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Simulated Driving Performance among Daily and Occasional Cannabis Users

Authors:

Ashley Brooks-Russell, PhD, MPH[a]
Tim Brown, PhD[c]
Kyle Friedman, MA[b]
John Schwarz, PhD[b]
Karen A. Ryall, PhD[b]
Elise Amioka, MS[b]
Gregory Dooley, PhD[d]
George Sam Wang, MD[e]
Julia Wrobel, PhD[f]
Benjamin Steinhart[f]
Gary Milavetz, PharmD[c]
Michael J. Kosnett, MD, MPH[gh]

Affiliations
[a]Department of Community and Behavioral Health, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado
[b]Rocky Mountain Poison and Drug Safety, Denver Health, Denver, Colorado
[c]National Advanced Driving Simulator, University of Iowa, Iowa City, Iowa
[d]Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, Colorado
[e]Department of Pediatrics, CU School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado
[f] Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado
[g]Department of Medicine, CU School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado
[h]Department of Environmental and Occupational Health, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado

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Abstract
Objective: Daily cannabis users develop tolerance to some drug effects, but the extent to which this diminishes driving impairment is uncertain. This study compared the impact of acute cannabis use on driving performance in occasional and daily cannabis users using a driving simulator.

Methods: We used a within-subjects design to observe driving performance in adults age 25 to 45 years with different cannabis use histories. Eighty-five participants (43 males, 42 females) were included in the final analysis: 24 occasional users (1 to 2 times per week), 31 daily users and 30 non-users. A car-based driving simulator (MiniSim™, National Advanced Driving Simulator) was used to obtain two measures of driving performance, standard deviation of lateral placement (SDLP) and speed relative to posted speed limit, in simulated urban driving scenarios at baseline and 30 minutes after a 15 minute *ad libitum* cannabis smoking period. Participants smoked self-supplied cannabis flower product (15% to 30% tetrahydrocannabinol (THC). Blood samples were collected before and after smoking (30 minutes after the start of smoking). Non-users performed the same driving scenarios before and after an equivalent rest interval. Changes in driving performance were analyzed by repeated measures general linear models.

Results: Mean whole blood THC cannabinoids concentrations post smoking were use THC = 6.4 ± 5.6 ng/ml, THC-COOH = 10.9 ± 8.79 ng/mL for occasional users and THC = 36.4 ± 37.4 ng/mL, THC-COOH = 98.1 ± 90.6 ng/mL for daily users. On a scale of 0 to 100, the mean post-use score of subjective high was similar in occasional users and daily users (52.4 and 47.2, respectively). In covariate-adjusted analysis, occasional users had a significant increase in SDLP in the straight road segment from pre to post compared to non-users; non-users decreased by a mean of 1.1 cm (25.5 cm to 24.4 cm) while occasional users increased by a mean of 1.9 cm (21.7 cm to 23.6 cm; p=0.02). Daily users also increased adjusted SDLP in straight road segments from baseline to post-use (23.2 cm to 25.0 cm), but the change relative to non-users was not statistically significant (p=0.08). The standardized mean difference in unadjusted SDLP from baseline to post-use in the straight road segments comparing occasional users to non-users was 0.64 (95% CI 0.09 – 1.19), a statistically significant moderate increase. When occasional users were contrasted with daily users, the baseline to post changes in SDLP were not statistically significant. Daily users exhibited a mean decrease in baseline to post-use adjusted speed in straight road segments of 1.16 mph; a significant change compared to slight speed increases in the non-users and occasional users (p=0.02 and p=0.01, respectively).

Conclusion: We observed decrements in driving performance assessed by SDLP after acute cannabis smoking that was statistically significance only in the occasional users. Direct contrasts between the occasional users and daily users in SDLP were not statistically significant. Daily users drove slower after cannabis use as compared to the occasional use group and non-users. The study results do not conclusively establish that occasional users exhibit more driving impairment than daily users when both smoke cannabis *ad libitum*.

Keywords
Drug impaired driving; driving simulator; cannabis use; drug tolerance; lateral control; cannabis impaired driving

1. Introduction

After alcohol, cannabis (primary active agent tetrahydrocannabinol, THC) is the most frequently detected drug in fatally injured drivers in the U.S.[1] Driving after cannabis use may be increasing in frequency due to its increased legal availability for medicinal or recreational purposes in the U.S. and globally. Epidemiological data have associated cannabis use, evidenced by delta-9 THC in blood, with an approximately two fold increase in motor vehicle crash risk, particularly those with fatal outcomes.[3-6] However, the epidemiological data has largely been unable to determine the temporal relationship, or recency, between a driver's last cannabis use and a motor vehicle crash, or to assess the impact of a driver's cannabis use history, and hence potential tolerance to cannabis-induced impairment.

There is growing evidence that people who use cannabis frequently, such as daily and multiple times a day, may develop tolerance to impairing effects of THC.[7-10] A recent systematic review and meta-analysis have concluded that the acute pharmacodynamic effects of cannabis depend on the history of previous cannabis use; the impairing effects of cannabis tend to be of a lesser magnitude and shorter duration in daily or frequent users compared to occasional users.[8,10]

Research that has investigated the impact of cannabis use history on driving performance is sparse. An on-the-road driving study observed oral low dose synthetic THC (dronabinol 10 mg or 20 mg) acutely reduced road tracking and car following skill in occasional but not heavy cannabis users.[11] In another on road study, Arkell and colleagues found standard deviation of lateral placement (SDLP) increased 2.33 cm at 40 minutes following consumption of THC-dominant cannabis, among a sample of 26 occasional cannabis users.[12] Studies with hi-fidelity driving simulators offer the opportunity to investigate the acute effects of cannabis use on driving skills in a controlled setting. These studies, including a recent meta-analysis of driving

performance and related skill, have found an increase in lateral movement within a lane following acute cannabis use.[10,13]

