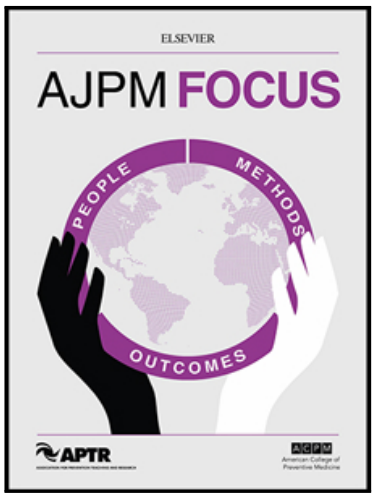

The effects of cannabidiol on the driving performance of healthy adults: a pilot randomized clinical trial

Toni Marie Rudisill PhD , Karen (Kim) Innes PhD , Sijin Wen PhD , Treah Haggerty MD , Gordon S. Smith MB ChB

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Authors' Names and Affiliations:

Toni Marie Rudisill, PhD[1], Karen (Kim) Innes, PhD[1], Sijin Wen, PhD[1], Treah Haggerty, MD[2], Gordon S. Smith, MB ChB[1]

[1] Department of Epidemiology and Biostatistics, West Virginia University, Morgantown, West Virginia, USA

[2] Department of Family Medicine, West Virginia University, Morgantown, West Virginia, USA

Corresponding Author:

Toni Marie Rudisill, MS, PhD

Department of Epidemiology and Biostatistics

West Virginia University, School of Public Health

PO BOX 9190

Morgantown, WV 26506 USA

Email: trudisill@hsc.wvu.edu; Telephone: 717-817-3028

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HIGHLIGHTS

- **A side effect of cannabidiol is drowsiness, which could impact driving.**
- **This pilot trial investigated oral cannabidiol's impact on simulated driving.**
- **Slight detriments to performance were noted.**
- **The study was statistically underpowered.**
- **Additional research is needed to determine if cannabidiol impacts driving.**

ABSTRACT

Introduction: A common side effect of cannabidiol is drowsiness, which could impact safe driving. This study's purpose was to determine feasibility and whether cannabidiol impacts simulated driving performance.

Methods: This was a randomized, parallel-group, sex-stratified, double-blind, pilot trial which consisted of a volunteer sample of healthy, currently driving, college students. Participants were randomized and allocated to receive placebo (N=19) or 300 mg cannabidiol (N=21) via oral syringe. Participants completed a ~40-minute driving simulation. A post-test survey assessed acceptability. The primary outcomes were mean standard deviation of lateral position, total percent time the individual drove outside travel lanes, total collisions, time to initial collision, and mean brake reaction time. Outcomes were compared between groups using Student's T-tests and Cox proportional hazards models.

Results: None of the relationships were statistically significant, but the study was underpowered. Those receiving cannabidiol experienced slightly more collisions (0.90 vs 0.68, p=0.57), had slightly higher mean standard deviation of lateral position, and slower brake reaction times (0.60 vs. 0.58 seconds, p=0.61) compared to placebo. Participants were satisfied with their experience.

Conclusions: The design was feasible. Larger trials may be warranted as it is unclear whether the small differences in performance seen in CBD group were clinically relevant.

KEY WORDS: Cannabidiol; Cannabis; Driving performance; Simulation

ABBREVIATIONS: CBD=Cannabidiol; CI=Confidence interval; HR=Hazard ratio; mg=milligram; P=probability; RCT=Randomized clinical trial; SDLP=Standard deviation of lateral position; THC= Delta-9 tetrahydrocannabinol

