

Effects of therapeutic cannabis on simulated driving: A pilot study

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Abstract

Background: Although medical cannabis has been available to Canadians since 2001, there is little research on the effects of cannabis on driving in individuals who use cannabis medically. This pilot study sought to determine the effects of therapeutic cannabis use on simulated driving. **Methods:** Eligible participants reported daily use of cannabis for therapeutic purposes, with a medical authorization. Prior to the test session, participants were asked not to smoke their regular dose. Participants (n=14) completed self-report questionnaires, including subjective effects questionnaires (visual analog scales), the Addiction Research Centre Inventory (ARCI), and Profile of Mood States (POMS), and provided blood (for determination of THC and metabolites). They also drove a simulator both before and after smoking their usual daily dose of cannabis. Outcome measures on simulated driving consisted of overall mean speed, straightaway mean speed, straightaway lateral control, and brake latency. Speed and lateral control were also measured under cognitive load. **Results:** After smoking cannabis, overall mean speed was reduced. No effects of therapeutic cannabis were found on straightaway mean speed or straightaway lateral control for either condition (standard or cognitive load) or on brake latency. After smoking therapeutic cannabis in the lab, changes in speed and lateral control were negatively correlated with the amount of cannabis smoked per day. Prior to smoking therapeutic cannabis in the lab, under baseline conditions, speed and lateral control under cognitive load were also correlated with the amount of cannabis used per day. Therapeutic cannabis use increased subjective reports and blood levels of THC and metabolites. **Conclusions:** The present study suggests that, even with repeated daily use, cannabis consumption among therapeutic users may alter driving behavior. This has implications for road safety and use of cannabis for therapeutic purposes.

Keywords: cannabis; driving; medicinal cannabis; weaving; speed

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Introduction

With the growing legalization of cannabis for non-medical use, assessing the outcomes of cannabis use in the population is of increasing significance (Fischer, Murphy, Kurdyak, Goldner, & Rehm, 2015). According to data from the Canadian Cannabis Survey (CCS) (HealthCanada, 2018), 13% of respondents indicated that they used cannabis for therapeutic purposes. In terms of driving, 39% of CCS respondents who had used cannabis in the past 12 months also reported driving within two hours of consumption (HealthCanada, 2018). Although it is still too early to know whether driving under the influence of therapeutic cannabis will increase post-legalization (Hall & Lynskey, 2016), evidence-informed understanding of the impacts of therapeutic

cannabis use on driving and greater knowledge of the characteristics of therapeutic users is needed.

Epidemiological studies have found an increased risk of motor vehicle collisions in motorists that are under the influence of cannabis (Bondallaz et al., 2016; Sayer et al., 2014). Driving simulators provide a safe means to study the effects of drugs on driving. In this regard, consistent with epidemiological data, some studies with driving simulators have found an increase in collisions after use of cannabis (Ogourtsova, Kalaba, Gelinis, Korner-Bitensky, & Ware, 2018; Ronen et al., 2008). Simulator studies have looked at a number of variables that may influence driving after cannabis use, most commonly speed (Anderson, Rizzo, Block, Pearlson, & O'Leary, 2010; Arkell et al., 2019; Lenne et al., 2010; Ronen et al., 2010; Ronen et al., 2008) and 'weaving' (i.e. standard deviation of lateral

position; SDLP) (Arnell et al., 2019; Bosker et al., 2012; Micallef et al., 2018; Ronen et al., 2010; Ronen et al., 2008; Veldstra, Bosker, de Waard, Ramaekers, & Brookhuis, 2015). Where effects have been found, the most consistent are on SDLP (Arnell et al., 2019; Bosker et al., 2012; Micallef et al., 2018; Ronen et al., 2010; Ronen et al., 2008; Veldstra et al., 2015); but see (Micallef et al., 2018; Ogourtsova et al., 2018), and sometimes speed (Lenne et al., 2010; Ronen et al., 2008), but not always (Anderson et al., 2010; Arnell et al., 2019; Ogourtsova et al., 2018; Ronen et al., 2010). Other studies have also found decreased steering control (Lenne et al., 2010; Ronen et al., 2010; Ronen et al., 2008), longer reaction time (Lenne et al., 2010), and increased headway (Lenne et al., 2010). No effects were found on brake latency (Liguori, Gatto, & Jarrett, 2002; Liguori, Gatto, & Robinson, 1998). In our recent study of the effects of smoked cannabis on the simulated driving performance of young recreational cannabis users, we observed that those driving 30 minutes after smoking cannabis demonstrated significant reductions in speed, both driving as usual and also driving under conditions of increased task demands (Brands et al., 2019).

At present, to the best of our knowledge, there have been no studies of the effects of therapeutic cannabis use on driving. Therapeutic users often use cannabis frequently, or daily (Goulet-Stock et al., 2017), and the few studies centered on the effects of repeated, or frequent, cannabis use on simulated driving have yielded equivocal results. In one study, driving errors following the smoking of cannabis were worse in regular cannabis users compared to non-regular users (Downey et al., 2013). This suggests that repeated users do not habituate to the effects of cannabis on driving, consistent with evidence for impaired driving in one study of habitual cannabis users (Tank et al., 2019). In other studies, weaving was more evident in occasional users, as compared to regular users, after oral synthetic THC (dronabinol) (Bosker et al., 2012) or smoked cannabis (Hartley et al., 2019), suggesting that regular users may be tolerant to the effects of cannabis.

