



Original Investigation | Public Health

Dose-Dependent Effects of Cannabis Edibles on Simulated Driving Performance

A Randomized Clinical Trial

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Abstract

IMPORTANCE Use of cannabis edibles is increasing, yet little is known about the impact of edibles on driving, which is particularly important in the context of per se thresholds (commonly 2 or 5 ng/mL) used to enforce cannabis-impaired driving laws.

OBJECTIVE To determine whether driving simulator performance is dose-dependently impaired by commercially available edible cannabis.

DESIGN, SETTING, AND PARTICIPANTS This randomized, double-blind, placebo-controlled, crossover clinical trial was completed at a single-site tertiary care academic hospital in Toronto, Ontario, Canada, between September 2024 and April 2025. Participants were healthy adults aged 19 to 45 years endorsing at least weekly cannabis use and monthly use of cannabis edibles.

INTERVENTIONS Edible (oral) delta-9-tetrahydrocannabinol (THC) was administered to all participants in soft-chew gummies, 0 or 2 mg each, to achieve doses of 0, 2, 10, and 20 mg.

MAIN OUTCOMES AND MEASURES Standard deviation of lateral position (SDLP) in simulated driving scenarios at 2 and 5 hours after THC exposure was the primary outcome (reported as difference in means [95% CIs]) assessed in the intention-to-treat population. Secondary outcomes included driving simulator standard deviation of speed (SDS) and reaction time (RT), self-reported driving willingness and perceived ability, and whole-blood THC and metabolite levels.

RESULTS Of 85 potential participants, 52 were enrolled as eligible, 10 withdrew before receiving a dose of THC, and 2 were removed from the analysis. Thus, 40 participants (20 [50.0%] female and 20 [50.0%] male) were included in the analysis (mean [SD] age, 30.4 [6.9] years). Relative to placebo, SDLP was significantly increased at 20 mg (3.3 [95% CI, 2.4 to 4.3] cm; $P < .001$) and 10 mg (2.0 [95% CI, 1.0 to 2.9] cm; $P < .001$), but not 2 mg (0.7 [95% CI, -0.3 to 1.6] cm; $P = .16$). The secondary driving measures RT and SDS were also negatively influenced by THC exposure. For example, compared with placebo, RT was significantly higher at 20 mg (difference in means, 0.034 [95% CI, 0.018 to 0.050] s; $P < .001$) and SDS was significantly increased at 20 mg (difference in means, 0.469 [95% CI, 0.154 to 0.784] km/h; $P = .004$). Self-reported driving measures were dose-dependently decreased by THC dose. For example, compared with placebo, willingness to drive was significantly decreased at 20 mg (difference in means, -2.113 [95% CI, 1.166-1.821]; $P < .001$), as was participant-perceived driving ability (difference in means, -1.694 [95% CI, 1.422-1.966]; $P < .001$). Whole-blood THC concentrations (peaks of 3.4 and 1.6 ng/mL at 20 and 10 mg, respectively) were near or below common per se thresholds for driving.

(continued)

Key Points

Question Do commercially available cannabis edibles dose-dependently impair driving simulator performance?

Findings In this randomized clinical trial including 40 adults who used cannabis regularly, edible delta-9-tetrahydrocannabinol (THC) dose-dependently increased the standard deviation of lateral position measured in a driving simulator 2 and 5 hours after THC exposure, with blood THC concentrations that peaked between 1.6 and 3.4 ng/mL.

Meaning Findings indicate that commercially available cannabis edibles dose-dependently impaired lateral vehicular control in a driving simulator at blood THC concentrations below common per se thresholds.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this crossover randomized clinical trial of driving performance after exposure to THC edibles, THC dose-dependently impaired simulated driving performance at blood THC concentrations below per se thresholds commonly used for roadside enforcement.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT06595576](https://clinicaltrials.gov/ct2/show/study/NCT06595576)

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Introduction

Meta-analyses have shown an association between cannabis use and risk of collision involvement¹⁻³ although there are limitations of epidemiologic studies (eg, delays between law enforcement dispatch and blood draws,⁴ the long elimination half-life of cannabinoids⁵). Driving simulator and on-road studies have provided causal evidence of differences in driving behavior under the influence of cannabis, such as decreased lane control and speed.⁶ However, most studies administered inhaled cannabis, which may not generalize to newer noninhaled products with different pharmacokinetics and time course of effects that are available in the increasingly diversified cannabis retail market.^{7,8}

