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ORIGINAL INVESTIGATION

Combined effect of alcohol and cannabis on simulated driving

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Abstract

Rationale With alcohol and cannabis remaining the most commonly detected drugs in seriously and fatally injured drivers, there is a need to understand their combined effects on driving.

Objectives The present study examined the effects of combinations of smoked cannabis (12.5% THC) and alcohol (target BrAC 0.08%) on simulated driving performance, subjective drug effects, cardiovascular measures, and self-reported perception of driving ability.

Methods In this within-subjects, double-blind, double-dummy, placebo-controlled, randomized clinical trial, cannabis users (1–7 days/week) aged 19–29 years attended four drug administration sessions in which simulated driving, subjective effects, cardiovascular

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measures, and whole blood THC and metabolite concentrations were assessed following placebo alcohol and placebo cannabis (<0.1% THC), alcohol and placebo cannabis, placebo alcohol and active cannabis, and alcohol and active cannabis.

Results Standard deviation of lateral position in the combined condition was significantly different from the placebo condition ($p < 0.001$). Standard deviation of lateral position was also significantly different from alcohol and cannabis alone conditions in the single task overall drive ($p = 0.029$ and $p = 0.032$, respectively), from the alcohol alone condition in the dual task overall drive ($p = 0.022$) and the cannabis alone condition in the dual task straightaway drive ($p = 0.002$). Compared to the placebo condition, the combined and alcohol conditions significantly increased reaction time. Subjective effects in the combined condition were significantly greater than with either of the drugs alone at some time points, particularly later in the session. A driving ability questionnaire showed that participants seemed unaware of their level of impairment.

Conclusion Combinations of alcohol and cannabis increased weaving and reaction time, and tended to produce greater subjective effects compared to placebo and the single drug conditions suggesting a potential additive effect. The fact that participants were unaware of this increased effect has important implications for driving safety.

Keywords THC · Cannabis · Driving · Alcohol · Subjective effects · Weaving · Reaction time

Introduction

Alcohol is the most commonly detected drug in seriously and fatally injured drivers and cannabis is the second most commonly detected drug (Biecheler et al. 2008; Brubacher et al. 2016; Woodall et al. 2015). Combined alcohol and cannabis use is frequently reported by non-medical users of cannabis (Boak et al. 2020) and this combination is often reported in studies of fatally and non-fatally injured drivers (Brubacher et al. 2016). With increasing legalization of non-medical use of cannabis, understanding the effects of cannabis combined with alcohol on driving and other health-related outcomes is of growing importance.

Meta-analyses of epidemiological studies concluded that driving under the influence of cannabis leads to an increase in collision risk (Asbridge et al. 2012; Li et al. 2012). The most consistent findings from driving simulation studies are that cannabis detrimentally affects measures of lane control (Arkell et al. 2019; Bramness et al. 2010; Hartman et al. 2015; Lenne et al. 2010; Micallef et al. 2018; Ramaekers et al. 2000; Robbe 1998; Ronen et al. 2008), reduces speed (Anderson et al. 2010; Brands et al. 2019; Hartman et al. 2016; Lenne et al. 2010; Ronen et al. 2010; Ronen et al. 2008), slows reaction time (Lenne et al. 2010; Ronen et al. 2008), and decreases steering control (Ronen et al. 2010). However, there are studies that did not find a decrease in speed (Ogourtsova et al. 2018; Robbe 1998) or a decrease in lane control (Anderson et al. 2010; Brands et al. 2019; Ogourtsova et al. 2018; Ronen et al. 2010).

The harmful effects of alcohol on driving and collision risk are well known, with the risk of collision involvement increasing exponentially as blood alcohol concentration (BAC) increases (Voas et al. 2012). Alcohol consumption leads to impairment of driving ability by influencing psychomotor skills, reaction time, the ability to keep a vehicle within traffic lanes and focus on more than one task, vigilance, and speed control, and by increasing aggression and decreasing hazard perception (Moskowitz and Florentino 2000). Alcohol at a BAC of 0.05% also disrupts the coordinated movement of the eyes (horizontal nystagmus) and reduces peripheral vision (tunnel vision) (Marcinkova et al. 2019). In a review by Moskowitz and Florentino (2000), the majority of studies reported significant impairment in driving-related skills at a BAC of 0.05%, while more than 94% of studies reported impairment in these tasks at a BAC of 0.08%.

A small number of studies have examined the combined effects of alcohol and cannabis on driving, showing an increase in standard deviation of lateral position (SDLP) (Hartman et al. 2015; Ramaekers et al. 2000), reaction time (Ramaekers et al. 2000), steering wheel deviation, and elevated lane deviations (Ronen et al. 2010). The effects on speed are less consistent, with one study demonstrating a reduction in time spent driving over the speed limit, while Δ^9-tetrahydrocannabinol (THC) concentrations were high (Hartman et al. 2016) and another showing no effects on speed (Ronen et al. 2010). In general, as with studies of fatigue and individual drugs (Vinckenbosch et al. 2020), it appears that SDLP may be the measure most consistently affected by combined alcohol and cannabis use, with effects on other measures appearing less consistently. This variation in results may be related to variations in doses of alcohol and cannabis used in previous studies. The target breath alcohol concentrations (BrACs) varied from 0.04 to 0.07% while the cannabis THC concentrations varied from 1.78 to 6.7% (Downey et al. 2013; Hartman et al. 2015, 2016; Ramaekers et al. 2000; Ronen et al. 2010).

Drivers may not be aware of the effects of alcohol and cannabis on their driving abilities. One study of therapeutic cannabis users observed that they felt there was little risk associated with driving after the use of cannabis (Di Ciano et al. 2020). Another study showed that individuals believed their driving ability may be more negatively impacted by alcohol than cannabis (Watson et al. 2019). However, no studies reported individuals' assessments of the combined effects of cannabis and alcohol on their driving abilities.

The potency of non-medical cannabis is increasing in recent years, with one report showing the average THC level in the USA increasing from 8.9% THC in 2008 to 17.1% THC in 2017 (Chandra et al. 2019). Since alcohol and cannabis is a common combination for non-medical drug users (Boak et al. 2020), there is an increasing need to understand the effects of combined use, particularly with a higher dose of THC, on driving and related measures. The purpose of the present study was to add to the previous findings in the literature by examining the effects of cannabis with a higher THC concentration (12.5% THC; approximately 93.75 mg) and alcohol (target BrAC of 0.08%; the Criminal Code per se drink-drive limit in Canada) on simulated driving performance, self-reported drug effects, cardiovascular measures, and self-reported perception of driving ability.

Methods

Trial design

This was a within-subject, double-blind, double-dummy, placebo-controlled, randomized clinical trial assessing the impact of alcohol and cannabis, alone and combined, on driver behavior conducted at a single site in Toronto, Ontario, Canada, at the Centre for Addiction and Mental Health (CAMH). The study was reviewed and approved by both the CAMH Research Ethics Board (123/2015) and Health Canada Research Ethics Board (2015-0018), was in accordance with the Declaration of Helsinki, and was registered on clinicaltrials.gov (NCT03106363). The study included the following four conditions: (1) placebo alcohol and placebo cannabis; (2) an intoxicating dose of alcohol and placebo cannabis; (3) placebo alcohol and active cannabis; and (4) an intoxicating dose of alcohol and active cannabis. After initial eligibility was determined through the CAMH secure REDCap database (Harris et al. 2009) or telephone prescreener, participants provided written informed consent at a session in which their eligibility was further determined. The study involved a total of 6 sessions: one eligibility assessment, one practice session, and four drug administration sessions (one for each condition), separated by at least 72 h. The order of the four test sessions was randomized. The CAMH Research Pharmacy prepared the cannabis cigarettes and alcohol beverages and maintained the randomization codes. This was a computer-generated list by the Research Pharmacy and was concealed from personnel involved in running the trial. There were 24 orders of conditions, with dropouts being replaced. In total, each order was presented a maximum of 2–3 times. The CAMH Clinical Laboratory performed all clinical and specialty tests, including the quantitative determination of the THC and metabolite concentrations in whole blood.