Some of these studies have investigated differences in performance between occasional and daily users.[12-17] For example, Brands and colleagues conducted a double-blind, placebo-controlled trial and observed decreased speed at 30 minutes after smoking 12.5% THC cannabis among weekly users. They also found that SDLP decreased (improved) in the subgroup with the highest blood THC , but this effect was marginally significant (p=.05).[14] Two recent randomized placebo-controlled trials observed an increase in SDLP after acute smoking of cannabis by occasional users,[12 15] one by Micallef and colleagues with a sample of males[15] and another by Hartman and colleagues with a placebo, low (2.9% THC) or high (6.7% THC) dose condition.[17] Thus, the emerging literature suggests that people who use cannabis daily may not experience the same decrements in driving performance as people who use occasionally.

The purpose of the present study was to investigate, using a high fidelity driving simulator, the impact of cannabis use history on the acute effects of cannabis smoking on driving performance. Our study employed an observational design to study how participants' driving changed after they consumed self-supplied high potency cannabis flower product typically available in states with a legal retail cannabis market.

2. Materials and Methods

2.1 Participants

We recruited healthy adults (ages 25-45) with a valid driver's license in the Denver area between October 2018 and February 2020 using posters and cards placed at retail stores, including cannabis dispensaries, campus buildings, email lists, paid advertisements in local

newspapers, and local news coverage. Prospective participants completed a web-based survey to assess eligibility criteria. Key eligibility criteria included a minimum driving frequency of 20 miles per week and at least four days per month, cannabis use either on a daily basis or weekly basis, and willingness to smoke at least 2 inhalations of cannabis flower product with between 15 and 30 percent total THC and less than 2% CBD (cannabidiol). There were additional exclusion criteria related to use of cannabis and use of the driving simulator or other study assessments such as history of drug or alcohol dependence, body mass index above 35, color-blindness, currently pregnant, and employment in a job with shift work or over-night shifts. If determined to be eligible the participant was invited to provide contact information to research staff. Participants were enrolled into one of three groups, according to age and gender quotas, and frequency of cannabis use: (1) daily cannabis use defined as smoking or vaping cannabis flower product at least one time per day, every day of the week for 30 days prior to enrollment; (2) occasional cannabis use defined as smoking or vaping cannabis flower product on at least one day but no more than two days per week in the 30 days prior to enrollment; and (3) non-use defined as having used cannabis at least once in the past but no use in the month prior to enrollment.

2.2 Data collection

The study utilized a within-subjects design comparing pre and post consumption driving performance. To account for learning or testing effects, we included a non-use comparison group that completed the same protocol except for the cannabis use. Participants who met the inclusion and exclusion criteria on web-based screening were invited to an in-person screening visit. At this screening visit, eligibility criteria were reviewed and confirmed. Each participant completed

an alcohol breath test (Lifeloc FC10™) to screen for acute alcohol use, provided a urine sample to test for illicit drug use or use of prescription drugs not prescribed (30 mL Alere brand 13-panel iCup®), and completed a practice driving session (approximately 10 minutes) to familiarize themselves with the driving simulator. The simulator practice session facilitated elimination of participants reporting headache, dizziness, or other features of "simulator sickness syndrome" that may occur.[18] A second visit, for data-collection, was scheduled within 10 days, and typically less than a week from the first visit.

For the data collection visit, participants were instructed not to use inhaled cannabis for at least 8 hours and not to use edible cannabis for at least 12 hours before the appointment. Their cannabis use pattern between the screening visit and data collection visit was also verified by review of a participant's diary of the time and amount of all cannabis use, other medication and drug use, and sleep duration. Participants again completed an alcohol breath test and provided a urine sample to screen for acute alcohol or other drug use. They performed another brief practice drive on the simulator that was not used to assess performance. They then completed a number of baseline assessments including simulator driving, blood draw for cannabinoids, baseline measurements of blood pressure and pulse, and other psychomotor assessments not reported here. Participants who were occasional or daily users were then observed to smoke or vaporize their own cannabis flower while seated in a recliner in a dedicated ventilated room.

Cannabis use was observational in nature. Participants self-procured cannabis flower and brought it in original packaging from a state-licensed Colorado dispensary to verify the percent total THC (required to be between 15 and 30%, and less than 2% cannabidiol (CBD) by weight). Participants smoked the cannabis flower *ad libitum* and were specifically instructed to smoke or vape during a 15 minute interval "the amount you most commonly use for the effect you most

commonly desire." In order to measure the mass of cannabis flower combusted by each participant in the process or smoking or vaping, the initial and remaining quantity of cannabis brought to the session by each participant was weighed before and after use using a scale measuring with a precision of 1 mg. Participants in the non-use group were invited to relax for the equivalent amount of time.

At baseline and 30 minutes after the start of smoking a certified phlebotomist collected approximately 10mL of blood using standard sterile phlebotomy techniques into grey-top tubes (BD brand vacutainer tubes, containing 100mg sodium fluoride and 20 mg potassium oxalate additive) and stored at approximately 4°C (39.2°F) for analysis within 30 days. Whole blood samples were shipped on cold packs to the Colorado State University Analytical Toxicology Laboratory for analysis. Participants began their post-smoking driving simulator session 15 minutes after the post-smoking blood collection (30 minutes after the end of the smoking session).

Participants were provided with $20 for completing the first session and $120 for the second session. All cannabis using participants were transported from the study site after the smoking session by a designated sober driver. Written informed consent was obtained and the study was approved by the Colorado Multiple Institutional Review Board.