In the United States, the use of cannabis edibles substantially increased following state legalization of recreational cannabis, becoming the second most commonly used cannabis product.⁹ Prevalence of edible cannabis use has similarly increased in Canada, with 55% of Canadians who used cannabis in 2024 reporting use of edibles.¹⁰ Two previous studies examined the effects of cannabis edibles on driving using a naturalistic design in which participants sourced their own cannabis products.^{11,12} However, in order to inform impaired driving policy, placebo-controlled laboratory studies using standardized dosing are needed. Such studies are particularly important in the context of per se laws that establish criminal offenses based on specified drug concentrations in a driver's body, including the Canadian Criminal Code, which specifies threshold driving limits of 2 to 5 ng/mL and 5 ng/mL or higher for delta-9-tetrahydrocannabinol (THC), and similar 5 ng/mL per se thresholds in some US states.¹³ Oral formulations of THC have different pharmacokinetics that influence the onset, magnitude, and duration of effects,⁵ and therefore may impact the utility of per se thresholds. Since oral THC administration leads to lower peak blood THC concentrations,¹⁴ it is possible that driving-relevant impairment may be present after oral THC exposure in the absence of elevated blood THC. The potential decoupling of blood THC and impairment is further underscored by its pharmacokinetic-pharmacodynamic relationships, which typically show a counterclockwise hysteresis loop (ie, the same concentration of THC can elicit different effects depending on the temporal sequence in which the effect is measured due to a distribution delay to the active site), an effect that may actually differ when THC is inhaled or taken orally.¹⁵

The primary objective of the present study was to examine the dose-dependent effects of edible THC (0, 2, 10, and 20 mg) on simulated driving performance among adults who regularly use cannabis. Standard deviation of lateral position (SDLP), which represents the variability of a vehicle's position from the center of the lane, was our registered primary outcome variable since it is a standard and validated measure of drug-related driving impairment¹⁶ and has shown sensitivity to cannabis impairment.^{17,18} We included secondary measures of simulated driving performance, self-reported effects, and blood cannabinoid levels. Our primary focus was the acute effects (2 and 5 hours after THC exposure), with a secondary focus on potential residual (next-day) effects 24 hours after the exposure.

Methods

The study was a randomized, double-blind, placebo-controlled, counterbalanced, crossover clinical trial assessing the effects of a range of THC doses (0, 2, 10, and 20 mg) in cannabis edibles on driving

simulator performance. The full clinical protocol is provided in [Supplement 1](#), and an outline of the study design is provided in the eFigure in [Supplement 2](#). The trial was conducted at a single hospital site, the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, Canada, between September 2024 and April 2025. The trial was reviewed and approved by the CAMH Research Ethics Board and the Health Canada and Public Health Agency of Canada Research Ethics Board. All participants provided written informed consent. This report follows the Consolidated Standards of Reporting Trials ([CONSORT](#)) guideline for randomized clinical trials.¹⁹

Participants

Most participants were recruited via advertisements posted in public transit areas throughout Toronto (other methods included recontact lists and social media). Participants were compensated CA\$800 at completion, which was prorated for partial completion. To be enrolled, participants had to be healthy adults aged 19 to 45 years who reported recreational use of cannabis at least 1 day per week and use of edibles at least 1 day per month. Participants were required to have a full driver's license for at least 12 months, no severe medical or psychiatric conditions or substance use disorders, and no regular use of medication that could impact performance. Full eligibility criteria are provided in the eMethods in [Supplement 2](#). Race and ethnicity were assessed to more fully characterize the sample. The self-reported race and ethnicity categories were based on options provided by the researchers. They included Asian; Black; Latin, Central, or South American; mixed heritage; and White as well as the option to write in other or none of these options. Race categories with few participants were combined for the purpose of reporting to avoid identifying participants. The full question and response options for race and ethnicity are included in the eMethods in [Supplement 2](#).

Procedures

Prescreening occurred over the phone or online using REDCap.²⁰ Potentially eligible participants were invited to come to CAMH for an in-person eligibility assessment, where written informed consent was obtained by trained study staff prior to initiating study procedures. Participants meeting eligibility criteria came to the laboratory for a total of 10 sessions: an eligibility assessment, a practice session, 4 acute test sessions, and 4 next-day test sessions. Participants were asked to refrain from personal use of cannabis for 72 hours before practice and test sessions (eMethods in [Supplement 2](#)).

Practice and test sessions commenced with a breath test, pregnancy test (for individuals with childbearing potential), and a point-of-care urine toxicology screen and saliva sample for detection of THC. During the practice session, information was collected on cannabis and other drug use, driving attitudes, demographics, and other personality and individual difference measures, and participants practiced all study tasks, including driving simulator scenarios. Participants then returned to the laboratory for 4 cannabis exposure sessions separated by intervals of approximately 1 week. Baseline procedures included blood and oral fluid sample collection for determination of baseline concentrations of THC, 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THC-COOH) and completion of a practice driving trial followed by baseline driving trials. Participants then consumed the cannabis edibles (time 0 marked the end of edible THC ingestion). Simulated driving trials, subjective driving measures, and blood collections were repeated at 2 and 5 hours after exposure, whereas a visual analogue scale (VAS) was administered immediately after exposure, and then at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 5.0 hours after exposure. Participants also completed a verbal recall task and other subjective effects measures, which will be reported elsewhere. Participants returned approximately 24 hours after the time of edible exposure for a next-day test session.

