Clinical Trial Protocol with Statistical Analysis Plan

Study: The Effects of Cannabidiol on the Driving Ability of Healthy Adults: a Clinical Trial

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PI: Toni Marie Rudisill, MS, PhD

Protocol Number & Study Protocol Title

The effects of cannabidiol on the driving ability of healthy adults: a clinical trial

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Abbreviations List

AE=Adverse event
BRT=Brake reaction time
CBD=Cannabidiol
CO-I=Co-investigator
DSST=Digital Symbol Substitution Test
IRB=Institutional Review Board
IT=Information Technology
PHI=Protected health information
PI=Principal Investigator
PVT=Psychomotor Vigilance Test
SRT=Simple Reaction Time test
SSS=Stanford Sleepiness Scale
THC= Delta-9-tetrahydrocannabinol
TMT=Trail Making Test
US=United States
VAMS=Visual Analog Mood Scale
WVU=West Virginia University

Section I: Team and Research Summary

Study Team Composition

Toni Marie Rudisill, MS, PhD: Principal Investigator/Project Director.
Dr. Rudisill is a Research Assistant Professor in the Department of Epidemiology at the West Virginia University (WVU) School of Public Health. She is an injury epidemiologist and experienced traffic safety researcher with numerous manuscripts related to drug-impaired driving. Even though she is an early-stage investigator, Dr. Rudisill has been the Co-I on multiple federal and state grants. Dr. Rudisill will oversee all aspects of this study including staff, data collection, data management, data analysis, summarization of findings, drafting manuscripts and progress reports, dissemination of findings, and fiscal oversight of the project.

Karen (Kim) Innes, PhD, MSPH: Co-Investigator.
Dr. Innes is a Professor in the Department of Epidemiology at the West Virginia University School of Public Health**.** She is an experienced clinical researcher and epidemiologist and has extensive background and expertise in clinical trials, survey research, chronic disease epidemiology, public health, and behavioral medicine, and have been continuously grant-funded as a PI/Co-PI in clinical intervention and epidemiologic research since 1998**.** She has authored over 230 peer-reviewed articles. Dr. Innes will support Dr. Rudisill in all aspects of the conduct of this study.

Gordon Smith, MD, MPH: Co-Investigator.
Dr. Smith, a Stewart M. and Joyce N. Robbins Distinguished Professor of Epidemiology, is an internationally renowned physician-epidemiologist with expertise in injury epidemiology, traffic safety, and substance use at WVU. He has continuously maintained research funding from the NIH and CDC. To date, he has published over 200 peer reviewed manuscripts. Dr. Smith will support Dr. Rudisill in all aspects of this study including training staff, data collection, data management, data analysis, summarization of findings, drafting manuscripts and progress reports, dissemination of findings.

Sijin Wen, MA, MS, PhD: Co-Investigator.
Dr. Wen is an Associate Professor in the Department of Biostatistics at the West Virginia University School of Public Health. Dr. Wen has extensive expertise in the preclinical and clinical studies. Dr. Wen will support Dr Rudisill in the statistical analysis of this study.

Dr. Treah Haggerty, MD, MS: Physician
Dr. Haggerty is an Associate Professor and practicing physician in the Department of Family Medicine at West Virginia University Medicine. She is located at the West Virginia University Health Sciences Center and will serve as the consulting physician for this study. She will be available on site for consultation should medical issues arise during testing.

OTHER PERSONNEL

Oscar Oviedo-Trespalacios, MSc, PhD: Consultant.
Dr. Oviedo-Trespalacios is a Strategic Research Fellow at the Centre for Accident Research and Road Safety in Queensland, Australia. He is an expert in using driving simulators and technology in transportation safety research. He will serve as a consultant-in-kind to Dr. Rudisill regarding the driving simulation aspect of this study.

Hourly Graduate Research Assistant: To be determined.

The PI will hire a graduate student to assist with the completion of this project. This individual will assist with the PI with various tasks such as overseeing the allocation of study groups, administering the study drug and tests, data collection, data management, manuscript preparation, and data dissemination.

Cynthia Fisher-Duda: Study Coordinator
Ms. Fisher-Duda will serve as the Study Coordinator for this project. She will assist the PI with the completion of this project such as recruiting, consenting participants, overseeing the allocation of study groups, administering the study drug and tests, data collection, data management.

Michelle L. Chidester: Study Personnel
Ms. Chidester will serve as additional study personnel for this project. She will assist the PI with the completion of this project such as completing IRB submissions, amendments and regulatory document collections.

Research Summary

Study Population – Forty overall healthy adults will be recruited and randomized to receive either 300 mg of CBD (N=20) or placebo (N=20). The criteria for eligibility are as follows: 1) the participant must be currently enrolled as a WVU student, 2) be 18-30 years of age at time of study, 3) have a current drivers' license issued from any state in the United States, 4) has driven at least once in the past 30 days 5) is able to speak and read English, 6) is willing to be randomized and comply with study requirements including a urine drug test on the day they consent to participate in the experiment and complete a test drive to ensure the absence of simulation sickness, 7) not currently taking any daily prescription medications other than birth control, 8) have not been diagnosed with any serious chronic disease by a licensed healthcare provider (including but not limited to Alzheimer's and related dementias, Parkinson's disease or other neurodegenerative disorder, major depressive or anxiety disorder, schizophrenia or other serious mental illness, arrhythmias, cataracts, glaucoma, chronic obstructive pulmonary disease, diabetes, epilepsy, sleep apnea, and fibromyalgia), and 9) has an individual able to drive them home after testing or is willing to be driven home by study staff after testing completion.

Participants will be excluded if they 1) currently smoke or use tobacco products, 2) have used illegal drugs (including cocaine/crack, heroin, methamphetamine, 3,4-methylenedioxy-methamphetamine, inhalants, phencyclidine, lysergeic acid, mushrooms, or marijuana) in the past 30 days, 3) has consumed CBD in the past 7 days, or 4) is currently pregnant or lactating. The health conditions and substances noted above have all been associated with changes in driving ability or performance. Also, limiting participants to those who are currently not using illegal drugs, tobacco products, and prescription medications may help minimize bias potentially caused by drug interactions with CBD or known impediments to driving performance from the medications themselves. Because the safety of CBD on fetuses or neonates is unknown, individuals who are pregnant or lactating are excluded for safety reasons.

