Cannabis and Cannabinoid Research
Volume X, Number X, 2023

DOI: 10.1089/can.2022.0310

Longitudinal Associations Between Cannabis Use and Cognitive Impairment in a Clinical Sample of Middle-Aged Adults Using Cannabis for Medical Symptoms

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Abstract

Introduction: Cannabis use to alleviate medical symptoms is increasing in middle-aged and older adults. Cognitive impairment associated with cannabis use may be especially detrimental to these understudied age groups. We hypothesized that among middle-aged and older adults who used cannabis for 12 months, frequent (≥3 days/week) compared with nonfrequent (≤2 days/week) use will be associated with cognitive impairment.

Materials and Methods: We performed secondary analysis on data from a clinical trial of cannabis use for medical symptoms. Participants ($n = 62$) were ≥45 years, and completed a baseline and at least one postbaseline visit. Cognitive domains were assessed through the Cambridge Neuropsychological Test Automated Battery. Cannabis use was assessed prospectively through daily smartphone diaries. Frequency of cannabis use was a binary predictor in a mixed-effects logistic regression model predicting cognitive impairment adjusted for baseline cognitive functioning.

Results: At baseline, participants were primarily nonfrequent cannabis users; however, in all other time periods, most participants were frequent users (range: 55–58%). Cognitive outcomes did not differ between frequent and nonfrequent cannabis users. However, in sensitivity analyses, respondents with problematic cannabis use scored significantly worse on one cognitive domain compared to those without problematic cannabis use.

Conclusions: In a clinical sample of adults aged ≥45 years, no longitudinal associations were found between cannabis use and cognitive functioning. However, a few significant associations were observed between problematic use and cognitive functioning. Further research is needed to assess the impact of cannabis use on adults, particularly those aged ≥65 years, and to investigate potential subtler influences of cannabis use on cognition. ClinicalTrials.gov ID: NCT03224468.

Keywords: cognitive impairment; medical marijuana; cannabis use disorder; cannabis; aging; neurocognition

Introduction

In recent decades, dramatic increases have been observed in the prevalence of cannabis use among middle-aged (45–64 years) and older adults (≥65 years) with national estimates ranging from 57.8% to 250% increases.[1–3] This upward trend, which is expected to continue,[4,5] may be driven by decriminalization of marijuana,[6,7] increasing beliefs in the therapeutic benefits of cannabis for aging-related medical conditions,[8] and decreasing perception of cannabis as a risky substance.[5] While much attention on cannabis-related harm has focused on adolescents and young adults, emerging literature suggests that middle-aged and older adults are particularly vulnerable to adverse effects of cannabis,[9] such as falls,[10] other injury and subsequent emergency department visits,[11] and physical[12] and cognitive decline.[13,14]

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Cannabis can alter brain function, especially in networks that support learning,[15] memory,[16] attention,[17] and cognitive control and reward processing.[18–20] Considering changes in brain plasticity and cognitive decline associated with normal aging,[21] middle-aged and older adults may be vulnerable to cannabis-related cognitive impairment.[22,23] Nevertheless, to-date, middle-aged and older adults remain the most understudied age groups of cannabis users.

A recent systematic review assessing neurocognitive effects of cannabis in middle-aged and older adults[23] called for more high-quality, longitudinal analyses. Those studies that did show associations with cognitive impairment showed a dose-dependent effect; categorical frequency of use was typically the predictor. These studies were heterogeneous in methods and samples, including whether use was recreational or medical.

Those who use cannabis recreationally may not necessarily be comparable with those who use it medically in terms of frequency and amount of use, potency of consumed products, and other clinical characteristics (e.g., differences in baseline psychopathology).[24] Because of the therapeutic benefits of cannabis and the prevalence of disease and discomfort in older age that could be alleviated by cannabis,[8] it is critically important to ensure that cannabis does not have deleterious cognitive effects.

We performed a secondary analysis on data from a pragmatic clinical trial of cannabis use for medical symptoms (NCT03224468). We assessed the effect of frequency of cannabis use on three cognitive domains in adults aged ≥45 years, hypothesizing that frequent (≥3 days/week) users are more likely to have worse cognitive functioning at the end of 12 months of use compared with nonfrequent (≤2 days/week) users.

Materials and Methods

Study design and participants

We used data from a single-site, randomized, pragmatic single-blind trial (NCT03224468) conducted in the Greater Boston area from July 1, 2017 to July 31, 2020. Adults 18–65+ years ($n=269$) with no prior history of cannabis use disorder (CUD) or heavy cannabis use who expressed their interest in using cannabis to treat pain, insomnia, anxiety, and/or depression were recruited from clinical and community sites.

Participants were randomly assigned to either an active cannabis arm ($n=173$) or a waitlist control arm ($n=96$). Participants were assessed at baseline and 1, 3, 6, and 12 months for cannabis use behaviors, development of CUD, and neurocognitive performance. Study procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Mass General Brigham Human Research Committee. Written informed consent was obtained from all study participants, and they received financial compensation for participation. Further information on inclusion/exclusion criteria, randomization, and masking can be found elsewhere.[25]

Outcomes

Cognitive outcomes were assessed at baseline and 1, 3, 6, and 12 months using the Cambridge Neuropsychological Test Automated Battery (CANTAB® Cognition).[26] Three cognitive domains were included as outcomes, based on several cognitive tasks: (1) Attention and Psychomotor Speed domain (Rapid Visual Information Processing task; Attention Switching task); (2) Memory domain (Verbal Recognition Memory task; Paired Associates Learning task); and (3) Executive Function domain (Spatial Working Memory task). Alternate forms of CANTAB tasks were administered when available to minimize practice effects.

Predictors

At each time point, participants were queried about cannabis use-related variables. The primary predictor was a binary variable indicating frequency of cannabis use at each timepoint (≥3 days/week; ≤2 days/week). This variable was recoded from an original continuous frequency of cannabis use variable measured using smartphone diaries.

Demographic variables

Sociodemographic variables included sex (male, female), age (45–64 years, ≥65 years), race (Caucasian, African American, Multiracial, Asian), ethnicity (Hispanic, non-Hispanic), educational level (less than high school, high school/GED completion, part-time college), and employment status.

Cannabis use-related covariates included the following: number of days since last used cannabis, CUD (yes, no), and problematic cannabis use (assessed using the Cannabis Use Disorder Identification Test-Revised [CUDIT-R] score).

Statistical analysis

The analytic sample included participants who were ≥45 years, and completed randomization, baseline assessment, and at least one postbaseline visit ($n=62$). Respondents were primarily middle-aged adults, and

only two participants were older adults (≥65 years). We fit a linear mixed-effects model to each outcome with a participant-varying intercept to account for the longitudinal design of the study. We used the Proc Mixed procedure from SAS statistical software to obtain model estimates. We fit two models, one with and one without an adjustment for baseline cognitive functioning. Our key effect of interest was the differences in cognitive scores between participants who reported using cannabis ≥3 days/week and those who reported using ≤2 days/week.

In similar models as part of sensitivity analyses, three newly constructed variables were created and modeled as predictors: (1) A 3-level variable indicating trajectory of cannabis use (i.e., whether frequency of use increased, decreased, or did not change over the study period); (2) a 3-level variable indicating frequency of cannabis use relying on a different cutoff for (≥5 days/week; 3–4 days/week; ≤2 days/week); and (3) a binary variable indicating problematic cannabis use (yes; no) based on CUDIT-R. Statistical tests with $p < 0.05$ uncorrected were considered significant.

Results

Sample characteristics over time

Sociodemographic characteristics and cannabis use-related variables are shown for each assessment period (Table 1). Across all assessments, participants ($n = 62$) were primarily female, between 45 and 64 years of age, Caucasian, non-Hispanic, employed, and had completed part of graduate or professional school.

At baseline, participants were primarily nonfrequent cannabis users (using ≤2 days/week); however, in all other time periods, the majority of participants were frequent users (range: 55–59%).

Table 1. Sociodemographic Characteristics and Cannabis Use-Related Variables Among Adults Aged ≥45 Years

Characteristic	Baseline ($n=62$)	1 Month ($n=62$)	3 Months ($n=59$)	6 Months ($n=54$)	12 Months ($n=49$)
Gender					
Female, *n* (%)	38 (61.29)	38 (61.29)	37 (62.71)	34 (62.96)	31 (63.27)
Male, *n* (%)	24 (38.71)	24 (38.71)	22 (38.71)	20 (38.71)	18 (36.73)
Age categories (years)					
45–64, *n* (%)	60 (96.77)	60 (96.77)	57 (96.61)	52 (96.30)	47 (95.92)
≥65, *n* (%)	2 (3.23)	2 (3.23)	2 (3.39)	2 (3.70)	2 (4.08)
Age, years, mean (SD)	55.02 (5.87)	55.02 (5.87)	54.88 (5.97)	55.26 (6.00)	55.67 (5.93)
Race					
Caucasian, *n* (%)	55 (88.71)	55 (88.71)	53 (89.83)	49 (90.74)	46 (93.88)
African American, *n* (%)	5 (8.06)	5 (8.06)	5 (8.47)	4 (7.41)	2 (4.08)
Asian, *n* (%)	1 (1.61)	1 (1.61)	1 (1.69)	1 (1.85)	1 (2.04)
Multiracial, *n* (%)	1 (1.61)	1 (1.61)	0 (0.00)	0 (0.00)	0 (0.00)
Ethnicity					
Hispanic, *n* (%)	2 (3.23)	2 (3.23)	2 (3.39)	1 (1.85)	1 (2.04)
Education level					
Less than high school, *n* (%)	1 (1.61)	1 (1.61)	1 (1.69)	1 (1.85)	1 (2.04)
High school/GED, *n* (%)	3 (4.84)	3 (4.84)	1 (1.69)	0 (0.00)	0 (0.00)
Part college, *n* (%)	11 (17.74)	11 (17.74)	11 (18.64)	11 (20.37)	10 (20.41)
College (2 years), *n* (%)	1 (1.61)	1 (1.61)	1 (1.69)	1 (1.85)	1 (2.04)
College (4 years), *n* (%)	14 (22.58)	14 (22.58)	14 (23.73)	13 (24.07)	11 (22.45)
Part graduate/professional school, *n* (%)	32 (51.61)	32 (51.61)	31 (52.54)	28 (51.85)	26 (53.06)
Employment status					
Unemployed, *n* (%)	18 (29.03)	18 (29.03)	16 (27.12)	15 (27.78)	13 (26.53)
Employed, *n* (%)	44 (70.97)	44 (70.97)	43 (72.88)	39 (72.22)	36 (73.47)
Cannabis use-related variables					
No. of days since last used cannabis, mean (SD)	4.48 (5.20)	2.33 (3.87)	2.87 (6.04)	8.12 (19.14)	7.82 (18.30)
Cannabis use frequency					
≥3 days/week, *n* (%)	11 (17.74)	36 (58.06)	35 (59.32)	30 (55.56)	27 (55.10)
≤1–2 days/week, *n* (%)	51 (82.26)	26 (41.94)	24 (40.68)	24 (44.44)	22 (44.90)
Cannabis use disorder					
Yes, *n* (%)	0 (0.00)	2 (3.23)	2 (3.39)	6 (11.11)	4 (8.16)
No, *n* (%)	62 (100.00)	60 (96.77)	57 (96.61)	48 (88.89)	45 (91.84)
CUDIT-R score, mean (SD)	1.81 (2.33)	3.55 (2.86)	3.80 (2.85)	5.00 (2.53)	4.10 (3.03)
CUDIT-R, categories					
0–7, *n* (%)	60 (96.77)	57 (91.94)	51 (86.44)	46 (85.19)	41 (83.67)
≥8, *n* (%)	2 (3.23)	5 (8.06)	8 (13.56)	8 (14.81)	8 (16.33)

CUDIT-R, Cannabis Use Disorder Identification Test-Revised; GED, General Educational Development; SD, standard deviation.

Associations with cognitive functioning

There were no significant longitudinal associations between frequency of cannabis use and any of the cognitive outcomes included in analyses (Table 2). In sensitivity analyses, no significant differences in cognitive outcomes were found between cannabis users with different trajectories of cannabis use (Supplementary Table S1). Similarly, no significant differences in cognitive outcomes were observed between cannabis users with different frequency cutoffs (Supplementary Table S2). Participants with problematic cannabis use, as indicated by a CUDIT-R score of ≥ 8, performed significantly worse on rapid visual information processing. No significant differences were found on other cognitive tasks (Supplementary Table S3).

Discussion

The aim of this secondary analysis was to determine whether cognitive impairment as measured by the CANTAB was longitudinally associated with frequency of cannabis use in a clinical sample of people aged ≥ 45 years who used cannabis as part of a pragmatic trial. At baseline, participants were largely nonusers or light users, while at 12 months over half of participants became heavy users. Despite the increase in cannabis use, we did not find declines in cognitive scores across several domains.

Conversely, findings did provide some indications of cognitive deterioration within two specific cognitive domains among participants with problematic cannabis use. This study provides real-world, prospective, longitudinal effect sizes and variation for both frequency of use and for cognitive outcomes in an understudied age group of cannabis users (≥ 45 years) in a setting where access to cannabis has been made available. Importantly, this study includes a baseline measurement of cognitive functioning before cannabis exposure.

Existing data on the relationship between frequency of cannabis use and cognitive functioning in middle-aged adults show mixed results with highly heterogeneous methods and samples across studies.[23] A longitudinal, prospective study assessing the aging population ($n = 3385$)[27] showed associations between both current and past (without current) cannabis exposure and declining verbal memory, which appeared to be dose dependent; however, this study did not assess cognitive functioning at baseline, only at the final timepoint (year 25), assessed recreational use instead of medical use, and measured use infrequently.