Drug Administration

Cannabis soft chew candy edibles (2 mg of THC) and matching placebo edibles were obtained from Indiva, a licensed producer in Canada. The THC conditions were generated by combining the active and placebo candy edibles to achieve 4 doses of THC: placebo (0 mg), low dose (2 mg), medium dose (10 mg) and high dose (20 mg). For example, in the low-dose condition, participants received one

2-mg THC candy and 9 placebo candies. The CAMH Research Pharmacy was responsible for cannabis storage and accountability and also maintained study randomization codes. Participants were block randomized (in blocks of 4) to 1 of 4 sequences of drug dose exposure, which were counterbalanced.

Driving Simulation

For details of the driving simulator (VS500M, Virage), see previous studies conducted by members of our team.^{21,22} Each drive included 3 scenarios. The first 2 scenarios were nearly identical drives on a rural road, but 1 had no distractor task (single task), whereas the other scenario (dual task) had an added secondary task (counting backward by 3's from a large, randomly generated number). The third scenario captured reaction time (RT). The simulator-based RT judgment task instructed participants to stop when they saw a stop sign directly facing them, but not to stop when they saw a stop sign at an angle. Because the results for single-task and dual-task scenarios were nearly identical, outcomes from single-task scenarios are presented in the main text, while dual-task results are available in the eResults in [Supplement 2](#).

Outcome Measures

Our registered primary outcome measure was SDLP (in meters), which was based on global performance throughout the entire driving scenario. Secondary driving outcome measures included mean speed, standard deviation of speed, and maximum speed, all in kilometers per hour, and RT assessed in seconds. RT was measured in the RT scenario only and was the mean of the RTs across the 7 correct stops within each scenario.

Subjective effects measures were included to complement the objective simulator data (eg, to determine whether participant self-report of drug effects matched changes in performance). Before and after each drive, participants were asked to self-report their willingness to drive ("How willing would you be to drive a real vehicle?") and their perceived driving ability ("How do you think you will perform/performed during the driving simulation?"). Self-report driving measures did not differ before or after the drives; thus, only the data collected before the drives are presented in the main text, with the remainder of the data reported in the eResults in [Supplement 2](#). VAS ratings to assess subjective intoxication included "I feel this effect" (effect) and "I feel this high" (high), which were rated on a scale from 0 to 100, with higher values indicating a greater degree of subjective effect or intoxication.

The levels of THC, THC-COOH, and 11-OH-THC were quantified in whole blood. A previous publication¹⁸ by members of our team provides the details. Adverse events (AEs) were assessed at each study visit using a standardized institutional AE reporting form that captures the nature, severity, seriousness, and attribution of each AE.

Note that some preregistered secondary outcomes (ie, Addiction Research Centre Inventory; Profile of Mood States; Verbal Free Recall Task; blood concentrations of mitochondrial DNA; and blood concentrations of endocannabinoids) are not reported here. These outcomes address secondary research aims that will be presented in subsequent papers.

Sample Size

Our target sample size of 36 participants who completed the study was based on a previous study of smoked cannabis by members of our team.¹⁸ A significant main effect of THC condition on SDLP was observed with 35 participants who completed the study ($F_{3,231} = 15.9$; $P < .001$).

Statistical Analysis

Data analysis was conducted in IBM SPSS, version 27 (SPSS Inc). All variables were subjected to descriptive analyses (measures of central tendency and variance). To answer the main research questions, linear mixed effects modeling was used, with time (2 and 5 hours), session (1 to 4), condition (placebo or low, medium, and high THC dose), order (the order of conditions the participant was randomized to receive), and baseline value of the outcome as fixed effects and with

participant as the random intercept. The interaction of dose and time was also entered into the model as a fixed effect; the study was not powered to detect an interaction; this term is presented to explore potential time variance of dose effects and should be interpreted as exploratory. The primary interest was the overall condition effect, which was considered significant when the *P* value for the *F* test was lower than .05, taking into account 1 primary outcome measure (SDLP). When the overall condition effect was statistically significant, pairwise comparisons were reported to understand dose-related effects. Since we expected different variance in outcome measures at the residual (24-hour) visit, we performed separate models to test for residual effects, which were identical to the acute effects models but without the factor of time. All analyses were conducted for the intention-to-treat population. All statistical tests were 2-sided, and values of *P* < .05 were considered statistically significant.

Results

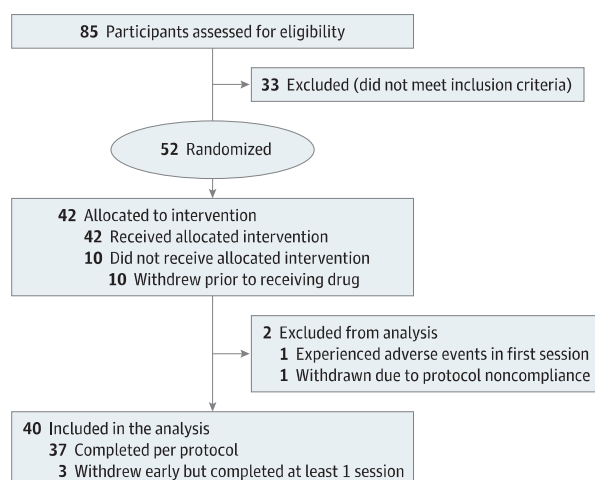
Participants

The analysis included 40 participants (20 [50.0%] female and 20 [50.0%] male; mean [SD] age, 30.4 [6.9] years). Most participants self-reported their race and ethnicity as Asian (12 [30.0%]) or White (20 [50.0%]). We prescreened 2619 participants and screened 85 participants on-site (**Figure 1**). Of them, 33 participants were ineligible for the study based on on-site screening (eResults in [Supplement 2](#)); thus, 52 participants were enrolled and randomized. Ten enrolled participants withdrew from the study without receiving the study drug. One participant did not complete a full study visit, and 1 participant was withdrawn for protocol noncompliance. Thus, we included data from 40 participants who completed at least 1 drug exposure visit (37 completed all study procedures). See **Table 1** for demographic and substance use characteristics of the sample.