Study Design – This is a randomized, parallel-group, double-blind, exploratory two-arm trial to assess the effects of CBD on driving ability along with changes in psychological status (e.g., sedation) and cognitive function. Forty healthy West Virginia University (WVU) students will be recruited for this study. Email notifications about the study will be sent to the student body and flyers will be posted on boards throughout campus; this type of recruitment has been successful in our other studies. Interested students can contact study personnel. Study personnel will tell them about the study and pre-screen participants using a standardized checklist. If students are eligible and still want to participate, they will be asked to meet at the research office. After eligibility is reassessed and consent is obtained, the individual will be allocated and randomized to receive: (1) 300 mg of pure CBD oil or (N=20) (2) placebo matched in appearance and taste (N=20). After consuming the study drug, each individual will participate in a 25–35-minute driving simulation (which includes a practice drive and brake reaction test (BRT)) and have their driving performance measured. To assess changes in mental status (i.e., sedation and drowsiness) and drug impairment-related cognitive

function, the VAMS, SSS, DSST, PVT, SRT, and TMT will also be administered to participants at baseline (prior to study drug consumption) and following completion of the driving simulation test. The primary outcome of this study will be driving performance, quantified using measures strongly associated with collision risk including number of lane departures, standard deviation of lateral position (i.e., weaving), brake reaction time, and collision occurrence. Secondary outcomes will be pre-post changes in well-validated measures of mental sedation (VAMS, SSS) and cognitive function (DSST, TMT, PVT, SRT). We will also collect baseline demographic, health, and driving history data along with data at the end of the survey to assess participant satisfaction and tests of blinding. The entire protocol for each participant will be completed in one day and should take 4-4.5 hours to complete. We chose a parallel design as opposed to a cross-over design to minimize participant burden (i.e., to avoid 2 testing sessions) and facilitate retention. As CBD is a legal nutraceutical that can be obtained over the counter, and it typically is well-tolerated, this study is minimal risk. All data will be deidentified and stored on a secure server that is compliant with WVU Information Technology (IT) Department. An overview of the protocol is below.

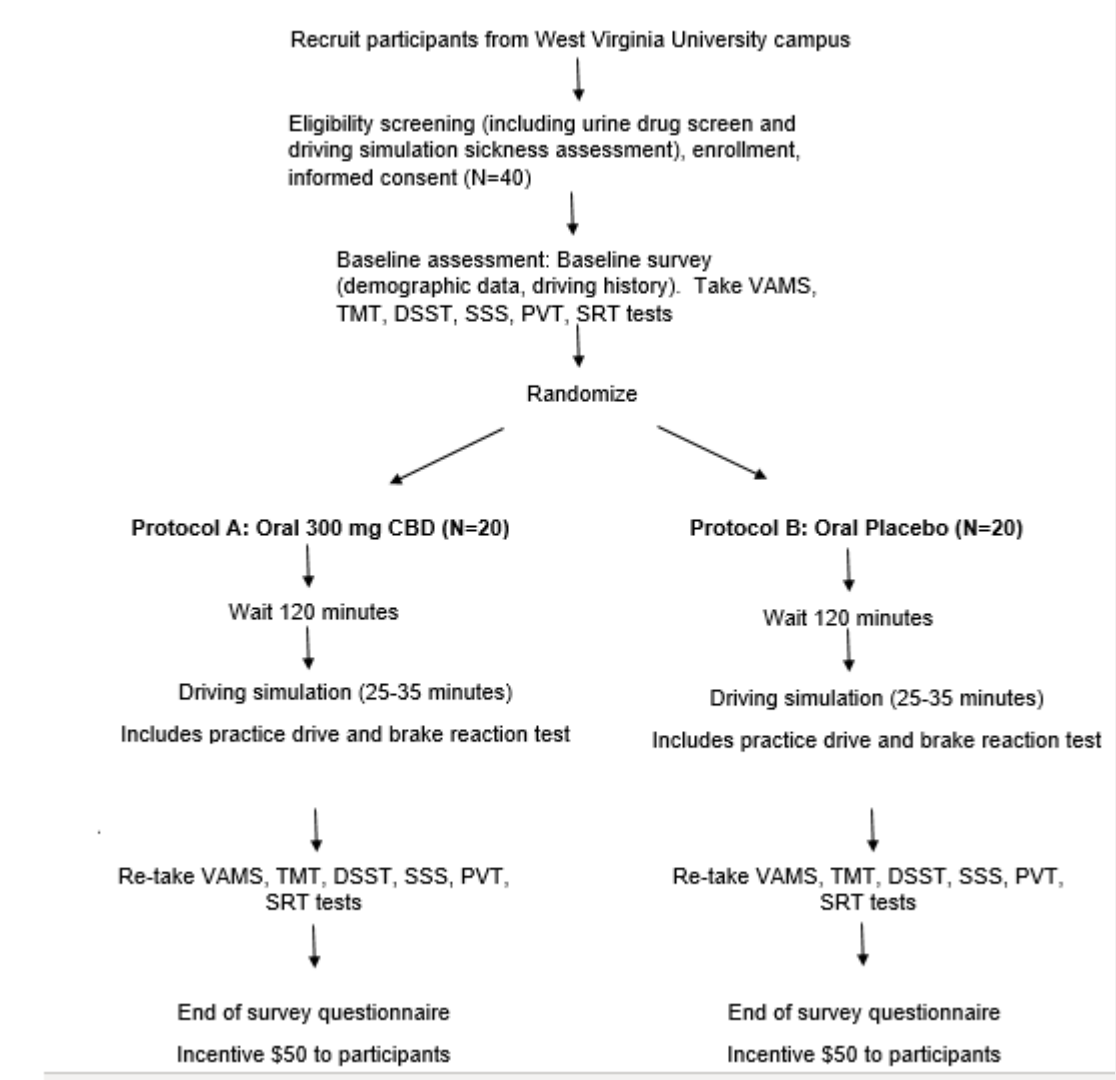

Figure 1. Overview of protocol

Study Duration – 24 months

Background & Significance

BACKGROUND. Drug-impaired driving has outpaced alcohol-impaired driving in the United States (US) partly due to the passage of state medical and recreational marijuana use laws and the national opioid epidemic.[1-4] Delta-9-tetrahydrocannabinol (THC), the psychoactive component of marijuana (*Cannabis sativa*), is consistently the most prevalent drug identified among drivers nationally and its detection has increased nearly 50% since 2007.[1,5-7] THC is known to impair drivers' psychomotor function, divided attention, lane tracking, and cognitive function, which can increase their risk of motor vehicle collision.[8-13] While knowledge of the pharmacodynamic and pharmacokinetic properties of marijuana are expanding, virtually nothing is known regarding the effects of cannabidiol (CBD), the non-psychoactive component of marijuana, and its relationship with driver performance,[14-16] despite rapidly increasing use and health claims.