Another large ($n = 1897$) study[28] found between-person but not within-person differences in cognition based on frequency of use, and concluded that the poorer verbal recall seen in mid-life users compared with nonusers was not due to current cannabis use. Other studies[29–31] assessed cannabis use in the context of dementia, Parkinson's disease, human immunodeficiency virus, and other diseases.

This analysis has limitations. Although the cognitive assessment in this study was objective, these tests are not as reliable[32] or valid as in-person interviewer assessments; practice effects may have been significant[32] although minimized in this study when possible. In addition, it is important to note that only one to two tasks were conducted for each cognitive domain in our study. To obtain a more comprehensive assessment of cognition, future studies should incorporate a wider range of tasks.

As the original trial was not designed to specifically assess older participants, the sample may have been underpowered to detect subtle cognitive effects in this age group. Importantly, the sociodemographic distribution is not representative of the general population; this was a clinical sample of people who expressed their interest in therapeutic use of cannabis, and does not assess effects of recreational use or use in otherwise healthy adults. The majority of participants were aged 45–64 years, so this

Table 2. Differences in Mean Scores of Cognitive Outcomes Between Nonfrequent (≤ 2 Days/Week) and Frequent (≥ 3 Days/Week) Adult Cannabis Users Ages ≥ 45 Years ($n = 62$)

Cognitive outcome	Beta (SE)	*T*	*p*	LCI	UCI
Attention and psychomotor speed					
Attention switching tasks					
Task 1*	5.28 (13.55)	0.39	0.6987	−22.12	32.69
Task 2*	−28.32 (27.53)	−1.03	0.3099	−84.01	27.36
Rapid visual information processing					
Task 1**	0.37 (0.18)	1.91	0.0635	−0.02	0.69
Memory					
Verbal recognition memory task					
Task 1**	−0.35 (0.22)	−1.60	0.1176	−0.80	0.093
Task 2**	−0.61 (0.84)	−0.73	0.4703	−2.31	1.08
Paired associative learning task					
Task 1**	−4.59 (2.98)	−1.54	0.1311	−10.62	1.43
Executive function					
Spatial working memory					
Task 1**	0.84 (4.42)	0.19	0.8496	−8.09	9.77

Mixed-effects model adjusted for baseline cognitive functioning comparing cognitive outcomes between frequent and nonfrequent cannabis users. Cognitive outcomes were assessed using the Cambridge Neuropsychological Test Automated Battery.

*Higher scores indicate better performance.

**Higher scores indicate worse performance.

LCI, lower confidence interval; SE, standard error; UPI, upper confidence interval.

limits generalizability to older adults ($n = 2$). Further longitudinal studies that account for cognitive effects of cannabis use in adults ≥65 years are warranted.

In addition, this sample was primarily White and female; studies in more diverse samples are needed. Although this analysis spans a year, other studies[27,28] that have shown associations between cognitive impairment and frequency of use were longer in duration and had larger sample sizes; it is possible that had this study been longer or larger, different results may have been seen.

Furthermore, it is important to consider that a portion of the study period coincided with the COVID-19 pandemic. Given the potential influence of this period on changes in the prevalence and frequency of cannabis use,[33] as well as the impact on cognitive functioning among individuals recovering from COVID-19,[34] the results of our study may have been affected by the study period. Future studies examining the associations between cannabis use and cognitive functioning should take this into account.

Conclusion

In a clinical sample of adults aged ≥45 years, who expressed their interest in using cannabis before participating in a trial, frequency of cannabis use was not associated with cognitive impairment. However, noteworthy associations were observed between problematic cannabis use and cognitive functioning within certain cognitive domains. More comprehensive studies using more reliable measures of cognitive impairment are needed to answer this question of safety for middle-aged and older adults using cannabis.

Authors' Contributions

O.L. contributed to conceptualization; formal analysis; and writing—original draft. K.W.P. performed formal analysis; software; and writing—review and editing. R.M.S. designed conceptualization; data curation—review and editing. J.M.G. assisted with conceptualization; writing—original draft; writing—review and editing; resources; data curation; and supervision.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This research was supported by the National Institute of Drug Abuse: PI J.M.G. (R01DA051540); PI O.L. (K23DA057417).

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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Cite this article as: Livne O, Potter KW, Schuster RM, Gilman JM (2023) Longitudinal associations between cannabis use and cognitive impairment in a clinical sample of middle-aged adults using cannabis for medical symptoms, *Cannabis and Cannabinoid Research* X:X, 1–6, DOI: 10.1089/can.2022.0310.

Abbreviations Used

CANTAB = Cambridge Neuropsychological Test Automated Battery
CUD = cannabis use disorder
CUDIT-R = Cannabis Use Disorder Identification Test-Revised
GED = General Educational Development

Original Paper

Effects of cannabidiol on simulated driving and cognitive performance: A dose-ranging randomised controlled trial

Journal of Psychopharmacology
2022, Vol. 36(12) 1338–1349

DOI: 10.1177/02698811221095356
journals.sagepub.com/home/jop

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Abstract

Background: Cannabidiol (CBD), a major cannabinoid of *Cannabis sativa*, is widely consumed in prescription and non-prescription products. While CBD is generally considered 'non-intoxicating', its effects on safety-sensitive tasks are still under scrutiny.
Aim: We investigated the effects of CBD on driving performance.
Methods: Healthy adults ($n=17$) completed four treatment sessions involving the oral administration of a placebo, or 15, 300 or 1500 mg CBD in a randomised, double-blind, crossover design. Simulated driving performance was assessed between ~45–75 and ~210–240 min post-treatment (Drives 1 and 2) using a two-part scenario with 'standard' and 'car following' (CF) components. The primary outcome was standard deviation of lateral position (SDLP), a well-established measure of vehicular control. Cognitive function, subjective experiences and plasma CBD concentrations were also measured. Non-inferiority analyses tested the hypothesis that CBD would not increase SDLP by more than a margin equivalent to a 0.05% blood alcohol concentration (Cohen's $d_z=0.50$).
Results: Non-inferiority was established during the standard component of Drive 1 and CF component of Drive 2 on all CBD treatments and during the standard component of Drive 2 on the 15 and 1500 mg treatments (95% CIs < 0.5). The remaining comparisons to placebo were inconclusive (the 95% CIs included 0 and 0.50). No dose of CBD impaired cognition or induced feelings of intoxication ($ps > 0.05$). CBD was unexpectedly found to persist in plasma for prolonged periods of time (e.g. >4 weeks at 1500 mg).
Conclusion: Acute, oral CBD treatment does not appear to induce feelings of intoxication and is unlikely to impair cognitive function or driving performance (Registration: ACTRN12619001552178).

Keywords

Cannabidiol, cognition, driving simulation, medicinal cannabis, psychomotor

Introduction

Cannabidiol (CBD) is a terpenophenolic cannabinoid found in the *Cannabis sativa* plant (ElSohly et al., 2017). CBD has shown considerable therapeutic potential in recent clinical trials (Millar et al., 2019) and is increasingly being used to treat anxiety, epilepsy, chronic pain and other conditions (Arnold et al., 2020). While some CBD products are prescribed (e.g. Epidiolex), the use of non-prescription CBD is also common in Europe and North America where CBD-containing 'nutraceuticals' can be purchased over the counter (Goodman et al., 2020; Manthey, 2019). Unlike the other major plant-derived cannabinoid, Δ^9-tetrahydrocannabinol (Δ^9-THC) (Arkell et al., 2019, 2020), CBD does not appear to 'intoxicate' or have readily discernible subjective effects (Arkell et al., 2020; Arndt and de Wit, 2017; Spindle et al., 2020). However, the impact of CBD on cognitively demanding, safety-sensitive tasks, such as driving, is worthy of investigation, given the substantial and increasing community use.

While several studies have indicated that CBD does not impair cognitive performance on discrete neuropsychological tests (McCartney et al., 2020), only one has directly investigated its effects on driving performance (Arkell et al., 2020). This randomised, placebo-controlled trial involving occasional

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cannabis users found that vaporised cannabis containing 13.75 mg of CBD (<1.0% Δ^9-THC) did not increase *standard deviation of lateral position* (SDLP), a well-established marker of impaired driving (Verster and Roth, 2011), during an on-road driving test. Measures of cognitive function and subjective intoxication (e.g. feeling 'stoned', 'sedated', 'relaxed', 'anxious') were also unaffected by CBD (Arkell et al., 2020). Thus, low doses of vaporised CBD appear unlikely to impair driving performance.

While reassuring, it should be noted that most clinical trials administer CBD orally (e.g. in a solution/oil, capsule or spray) rather than via vaporisation (Millar et al., 2019) and that nutraceuticals and prescription CBD products are often designed for oral ingestion (e.g. oils, capsules, edibles) (McGregor et al., 2020). Route of administration has a profound effect on the pharmacokinetics of CBD, with inhalation producing a rapid and transient peak in blood CBD concentrations and oral consumption eliciting lower peak concentrations hours later (Millar et al., 2018). Dose is another important factor: while nutraceuticals usually contain small amounts of CBD (e.g. ~10–20 mg/mL) (McGregor et al., 2020), the anxiolytic (~300–600 mg) (Bergamaschi et al., 2011; Crippa et al., 2011; Linares et al., 2019; Zuardi et al., 1993), anti-psychotic (~600–1280 mg/d) (Boggs et al., 2018; Leweke et al., 2012; Zuardi et al., 2009) and anticonvulsant (5–20 mg/kg/d) (Devinsky et al., 2017, 2018; Thiele et al., 2018) effects of CBD are only well documented at higher doses.

The current randomised controlled trial (RCT) investigated the effects of acute, oral CBD treatment at doses of 15, 300 and 1500 mg on simulated driving performance, cognitive function and subjective experiences. A non-inferiority approach was used to test the hypothesis that CBD would not increase SDLP by more than the non-inferiority margin (Δ), equivalent to a 0.05% blood alcohol concentration (BAC) (McCartney et al., 2020). This is the legal BAC limit for driving in many jurisdictions (Furtwaengler and De Visser, 2013) and therefore represents the largest 'tolerable' amount of driver impairment.

Methods

This investigation was approved by the University of Sydney's Human Research Ethics Committee (2019/474) and conducted at the Woolcock Institute of Medical Research, Sydney, Australia in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki (1983), and local regulations. The trial protocol is published elsewhere (McCartney et al., 2020) and registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12619001552178).

Study design

Participants completed four treatment sessions involving the oral administration of either placebo or 15, 300 or 1500 mg CBD (CBD-15, CBD-300 and CBD-1500) in a randomised, double-blind, crossover design. Sessions were separated by a washout period ⩾7 days and completed within a maximum of 60 days (median (interquartile range; IQR) washout of 7.5 (7) days). Participants were instructed to avoid using illicit drugs (including cannabis) throughout their involvement.

Participant population

Healthy individuals aged between 18 and 65 years who had held a full (unrestricted) driver's licence for ⩾1 year and had not used cannabis in ⩾3 months were eligible to participate. Exclusion criteria were as follows: (1) a clinically significant prior adverse response to cannabis, cannabinoid products or synthetic cannabinoids; (2) a current sleep disorder; (3) current suicidal ideation; (4) a history of (a) drug (including cannabis) and/or alcohol dependence or (b) attempted suicide; (5) a major psychiatric disorder within the last 12 months (except clinically-managed mild depression or anxiety); (6) a body mass index > 30 kg/m^2; (7) a high habitual caffeine intake (i.e. >300 mg/d); (8) current use of medications that (a) induce or inhibit the cytochrome (CYP) 450 enzyme system or (b) are metabolised by CYP enzymes that are inhibited by CBD; (9) current use of anticonvulsant medications; (10) required to complete drug testing for cannabis; (10) unwillingness to (a) adhere to pre-trial procedures (see section 'Experimental procedures') or (b) refrain from using illicit drugs throughout participation; (11) high likelihood of experiencing simulator sickness; and (12) pregnant or lactating.

All volunteers completed an initial eligibility screen where they were informed of the study requirements and risks before providing written informed consent and being assessed for eligibility by an investigator and independent physician. Eligible participants then practised the full, ~30 min simulated drive and cognitive function tests to reduce learning effects. The eligibility criteria and the recruitment and screening processes are detailed further elsewhere (McCartney et al., 2020).

Experimental procedures

Participants were instructed to abstain from alcohol (⩾24 h) and caffeine (⩾12 h), keep a 24-h diet record (or, if this was not their first session, to replicate the diet they consumed before this) and spend ⩾8 h in bed overnight prior to each session.

Participants arrived at the laboratory between ~07:00 and 09:00 h following an overnight fast and verbally acknowledged compliance with the pre-trial procedures. Breath (Alcotest®, Dräger, Lübeck, Germany), drug (DrugCheck® NxStep Onsite Urine Drug Test), hydration (Palette Digital Refractometer, ATAGO, USA) and pregnancy (Human Chorionic Gonadotrophin Cassette, Alere™) tests were also performed (as applicable) to verify abstinence from alcohol, cannabis and illicit drugs and to rule out dehydration and pregnancy (McCartney et al., 2020).

Each treatment session involved eight 'blocks' of testing: 'Baseline' (pre-treatment), 'Pre-Drive 1' (between 15 and 45 min post-treatment), 'Drive 1' (between 45 and 75 min post-treatment), 'Post-Drive 1' (between 75 and 95 min post-treatment), 'Halfway' (between 140 and 150 min post-treatment), 'Pre-Drive 2' (between 180 and 210 min post-treatment), 'Drive 2' (between 210 and 240 min post-treatment) and 'Post-Drive 2' (between 240 and 260 min post-treatment). The specific assessments completed during each block are described below and summarised in Table 1 of McCartney et al. (2020). Treatments were administered on completion of the Baseline tests alongside a standardised breakfast; a light standardised snack was also provided ~150 min post-treatment. Participants indicated which treatment they thought they had received and their confidence in this guess

Table 1. Participant characteristics.