Participants

Healthy young adults were recruited through community and public transit advertisements in Toronto between May 2017 and November 2019. Inclusion criteria were as follows: (1) use of cannabis at least once per week; (2) males who report consuming at least 5 drinks and females at least 4 drinks in about 2 h in the past 6 months and at least one episode of rapid alcohol consumption in the past 6 months (3 or more drinks over a span of 1 h); (3) 19–29 years of age. This age range was selected to target young adults, who are the most likely to use cannabis and to drive after using cannabis. It also excluded participants who were under the legal drinking and cannabis use age in the province of Ontario; (4) holds a class G or G2 Ontario driver's license (or equivalent from another jurisdiction) for at least 12 months; (5) willing to abstain from using alcohol for 48 h and cannabis for 72 h prior to sessions; (6) willing to abstain from all other drugs not prescribed for medical purposes for the duration of the study; (7) provides written and informed consent. Exclusion criteria were as follows: (1) urine toxicology screens negative for cannabinoids upon eligibility assessment, below 15 ng/mL; (2) diagnosis of severe medical or psychiatric conditions; (3) females who were pregnant, breastfeeding, or were trying to become pregnant; (4) meets criteria for current or lifetime alcohol or substance dependence (DSM-IV); (5) is a regular user of medications that affect brain function (e.g., antidepressants, benzodiazepines, stimulants); (6) taking medications or has any medical condition for which alcohol is contraindicated; (7) first-degree relative diagnosed with schizophrenia; (8) severe allergy to citrus (lemon-lime).

Drug administration

Alcohol was administered with a target BrAC of 0.08%. This was achieved by providing participants with approximately 1.5 g of alcohol per liter of body water. The amount of body water was determined using pre-established equations that differed for males and females (Watson et al. 1980). Alcohol was provided in the form of a chilled beverage of 80-proof vodka mixed with tonic water in a 1:3 ratio. The placebo alcohol was administered as beverages containing tonic water at an equivalent volume as the alcohol beverage. All beverages were capped with a few milliliters of lemon-lime juice with a minimal amount of vodka capped on top and on the rim of the glass to enhance alcohol cues. In addition, all beverages were divided into three equal portions, and participants were asked to consume each portion over a period of 5 min, for a total of 15 min. Three minutes after the completion of the alcohol consumption, participants were asked to rinse their mouths with water.

In both the active and placebo conditions, participants were given a single cigarette that contained approximately 750-mg

plant material. The cannabis in the active condition contained 12.5% ± 2% THC (approximately 94 mg THC) and was obtained from Aurora Cannabis Enterprises Inc., a licensed producer approved by Health Canada. Placebo cannabis (<0.1% THC) was provided by the National Institute of Drug Abuse (NIDA) Drug Supply Program. Procedures for handling and administration of cannabis were identical to those described previously (Brands et al. 2019). Briefly, participants were instructed to smoke ad libitum, over the course of 10 min in a negative airflow room with external ventilation in the CAMH hospital, designated for research studies on smoking of cannabis and tobacco.

Driving simulator

The CAMH Virage VS500M simulator features 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 55-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 (Brands et al. 2019).

Custom driving simulation scenarios were all programmed on the same 9-km 2-lane rural highway. Participants were instructed to maintain a speed of 80 km/h and drive in the center of the lane to the best of their ability, to stay on the main road and drive as they normally would, and to interact with other vehicles and obstacles as they would in the real world. Each of the scenarios programmed two interactions with other vehicles: a slow moving vehicle and a disabled vehicle at roadside. Also included in each scenario was a stretch of 1600-m straight road with no oncoming traffic (straightaway). The order in which these were encountered varied for each scenario. Driving assessment included both a single and a dual task simulation, with the dual task simulation always immediately following the single task simulation. In this dual task simulation, participants counted backwards by 3's from a random number between 700 and 999 while driving (Lansdown and Saunders 2012; North and Hargreaves 1999). The addition of a counting backwards task has a long history of use to increase the complexity of cognitive and other tasks (Peterson and Peterson 1959). Data generated during the slow moving and disabled vehicle portions of the drives were not included in our analysis. Data were recorded at a frequency of 10 Hz.

A separate driving simulation scenario was programmed to measure reaction time in terms of brake pedal latency. This scenario consisted of an endless 4-lane highway where participants were instructed to drive at 100 km/h, while remaining in the second lane to the right. When presented with a true stop sign (stop sign facing them), they were to come to a complete stop as quickly as possible. When presented with a false stop sign (stop sign facing away from them), they were to maintain their speed. During each trial, a total of 10 stop signs appeared suddenly at the far right lane: 7 of them were true and 3 of them were false. Data were recorded at a frequency of 60 Hz. The total time spent driving all three driving simulations was approximately 30 min.

Procedure

Eligibility assessment Participants deemed eligible on the phone or via an online pre-screener were invited for an in-person eligibility assessment. Participants were required to provide a urine sample for point-of-care drug testing (Quickscreen™ CLIA-Waived 14-panel Multi Drug Test: cannabis; cocaine; opiates/morphine; methamphetamine; amphetamine; benzodiazepines; barbiturates; methadone; buprenorphine; tricyclic antidepressants; MDMA; oxycodone; phencyclidine; EDDP) and pregnancy test (BFP Pregnancy Test Strips by Fairhaven Health) for females. A positive result for 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) was needed in order to avoid enrolling participants who were naïve to cannabis. Participants underwent a medical assessment and were screened for psychiatric disorders using the Structured Clinical Interview for DSM-IV non-patient edition. Finally, blood samples were collected for routine biochemistry and hematology. Eligible participants were instructed not to drive to CAMH for test sessions.

Ongoing eligibility at the beginning of every session was determined with the collection of a breath sample to confirm a BrAC of 0% (Alert™ J5 model, Alcohol Countermeasure Systems), a saliva THC test (Securetec DrugWipe® 3S, 25 ng/mL THC) to confirm abstinence from cannabis, and a point-of-care urine test to rule out other drug use. Female participants also had urine collected for point-of-care pregnancy testing.

Practice session During this session, participants completed a self-report questionnaire (demographics, driving behavior) and practiced responding to the subjective effects using visual analog scales (VAS) questions and driving on the simulator.

Drug administration sessions All four of the drug administration sessions were identical with the only difference being the alcohol and/or cannabis exposure conditions. Each drug administration session was separated by at least 72 h. The schedule of drug administration and data collection in each session is summarized in Table 1. Participants completed baseline subjective effects questionnaires, the driving simulation scenarios, and a perceived driving ability questionnaire. Also at baseline, cardiovascular measures (blood pressure and heart rate) and a blood sample (for quantitative determination of THC and its two major metabolites, 11-hydroxy-tetrahydrocannabinol (11-OH-THC) and THCCOOH) were collected. Once all baseline measures were completed, participants were administered alcohol.

Table 1 Schedule of drug administration and data collection. Time 0 is completion of the alcohol exposure procedure

	Eligibility Assessment	Practice Session	Drug Administration Sessions: Alcohol Exposure (-15 to 0 min) ↓		Cannabis Exposure (15 to 25 min) ↓							
Approximate Time			-2 h	-30 min	15 min	30 min	45 min	75 min	2 h	3 h	4 h	5 h
Driving Simulation Trial		x		x			x					
Breathalyzer	x	x	x		x	x	x	x	x	x	x	x
Physical exam, psychiatric exam (SCID)	x											
Vital signs	x		x		x	x	x	x	x	x	x	x
Urine: point-of-care drug screen	x	x	x									
Urine: point-of-care pregnancy test	x		x									
Blood: biochemistry, hematology	x											
Blood: THC and metabolites quantification			x				x					
Self-report questionnaire		x										
VAS		x	x		x	x	x	x	x	x	x	x
Saliva: point-of-care THC test		x	x				x					x
Perceived driving ability				x			x					
Reminder to refrain from driving For 24 h												x

Completion of this task was considered time 0. Cardiovascular measures, BrAC, and VAS assessing subjective drug effects were collected 15 min after the alcohol administration and the cannabis administration followed. Cardiovascular, BrAC, and VAS were subsequently collected at 30, 45, 75 min, and then hourly until 5 h after the alcohol administration. A second blood sample and saliva test were collected 45 min after alcohol administration (15–20 min after smoking) and this was followed by the driving trial and perceived driving ability questionnaire. Driving occurred 45 min after alcohol administration in order to capture effects during peak levels of BrAC and peak THC effects. For the remainder of the day, participants were seated in a lounge area where they were offered lunch and snacks. If their BrAC was still greater than 0.04% at the 5-h mark, participants were required to remain on site until it had dropped below this level. Upon completion of the session participants were provided with a taxi chit and study personnel ensured that they got in the taxi to be taken home.

