Effect of cannabidiol and delta-9-tetrahydrocannabinol on driving performance: a randomized clinical trial

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Key Points

Question: What is the magnitude and duration of driving impairment following vaporization of cannabis containing varying concentrations of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)?

Findings: In this cross-over clinical trial that included 26 healthy participants who underwent on-road driving tests, the standard deviation of lateral position (SDLP, a measure of lane weaving, swerving, and overcorrecting) at 40-100 minutes following vaporized consumption of CBD-dominant cannabis, THC-dominant cannabis, THC/CBD-equivalent cannabis, and placebo was 18.21 cm, 20.59 cm, 21.09 cm and 18.26 cm, respectively. At 240-300 minutes, the SDLP was 19.03 cm, 20.59 cm, 19.88 cm and 19.37 cm. Compared with placebo, SDLP with THC-dominant and THC/CBD-equivalent cannabis was significantly greater at 40-100 minutes but not 240-300 minutes after consumption; there were no significant differences between CBD-dominant cannabis and placebo.

Meaning: Although this study did not find statistically significant differences in driving performance during experimental on-road driving tests between CBD-dominant cannabis and placebo, the effect size may not have excluded clinically important impairment, and the doses tested may not necessarily represent common usage.

Abstract

Importance: Cannabis use has been associated with increased crash risk, but the effect of cannabidiol (CBD) on driving is unclear.

Objective: To determine the driving impairment caused by vaporized cannabis containing Δ^9-tetrahydrocannabinol (THC) and CBD.

Design, Setting and Participants: A double-blind, within-participants, randomized clinical trial was conducted at the Faculty of Psychology and Neuroscience at Maastricht University in the Netherlands between 20th May 2019 and 27th March 2020. Participants (n=26) were healthy, occasional cannabis users.

Interventions: Participants vaporized THC-dominant, CBD-dominant, THC/CBD-equivalent, and placebo cannabis. THC and CBD doses were 13.75 mg. Order of conditions was randomized and balanced.

Main Outcome and Measure: The primary endpoint was standard deviation of lateral position (SDLP; a measure of lane weaving) during 100 kilometre, on-road driving tests that commenced at 40 min and 240 min after cannabis consumption. At calibrated blood alcohol concentrations (BACs) of 0.02% and 0.05%, SDLP is increased relative to placebo by 1.12 cm and 2.4 cm, respectively.

Results: Among 26 randomized participants (mean [SD] age, 23.2 [2.6] years; 16 females), 22 (85%) completed all eight driving tests. At 40-100 min, the SDLP was 18.21 cm (CBD), 20.59 cm (THC), 21.09 cm (THC/CBD) and 18.28 cm (placebo). SDLP was significantly increased by THC-dominant (+2.33 cm, 95% CI: .80 - 3.86, *P* <.001) and THC/CBD-equivalent (+2.83 cm, 95% CI: 1.28 – 4.39, *P* <.001) cannabis, but not CBD-dominant cannabis (-.05 cm, 95% CI: -1.49 – 1.39, *P* >.99), relative to placebo. At 240-300 min, the

SDLP was 19.03 cm (CBD), 19.88 cm (THC), 20.59 cm (THC/CBD) and 19.37 cm (placebo). The SDLP did not differ significantly in the CBD (-.34 cm, 95% CI -1.77 – 1.10, P >.99), THC (.51 cm, 95% CI -1.01 – 2.02, P >.99) or THC/CBD (1.22 cm, 95% CI -0.29 – 2.72, P = .20) conditions, relative to placebo. Out of 188 test drives, 16 (8.5%) were terminated due to safety concerns.

Conclusions and Relevance: In a cross-over clinical trial that assessed driving performance during on-road driving tests, the SDLP following vaporized THC-dominant and THC/CBD-equivalent cannabis compared with placebo was significantly greater at 40-100 minutes but not 240-300 minutes after vaporization; there were no significant differences between CBD-dominant cannabis and placebo. However, the effect size for CBD-dominant cannabis may not have excluded clinically important impairment, and the doses tested may not represent common usage.

Trial Registration: European Clinical Trials Database: 2018-003945-40.

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Introduction

Epidemiological studies have indicated that cannabis is associated with increased crash risk and culpability[1,2]. Acute cannabis intoxication increases standard deviation of lateral position (SDLP)[3], an index of lane weaving, swerving and overcorrecting that is a validated measure of alcohol-and drug-induced driving impairment[4].

