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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