Although little is known about CBD's effects, it is a legal substance in the US and is currently being added to a myriad of foods, beverages, tobacco products, and dietary supplements in oil or tincture form.[17,18] CBD is immensely popular and sales are projected to hit $23 billion per year by 2025.[19] A survey of US CBD consumers (N=2,409) revealed that many individuals purchase the product for general wellness or recreation (38%), but most use CBD to treat a medical condition (62%), such as pain, anxiety, depression, or insomnia.[20] Whether CBD actually helps these maladies is unclear; peer-reviewed placebo-controlled studies of CBD have only been conducted in small, unique clinical populations suffering from conditions such as post-traumatic stress, addiction, anxiety, multiple sclerosis, epilepsy, psychosis, movement disorders, or insomnia.[21-40] While most studies involving clinical populations show that CBD is well-tolerated in high doses, it is not without its side effects; patients often claim to experience drowsiness and sedation.[41-44] In fact, the Food and Drug Administration package insert for Epidiolex, which is prescription CBD oil for Lennox-Gastaut and Dravet syndromes in children, contains a warning about sedation and potential driver impairment.[45] However, the effects of CBD in healthy adult populations is severely lacking, especially with regard to effects on driving.

To our knowledge, only 16 placebo-controlled peer-reviewed studies of CBD have been conducted to date in healthy volunteers; most of these studies have been conducted using males and virtually all have involved South American or European populations.[44,46-59] The sample sizes are small with 79% of these studies having fewer than 16 people (range 5-57 participants); all these studies have suggested that CBD is sedating and anxiolytic but were not statistically significantly different from the effects of placebo, which is likely driven by the very small sample sizes.[44,46-59] Surveys indicate that females appear to use CBD more than males, but the known effects of CBD are virtually unstudied in healthy females.[20] Thus, it appears that CBD is likely sedating, but it has not been formally assessed in a placebo-controlled trial in a healthy US population consisting of both sexes. Additionally, to date, no peer-reviewed studies have investigated whether CBD alone affects the driving ability of healthy adults.

Thus, the **objectives** of this application are to investigate the effects of CBD on driving performance, psychological status (i.e., mood, drowsiness, sedation), and cognitive function in healthy adults aged 18-30 years. Driving performance will be assessed using a driving simulator, which directly correlates with actual driving ability, [60-64] while cognitive function and psychological status will be assessed using a battery of well-validated instruments widely used in the evaluation of drug impairment.[65,66] Given that CBD products are growing exponentially in popularity among all age groups,[20] and their effects in a healthy population are understudied, the **positive impact** of this study is the collection of essential preliminary data regarding the potential adverse effects of CBD, which may unknowingly put drivers and other road users at increased risk of motor vehicle collision and subsequent morbidity and mortality.

SIGNIFICANCE. West Virginia has a traffic fatality rate that is 70% greater than the national rate.[67] While the exact reason for this disparity is unclear, previous studies have suggested that drug impaired driving may be partly responsible.[68] Not only is the traffic fatality rate elevated in WV, but our preliminary studies indicate that CBD consumption is high as well. Among WVU students, our preliminary study found that 60% of drivers surveyed had consumed CBD (see section C.5.4.1). This demonstrates the high usage in the population and the need to determine if CBD is safe for drivers to consume not only nationally, but also in WV, which already suffers from such a disparate traffic fatality rate. These findings could facilitate public health intervention, driver education, and/or legislative initiatives to protect this high-risk population of drivers.

Objectives

The **objective/purpose** of this study is to investigate the effects of CBD on driving performance, psychological status (i.e., mood, sedation, drowsiness), and cognitive function in healthy adults aged 18-30 years. This is because CBD is widely sold and consumed and there is some evidence that it may be sedating; however, this has never been evaluated in healthy adults. The **primary outcome** of this study will be driving performance, quantified using measures strongly associated with collision risk, including number of lane departures, standard deviation of lateral position (i.e., weaving), brake reaction time, and collision occurrence. Driving performance will be assessed using a driving simulator. **Secondary outcomes** will be changes in well-validated measures of mental sedation and cognitive function which includes performance on the VAMS, SSS, TMT, DSST, PVT, SRT. The VAMS and SSS are Likert-type scales which assess mental and physical sedation and sleepiness, respectively, at that moment and time. VAMS consists of 16 questions, while SSS only consists of 1. These measures can be summed with higher scores equating to more sedation. The SSS will be summed with greater perceived sleepiness receiving a larger score, similar to the VAMS. The DSST measures psychomotor speed, attention and working memory by requiring participants to translate numbers into symbols; the test is scored by the degree of completion and accuracy over a timed 90 second period. The TMT measures executive function and consists of two parts; the first part requires participants to connect numbers in ascending order, while the second part requires individuals to connect numbers and letters in sequence. The test is scored by the time it takes to accurately complete each test. Increases in time correlate with greater impairment. PVT and SRT are tests given on a computer tablet. They both measure participants reactions to stimuli.

Study Design & Methodology

This is a randomized, parallel-group, double-blind, exploratory two-arm trial to assess the effects of CBD on driving ability along with changes in psychological status (e.g., sedation) and cognitive function. Thus, the data will be collected prospectively. The methodology of the study is below.

Study Design and Protocol Overview. We propose a randomized, parallel-group, double-blind, exploratory two-arm trial to assess the effects of CBD on driving ability along with changes in psychological status (i.e., mood, drowsiness, sedation) and cognitive function. Forty healthy West Virginia University (WVU) students will be allocated and randomized to receive: (1) 300 mg of pure CBD oil or (N=20) (2) placebo matched in appearance and taste (N=20). After consuming the study drug, each individual will participate in a 25–35-minute driving simulation, which includes a practice drive and brake reaction test, and their driving performance measured. To assess changes in psychological status (i.e., mood, drowsiness, sedation) and drug impairment-related cognitive function, the VAMS, SSS, DSST, TMT, PVT, SRT will also be administered to participants at baseline (prior to study drug consumption) and following completion of the driving simulation test. The primary outcome of this study will be driving performance, quantified using measures strongly associated with collision risk including number of lane departures, standard deviation of lateral position (i.e. weaving), reaction time, and collision occurrence.[78-80] Secondary outcomes will be pre-post changes in well-validated measures of mood, drowsiness, mental sedation (VAMS, SSS) and cognitive function (DSST, TMT, PVT SRT).[69-76] We will also collect baseline demographic, health (including body mass index), and driving history data, including driving habits, along with data at the end of the survey to assess participant satisfaction and tests of

blinding. The entire protocol will be completed in one day and should take 4-4.5 hours to complete for each participant. We chose a parallel RCT design as opposed to a cross-over RCT to minimize participant burden, while still being able to study both within individual (i.e., test battery results) and between group effects (i.e., simulator and test battery performance).