Cannabis chemovars can be broadly categorized into three chemotypes: tetrahydrocannabinol (THC)-dominant, cannabidiol (CBD)-dominant and THC/CBD-equivalent[5]. THC-dominant products are typically used for intoxication while CBD-dominant products, which are presumed not to be intoxicating, are prescribed for the treatment of epilepsy, anxiety, psychosis and neurological disorders[6]. THC/CBD-equivalent products are sometimes consumed with the expectation that CBD can ameliorate THC-related symptoms such as anxiety, paranoia and cognitive impairment[7]. Although some research has suggested an absence of cognitive, psychomotor, or subjective effects with oral and vaporized CBD[8], sedation and somnolence are sometimes reported with CBD, albeit usually in the presence of other drugs[8,9], but which nonetheless could affect driving.

Cannabis can be smoked or ingested, but vaporization is an increasingly popular method of administration[10,11]. The present study investigated the effects of vaporized THC-dominant (THC), THC/CBD-equivalent (THC/CBD) and CBD-dominant (CBD) cannabis on driving performance, cognitive function, and subjective experiences.

Methods

The study was approved by the Medical Ethics Committee of Maastricht University and conducted in accordance with the ethical standards of the Helsinki Declaration. The trial protocol including the statistical analysis plan is provided in Supplement 1.

Participants

Healthy volunteers with a history of occasional cannabis use were recruited via advertisement, social media (e.g. Facebook) and word of mouth. Inclusion criteria were: aged 20-50 years; self-reported cannabis use <2 times/week in the past 12 months and >10 lifetime exposures; in possession of a valid driver license with at least 2 years driving experience and driving >2000 km/year, and; body mass index (BMI) between 20 and 28.

Exclusion criteria were: presence of any major medical, endocrine or neurological condition; history of drug abuse or addiction; current or history of psychiatric disorder; current use of medications known to affect driving; active hypertension; pregnancy; history of cardiac dysfunction, and; any serious prior adverse response to cannabis. Participants meeting eligibility criteria underwent a comprehensive medical examination involving a medical history review, electrocardiogram, blood testing (hematology and serology) and physical examination. All participants provided written informed consent prior to participation.

Study Design and Procedures

This double-blind, within-participants crossover study included four experimental sessions that were scheduled ≥1 week apart to avoid potential drug carryover effects. Participants were required to abstain from cannabis and other drugs for the duration of the study, and from alcohol for 24 h prior to each session. Prior to the first experimental session, participants completed a practice session to familiarize them with the on-road driving test and cognitive test procedures. For experimental sessions, participants vaporized cannabis containing 13.75 mg THC (THC condition), 13.75 mg THC & 13.75 mg CBD (THC/CBD condition), 13.75 mg CBD (CBD condition) or placebo (PLA condition). Study drugs were prepared in advance by J.R. and E.T. according to a computer-generated balanced, randomization schedule with a block size of 6 (based on expected recruitment of 24 participants). Investigators conducting test days (T.A./F.V.) and participants were blind to the

randomization schedule. The study was conducted between May 2019 and March 2020 at the Faculty of Psychology and Neuroscience at Maastricht University.

Experimental Sessions

The Box shows the order of events during the four experimental sessions. Upon participant arrival, a zero breath alcohol concentration was confirmed via breathalyzer (Alcotest 5510, Draeger, Lübeck, Germany) and oral fluid was screened (DrugTest 5000, Dräger, Lübeck, Germany) to identify any recent use of cannabis, cocaine, opiates, amphetamine, methamphetamine or MDMA. Following baseline measurements of cardiovascular measures and self-reported drug effects, a catheter was inserted into the participant's non-dominant arm and the first blood sample was collected. Participants then inhaled THC, THC/CBD, CBD or placebo. Driving tests occurred at 40-100 min and 240-300 min post-vaporization. Cognitive tests were conducted at 5, 135 and 205 min. Blood samples, blood pressure and heart rate were collected at baseline and at 0, 25, 130, 200 and 320 min. Subjective drug effects were assessed at baseline and at 0, 25, 130, 200 and 240 min. Baseline refers to pre-drug administration while 0 min represents the end of drug administration.