Primary Outcome

There was a significant main effect of THC dose on SDLP under full attention, that is, during the single task of driving ($F_{3,214} = 19.24$; $P < .001$), but no significant dose by time interaction (**Figure 2A**). The effect was dose-related, as all doses significantly differed from one another (2 vs 10 mg difference in means, 0.013 [95% CI, 0.004-0.022] m; $P = .007$; 2 vs 20 mg difference in means, 0.027 [95% CI, 0.017-0.036] m; $P < .001$; and 10 vs 20 mg difference in means, 0.014 [95% CI, 0.004-0.023] m; $P = .005$), except 2 mg vs placebo (difference in means, 0.007 [95% CI, -0.003 to 0.016] m; $P = .16$) (eTable 3 in [Supplement 2](#)). Compared with placebo, SDLP was higher at 20 mg (difference in means,

Figure 1. Participant Flow Diagram Based on the Consolidated Standards of Reporting Trials Guideline



0.033 [95% CI, 0.024-0.043] m; $P < .001$) and 10 mg (difference in means, 0.020 [95% CI, 0.010-0.029] m; $P < .001$).

Secondary Driving Simulator Outcomes

Acute Effects 2 and 5 Hours After Drug Exposure

There was a significant main effect of THC dose on RT ($F_{3,236} = 6.07$; $P < .001$) but no dose-by-time interaction. Compared with placebo, RT was significantly higher at 20 mg (difference in means, 0.034 [95% CI, 0.018-0.050] s; $P < .001$) and 2 mg (difference in means, 0.017 [95% CI, 0.000-0.033] s; $P = .047$) but not 10 mg (difference in means, 0.009 [95% CI, -0.007 to 0.026] s; $P = .27$) (Figure 2B; eTable 3 in Supplement 2). In addition, RT at 20 mg differed significantly from the 10-mg (difference in means, 0.025 [95% CI, 0.009-0.041; $P = .003$) and 2-mg (difference in means, 0.018 [95% CI, 0.001-0.034; $P = .03$) doses, but RT at 10 mg was not different from 2 mg (difference in means, 0.007 [95% CI, -0.009 to 0.024]; $P = .37$).

There was a significant main effect of THC dose on standard deviation of speed (SDS) ($F_{3,255} = 4.45$; $P = .005$) but no dose by time interaction. SDS was significantly elevated at 20 mg compared with 10 mg (difference in means, 0.395 [95% CI, 0.082-0.708] km/h; $P = .01$), 2 mg (difference in means, 0.523 [95% CI, 0.211-0.835] km/h; $P < .001$), and placebo (difference in means, 0.469 [95% CI, 0.154-0.784] km/h; $P = .004$) (eTable 3 in Supplement 2). The 10-mg and 2-mg doses did not differ from placebo or from one another. There were no effects of THC dose on mean speed or maximum speed.

Table 1. Demographic and Substance Use Characteristics of the Full Sample

Characteristic	Participants
Total No.	40
Sex assigned at birth, No. (%)	
Male	20 (50.0)
Female	20 (50.0)
Gender, No. (%)	
Male	19 (47.5)
Female	18 (45.0)
Nonbinary	3 (7.5)
Age, mean (SD) [range], y	30.4 (6.9) [19.0-43.0]
Race and ethnicity, No. (%) ^a	
Asian	12 (30.0)
White	20 (50.0)
Other	8 (20.0)
Educational attainment, No. (%)	
High school	5 (12.5)
College	9 (22.5)
Undergraduate degree	20 (50.0)
Professional or graduate degree	6 (15.0)
Age of initiation of cannabis use, mean (SD) [range], y	20.1 (5.7) [14.0-42.0]
Age of initiation of weekly cannabis use, mean (SD) [range], y	24.3 (6.4) [15.0-42.0]
Weekly frequency of smoked cannabis, median (IQR) [range], No. days per week ^b	1.5 (0.3-3.2) [0.0-7.0]
Weekly frequency of edible cannabis, median (IQR) [range], No. days per week ^b	0.6 (0.3-1.4) [0.0-6.4]
Drove under the influence of cannabis in the past 12 mo, No. (%)	4 (10.0)
Current tobacco use, No. (%)	5 (12.5)
Alcohol use in the past 12 mo, No. (%)	38 (95.0)
Baseline blood delta-9-tetrahydrocannabinol concentration per session, mean (SD) [range], ng/mL	
Session 1 (valid n = 39)	0.22 (0.55) [0.00-2.90]
Session 2 (valid n = 38)	0.26 (0.60) [0.00-3.00]
Session 3 (valid n = 35)	0.15 (0.39) [0.00-1.80]
Session 4 (valid n = 37)	0.14 (0.27) [0.00-1.00]

^a Full race and ethnicity options are included in the eMethods in Supplement 2. Other included Black; Latin, Central, or South American; and mixed heritage.