An interesting observation in this latter study is that differences between occasional and frequent users of cannabis were also evident following placebo, suggesting that frequent therapeutic users of cannabis may demonstrate different driving abilities even at baseline. Indeed, in a cross-sectional study, it was found that participants who used cannabis at least 4 times a week had slower mean speeds, and were relatively slower than the car in front of them, as compared to a group of infrequent cannabis users. (Doroudgar et al., 2018). The frequent users of cannabis also had mean blood THC levels above the legal cut-off of 5 nanograms/ml. Thus, detriments in baseline driving performance may be related to residual

levels of THC, as the authors propose (Doroudgar et al., 2018).

The above-mentioned studies of the effects of repeated cannabis use on driving also assayed levels of Δ -9-tetrahydrocannabinol (THC) in the blood after administration of cannabinoids. In all studies, levels of THC were higher in the blood of frequent users of cannabis, as compared to occasional users (Bosker et al., 2012; Downey et al., 2013). The findings of increased levels of THC in frequent cannabis users speaks to the importance of further delineating the relationship of THC to changes in driving. Given the mixed findings with respect to the effects of repeated cannabis on driving, it is not clear if these increased levels of THC in the blood are associated with decrements in driving behavior. An increasing number of jurisdictions worldwide are considering or implementing non-zero *per se* limits for THC detected in drivers, and research to identify scientifically supported limits is ongoing (Hedlund, 2015; Watson & Mann, 2016).

The purpose of the present pilot study was to study simulated driving in therapeutic cannabis users who were asked to smoke their usual dose of cannabis before driving the simulator. Driving was measured, and subjective effects questionnaires were administered both before and 30 minutes after smoking cannabis. Blood was also collected at these time points for determination of levels of THC and its metabolites. It was hypothesized that therapeutic cannabis would affect driving, increase blood levels of THC, and yield subjective effects.

Materials and Methods

Study participants were recruited through advertisements in local social media and posters in the community. Inclusion criteria were: 1) males and females aged 19 years and older; 2) daily use of cannabis and an authorization to use cannabis for therapeutic purposes; 3) holds a valid class G or G2 Ontario driver's licence (or equivalent from another jurisdiction); 4) willing to abstain from alcohol and other drugs (other than nicotine and drugs required for treatment of a medical condition) for 48 hours prior to study session; and 5) provides written and informed consent. Exclusion criteria were: 1) use of psychoactive medications or drugs other than cannabis, prescription opioids, or nicotine; and 2) self-reported current alcohol or other drug dependence.

Participants were screened for eligibility over the telephone through self-reports. Upon eligibility confirmation by telephone, participants were asked to attend the Centre for Addiction and Mental Health (CAMH), a large addiction and mental health teaching and research hospital in Toronto, Canada, for one study

session. Participants were instructed not to smoke their first daily dose of cannabis prior to coming to CAMH on the day of testing, and not to use alcohol or drugs other than cannabis (unless required for treatment of a medical condition, and excluding nicotine) during the 48 hours prior to attending their session. This study received ethical approval from the Research Ethics Boards of both CAMH and Health Canada. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Study session: Upon attending the lab, participants provided informed consent. Participants provided a urine sample to screen for recreational drugs and a saliva sample to screen for use of cannabis. A DrugWipe (Alcohol Countermeasure Systems) with a 10 ng/ml cut-off was used to screen for cannabis use. A breathalyzer was also performed to verify that participants had not consumed alcohol prior to study participation. Participants were then asked to provide a blood sample for measurement of Δ -9-tetrahydrocannabinol (THC) and metabolites (11-nor-9-carboxy- Δ 9-tetrahydrocannabinol (THC-COOH) and 11-hydroxy- Δ 9-tetrahydrocannabinol (11-OH-THC)), both before smoking their own usual dose of a cannabis cigarette and 30 minutes after smoking. After completing an initial practice session on the driving simulator to mitigate possible practice effects on driving outcomes, participants were asked to drive the simulator (Virage model VS500M) before and 30 minutes after smoking the cigarette.

The Profile of Mood States (POMS) (Pollock, Cho, Reker, & Volavka, 1979), Addiction Research Centre Inventory (ARCI, short form 49 item) (Haertzen & Hickey, 1987), and Visual Analogue Scales (VAS) were administered to measure subjective drug effects before and 30 minutes after cannabis exposure. For the ARCI, the subscales were: amphetamine, morphine-benzedrine, lysergic acid diethylamine, benzedrine, pentobarbital-chlorpromazine-alcohol, euphoria, and sedation. For the POMS, the subscales were: Tension-Anxiety, Anger-Hostility, Depression-Dejection, Friendliness, Fatigue, Confusion, Vigor, Elation, Arousal, and Positive Mood. For the VAS, the measures were: 'I feel this effect', 'I feel this high', 'I feel the good effects', 'I feel the bad effects', 'I like cannabis', 'This feels like cannabis', and 'I feel the rush'. All subjective effects questionnaires were administered by computer.