INTRODUCTION

The United States Food and Drug Administration approved Epidiolex, which is prescription cannabidiol (CBD) oil, for the treatment of Dravet and Lennox-Gastaut Syndromes and Tuberous Sclerosis Complex in children. [1, 2] A legislative change in 2018, allowed non-prescription CBD oil to be sold over the counter and it is being added to numerous products that target the general consumer. [3] Non-prescription products tend to contain lower amounts of CBD than prescription. [4] Published randomized placebo-controlled clinical trials (RCTs) of CBD's effectiveness are limited and predominately focused on clinical populations suffering from neurological or neuropsychiatric conditions. [5-24] A common side effect of CBD is drowsiness, which could impact driving performance. [25-28] However, only one published RCT investigating the effects of smoked non-prescription CBD on driver performance exists. [29] In that study, the primary outcome was standard deviation of lateral position (SDLP), which measures weaving, and is a common indicator of impairment. [30, 31] That study found that SDLP did not differ between CBD and placebo groups nor did their cognitive test performance. [29] Previous studies which investigated CBD's effects on cognition or psychomotor function in healthy adults have also found limited effects. [32-40]

Given the lack of RCTs in healthy adults, the primary aims of this study were to assess the feasibility/acceptability of a RCT using ingested non-prescription CBD oil and compare measures of simulated driving performance among participants randomized to CBD vs. placebo.

MATERIALS AND METHODS

Study design and participants

This study was a randomized, parallel-group, double-blind, two-arm, pilot, feasibility trial. A parallel design was chosen over a crossover design to maximize participant retention and minimize missing data.[41] Eligibility criteria were: 1) enrolled as a student, 2) 18-30 years old, 3) possessed a valid drivers' license, 4) driven ≥1 time in the past month, 5) could read English, 6) willing to take a urine drug test and complete a test drive to ensure absence of simulation sickness, 7) not taking any prescription medications (excluding birth control), 8) not diagnosed with any serious chronic disease 9) had an individual willing to drive them home post-testing. Participants were excluded if they used tobacco, used CBD in the past 7 days, used illegal drugs in the past month, or were pregnant/lactating. The study took place at West Virginia University between April 2021-January 2022. The study was approved by West Virginia University's Institutional Review Board (ID# 2007073792) and registered on www.clinicaltrials.gov (NCT04590495).

Sample size

Sample size was calculated using GPower 3.1 *apriori*.[42] As one outcome was between-group differences in mean SDLP, an omnibus one-way analysis of variance test was chosen. Assuming a large effect size (0.50), alpha=0.05, and 80% power, the analysis recommended 34 participants. Accounting for 15% attrition, 40 participants were targeted. Because no published data regarding CBD's effects on driving existed at conceptualization and prior trials documented anxiolytic effects starting at 300mg in healthy adults,[38, 43, 44] we initially posited that participants receiving CBD would show larger differences in performance than placebo.

Recruitment, screening, and enrollment

Email advertisements were sent to all students. Using a standardized checklist, 58 individuals were screened and scheduled for testing. All participants received pre-visit instructions. At the laboratory, personnel re-screened participants; if participants did not follow pre-visit instructions, their appointment was rescheduled. Written consent was obtained. After consenting, participants provided urine samples, which were immediately analyzed. If a participant's sample tested negative, they completed a 10-minute practice drive on the simulator, which provided practice and screen for simulation sickness.[45] If sickness occurred, the individual was ineligible. Forty individuals completed the consent process and enrolled.

Study procedure overview

After enrollment, all participants completed a standardized, demographic survey and six cognitive/psychomotor tests (see Appendix). Participants were then randomized and allocated to a treatment group. Participants were provided a standardized breakfast and then waited 120 minutes for absorption, which was chosen based on the pharmacokinetics of CBD along with the consideration of participant burden. [28, 46] Participants completed the driving simulation and were re-administered the cognitive/psychomotor tests. Lastly, participants received compensation after completing a questionnaire which inquired about the acceptability of procedures and a test of blinding. The procedure lasted 4-4.5 hours (Figure 1).