Study Population, Eligibility, Setting, and Recruitment. Forty healthy adults will be recruited and randomized to receive either 300 mg of CBD (N=20) or placebo (N=20). The criteria for eligibility are as follows: 1) the participant must be currently enrolled as a WVU student, 2) be 18-30 years of age at time of study, 3) have a current drivers' license issued from any state in the United States, 4) has driven at least once in the past 30 days 5) is able to speak and read English, 6) is willing to be randomized and comply with study requirements including a urine drug test on the day they consent to participate in the experiment and complete a test drive to ensure the absence of simulation sickness, 7) not currently taking any daily prescription medications other than birth control, 8) have not been diagnosed with any serious chronic disease by a licensed healthcare provider (including but not limited to Alzheimer's and related dementias, Parkinson's disease or other neurodegenerative disorder, major depressive or anxiety disorder, schizophrenia or other serious mental illness, arrhythmias, cataracts, glaucoma, chronic obstructive pulmonary disease, diabetes, epilepsy, sleep apnea, and fibromyalgia), and 9) has an individual able to drive them home after testing or is willing to be driven home by study staff after testing completion.

Participants will be excluded if they 1) currently smoke or use tobacco products, 2) have used illegal drugs (including cocaine/crack, heroin, methamphetamine, 3,4-methylenedioxy-methamphetamine, inhalants, phencyclidine, lysergeic acid, mushrooms, or marijuana) in the past 30 days, 3) has consumed CBD in the past 7 days, or 4) is currently pregnant or lactating. The health conditions and substances noted above have all been associated with changes in driving ability or performance.[86-115] Also, limiting participants to those who are currently not using illegal drugs, tobacco products, and prescription medications may help minimize bias potentially caused by drug interactions with CBD or known impediments to driving performance from the medications themselves.[84] Participants will be recruited from WVU. Email notifications about the study will be sent to the student body and flyers will be posted on boards throughout campus; this type of recruitment has been successful in other studies.[116] The study will take place at the WVU Health Sciences Center.

Consent, Screening, and Baseline Assessments. Students who are interested in participating in the study will be contacted via study personnel. Participants will be given a brief overview of the study and its purpose and will be initially screened for eligibility using a standardized screening checklist. If the individual meets the inclusion and exclusion criteria, they will be invited to participate in the study. Participants will be given a list of instructions prior to their assessment. While participants should not be taking any routine prescription medications as part of the inclusion criteria, they will be told to abstain from taking any other types of medications including nutraceuticals, over-the-counter medications, vitamins, supplements 24 hours prior to coming to their appointment. Caffeine and alcohol should also not be consumed within 10 hours of their appointment. They will be instructed to get at least 6 hours of sleep the night prior and to only consume water prior to their scheduled visit.

At the research office, study personnel will explain the requirements, re-screen the participant, and review the consent form with each individual in a private room and obtain signed consent. After consenting, the participant will be asked to provide a urine sample which will be analyzed immediately onsite for potentially impairing or illicit drugs via a rapid urine test. If the individual tests positive for any potentially impairing substance, they will not be able to participate in the study. Anyone who tests positive for a drug will be referred to the Carruth Center on campus. If a participant's sample tests negative, they will then be allowed to practice on the driving simulator for approximately 10 minutes prior to engaging in any other study activities. This is necessary as some individuals who are prone to motion sickness may experience brief, mild nausea (e.g., simulator sickness).[85] If there is evidence of simulator sickness, the individual will not be able to participate in the study, as they will likely not be able to complete the

protocol. Any reasons as to why an individual is not eligible to participate will be documented in a screening log. If no simulation sickness is observed, the student will then take the standardized and pilot-tested baseline survey regarding their demographics, health (including body mass index), and driving history along with the VAMS, SSS, TMT, DSST, PVT, and SRT tests.

These tests have all been deemed valid and reliable instruments and have been described in detail elsewhere. [69-76,78,117-119] The tests will be administered by trained study personnel via a computer tablet and/or paper and pencil; personnel will then transfer the collected data to a secure, electronic database. Participants will also be given a standardized breakfast after baseline assessment.

Allocation, Randomization and Blinding. Participants will be randomized immediately after baseline assessments are completed to the CBD (N=20) or placebo group (N=20) using a sex-stratified 1:1 random block design to ensure equal distribution among treatment groups and sex.[120] The participant and the PI will be unaware of group assignment (i.e. double-blind). Dr. Wen, who will not have contact with participants, will generate a randomized assignment master list and provide sequentially numbered envelopes containing group assignment to the team member that helps consent participants. This team member will assign the unique number from the next envelope in sequence as the participant's study identification number and will record the participant's information in a secure, electronic master database.

Intervention. Protocol A consists of a 300 mg dosage of CBD oil which will be consumed orally. This dosage was chosen as it has been used in other studies consisting of both healthy and clinical populations and is well-tolerated with no major adverse events.[46,51,52,54,55,59,121-123] CBD will be obtained from Zatural, a CBD manufacturer from Eden, Idaho. The CBD oil will be tested by Botanacor Laboratories (Denver, CO) for microbials, potency, heavy metals, trace THC, pesticides, and residual solvents to ensure purity, label accuracy, and safety; copies of laboratory reports will be maintained on premise. Protocol B is a placebo matched on appearance to the treatment (i.e., avocado oil potentially colored with food coloring). Both the CBD oil and placebo will be matched on taste (i.e., peppermint-flavored oil) prior to dispensing to each participant. After consumption of the respective protocol drug, the participant will be given a standardized meal and will then wait for 120 minutes to allow for digestion and for CBD to begin taking effect; this time frame was chosen based on the pharmacodynamics of CBD along with the consideration of participant burden (max absorption 2-5 hours).[44,124] Next, individuals will undergo a driving simulation and all participants will drive the same course. The simulator presents the individual with real life driving scenarios and is equipped with screens, a steering wheel, signals, and pedals (Figure 2). The participant will be instructed to drive the course for 25-35 minutes (this includes a practice drive and brake reaction time (BRT)). They will be instructed to follow normal driving rules, follow speed limits, and maintain constant speed and position within the lane, and brake when necessary. The simulation will include highway, suburban, rural, and urban driving scenarios which will incorporate turns, changes in speed, and avoidance of cars/pedestrians; this course sequence and times were chosen to minimize simulator sickness.[125] The simulator can monitor numerous aspects of drivers' performance and collect the data which is then downloaded and analyzed. Since we are investigating sedation and potential impairment, BRT, lateral position in the lane, lane departures, and collisions are the most telling performance measures. [79,80] After the simulation, participants will retake the VAMS, SSS, TMT, DSST,

Figure 2

PVT, SRT and complete an end of study questionnaire. The questionnaire will inquire about acceptability and tests of blinding.