2.3 Measures

2.3.1 Cannabinoids Analysis by LC-MS/MS

Whole blood samples were prepared for LC-MS/MS analysis by using solid phase extraction following a published methodology by Schwope et al. 2011.[19] Prepared calibrators, controls, and samples were analyzed with an Agilent 1290 Ultra High Performance Liquid

Chromotography (UHPLC) coupled to an Agilent 6460 triple quadruple mass spectrometer equipped with an Agilent Jet Stream electrospray ionization source (Agilent, Santa Clara, CA). Cannabinoids were first chromagraphically separated on a Restek Raptor Biphenyl column (2.1 x 100 mm, 5 μm) held at 40°C. A sample volume of 10 μL was injected and a mixture of water with 5 mM ammonium acetate/0.1% acetic acid (A) and 15% methanol in acetonitrile (B) at a flow rate of 0.4 mL/min. The gradient elution used was 30% B for 1 minute, increasing to 100% B at 7 minutes, and held at 100% B for 3 minutes. The ionization source conditions used were as follows: nebulizer 45 psi; gas flow of 12 L/min at 330°C; sheath gas flow of 12 L/min at 390°C. The electrospray ionization polarity was set to positive for tetrahydrocannabinol (THC). Negative ionization was used for THC-COOH (11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol). Two ion transitions (m/z) were monitored for each analyte and corresponding deuterium labeled internal standard. These ion transitions and corresponding fragmentor and collision energy voltages are displayed in Supplemental Data Table 1.

Compound identifications were confirmed by retention time and the product ion ratios (± 20%). The data collection and processing were performed by using Agilent MassHunter Quantitative software (v.B.08.01). Quantitation was performed with linear regression using 6 point calibration curves. LOQ were 0.5 ng/mL for THC, and 2.5 ng/mL for THC-COOH. LOD were 0.2 ng/mL for THC and 1 ng/mL for THC-COOH.

2.3.2 Driving Simulator

Driving performance was assessed using the miniSim™ developed and provided by the National Advanced Driving Simulator (NADS) at the University of Iowa. The miniSim is a PC-based research driving simulator with a quarter cab with three 48" 1080p LED Active Backlit

LCD displays that provide a forward field of view of 141.4◦ horizontal by 27.5◦ vertical at a 48 inch viewing distance. The simulator includes a real vehicle seat, steering wheel with column gear selector, and pedals with an active steering loader with DC motor/microprocessor control. The sound system includes a 2.1-channel sound system with a vibration transducer under the seat and an audio amplifier with external controls. Data is sampled at 60 Hz.

Participants completed four sequential driving scenarios for a baseline ("pre") driving period and four sequential driving scenarios after smoking cannabis (the "post" use period). Each scenario lasted approximately 5-10 minutes, resulting in a total driving period duration of approximately 20-30 minutes. The scenarios in the baseline driving period were paired with a scenario in the post-use driving period that were intended to test the same skill albeit in a driving simulation setting that visually appeared different. For each scenario pair, the period in which a particular scenario was presented to the driver as well as the sequence it was presented within a period (occurring first, second, third or fourth in each period) were randomized and balanced to minimize practice effects. The driving scenarios included urban and rural highway driving segments. The posted speed limit of the urban segments was 25-35 miles per hour (mph) and those of the rural highway segments was 45-65 mph. Other traffic was varied throughout the drives and pedestrians and other features were present in the drives. Identical standardized instructions were read to each participant regarding operation of the simulator. The researcher supervising data collection during the simulator sessions was not blinded to the participant's status as a cannabis user or non-using comparison participant, but was blinded to the amount of cannabis each participant consumed and their self-reported measures of drug effect.

In this study we focus on two primary outcomes of (1) standard deviation of lateral placement and (2) mean speed driven above or below the posted speed limit. These were

assessed during an urban driving scenario (see Supplemental Table 2 for further details about the scenarios). Because drivers typically reduce speed and SDLP in sections of roadway with curved segments compared to those with entirely straight segments, the speed relative to the posted speed limit and SDLP were assessed separately for curved urban segments and straight urban segments.

2.3.3 Self-reported measures

At 40 minutes after the start of the smoking session (five minutes before the post-smoking driving period), participants completed brief self-assessments. Subjective drug affect was measured with a visual analog scale where participants were asked to mark the point on the line indicating "how high you are feeling right now" ranging from "not high at all (0 cm)" to "most high ever (100 cm)" Similarly, participants were ask to mark on a line, "how confident you are if you had to drive right now" ranging from "I am not confident (0 cm)" to "I am confident (100 cm)." Finally, participants completed the Karolinska Sleepiness Scale[20] indicating their perceived level of sleepiness during the past 5 minutes on a 9 point scale ranging from "extremely alert" to "very sleepy, great effort to keep awake, fighting sleep."

2.4 Analysis

We based sample size calculations on our primary driving-related measure of standard deviation of lateral placement (SDLP). We estimated that a sample of 30 participants per user group would provide 90% power to detect a mean change in standard deviation of lateral placement (SDLP) of 3.6 cm in SDLP between user groups with a two-tailed alpha level of 0.05.[21] [22]Driving performance measures were analyzed using repeated measures general linear

models with the following effects entered into each model: user group (non-users, occasional users, and daily users), period (baseline vs. post-cannabis), gender, age, order of simulator scenarios, the interaction between period and scenario order, and the interaction between user group and period. Age and gender were included a priori as covariates because of other studies identifying their frequent significance as predictor variables in driving simulator outcomes.[14,23-25] Mean driving speed was included as a covariate in the models for SDLP. The difference in the covariate-adjusted least-squared mean between the baseline period and the post-period was calculated and assessed for statistical significance for each user group (occasional smokers, daily smokers, and non-users). Pre- versus post-period least squared mean differences for each user group were contrasted with each other (occasional user versus non-user, daily user versus non-user, occasional versus daily user) to assess the significance of cannabis use history on driving performance. The significance threshold was set at $p < 0.05$ and all analyses were performed using SAS v9.4.