^b Weekly frequency of cannabis use was the mean across the past 30 days using the timeline followback; smoked and edible cannabis use were indicated separately; thus, some participants report 0 days of either smoked or edible cannabis.

Residual Effects, 24 Hours After Drug Exposure

There was a significant effect of THC dose on maximum speed ($F_{3,108} = 2.94$; $P = .04$), which was higher at 20 mg (difference in means, 2.019 [95% CI, 0.528-3.510] km/h; $P = .008$) and 10 mg (difference in means, 1.640 [95% CI, 0.119-3.161] km/h; $P = .04$) compared with placebo (eTable 5 in Supplement 2). There was no evidence of residual dose-related differences in any other driving measure.

See eResults in Supplement 2 for dual-task driving outcomes. See eTables 1 to 5 in Supplement 2 for all model parameters, estimated marginal means for all doses, and pairwise comparisons for the main effects of dose.

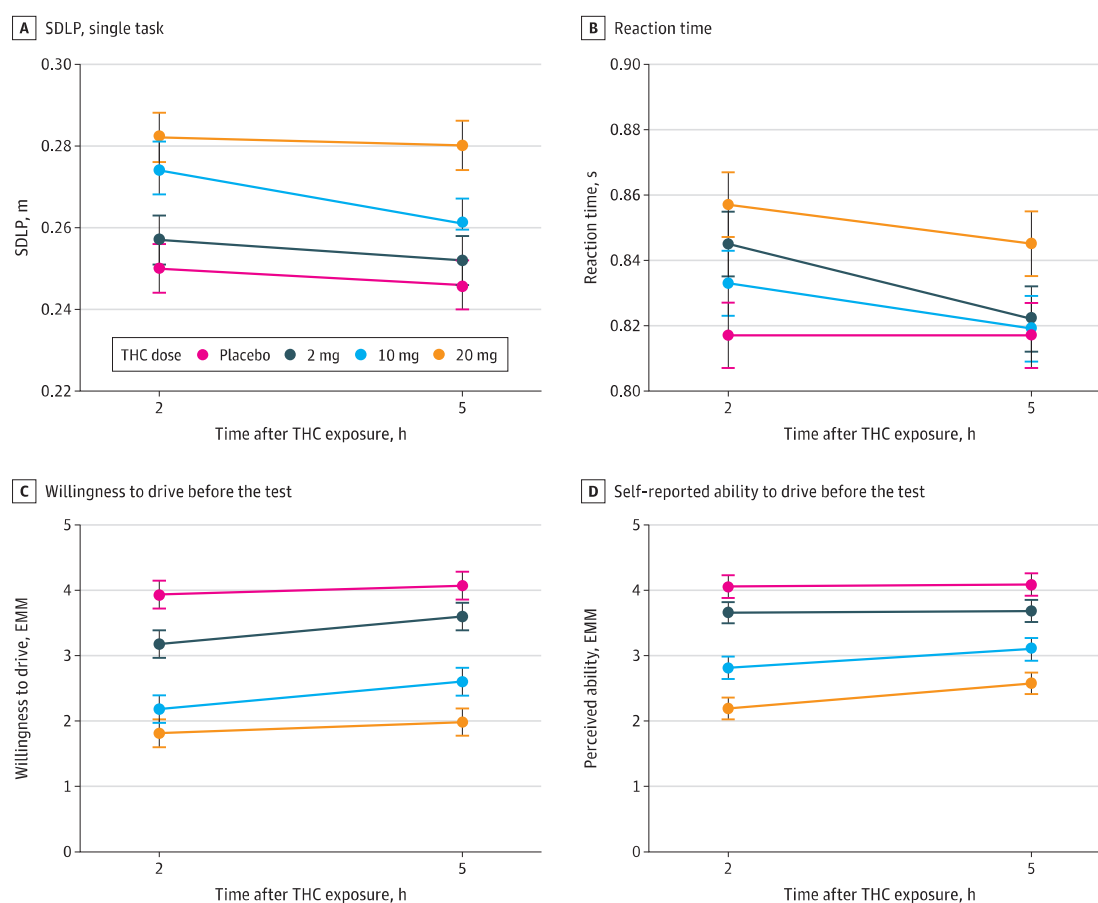
Self-Reported Driving Measures, Before Driving

Acute Effects

There was a significant main effect of THC dose on willingness to drive before operating the simulator ($F_{3,256} = 64.74$; $P < .001$) but no dose-by-time interaction. Effects were dose-dependent, as every pairwise comparison was significant (Figure 2C; eTable 8 in Supplement 2). Compared with placebo, willingness to drive was significantly decreased at 20 mg (difference in means, 2.113 [95% CI, 1.166-1.821]; $P < .001$), 10 mg (difference in means, 1.617 [95% CI, 1.282, 1.951]; $P < .001$), and 2 mg (difference in means, 0.620 [95% CI, 0.286-0.953]; $P < .001$).