Outcomes

Our primary outcome was simulated driving performance, which was operationalized with measures of SDLP, the mean and standard deviation of speed (km/h), maximum speed, and reaction time. Our speed variables and the lateral control variable were assessed for the complete drive and the straightaway section of the driving simulation scenario. Lateral control was operationalized as the SDLP in meters, using the lateral distance between the driver's car and the center of the driver's original lane, as a vector quantity. Speed variables and SDLP were assessed under single and dual task simulations. Reaction time, which utilized a separate third driving simulation scenario, was defined as the time taken (seconds) by the driver to hit the brake pedal once the stop sign appeared.

Our secondary outcomes reported here were subjective drug effects (measured by VAS), cardiovascular measures, and BrAC. The VAS consisted of 11 items, which participants rated on a scale of 0–100 (REDCap). In addition, participants were asked to rate their demonstrated driving skill on a Likert scale of 1 (demonstrated poor driving skills) to 5 (demonstrated excellent driving skills).

Whole blood THC, 11-OH-THC, and THCCOOH were quantified in the baseline and + 45-min blood samples. This was done by purification by solid phase extraction followed by derivatization and analysis by gas chromatography mass spectrometry. Limits of quantification (LOQ) were 0.5 ng/mL for THC and 1.0 ng/mL for 11-OH-THC and THCCOOH. For statistical analysis, all values below the LOQ were entered as a

zero. Procedures were identical to those described previously (Brands et al. 2019).

Throughout the study, participants were monitored for any adverse events (AEs) using a modified version of the Systematic Assessment for Treatment Emergent Effects (SAFTEE) questionnaire (Guy et al. 1986; Rabkin and Markowitz 1986). AEs were coded based on a list of preferred terms, and the date of onset, duration, severity, relationship to study drug, and action taken were recorded. In the event that an AE did not match the SAFTEE preferred terms, an alternate term was used. Some participants experienced multiple AEs; each AE was coded separately.

Sample size

The study intended to recruit 70 participants, in order to achieve the target sample of 50 participants. This sample size would provide power of 0.89 (Cohen's $d = 0.89$) to detect a medium effect size in a two-tailed F-test of a within-subjects main effect of one drug following drug administration. It would also provide power > .90 to detect a significant interaction with a medium effect size.

Approval for an interim analysis was requested from the REB. Conducting an interim analysis is standard for clinical trials in order to determine the efficacy of the trial partway through. This allows checking if it warranted stopping the trial since it is not justified to keep going if there is an effect with a smaller sample size. The analysis was conducted with $n = 20$ participants and SDLP was used as the primary measure. It was determined that stopping the study at a smaller sample size was warranted as we were powered to see an effect with 27 participants, so the study continued until 30 participants completed the study.

Statistical analysis

Primary outcomes Driving measures were analyzed with repeated-measures analyses of variance (ANOVAs) using the within-subjects factor condition (placebo, alcohol, cannabis, alcohol+cannabis) for both the baseline and post-drug administration. To determine whether there was an effect of sex on driving, driving data were also analyzed using mixed ANOVAs with condition (4 levels) as the within-subjects factor and Sex (2 levels) as the between-subjects factor. Significant effects were followed by planned comparisons of each condition to each other.

Secondary outcomes Subjective and cardiovascular effects were analyzed with condition (4 levels) × Time (9 levels) repeated-measures ANOVAs. BrACs were analyzed with condition (2 levels; alcohol, combined) × Time (9 levels) repeated-measures ANOVAs. Whole blood THC and metabolites (11-OH-THC and THCCOOH) concentrations were analyzed with condition (4 levels) × Time (2 levels) repeated-measures ANOVAs. Significant interactions were followed by planned comparisons of each condition at each time point. The driving ability question was analyzed with a one-way non-parametric analysis (Friedman test) of the effects of condition followed by planned comparisons of placebo to each drug condition, cannabis to alcohol and each drug condition to the drug conditions combined, analyzed with non-parametric statistics. Smoking topography measures (amount smoked in grams and smoking duration) were analyzed with one-way repeated-measures ANOVAs on the effect of condition (placebo, alcohol, cannabis, alcohol+cannabis). Estimated THC dose was analyzed with one-way repeated-measures ANOVAs on the effect of condition (cannabis, alcohol+cannabis).

For all analyses, a p value of ≤ 0.05 was adopted for significance. For all repeated-measures analyses, Geisser-Greenhouse corrections are reported as needed. Data were analyzed with SPSS version 25. Missing data were replaced with the group mean to allow for analysis. Three participants had missing VAS values, due to data not being saved or research personnel forgetting to provide the questions to participants (one at 15 min post-administration in the alcohol session, one at 45 min post-administration in the combined condition, and one at 300 min post-administration in the alcohol condition). Six participants had missing reaction time data, four due to failure of the simulator to generate the data (one in the alcohol condition, two in the cannabis condition, and one in the combined condition), and two participants due to missing one or more true stop sign (one in the alcohol condition and one in the cannabis condition).

Results

Participants

Of the 30 participants that completed the study, 28 (16 males and 12 females) were included in the final analyses. One participant was removed due to a suspected breach of protocol (did not abstain from cannabis use for 72 h) and the other was removed for not following study personnel instruction. The demographics of the remaining participants are presented in Table 2.

Primary outcome measures

ANOVAs on the effect of condition on baseline driving measures revealed no significant effects for both single and dual task simulations (see Table 3). No interactions or main effects

Table 2 Participant characteristics (mean (standard error of the mean), [range])

Sex	16 males 12 females
Age	22.54 (0.48)
Race/ethnicity	10 White European 3 Asian-East 7 White North American 3 mixed heritage 2 Asian-South 2 Latin American 1 Asian-South East
Height (m)	1.72 (0.02)
Weight (kg)	72.93 (2.39)
BMI (kg/m^2)	24.50 (0.64)
Cannabis use frequency (days/week)	2.93 (0.30), [1–7]
Alcohol drinking frequency (days/week)	2.08 (0.27), [0.46–7]

were found in the sex differences analysis. ANOVAs on the effect of condition on driving measures post-drug administration revealed significant effects for SDLP under both single [$F(2.361, 63.736) = 7.650$, $p = 0.001$] and dual task simulations [$F(1.806, 48.761) = 8.356$, $p = 0.001$], for straightaway SDLP under both single [$F(2.006, 54.150) = 3.316$, $p = 0.044$] and dual task simulations [$F(3, 81) = 9.791$, $p < 0.001$], for overall standard deviation of speed in the dual task condition [$F(1.547, 41.770) = 5.142$, $p = 0.016$] and straightaway standard deviation of speed in the dual task condition [$F(3, 81) = 2.989$, $p = 0.036$], for overall maximum speed in the dual task condition [$F(2.151, 58.074) = 4.265$, $p = 0.017$] and straightaway maximum speed in the dual task condition [$F(2.149, 58.030) = 3.904$, $p = 0.023$]. There was also a significant effect of condition on reaction time [$F(3, 81) = 3.884$, $p = 0.012$]. As for the analysis on sex differences, no interactions or main effects were found.