In addition to examining contrasts based on centimeters of SDLP, we assessed the impact of cannabis use history on SDLP by calculating the standardized mean difference of the baseline to post -use change in unadjusted SDLP among user groups. The standardized mean difference between two groups was calculated using the following formula: $(\Delta Mt - \Delta Mc)/(\text{Standard Deviation}_{pooled})$ where ΔMt was the post to baseline change in SDLP in either daily or occasional smokers and ΔMc was the post to baseline change in SDLP for the non-users (controls). The pooled standard deviation was calculated as $\sqrt{\frac{SD_t^2 + SD_c^2}{2}}$.

A total of 118 participants were enrolled. Participants were excluded from the final analysis dataset for the following reasons: 12 did not return for their second visit; 2 participants experienced dizziness and nausea related to the simulator test drive at the screening visit and

withdrew; 8 were excluded because the post use blood venipuncture was unsuccessful; 1 was excluded due to failure to obtain simulator data at post-use due to technical difficulties. An additional 4 participants who were enrolled in the occasional use were excluded based on baseline blood THC-COOH levels that were >68 ug/mL. This was higher than all but 9 participants in the daily user group, and was judged to be inconsistent with self-reported occasional cannabis use. Finally, 6 participants were excluded for post-use blood THC values <1.0 ug/mL. It is possible that these participants did not sufficiently inhale the cannabis they smoked or vaped, or that the actual concentration of THC in the cannabis they used was much lower than the concentration stated on the product label. As these participants would be considered nonusers based on the limit of detection of THC of 1 ug/mL used in many forensic drug assays, we did not include them. The baseline urine drug screen verified no evidence of recent cannabis use among the non-use group. Confidence that the enrolled cannabis users had adhered to the request to avoid consuming cannabis for at least 8 hours prior to the study session was gleaned from the post-hoc observation that at baseline the molar ratio of the sum of blood THC + blood THC-OH divided by THC-COOH, a measure of recency of use sometimes referred to as the cannabis influence factor[26], was less than 0.34 in all subjects. These values are consistent with the inference of no use within at least the past 2 hours.[26] The decision to exclude participants was made prior to data analysis. Thus, the final analysis sample was n=85 (daily use n=31, occasional use n=24, no current use, n=30).

3. Results

3.1 Participant characteristics

Eighty-five healthy adults (43 men, 42 women, ages 21 to 45; 31 with daily use, 24 with occasional use, and 30 with no current use) completed the study (Table 1). Participants were predominantly non-Hispanic whites with post-secondary school education. Due to recruitment quotas, user groups were relatively balanced in age and gender.

Driving experience was approximately equivalent across groups ranging from an average of 13.5 years among those using cannabis occasionally and 15.9 years among those who do not currently use (Table 1). Among the two groups of participants currently using cannabis the mean age of first use for those using daily and occasionally was 17.1 and 17.6 years, respectively. Consistent with eligibility criteria, those who use daily reported cannabis use on 29.7 of the past 30 days, a mean of 7 days a week and a mean of 4.9 times a day. Among those who use occasionally, they reported using a mean of 5.7 days in the past 30 days, 1.5 days in a typical week, and 1.4 times per day on the days used.

3.2 Cannabis use and drug effects

Among those who use daily and occasionally, the mean THC concentration of their purchased retail cannabis product was 22.1% (SD 3.0) and 21.1%, (SD 3.6) respectively (Table 2). Consistent with the protocol, no product contained more than 2% CBD. During the up to 15 minutes allotted for cannabis use, those who use daily smoked a mean of 417.3 milligrams, taking a mean of 21 inhalations, and smoking over 10 minutes. Those who use occasionally smoked a mean of 149.3 milligrams, taking 9 inhalations over 6 minutes. Among those who use daily 14 smoked using a joint, 15 used a pipe (“bowl”), 1 used a blunt and 1 bong. Among those who use occasionally, 9 smoked a joint, 12 used a pipe (“bowl”), 1 used a “one hitter” pipe, 1 used a bong, and 1 used a vaporizer (data not shown).

Blood cannabinoid values (THC and THC- COOH) at baseline and post use for the two user groups are presented in Table 3. At baseline, the group not using cannabis had no detectable THC or other cannabinoids in their blood at baseline (data not shown). At baseline, among those using daily, the mean blood THC level was 5.0 ng/mL, THC-COOH was 57.5 ng/mL, which rose to 36.4 ng/mL (THC) and 98.1 ng/mL (THC-COOH) at 30 minutes after the start of smoking (15 minutes after the end of the smoking period; Table 3). Among the group using cannabis occasionally, the mean baseline blood THC was non-detectable (<LOD = 0.2 ng/mL) and mean THC-COOH was 1.3 ng/mL, which rose to 6.4 ng/mL (THC) and 10.9 ng/mL (THC-COOH) at post-use (Table 3). Participants were asked to rate the drug effect on a visual analog scale ranging from 0 to 100 for the "high" and for confidence in the ability to drive. At post-use the feeling of high was a mean of 47 for those in the daily use group and 52 for those in the occasional use group. At post-use, driving confidence was 61.4 (out of 100) for daily users compared to 38.4 for occasional users, and the change in driving confidence from pre to post use between these groups (using a t-test) was statistically significantt(Table 3).