Participant Compensation and Safety. All individuals who complete the study will receive a $50 -gift card for their time and participation. All participants will be encouraged to report any adverse events (AE) to study staff during and after their participation in the study (i.e., up to 24 hours afterwards) and a physician (Dr. Haggerty) is available if needed. However, the half-life of consumed CBD is approximately 17 hours.[44,124]The PI will report AEs to the WVU Institutional Review Board (IRB). All study personnel will have completed Human Subjects Training and the PI will obtain WVU IRB approval prior to study inception. As part of the inclusion criteria of the study, participants will be required to have a friend take them home after testing or they must agree to be transported home by study staff. We will also advise all study participants not to drive 24 hours post-testing for safety purposes**.**

Data Collection, Management and Analysis. All collected data will be entered by study staff into the secure, de-identified database and maintained in accordance with WVU IRB and Information Technology. All analyses will be performed in SAS (Cary, NC). The variables to be collected and their source are summarized in **Table 2**. Missing data will be multiply imputed to allow inclusion of all participants regardless of compliance.[126-128] We will perform both an intent-to-treat analysis based on initial assignment and a protocol analysis, excluding those who fail to complete the study.[129] Both between and within-group analyses will be conducted. Demographic characteristics and driving habits will be compared between groups via descriptive statistics to ensure proper randomization; we will also investigate tests of blinding by comparing accuracy of group assignment (perceived group assignment will be asked on end of study survey). If differences are noted, models can be adjusted. For between group effects, the data will be compared using Student's T-tests and/or ANOVA for continuous variables if the data are normally distributed; if non-normally distributed a Mann-Whitney test may be utilized.[130] For within group effects, the data will be compared using paired Student's T-tests (for normally distributed continuous paired observations) or Wilcoxon signed-rank test (for those continuous paired observations not normally distributed). We will perform a correlation using Pearson's R test between the variables collected for Aims 1 and 2, both between and within groups, to assess whether driving performance is

Table 2. Overview of proposed variables to be collected and for CBD study[a]

Aim	Variables	Source
	Socio-demographics, driving history, health	Baseline questionnaire
Aim 1. Determine the effects of CBD on the driving performance of healthy adults aged 18-30 years.	Driving performance • Number of lane departures • Number of collisions • Mean brake reaction time to stimuli • Mean standard deviation of lateral position in lane under consistent speed	Driving simulation
Aim 2. Determine the effects of CBD on participants psychological status and cognitive function.	Sedation • Self-reported sleepiness • Mental sedation: Sum of scores from questions 1,4,11,13 on VAMS-higher scores indicate more mental sedation • Physical sedation: Sum of scores from questions 3,5,6,16 on VAMS—higher scores indicate more physical sedation Cognitive function • Number of symbols completed within 60 seconds • Number of correct symbols completed within 60 seconds • Time to accurately complete Part A and Part B • Mean reaction time to stimuli • Mean reaction time to stimuli	SSS VAMS VAMS DSST TMT PVT SRT
Aim 3. Determine the relation of driving performance to changes in psychological and cognitive status.	Correlation between variables in Aims 1 and 2	Driving simulation outcomes, SSS, VAMS, DSST, TMT, PVT, SRT

a: All measures will be assessed between treatment and placebo groups. DSST, SSS, TMT, PVT, SRT and VAMS scores will also be compared within subjects to gauge changes overtime.

correlated with psychological or cognitive testing measures. Data will also be analyzed via sex as well.

As one can see, there is minimal risk to participants. There is no direct benefit to participants. However, there are potential benefits to society that offset the potential risks of this study, which are minimal. The findings of this study will be extremely informative to the public, medical providers, policy makers, and public health practitioners. Cannabidiol is commonly used drug, yet its effects in healthy populations are virtually unknown. Thus, the risk vs. benefit is reasonable.

Target Population & Recruitment Methods

Our sample size is 40 individuals. We chose this number based on an a priori power analysis.

Our inclusion and exclusions criteria are as follows: 1) the participant must be currently enrolled as a WVU student, 2) be 18-30 years of age at time of study, 3) have a current drivers' license issued from any state in the United States, 4) has driven at least once in the past 30 days 5) is able to speak and read English, 6) is willing to be randomized and comply with study requirements including a urine drug test on the day they consent to participate in the experiment and complete a test drive to ensure the absence of simulation sickness, 7) not currently taking any daily prescription medications other than birth control, 8) have not been diagnosed with any serious chronic disease by a licensed healthcare provider (including but not limited to Alzheimer's and related dementias, Parkinson's disease or other neurodegenerative disorder, major depressive or anxiety disorder, schizophrenia or other serious mental illness, arrhythmias, cataracts, glaucoma, chronic obstructive pulmonary disease, diabetes, epilepsy, sleep apnea, and fibromyalgia), and 9) has an individual able to drive them home after testing or is willing to be driven home by study staff after testing completion.

Participants will be excluded if they 1) currently smoke or use tobacco products, 2) have used illegal drugs (including cocaine/crack, heroin, methamphetamine, 3,4-methylenedioxy-methamphetamine, inhalants, phencyclidine, lysergeic acid, mushrooms, or marijuana) in the past 30 days, 3) has consumed CBD in the past 7 days, or 4) is currently pregnant or lactating. The health conditions and substances noted above have all been associated with changes in driving ability or performance. Also, limiting participants to those who are currently not using illegal drugs, tobacco products, and prescription medications may help minimize bias potentially caused by drug interactions with CBD or known impediments to driving performance from the medications themselves.

Thus, we needed to specify the inclusion and exclusion criteria to avoid confounding. We wanted a healthy population of drivers (i.e., not on medications nor without complex health conditions) to minimize confounding. Drivers older than 30 will probably be more likely to take medications and/or be diagnosed with a chronic condition. As long as a student meets the inclusion and exclusion criteria, they will be able to participate. Thus, we will not limit anyone by gender or race. As mentioned previously, we will recruit via flyers/posters and via emails to the student body. All study advertisement will state that this is a research project conducted by the Department of Epidemiology, the PI's contact information will be included along with the time commitment, inclusion/exclusion criteria, voluntary participation and that the WVU IRB approval is on file.