Characteristic	Participants ($n=17$)
Sex (M/F) (n)	10/7
Age (years)	27.9 (7.0)
Weight (kg)	67.4 (23.0)
Body mass index (kg/m^2)	22.0 (4.3)
Unsupervised driving experience[a] (years)	9.9 (6.7)
Last month driving frequency (day/week)	4 (5)
Last month driving distance (km/week)	80 (75)
Lifetime cannabis exposures (n)	
⩽10 uses	6
>10 uses	10
No use	1
Time since last cannabis use (n)	
3–6 months	3
6–12 months	5
1–2 years	3
2–4 years	2
>4 years	3
Lifetime CBD exposures (n)	
⩽10 uses	1
>10 uses	2
No use	14
Time since last CBD use (n)	
3–6 months	0
6–12 months	2
1–2 years	1
2–4 years	0
>4 years	0

M: males; F: females; CBD: cannabidiol; IQR: interquartile range.
Values are median (IQR) and frequency (n) as appropriate.
[a]Years in possession of a driver's licence (includes time with a probationary licence).

(on a 4-point Likert-type scale; 1 = 'not at all' to 4 = 'extremely') at the end of each session.

Study treatments

The investigational product (GD Cann®–C; GD Pharma Pty Ltd, Norwood, South Australia, Australia) was an oral formulation of synthetic CBD (100 mg/mL) in medium-chain triglyceride (MCT) oil; the placebo was MCT oil (only). It was administered in different volumes (i.e. 150 µL, 3.0 mL or 15 mL) containing 15, 300 or 1500 mg CBD. Each dose was made up to a total equivalent volume of 15 mL via the addition of placebo oil and administered (via oral ingestion) in a high-fat supplement (100 mL; 50 g fat) (Calogen®, Nutricia, Macquarie Park, Australia) intended to increase the bioavailability of CBD (Birnbaum et al., 2019; Taylor et al., 2018). Neither the placebo nor active treatment contained any other cannabinoids (including Δ^9-THC) or cannabis constituents (e.g. flavonoids, monoterpenes, sesquiterpenes). The products did not differ noticeably in their visual appearance or smell and the preparations administered carried no 'treatment-identifying' information (e.g. coded letters or numbers).

Randomisation

Participants were assigned to one of four possible treatment orders (Figure 1) in a 1:1:1:1 ratio using a pre-populated randomisation schedule. The four orders constituted a Latin square and the schedule was randomly generated in a series of balanced blocks by an independent statistician using SAS (v9.4, Cary, NC) as described elsewhere (McCartney et al., 2020). Only the statistician and those individuals involved in treatment preparation had access to the randomisation schedule (and neither had any contact with participants).

Data collection

Simulated driving. Driving performance was measured 45–75 and 210–240 min post-treatment using a fixed-base driving simulator equipped with standard vehicle controls and a custom-built scenario that has demonstrated sensitivity to the effects of Δ^9-THC (SCANeR Studio Simulation Engine, v1.6r85, OKTAL, Paris, France) (Arkell et al., 2019). The timing of the second drive was selected to approximately coincide with peak plasma CBD concentrations reported at ~3 h after consuming 25 or 300 mg CBD (Birnbaum et al., 2019; Knaub et al., 2019) and ~4 h after consuming 1500 mg CBD (Taylor et al., 2018). The driving test incorporated two activities detailed elsewhere (McCartney et al., 2020): (1) a 7-min 'car following' (CF) component during which participants maintained what they considered a 'safe distance' between themselves and a lead vehicle accelerating and decelerating (90–110 km/h) at 30 s intervals and (2) a ~25-min 'standard' component (formally termed 'secondary' component; Arkell et al., 2019; McCartney et al., 2020) along highway and rural roads with posted speed limits of 110 and between 60–100 km/h, respectively. SDLP was measured throughout both components. Car following distance ('headway') and standard deviation (SD) of headway were measured during the CF component (only) and speed and SD of speed were measured during the standard component (only). Data were automatically recorded by the simulator's software programme at a rate of 20 Hz and all artefacts were removed manually by the same (blinded) investigator using a systematic approach: 10 s of data were removed immediately prior to and following each intentional lane crossing and 60 s were removed immediately prior to and following each 'incident' (two hazards and two sets of traffic lights) using timestamps recorded by the driving simulator software. The data collected during each incident were also removed. Artefacts were only present in the standard component of the drive. Participants were instructed to follow all road rules and drive in the centre of their lane.

Cognitive function. Cognitive function was assessed at Baseline, Pre-Drive 1 and Pre-Drive 2 using three computerised tasks that have previously demonstrated sensitivity to the effects of Δ^9-THC (Arkell et al., 2019, 2020; Schlienz et al., 2020; Spindle et al., 2018): the Digit Symbol Substitution Task (DSST) (~1.5 min), Divided Attention Task (DAT) (~4 min) and Paced Serial Addition Task (PSAT) (~3 min). The DRUID® task (~2 min), a computerised application ('app') designed to measure drug and/or alcohol-induced impairment, was also completed at these times (Richman and May, 2019). The app generates an overall impairment score between 0 and 100, with higher

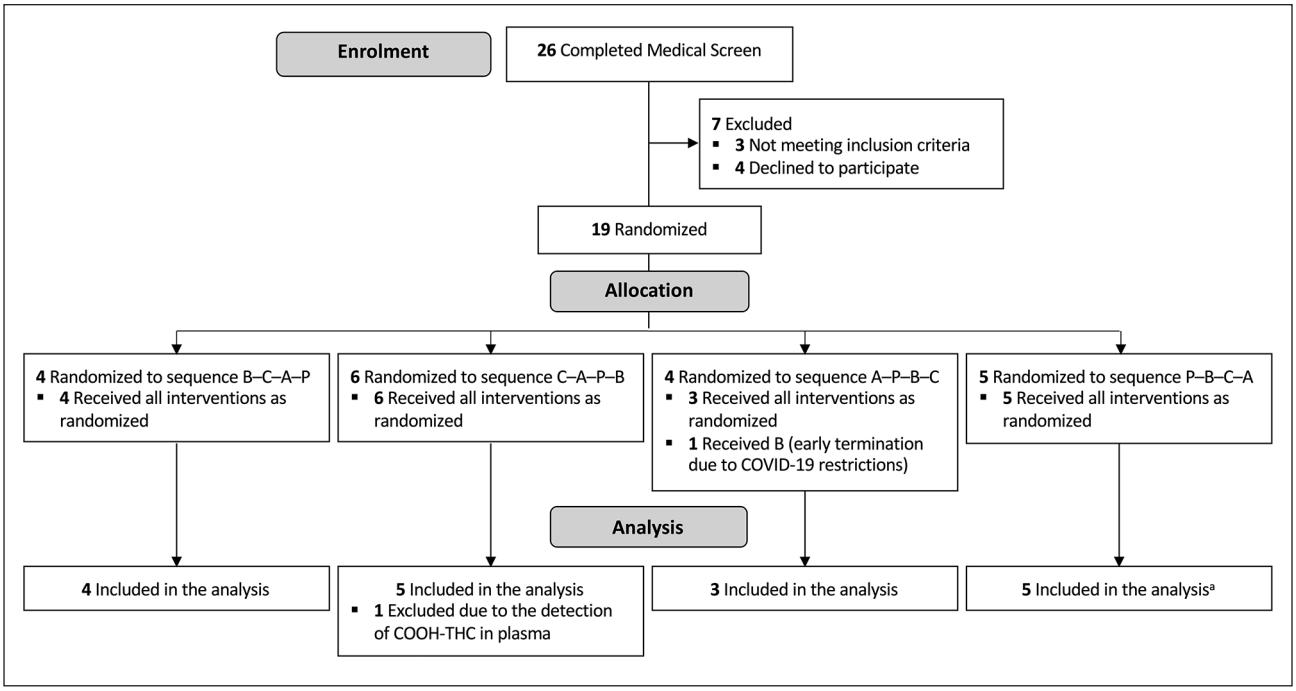

Figure 1. CONSORT diagram. A: 1500 mg CBD; B: 15 mg CBD; C: 300 mg CBD; P: Placebo. [a]One participant failed to complete the 'Standard Drive' on each testing occasion and was therefore omitted from the analysis of these outcomes.

scores indicating increased impairment. A 10-min Psychomotor Vigilance Task (PVT) (i.e. simple reaction time test) was also performed Post-Drives 1 and 2. These tasks and their associated outcome measures are detailed elsewhere (McCartney et al., 2020). All automatically generated 'alternate versions' (i.e. with different stimuli) on each testing occasion to reduce learning effects.

Subjective experiences. Subjective feelings, namely 'stoned', 'sedated', 'alert', 'anxious' and 'sleepy', were measured at all time points using 100 mm visual analogue scales (VAS), where 0 represented 'not at all' and 100 represented 'extremely'. State anxiety was also measured at these times using the 6-item Short Form State and Trait Anxiety Inventory (STAI-S) (Marteau and Bekker, 1992). After reversing the scores on 'positive' items, the total STAI score was summed and multiplied by 20/6 to generate a result comparable to that obtained on the full, 20-item STAI-S (Marteau and Bekker, 1992). Driving self-efficacy was measured Pre-Drives 1 and 2 using the Adelaide Driving Self Efficacy Scale (ADSES) (George et al., 2007).

Plasma cannabinoid concentrations. Blood was collected into 10 mL pre-treated EDTA vacutainers (Becton, Dickinson and Company, Franklin Lakes, USA) via an indwelling venous cannula at Baseline and Pre- and Post-Drives 1 and 2. Samples were centrifuged at 2500*g* for 15 min (4°C) and the plasma supernatant was stored at −80°C. Plasma was thawed for analysis via ultra-high performance liquid chromatography-tandem mass spectrometry using previously validated methods (Kevin et al., 2021). Target analytes were CBD, Δ^9-THC and their major phase-I metabolites.

Cardiovascular measures. Seated heart rate (HR) and blood pressure (BP) were measured at all time points using an automated sphygmomanometer (M2 Basic, Omron Corporation, Kyoto, Japan). Measures were taken in duplicate or triplicate if systolic BP differed by >15 mmHg, then averaged.

Primary outcome

The primary outcome was SDLP on the simulated driving tests. SDLP is a well-established measure of impaired driving and has been shown to increase dose-dependently with the administration of intoxicating and sedative drugs (e.g. alcohol, Δ^9-THC, benzodiazepines) (Dassanayake et al., 2011; Irwin et al., 2017; Veldstra et al., 2015).

Statistical methods

The primary outcome was subjected to non-inferiority analysis. Δ was defined a priori as a Cohen's d_z effect of 0.50 on the basis of analyses suggesting that a 0.05% BAC (i.e. the largest 'tolerable' amount of driver impairment) has an effect of this magnitude on SDLP (see McCartney et al., 2020, for details). Non-inferiority is therefore established if the upper 95% confidence interval (CI) is <0.50. Indeed, this is the preferred way in which to demonstrate that one treatment is not worse than another (Althunian et al., 2017). Note that Δ was not based on prior studies of cannabis or THC as there is limited value in showing CBD is less impairing than a substance that is typically prohibited among drivers (Perkins et al., 2021). Note also that although they could differ in their sensitivity to impairment, the same Δ was used to analyse SDLP data from the standard and CF components of the drive. This was because we did not have a direct measure of alcohol's effects on our specific driving scenario and instead used data from several other studies to obtain the best possible estimate

(see McCartney et al., 2020, for details). Indeed, it would have been difficult to estimate the magnitude of difference (if one exists) between CF and non-CF drives using this approach.

Cohen's d_z effect estimates were calculated by standardising the mean difference between placebo and each intervention performance score against the SD of the performance change (SDΔ) (Lakens, 2013). The standard error (SE) was derived using the Hedges and Olkin approximation adapted for a repeated-measures design (Borenstein et al., 2009; Goulet-Pelletier and Cousineau, 2018b):

$$SE_d = \sqrt{\left(\frac{1}{n} + \frac{d^2}{2n}\right) \times 2 \times (1 - R)} \quad (1)$$

where SE_d is the SE of Cohen's d, d is Cohen's d_z, n is the sample size and R is the correlation coefficient. SE_d values were then divided by a factor of $\sqrt{2(1-R)}$ to derive the SE for Cohen's d_z specifically (Goulet-Pelletier and Cousineau, 2018a, 2018b) and used to calculate 95% CIs. (Note: one participant failed to complete the standard component of each drive (see section 'Expectancies and adverse events') and was therefore omitted from the relevant non-inferiority analyses and the statistical analyses of speed and SD of speed described below.)

Secondary outcomes were analysed using linear mixed-effects models and the 'lme4' and 'emmeans' packages (Bates et al., 2012; Singmann et al., 2019) in RStudio (Version 4.0.1). Variables that were measured at Baseline were analysed as the *change from Baseline* (i.e. the Baseline measure was subtracted from each measure obtained during a given treatment session prior to analysis); the remainder were analysed as 'raw scores'. The models included Treatment, Time, and the Treatment × Time interaction as fixed effects (as appropriate) and the participant as a random effect. Models were generated using the restricted maximum likelihood (RML) criterion and no covariance structure was specified (unstructured). The data were log-transformed and reanalysed in the event that residuals were non-normally distributed (Shapiro–Wilk test, $p < 0.05$). The first model was retained if the log transformation did not improve normality (Schielzeth et al., 2020). Effect sizes were calculated as partial eta squared (η_p^2). Two-sided (Bonferroni corrected) pairwise comparisons were used to compare estimated marginal means across Treatment, Time or Treatment and Time if a significant effect of Treatment, Time, or a Treatment × Time interaction was observed, respectively. For each variable, the Bonferroni correction was proportional to the total number of post hoc comparisons performed (e.g. six if a main effect of Treatment was observed). Normally and non-normally distributed data are presented as Mean ± SE and median (IQR), respectively unless otherwise stated. Statistical significance was accepted as $p < 0.05$.