3.3 Driving Performance

Table 4 presents adjusted least squared means at baseline and post-use for each of the groups for driving simulator outcomes (Supplemental Table 4 presented unadjusted means and standard deviations). There were no significant changes in driving performance from baseline to post among the group not using cannabis. Among the occasional use group there was a small but significant increase in SDLP from baseline to post use on the straight road segment (1.9 cm, p=.02), which approached significance (2.6 cm, p=.06) on the curved road segments. Daily users displayed a small but significant increase in SDLP on the curved road segments (1.9 cm, p=.02)

but not the straight road segment. There were significant group differences in the relative change in SDLP from baseline to post use in the drive with straight road segments for the occasional use group compared to the non-user group ($p = 0.02$). Non-users decreased SDLP by a mean of 1.1 cm while occasional users increased SDLP by a mean of 1.9 cm. (Figure 1). The standardized mean difference in unadjusted SDLP from baseline to post-use in the straight road segments comparing occasional users to non-users was 0.64 (95% CI 0.09 – 1.19), a statistically significant increase. There were no significant differences between either user group and nonusers in relative change in SDLP (baseline versus post) in curved segments of the drive, whether measured in centimeters or as a standardized mean difference. When occasional users were contrasted with daily users, none of the baseline to post changes in SDLP were significant, whether compared in centimeters adjusted for speed and other covariates (Table 4), or as unadjusted values compared in terms of standardized mean differences (See Supplemental Table 3).

Studies have associated a blood alcohol concentration of 0.05% with an increment in unadjusted SDLP of 2.0 cm or 2.1 cm at highway speeds.[17,27] Applying a baseline to post-use increment in unadjusted SDLP of 2.1 cm as a measure of clinically significant driving impairment, the odds ratio that the occasional users, as compared to non-users, had an increase of a SDLP of $\geq$ 2.1 cm in the straight road segments was 2.33 (95% CI: 0.76 – 7.12). The corresponding odds ratio for daily users compared to nonusers was 1.69 (95% CI 0.58 – 4.83).

Daily users exhibited a small but significant mean decrease of 1.16 mph ($p = 0.02$) in their average speed relative to the posted speed limit on straight road segments from baseline to post use, and a mean decrease of 0.79 mph which approached significance ($p=.06$) on curved road segments (Table 4). The change in speed (baseline to post) in the roadway with straight

segments following acute cannabis use was significantly different in the daily use group compared to those with no use (p=.02) and occasional use group (p=.01) with those in the daily use driving slower at post use (Figure 1). The change in speed in an urban roadway with curved segments approached statistical significance d in the daily use group compared to the occasional (p=.06) with those in the daily use group driving slower at post use (Figure 1).

4. Discussion

This study aimed to examine acute effects of cannabis on driving performance among those who use cannabis occasionally compared to those who use daily. We hypothesized that those in the occasional use group would experience relatively more impairment than the daily use group due to some tolerance to the acute effects of cannabis among the latter. To take into account possible learning effects inherent to participating in a novel driving simulation environment twice within two hours, the protocol included a group that did not use cannabis. Our primary outcome measure was standard deviation of lateral placement (SDLP), a measure of lateral control over a vehicle that in a broader sense reflects the extent of weaving within a lane. SDLP has been found to be sensitive to the impairing effects of cannabis and alcohol in on-the-road and driving simulator investigations.[12,15,17,27] We observed that occasional users and the daily users tended to increase their SDLP after smoking cannabis, with a statistically significant increase for occasional users in urban straight road segments and for daily users in urban curved road segments. In covariate-adjusted analysis, only the mean increase in SDLP of 1.9 cm in urban straight road segments in the occasional users compared to the mean decrease of 1.1 cm in the non-users achieved statistical significance. In these straight road segments, the standardized

mean difference in the change in unadjusted SDLP (post minus baseline) for the occasional users compared to the non-users was also statistically significant.

Our analysis did not intend to investigate factors responsible for potential differences in baseline SDLP in nonusers, occasional users, and daily users. Rather, using a within subject design, it focused on comparing changes from baseline SDLP associated with acute cannabis use in these three groups. The mean, SD, and range in unadjusted SDLP on urban straight road segments in the non-users during their first driving session was 25.7 cm, 5.75 cm, and 15.3 to 40.5 cm, respectively. It may be noted that the inter-group difference in the baseline least-squared adjusted mean SDLP for urban straight road segments comparing the non-user group (25.5 cm) and the occasional user group (21.7 cm) of 3.8 cm exceeded the intra-group change of 1.9 cm in SDLP associated with acute use of cannabis in the occasional users. SDLP in healthy, sober adults is characterized by a relatively wide normative range, which depends in part on the nature of the test course or platform, the speed driven, the experience and attentiveness of the driver, their age, and other less defined factors.[28,29] For example, in one naturalistic study of on-the-road driving, the mean and standard deviation of 57 normal adults driving approximately 37 to 47 miles per hour on straight highway segments was 16 cm $\pm$ 2.9 cm.[30] In a driving simulator study of acute cannabis use in 18 occasional cannabis users driving at approximately 55 mph on straight highway segments, baseline (i.e. post-placebo) mean, SD, and range of SDLP was 28.8 cm, 17.8 cm, and 24.7 – 44.8 cm, respectively. In that same study, the estimated increase in SDLP associated with acute cannabis smoking that resulted in an increase in blood THC from zero to 7 ng/ml was 1.8 cm, a fraction of the baseline range and variability.[17] Thus, in the present study, as in others, the increment in SDLP associated with acute cannabis observed in occasional

users, while statistically significant, was less than the natural variability in SDLP found in healthy, adult drivers.