Risk & Benefit

Risk –There is minimal risk to participants. The first concern may be the small risk of a data breaches. However, this should be minimal as participants will be assigned an identification/study number. All other data will be stored on a secure virtual environment maintained by WVU's Information Technology department that only study personnel will have access to. A second minimal concern is momentary motion sickness from the driving simulator (e.g., simulator sickness); some individuals may report feeling brief nausea from the simulator. It typically clears immediately when the simulation is stopped. If participants experience this, the trial will stop immediately. The third risk involves the CBD itself. CBD comes from the Cannabis Sativa plant that must have <0.3% delta-9-tetrahydrocannabinol (THC) by federal law. THC is the psychoactive component of Cannabis. Thus, the CBD oil can contain very trace amounts of THC; thus, it is theoretically possible that an individual could test positive for THC/marijuana on an administered drug test. The CBD oil obtained for this study will be obtained from Zatural, a CBD manufacturer from Eden, Idaho. Zatural does attempt to remove THC from their product. The CBD oil will be tested by Botanacor Laboratories (Denver, CO) for microbials, potency, heavy metals, trace THC, pesticides, and residual solvents to ensure purity, label accuracy, compliance, and safety. Testing of the product has shown that it is free of microbials, heavy metals, pesticides, and residual solvents. Potency tests have shown that the concentration of CBD is accurate and that THC and THCa (a chemical precursor of THC) were not detected by this test's level of quantitation. Trace THC tests, which have a very low level of quantitation (i.e., 0.001%), detected no THCa, and 0.006% THC, which is well below acceptable limits (legal limit is 0.3%). Copies of laboratory reports will be maintained on premise. There are additional minimal risks with the CBD itself. Very little research exists on the effects of CBD even though it is a legal product. The CBD used in this study is a nutraceutical and it is not regulated by the United States Food and Drug Administration. The United States Food and Drug Administration does regulate Epidiolex, which is the prescription version of CBD oil prescribed to treat seizure disorders. According to the package insert for Epidiolex (available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf) and the United States Food and Drug Administration website (available at: https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis), several side effects of prescription CBD oil have been noted and could potentially harm participants. Prescription CBD oil can cause liver injury/hepatic dysfunction by elevating liver enzymes such as alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). Prescription CBD oil can interact with other drugs or alcohol the participant may be taking potentially resulting in serious side effects. Mainly, using CBD oil with alcohol or other drugs, especially those used to treat anxiety, panic, stress, or sleep disorders, could slow brain activity, and increase the risk of sedation and/or drowsiness, which could lead to injury. Prescription CBD oil has also been shown to impact the gastrointestinal tract with side effects such as decreased appetite, diarrhea, weight loss, gastroenteritis, and abdominal pain/discomfort. Prescription CBD oil has also been shown to affect the nervous system and cause somnolence (drowsiness or sleepiness), lethargy, fatigue, malaise, insomnia, poor sleep quality, irritability, agitation, aggression, anger, drooling, or gait disturbances. Anti-epileptic drugs, such as prescription CBD oil, have been associated with suicidal behavior and/or suicide ideation. Prescription CBD oil has also caused hypersensitivity reactions, rashes, hypoxia, respiratory failure, and infection. Studies in animals exposed to CBD oil have also shown male reproductive toxicity, or damage to fertility in males or male off-spring of women who have been exposed to CBD oil. For this study, we are using 300 mg of CBD which is a relatively small dose. This dosage was chosen as it has been used in other studies consisting of both healthy and clinical populations and is generally well-tolerated with no major adverse events; most studies use 150-600 mg, while some have used >1,200 mg.[46,51,52,54,55,59,121-123]

Benefit –There is no direct benefit to participants. However, there are potential benefits to society that offset the potential risks of this study, which are minimal. The findings of this study will be extremely informative to the public, medical providers, policy makers, and public health practitioners. Cannabidiol is commonly used nutraceutical, yet its effects in healthy populations are virtually unknown. Thus, the risk vs. benefit is reasonable.

Statistical Analysis Plan

All collected data will be entered by study staff into the secure, de-identified database and maintained in accordance with WVU IRB. All analyses will be performed in SAS (Cary, NC). The primary outcome of this study will be driving performance, including number of lane departures, standard deviation of lateral position (i.e., weaving), mean brake reaction time, and number of collisions (Aim 1). Secondary outcomes will be pre-post changes in well-validated measures of mental sedation (SSS, VAMS) and cognitive function (DSST, TMT, PVT, SRT) (Aim 2). The variables that will be collected and their source are summarized in Table 2. Missing data will be multiply imputed to allow inclusion of all participants regardless of compliance.[118-120] We will perform both an intent-to-treat analysis based on initial assignment and a protocol analysis, excluding those who fail to complete the study.[121]Both between and within-group analyses will be conducted. Demographic characteristics will be compared between groups via descriptive statistics to ensure proper randomization; we will also investigate tests of blinding by comparing accuracy of group assignment (perceived group assignment will be asked on end of study survey). For between group effects, the data will be compared using Student's T-tests and/or ANOVA for continuous variables if the data are normally distributed; if non-normally distributed a Mann-Whitney test may be utilized.[122] For within group effects, the data will be compared using paired Student's T-tests (for continuous paired observations which are normally distributed) or Wilcoxon signed-rank test (for continuous paired observations which are not normally distributed). We will perform a correlation using Pearson's R test between the variables collected for Aims 1 and 2, both between and within groups, to assess whether driving performance is correlated with psychological or cognitive testing measures. Data will also be analyzed via sex.

Table 2. Overview of proposed variables to be collected and for CBD study[a]

Aim	Variables	Source
	Socio-demographics, driving history, health	Baseline questionnaire
Aim 1. Determine the effects of CBD on the driving performance of healthy adults aged 18-30 years.	Driving performance • Number of lane departures • Number of collisions • Mean brake reaction time to stimuli • Mean standard deviation of lateral position in lane under consistent speed	Driving simulation
Aim 2. Determine the effects of CBD on participants psychological status and cognitive function.	Sedation • Self-reported sleepiness • Mental sedation: Sum of scores from questions 1,4,11,13 on VAMS-higher scores indicate more mental sedation • Physical sedation: Sum of scores from questions 3,5,6,16 on VAMS—higher scores indicate more physical sedation Cognitive function • Number of symbols completed within 60 seconds • Number of correct symbols completed within 60 seconds • Time to accurately complete Part A and Part B • Mean reaction time to stimuli • Mean reaction time to stimuli	SSS VAMS VAMS DSST TMT PVT SRT
Aim 3. Determine the relation of driving performance to changes in psychological and cognitive status.	Correlation between variables in Aims 1 and 2	Driving simulation outcomes, SSS, VAMS, DSST, TMT, PVT, SRT
a: All measures will be assessed between treatment and placebo groups. DSST, SSS, TMT, PVT, SRT and VAMS scores will also be compared within subjects to gauge changes overtime.		

Sample Size – We conducted an analysis to ensure adequate sample size and power. The analysis was based on mean reaction time, which is one of the primary outcomes between groups. A total sample size of 26 students with a large effect size of 0.7 and α=0.05 using a two-sided, two-sample equal variance t-test achieves 80% power to reject the null hypothesis of equal means.[131] Thus, our total sample size (N=40) should be more than adequate for this study.

Data Safety Monitoring – A Data Safety Monitoring Board will not be appointed for this study unless required.