Follow-up comparisons revealed significant differences (see Table 4) between conditions. Under the single task simulation, significant differences were observed on the SDLP measure. For overall driving, clear additive effects were seen. The alcohol, cannabis, and combined condition showed significantly higher SDLP than placebo ([$t(27) = -2.179$, $p = 0.038$], [$t(27) = -3.181$, $p = 0.004$], [$t(27) = -4.783$, $p < 0.001$], respectively), and the combined condition showed significantly higher SDLP measures than both alcohol [$t(27) = -2.313$, $p = 0.029$] and cannabis [$t(27) = -2.259$, $p = 0.032$] conditions, which did not differ from each other. Further evidence for additive effects was observed on straightaway SDLP, where the combined condition, but not the alcohol or cannabis only conditions, showed significantly higher SDLP than placebo [$t(27) = -2.860$, $p = 0.008$]. No other comparisons were significant. Additional evidence was observed for additive effects under the dual task simulation, while in some instances it appeared that alcohol effects were predominant. For overall driving, the alcohol, cannabis, and combined

Table 3 Primary driving outcome measures for single task and dual task driving simulations by condition pre drug administration (mean (standard error of the mean)). Standard deviation of lateral position (SDLP) is in m. All speed measures are in km/h. Reaction time is presented in s

	Single task driving simulation							
	Overall				Straightaway			
	SDLP	Mean speed	Standard deviation of speed	Max speed	SDLP	Mean speed	Standard deviation of speed	Max speed
Pla	0.31 (0.01)	83.03 (1.08)	4.79 (0.67)	93.91 (1.27)	0.27 (0.02)	83.92 (1.18)	2.47 (0.22)	89.23 (1.41)
Alc	0.31 (0.01)	82.87 (0.78)	3.97 (0.26)	93.51 (1.42)	0.28 (0.02)	83.36 (1.16)	2.91 (0.25)	89.70 (1.55)
Can	0.31 (0.01)	82.81 (0.99)	3.85 (0.24)	93.63 (1.56)	0.27 (0.02)	83.18 (1.03)	2.37 (0.22)	88.18 (1.38)
Alc-Can	0.31 (0.02)	82.72 (0.82)	4.29 (0.32)	93.81 (1.60)	0.27 (0.02)	82.71 (0.76)	2.41 (0.21)	87.97 (1.02)
	Dual task driving simulation							
	Overall				Straightaway			
	SDLP	Mean speed	Standard deviation of speed	Max speed	SDLP	Mean speed	Standard deviation of speed	Max speed
Pla	0.28 (0.01)	83.56 (1.01)	4.99 (0.26)	96.34 (1.36)	0.24 (0.01)	83.59 (1.07)	3.16 (0.31)	90.22 (1.24)
Alc	0.28 (0.01)	82.88 (0.92)	5.04 (0.28)	96.67 (1.48)	0.24 (0.01)	83.37 (1.15)	3.00 (0.26)	89.32 (1.45)
Can	0.28 (0.01)	82.33 (0.84)	4.94 (0.34)	94.67 (1.35)	0.23 (0.01)	82.54 (1.02)	3.14 (0.33)	89.25 (1.38)
Alc-Can	0.29 (0.02)	82.30 (0.83)	5.21 (0.40)	95.34 (1.46)	0.22 (0.01)	82.77 (0.85)	3.00 (0.29)	88.62 (0.99)
	Reaction time							
Pla	0.99 (0.03)							
Alc	1.00 (0.03)							
Can	0.97 (0.02)							
Alc-Can	0.97 (0.02)							

Table 4 Primary driving outcome measures for single task and dual task driving simulations by condition post-drug administration (mean (standard error of the mean)). Standard deviation of lateral position (SDLP) is in m. All speed measures are in km/h. Reaction time is presented in s

	Single task driving simulation							
	Overall				Straightaway			
	SDLP	Mean speed	Standard deviation of speed	Max speed	SDLP	Mean speed	Standard deviation of speed	Max speed
Pla	0.30 (0.01)	84.07 (0.84)	4.72 (0.55)	93.85 (3.01)	0.27 (0.01)	83.86 (0.86)	3.04 (0.42)	90.01 (1.37)
Alc	0.32^{P} (0.01)	85.06 (1.38)	5.80 (0.78)	98.85 (3.02)	0.30 (0.01)	86.71 (1.90)	3.39 (0.40)	93.76 (2.38)
Can	0.33^{P} (0.01)	83.27 (0.78)	4.37 (0.47)	94.64 (1.65)	0.29 (0.02)	83.60 (1.08)	3.08 (0.49)	90.09 (1.79)
Alc-Can	0.37^{P,A,C} (0.02)	84.64 (1.82)	4.81 (0.44)	97.76 (2.41)	0.34^{P} (0.03)	86.37 (2.43)	3.14 (0.28)	93.19 (2.49)
	Dual task driving simulation							
	Overall				Straightaway			
	SDLP	Mean speed	Standard deviation of speed	Max speed	SDLP	Mean speed	Standard deviation of speed	Max speed
Pla	0.28 (0.01)	83.23 (0.94)	4.92 (0.29)	95.84 (1.43)	0.24 (0.01)	83.27 (1.13)	3.26 (0.26)	90.24 (1.50)
Alc	0.33^{P} (0.01)	87.34 (2.10)	6.38^{P} (0.59)	102.84^{P} (2.91)	0.30^{P} (0.02)	89.30 (2.96)	4.17^{P} (0.41)	97.59^{P} (2.98)
Can	0.32^{P} (0.02)	83.45 (1.09)	5.15^{A} (0.36)	97.04^{A} (1.73)	0.27 (0.01)	84.38 (1.39)	3.21^{A} (0.27)	91.27^{A} (1.78)
Alc-Can	0.38^{P,A} (0.02)	85.25 (2.27)	6.06^{P,C} (0.39)	101.08^{P} (2.68)	0.33^{P,C} (1.02)	85.46 (2.62)	3.74 (0.37)	93.16 (2.45)
	Reaction time							
Pla	0.99 (0.03)							
Alc	1.04^{P} (0.02)							
Can	0.99 (0.03)							
Alc-Can	1.04^{P,C} (0.02)							

$^{P}p < 0.05$, different from placebo; $^{A}p < 0.05$ different from alcohol; $^{C}p < 0.05$, different from cannabis

condition showed significantly higher SDLP than placebo ([$t(27) = -4.019$, $p < 0.001$], [$t(27) = -2.815$, $p = 0.009$], [$t(27) = -6.047$, $p < 0.001$], respectively). As well, the combined condition showed significantly higher SDLP than the alcohol condition [$t(27) = -2.437$, $p = 0.022$], but not the cannabis condition. On the straightaway, the alcohol and combined condition showed significantly higher SDLP than placebo ([$t(27) = -3.925$, $p = 0.001$], [$t(27) = -4.736$, $p < 0.001$], respectively). As well, the combined condition showed significantly higher SDLP than the cannabis condition [$t(27) = -3.512$, $p = 0.002$]. For overall driving, the standard deviation of speed for the alcohol and combined condition was significantly higher than placebo ([$t(27) = -2.712$, $p = 0.011$], [$t(27) = -4.457$, $p < 0.01$], respectively) and cannabis conditions ([$t(27) = 2.065$, $p = 0.049$], [$t(27) = -3.625$, $p = 0.001$], respectively). Maximum speed for the alcohol and combined condition was significantly greater than placebo ([$t(27) = -2.717$, $p = 0.011$], [$t(27) = -2.337$, $p = 0.027$], respectively) and the alcohol condition significantly greater than the cannabis condition [$t(27) = 2.454$, $p = 0.021$]. On the straightaway, the alcohol condition showed significantly higher standard deviation of speed and maximum speed than placebo ([$t(27) = -2.582$, $p = 0.016$], [$t(27) = -2.508$, $p = 0.018$], respectively) and cannabis condition ([$t(27) = 2.245$, $p = 0.033$], [$t(27) = 2.523$, $p = 0.018$], respectively), but did not differ from the combined condition. On the measure of reaction time, the alcohol and combined conditions were significantly slower than the placebo condition ([$t(27) = -2.227$, $p = 0.034$], [$t(27) = -2.784$, $p = 0.010$], respectively). As well, the combined condition showed significantly slower reaction time than the cannabis condition [$t(27) = -3.078$, $p = 0.005$].