SDLP has been favored as an outcome measure in driving impairment research because it is a sensitive indicator of performance that can be measured in both on-the-road driving protocols and driving simulators.[27,31] SDLP represents a continuous tracking task that may be affected by drug actions that decrease driver vigilance or that impair reaction time, visuomotor coordination or hand steadiness. In a recent meta-analysis of data from 32 studies using car and PC-based simulator platforms, a blood alcohol concentration of 0.05 percent was associated with a 2.0 cm increase in SDLP.[27] Similarly in the present investigation a mean increase in blood THC concentration of occasional users to 6.4 ng/mL was associated with a covariate adjusted mean increase in SDLP of 1.9 cm.

Other recent studies using car-based simulator platforms.[14,15,17,32,33] and on the road testing[12,21,34] to investigate within-person changes in SDLP associated with acute cannabis smoking have reported variable findings. Inter-study comparisons of changes in SDLP expressed in centimeters must be undertaken cautiously in light of differences in the simulator platforms and the nature of the simulated driving scenarios utilized in different studies. SDLP tends to increase as vehicle speed increases and as road curvature increases.[30] In the present study, SDLP was assessed in a simulated urban environment where the slower speed of travel (speed limit 25 miles per hour) would tend to decrease SDLP relative to simulations conducted at faster highway speeds, but where distractions including storefronts, lighted signage, intersections, and pedestrians close to the roadway may increase SDLP relative to limited access highway scenarios. Our observation of significant cannabis-related inter-group increases in SDLP in the straight road segments but not in the curved road segments may be a consequence of the more

prominent roadside distractions in the former. In the meta-analysis by Irwin et al. of alcohol impaired driving,[27] the effect of different driving simulator platforms on outcome was mitigated by expressing the change in SDLP in terms of standardized mean differences. The weighted mean effect of acute alcohol consumption (blood alcohol range 0.033 to 0.110 percent) on standardized mean difference in SDLP was 0.23.[27] By comparison, the standardized mean difference in SDLP associated with acute cannabis use by occasional users in the present study of 0.64 (95% CI 0.09 – 1.19) represents a more pronounced effect. The implication that a drug-induced increase in SDLP will be associated with an increased crash risk is inferential. As noted in an analysis by Owens and Ramaekers, alcohol-induced increases in SDLP are highly correlated with alcohol-induced increases in crash risk, as is diazepam-induced increase in SDLP and diazepam-induced change in crash risk as a function of time after inception of medication usage. [35] In on-the road placebo-controlled studies of hypnotic drugs, SDLP was correlated with the number of excursions out of lane.[36] Quantitative predictions linking cannabis-associated increases in SDLP with increased crash risk might emerge in the future if an enlarging body of research demonstrates consistent dose-response relationships between indicators of acute cannabis use and epidemiological crash risk data.

Our secondary outcome was speed. The daily use group drove slower after smoking cannabis in urban straight road segments. The occasional use group drove faster after smoking cannabis, but not significantly. In covariate-adjusted analysis, the change among daily users (to drive slower) was significantly different from both the occasional and non-using group in the straight segment. Our findings are somewhat inconsistent with prior studies that found a decline in speed among occasional users after smoking cannabis[14,17] whereas we observed this for daily users and not occasional users. It is possible that daily users have increased familiarity with driving after

smoking and may have approached the driving task with more caution or learned vigilance as a compensatory tactic to driving after smoking. We found that daily and occasional users experienced similar levels of self-reported drug effects and yet daily users had significantly higher levels of driving confidence, which may be supporting evidence for this idea.

Overall, the findings related to SDLP and speed do not provide clear evidence that occasional users have worse driving performance after cannabis than daily users. Our study allowed participants to smoke what they are accustomed to using, rather than providing the same amount of cannabis to both occasional and daily users. We found that daily users consumed more cannabis than occasional users, and achieved higher blood THC concentrations, while reporting similar subjective drug effects. In this regard, we found evidence of tolerance. Given the emerging and somewhat inconsistent evidence for tolerance to the effects of cannabis relevant for driving performance,[7,8] this question is worthy of future study. To our knowledge, the only other driving simulator study to have directly compared the impact of acute cannabis smoking on SDLP in occasional and daily users reported no significant impact in either group.[37]

4.1 Limitations

This study has several limitations. Our assessment of driving performance using SDLP was conducted in urban drive simulations where the speed limit was either 25 or 35 miles per hour; SDLP at higher speeds on simulated highway segments, the focus of several other studies, was not examined. We also used an observational design rather than an experimental design which limits our ability to quantify how much cannabis was consumed. Although this is an important limitation, this approach allowed us to study cannabis use under real-world conditions with participants using typical concentration cannabis flower products they purchased at state-licensed

dispensaries. Even under experimental conditions there is evidence that research participants self-titrate cannabis consumptions which undermine efforts to standardize dose.[38,39] Extremes of age and years of driving experience are known to influence driving skill, with young and/or inexperienced drivers, and elderly drivers, exhibiting impaired performance and increased collision risk.[23-25] To increase the likelihood we could observe an impact of cannabis that would not be obscured by dominant age and driving experience effects, we limited enrollment to participants 25 to 45 years of age, with active licensure and automobile insurance, who drove on average ≥ 4 days per month and ≥ 650 miles in the prior six months. Despite this, we observed relatively large inter-individual variation in many performance measures which may have limited our ability to observe significant differences between cannabis user groups. We recruited participants who either used occasionally (weekly) or daily by setting eligibility on the number of days used in a week. However, there remains variability in frequency of use as it relates to the number of times used per day, amount used per day, and the concentrations of products used per day. These inter-individual variations may have also contributed to reduced power to detect differences between groups. Future research should continue to explore how history of use relates to the acute effects of cannabis use.