Prior to driving the simulator, participants completed a questionnaire that assessed their demographics, concurrent drug use, cannabis use, and therapeutic cannabis use while driving. Questionnaire data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools, hosted at CAMH (Harris et

al., 2009). REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Driving simulator: The CAMH Virage VS500M simulator consists of the driver's side instrument cluster, steering wheel, controls, and center console of a General Motors compact car. The steering wheel provides dynamic force feedback, as do the brake and accelerator pedals. The visual system consists of three 50-inch screens providing a 180° field of view in the front, and two 17-inch side displays providing visual feedback for the left and right blind zones.

Two of the driving scenarios (to measure speed and lateral control) were programmed on the same 9-km stretch of rural highway with posted speed limits of 80 km/hr, and included periodic driving interactions (e.g. slowly moving vehicle, disabled vehicle at roadside) that differed for each scenario. The road was a single lane, with a lane in the opposite direction. Participants could change lanes if they wished. Participants were instructed to drive as they normally would, allowing for assessment of driver behavior (i.e. how a driver chooses to operate the vehicle) as opposed to one's ability to perform certain driving skills. For the first rural highway scenario, participants drove the simulator under standard conditions, and for the second they drove under conditions of increased cognitive load for the entire session, where they were instructed to count backwards by threes from a randomly selected 3-digit number^{21,22}. The addition of a counting backward task has a long history of use to increase the complexity of cognitive and other tasks²³.

The third driving scenario, designed to measure brake latency, was programmed on a 4-lane expressway with a speed limit of 100 km/hr. Prior to the drive, participants were instructed to drive at the posted speed limit and to brake in response to stop signs that periodically appeared at the roadside. Consistent with a choice reaction time task (Risser et al., 2008; Sommer et al., 2008), participants were required to brake in response to 7 of the 10 appearing stimuli (which of the 7 trials requiring the participant to brake differed for each scenario, as did the timings between all trials). Participants were instructed to brake as quickly as possible and come to a complete stop if a stop sign appeared facing them, on the right side of the road. If a stop sign appeared at an angle, they were instructed to keep driving, and not brake at all.

The first two practice scenarios were the same as the first two testing scenarios, but with more objects on the road. The practice scenario for brake latency presented stop signs in a different order and with different timings than any of the testing scenarios. The scenarios (including both standard and cognitive load conditions) were presented in the same order for all participants.

Outcome measures: Our driving outcome variables of interest were brake latency, straightaway mean speed, overall mean speed, and straightaway lateral control; the latter three measures were most commonly affected by cannabis in previous research (Anderson et al., 2010; Downey et al., 2013; Hartman et al., 2015; Lenne et al., 2010; Ronen et al., 2010). Lateral control was operationalized as the standard deviation of the absolute distance between the centre of the simulated vehicle and the centre of the lane in which the participant was driving, in meters. Straightaway lateral control and straightaway mean speed were calculated from a straightaway section (i.e. a straight stretch of road approximately 1.6 km in length without any traffic control signals or other moving vehicles). For the overall mean speed measure, data collected throughout the entire scenario were included, where participants had to manoeuvre or brake in response to stimuli. Speed and lateral control variables were assessed under both single task and cognitive load scenarios.

Statistical Analyses:

Effects of therapeutic cannabis on driving variables: The driving variables (straightaway lateral control, straightaway lateral control under cognitive load, straightaway mean speed, straightaway mean speed under cognitive load, overall mean speed, and overall mean speed under cognitive load) were analysed with two-way Condition (standard, cognitive load) X Time (pre, post) repeated-measures ANOVAs. Where a significant effect of Time was revealed, THC pre-cannabis was entered as a covariate into an ANCOVA, to determine whether THC at baseline had an effect on driving. Latency was analysed with a *t*-test comparing pre and post cannabis measures.

Levels of THC and metabolites in blood and subjective scores after therapeutic cannabis: Levels of THC and each metabolite, as well as each VAS score and ARCI and POMS subscale, were analysed with paired *t*-tests comparing the value before cannabis (pre) to the value after cannabis (post).

Correlations: Correlations between a number of variables and driving measures before smoking cannabis were conducted. The variables entered into the correlation were: 1) number of times per day that cannabis is smoked; 2) amount of cannabis used per occasion; 3) grams used per

day (calculated as variable 1 multiplied by variable 2); and 4) levels of THC and metabolites before smoking cannabis.

The changes in driving (post cannabis – pre cannabis) were also correlated with the above-mentioned demographic variables, the change in weight of the cigarette, and the time taken to smoke the cigarette. Correlation coefficients were also conducted between changes in driving measures after smoking and changes in THC and metabolites (post cannabis – pre cannabis).

Data were analysed with SPSS version 25. A significance level of $p \leq 0.05$ was adopted for all analyses.

Results

A total of 14 participants completed the simulator trials. Three withdrew due to an experience of simulator sickness, a vertigo-like reaction to interacting with a driving simulator. One participant tested positive for use of recreational drugs, and another experienced negative effects of having refrained from smoking cannabis that day; these two participants were also withdrawn from the study. All participants that completed the study screened negative for recreational drugs, and 10 screened negative for THC in saliva.

Demographics: Most participants were male ($n=11$), with an average age \pm SEM of 42 ± 9 . Seven of the participants reported using cannabis five or more times per day. All participants had authorization to use medical cannabis. The average (\pm SEM) amount used per occasion was 1.1 ± 1.1 grams. The average amount used per day (amount per occasion X number of occasions per day) was 4.8 ± 5.7 grams. Of the 14 participants, 5 reported taking cannabis for pain, 1 for anxiety, and 8 for multiple conditions.