Perceived driving ability before driving in the simulator showed an identical pattern (main effect of dose: $F_{3,254} = 59.57$; $P < .001$) (Figure 2D). Compared with placebo, perceived driving ability was

Figure 2. Line Graphs Depicting Model-Estimated Marginal Means (EMMs) for Objective Driving Simulator Measures and Subjective Self-Reported Driving Measures, by Delta-9-Tetrahydrocannabinol (THC) Dose and Time



Data points represent EMMs with SEs. SDLP indicates standard deviation of lateral position.

significantly decreased at 20 mg (difference in means, 1.694 [95% CI, 1.422-1.966]; $P < .001$), 10 mg (difference in means, 1.118 [95% CI, 0.844-1.392]; $P < .001$), and 2 mg (difference in means, 0.401 [95% CI, 0.129-0.672]; $P = .004$) (eTable 8 in [Supplement 2](#)).

Residual Effects

There were no effects of THC dose 24 hours after THC exposure on self-reported driving measures.

See eResults in [Supplement 2](#) for ratings after driving the simulator and eTables 6-10 in

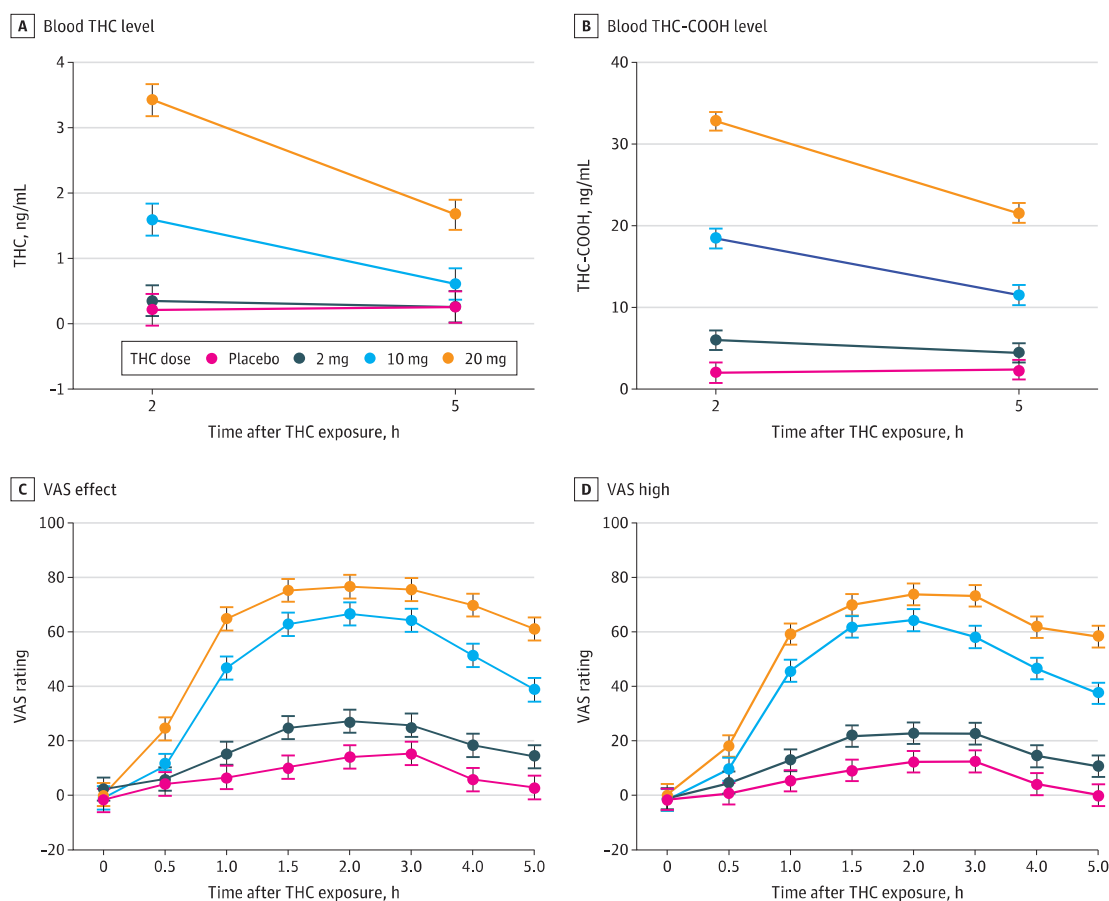
[Supplement 2](#) for all model parameters, estimated marginal means for all doses, and pairwise comparisons for the main effects of dose.