Results

Participant characteristics

Recruitment for this trial commenced in November 2019 and concluded 12 months later. Nineteen participants were initially randomised (Figure 1). However, one was unable to complete all four treatment sessions within the 60-day (drug expiration) period due to a university-wide suspension on face-to-face research during the SARS-CoV-2 pandemic. Another had detectable levels of 11-COOH-Δ^9-THC in plasma (at Baseline) suggesting she had not abstained from cannabis. Both individuals (females) were removed from the final sample. (Note: The retrospective exclusion of the latter participant did not influence the primary outcome; see Figure S1.) The characteristics of the 17 remaining participants are summarised in Table 1. Baseline urine specific gravity (hydration status) ($F_{[3, 48]} = 0.745$, $p = 0.531$) and self-reported (pre-trial) sleep duration ($F_{[3, 48]} = 0.348$, $p = 0.791$) did not differ across treatments.

The target sample size of 27 (see McCartney et al., 2020) could not be reached within the available resources due to the abovementioned suspension of face-to-face research. A smaller than anticipated sample size in a non-inferiority trial would be expected to yield Cohen's d_z effect estimates with wider 95% CIs, increasing the likelihood of an inconclusive result (i.e. where the 95% CI includes 0 and 0.50 – and the 'true' result, inferior or non-inferior, remains to be determined) without compromising the validity of any 'non-inferior' results (Schönbrodt and Perugini, 2013). There is also some risk of 'non-inferior (inferior)' results (i.e. where the 95% CI does not include 0 or 0.50) being mistaken for 'standard' non-inferior results (i.e. where the 95% CI includes 0 but not 0.50); however, both still indicate non-inferiority (i.e. the 95% CI is <0.5) (see also Figure 1 in McCartney et al., 2020).

Primary outcome

The non-inferiority analysis of the primary outcome (SDLP) is displayed in Figure 2; Mean ± SD values are presented in Table 2. Non-inferiority to placebo was established during the standard component of Drive 1 (CBD-15: –1.60 ± 1.31 cm; CBD-300: –0.94 ± 1.25 cm; CBD-1500: –0.87 ± 1.17 cm) and the CF component of Drive 2 (CBD-15: –0.45 ± 1.49 cm; CBD-300: –0.71 ± 1.10 cm; CBD-1500: –1.24 ± 1.28 cm) on all CBD treatments and during the standard component of Drive 2 on CBD-15 (–0.44 ± 1.18 cm) and CBD-1500 (–0.64 ± 1.51 cm). The remaining comparisons (to placebo) were inconclusive (i.e. the 95% CIs included both 0 and 0.50) (CBD-15 on CF Drive 1: +1.04 ± 1.18 cm; CBD-300 on CF Drive 1: +1.43 ± 1.16 cm; CBD-1500 on CF Drive 1: +1.39 ± 0.82 cm; CBD-300 on standard Drive 2: +0.06 ± 1.07 cm). The same results were obtained when the analysis was performed using an unstandardised Δ (see Figure S19). Note also that the numeric differences in SDLP on the standard and CF components of the drive (Table 2) are likely due, in part, to the latter being conducted on a large highway with gentle contours, and part of the former being conducted on a windier rural road.

Secondary outcomes

Measures of driving performance are summarised in Table 2. Measures of cognitive function, subjective experiences and cardiovascular function are displayed in Figures S2–S9; note that 'raw scores' for variables that were measured at Baseline (and therefore analysed as the *change from Baseline* as described in section 'Statistical methods') are also presented in Figures S10–S15. These data were included for completeness and were not subjected to statistical analysis. The results of the statistical comparisons are summarised in Table 3.

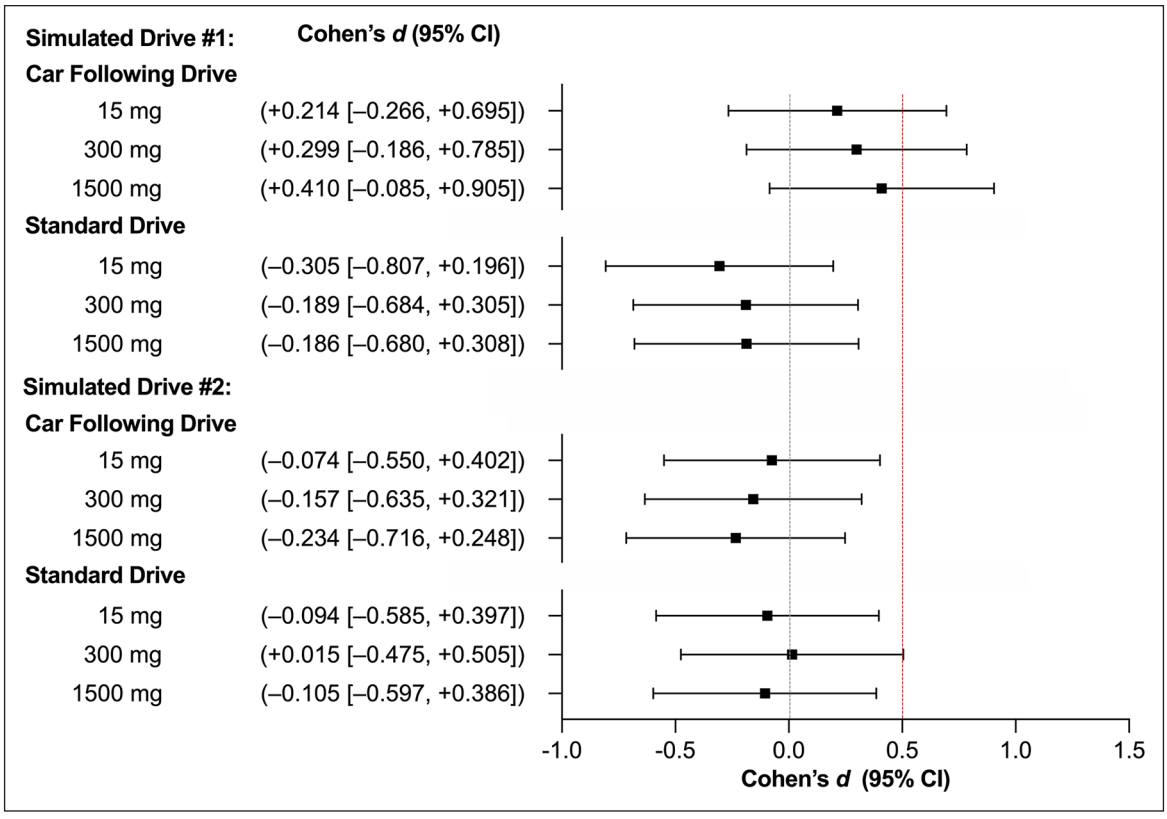

Figure 2. SDLP effect sizes ($n=17$ on Car Following Drives and $n=16$ on Standard Drives). Values are Cohen's d_z (95% CI) (all comparisons to Placebo). Red line represents the non-inferiority margin (Δ). CI: confidence interval. Drive 1 was completed 45–75 min post-treatment and Drive 2 was completed 180–210 min post-treatment.

Table 2. Measures of simulated driving performance.

	Simulated drive 1				Simulated drive 2			
	Placebo	15 mg	300 mg	1500 mg	Placebo	15 mg	300 mg	1500 mg
Car Following component								
SDLP (cm)	20.0 ± 4.2	21.0 ± 5.4	21.4 ± 3.7	21.4 ± 4.3	21.7 ± 5.5	21.2 ± 5.1	21.0 ± 5.4	20.4 ± 5.5
Headway (m)	81.5 ± 66.2	102.5 ± 93.0	96.7 ± 103.2	89.7 ± 81.8	90.8 ± 73.4	102.6 ± 109.3	93.9 ± 73.2	93.0 ± 86.1
SD Headway (m)	18.3 ± 7.8	27.2 ± 21.2	22.5 ± 16.3	20.7 ± 12.6	26.9 ± 23.8	26.6 ± 20.3	25.4 ± 11.2	22.6 ± 11.0
Standard component[a]								
SDLP (cm)	34.4 ± 5.1	32.8 ± 4.8	33.4 ± 6.2	33.5 ± 5.9	34.3 ± 4.9	33.9 ± 6.1	34.4 ± 4.0	33.7 ± 6.2
Speed (km/h)	100.1 ± 6.2	98.9 ± 6.4	99.0 ± 5.1	99.7 ± 5.4	103.2 ± 11.7	100.6 ± 5.4	101.1 ± 5.5	101.3 ± 7.0
SD Speed (km/h)	13.0 ± 2.4	14.1 ± 3.6	12.2 ± 2.0	12.9 ± 2.5	13.5 ± 3.1	12.8 ± 3.1	12.2 ± 2.4	12.5 ± 2.9

SD: standard deviation; SDLP: standard deviation of lateral position.
Values are Mean ± SD.
[a]Sample size was $n=16$ as one participant failed to complete the Standard Drive on each occasion (see section 'Expectancies and adverse events').
Drive 1 was completed ~45–75 min post-treatment and Drive 2 was completed ~180–210 min post-treatment. The measures obtained during the standard component of these simulated drives may not be directly comparable to those obtained during previous studies utilising the same task as artefacts (e.g. lane crossing events) were removed in a subtly different (though in both cases, systematic) way.

Driving performance. Speed differed across Time (Table 3) with participants travelling faster during Drive 2 than Drive 1 ($p=0.005$; Table 2). No other significant differences were observed.

Cognitive function. Tracking error, that is, the mean distance between the cursor and the target, on the DAT indicated an effect of Treatment (Table 3; Figures S3 and S11) with less error (relative to baseline) observed on CBD-300 (–0.16 ± 0.31 vs +1.21 ± 0.43, $p=0.011$) and CBD-1500 (–0.19 ± 0.43 vs +1.21 ± 0.43, $p=0.007$) than CBD-15. No other significant differences were observed.

Subjective experiences. VAS ratings of stoned, sedated, alert and sleepy as well as scores on the ADSES and STAI

Table 3. Results of the statistical analyses of driving performance, cognitive function, subjective experiences, and cardiovascular parameters ($n = 17$).

Outcome	Treatment effect			Time effect			Interaction effect		
	F-ratio	*p*-value	η_p^2	*F*-ratio	*p*-value	η_p^2	*F*-ratio	*p*-value	η_p^2
Driving performance									
SDLP (CF)	–	–	–	0.018	0.893	<0.01	–	–	–
Headway	0.700	0.553	0.02	0.746	0.389	<0.01	0.311	0.816	<0.01
SD Headway	0.508	0.677	0.03	3.81	0.053	0.03	0.684	0.563	0.03
SDLP (Standard)	–	–	–	0.850	0.359	<0.01	–	–	–
Speed	1.15	0.329	0.03	**8.37**	**0.005**	**0.07**	0.160	0.922	<0.01
SD Speed	2.35	0.076	0.06	1.18	0.278	0.01	1.24	0.297	0.03
Cognitive function									
DSST									
Correct responses	0.325	0.807	<0.01	1.77	0.186	0.02	0.113	0.952	<0.01
Response accuracy	0.637	0.593	0.02	<0.001	0.982	<0.01	0.234	0.872	<0.01
DAT									
Tracking error	**4.75**	**0.004**	**0.11**	0.211	0.647	<0.01	0.742	0.529	0.02
Hits	0.476	0.700	0.01	0.167	0.684	<0.01	0.085	0.968	<0.01
Response time	1.67	0.176	0.04	0.105	0.746	<0.01	1.09	0.356	0.03
PSAT									
Correct responses	2.49	0.064	0.06	0.040	0.841	<0.01	0.118	0.949	<0.01
Response time	2.54	0.060	0.06	0.731	0.394	<0.01	0.429	0.733	0.01
DRUID									
Total score	1.03	0.381	0.03	0.347	0.557	<0.01	0.521	0.669	0.01
PVT									
Response time	1.09	0.353	0.03	0.243	0.623	<0.01	0.118	0.949	<0.01
Lapses	1.87	0.138	0.05	0.001	0.973	<0.01	0.405	0.749	0.01
Subjective experiences									
Stoned	1.04	0.377	0.01	**5.39**	**<0.001**	**0.07**	0.535	0.891	0.02
Sedated	0.500	0.682	<0.01	**8.03**	**<0.001**	**0.10**	0.569	0.867	0.02
Alert	2.07	0.104	0.02	**3.19**	**0.014**	**0.04**	0.190	0.999	<0.01
Anxious	**7.54**	**<0.001**	**0.07**	0.545	0.703	<0.01	0.200	0.999	<0.01
Sleepy	2.27	0.081	0.02	**11.7**	**<0.001**	**0.13**	0.613	0.831	0.02
State anxiety	2.20	0.088	0.02	**2.42**	**0.048**	**0.03**	0.389	0.967	0.02
Driving self-efficacy	0.654	0.581	0.02	**8.37**	**0.005**	**0.07**	0.386	0.762	0.01
CV Function									
Heart rate	1.40	0.243	0.01	1.96	0.100	0.03	0.263	0.994	0.01
Systolic BP	2.27	0.080	0.02	0.965	0.427	0.01	0.810	0.640	0.03
Diastolic BP	1.93	0.125	0.02	**2.71**	**0.031**	**0.03**	0.415	0.957	0.02