Randomization, treatment allocation, and blinding

Participants were randomized to receive either CBD (N=21) or placebo (N=19) using a 1:1 stratified randomly varying block technique; [47] the stratification variable was participants' sex as driving behaviors and risk tolerances differ between the sexes. [48, 49] The study statistician, who had no contact with participants, prepared the randomization schedule. Following this schedule, staff sequentially placed small cards labeled A or B into opaque envelopes, sealed, and stacked them. When a participant was enrolled, the top envelope was removed. Both the Principal Investigator, staff delivering the treatment, those assisting with data collection, and participants were blinded to treatment assignment.

Intervention

Study drugs

Treatment A (i.e., placebo) consisted of avocado oil while Treatment B was 300 mg of CBD oil. This dosage was chosen as it was used and well-tolerated in other studies. [24, 38, 40, 43] Both treatments were identically flavored prior to dispensing. The CBD was purchased from Zatural (Idaho). As previous studies found that non-prescription CBD products are often mislabeled or contain high levels of Delta-9 tetrahydrocannabinol (THC), [50] the product was tested by an independent third-party laboratory prior to use (e.g., Botanacor Laboratories, Colorado). Testing revealed that the labeling was accurate with virtually no THC present (i.e., 0.006%).

Driving simulation

All participants (N=40) received instructions and underwent an identical driving simulation using the STISIM Drive M1000 simulator. The simulator was equipped with one screen, steering wheel, controls, brake and accelerator pedals. Participants completed a practice drive (~5 minutes), brake reaction test (~5 minutes), and primary study drive (~25 minutes), which included urban, suburban, and rural highway segments that entailed adjustments to speed, avoidance of objects, turns, and navigational instructions.

Measures of feasibility, acceptability, and blinding

At study completion, participants completed a questionnaire that contained structured and open-ended questions to assess the acceptability of procedures. An additional question asked what treatment they thought they received. The number of adverse events were used to gauge

acceptability of procedures. Participants were contacted twice within 24 hours post-testing to discern adverse event occurrence.

Measures of driving performance

Five primary outcomes and 3 secondary outcomes were collected. The primary outcome was SDLP, which was measured in two separate segments of the main study drive (e.g., SDLP#1 occurred earlier in drive and SDLP#2 occurred at the end). SDLP is calculated by taking the standard deviation of the vehicle's lateral position which is the distance in feet between the vehicle's center in respect to the roadway's center line. Greater SDLP is associated with more impaired driving.[30, 31] The second outcome was the total percent time the participant spent driving beyond the roadway's center line or shoulder. The third outcome was total collisions. The time to initial collision (i.e., fourth outcome) was the time that elapsed from the beginning of the simulation to the time of first collision. The fifth outcome was mean brake reaction time which was the average time (seconds) it took the participant to hit the brake after being exposed to stimuli. Secondary outcomes included the percentage of time that the participant spent driving over the designated speed limit, total time it took the participant to complete the study drive, and turn signal performance. This was the proportion of 'good' turn signal use out of total possible turn signal maneuvers. The simulator considered 'good performance' instances when the driver correctly signaled for a turn/lane change in advance. This value ranged from 0-1, with values closer to 1 indicating better performance.

Statistical analyses

All quantitative analyses were performed using SAS version 9.4. Only an intent-to-treat analysis was performed as no enrolled participants failed to complete the study. Demographic characteristics and tests of blinding were compared between groups using Chi Square, Fisher's Exact, or Student's T tests. To compare between group differences in driving outcomes and study satisfaction, the data were analyzed using a Negative Binomial Regression, Student's T, or Mann-Whitney U tests. To compare the time until first collision between treatment groups, Cox proportional hazards models were employed; Schoenfeld residuals were analyzed to ensure the proportional hazards assumptions were not violated. [51] A Kaplan Meier curve was plotted along with a Log-rank test to compare treatment groups. [52] Free text responses were analyzed via qualitative content analyses. [53] All analyses utilized two tailed hypothesis tests with $\alpha=0.05$. Effect sizes were calculated using Cohen's D. [54]

RESULTS

Between April 15-Nov 30, 2021, ninety-six individuals were pre-screened by research personnel. A total of 40 individuals were enrolled and completed the study. There were no missing data (Figure 1).

