration when conducting controlled administration studies or interpreting cannabinoid concentrations. Observation of partial tolerance to subjective or cardiovascular effects in frequent smokers after inhaled cannabis may be confounded by allowing participants to consume doses *ad libitum*. In contrast, administration of oral cannabis eliminates the ability to titrate, and tolerance can be more easily observed. Users should be warned against self-administering too high a dose too quickly to overcome this tolerance, which may lead to unintended adverse events. This is particularly concerning as cannabis-containing edibles become more prevalent; there is great uncertainty in the THC content of commercial edible products; 23% of tested products under-labeled THC content (Vandrey et al., 2015). Additionally, these data offer compelling evidence for the strength of vaporized cannabis over smoking or oral routes for medicinal administrations; effects occur quickly and doses can be titrated without exposure to CO. These results have strong implications for safety and abuse liability assessments by demonstrating how results may differ depending on study population, dose administration route, or how dosing is controlled.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Contributors

Dr. Huestis (principal investigator) was responsible for all aspects of the study and designed the protocol with Dr. Swortwood and Mr. Newmeyer. Dr. Swortwood and Mr. Newmeyer were responsible for data collection and review of study methods. Dr. Abulseoud was responsible for reviewing participant eligibility, and ensuring their safety during the study. Mr. Newmeyer was responsible for data analysis and drafting the manuscript. All authors contributed to and approved the final manuscript.

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