Subjective Effects

Acute Effects

There were significant dose by time interactions for VAS ratings of effect (ie, participant response to "I feel a drug effect") ($F_{21,1138} = 11.77$; $P < .001$) and high (ie, participant rating for "I feel this high") ($F_{21,1138} = 12.32$; $P < .001$). Mean ratings showed similar patterns over time for both outcomes. There was no evidence of a dose-related difference immediately after ingestion of the THC edible. At 0.5 hours, VAS ratings were increased only at 20 mg. At 1 hour, VAS ratings were increased at both 20 and 10 mg. From 1.5 to 5 hours, all pairwise comparisons were significant (**Figure 3C and D**; eTable 13 in [Supplement 2](#)).

Figure 3. Line Graphs of Model-Estimated Marginal Means (EMMs) for Blood Cannabinoid Levels and Visual Analogue Scale (VAS) Ratings, by Delta-9-Tetrahydrocannabinol (THC) Dose and Time



Data points represent EMMs with SEs. THC-COOH indicates 11-nor-9-carboxy-THC.

Residual Effects

There were no statistically significant differences in any measure 24 hours after THC exposure. See eTables 11-15 in [Supplement 2](#).

Blood Cannabinoids

Acute Effects

There were significant dose-by-time interactions for whole blood THC levels ($F_{3,239} = 6.60$; $P < .001$) (Figure 3A), THC-COOH ($F_{2,241} = 12.34$; $P < .001$) (Figure 3B), and 11-OH-THC ($F_{3,245} = 28.97$; $P < .001$). Blood THC concentrations peaked 2 hours after exposure (0.4 ng/mL for 2 mg, 1.6 ng/mL for 10 mg, and 3.4 ng/mL for 20 mg). Two hours after exposure, THC levels showed dose-dependent increases (eg placebo vs 10 mg difference in means, 1.370 [95% CI, 0.724-2.034] ng/mL and placebo vs 20 mg difference in means, 3.213 [95% CI, 2.558-3.868] ng/mL), with all pairwise comparisons significantly different at $P < .001$, except 2 mg vs placebo, which was not significantly different (eTable 18 in [Supplement 2](#)). By 5 hours, whole blood THC levels remained significantly elevated only at the 20-mg dose compared with all other conditions (vs placebo: difference in means, 1.411 [95% CI, 0.766-2.057] ng/mL; $P < .001$; vs 2 mg: difference in means, 1.411 [95% CI, 0.770-2.051] ng/mL; $P < .001$; vs 10 mg: difference in means, 1.411 [95% CI, 0.418-1.704] ng/mL; $P = .001$). Of 294 valid blood THC values (at both 2 and 5 hours), only 8 values were above 5 ng/mL (7 at 20 mg and 1 at 10 mg). Whole blood levels of THC-COOH and 11-OH-THC showed identical patterns of dose-dependent differences, with all pairwise comparisons significant at 2 hours and all comparisons except 2 mg vs placebo significant at 5 hours (eTable 18 in [Supplement 2](#)).

Residual Effects

There were no differences in blood THC levels at 24 hours for any comparison, but there were significant main effects of dose for THC-COOH ($F_{3,95} = 43.07$; $P < .001$) and 11-OH-THC ($F_{3,99} = 6.00$; $P < .001$). Both metabolites were significantly higher at 20 mg compared with all other conditions (eg, for THC-COOH placebo vs 20 mg difference in means, 7.925 [95% CI, 6.416-9.435] ng/mL; $P < .001$; and for 11-OH-THC placebo vs 20 mg, difference in means, 0.126 [95% CI, 0.060-0.191] ng/mL; $P < .001$), while 10 mg had a higher THC-COOH level compared with placebo (difference in means, 2.406 [95% CI, 0.866-3.946] ng/mL; $P = .003$) (eTable 18 in [Supplement 2](#)). See eTables 16-20 in [Supplement 2](#).

Adverse Events

In total, 22 AEs were recorded across 42 randomized participants ([Table 2](#)). Headaches (5 occurrences) and dizziness or nausea (4 occurrences) were the most common. Of 22 AEs, 8 were recorded in the high-dose session, 2 in the medium-dose session, 5 in the low-dose session, and 7 in

Table 2. Adverse Events Recorded for 42 Randomized Participants Who Received at Least 1 Dose of Delta-9-Tetrahydrocannabinol (THC)

Adverse event	No. of events						Study-related ^a
	Total	Placebo	2 mg of THC	10 mg of THC	20 mg of THC	Study-unrelated	
Headache	5	3	1	0	1	2	3
Dizziness and nausea	4	1	1	0	2	0	4
Cold or flu symptoms	3	2	0	1	0	3	0
Cramps	2	0	1	0	1	1	1
Anxiety	2	0	0	0	2	1	1
Pain at blood draw site	2	1	1	0	0	0	2
Accidental injury	1	0	1	0	0	1	0
Ear infection	1	0	0	1	0	1	0
Vomiting	1	0	0	0	1	0	1
Diarrhea	1	0	0	0	1	0	1
Total	22	7	5	2	8	9	13

^a Judged by a qualified investigator (B.L.F.) as possibly, probably, or definitely related to the intervention or study procedures.

the placebo session. We deemed 8 AEs unrelated to the study intervention or procedures, whereas 13 AEs were judged as possibly, probably, or definitely related to the study intervention or procedures. No serious AEs occurred, and no AEs were judged as severe or moderate in intensity (all were rated as mild).