Demographic characteristics were similar between CBD and placebo groups (Table 1). Overall, the participants averaged 21.2 ± 2.7 years of age, 48% were male, and 85% were non-Hispanic white.

Primary and secondary study outcomes are shown by group in Table 2. None of the relationships were statistically significant. However, the CBD group performed slightly worse on all primary and secondary outcomes. Those receiving CBD drove slower and spent less time speeding. Calculated effect sizes ranged from 0.03-0.36.

Though not statistically significant, the survival analyses (shown here) determined that participants who received CBD were 35% more likely to experience a collision compared to placebo (Hazard ratio (HR)=1.36, 95% confidence interval (CI) 0.54, 3.44). The Kaplan Meier curve is shown in Figure 2.

As for acceptability/feasibility of the study, results of the qualitative analysis are shown in Appendix Table 1. Most participants enjoyed the way the study was designed or how it was structured (85%). Most participants were highly satisfied with their experience irrespective of group assignment (Appendix Table 2). Only 26% of those who received placebo and 48% who received CBD correctly identified their group allocation (Appendix Table 3).

DISCUSSION

The findings demonstrated that the protocol was safe, feasible, and acceptable to participants. No enrolled participants were lost to attrition and no adverse events were reported.

This study also found that primary and secondary driving performance outcomes did not differ statistically between the placebo and CBD groups. These findings were similar to the Arkel et al crossover RCT that investigated smoked CBD on driver performance. However, this study's findings need to be interpreted with caution for two important reasons. First, this study was statistically underpowered. The study was initially powered at 0.5 but effect sizes were found to range from 0.03-0.36. Secondly, the CBD group performed slightly worse across all outcomes compared to the placebo group. It is unclear whether these small performance deficits would be clinically relevant and result in impaired driving. Impaired drivers typically have problems maintaining lane position and speed, commit more errors, and have slower reaction times than those not impaired. [55]

Nevertheless, these findings have public health implications. CBD is being added unscrupulously to food and hygienic products, but its effects are understudied. Previous research has shown that many CBD products are mislabeled and contain more THC than allowed by law and THC alone can negatively impact safe driving. [29, 50] Even if CBD's effects are small, it is unclear whether compensatory measures such as getting more rest or using caffeine post-consumption is enough to counterbalance CBD's effects. Additional research clearly is needed.

Limitations

Only one dosage of CBD was utilized, and this may not reflect "normal" use. Participants were recruited from a university so results may not be generalizable to the general population. While a placebo group was utilized, a positive control group was not used. Lastly, CBD's max absorption occurs 2-5 hours post-consumption.[28, 46] To balance participant burden, a two-hour waiting period between dosing and simulation was chosen. It is possible that the full effect of the drug was not reached amongst some participants.

CONCLUSION

This study found that an RCT of CBD is feasible. While no relationships were statistically significant, the study was underpowered. Those randomized to CBD performed slightly worse on all study outcomes and it is unclear if these deficits are indicative of impairment. Larger RCTs are warranted.

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TABLES

Table 1. Demographics of study participants by treatment group (N=40)

Characteristic	Overall (N=40)	CBD (N=21)	Placebo (N=19)	P
Age in years, mean (SD)[a]	21.2 (2.7)	21.4 (2.8)	21.0 (2.7)	0.57
Male, N (%)[b]	19 (47.5)	10 (47.6)	9 (47.4)	0.99
White, N (%)[c]	34 (85.0)	18 (85.7)	16 (84.2)	1.00
BMI, mean (SD)[d]	26.0 (5.2)	26.3 (6.3)	25.6 (3.6)	0.70
Undergraduate student, N (%)[b]	28 (70.0)	13 (61.9)	15 (79.0)	0.24
Employed full or part-time, N (%)[b]	21 (52.5)	11 (52.4)	10 (52.6)	0.99
Hours spent playing video games per week [a]	7.1 (10.2)	5.6 (5.1)	8.6 (13.8)	0.66
Miles driven per week, mean (SD) [a]	49.5 (52.7)	49.9 (60.5)	48.9 (43.7)	0.60
Risky driving score, mean (SD) [d]	8.4 (6.4)	6.8 (6.5)	10.2 (5.9)	0.09
Ever used CBD, N (%)[c]	9 (23.1)	4 (19.1)	5 (27.8)	0.71