Secondary outcome measures

Subjective effects Condition × Time ANOVAs revealed a significant interaction for all VAS measures: "I feel this effect" [$F(7.770, 209.785) = 14.513$, $p < 0.001$]; "I like this drug" [$F(9.297, 251.011) = 5.969$, $p < 0.001$]; "I feel the good effects" [$F(7.542, 203.621) = 9.097$, $p < 0.001$]; "I feel the bad effects" [$F(7.557, 204.028) = 4.191$, $p < 0.001$]; "I feel the rush" [$F(7.774, 209.907) = 7.951$, $p < 0.001$]; "I feel dizzy" [$F(7.422, 200.407) = 2.1$, $p = 0.042$]; "I feel high" [$F(7.213, 194.752) = 13.049$, $p < 0.001$]; "I feel drunk" [$F(7.592, 204.988) = 13.46$, $p < 0.001$]; "I feel exhilarated" [$F(8.499, 229.460) = 5.922$, $p < 0.001$]; "I feel drowsy" [$F(8.719, 235.407) = 2.418$, $p = 0.013$]; "I feel nauseated" [$F(7.936, 214.267) = 2.266$, $p = 0.024$]. Follow-up comparisons revealed some differences between conditions (see Fig. 1 and Table 5). Drug effects, where individual effects of alcohol and cannabis differed from placebo following exposure, were observed on nearly all measures ($p < 0.05$). However, for alcohol, significant differences from placebo at only one time point were seen for "nauseated." As well, no effects of cannabis were seen for "drunk," and only two

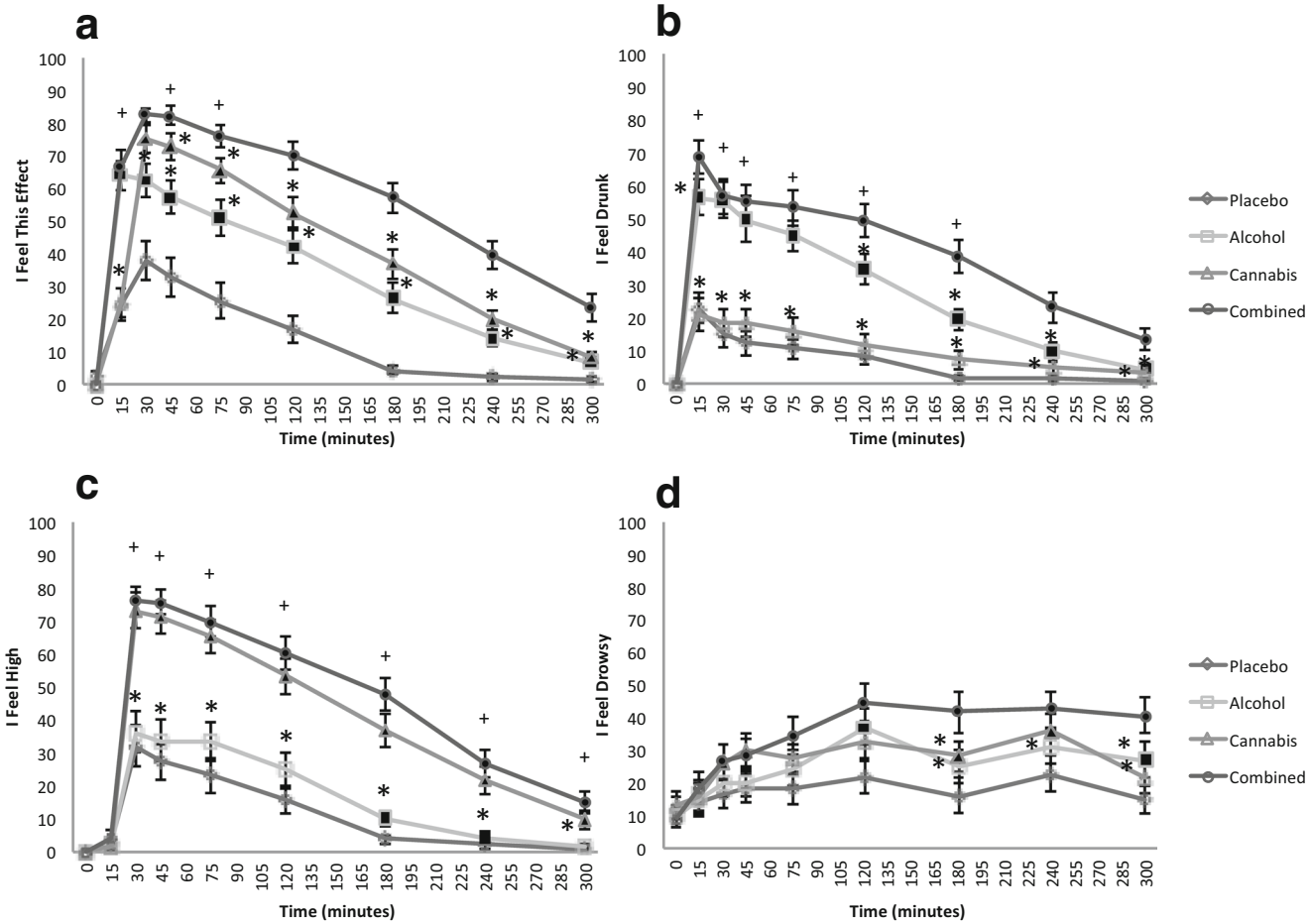

Fig. 1 Visual analog scale ratings of (**a**) "I feel this effect," (**b**) "I feel drunk," (**c**) "I feel high," and (**d**) "I feel drowsy" from baseline to 300 min after alcohol exposure. Data are presented as mean ± SEM. Dark symbols $p < 0.05$, different from placebo; *$p < 0.05$ different from alcohol and cannabis combined; $^{+}p < 0.05$ cannabis different from alcohol

of the post-consumption alcohol measures differed from placebo for "high." Substantial evidence for additivity of effects, where the combined effects of alcohol and cannabis were significantly greater than the effects of either drug alone, was seen on nearly all measures. An exception to this was on the measure of high, where the effect of cannabis and alcohol together did not differ from the effect of cannabis alone. At the 5-h assessment, we still observed significant individual drug effects on most measures, and as well in the combined condition we observed significant differences from one or both individual drug conditions on all measures except for "rush" and "nauseated." Analysis of the driving ability questionnaire with Friedman test revealed a significant effect only at 45 min post-alcohol (see Table 6; 45 min: χ^2 (3) = 18.767, $p < 0.001$; baseline: χ^2 (3) = 2.481, $p > 0.05$). Comparisons of each condition to each other at 45 min with Wilcoxon test revealed differences between placebo and each of the alcohol and/or cannabis conditions, with no evidence of additivity, meaning there was no difference between the combined condition and the single drug conditions.

Cardiovascular measures Condition × Time ANOVAs revealed a significant interaction for heart rate [$F(7.975, 215.320) = 16.856$, $p < 0.001$]. Follow-up comparisons revealed some differences between conditions ($p < 0.05$). Drug effects, where individual effects of alcohol and cannabis and their combination differed from placebo following exposure, were observed at nearly all time points (see Fig. 2). Substantial increases in heart rate in the first hour appeared primarily due to cannabis. After the first hour, both drugs appeared to increase heart rate somewhat, with some evidence for additivity of effects. Condition × Time ANOVAs revealed a significant interaction for systolic [$F(7.640, 206.208) = 2.623$, $p = 0.010$] and diastolic blood pressure [$F(24, 648) = 2.353$, $p < 0.001$]. Follow-up comparisons revealed some differences between conditions ($p < 0.05$; see Fig. 2). These effects were complex, with increases in both measures seen in the first hour following drug administration, but increases appearing larger for cannabis for systolic blood pressure. Following the first hour, blood pressure measures tended to decline, with these declines appearing most pronounced in the combined condition.

Table 5 Visual analog scale measures by condition and time in min (presented as mean (standard error of the mean)