Our study was powered to detect a group-level difference in SDLP of. 3.6cm. However, if the true effect size were smaller, such as 2.4 cm, then our study, at 64 percent power, may have been underpowered to detect this difference. Those interested in a smaller effect size should keep this in mind when planning future studies and may need to collect data from more subjects. However, our study was appropriately powered to detect within-individual changes in SDLP.

The external generalizability of our participants is not fully known. We were successful in recruiting both men and women across the eligible age range, but the large majority of our

participants were non-Hispanic white and those who used occasionally and in the non-user group reported more education than daily user group. Although we attempted to recruit equal numbers of participants who used occasionally and daily, our final analysis sample had fewer participants that used occasionally. It was challenging to recruit participants with a sustained pattern of weekly but less than daily or near daily use. This may not be surprising considering the prevalence of cannabis use frequency in Colorado where among those use currently use cannabis, nearly half (48.2%) use daily or nearly daily whereas 31.6% use between 4 and 19 days per month.[40]

4.2 Conclusion

In this study of the acute effects of cannabis use on driving performance among participants with a history of using cannabis daily or occasionally, we found evidence for decrements of driving performance in both groups relative to baseline for SDLP, that was of moderate size and statistical significance only in the occasional users. Small, statistically significant decreases in speed were observed in the daily use group. Since direct contrasts between the occasional users and daily users in SDLP were not statistically significant, the study results do not conclusively establish that occasional users exhibit more driving impairment than daily users when both smoke cannabis ad libitum. Future research should examine a greater range of cannabis intoxication with continued attention to the role of cannabis use history and tolerance on impairment.

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Table 1. Participant demographic characteristics, and driving and cannabis use experience

	Participant Group		
	Daily use n=31 % (n)	Occasional use n=24 % (n)	No current use n=30 % (n)
Gender			
Male	17 (54.8%)	14 (58.3%)	12 (40.0%)
Female	14 (45.2%)	10 (41.7%)	18 (60.0%)
Age			
25-35	22 (71.0%)	20 (83.3%)	20 (66.7%)
36-45	9 (29.0%)	4 (16.7%)	10 (33.3%)
Ethnicity			
Non-Hispanic	25 (80.6%)	21 (87.5%)	26 (86.7%)
Hispanic	6 (19.4%)	2 (8.3%)	4 (13.3%)
Unknown	0 (0.0%)	1 (4.2%)	0 (0.0%)
Race			
White	26 (83.9%)	23 (95.8%)	26 (86.7%)
Other[a]	5 (16.1%)	0 (0.0%)	3 (10.0%)
Unknown	0 (0.0%)	1 (4.2%)	1 (3.3%)
Education			
High school and some college	15 (48.4%)	4 (16.7%)	4 (13.3%)
Completed college	14 (45.2%)	12 (50.0%)	14 (46.7%)
Graduate degree	2 (6.5%)	8 (33.3%)	12 (40.0%)
Driving Experience, Cannabis use			
	Mean (SD)	Mean (SD)	Mean (SD)
Driving experience, years	15.3 (5.7)	13.5 (5.6)	15.9 (5.2)
Age at first use, years	17.1 (5.8)	17.6 (4.7)	18.5 (4.6)
Lifetime years smoked	15.6 (7.6)	13.4 (6.9)	--
Number of days used, past 30	29.7 (1.3)	5.7 (2.6)	--
Number of days use per week, past 30	7.0 (0.0)	1.5 (0.5)	--
Times used per day on average, past 30	4.9 (4.6)	1.4 (0.9)	--

[a] "Other" includes African American/Black, American Indian/Alaska Native, Asian and multiracial

Table 2. Characteristics of cannabis use during observed smoking

	Participant group					
	Daily use n=31			**Occasional use** n=24		
	mean (SD)	median	range	mean (SD)	median	range
Concentration used (%THC)	22.1 (3.0)	22.2	(15.0, 27.5)	21.1 (3.6)	20.1	(15.3, 29.7)
Weight combusted (milligrams)	417.3 (316.5)	332.0	(29.0, 1,101.0)	149.3 (125.0)	113.0	(6.0, 463.0)
Number of inhalations	21.0 (13.4)	17.0	(2.0, 49.0)	9.0 (5.1)	8.0	(2.0, 21.0)
Total time smoked (minutes)	10.4 (4.2)	12.0	(0.0, 15.0)	5.9 (3.5)	5.0	(1.0, 13.0)

Table 3. Blood cannabinoid concentrations and perceived drug effect before and after observed cannabis smoking

	Daily use n=31						Occasional use n=24					
	Baseline			**Post-use**			**Baseline**			**Post-use**		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Whole Blood Concentrations												
THC (ng/mL)*	5.0 (6.4)	2.5	(<LOD, 26.0)	36.4 (37.4)	24.8	(1.3, 146.7)	< LOD	< LOD	(0.0, 0.0)	6.4 (5.6)	5.6	(1.0, 29.6)
THC-COOH (ng/mL)*	57.5 (49.5)	34.8	(3.5, 178.4)	98.1 (90.6)	59.1	(8.2, 341.7)	1.3 (2.81)	< LOD	(0.0, 11.2)	10.9 (8.79)	8.2	(3.2, 46.0)
Self-reported drug effects												
VAS of High	0.6 (1.6)	0.0	(0.0, 8.0)	47.2 (16.6)	46.0	(13.0, 81.0)	1.0 (2.3)	0.0	(0.0, 8.0)	52.4 (15.7)	55.8	(16.0, 79.0)
VAS of Driving confidence *	99.6 (0.8)	100.0	(96.0, 100.0)	61.4 (32.8)	70.0	(0.0, 100.0)	99.4 (1.3)	100.0	(95.0, 100.0)	38.4 (32.9)	28.0	(0.0, 97.0)