Abbreviations: BMI=Body mass index; N=total; P=probability value; SD=standard deviation

a: P-value calculated via Mann Whitney U Test comparing CBD to placebo group

b: P-value calculated via Chi Square test comparing CBD to placebo group

c: P-value calculated via Fisher's Exact test due to small cell counts comparing CBD to placebo group

d: P-value calculated via Student's T-test comparing CBD to placebo group

Table 2. Primary and secondary performance outcomes by treatment group

Outcome	CBD (N=21)		Placebo (N=19)		P	ES[e]
	Mean	(SD)	Mean	(SD)		
Total collisions[a]	0.90	1.09	0.68	0.95	0.52	0.23
Percent time out of lane[b]	4.41	2.44	4.34	2.09	0.95	0.03
SDLP#1[b]	4.37	2.22	3.88	2.49	0.90	0.20
SDLP #2[b]	1.07	0.77	0.98	0.44	0.63	0.20
Percent time speeding[b]	5.83	6.02	8.27	9.58	0.27	0.25
Turn signal performance[c,d]	0.51	0.13	0.54	0.10	0.54	0.30
Drive time (seconds)[c]	1,309	58	1,281	78	0.20	0.36
Mean brake reaction time[b]	0.60	0.11	0.58	0.12	0.61	0.17

Abbreviations: CBD=Cannabidiol; ES=Effect size; P=Probability value; SD=Standard deviation; SDLP=Standard deviation of lateral position

a: P-value obtained from Negative Binomial regression comparing CBD to placebo

b: P-values obtained via Mann Whitney U test comparing CBD to placebo

c: P-values obtained via Student's T-Tests comparing CBD to placebo

d: Turn signal performance was the proportion of 'good' turn signal usage out of total possible turn signal maneuvers. This value ranges from 0 to 1. Values closer to 1 indicate better performance

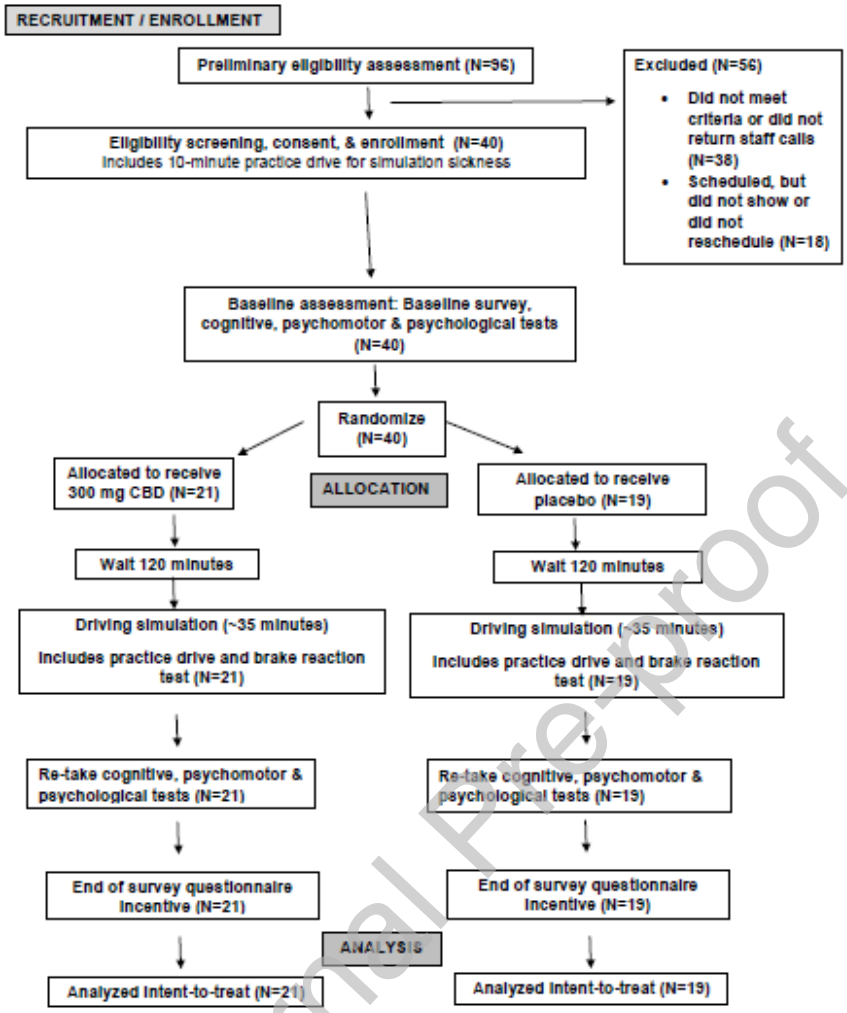
e: Effect sizes were calculated by subtracting the mean of the placebo group from the