–: not applicable; CF: car following drive; CV: cardiovascular; DAT: Divided Attention Task; DSST: Digit Symbol Substitution Task; PSAT: Paced Serial Addition Task; PVT: Psychomotor Vigilance Test; Standard: standard drive; SD: standard deviation; SDLP: standard deviation of lateral position; BP: blood pressure.
Bold *p*-values are significant ($p < 0.05$).

questionnaires differed across Time but did not indicate effect of Treatment or a Treatment × Time interaction (Table 3; Figures S7, S8 and S14). Relative to baseline, participants felt

1. More stoned Post-Drive 1 ($+4 \pm 2$ mm) than Pre-Drive 1 ($+1 \pm 1$ mm, $p = 0.006$), Pre-Drive 2 ($+1 \pm 1$ mm, $p = 0.001$) and Post-Drive 2 ($+1 \pm 1$ mm, $p = 0.002$);
2. More sedated ($ps < 0.002$) Post-Drive 1 ($+10 \pm 5$ mm) than Pre-Drive 1 ($+2 \pm 2$ mm), Halfway ($+4 \pm 3$ mm), Pre-Drive 2 ($+3 \pm 2$ mm) and Post-Drive 2 ($+4 \pm 3$ mm);
3. Less alert Post-Drive 1 than Pre-Drive 2 (-2 ± 5 vs $+7 \pm 5$ mm, $p = 0.021$);
4. Sleepier ($ps < 0.001$) Post-Drive 1 ($+11 \pm 5$ mm) than Pre-Drive 1 (-3 ± 3 mm) and Pre-Drive 2 ($+1 \pm 5$ mm);
5. Sleepier Post-Drive 2 ($+6 \pm 5$ mm) than Pre-Drive 1 (-3 ± 3 mm, $p < 0.001$) and Pre-Drive 2 ($+1 \pm 5$ mm, $p = 0.027$);
6. Sleepier Halfway than Pre-Drive 1 ($+6 \pm 5$ vs -3 ± 3 mm, $p = 0.004$).

Driving self-efficacy was also higher Pre-Drive 2 than Pre-Drive 1 (108 ± 4 vs 103 ± 5, $p = 0.005$). Post hoc comparisons for state anxiety did not reach statistical significance ($ps > 0.10$). These observations suggest the driving tests induced some degree of fatigue.

VAS ratings of anxiousness indicated an effect of Treatment (Table 3; Figures S7 and S14) with higher ratings (relative to baseline) observed on placebo ($+0 \pm 1$ mm) than CBD-300

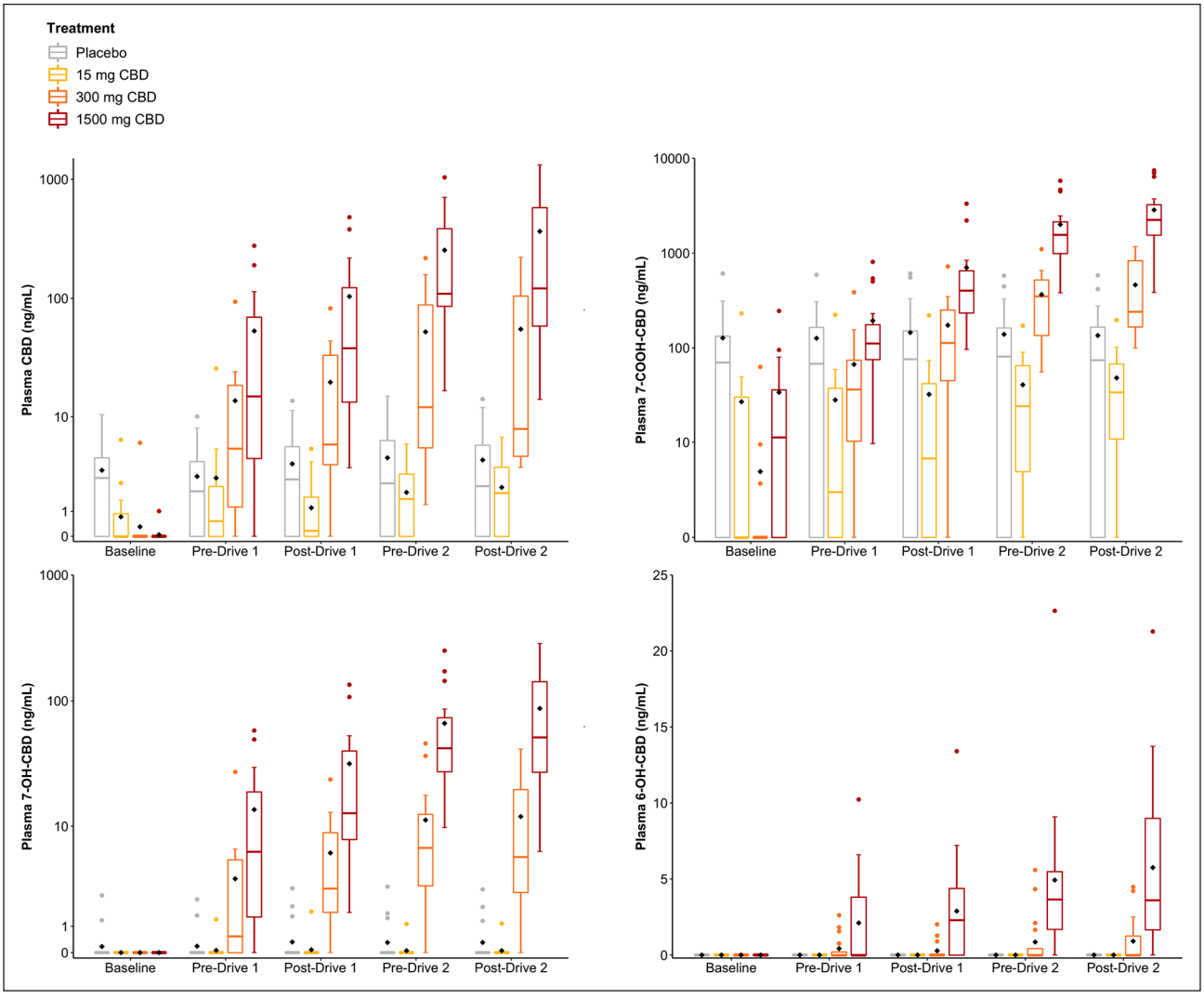

Figure 3. Plasma CBD, 7-COOH-CBD, 7-OH-CBD and 6-OH-CBD and concentrations ($n=17$). Baseline is pre-treatment; Pre-Drive 1 is ~45 min post-treatment, Post-Drive 1 is ~75 min post-treatment, Pre-Drive 2 is ~210 min post-treatment and Post-Drive 2 is ~240 min post-treatment. Grey: Placebo, Yellow: 15 mg CBD; Orange: 300 mg CBD and Red: 1500 mg CBD. The black diamond represents the mean value.

(–6 ± 4 mm, $p<0.001$) and CBD-1500 (–4 ± 3 mm, $p=0.033$) and on CBD-15 (+0 ± 2 mm) than CBD-300 (–6 ± 4 mm, $p=0.001$) and CBD-1500 (–4 ± 3 mm, $p=0.040$). No other significant differences were observed.

Cardiovascular function. Diastolic BP indicated an effect of Time (Table 3; Figures S9 and S15) with higher BP (relative to baseline) observed Pre-Drive 1 than Post-Drive 1 (–4.6 ± 6.0 vs −2.0 ± 6.1 mmHg, $p=0.025$). No other significant differences were observed.

Plasma cannabinoid concentrations

Plasma CBD, 7-COOH-CBD, 7-OH-CBD and 6-OH-CBD concentrations are presented in Figure 3. Several participants were unexpectedly found to have detectable levels of CBD and CBD metabolites in plasma at Baseline on (and throughout) their placebo trial (CBD: $n=12$, mean (range)=4.7 (1.4–10.4) ng/mL; 7-COOH-CBD: $n=12$, 180 (61–609) ng/mL; 7-OH-CBD: $n=2$, 1.9 (1.3–2.5) ng/mL) (Figure S16). Each of these individuals received CBD-1500 at their last visit between 7 and 29 days earlier suggesting that this high dose produced prolonged residual concentrations of CBD and CBD metabolites in plasma. (Note: The Latin square generated during randomisation was 'unbalanced' such that each treatment was not preceded equally often by every other treatment; Figure 1.) Indeed, we identified a moderate, though not statistically significant, negative (Spearman's) correlation between residual plasma CBD concentrations and the length of the washout period (in days) among these 12 individuals ($R=0.53$, $p=0.075$).

Some participants also had detectable levels of CBD and CBD metabolites in plasma at Baseline on their CBD-15 trial (CBD: $n=5$; mean (range)=2.5 (0.8–6.3) ng/mL; 7-COOH-CBD: $n=7$; 62 (15–230) ng/mL) (Figure S16). Each of these individuals received placebo at their last visit but CBD-1500

between 14 and 39 days earlier. CBD and 7-COOH-CBD were also detected in plasma at Baseline on a number of CBD-300 (CBD: $n=1$; 7-COOH-CBD: $n=3$) and CBD-1500 (CBD: $n=1$; 7-COOH-CBD: $n=11$) trials (Figure S16). Δ^9-THC, 11-COOH-Δ^9-THC and 11-OH-Δ^9-THC were not detected in any of the samples obtained from the 17 included participants.

Expectancies and adverse events

Participants correctly identified the treatment received on 11 (16%) occasions (Placebo: 3 (18%); CBD-15: 3 (18%); CBD-300: 4 (24%); CBD-1500: 1 (6%)) (Figure S17). Individuals were *not at all* ($n=4$), *somewhat* ($n=2$), *moderately* ($n=4$) and *extremely* ($n=1$) confident they had correctly guessed their assigned treatment in each instance.

No serious adverse events occurred. One participant fainted during the Baseline blood draw; she completed the treatment session; however, her involvement in the trial was ultimately terminated due to the abovementioned suspension of face-to-face research. A second participant felt nauseated ~20 min into the first driving test (after receiving the placebo treatment) and later vomited (despite having practised the driving test without complications during the eligibility screen). She completed the treatment session, but only performed the CF component (i.e. first ~7 min) of each subsequent drive (see section 'Statistical methods'). The participant appeared to drive similarly during the CF component of her first and subsequent driving tests and her exclusion did not influence the primary outcome (Figure S18).

Discussion

This study investigated the effects of acute, oral CBD treatment on simulated driving performance, cognitive function and subjective experiences. A non-inferiority design was used to test the hypothesis that CBD would not increase SDLP by more than Δ, the approximate level of impairment observed at 0.05% BAC. With recent evidence suggesting that low doses of vaporised CBD do not impair driving performance (Arkell et al., 2020), and additional reports that CBD (in general) does not affect cognitive function or induce feelings of intoxication (Arkell et al., 2020; Arndt and de Wit, 2017; Spindle et al., 2020), the expectation was that orally administered CBD would not influence these outcomes, even at high doses.

The effects of CBD on SDLP during Drive 2 (~3.5–4 h post-treatment) support this hypothesis. Indeed, neither CBD-15, CBD-300 nor CBD-1500 appeared to increase SDLP during the CF or standard components of this drive, though CBD-300 *technically* had an inconclusive effect on the latter with the upper 95% CI *just* exceeding (+0.005) the non-inferiority margin. The average increase in SDLP on this treatment and task was negligible (+0.06 cm).

While all three CBD treatments also demonstrated non-inferiority during the standard component of Drive 1 (~45–75 min post-treatment), suggesting no effect on SDLP, their effects on the CF component were inconclusive, that is, these analyses were underpowered to determine the impact of CBD. As CBD did not affect SDLP during the standard component of this drive and plasma CBD concentrations were lower at this time than during Drive 2, where non-inferiority was established, it seems likely that a larger participant sample would yield a 'non-inferior' result. However, it is important to acknowledge that the CF task has demonstrated greater sensitivity to Δ^9-THC-induced impairment than the standard drive (Arkell et al., 2019). In addition, we cannot rule out the possibility that CBD has 'phasic' pharmacological effects, for example, stronger (or differing) effects on initial exposure than at maximum plasma concentrations (C_{max}). On the contrary, the average 'change' in SDLP observed (during CF) on each of these treatments (+1.0–1.4 cm) was smaller than typically reported during intoxication with other drugs (e.g. ~2.5 cm) (Verster and Roth, 2011) (see also Figure S19) – and considerably less than previously observed with 13.75 mg Δ^9-THC in another RCT employing exactly the same simulated driving test (~3.9 cm) (Arkell et al., 2020).

The effects of CBD on cognitive function and subjective experiences were also investigated. However, unlike SDLP, these data were analysed in an exploratory fashion using traditional, statistical techniques (i.e. test of 'superiority') as it would have been difficult to define Δ for each individual outcome. No dose of CBD impaired performance on the DSST, DAT, PSAT, PVT or DRUID® task. However, tracking performance on the DAT did differ among active treatments with more error observed on CBD-15 than CBD-300 and CBD-1500. This finding is somewhat difficult to interpret as no significant differences to placebo were observed, that is, it is unclear whether CBD-15 impaired or CBD-300 and CBD-1500 enhanced tracking performance (or both). The fact that (1) no other cognitive effects were observed; (2) studies do not typically detect significant effects of CBD on cognitive function (McCartney et al., 2020); and (3) 10 different cognitive function variables were measured suggests that the result could be a Type II Error. The only subjective measure to demonstrate an effect of treatment in this trial was 'anxiousness', with marginally higher VAS ratings (~5 mm) observed on placebo and CBD-15 than CBD-300 and CBD-1500. This finding adds to a growing body of evidence that CBD has anxiolytic properties (Bergamaschi et al., 2011; Crippa et al., 2011; Linares et al., 2019; Zuardi et al., 1993). Overall, these observations suggest that CBD does not impair cognitive function or induce feelings of intoxication. However, it is important to acknowledge that, given our relatively small sample size, these superiority analyses could have been underpowered to detect otherwise significant effects.