The mean amount smoked of the cannabis cigarette in the laboratory was 387 ± 56.0 mg (mean \pm SEM). There was no correlation between the amount smoked per occasion and the amount smoked in controlled laboratory conditions ($p=.122$). Of the 14 participants in the therapeutic group, 4 reported smoking a strain with over 20% THC, 6 reported smoking a strain with 15-20% THC, and 2 smoked cannabis with 10-15% THC. One participant smoked a high cannabidiol (CBD) strain with less than 1% THC. Eight reported smoking low CBD strains, but 4 participants did not provide the CBD content. One participant did not report what they smoked during the laboratory test.

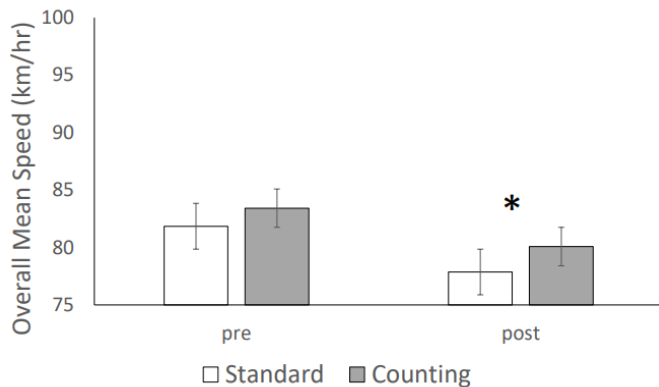
Self-reported driving under the influence of cannabis: Of the 14 participants, 8 reported that, within the past year, they had consumed cannabis within 1 hour of driving. Of these, 9 reported 'no risk' or 'slight risk' of driving after cannabis use. Participants reported that cannabis affected them in a number of ways. For example, three participants

reported no difference in driving after using cannabis, and one mentioned that their driving was ‘not the best’ after driving. Two reported that their driving improved. One reported being more cautious. One reported being more focused and drove slower because they were more paranoid.

Effects of therapeutic cannabis on simulated driving: Therapeutic cannabis reduced overall mean speed, as revealed by an effect of Time in a Condition X Time ANOVA ($F(1, 13)=10.395, p=0.007$). Entering THC (ng/ml) at baseline as a covariate in an ANCOVA did not affect this, as an effect of Time was still revealed ($p=0.05$; Figure 1).

Figure 1

Overall Mean Speed (\pm SEM) in km/hr before or 30 minutes after smoking therapeutic cannabis

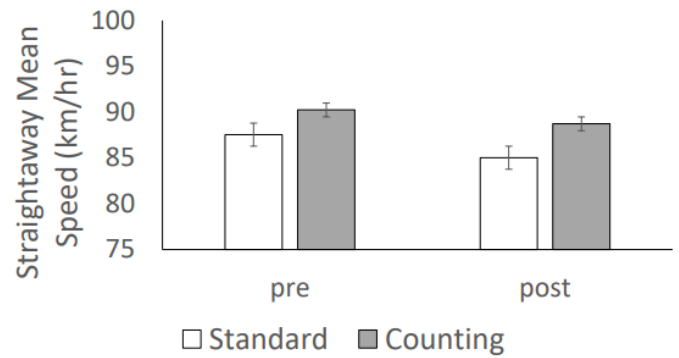


Note. * $p<0.05$, effect of Time (Time X Condition ANOVA); open and grey bars represent standard and cognitive load cognitions, respectively.

For straightaway mean speed and straightaway lateral control, two-way Condition X Time ANOVAs revealed no significant effects. Analysis of brake latency also did not reveal an effect of cannabis ($p>0.05$; see Figures 2-4).

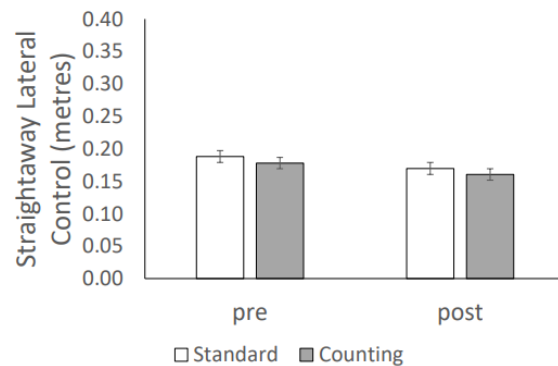
Figure 2

Straightaway Mean Speed (\pm SEM) in km/hr before or 30 minutes after smoking therapeutic cannabis.



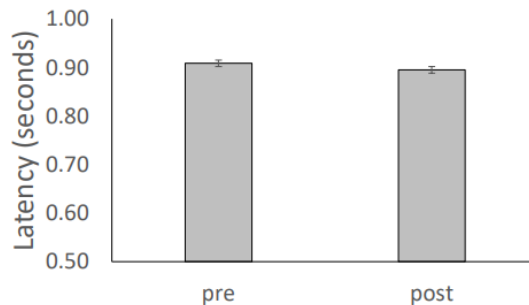
Note. Open and grey bars represent standard and cognitive load conditions, respectively. (Brands et al., 2019).

Figure 3: *Straightaway Lateral Control (\pm SEM) in meters before or 30 minutes after smoking therapeutic cannabis.*



Note. Open and grey bars represent standard and cognitive load conditions, respectively (Brands et al., 2019).