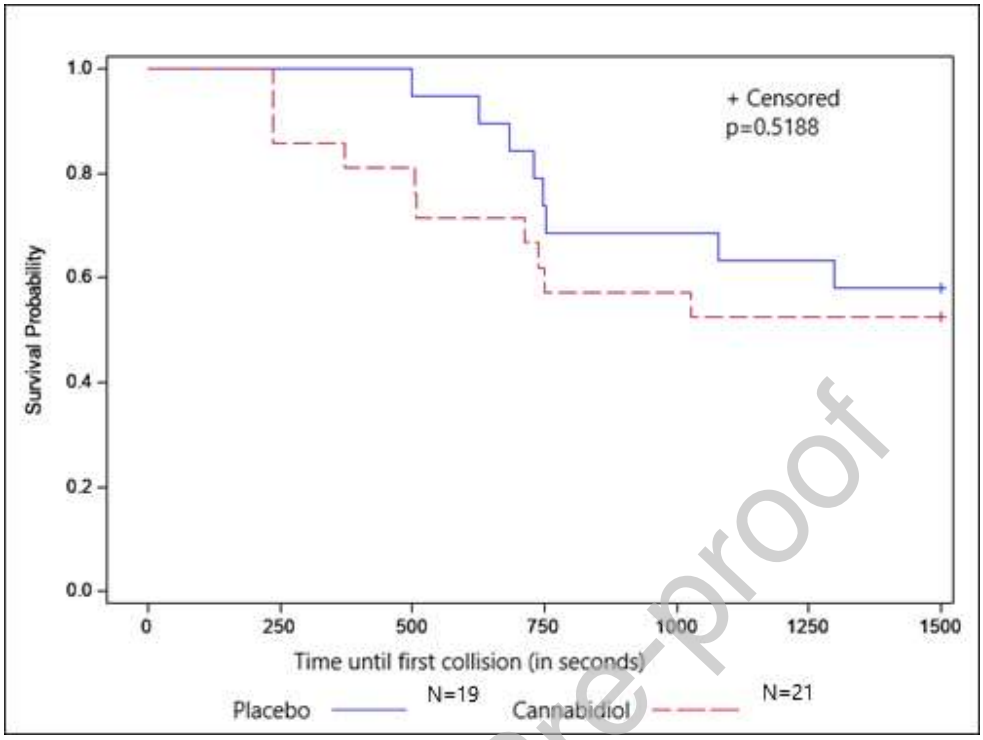
mean of the CBD group and dividing this difference by the placebo group's standard deviation (i.e., Cohen's D)

FIGURE LEGENDS

Figure 1. Study flow diagram. Overview of study procedures

Figure 2. Time until first collision by treatment group. Differences between those receiving cannabidiol vs. placebo were compared using the Log rank test.





Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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