Study Drugs

THC-dominant (THC 22% / CBD <1.0%), CBD-dominant (THC<1% / CBD 9%) and placebo (<0.2% total cannabinoid content) cannabis varieties (Bedrocan, Netherlands) were used to deliver target doses of 13.75 mg THC, 13.75 mg THC/CBD and 13.75 mg CBD. Placebo cannabis was added to active cannabis varieties so that each treatment contained target doses of THC and CBD within 215 mg total plant material. Study drugs were vaporized at 200^{o}C (Mighty Medic, Storz & Bickel, Tuttlingen, Germany) according to a standardized procedure (inhale 5 seconds, hold 3 seconds, exhale, and rest for 30 seconds; minimum of 10 inhalations and continued if necessary until vapor no longer visible).

Subjective Drug Effects

Subjective drug effects were assessed using 7 visual analog scales (VAS) with 10 cm lines ranging from 0 (lowest score) – 10 (highest score)[12]. Participants rated the following: "Strength of Drug Effect" (No effect - Very strong), "Liking of Drug Effect" (Dislike Very Much – Like Very Much), "Stoned" (Not Stoned – Very Stoned), "Sedated" (Not Sedated – Very Sedated), "Relaxed" (Not Relaxed – Very Relaxed), "Anxious" (Not Anxious – Very Anxious) and "Confident to Drive" (Not Confident - Very Confident). Perceived driving quality was assessed after each driving test using the following VAS items: "How would you rate the quality of your driving just now?" (Very Poor – Very Good) and "Do you think your driving was impaired?" (Not at All – Very Much). Anxiety was further assessed using the state subscale of the State Trait Anxiety Inventory (STAI) which consists of 20 statements that are rated on 4-point Likert scales ranging from "Not at All" (1) to "Very Much So" (4). Possible scores range from 20-80, with higher scores indicating greater anxiety[13].

Driving Tests

The on-road driving test (road tracking test[14]) ran for approximately 60 min. Participants drove a specially instrumented vehicle over a 100-km highway circuit while maintaining a constant speed (95 km/h) and a steady lateral position in the right (slower) traffic lane. Participants were accompanied by a licensed driving instructor who had access to dual vehicle controls (accelerator and brake pedals).

Cognitive and Psychomotor Measures

Cognitive and psychomotor performance was assessed using 4 computerized tasks that have proven sensitive to THC impairment[12,15,16]. These were: the Digit Symbol Substitution Task (DSST)[17], Divided Attention Task (DAT)[18], Paced Serial Addition Task (PSAT)[19] and Tower of London (TOL)[20]. Participants also completed the Emotional Stroop Task (EST)[21]. These tasks assess processing speed (DSST; PSAT), divided attention (DAT), psychomotor function (DAT), working memory (PSAT) and decision making and cognitive flexibility (TOL, EST). The DSST, DAT and PSAT were completed in this order at 5 min and at 205 min post-

vaporization, while the EST and TOL were completed once in each session at 5 min and 135 min, respectively. Further details are provided in eMethods 1 (Supplement 2).

Blood collection and plasma cannabinoid analyses

Blood was collected via indwelling peripheral venous catheter into 10 mL purple-top (EDTA) Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) and centrifuged at 3000 *x g* for 10 min. The supernatant plasma was then decanted and stored in 2 mL cryotubes at −20°C. Plasma was subsequently thawed for analysis via liquid chromatography-tandem mass spectrometry (LC-MS/MS) according to published methods[22,23]. Target analytes included THC, 11-OH-THC, 11-COOH-THC and CBD. Further details of these analyses are provided in eMethods 2 (Supplement 2).

Outcomes

The prespecified primary endpoint was mean SDLP during the on-road driving test. Lateral position, which is the distance between the vehicle and the lane boundary to the left of the vehicle, was recorded by a camera mounted on to the roof of the vehicle and sampled continuously at 4 Hz. Larger numbers indicate greater variability (i.e. reduced stability) in lane positioning. A 2.4 cm drug *versus* placebo increase in SDLP is typical of a driver with a blood alcohol concentration (BAC) of 0.05% and is thought to indicate the lower limit of clinically relevant driving impairment[4].

Other endpoints for the primary outcome were mean speed and standard deviation of speed, which were recorded electronically by an on-board computer. Secondary outcomes included cognitive and psychomotor performance measures as described above, subjective drug effects (0-10 cm VAS items as described above), cardiovascular measures (blood pressure, mmHg; heart rate, bpm), and plasma cannabinoid concentrations (ng/mL).

Post-hoc outcomes were the proportions of participants showing impairment or improvement in relation to SDLP changes associated with BACs of 0.02% (1.12 cm)[24] and 0.05% (2.4 cm)[4], two common legal driving limits.