Note. LOD = limit of detection = 0.2 ng/mL; VAS = Visual Analog Score, ranged from 0-100

*Denotes statistically significant t-test, unequal variances, comparing pre-post differences in daily use vs. occasional use groups at alpha = 0.05

Table 4. Adjusted models comparing driving performance by cannabis use group

	No use			Occasional use			Daily use			*Comparisons between groups, P-values*		
	Pre	Post	*p*	Pre	Post	*p*	Pre	Post	*p*	Daily v. no use	Occ v. No use	Daily v. Occ.
SDLP, urban straight road segments (cm)[a]	25.5	24.4	.24	21.7	23.6	**.02**	23.2	25.0	.18	0.08	**0.02**	0.99
SDLP, urban curved road segments (cm)[a]	26.6	27.7	.15	24.0	26.3	.06	23.8	25.7	**.02**	0.48	0.42	0.82
Mean speed relative to speed limit, urban straight road segments (mph)	2.88	3.32	.38	2.75	3.33	.16	3.07	1.91	**.02**	**0.02**	0.83	**0.01**
Mean speed relative to speed limit, urban curved road segments (mph)	-2.36	-2.12	.62	-2.67	-1.89	.31	-2.55	-3.34	.06	0.11	0.61	**0.06**

Note. Values shown are covariate adjusted least-squared means.
SDLP is standard deviation of lateral placement; mph is miles per hour
All models adjusted for gender, age, ordering of simulator scenarios, period (baseline vs. post-use), and interaction of period and order
[a]models adjusted for speed

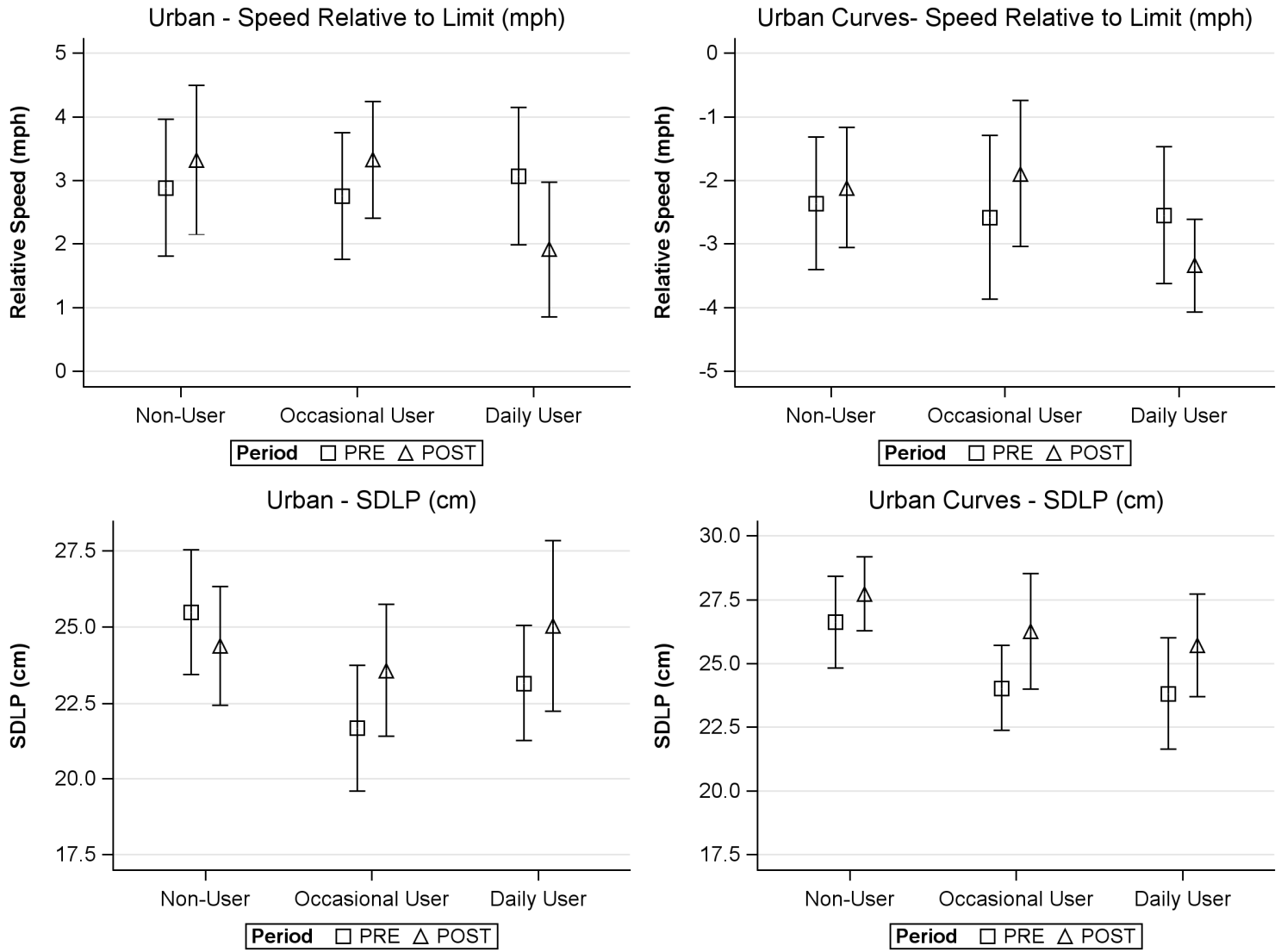

Figure 1. Plots of driving simulator outcomes by cannabis use group at baseline (PRE) and after (POST) cannabis use. *Note*. Boxes represent the mean and error bars represent 95% confidence intervals.