Safety Monitoring & Unanticipated Event Reporting

Study personnel will ensure that potential study participants fully understand study procedures and requirements before signing the consent, stress that they are under no obligation to participate and refusal to enroll in the study will in no way affect their care or university standing, and that they are fully aware that they can withdraw from the study at any time. In addition, all participants and study team members will be encouraged to report any adverse events (AE). The PI will promptly report AEs to the Institutional Review Board according to protocol and Institutional Review Board policies; complete an AE form and grade the AE. If any AE is considered serious and unexpected, the event must be reported to the IRB within 7 days from the time the study team receives knowledge of the event. Likewise, any unanticipated problems that occur will be reported to the Institutional Review Board within 7 days from the time the study team received knowledge of the event. Monitoring of this study will be performed by the PI through annual review. In addition, the PI and other key personnel, will review any adverse events as they may occur in each subject, both during testing and afterward. No significant AEs are anticipated but should any occur the event will be promptly reported to the Institutional Review Board. Any unanticipated or serious AE will require re-evaluation of the risk of the study. Study staff will contact all participants 8-12 hours post testing and approximately 24 hours post testing to ensure no AEs occurred. We will advise all study participants not to drive 24 hours post-testing. As part of the inclusion criteria of the study, participants will need to have a friend escort them home after testing or they must agree to being brought home by study staff. Dr. Haggerty will also be available during testing incase issues arise during testing.

Study Duration & Timeline

The projected timeline of this study is below. It should take 24 months to complete.

C5.14. Projected Timeline (task and months to complete)																							
TASK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
1. Recruitment	X	X																						
2. Conduct testing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
3. Data management & analysis																		X	X	X	X			
4. Manuscript preparation																				X	X	X	X	
5. Dissemination																							X	X

Section III: Informed Consent Process

Protected Health Information (PHI)

There will be PHI collected from this study. This will mainly come from the consent process. We will obviously collect the person's name on the consent form. After this, they will be assigned a study identification number and everything else will be de-identified. We will ask if they have any chronic medical conditions or take medication or illegal drugs. If they do, they can't participate in the study.

Informed Consent Process

Dr. Rudisill or her designee will perform the written consent process, which will take place in her office which is private. The Informed Consent Form (ICF) will be written in lay terms and at a 6th grade reading level. All study participants will be 18 or over so assent will not be necessary.

Confidentiality & Privacy

Confidentiality – All data collected will be kept for a minimum of 3 years after the conclusion of the research project. Physical copies of data collected will be locked in a drawer or file cabinet, within the PI's locked office. Digital data will be stored on an encrypted, password protected database located on a secure server maintained by WVU IT Department. All participant identifiers will be stored separately from the data collected.

Privacy – Data will be stored securely to protect the privacy of participants. Only the minimum amount of data will be collected to ensure participant privacy. The driving simulation and neurocognitive tests will occur in a quiet, secured office to maintain privacy.

A Federal Certificate of Confidentiality will be obtained if necessary to further protect participants.

Section IV: Other Considerations

Conflict of Interest

The PI and Co-Investigators have no conflicts of interest.

Publications, Presentations, & References

The PI will likely present the results of this study at one of the following conferences: Transportation Research Board, Society for the Advancement of Violence and Injury Prevention, American Public Health Association.

The PI will likely publish the results of this study in one of the following journals: American Journal of Epidemiology, Injury Prevention

References

1. Berning A, R C, K. W. Results of the 2013-2014 National Roadside Survey of Alcohol and Drug Use by Drivers. Washington DC: National Highway Traffic Safety Administration; 2015.

2. Brady JE, Li G. Prevalence of alcohol and other drugs in fatally injured drivers. Addiction 2013;108(1):104-114.

3. Wilson FA, Stimpson JP, Pagan JA. Fatal crashes from drivers testing positive for drugs in the U.S., 1993-2010. Public Health Rep 2014;129(4):342-50.

4. Rudisill TM, Zhao S, Abate MA, Coben JH, Zhu M. Trends in drug use among drivers killed in U.S. traffic crashes, 1999-2010. Accid Anal Prev 2014;70:178-87.

5. Lacey JH, Kelley-Baker T, Furr-Holden D, Voas RB, Romano E, Ramirez A, et al. 2007 National roadside survey of alcohol and drug use by drivers: drug results In: National Highway Traffic Safety Administration, editor. Washington DC, 2009.

6. Walsh JM, Flegel R, Atkins R, Cangianelli LA, Cooper C, Welsh C, et al. Drug and alcohol use among drivers admitted to a Level-1 trauma center. Accid Anal Prev 2005;37(5):894-901.

7. Terhune KW, Hendricks DL, Michalovic YG, Bogeman SC, Santiga P, Blomberg R, et al. The incidence and role of drugs in fatally injured drivers. In: National Highway Traffic Safety Administration, editor. Washington DC, 1992.

8. Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem 2013;59(3):478-92.

9. Hartman RL, Brown TL, Milavetz G, Spurgin A, Pierce RS, Gorelick DA, et al. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol Depend 2015;154:25-37.

10. Hartman RL, Brown TL, Milavetz G, Spurgin A, Pierce RS, Gorelick DA, et al. Cannabis effects on driving longitudinal control with and without alcohol. J Appl Toxicol 2016;36(11):1418-29.

11. Moskowitz H. Marihuana and driving. Accid Anal Prev. 1985 Aug;17(4):323-45.

12. Ramaekers JG, Robbe HW, O'Hanlon JF. Marijuana, alcohol and actual driving performance. Hum Psychopharmacol 2000;15(7):551-558.

13. Robbe H, JF OH. Marijuana and actual driving performance. In: Dept of Transporttion, editor. Washington DC, 1993.

14. Andre CM, Hausman J-F, Guerriero G. Cannabis sativa: The Plant of the Thousand and One Molecules. Front Plant Sci. 2016; 7:19-.

15. Bhattacharyya SSS. Opposite effects of -9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35(3):764-774.

16. Millar SA, Stone NL, Yates AS, O'Sullivan SE. A Systematic Review on the Pharmacokinetics of Cannabidiol in Humans. Front Pharmacol 2018;9:1365.

17. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold OnlineLabeling Accuracy of Cannabidiol Extracts Sold OnlineLetters. JAMA 2017;318(17):1708-1709.

18. Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. JAMA 2015;313(24):2491-3.

19. Mikulic M. Total U.S. cannabidiol consumer sales from 2014 to 2022. Statista 2019 [22 Aug 2019]; Available from: http://statista.com/statistics/760498/total-us-cbd-sales/.

20. Corroon J, Phillips JA. A Cross-Sectional Study of Cannabidiol Users. Cannabis Cannabinoid Res 2018;3(1):152-161.

21. Peres FF, Lima AC, Hallak JEC, Crippa JA, Silva RH, Abílio VC. Cannabidiol as a promising strategy to treat and prevent movement disorders? Front Pharmacol. 2018; 9.

22. Premoli M, Aria F, Bonini SA, Maccarinelli G, Gianoncelli A, Pina SD, et al. Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. Life Sci. 2019; 224:120-7.