One limitation of this investigation is that 12 participants were unexpectedly found to have low but detectable levels of CBD in plasma on their placebo trial. Each of these individuals had received CBD-1500 at their last visit (up to 29 days earlier) suggesting it was residual from this high dose. Indeed, cannabinoids are highly lipophilic molecules and the persistence of Δ^9-THC in biological matrices despite weeks or months of abstinence is a well-documented phenomenon believed to reflect its retention in adipose tissue (Wong et al., 2013). The current observation suggests that CBD may be retained in a similar manner, an effect that, to our knowledge, has not been well described in previous pharmacokinetic studies. A key phase-one trial (Taylor et al., 2018) during which participants were administered 1500, 3000 or 4500 mg CBD followed by two separate 1500 mg doses at intervals of ⩾7 days did not appear to report their participants' baseline (pre-treatment) plasma CBD concentrations (i.e. after prior dosing). The authors simply noted that their statistical analyses 'suggested' residual CBD was present in plasma after the

washout period (Taylor et al., 2018). Another study (Taylor et al., 2020) observed mean plasma CBD concentrations of ~30 ng/mL 2 weeks after administering 750 mg CBD twice daily for 4 weeks. It is important to recognise that the residual CBD detected in the current investigation is unlikely to reflect 'other' recent CBD use (i.e. outside of the trial) as CBD is not available (legally) without a prescription in Australia (McGregor et al., 2020) and was not detected in any Baseline oral fluid samples (i.e. the presence of CBD in oral fluid would indicate recent use) (data published elsewhere; McCartney et al., 2022).

It is important to consider the extent to which this residual CBD affected driving performance and/or other outcomes on the placebo treatment. In this regard, it is worth noting that residual plasma CBD concentrations were very low (e.g. at Baseline on the placebo treatment ($n=12$), mean (range)=4.7 (1.4–10.4) ng/mL) and similar to the (peak) plasma CBD concentrations observed on the 15 mg CBD treatment (4.7 (0.0–25.7) ng/mL) (when no CBD was present at Baseline). This is important because no RCTs appear to have detected meaningful phenotypic effects of CBD at doses <200 mg (Chagas et al., 2014; Freeman et al., 2020; Jadoon et al., 2016; Linares et al., 2019; Lopez et al., 2020; Naftali et al., 2017; Zuardi et al., 2017). It is therefore unlikely that these low, residual levels of CBD influenced performance.

Second, no obvious or substantial differences in SDLP were observed among those participants who did ($n=12$) *versus* did not ($n=5$) have residual CBD in plasma on their placebo trial (Table S1). Indeed, these groups had very similar (i.e. differed by ⩽ 1.0 cm) average SDLP values on the CF component of Drives 1 and 2 and the Standard component of Drive 2. Thus, while results should be interpreted with some caution, this residual CBD appears unlikely to have had a major effect on the current trial. Future studies should, however, take care to measure plasma CBD concentrations (as this is not frequently done; Millar et al., 2019) and be mindful that CBD doses ⩾300 mg may not 'washout' within 7 days. Whether 7-COOH-CBD and 7-OH-CBD, also present in plasma on the placebo trial, can elicit pharmacological effects in humans is yet to be established (Ujváry and Hanuš, 2016).

The current trial administered CBD in combination with a high fat supplement as previous studies have found that the administration of a high-fat meal greatly increases plasma CBD concentrations (Birnbaum et al., 2019; Taylor et al., 2018). Unfortunately, plasma CBD concentrations varied among participants (as is typical) and did not appear elevated above 'usual' levels observed in fasted participants (although C_{max} could not be reliably estimated and a 'no supplement' control was not used).

Conclusion

The results of this study suggest that acute, oral CBD treatment at doses up to 1500 mg does not induce feelings of intoxication and is unlikely to impair cognitive function or driving performance. However, further research is required to confirm no effect of CBD on safety-sensitive tasks in the hours immediately post-treatment and with chronic administration.

Acknowledgements

The authors would like to thank Dr Melissa Benson, Zoe Schrire, Sarah Abelev, Jun Zhi Teh, and Isobel Lavender for their assistance with trial activities; Dr Yizhong Zheng, Dr Tom Altree, and Dr Henry Ainge-Allen for their assistance conducting medical screens; Dr Lewis Martin for his statistical advice and all of the participants in the trial. We are grateful to Barry and Joy Lambert and family for their ongoing support of the research activities of the Lambert Initiative for Cannabinoid Therapeutics.

Author contributions

D.M., A.S.S., C.I., R.R.G., C.M.H. and I.S.M. contributed to the conception and design of the research project; D.M. and A.S.S. were involved in data acquisition; P.T.D. and R.C.K. were involved in biospecimen analysis; C.I. was involved in developing the simulated driving test; D.M. and I.S.M. contributed to the analysis and interpretation of the research data; and all authors were involved in drafting and critically revising the manuscript and approved the final submitted version.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: D.M., A.S.S., P.T.D., R.C.K. and I.S.M. receive salary support from the Lambert Initiative for Cannabinoid Therapeutics. I.S.M. also acts as a consultant to Kinoxis Therapeutics and is an inventor on several patents relating to novel cannabinoid therapeutics. The other authors have no conflicts of interest to disclose.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This research project was funded by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for medicinal cannabis research at the University of Sydney.

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Supplemental material

Supplemental material for this article is available online.

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JAMA | Original Investigation

Effect of Cannabidiol and Δ^9-Tetrahydrocannabinol on Driving Performance
A Randomized Clinical Trial

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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 May 20, 2019, and March 27, 2020. Participants (N = 26) were healthy occasional users of cannabis.

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 OUTCOMES AND MEASURES The primary end point was standard deviation of lateral position (SDLP; a measure of lane weaving) during 100 km, on-road driving tests that commenced at 40 minutes and 240 minutes after cannabis consumption. At a calibrated blood alcohol concentration (BAC) of 0.02%, SDLP was increased relative to placebo by 1.12 cm, and at a calibrated BAC of 0.05%, SDLP was increased relative to placebo by 2.4 cm.

RESULTS Among 26 randomized participants (mean [SD] age, 23.2 [2.6] years; 16 women), 22 (85%) completed all 8 driving tests. At 40 to 100 minutes following consumption, the SDLP was 18.21 cm with CBD-dominant cannabis, 20.59 cm with THC-dominant cannabis, 21.09 cm with THC/CBD-equivalent cannabis, and 18.28 cm with placebo cannabis. SDLP was significantly increased by THC-dominant cannabis (+2.33 cm [95% CI, 0.80 to 3.86]; $P < .001$) and THC/CBD-equivalent cannabis (+2.83 cm [95% CI, 1.28 to 4.39]; $P < .001$) but not CBD-dominant cannabis (−0.05 cm [95% CI, −1.49 to 1.39]; $P > .99$), relative to placebo. At 240 to 300 minutes following consumption, the SDLP was 19.03 cm with CBD-dominant cannabis, 19.88 cm with THC-dominant cannabis, 20.59 cm with THC/CBD-equivalent cannabis, and 19.37 cm with placebo cannabis. The SDLP did not differ significantly in the CBD (−0.34 cm [95% CI, −1.77 to 1.10]; $P > .99$), THC (0.51 cm [95% CI, −1.01 to 2.02]; $P > .99$) or THC/CBD (1.22 cm [95% CI, −0.29 to 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 crossover 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 to 100 minutes but not 240 to 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 EU Clinical Trials Register: 2018-003945-40

Editorial page 2163

Related article page 2144

Supplemental content

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JAMA. 2020;324(21):2177-2186. doi:10.1001/jama.2020.21218

Epidemiological studies have indicated that cannabis is associated with increased crash risk and culpability.[1,2] Acute cannabis intoxication increases the 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 3 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.

Key Points

Question What is the magnitude and duration of driving impairment following vaporization of cannabis containing varying concentrations of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD)?

Findings In this crossover 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 to 100 minutes following vaporized consumption was 18.21 cm for CBD-dominant cannabis, 20.59 cm for THC-dominant cannabis, 21.09 cm for THC/CBD-equivalent cannabis, and was 18.26 cm for placebo. At 240 to 300 minutes, the SDLP was 19.03 cm for CBD-dominant cannabis, 20.59 cm for THC-dominant cannabis, 19.88 cm for THC/CBD-equivalent cannabis, and 19.37 cm for placebo. Compared with placebo, SDLP with THC-dominant and THC/CBD-equivalent cannabis was significantly greater at 40 to 100 minutes but not 240 to 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.

Methods

The study was approved by the medical ethics committee of Maastricht University and conducted in accordance with the ethical standards of the Declaration of Helsinki. 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, and word of mouth. Inclusion criteria were age between 20 and 50 years, self-reported cannabis use less than 2 times per week in the past 12 months and more than 10 lifetime exposures, possession of a valid driver's license with at least 2 years' driving experience and driving more than 2000 km per year, and body mass index (calculated as weight in kilograms divided by height in meters squared) 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 4 experimental sessions that were scheduled at least 1 week apart to avoid potential drug carryover effects. Participants were required to abstain from use of cannabis and other drugs for the duration of the study and from use of alcohol for 24 hours 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 and 13.75 mg CBD (THC/CBD condition), 13.75 mg CBD (CBD condition), or placebo (placebo condition). Study drugs were prepared in advance (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. and 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 order of events during the 4 experimental sessions is shown in eTable 1 in Supplement 2. Upon participant arrival, a zero breath alcohol concentration was confirmed via breathalyzer (Alcotest 5510, Dräger), and oral fluid was screened (DrugTest 5000, Dräger) to identify any recent use of cannabis, cocaine, opiates, amphetamine, methamphetamine, or 3,4-methylenedioxymethamphetamine (MDMA [otherwise known as ecstasy]). Following baseline measurements of cardiovascular measures and self-reported drug effects, a catheter was inserted into the participant's nondominant arm and the first blood sample was collected. Participants then inhaled THC,

THC/CBD, CBD, or placebo. Driving tests occurred at 40 to 100 minutes and 240 to 300 minutes postvaporization. Cognitive tests were conducted at 5, 135, and 205 minutes postvaporization. Blood samples, blood pressure, and heart rate were obtained at baseline (indicates predrug administration), and at minute 0 (indicates the end of drug administration), and at 25, 130, 200, and 320 minutes postvaporization. Subjective drug effects were assessed at baseline and at 0, 25, 130, 200, and 240 minutes postvaporization.

Study Drugs

THC-dominant (THC 22% and CBD<1%), CBD-dominant (THC<1% and CBD 9%) and placebo (<0.2% total cannabinoid content) cannabis varieties (Bedrocan) 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 °C (Mighty Medic, Storz & Bickel) according to a standardized procedure (inhale 5 seconds, hold 3 seconds, exhale, and rest for 30 seconds; minimum of 10 inhalations and repeated 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) to 10 (highest score).[12] Participants rated the following: Strength of drug effect (*No effect* to *Very strong*), Liking of drug effect (*Dislike very much* to *Like very much*), Stoned (*Not stoned* to *Very stoned*), Sedated (*Not sedated* to *Very sedated*), Relaxed (*Not relaxed* to *Very relaxed*), Anxious (*Not anxious* to *Very anxious*), and Confident to drive (*Not confident* to *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* to *Very good*) and Do you think your driving was impaired? (*Not at all* to *Very much*). Anxiety was further assessed using the state subscale of the State Trait Anxiety Inventory, which consists of 20 statements that are rated on a 4-point Likert scale (range, 1-4 [*Not at all* to *Very much so*]). Possible score totals range from 20 to 80 with higher scores indicating greater anxiety.[13]

Driving Tests

The on-road driving test (road-tracking test[14]) ran for approximately 60 minutes. Participants drove a specially instrumented vehicle over a 100-km highway circuit while maintaining a constant speed (95 km/h [59 mph]) 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,[17] Divided Attention Task,[18] Paced Serial Addition Task,[19] and Tower of London.[20] Participants also completed the Emotional Stroop Task.[21]

These tasks assess processing speed (Digit Symbol Substitution Task; Paced Serial Addition Task), divided attention (Divided Attention Task), psychomotor function (Digit Symbol Substitution Task; Divided Attention Task), working memory (Paced Serial Addition Task), and decision-making and cognitive flexibility (Tower of London; Emotional Stroop Task). The Digit Symbol Substitution Task, Divided Attention Task, and Paced Serial Addition Task were completed in this order at 5-minutes postvaporization and at 205 minutes postvaporization. The Emotional Stroop Task and Tower of London were completed once in each session at 5 minutes postvaporization and at 135 minutes postvaporization. Further details are provided in eMethods 1 in 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) and centrifuged at 3000*g* for 10 minutes. 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 in Supplement 2.