Discussion

We examined the dose-dependent effects of THC edible exposure on driving simulator performance. SDLP (our primary outcome) was dose-dependently increased after ingestion of THC, with significant differences from placebo at the 10- and 20-mg doses but not the 2-mg dose. While THC did not acutely affect mean or maximum speed, the SDS was elevated at 20 mg. RT was elevated at the 2- and 20-mg doses, which was the only evidence of driving differences at 2 mg. There were minimal residual driving effects at 24 hours; only maximum speed was increased at THC doses of 10 and 20 mg. Self-reported willingness to drive and perceived driving ability were dose-dependently decreased by THC, with the greatest decreases at the 20-mg dose. Acute subjective intoxication was captured in VAS ratings, which showed dose-dependence, although no evidence of residual subjective intoxication.

These current results align with those from a previous study by members of our team¹⁸ assessing dose-related effects of smoked cannabis on driving simulator performance, which followed an identical study design and found that THC negatively impacted SDLP, SDS, and reaction time (especially at the highest dose), with no impact on mean speed. Dose-related effects were similar in magnitude between edible and smoked cannabis (eg, relative to placebo, high-dose edibles increased SDLP by 3.3 cm, whereas high-potency smoked cannabis increased SDLP by 4.1 cm), despite nearly 10-fold lower peak blood THC concentrations with edibles (eg, high-dose condition: 3.4 ng/mL in the current study; 30.3 ng/mL in the previous smoked cannabis study).¹⁸ Our results have clinical significance, as prior work has suggested a difference of 2.4 cm in SDLP is a meaningful indicator of impairment, equivalent to a blood alcohol concentration of 0.05%.²³ However, the SDLP increase we saw was smaller than the SDLP difference Won and colleagues¹² found in their occasional use group (3.9-4.4 cm) after they ingested a mean of 7.5 mg of THC, which may reflect differences in the participant samples (eg, frequency of cannabis use).

Low peak THC concentrations after edible THC exposure were expected based on general pharmacokinetic principles and are consistent with prior studies comparing blood THC levels across routes of administration,^{5,24} yet present challenges to the enforcement of impaired driving legislation using approved drug screening equipment.^{6,25,26} In our study, all observed peak THC concentrations, including in the high and medium dose conditions (3.4 and 1.6 ng/mL, respectively), were near or below common per se thresholds (eg, the 5 ng/mL hybrid offense threshold in Canada¹³ or the lower 2 ng/mL threshold used in many jurisdictions), yet participants demonstrated clear evidence of both objective and subjective driving impairment. Thus, increasing use of edible THC products may present a unique challenge to enforcement of per se legislation.

Limitations

Our study has limitations. First, our primary driving scenarios consisted of a straightforward rural drive with minimal distractors, which may not generalize to more complex driving environments (eg, urban roads with heavy traffic). Further, we limited our focus to measures of lane control, speed, and RT; other driving measures, such as headway and braking dynamics, should be considered in future studies. Relatedly, we interpreted clinical significance based on change in our primary outcome variable (SDLP) and in relation to the well-established impairment in SDLP at a blood alcohol concentration of 0.05%. This approach may not be sufficient to inform road safety, as different drugs can lead to different patterns of functional impairment. For example, THC (at the doses we tested) may lead to similar impairment in SDLP as alcohol, while other measures of driving performance we did not measure (eg, hazard perception) may be more or less impacted by THC than by alcohol.

Future work is needed to establish broader patterns of driving impairment across diverse substances and comparability with alcohol to benchmark driving impairment in simulator studies. Second, our drives were completed at 2, 5, and 24 hours after ingestion of THC, and thus duration of driving impairment between 5 and 24 hours is unknown. Finally, our sample was restricted to young and middle-aged adults who use cannabis regularly for nonmedical reasons; findings may not generalize to youth or older adults or people who use cannabis at different frequencies or for medical reasons.

Conclusions

This placebo-controlled, crossover randomized clinical trial found significant evidence of dose-related impairment of driving simulator performance 2 and 5 (but not 24) hours after ingestion of THC edibles among adults who used cannabis regularly. We found decreased lane control, increased speed variability, and increased RT, especially at the highest dose (20 mg), with minimal evidence of changes in driving performance at the low dose (2 mg). Objective measures of driving simulator performance aligned with self-reported data suggesting that participants were less willing to drive and perceived lower driving ability in a dose-dependent manner, even at the low dose. Whole-blood THC levels were below the commonly used 5 ng/mL per se threshold in all dose conditions, suggesting that THC edibles may present unique challenges for roadside enforcement.

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Author Contributions: Dr Le Foll had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eMethods.

eFigure. Study design

eResults.

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eTable 3. Pairwise comparisons for main effects of THC dose on driving simulator measures (acute)

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eTable 6. Linear mixed model parameters for subjective, self-reported driving outcomes showing dose by time interaction and main effect of dose (acute phase) and main effect of dose (residual phase)

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SUPPLEMENT 3.
Data Sharing Statement