Statistical Analysis

Sample size was determined by power calculation using the effect size obtained in a previous study of dronabinol (10-20 mg THC) on SDLP during on-road driving[25]. This indicated that 20 participants were needed to detect an equivalent effect (Cohen's f = 0.62; ΔSDLP = ~1.94 cm; approx. 0.04% BAC[26]) with 95% power.

Available data from all 26 participants were analyzed according to randomization group in SPSS v25 (IBM Corp., Armonk, NY) using linear mixed-effects models. Model parameters included condition, time and condition*time as fixed effects and a random intercept. A first-order autoregressive (AR1) residual covariance structure was used as it consistently provided the lowest Schwarz's Bayesian Information Criterion (BIC) model fit values. The restricted maximum likelihood method (REML) was used as it provides an unbiased estimation of the variance parameters when the data are unbalanced. Missing data were handled using listwise deletion.

If a significant main effect of condition or a significant condition*time interaction was observed, 2-sided pairwise comparisons compared means across conditions at each level of time. To control the family-wise Type 1 error rate, a Bonferroni correction was applied such that significance values were multiplied by 6, the total number of comparisons. The predefined comparisons of interest were: THC vs. PLA, THC/CBD vs. PLA, CBD vs. PLA and THC vs THC/CBD. Statistical significance was set at P <0.05. Analyses including only completing participants (n=22) did not differ meaningfully from the full results presented here (eTable 1).

Results

Table 1 presents the characteristics of the 26 participants who were enrolled into the study and randomized. Complete results of statistical analyses (eTable 2) including pairwise comparisons (eTables 3-7) are provided in Supplement 2. Figure 1 shows the flow of participants through the study.

Primary Outcome

A significant main effect of condition was found for SDLP (*P* <.001) (Figure 2). Pairwise comparisons revealed increased SDLP in both the THC and THC/CBD conditions relative to placebo at 40-100 min (2.33 cm, 95% CI 0.08 – 3.86, *P* <.001; 2.83 cm, 95% CI 1.28 – 4.39 cm, *P* <.001) but not 240-300 min (0.51 cm, 95% CI -1.01 – 2.02, *P* >.99; 1.22 cm, 95% CI -0.29 – 2.72, *P* = .20) . CBD did not affect SDLP relative to placebo (40-100 min: -0.05 cm, 95% CI -1.49 – 1.39, *P* >.99; 240-300 min: -0.34 cm, 95% CI -1.77 – 1.10, *P* >.99) and there was no significant difference between the THC/CBD and THC conditions (40-100 min: 0.50 cm, 95% CI -1.10 – 2.10, *P* >.99; 240-300 min: 0.71 cm, 95% CI -0.83 – 2.25, *P* >.99). No significant differences were observed across conditions for mean speed (*P* = .56) or standard deviation of speed (*P* = .67). At 40-100 min, mean speed was 92.53 km/h (CBD), 91.82 km/h (THC), 92.86 km/h (THC/CBD) and 92.65 km/h (placebo); at 240-300 min, mean speed was 92.64 km/h (CBD), 93.00 km/h (THC), 93.01 km/h (THC/CBD) and 92.75 km/h (placebo). At 40-100 min, mean standard deviation of speed was 3.06 km/h (CBD), 3.32 km/h (THC), 3.18 km/h (THC/CBD) and 2.93 km/h (placebo); at 240-300 min, mean standard deviation of speed was 3.29 km/h (CBD), 3.26 km/h (THC), 3.37 km/h (THC/CBD) and 3.40 km/h (placebo).

Secondary Outcomes

At the end of each driving test, participants rated their driving as significantly more impaired relative to placebo in the THC condition (100 min: 4.15, 95% CI 2.29 – 6.02, *P* <.001; 300 min: 2.27, 95% CI 0.41 – 4.12, *P* = .008) and the THC/CBD condition (100 min: 4.09, 95% CI 2.20 – 5.98, *P* <.001; 300 min: 2.70, 95% CI -.93 – 4.57, *P* =.001) (Figure 3). Participants rated the quality of their driving as significantly worse relative to placebo at the end of the first driving test only (THC: -1.95, 95% CI -3.64 – -0.26, *P* =.01; THC/CBD: -2.14, 95% CI -3.83 – -0.44, *P* =.006) (eFigure 1).There was a main effect of condition for “Confident to Drive” (*P* <.001), with ratings decreased in the THC and THC/CBD conditions relative to placebo at 0 min (-4.3, 95% CI -5.61 – -2.98, *P* <.001; -2.48, 95% CI -3.81 – -1.14, *P* <.001),