Figure 4: *Latency (\pm SEM) in seconds before or 30 minutes after smoking therapeutic cannabis*



Effects of therapeutic cannabis on blood levels of THC and subjective measures: Analysis of blood levels of THC and metabolites with *t*-tests revealed that levels were significantly higher after smoking therapeutic cannabis (THC: $t(13)=-6.510, p<0.001$; 11-OH-THC: $t(13)=-5.953,$

$p < 0.001$; THC-COOH: $t(13) = -4.869$, $p < 0.001$). For the VAS, the difference between pre-cannabis and post-cannabis was also significant for all measures except for 'I feel the bad effects' ('I feel this effect': $t(13) = -11.394$, $p < 0.001$; 'I feel this high': $t(13) = -7.401$, $p < 0.001$; 'I feel the good effects': $t(13) = -18.101$, $p < 0.001$; 'I like cannabis': $t(13) = -7.156$, $p < 0.001$; 'This feels like cannabis': $t(13) = -14.864$, $p < 0.001$; 'I feel the rush': $t(13) = -4.698$, $p < 0.001$). See Table 1.

Table 1

Mean \pm SEM measures of THC and metabolites and scores on VAS before (pre) and after (post) smoking therapeutic cannabis

Blood Measure	Pre	Post
THC	3.99 \pm 0.93	19.56 \pm 3.01*
THC-COOH	45.04 \pm 10.52	63.46 \pm 12.23*
11-OH-THC	1.51 \pm 0.38	4.78 \pm 0.74*
VAS	Pre	Post
I feel this effect	4.43 \pm 3.62	69.00 \pm 6.01*
I feel this high	4.29 \pm 3.61	59.79 \pm 7.34*
I feel the good effects	1.93 \pm 1.65	75.71 \pm 4.09*
I feel the bad effects	4.43 \pm 4.43	11.14 \pm 4.56
I like cannabis	14.86 \pm 8.57	81.29 \pm 5.39*
This feels like cannabis	5.36 \pm 4.27	89.57 \pm 4.23*
I feel the rush	0.86 \pm 0.72	39.86 \pm 8.50*

* $p < 0.05$ pre vs post, t -tests.

Analysis of the ARCI and POMS with paired t -tests from baseline to 30 minutes after smoking cannabis revealed no significant effects for any of the POMS subscales. For the ARCI, the subscales of 'amphetamine' ($t(13) = -2.347$, $p = 0.035$) and 'euphoria' ($t(13) = -2.188$, $p = 0.047$) were significantly increased after smoking.

Correlations between demographic variables, THC and metabolites and simulated driving: It was observed that two participants smoked a great deal of cannabis per day (15 grams and 20 grams). An outlier test revealed that the more extreme value was an outlier and this data was removed from analysis, resulting in a sample size of 13. Results of the correlational analysis are provided in Table 2. Of note, driving measures under cognitive load before

smoking cannabis were correlated with the amount smoked per occasion and the number of grams smoked per day. After smoking cannabis, the change in driving scores was also correlated with the amount used per occasion/day, and the time taken to smoke the cannabis in the lab.

Discussion

The purpose of the present pilot study was to investigate the effects of therapeutic cannabis use on simulated driving. It was found that therapeutic cannabis reduced overall mean speed with no effects on straightaway mean speed, straightaway lateral control, or brake latency. After smoking therapeutic cannabis, changes in speed and lateral control were correlated with the amount smoked per day as well as the amount smoked during the test session. Therapeutic cannabis users had elevated THC and metabolite levels at baseline; smoked cannabis increased these levels. Under conditions of cognitive load prior to smoking cannabis, speed measures and lateral control were correlated with the amount of cannabis used per day in therapeutic users.

The main finding that therapeutic cannabis use decreased overall mean speed is consistent with some previous studies, which found that recreational cannabis use decreased measures of speed (Lenne et al., 2010; Ronen et al., 2008). As mentioned in the Introduction, not all reports have found decreased speed in response to recreational cannabis (Anderson et al., 2010; Arkell et al., 2019; Ogourtsova et al., 2018; Ronen et al., 2010). Where decreases have been found, it has been suggested that these decreases are compensatory (Ward & Dye, 1999) as cited in Ronen et al., (2008), and this may be the case for those who use cannabis for therapeutic purposes. The reason for the discrepancy in findings of the various studies is not known, but may be related to the driving scenarios used. Indeed, in the present study, therapeutic cannabis users did not demonstrate overall effects on straightaway mean speed. Measures of overall mean speed would have included challenges in the roadside, such as passing a slow-moving vehicle. Decreases in overall mean speed may therefore represent an attempt by the driver to compensate for obstacles on the road, an effect which may be enhanced by cannabis.

Several previous studies have reported that drivers 'weave' more after smoking cannabis (Arkell et al., 2019; Bosker et al., 2012; Micallef et al., 2018; Ronen et al., 2010; Ronen et al., 2008; Veldstra et al., 2015), measured as an increase in SDLP or other measures of lateral control. It should be mentioned that, in the present study, therapeutic users of cannabis did not demonstrate changes in lateral control after smoking therapeutic cannabis. It is possible that our measures were not as sensitive as those used in previous studies. As well, drivers in our study were

instructed to drive as they normally would, while in some other studies instructions emphasized maintaining a specified speed, meaning that participants in the present study could have maintained their lane control as a result of reducing their speed, (Brands et al., 2019).