Time in min										
		0	15	30	45	75	120	180	240	300
Like	Pla	0.18	28.11	41.64	35.86	26.25	24.39	15.32	3.75	1.25
		(0.15)	(5.60)	(6.49)	(6.08)	(6.07)	(5.91)	(5.04)	(2.19)	(0.61)
	Alc	0.00	58.93^{P}	62.14^{P}	59.14^{P}	53.00^{P}	39.14^{P}	27.79	15.43^{P}	7.89^{P}
		(0.00)	(6.67)	(6.31)	(6.12)	(6.41)	(5.07)	(5.05)	(3.65)	(2.68)
	Can	0.36	24.21^{A}	67.61^{P}	63.29^{P}	61.75^{P}	52.39^{P}	44.50^{P,A}	27.00^{P,A}	17.25^{P}
		(0.23)	(5.10)	(3.93)	(4.10)	(4.44)	(5.26)	(5.26)	(4.50)	(4.04)
	Alc-Can	0.07	58.25^{P,C}	77.75^{P,A,C}	76.07^{P,A,C}	67.86^{P}	58.70^{P,A}	50.75^{P,A}	38.46^{P,A}	23.04^{P,A}
		(0.05)	(5.79)	(3.24)	(3.24)	(4.61)	(5.02)	(5.01)	(5.38)	(4.87)
Good	Pla	0.21	29.07	42.86	36.04	28.54	21.57	7.21	3.07	0.75
		(0.21)	(5.43)	(6.86)	(6.40)	(6.43)	(5.38)	(2.77)	(1.79)	(0.42)
	Alc	0.00	69.68^{P}	71.82^{P}	58.50^{P}	56.89^{P}	45.00^{P}	26.21^{P}	15.54^{P}	6.91^{P}
		(0.00)	(4.51)	(4.51)	(5.44)	(5.98)	(5.48)	(4.70)	(3.28)	(2.03)
	Can	2.93	28.36^{A}	69.25^{P}	64.25^{P}	61.00^{P}	55.75^{P}	42.61^{P,A}	27.43^{P,A}	14.11^{P,A}
		(2.67)	(5.48)	(3.67)	(4.01)	(4.70)	(4.60)	(5.28)	(4.60)	(4.04)
	Alc-Can	0.14	65.89^{P,C}	80.04^{P,C}	79.96^{P,A,C}	66.79^{P}	61.32^{P,A}	54.43^{P,A,C}	37.43^{P,A}	20.89^{P,A}
		(0.14)	(4.63)	(2.71)	(3.00)	(3.79)	(4.31)	(4.48)	(5.51)	(4.85)
Bad	Pla	0.14	11.11	6.54	5.61	5.54	6.64	2.11	3.54	1.96
		(0.11)	(3.37)	(1.97)	(2.15)	(1.70)	(2.66)	(0.96)	(2.27)	(1.11)
	Alc	0.07	12.75	13.39^{P}	11.86	12.71^{P}	20.00^{P}	11.61^{P}	10.50	10.75^{P}
		(0.05)	(4.25)	(3.40)	(3.01)	(3.46)	(4.47)	(3.78)	(4.55)	(3.61)
	Can	0.25	16.25	30.14^{P,A}	27.50^{P,A}	23.93^{P,A}	16.46^{P}	10.96^{P}	11.25^{P}	4.79
		(0.13)	(4.84)	(5.03)	(4.48)	(4.50)	(3.72)	(2.85)	(3.13)	(1.44)
	Alc-Can	0.00	19.60	22.43^{P,A,C}	22.29^{P,A}	24.75^{P,A}	30.54^{P,A,C}	22.57^{P,A,C}	20.54^{P,C}	14.89^{P,A,C}
		(0.00)	(5.09)	(4.29)	(3.85)	(4.63)	(4.82)	(4.13)	(4.28)	(4.11)
Rush	Pla	0.14	12.57	14.32	9.82	13.71	5.04	1.89	1.04	0.43
		(0.08)	(4.13)	(4.07)	(3.61)	(4.06)	(1.95)	(0.92)	(0.49)	(0.26)
	Alc	0.04	48.43^{P}	43.25^{P}	38.39^{P}	29.86^{P}	20.64^{P}	7.21^{P}	5.46^{P}	1.85
		(0.04)	(5.73)	(5.31)	(5.72)	(5.42)	(4.24)	(2.11)	(1.90)	(0.85)
	Can	0.14	12.04^{A}	37.86^{P}	33.68^{P}	31.86^{P}	21.82^{P}	13.82^{P}	7.07^{P}	3.29
		(0.08)	(3.03)	(5.73)	(5.85)	(6.23)	(4.94)	(3.41)	(2.71)	(1.86)
	Alc-Can	0.11	41.37^{P,C}	57.86^{P,A,C}	58.61^{P,A,C}	38.29^{P}	34.79^{P,A}	23.96^{P,A,C}	18.96^{P,A,C}	5.93^{P}
		(0.11)	(5.92)	(4.53)	(4.43)	(5.48)	(5.28)	(4.18)	(4.42)	(2.69)
Dizzy	Pla	0.89	10.57	12.29	13.54	9.39	6.29	3.61	1.75	3.57
		(0.72)	(3.64)	(4.01)	(3.68)	(3.68)	(2.67)	(1.69)	(1.15)	(2.58)
	Alc	0.36	13.54	13.11	11.61	11.39	14.64	4.93	8.32^{P}	6.13
		(0.23)	(3.46)	(4.13)	(3.68)	(3.38)	(4.07)	(1.78)	(3.06)	(3.32)
	Can	0.29	10.93	22.39	21.54	20.25^{P,A}	15.00^{P}	12.39^{P}	8.14^{P}	3.75
		(0.29)	(4.18)	(5.21)	(5.24)	(4.77)	(4.65)	(4.18)	(3.40)	(2.28)
	Alc-Can	0.29	22.04^{P}	22.07^{P}	25.00^{P,A}	29.79^{P,A}	28.29^{P,A,C}	19.75^{P,A}	20.32^{P,A,C}	11.64^{P,A}
		(0.29)	(5.40)	(4.44)	(4.82)	(5.89)	(5.29)	(4.00)	(4.56)	(3.43)
Exhilarated	Pla	0.07	12.64	10.68	10.46	9.29	5.04	1.46	1.14	0.75
		(0.07)	(4.38)	(3.64)	(4.17)	(3.11)	(1.96)	(0.77)	(0.51)	(0.40)
	Alc	2.54	44.57^{P}	41.18^{P}	33.14^{P}	21.54^{P}	16.00^{P}	5.86^{P}	2.43	0.93
		(1.78)	(5.13)	(6.24)	(5.75)	(4.85)	(4.01)	(1.89)	(0.80)	(0.49)
	Can	0.64	11.57^{A}	33.36^{P}	32.39^{P}	25.86^{P}	16.50^{P}	11.86^{P}	6.61	5.07
		(0.39)	(3.70)	(5.15)	(5.94)	(5.76)	(4.50)	(3.78)	(3.18)	(2.71)
	Alc-Can	0.71	37.77^{P,C}	47.89^{P,C}	44.57^{P}	39.46^{P,A,C}	30.43^{P,A,C}	19.39^{P,A}	13.43^{P,A}	5.71^{P,A}
		(0.47)	(5.85)	(5.20)	(5.45)	(5.79)	(4.82)	(3.56)	(3.42)	(1.52)
Nauseated	Pla	0.14	11.29	5.00	6.46	4.61	4.00	2.39	2.86	3.86
		(0.11)	(3.56)	(1.91)	(2.55)	(1.68)	(1.35)	(1.21)	(1.24)	(2.28)
	Alc	0.32	10.18	7.64	8.00	3.82	11.39^{P}	6.11	6.54	8.61
		(0.22)	(3.87)	(3.12)	(3.13)	(1.34)	(3.83)	(2.21)	(2.91)	(3.39)
	Can	0.11	9.00	8.96	15.71^{P}	14.32^{P,A}	6.68	7.04	6.61	3.96
		(0.06)	(3.56)	(2.56)	(3.82)	(4.10)	(2.36)	(2.62)	(2.69)	(1.52)
	Alc-Can	0.29	18.28	16.00^{P,A}	17.18^{P,A}	20.82^{P,A}	17.18^{P,C}	16.39^{P,A,C}	8.25^{P}	9.68
		(0.11)	(4.48)	(3.70)	(4.02)	(5.24)	(4.67)	(4.46)	(2.20)	(3.79)

^{P} $p < 0.05$, different from placebo; ^{A} $p < 0.05$ different from alcohol; ^{C} $p < 0.05$, different from cannabis

Physiological measures No significant interactions were revealed by Condition × Time ANOVAs for BrACs ($p = 0.308$), indicating that BrAC measures did not differ between the alcohol and combined conditions (see Fig. 2). However, there was a main effect of time ($F(3.391, 91.549) = 270.293$, $p < 0.001$). The average BrAC measures at the time of driving in

Table 6 Driving ability questionnaire from a Likert scale of 1 (demonstrated poor driving skills) to 5 (demonstrated excellent driving skills), (presented as mean (standard error of the mean))

Time	Placebo	Alcohol	Cannabis	Alc-Can
Baseline	3.89 (0.19)	4.00 (0.14)	4.11 (0.18)	3.93 (0.13)
45 min	3.64 (0.15)	3.04^{P} (0.18)	2.71^{P} (0.22)	2.64^{P} (0.24)