Outcomes

The prespecified primary end point 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 onto the roof of the vehicle and sampled continuously at 4 Hz. Measurements of lateral position over the time of the driving test were averaged to yield the mean lateral position, and standard deviation was calculated to determine the mean SDLP. Larger numbers indicate greater variability (ie, reduced stability) in lane positioning. A 2.4-cm drug vs 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 end points 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 (previously described), subjective drug effects (0-10 cm VAS items as previously described), cardiovascular measures (blood pressure; heart rate), 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] 2 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

Table. Participant Demographics and Characteristics

Demographic/characteristic	Participants, No. (%)
No.	26
Women	16
Men	10
Age, mean (SD), y	23.2 (2.6)
Body mass index, mean (SD)[a]	21.4 (2.4)
Participants with at least some tertiary education, %	100
Episodes of cannabis use in past 3 mo, median (IQR)	4.5 (1-20)
Years in possession of driver's license, median (IQR)	5 (4-7)
Average No. of km driven per year, median (IQR)	4500 (3000-8000)
Ever driven while under the influence of cannabis	5 (19.2)
Weekly use of alcohol	10 (38.5)
Prior use of other drugs	
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)

Abbreviations: IQR, interquartile range; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine.

Conversion factor: To convert kilometers to miles, divide the value by 1.609.

[a] Calculated as weight in kilograms divided by height in meters squared.

(Cohen f = 0.62; ΔSDLP = 1.94 cm; approximately 0.04% BAC[26]) with 95% power.

Available data from all 26 participants were analyzed according to randomization group using SPSS version 25 (IBM Corporation) using linear mixed-effects models. Model parameters included condition, time and condition × time as fixed effects, and a random intercept. A first-order autoregressive residual covariance structure was used as it consistently provided the lowest Schwarz Bayesian Information Criterion model fit values. The restricted maximum likelihood method 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 I 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 placebo, THC/CBD vs placebo, CBD vs placebo and THC vs THC/CBD. Statistical significance was set at a *P* value of less than .05. Analyses including only completing participants (n = 22) did not differ meaningfully from the full results presented here (eTable 2 in Supplement 2).

Results

The **Table** presents the characteristics of the 26 participants who were enrolled into the study and randomized. Complete results of statistical analyses are found in eTable 3 (Supplement 2), and pairwise comparisons are found in eTables 4, 5, 6, 7, and 8 (Supplement 2). **Figure 1** shows the flow of participants through the study.

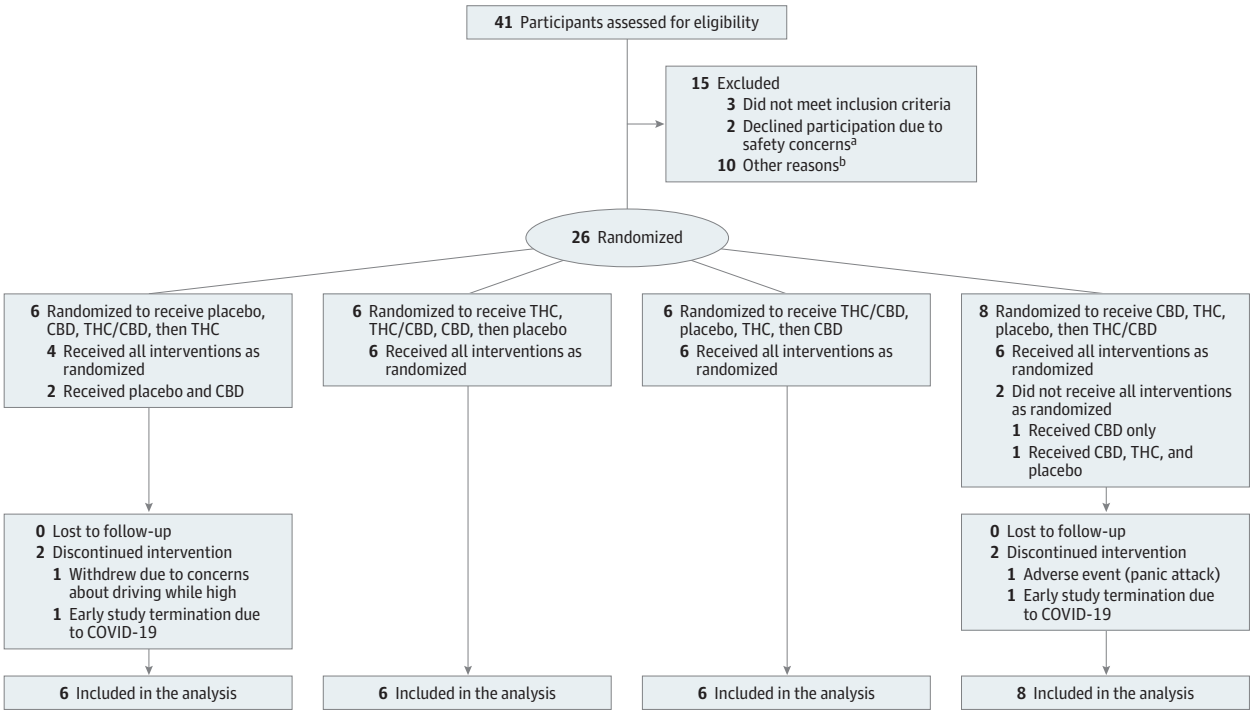
Primary Outcome

From 40 to 100 minutes, the mean lateral position was 86.94 cm (95% CI, 81.50 to 91.48) in the THC condition, 85.51 cm (95% CI, 81.81 to 89.21) in the THC/CBD condition, 84.07 cm (95% CI, 79.40 to 88.74) in the CBD condition, and 84.41 cm (95% CI, 80.01 to 88.82) in the placebo condition; from 240 to 300 minutes, the mean lateral position was 85.03 cm (95% CI, 80.88 to 89.17) in the THC condition, 84.04 cm (95% CI, 80.64 to 87.54) in the THC/CBD condition, 84.25 cm (95% CI, 79.85 to 88.65) in the CBD condition, and 83.68 cm (95% CI, 79.45 to 87.91) in the placebo condition. The overall range of mean lateral position values was 53.62 cm. A significant main effect of condition was found for SDLP ($P < .001$) (**Figure 2**). Pairwise comparisons revealed increased SDLP at 40 to 100 minutes in the THC condition compared with placebo (2.33 cm [95% CI, 0.08 to 3.86]; $P < .001$) and the THC/CBD condition compared with placebo (2.83 cm [95% CI, 1.28 to 4.39]; $P < .001$) but not at 240 to 300 minutes in the THC condition compared with placebo (0.51 cm [95% CI, −1.01 to 2.02]; $P > .99$) or the THC/CBD condition compared with placebo (1.22 cm [95% CI, −0.29 to 2.72]; $P = .20$). CBD did not affect SDLP compared with placebo at 40 to 100 minutes (−0.05 cm [95% CI, −1.49 to 1.39]; $P > .99$) or at 240 to 300 minutes (−0.34 cm [95% CI, −1.77 to 1.10]; $P > .99$), and there was no significant difference between the THC/CBD and THC conditions at 40 to 100 minutes (0.50 cm [95% CI, −1.10 to 2.10]; $P > .99$) or at 240 to 300 minutes (0.71 cm, [95% CI, −0.83 to 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 to 100 minutes, mean speed was 92.53 km per hour for CBD, 91.82 km per hour for THC, 92.86 km per hour for THC/CBD, and 92.65 km per hour for placebo. At 240 to 300 minutes, mean speed was 92.64 km per hour for CBD, 93.00 km per hour for THC, 93.01 km per hour for THC/CBD, and 92.75 km per hour for placebo. At 40 to 100 minutes, mean standard deviation of speed was 3.06 km per hour for CBD, 3.32 km per hour for THC, 3.18 km per hour for THC/CBD, and 2.93 km per hour for placebo. At 240 to 300 minutes, mean standard deviation of speed was 3.29 km per hour for CBD, 3.26 km per hour for THC, 3.37 km per hour for THC/CBD, and 3.40 km per hour for placebo.

Secondary Outcomes

At the end of each driving test, participants rated their driving as significantly more impaired compared with placebo in the THC condition (at 100 minutes, 4.15 [95% CI, 2.29 to 6.02]; $P < .001$, and at 300 minutes, 2.27 [95% CI, 0.41 to 4.12]; $P = .008$) and the THC/CBD condition (at 100 minutes, 4.09 [95% CI, 2.20 to 5.98]; $P < .001$, and at 300 minutes, 2.70 [95% CI, −0.93 to 4.57]; $P = .001$) (**Figure 3**). Participants rated the quality of their driving as significantly worse compared with placebo at 100 minutes (the end of the first driving test only) (THC, −1.95 [95% CI, −3.64 to −0.26]; $P = .01$,

Figure 1. Flow of Participants Through the Study of the Effects of CBD and THC on Driving Performance



CBD indicates cannabidiol condition; COVID-19, coronavirus disease 2019; THC, Δ9-tetrahydrocannabinol condition; THC/CBD, Δ9-tetrahydrocannabinol/cannabidiol condition.

[a] Safety concerns regarded driving under the influence of cannabis.

[b] Other reasons: 6 participants became unresponsive and could not be contacted, 3 were unable to meet study time commitments, and 1 underwent a medical screening that revealed a low red blood cell count.

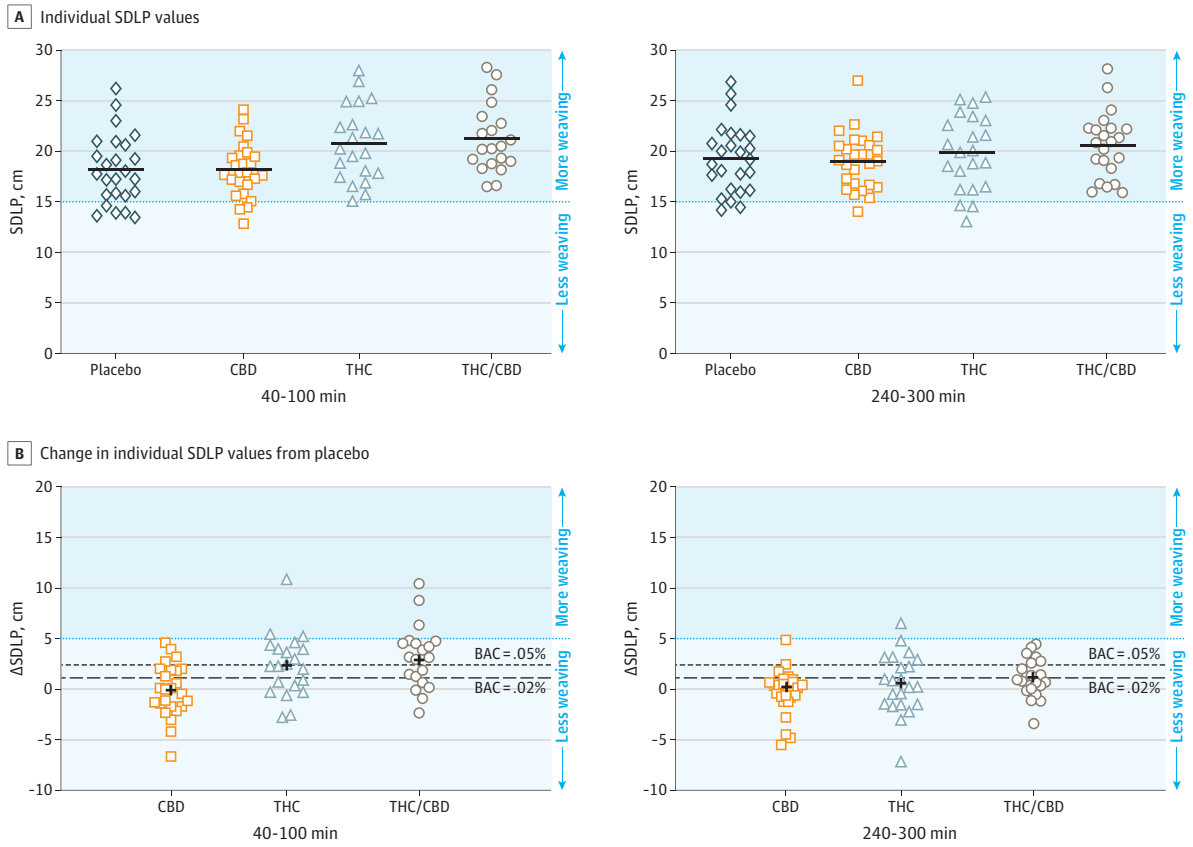
and for THC/CBD, −2.14 [95% CI, −3.83 to −0.44]; *P* = .006) (eFigure 1 in Supplement 2).

There was a main effect of condition for *Confident to Drive* (*P* < .001), with ratings decreased in the THC condition compared with placebo (at 0 minutes, −4.3 [95% CI, −5.61 to −2.98] [*P* < .001]; at 25 minutes, −3.65, [95% CI, −4.96 to −2.33] [*P* < .001]; and at 130 minutes, −2.18 [95% CI, −3.49 to −0.86] [*P* < .001]), decreased in the THC/CBD condition compared with placebo (at 0 minutes, −2.48 [95% CI, −3.81 to −1.14] [*P* < .001]; 25 minutes, −2.08 [95% CI, −3.41 to −0.75] [*P* < .001]; and at 130 minutes, −1.74 [95% CI, −3.07 to −0.41] [*P* = .003]) and with ratings greater in the THC/CBD condition compared with the THC condition (at 0 minutes, 1.82 [95% CI, −0.47 to 3.17] [*P* = .002]; and at 25 minutes, 1.57 [95% CI, 0.22 to 2.92] [*P* = .01]) (**Figure 4**). Results for other subjective drug effect measures are shown in eFigure 3 in Supplement 2, and results for the state subscale of the State Trait Anxiety Inventory are shown in eFigure 4 in Supplement 2. The rating of the *Strength of Drug Effect* was significantly lower in the THC/CBD condition than in the THC condition at 0 minutes (−1.67 [95% CI, −2.97 to −0.37]; *P* = .004) and at 25 minutes (−1.57 [95% CI, −2.87 to −0.27]; *P* = .01), and the rating of *Anxious* was significantly lower in the THC/CBD condition than in the THC condition at 0 minutes (−1.88 [95% CI, −2.99 to −0.76]; *P* < .001) and at 25 minutes (−1.14 [95% CI, −2.26 to −0.02]; *P* = .04).