After smoking therapeutic cannabis, changes in lateral control were found to be correlated with the amount smoked during the session and also the amount smoked per day; lateral control decreased with greater amounts smoked. Thus, it is possible that heavier use of therapeutic cannabis may result in greater changes in driving after smoking therapeutic cannabis. All participants in the present study were taking cannabis to treat an underlying condition; 5 of the 14 participants used cannabis mainly to treat pain and 8 for multiple conditions, including pain in some cases. It is known that pain can affect driving (Nilsen et al., 2011), and thus it is possible that use of therapeutic cannabis may affect performance decrements caused by pain or other underlying pathology. Indeed, changes in lateral control after smoking therapeutic cannabis were correlated with the amount of cannabis smoked per day, suggesting that those with more acute symptoms who take more cannabis may demonstrate greater reduction of symptom-induced changes in driving.

Even before smoking cannabis, changes in speed and lateral control under cognitive load were correlated with the amount smoked on a daily basis. Thus, it is possible that the underlying illness, or residual THC, may affect driving. Unfortunately, the present study did not collect data to determine the degree of pain or other malaise suffered, and therefore changes in baseline performance could be affected by the degree of symptomology. Further research is needed to disentangle these various effects on driving. If residual THC is impairing driving, then this has consequences for road safety, and suggests that people who use therapeutic cannabis must be aware of any residual effects of cannabis.

The finding of residual levels of THC in the blood is an important observation. The current legal limit of THC in Canada is 2-5 ng/ml, and on average, participants had 3.99 ng/ml of THC in the blood prior to smoking. This has important consequences for the use of therapeutic cannabis, and for establishing safe timelines of driving after use of therapeutic cannabis. It may be possible that therapeutic users of cannabis require a longer washout period before driving. This is especially important given that the amount of cannabis smoked per day was correlated with changes in speed and lateral control, findings which suggest that drivers may be impaired at baseline.

Limitations: Interpretations of this pilot study must be made in view of several limitations. First, study

participants smoked their own strain of cannabis. This may have introduced variability in the data, as the potency and cannabinoid composition of the cannabis were unknown. A second limitation is the inherent difficulty in definitively concluding that participants had not smoked cannabis on the day of testing. This leads to the possibility that the relationships seen in the baseline data in this study were related to recently smoked cannabis. The only method to definitively conclude that participants have not smoked cannabis on a given day is through inpatient studies, and these are beyond the scope of many investigations. A third limitation is related to the fact that there were no correlations between the amount smoked at home and the amount of cannabis consumed in the laboratory. Indeed, participants smoked more at home per occasion than in the one instance in the laboratory. This suggests that the results of the present study may have limited ecological validity, and future studies will need to investigate whether different doses of cannabis have different effects on therapeutic cannabis users. A fourth limitation relates to the use of straightaway road scenarios to measure lateral control. Straight roadways are less sensitive to changes in weaving than roads with curvatures. Thus, future studies will need to investigate the possibility that different road conditions may have varying effects on driving after the use of therapeutic cannabis. This last point is particularly germane given that there is some inconsistency in the driving simulator literature. For example, as mentioned in the Introduction, some, but not all, studies have found effects of cannabis on speed, and most studies have found effects on SDLP. Thus, differences may be related to the types of scenarios used. Finally, the sample size in the present study is limited. With a total sample of 14 participants, this study is nevertheless consistent with another recently published report (Arkell et al., 2019). Despite the relatively small sample size, we still saw effects on mean speed. However, there is a possibility that the lack of effect on lateral control may be related to a lack of statistical power. Visual inspection of the lateral control data suggests that our experimental design may not have been ideal for detecting changes in lateral control after cannabis (discussed above). Nevertheless, this study is a pilot study and suggests that further investigation of the effects of therapeutic cannabis on driving are warranted.

Author Disclosures

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Contributors: PDC oversaw the trial conduct, analyzed the data, and prepared the first draft of the manuscript; AM

collected the data; JM collected the data; AF collected the data; HH designed the questionnaire; CMW helped to design the study; TMW designed the questionnaire; REM helped to design the study; BLF provided medical oversight and helped to design the study; BB was the study PI, designed the study, and provided oversight. All authors assisted with data interpretation and approve the submitted manuscript.

Conflict of Interest: BLF has/will receive some in-kind donation of cannabis product from Canopy and Aurora and medication donation from Pfizer and Bioprojet, and was provided a coil for transcranial magnetic stimulation study from Brainsway. BLF has/will perform research with industry funding obtained from Canopy, Bioprojet, Alcohol Countermeasures, and Alkermes. BLF has received in-kind donations of nabiximols from GW Pharma for past studies funded by CIHR and NIH.