$^{P}p < 0.05$, different from placebo

the alcohol and combined conditions were 94.01 ± 5.14 mg/dL (mean ± SEM) and 92.30 ± 3.25 mg/dL, respectively. Condition × Time ANOVAs revealed significant interaction for blood THC [$F(1.463, 39.505) = 21.783$, $p < 0.001$], 11-OH-THC [$F(1.67, 45.077) = 16.265$, $p < 0.001$], and THCCOOH [$F(1.789, 48.302) = 37.707$, $p < 0.001$]. Follow-up comparisons revealed some differences between conditions ($p < 0.05$). Pre-drug administration concentrations of THCCOOH in the combined condition were significantly lower than the placebo and the alcohol only conditions. Post-drug administration concentrations of THC, 11-OH-THC, and THCCOOH in the cannabis alone and combined conditions were significantly higher than the alcohol alone and placebo conditions, confirming cannabis consumption. Additionally, the post-drug administration concentration of THCCOOH in the combined condition was significantly lower than the cannabis alone condition (see Table 7). Blood THC concentrations 15–20 min after smoking cannabis appeared unaffected by whether or not participants had also consumed alcohol. Interestingly, THCCOOH concentrations were significantly higher after smoking cannabis and consuming placebo alcohol, than after smoking cannabis and consuming alcohol.

Smoking topography ANOVAs on the effect of condition for the amount smoked in grams ($p = 0.808$), smoking duration ($p = 0.073$), and estimated THC dose ($p = 0.961$) revealed no significant effects (see Table 8).

Safety

A total of 30 AEs were recorded throughout the study. All AEs were of mild or moderate severity; no AEs were severe, and no serious adverse events (SAEs) occurred. The most common AEs were nausea/vomiting, pain at the site of blood draw, headache, dizziness, flu, and cold-like symptoms.

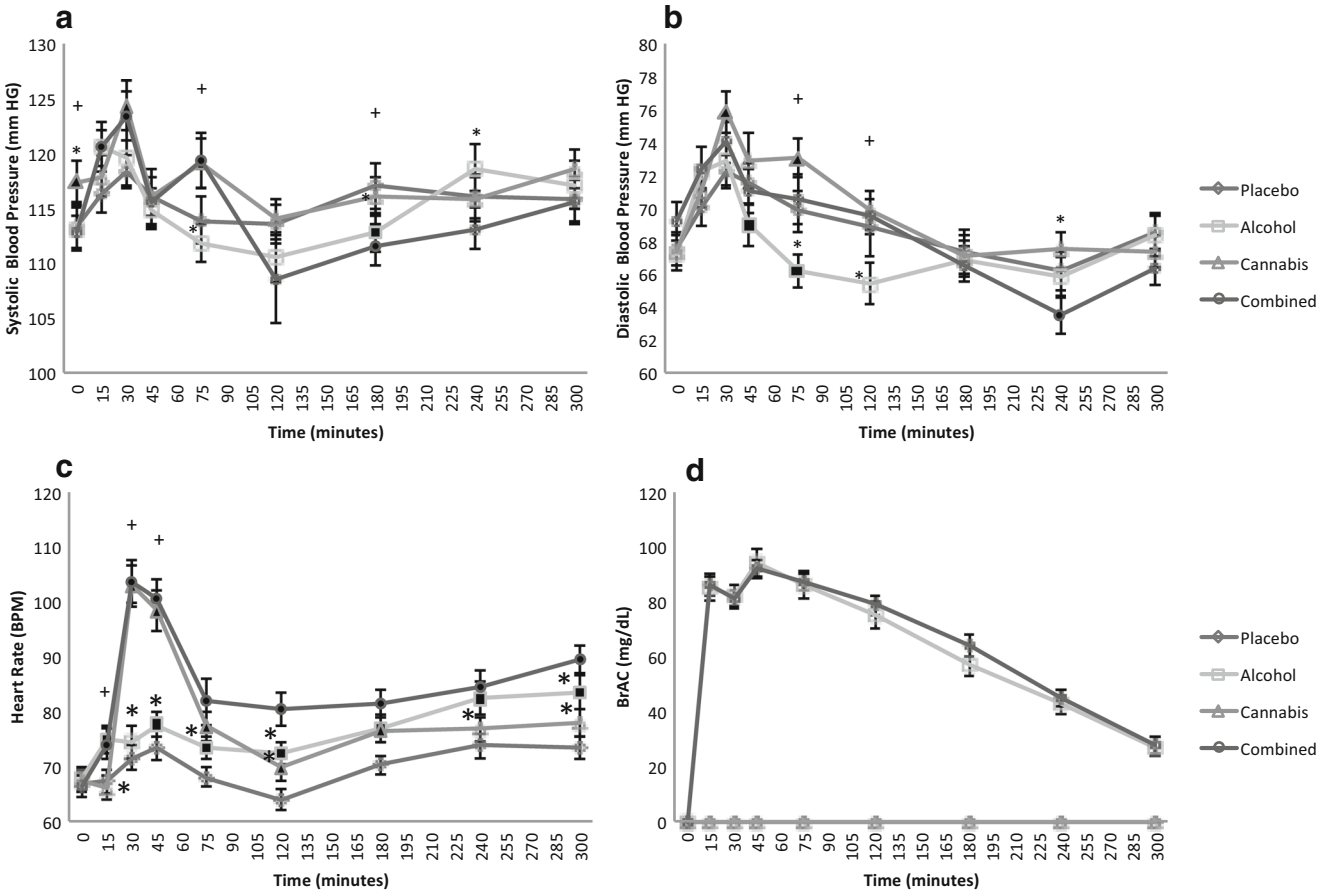

Fig. 2 (**a**) Systolic blood pressure, (**b**) diastolic blood pressure and (**c**) heart rate from baseline to 300 min after alcohol exposure, and (**d**) breath alcohol concentrations. Data are presented as mean ± SEM. Dark symbols $p < 0.05$, different from placebo; *$p < 0.05$ different from alcohol and cannabis combined; $^{+}p < 0.05$ cannabis different from alcohol

Table 7 Whole blood concentrations of THC and its metabolites before (pre) and after (post) smoking cannabis by condition (mean, median, [range])

Measure	Time	Placebo	Alcohol	Cannabis	Alc-Can
THC	Pre	0.12, 0.00, [0.00–1.97]	0.03, 0.00, [0.00–0.96]	0.12, 0.00, [0.00–1.45]	0.16 , 0.00, [0.00–2.92]
	Post	0.02, 0.00, [0.00–0.60]	0.08, 0.00, [0.00–1.55]	$7.12^{P,A}$, 4.93, [0.00–25.18]	$6.46^{P,A}$, 3.20, [0.00–30.80]
11-OH-THC	Pre	0.00, 0.00, [0.00–0.00]	0.00, 0.00, [0.00–0.00]	0.00, 0.00, [0.00–0.00]	0.00, 0.00, [0.00–0.00]
	Post	0.05, 0.00, [0.00–1.42]	0.00, 0.00, [0.00–0.00]	$1.49^{P,A}$, 1.17, [0.00–5.40]	$1.63^{P,A}$, 1.04, [0.00–8.10]
THCCOOH	Pre	0.97, 0.00, [0.00–6.50]	1.07, 0.00, [0.00–7.50]	0.78, 0.00, [0.00–6.30]	$0.49^{P,A}$, 0.00, [0.00–3.80]
	Post	0.87, 0.51, [0.00–5.00]	0.79, 0.00, [0.00–5.40]	$7.87^{P,A}$, 5.60, [0.00–23.51]	$5.56^{P,A}$, 3.66, [0.00–21.70]

All concentrations are in ng/mL. $^{P}p < 0.05$, different from placebo; $^{A}p < 0.05$ different from alcohol

Discussion

Both alcohol and cannabis are known to increase risk of collision involvement among drivers (e.g., Asbridge et al. 2012; Li et al. 2012; Voas et al. 2012). This study was undertaken to identify specific aspects of driving behavior that are affected by these drugs individually and in combination. We observed several effects of alcohol and cannabis on driving measures, both individually and combined. Alcohol alone resulted in significant increases in SDLP in both the single and dual task overall simulation as well as in the dual task straightaway simulation compared to placebo and a significant increase in the dual task overall and straightaway standard deviation of speed and maximum speed when compared to placebo and the cannabis alone condition. Cannabis alone resulted in significant increases in overall SDLP in the single task and dual task simulations, but did not impact straightaway SDLP or speed measures. The combination of both drugs led to a significantly greater increase in overall and straightaway SDLP, in the single and dual task drives. We found evidence for additivity of effects on the single task SDLP measure, where the combined effect of the drugs was significantly greater than the effect of each drug by itself. The combined condition also led to significant differences in the dual task overall standard deviation of speed, when compared to placebo and cannabis alone, and overall maximum speed when compared to placebo. Finally, both the alcohol alone and combined condition led to a slower reaction time than placebo. These findings provide support for the suggestion that, as with fatigue and individual effects of drugs (Vinckenbosch et al. 2020), the measure of SDLP may be most sensitive to the combined effects of alcohol and cannabis.