25 min (-3.65, 95% CI -4.96 – -2.33, *P* <.001; -2.08, 95% CI -3.41 – -0.75, P <.001) and 130 min (-2.18, 95% CI -3.49 – -0.86, *P* <.001; -1.74, 95% CI -3.07 – -0.41, *P* = .003) and greater in the THC/CBD condition relative to the THC condition at 0 min (1.82, 95% CI -0.47 – 3.17, *P* =.002) and 25 min (1.57, 95% CI 0.22 – 2.92, *P* = .01) (Figure 4). Results for other subjective drug effect measures are shown in eFigure 3 and results for the state subscale of the STAI are shown in eFigure 4. Ratings of "Strength of Drug Effect" and "Anxious" were significantly lower in the THC/CBD condition than in the THC condition at 0 min (-1.67, 95% CI -2.97 – -0.37, *P* = .004; -1.88, 95% CI -2.99 – -0.76, *P* <.001) and 25 min (-1.57, 95% CI -2.87 – -0.27, *P* =.01; -1.14, 95% CI -2.26 – -0.02, *P* = .04).

Cognitive performance results are shown in Figure 4 and eFigure 2. There was a significant main effect of condition for number correct and % correct on the DSST (*P* = .04, *P* = .03) but not number attempted (*P* = .26); tracking error and response time on the DAT (*P* = .02, *P* = .003); response time, number correct and % correct on the PSAT (*P* = .001, *P* <.001, *P* = .002), and; number correct and response time on the TOL (*P* = .03, *P* = .02). There was no effect of condition for either number correct or response time on the EST (*P* = .62, *P* = .82). The THC and THC/CBD conditions did not differ from placebo on any measures at 205 min, and the CBD condition did not differ from placebo on any measures at either timepoint (eTable 5).

Heart rate and blood pressure data are shown in eFigure 5. There was a significant condition*time interaction for systolic blood pressure (*P* =.001), although pairwise comparisons showed that neither THC nor THC/CBD differed significantly from placebo at any point in time (eTable 7). There was a main effect of condition on heart rate (*P* <.001) and a significant condition*time interaction (*P* <.001). eFigure 6 shows median (IQR) plasma cannabinoid concentrations over time. There was a significant main effect of condition, time and condition*time for all analytes (eTable 2).

Post-Hoc Outcomes

The proportions of participants showing impairment at 40-100 min at the 0.02% BAC criterion were 40% (CBD), 62% (THC) and 75% (THC/CBD). At 240-300 min, they were 16% (CBD), 36% (THC) and 50% (THC/CBD). The proportions of participants showing impairment at 240-300 min at the 0.05% BAC criterion were 16% (CBD), 48% (THC) and 60% (THC/CBD). At 240-300 min, they were 8% (CBD), 27% (THC) and 32% (THC/CBD). As shown in eTable 8, symmetry analysis revealed no significant difference in the proportion of participants showing impaired or improved driving in the CBD condition at either BAC criterion (0.02%, ΔSDLP = 1.12 cm; 0.05%, ΔSDLP = 2.4 cm). There was a significant difference for the THC and THC/CBD conditions at 40-100 min, with most participants showing impairment at both BAC criterion.

Adverse Events

One participant had a panic attack shortly after cannabis administration in the THC condition, leading to termination of that test day and withdrawal from the study. Out of 188 test drives that commenced, 16 (8.5%) were terminated by the driving instructor due to safety concerns. Of these terminated drives, 9 occurred during the first driving test (PLA: 2, CBD: 2, THC: 2, THC/CBD: 3) and 7 during the second test (PLA: 1, CBD: 1, THC: 2, THC/CBD: 3). All terminations in the second test were due to the participant appearing heavily fatigued while driving. There were no significant differences in terminations across conditions. In addition, three drives were cancelled prior to commencement (THC: 2, THC/CBD: 1) due to participant concerns about their ability to drive safely.

Discussion

In this randomized clinical trial, THC-dominant and THC/CBD-equivalent cannabis produced a short-term impairment during experimental on-road driving as indexed by a significant increase in SDLP measured 40-100 min following vaporization. In agreement with previous studies involving smoked cannabis or oral THC (dronabinol)[26,27], this impairment was modest in magnitude and similar to that seen in drivers with a 0.05% BAC (~2.4-2.5 cm[28]). SDLP in

the placebo and CBD conditions did not differ, indicating that CBD, when administered in a bolus dose via vaporization, did not impair driving.