Figure Captions

References

- Anderson, B. M., Rizzo, M., Block, R. I., Pearlson, G. D., & O'Leary, D. S. (2010). Sex differences in the effects of marijuana on simulated driving performance. *Journal of Psychoactive Drugs*, 42(1), 19-30. doi:10.1080/02791072.2010.10399782
- Arkell, T. R., Lintzeris, N., Kevin, R. C., Ramaekers, J. G., Vandrey, R., Irwin, C., Haber, P.S., McGregor, I. S. (2019). Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. *Psychopharmacology (Berl)*. doi:10.1007/s00213-019-05246-8
- Bondallaz, P., Favrat, B., Chtioui, H., Fornari, E., Maeder, P., & Giroud, C. (2016). Cannabis and its effects on driving skills. *Forensic Science International*, 268, 92-102. doi:10.1016/j.forsciint.2016.09.007
- Bosker, W. M., Kuypers, K. P., Theunissen, E. L., Surinx, A., Blankespoor, R. J., Skopp, G., Jeffery, W.K., Walls, H.C., van Leeuwen, C.J. Ramaekers, J. G. (2012). Medicinal Delta(9) -tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. *Addiction*, 107(10), 1837-1844. doi:10.1111/j.1360-0443.2012.03928.x
- Brands, B., Mann, R. E., Wickens, C. M., Sproule, B., Stoduto, G., Sayer, G. S., Burston, J., Pan, J.F., Matheson, J., Stefan, C., George, T.P., Huestis, M.A., Rehm, JLe Foll, B. (2019). Acute and residual effects of cannabis on driving simulator performance of young drivers: randomized clinical trial. *Drug and Alcohol Dependence*, 205:107641.
- Doroudgar, S., Mae Chuang, H., Bohnert, K., Canedo, J., Burrowes, S., & Perry, P. J. (2018). Effects of chronic marijuana use on driving performance. *Traffic Injury Prevention*, 19(7), 680-686. doi:10.1080/15389588.2018.1501800
- Downey, L. A., King, R., Papafotiou, K., Swann, P., Ogden, E., Boorman, M., & Stough, C. (2013). The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. *Accident Analysis and Prevention*, 50, 879-886. doi:10.1016/j.aap.2012.07.016
- Fischer, B., Murphy, Y., Kurdyak, P., Goldner, E., & Rehm, J. (2015). Medical marijuana programs - Why might they matter for public health and why should we better understand their impacts? *Preventive Medicine Reports*, 2, 53-56. doi:10.1016/j.pmedr.2014.12.006
- Goulet-Stock, S., Rueda, S., Vafaei, A., Ialomiteanu, A., Manthey, J., Rehm, J., & Fischer, B. (2017). Comparing Medical and Recreational Cannabis Users on Socio-Demographic, Substance and Medication Use, and Health and Disability Characteristics. *European Addiction Research*, 23(3), 129-135. doi:10.1159/000475987
- Haertzen, C. H., & Hickey, J. E. (1987). ARCI: measurement of euphoria and other drug effects. In M. A. Bozarth (Ed.), *Methods for Assessing the Reinforcing Properties of Abused Drugs* (pp. 489-524). New York: Springer-Verlag.
- Hall, W., & Lynskey, M. (2016). Why it is probably too soon to assess the public health effects of legalisation of recreational cannabis use in the USA. *Lancet Psychiatry*, 3(9), 900-906. doi:10.1016/S2215-0366(16)30071-2
- Harris, P. A., Taylor, R., Thielke, R., Payne, J. I., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, 42(2), 377-381.
- Hartley, S., Simon, N., Larabi, A., Vaugier, I., Barbot, F., Quera-Salva, M. A., & Alvarez, J. C. (2019). Effect of Smoked Cannabis on Vigilance and Accident Risk Using Simulated Driving in Occasional and Chronic Users and the Pharmacokinetic-Pharmacodynamic Relationship. *Clinical Chemistry* doi:10.1373/clinchem.2018.299727

- Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Pierce, R. S., Gorelick, D. A., . . . Huestis, M. A. (2015). Cannabis effects on driving lateral control with and without alcohol. *Drug and Alcohol Dependence, 154*, 25-37. doi:10.1016/j.drugalcdep.2015.06.015
- Health Canada. (2018). Canadian Cannabis Survey. Retrieved from <https://www.canada.ca/en/services/health/publications/drugs-health-products/canadian-cannabis-survey-2018-summary.html>
- Hedlund, J. (2015). *Drug-impaired driving: A guide for what States can do*. Washington, D.C.
- Lenne, M. G., Dietze, P. M., Triggs, T. J., Walmsley, S., Murphy, B., & Redman, J. R. (2010). The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. *Accident Analysis and Prevention, 42*(3), 859-866. doi:10.1016/j.aap.2009.04.021
- Liguori, A., Gatto, C. P., & Jarrett, D. B. (2002). Separate and combined effects of marijuana and alcohol on mood, equilibrium and simulated driving. *Psychopharmacology (Berl), 163*(3-4), 399-405. doi:10.1007/s00213-002-1124-0
- Liguori, A., Gatto, C. P., & Robinson, J. H. (1998). Effects of marijuana on equilibrium, psychomotor performance, and simulated driving. *Behavioural Pharmacology, 9*(7), 599-609.
- Micallef, J., Dupouey, J., Jouve, E., Truillet, R., Lacarelle, B., Taillard, J., Daurat, A., Authie, C., Rascol, O., Philip, P., Mestre, D. (2018). Cannabis smoking impairs driving performance on the simulator and real driving: a randomized, double-blind, placebo-controlled, crossover trial. *Fundamental and Clinical Pharmacology, 32*(5), 558-570
- Nilsen, H. K., Landro, N. I., Kaasa, S., Jenssen, G. D., Fayers, P., & Borchgrevink, P. C. (2011). Driving functions in a video simulator in chronic non-malignant pain patients using and not using codeine. *European Journal of Pain, 15*(4), 409-415. doi:10.1016/j.ejpain.2010.09.008
- Ogoursova, T., Kalaba, M., Gelinis, I., Korner-Bitensky, N., & Ware, M. A. (2018). Cannabis use and driving-related performance in young recreational users: a within-subject randomized clinical trial. *Canadian Medical Association Journal Open, 6*(4), E453-E462. doi:10.9778/cmajo.20180164
- Pollock, V., Cho, D. W., Reker, D., & Volavka, J. (1979). Profile of Mood States: the factors and their physiological correlates. *Journal of Nervous and Mental Disease, 167*(10), 612-614.
- Risser, R., Chaloupka, C., Grundler, W., Sommer, M., Hausler, J., & Kaufmann, C. (2008). Using non-linear methods to investigate the criterion validity of traffic-psychological test batteries. *Accident Analysis and Prevention, 40*, 149-157.
- Ronen, A., Chassidim, H. S., Gershon, P., Parmet, Y., Rabinovich, A., Bar-Hamburger, R., Cassuto, Y., . Shinar, D. (2010). The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. *Accident Analysis and Prevention, 42*(6), 1855-1865. doi:10.1016/j.aap.2010.05.006
- Ronen, A., Gershon, P., Drobiner, H., Rabinovich, A., Bar-Hamburger, R., Mechoulam, R., Cassuto, Y., Shinar, D. (2008). Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. *Accident Analysis and Prevention, 40*(3), 926-934. doi:10.1016/j.aap.2007.10.011
- Sayer, G., Ialomiteanu, A., Stoduto, G., Wickens, C. M., Mann, R. E., Le Foll, B., & Brands, B. (2014). Increased collision risk among drivers who report driving after using alcohol and after using cannabis. *Canadian Journal of Public Health, 105*(1), e92-93. doi:10.17269/cjph.105.4351
- Sommer, M., Herle, M., Hausler, J., Risser, R., Schutzhofer, B., & Chaloupka, C. (2008). Cognitive and personality determinants of fitness to drive. *Transportation Research Part F, 11*, 362-375.
- Tank, A., Tietz, T., Daldrup, T., Schwender, H., Hellen, F., Ritz-Timme, S., & Hartung, B. (2019). On the impact of cannabis consumption on traffic safety: a driving simulator study with habitual cannabis consumers. *International Journal of Legal Medicine, 133*(5), 1411-1420
- Veldstra, J. L., Bosker, W. M., de Waard, D., Ramaekers, J. G., & Brookhuis, K. A. (2015). Comparing treatment effects of oral THC on simulated and on-the-road driving performance: testing the validity of driving simulator drug research. *Psychopharmacology (Berl), 232*(16), 2911-2919. doi:10.1007/s00213-015-3927-9
- Ward, N. J., & Dye, L. (1999). Cannabis and driving: a literature review and commentary. *UK DETR Road Safety Research Report, 12*.
- Watson, T. M., & Mann, R. E. (2016). International approaches to driving under the influence of cannabis: A review of evidence on impact. *Drug and Alcohol Dependence, 169*, 148-155.

Table 2

Correlations (r_2) between driving measures and various demographic characteristics or blood levels of THC and metabolites of THC

Baseline	ovMS	OvMS_C	StrMS	StrMS_C	StrLatCont	StrLatCon_C	Latency
# Times/Day	0.332	0.341	0.295	0.414	0.246	0.514	0.244
Amt Smoked per Occasion	0.467	0.779*	0.425	0.673*	0.353	0.732*	-0.137
Grams Used Per Day	0.481	0.749*	0.447	0.692*	0.341	0.747*	-0.086
Baseline THC	0.167	0.229	0.256	0.401	0.484	0.45	0.321
Baseline THC-COOH	0.118	0.46	0.378	0.526	0.503	0.449	0.235
Baseline 11-OH-THC	0.412	0.282	0.449	0.515	0.571*	0.478	0.146
Change After Cannabis	ovMS	OvMS_C	StrMS	StrMS_C	StrLatCont	StrLatCon_C	Latency
# Times/Day	-0.197	0.113	-0.078	0.054	-0.041	-0.32	-0.388
Amt Smoked per Occasion	-0.564*	-0.578*	-0.691*	-0.734*	-0.589*	-0.835*	-0.049
Grams Used Per Day	-0.555*	-0.491	-0.649*	-0.647*	-0.506	-0.843*	-0.17
Change in Cigarette weight	-0.73*	-0.082	-0.285	-0.19	-0.523	-0.376	-0.124
Time Taken to Smoke	-0.673*	-0.548	-0.501	-0.742*	-0.546	-0.906*	-0.264
Change in THC	-0.24	0.341	0.175	0.425	0.182	0.255	0.235
Change in THC-COOH	0.029	0.18	-0.044	0.375	-0.057	0.359	0.473
Change in 11-OH-THC	-0.222	0.223	0.12	0.477	-0.054	0.511	0.518

* $p < 0.05$, significant correlations; OvMS: Overall Mean Speed; OvMS_C: Overall Mean Speed Cognitive Load; StrMS: Straightaway Mean Speed; StrMS_C: Straightaway Mean Speed Cognitive Load; StrLatCont: Straightaway Lateral Control; StrLatCon_C: Straightaway Lateral Control Cognitive Load; # Times/Day: Number of Smoking Occasions per day

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