In addition to evidence of additivity demonstrated on some of the driving measures, we also observed substantial further evidence for additivity on subjective drug effects data. The VAS scores suggest that participants were feeling effects under all drug conditions; however, in the combined condition, we found significantly greater effects than either of the drugs alone on almost all of the VAS measures. These effects seemed more pronounced later in the session for some VAS measures. As well, while effects on heart rate in the first hour appeared primarily driven by cannabis, after the first hour, some evidence for additivity of effects on heart rate was observed. Interestingly, while the driving ability questionnaire revealed that participants judged their ability to drive as significantly worse at 45 min after drug administration in all three conditions, there was no evidence for additive effects on this measure since their judgment did not differ between the combined condition and the single drug conditions.

Previous studies provided some evidence for an additive effect of the combination of cannabis and alcohol on driving measures (Downey et al. 2013; Hartman et al. 2015; Lamers and Ramaekers 2001; Liguori et al. 2002; Ramaekers et al. 2000), and the current results for SDLP support these findings. Hartman et al. (2015) estimated that a combination of 5 ng/mL THC with a BrAC of 0.05% would lead to a 3.4 centimeter (cm) increase in SDLP (Hartman et al. 2015). We observed that a combination of 6.5 ng/mL THC with a BrAC of 0.09% leads to a 7 cm increase in SDLP in the single task simulation and 10 cm in the dual task simulation when compared to placebo. The finding of greater effects in the present study points to the importance of dose when considering the combined effects on driving, with higher doses resulting in greater effects. Our results also show that the combination of both

Table 8 Smoking topography by condition (mean (standard deviation of the mean))

Measure	Placebo	Alcohol	Cannabis	Alc-Can
Amount smoked (mg)	617.46 (36.24)	629.36 (34.29)	609.04 (36.04)	607.61 (42.14)
Estimated THC (mg)			76.13 (4.51)	75.95 (5.27)
Smoking duration (min)	5.86 (0.46)	5.71 (0.46)	6.46 (0.50)	6.46 (0.53)

drugs led to a significant increase of 0.05 s in reaction time, when compared to placebo, which is in line with previous findings (Ramaekers et al. 2000). Also in line with previous findings (Hartman et al. 2016), are the effects on our speed measures under the combination of both alcohol and cannabis.

An interesting finding is the fact that participants seemed unaware of their level of impairment in the combined condition. When asked to rate their demonstrated driving skills, participants were aware of their impairment, as previously shown (Ramaekers et al. 2000); however, they did not rate their driving as poorer in the combined condition, compared to either of the single drug conditions. This is notable given that weaving was increased in the combined drug condition above that observed in the single drug conditions. Thus, drivers may not be aware of the additive effects of combinations of drugs, and this may have important implications for road safety.

Results from our cannabis alone condition are consistent with findings in the literature of an increase in weaving (Arkell et al. 2019; Bramness et al. 2010; Lenne et al. 2010; Micallef et al. 2018; Ramaekers et al. 2000; Robbe 1998; Ronen et al. 2008) and results from our alcohol alone condition are consistent with previous findings on weaving and speed (Irwin et al. 2017). The lack of effect of cannabis alone on reaction time contradicts previous findings (Lenne et al. 2010; Ronen et al. 2008); however, this may be due to methodological differences. Measuring reaction time with equipment that is not a standard part of vehicle operation (e.g., added button on steering wheel) may artificially increase reaction time when under the influence of cannabis. The brake pedal is part of standard vehicle operation, making measurement of reaction time with brake pedal latency more generalizable to real world conditions. Liguori et al. (2002) measured reaction time using brake pedal latency on a driving simulator and, consistent with the current study, found no effect of cannabis on reaction time. Another difference between the present findings and some previously published reports is the lack of effect of cannabis on our speed measures. In this study, not only were speed limits posted throughout the driving simulation but participants were also reminded of this at the beginning of each drive in the set of instructions presented on screen. In our previous studies where we observed that cannabis reduces speed, speed limits were posted throughout the drive; however, the set of instructions presented on screen asked participants to drive as they normally would (Brands et al. 2019; Di Ciano et al. 2020). This difference in the set of instructions may also be the reason why we saw no effects of cannabis on SDLP in our previous studies (Brands et al. 2019; Di Ciano et al. 2020), but saw effects in the current study, and is consistent with studies in the driving simulation literature showing that reduced speed is associated with reduced lane deviation (Zhou et al. 2008). Although this might not translate to a real world setting, in a highly controlled laboratory setting, our findings suggest the importance of the set of instructions provided to participants. With regard to the effects of alcohol on speed, some studies have reported higher speeds after consuming alcohol but this effect has not been consistently observed (Irwin et al. 2017). We did observe that alcohol tended to increase speed and speed variability, but only under dual task conditions, suggesting that this effect may be most likely to be observed when driving conditions are more complex.

Several limitations of this work should be considered when interpreting study findings. THC concentrations were sampled at only one time point after smoking the cannabis cigarette. Thus, the present study is not able to make conclusions about relationships between behavior and peak THC concentrations. Blood THC concentrations are obtained from an ad libitum smoking procedure, which does not allow control for variations between participants in smoking topography. Unequal number of puffs, duration of puffs, and breathhold would lead to different blood THC concentrations. As well, our driving simulation scenarios were relatively simple, and more complex scenarios (e.g., urban scenarios with more traffic and pedestrians) may produce different results. We also recognize that our study lacked a "true" control condition and in our placebo condition, it is possible that expectancy effects could have influenced results (e.g., Christiansen et al. 2017). The inclusion of a "true" control condition, in which participants would have received neither drug, while knowing that they had not received any drug, would have allowed us to evaluate these expectancy effects. Future work should include true control conditions to assess the extent to which these expectancy effects are present. Finally, participants drove 45 min after having completed the alcohol administration; at this time, some participants would have been on the ascending BAC limb while others would have been on the descending limb.

Conclusions

The present study is both replicating and extending previous observations with the demonstration that a moderate dose of cannabis in combination with an intoxicating dose of alcohol may adversely impact driving behavior. Using a higher dose of both alcohol and cannabis than has been administered in previous studies, the findings replicated the additive effects of cannabis and alcohol on SDLP in a sample of young nondependent participants. Replicating previous results using a different simulator and distinct scenarios strengthens the evidence of impairment of both cannabis and alcohol, individually and in combination. In addition, this study expands on the current literature by showing that participants appear to lack awareness of their greater level of impairment when under the influence of both drugs compared to either drug alone. More

research is warranted to understand the potential additive effects of cannabis and alcohol.

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Declarations

Conflict of interest Dr. Le Foll has obtained funding from Pfizer (GRAND Awards, including salary support) for investigator-initiated projects. Dr. Le Foll has some in-kind donation of cannabis product from Aurora and medication donation from Pfizer and Bioprojet and was provided a coil for TMS study from Brainsway. Dr. Le Foll has obtained industry funding from Canopy (through research grants handled by CAMH or University of Toronto), Bioprojet, ACS, and Alkermes. Dr. Le Foll has received in kind donations of nabiximols from GW Pharma for past studies funded by CIHR and NIH. Dr. George has partial salary support from NIDA (R21-DA-043949) and is a consultant to Frutarom. Dr. Huestis was a consultant to Canopy Health Innovations on medical cannabis study design, is a Science and Policy Advisor, PinneyAssociates, and President of Huestis & Smith Toxicology, LLC.

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