Cognitive performance results are shown in Figure 4 and in eFigure 2 in Supplement 2. There was a significant main effect of condition for number correct and percent correct on the Digit Symbol Substitution Task (*P* = .04; *P* = .03) but not number attempted (*P* = .26); tracking error and response time on the Divided Attention Task (*P* = .02; *P* = .003); response time, number correct, and percent correct on the Paced Serial Addition Task (*P* = .001; *P* < .001; *P* = .002); and number correct and response time on the Tower of London (*P* = .03; *P* = .02). There was no effect of condition for either number correct or response time on the Emotional Stroop Task (*P* = .62; *P* = .82). The THC and THC/CBD conditions did not differ from placebo on any measures at 205 minutes, and the CBD condition did not differ from placebo on any measures at either time point (eTable 6 in Supplement 2).

Heart rate and blood pressure data are shown in eFigure 5 in Supplement 2. 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 8 in Supplement 2). There was a main effect of condition on heart rate (*P* < .001) and a significant condition × time interaction (*P* < .001). eFigure 6 in Supplement 2 shows median (interquartile range) plasma cannabinoid concentrations over time. There was a significant main effect of condition, time, and condition × time for all analytes (eTable 3 in Supplement 2).

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



The x-axes indicate minutes postvaporization. Higher values on the y-axes indicate more weaving vs less weaving for lower values. A, The horizontal black bars indicate the mean standard deviation of lateral position (SDLP) in each condition. B, The dashed lines indicate the mean SDLP increase associated with a blood alcohol level (BAC) of 0.02% and 0.05%. The plus symbol shows the mean change in SDLP in each condition. CBD indicates cannabidiol; THC, Δ9-tetrahydrocannabinol.

Post Hoc Outcomes

The proportions of participants showing impairment at 40 to 100 minutes at the 0.02% BAC criterion were 40% (CBD), 62% (THC), and 75% (THC/CBD). At 240 to 300 minutes, the proportions showing impairment were 16% (CBD), 36% (THC), and 50% (THC/CBD). The proportions of participants showing impairment at 40 to 100 minutes at the 0.05% BAC criterion were 16% (CBD), 48% (THC), and 60% (THC/CBD). At 240 to 300 minutes, the proportions were 8% (CBD), 27% (THC), and 32% (THC/CBD). As shown in eTable 9 in Supplement 2, 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 to 100 minutes, with most participants showing impairment at both BAC criterion levels.

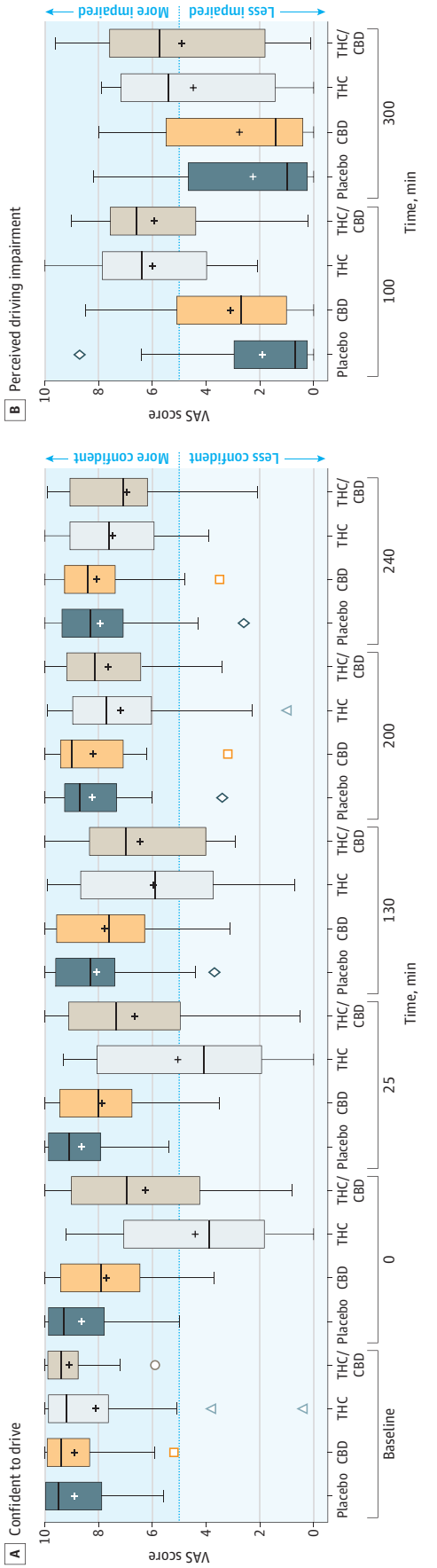
Adverse Events

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 (placebo [2], CBD [2], THC [2], THC/CBD [3]) and 7 during the second test (placebo [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, 3 drives were cancelled prior to commencement (THC [2] and 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 to 100 minutes 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

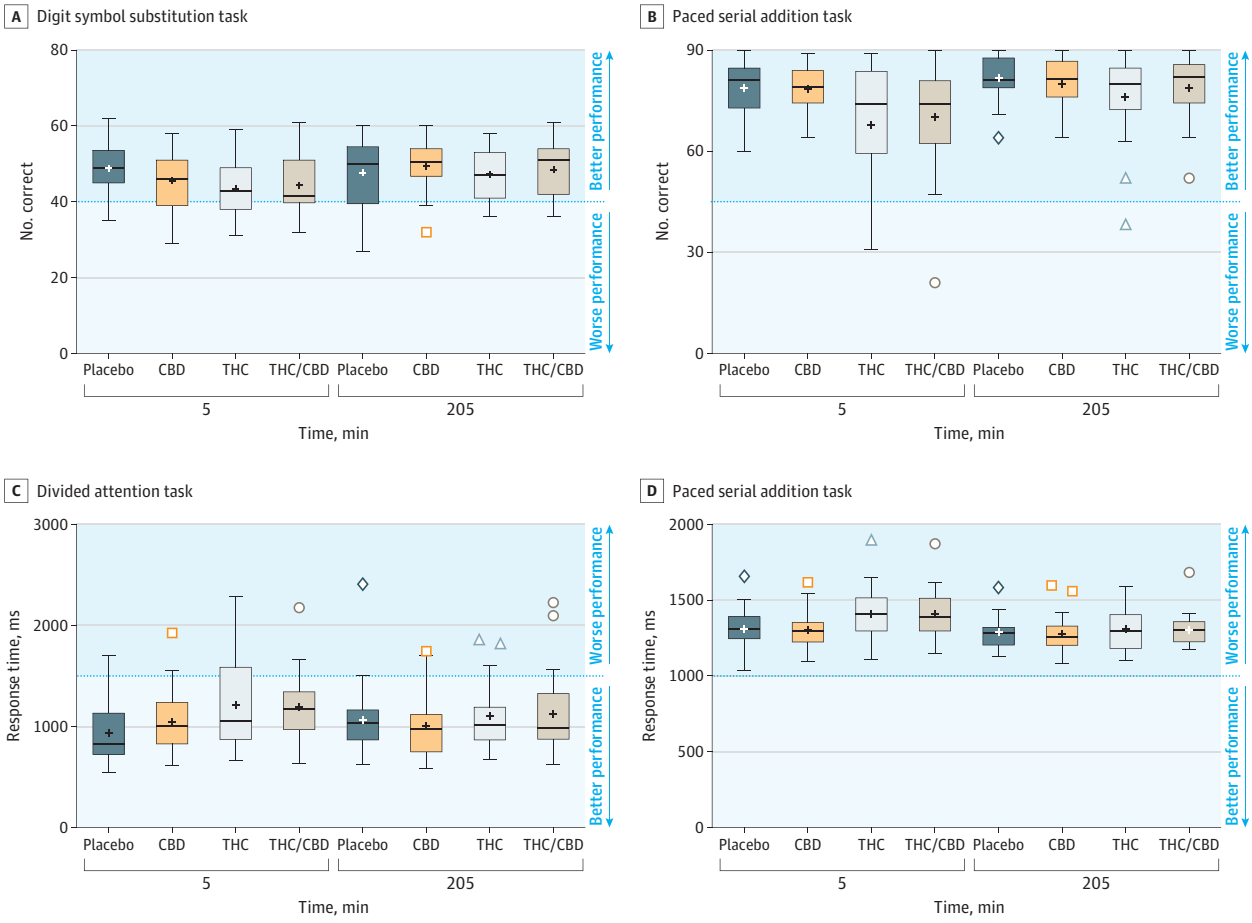
Figure 3. Confidence in Driving Ability Over Time and Perceived Driving Impairment at 2 Time Points



A, Baseline on the x-axis indicates predrug administration, minute 0 indicates the end of drug administration, all other values indicate time since vaporization. The visual analog scale (VAS) indicates mean values (range, 0-10 [not confident to very confident]). B, The VAS indicates mean values (range, 0-10 [less impaired to more impaired]) as assessed at the end of each on-road driving test.

Boxplot edges indicate the 25th and 75th quartile values. Horizontal bars indicate the median, and the plus signs indicate the mean. If there are no outliers (Q1 − 1.5 × [Q3 − Q1] and Q3 + 1.5 × [Q3 − Q1]), the whiskers indicate minimum and maximum values. Outliers (if present) are shown as colored symbols, the whiskers indicate the lowest and highest values that are not outliers. CBD indicates cannabidiol; THC, Δ9-tetrahydrocannabinol.

Figure 4. Performance on the Digit Symbol Substitution Task, Divided Attention Task, and Paced Serial Addition Task



Time points on the x-axis indicate time since vaporization. Boxplot edges indicate the 25th and 75th quartile values. Horizontal bars indicate the median, and the plus signs indicate the mean. If there are no outliers (Q1 − 1.5 × [Q3 − Q1] and Q3 + 1.5 × [Q3 − Q1]), the whiskers indicate minimum and maximum values. Outliers (if present) are shown as colored symbols, the whiskers indicate the lowest and highest values that are not outliers. CBD indicates cannabidiol; THC, Δ9-tetrahydrocannabinol. Additional outcome measures are shown in eFigure 2 in Supplement 2.

conditions did not differ, indicating that CBD, when administered in a bolus dose via vaporization, did not impair driving. During these driving tests, the overall range of lateral position values (ie, the actual distance between the vehicle and the lane boundary to the left of the vehicle) was approximately 54 cm.

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 compared with 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 coadministered CBD can reduce the euphoric, anxiogenic and subjective drug effects of THC.[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 240 to 300 minutes. 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 to 300 minutes 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 overrated their impairment, or this may have indicated subtle persistence of THC-induced impairment, perhaps combined with fatigue, causing subclinical SDLP increments (ie, <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 1 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 in which oral administration of CBD oils at doses of approximately 10 to 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 crossover 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 to 100 minutes but not 240 to 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.

ARTICLE INFORMATION

Accepted for Publication: October 9, 2020.

Author Contributions: Drs Arkell and Ramaekers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Arkell, Theunissen, McGregor, Ramaekers.
Acquisition, analysis, or interpretation of data: Arkell, Vinckenbosch, Kevin, McGregor, Ramaekers.
Drafting of the manuscript: Arkell, Kevin, McGregor, Ramaekers.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Arkell, Kevin, Ramaekers.
Obtained funding: McGregor, Ramaekers.
Administrative, technical, or material support: Vinckenbosch, Kevin, McGregor, Ramaekers.
Supervision: Theunissen, McGregor, Ramaekers.

Conflict of Interest Disclosures: Dr Kevin reported receipt of grants from The Lambert Initiative for Cannabinoid Therapeutics during the conduct of the study; and involvement as an expert witness in legal cases involving cannabis impairment.
Dr McGregor reported receipt of grants from the National Health and Medical Research Council of Australia, the Australian Research Council, and the Lambert Initiative for Cannabinoid Therapeutics during the conduct of the study; patents to WO2019071302 and WO2019227167 published, patents to WO2018107216A1, WO2017004674A1, and WO2011038451A1 issued and licensed, and patents to AU2017904438 and AU2019051284 pending; consultancy with Kinoxis Therapeutics around the development of noncannabinoid therapeutics; involvement as an expert witness in legal cases involving cannabis-induced impairment; and a speaker's honorarium from Janssen.
Dr Ramaekers reported receipt of grants from Lambert Initiative for Cannabinoid Therapeutics during the conduct of the study; and being president of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS). No other disclosures were reported.

Funding/Support: This study was funded by the Lambert Initiative for Cannabinoid Therapeutics at the University of Sydney.

Role of the Sponsor/Funder: The Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded independent research center at the University of Sydney, was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review and approval of the manuscript; and the decision to submit the manuscript for publication. The sponsor did not have the right to veto publication or control the decision regarding which journal the manuscript would be submitted to for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We are grateful to the following students from Maastricht University: Christin Büdenbender, BSc, Keziah Kusuma, BSc, Fabian Miramontes, BSc, Jacqueline Roux, BSc, and Dennis Ruesink, BSc, for their assistance with data collection. None of these individuals received compensation for their role in the study. We also wish to sincerely thank Peter Doohan, BSc (Hons), University of Sydney, for his assistance with the analysis of plasma samples. Peter Doohan received compensation for his role in the study.

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