This finding was validated by a post-hoc symmetry analysis which showed that drivers in the CBD condition were no more likely to show impairment than they were improvement relative to placebo at SDLP thresholds corresponding to BACs of 0.02% and 0.05%. Consistent with prior research[29], CBD-dominant cannabis also failed to produce significant cognitive or psychomotor impairment relative to placebo. While the doses of THC in the current study (13.75 mg) were moderate, they caused strong subjective effects including reduced confidence to drive. The presence of CBD did not reduce THC impairment of driving, although there were subtle differences in the subjective effects of THC-dominant and THC/CBD-equivalent cannabis despite near-identical THC plasma concentrations. THC/CBD-equivalent cannabis appeared to cause less anxiety, reduced strength of drug effects, and greater confidence to drive than THC-dominant cannabis, particularly at earlier time points. This agrees with prior, albeit limited, evidence that co-administered CBD can reduce THC euphoric, anxiogenic and subjective drug effects[30,31]. Other studies have failed to find such modulatory effects[7,12], suggesting they may be subtle and ephemeral in nature.

Previous on-road[26,32] and simulator[12,33] studies have described increased SDLP for up to 3 hours following inhaled cannabis. Consistent with this, the present study failed to detect changes in SDLP at 4-5 hours. Impairment could be extended with use of oral products[15], or with higher inhaled doses, and so these results should not be considered definitive. Confidence to drive only tracked SDLP to a limited extent while post-hoc evaluation of driving ability appeared more accurate, suggesting that participants were better able to evaluate their driving performance after the fact than predict it. This same pattern has been observed with other drugs known to impair driving, such as alcohol, alprazolam and zolpidem[34]. Participants considered their driving at 240-300 min to be significantly more impaired in the THC and THC/CBD conditions than in the placebo condition despite there being no difference across conditions in SDLP at that point in time. Participants may have

retrospectively over-rated their impairment, or this may have indicated subtle persistence of THC-induced impairment, perhaps combined with fatigue, causing subclinical SDLP increments (i.e. < 1.5 cm) that likely have limited real-world relevance.

Limitations

This study has several limitations. First, it was limited to healthy volunteers who were occasional cannabis users. The applicability of these findings to more frequent users including medical cannabis patients is unclear given that daily cannabis use may produce at least partial tolerance to the impairing effects of THC[35]. Second, only one dose of CBD and a single 1:1 ratio of CBD and THC were tested. The CBD dose used was also lower than that used in clinical practice for conditions such as pediatric epilepsy where oral administration of CBD oils at doses around 10-20 mg/kg is common[8]. Driving outcomes may differ with higher CBD and THC doses and different CBD:THC ratios. Retail CBD products in North America and other regions are not strictly regulated and so actual CBD content may be unknown or misrepresented[36]. Third, the confidence limits associated with change in SDLP in the CBD condition suggested the possibility of subclinical impairment similar to that seen at low BACs. While symmetry analysis suggested no difference in the proportion of impaired vs improved drivers in the CBD condition, these findings are exploratory and based on a small number of drivers and a single CBD dose. Fourth, this study was limited to a sample of young drivers with similar driving experience. Degree of driving impairment may differ as a function of driving experience as well as experience with cannabis and the driving task. Fifth, this study was powered to detect an effect of THC on driving and may have been underpowered to detect a difference between the THC and THC/CBD conditions.

Conclusions

In a cross-over clinical trial that assessed driving performance during on-road driving tests, the SDLP following vaporized THC-dominant and THC/CBD-equivalent cannabis compared with placebo was significantly greater at 40-100 minutes but not 240-300 minutes after

vaporization; there were no significant differences between CBD-dominant cannabis and placebo. However, the effect size for CBD-dominant cannabis may not have excluded clinically important impairment, and the doses tested may not represent common usage.

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Author Contributions:

Dr. Arkell and Dr. Ramaekers had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Sharing Statement: See Supplement 3.

References

1. Rogeberg O. A meta-analysis of the crash risk of cannabis-positive drivers in culpability studies-Avoiding interpretational bias. *Accid Anal Prev.* 2019;123:69-78.
2. Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction.* 2016;111(8):1348-1359.
3. Ramaekers JG. Driving Under the Influence of Cannabis: An Increasing Public Health Concern. *JAMA.* 2018;319(14):1433-1434.
4. Ramaekers JG. Drugs and Driving Research in Medicinal Drug Development. *Trends Pharmacol Sci.* 2017;38(4):319-321.
5. Jikomes N, Zoorob M. The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular Consumer Products. *Sci Rep.* 2018;8(1):4519.
6. Hill KP. Medical Use of Cannabis in 2019. *JAMA.* 2019;322(10):974-975.
7. Freeman AM, Petrilli K, Lees R, et al. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. *Neurosci Biobehav Rev.* 2019;107:696-712.
8. Chesney E, Oliver D, Green A, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. [published online ahead of print, 2020 Apr 8]. *Neuropsychopharmacology.* 2020.
9. Dos Santos RG, Guimaraes FS, Crippa JAS, et al. Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials. *Expert Opin Drug Metab Toxicol.* 2020;16(6):517-526.
10. Spindle TR, Bonn-Miller MO, Vandrey R. Changing landscape of cannabis: novel products, formulations, and methods of administration. *Curr Opin Psychol.* 2019;30(30):98-102.

11. Lintzeris N, Mills L, Suraev A, et al. Medical cannabis use in the Australian community following introduction of legal access: the 2018-2019 Online Cross-Sectional Cannabis as Medicine Survey (CAMS-18). *Harm Reduct J.* 2020;17:37.
12. Arkell TR, Lintzeris N, Kevin RC, et al. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. *Psychopharmacology (Berl).* 2019: 236(9):2713-2724.
13. Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs AG. Manual for the State-Trait Anxiety Inventory (Form Y). 1983. Consulting Psychologists Press, Inc.: Palo Alto.
14. O'Hanlon J. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol.* 1984;18(S1).
15. Vandrey R, Herrmann ES, Mitchell JM, et al. Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes. *J Anal Toxicol.* 2017;41(2):83-99.
16. Ramaekers JG, Moeller MR, van Ruitenbeek P, Theunissen EL, Schneider E, Kauert G. Cognition and motor control as a function of Δ9-THC concentration in serum and oral fluid: Limits of impairment. *Drug Alcohol Depend.* 2006;85(2):114-122.
17. Mcleod DR, Griffiths RR, Bigelow GE, Yingling J. An Automated Version of the Digit Symbol Substitution Test (Dsst). *Behav Res Meth Instr.* 1982;14(5):463-466.
18. Casswell S, Marks D. Cannabis Induced Impairment of Performance of a Divided Attention Task. *Nature.* 1973;241(5384):60-61.
19. Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. *Percept Mot Skills.* 1977;44(2):367-373.
20. Shallice T. Specific impairments of planning. *Philosophical Transactions of the Royal Society B: Biological Sciences.* 1982;298(1089):199-209.
21. Richards A, French CC, Johnson W, Naparstek J, Williams J. Effects of mood manipulation and anxiety on performance of an emotional Stroop task. *Br J Psychol.* 1992;83(4):479-491.

22. Kevin RC, Allsop DJ, Lintzeris N, Dunlop AJ, Booth J, McGregor IS. Urinary cannabinoid levels during nabiximols (Sativex®)-medicated inpatient cannabis withdrawal. *Forensic Toxicol.* 2017;35(1):33-44.
23. Schwope DM, Scheidweiler KB, Huestis MA. Direct quantification of cannabinoids and cannabinoid glucuronides in whole blood by liquid chromatography–tandem mass spectrometry. *Anal Bioanal Chem.* 2011;401(4):1273.
24. Jongen S, van der Sluiszen NNJJM, Brown D, Vuurman EFPM. Single- and dual-task performance during on-the-road driving at a low and moderate dose of alcohol: A comparison between young novice and more experienced drivers. *Hum Psychopharmacol Clin Exp.* 2018;33(3):e2661.
25. Veldstra JL, Bosker WM, de Waard D, Ramaekers JG, Brookhuis KA. Comparing treatment effects of oral THC on simulated and on-the-road driving performance: testing the validity of driving simulator drug research. *Psychopharmacology (Berl).* 2015;232(16):2911-2919.
26. Ramaekers JG, Robbe H, O'Hanlon J. Marijuana, alcohol and actual driving performance. *Hum Psychopharmacol Clin Exp.* 2000;15(7):551-558.
27. Bosker WM, Kuypers KP, Theunissen EL, et al. Medicinal Δ9-tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. *Addiction.* 2012;107(10):1837-1844.
28. Jongen S, Vermeeren A, van der Sluiszen N, et al. A pooled analysis of on-the-road highway driving studies in actual traffic measuring standard deviation of lateral position (ie,“weaving”) while driving at a blood alcohol concentration of 0.5 g/L. *Psychopharmacology (Berl).* 2017;234(5):837-844.
29. Spindle TR, Cone EJ, Goffi E, et al. Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. *Drug Alcohol Depend.* 2020:107937.

30. Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther.* 1976;19(3):300-309.
31. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by δ9-THC in normal subjects. *Psychopharmacology (Berl).* 1982;76(3):245-250.
32. Robbe H. Marijuana's impairing effects on driving are moderate when taken alone but severe when combined with alcohol. *Hum Psychopharm Clin.* 1998;13(S2):S70-S78.
33. Hartman RL, Brown TL, Milavetz G, et al. Cannabis effects on driving lateral control with and without alcohol. *Drug Alcohol Depend.* 2015;154:25-37.
34. Verster JC, Roth T. Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. *Psychopharmacology (Berl).* 2012;219(3):775-781.
35. Ramaekers JG, Mason NL, Theunissen EL. Blunted highs: Pharmacodynamic and behavioral models of cannabis tolerance. *Eur Neuropsychopharmacol.* 2020;36:191-205.
36. Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. *JAMA.* 2015;313(24):2491-2493.

Figure legends

Figure 1. Flow of Participants Through the Study.

PLA = placebo condition, CBD = CBD condition, THC/CBD = THC/CBD condition, THC = THC condition

Figure 2. The Standard Deviation of Lateral Position (SDLP) During On-Road Driving Tests

The top panel shows individual SDLP values during on-road driving tests at 40-100 min and 240-300 min post-vaporization. The horizontal line shows the mean SDLP in each condition. The bottom panel shows change in SDLP from placebo, with the dotted horizontal line representing the mean SDLP increase associated with a BAC of 0.02% and the dashed horizontal line the mean SDLP increase associated with a BAC of 0.05%. The plus symbol shows the mean change in SDLP in each condition.

Figure 3. Confidence in Driving Ability Over Time and Perceived Driving Impairment

The graph on the left shows mean (95% CI) visual analog scale (VAS, 0-10 cm) ratings of "Confident to Drive" (Not Confident – Very Confident). Time as shown on the x-axis indicates time since vaporization. BL = baseline. The boxplot on the right shows scores on the VAS (0-10 cm) item "Do You Think Your Driving Was Impaired?" (Not at All – Very Much So) as assessed at the end of each on-road driving test. The edges of the boxes represent the 25th and 75th quartile values. The horizontal line shows the median and the '+' shows the mean. If there are no outliers (Q1 − 1.5 × (Q3 − Q1) and Q3 + 1.5 × (Q3 − Q1)), the whiskers show minimum and maximum values. If there are outliers (shown as coloured symbols), the whiskers show the lowest and highest values that are not outliers.

Figure 4. Performance on the Digit Symbol Substitution Task (A), Divided Attention Task (B) and Paced Serial Addition Task (C-D)

Boxplots showing various outcome measures on the Digit Symbol Substitution Task (DSST), Divided Attention Task (DAT) and Paced Serial Addition Task (PSAT). The edges of the boxes represent the 25th and 75th quartile values. The horizontal line shows the median and the '+' shows the mean. If there are no outliers (Q1 − 1.5 × (Q3 − Q1) and Q3 + 1.5 × (Q3 − Q1)), the whiskers show minimum and maximum values. If there are outliers (shown as coloured symbols), the whiskers show the lowest and highest values that are not outliers. Time as shown on the x-axis indicates time elapsed since vaporization. Additional outcome measures are shown in eFigure 2.

Table 1. Participant demographics and characteristics

Demographic/characteristic	Participants (n=26)
Sex, no. participants,	
Female	16
Male	10
Age, mean (SD), y	23.2 (2.6)
BMI, mean (SD), kg/m^2	21.4 (2.4)
% participants with at least some tertiary education	100
Episodes of cannabis use in past 3 months, median (IQR)	4.5 (1-20)
Years in possession of driver license, median (IQR)	5 (4-7)
Average no. km driven per year, median (IQR)	4500 (3000-8000)
Ever driven while under the influence of cannabis, no. (%)	5 (19.2)
Weekly use of alcohol, no. participants (%)	10 (38.5)
Prior use of other drugs, no. participants (%)	
Psilocybin	7 (26.9)
Ecstasy/MDMA	6 (23.1)
Cocaine	4 (15.4)
LSD	3 (11.5)
Other	2 (7.7)
Amphetamine	1 (3.8)