23. Prud'Homme M, Cata R, Jutras-Aswad D. Cannabidiol as an intervention for addictive behaviors: A systematic review of the evidence. Subst Abuse. 2015; 9:33-8.

24. Rohleder C, Müller JK, Lange B, Leweke FM. Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence. Front Pharmacol. 2016; 7.

25. Soares VP, Campos AC. Evidences for the anti-panic actions of cannabidiol. Curr Neuropharmacol. 2017; 15:291-9.

26. Turna J, Syan SK, Frey BN, Rush B, Costello MJ, Weiss M, et al. Cannabidiol as a Novel Candidate Alcohol Use Disorder Pharmacotherapy: A Systematic Review. Alcohol Clin Exp Res. 2019; 43:550-63.

27. Zuardi AW, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, et al. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. Current Pharmaceutical Design 2012;18(32):5131-5140.

28. Bitencourt RM, Takahashi RN. Cannabidiol as a therapeutic alternative for post-traumatic stress disorder: From bench research to confirmation in human trials. Front Neurosci. 2018; 12.

29. Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a Potential Treatment for Anxiety Disorders. Neurotherapeutics 2015;12(4):825-836.

30. Burstein S. Cannabidiol (CBD) and its analogs: A review of their effects on inflammation. Bioorganic and Medicinal Chemistry 2015;23(7):1377-1385.

31. Celius EG, Vila C. The influence of THC:CBD oromucosal spray on driving ability in patients with multiple sclerosis-related spasticity. Brain and Behavior 2018;8(5).

32. de Mello Schier AR, de Oliveira Ribeiro NP, Coutinho DS, Machado S, Arias-Carrión O, Crippa JA, et al. Antidepressant-like and Anxiolytic-like effects of Cannabidiol: A chemical compound of cannabis sativa. CNS and Neurological Disorders - Drug Targets 2014;13(6):953-960.

33. de Mello Schier AR, de Oliveira Ribeiro NP, de Oliveira e Silva AC, Cecilio Hallak JE, Crippa JAS, Nardi AE, et al. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. Revista Brasileira de Psiquiatria 2012;34(S1):S104-S110.

34. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia (Series 4) 2014;55(6):791-802.

35. Guimarães Silva TB, Queiroz Balbino C, Moura Weiber AF. The relationship between cannabidiol and psychosis: A review. Annals of Clinical Psychiatry 2015;27(2):134-141.

36. Hermann D, Schneider M. Potential protective effects of cannabidiol on neuroanatomical alterations in cannabis users and psychosis: a critical review. Current Pharmaceutical Design 2012;18(32):4897-4905.

37. Lattanzi S, Brigo F, Cagnetti C, Trinka E, Silvestrini M. Efficacy and Safety of Adjunctive Cannabidiol in Patients with Lennox–Gastaut Syndrome: A Systematic Review and Meta-Analysis. CNS Drugs 2018;32(10):905-916.

38. Lattanzi S, Brigo F, Trinka E, Zaccara G, Cagnetti C, Del Giovane C, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs 2018;78(17):1791-1804.

39. Osborne AL, Solowij N, Weston-Green K. A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia. Neuroscience and Biobehavioral Reviews 2017;72:310-324.

40. Chagas MHN, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sobreira-Neto MA, Sobreira ET, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: A case series. Journal of Clinical Pharmacy and Therapeutics 2014;39(5):564-566.

41. Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res 2017;2(1):139-154.

42. Zhornitsky S, Potvin S. Cannabidiol in Humans--The Quest for Therapeutic Targets. Pharmaceuticals (14248247) 2012;5(5):529-552.

43. Bergamaschi MM, Queiroz RHC, Zuardi AW, Crippa JAS. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Current Drug Safety 2011;6(4):237-249.

44. Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. CNS Drugs 2018;32(11):1053-1067.

45. Food and Drug Administration. Full prescribing information. 2018; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

46. Borgwardt SJSSJ. Neural Basis of -9-Tetrahydrocannabinol and Cannabidiol: Effects During Response Inhibition. Biological Psychiatry 2008;64(11):966-973.

47. Consroe P, Carlini EA, Zwicker AP, Lacerda LA. Interaction of cannabidiol and alcohol in humans. Psychopharmacology (Berl) 1979;66(1):45-50.

48. Crippa JAdS, Zuardi AW, Garrido GEJ, Wichert-Ana L, Guarnieri R, Ferrari L, et al. Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow. Neuropsychopharmacology 2004;29(2):417-426.

49. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients. Pharmacology 1980;21(3):175-185.

50. Dalton WSWWS. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. Clinical Pharmacology and Therapeutics 1976;19(3):300-309.

51. Fusar-Poli PPP. Modulation of effective connectivity during emotional processing by sup9/sup - tetrahydrocannabinol and cannabidiol. International Journal of Neuropsychopharmacology 2010;13(4):421-432.

52. Fusar-Poli PPP. Distinct effects of A9-Tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Archives of General Psychiatry 2009;66(1):95-105.

53. Hollister LE. Cannabidiol and cannabinol in man. Experientia 1973;29(7):825-6.

54. Martin-Santos R, Crippa JA, Batalla A, Bhattacharyya S, Atakan Z, Borgwardt S, et al. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Current Pharmaceutical Design 2012;18(32):4966-4979.

55. Winton-Brown T. Modulation of auditory and visual processing by delta-9- tetrahydrocannabinol and cannabidiol: An fMRI study. Neuropsychopharmacology 2011;36(7):1340-1348.

56. Zuardi AW, Guimaraes FS, Moreira AC. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. Braz J Med Biol Res 1993;26(2):213-7.

57. Zuardi AW. Action of cannabidiol on the anxiety and other effects produced by sup9/sup-THC in normal subjects. Psychopharmacology 1982;76(3):245-250.

58. Linares IMP, Guimaraes FS, Eckeli A, Crippa ACS, Zuardi AW, Souza JD, et al. No acute effects of Cannabidiol on the sleep-wake cycle of healthy subjects: A randomized, double-blind, placebo-controlled, crossover study. Front Pharmacol. 2018; 9.

59. Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimarães FS, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Revista Brasileira de Psiquiatria 2019;41(1):9-14.

60. de Winter JC, de Groot S, Mulder M, Wieringa PA, Dankelman J, Mulder JA. Relationships between driving simulator performance and driving test results. Ergonomics 2009;52(2):137-153.

61. Qin Y, Xiong J, Jiang Y, et al. Simulator Evaluation of Drivers' Performance on Rural Highways in relation to Drivers' Visual Attention Demands. Advances in Mechanical Engineering. 2014;7(1):249275.

62. Philips B, Morton T. Making Driving Simulators More Useful for Behavioral Research— Simulator Characteristics Comparison and Model-Based Transformation. In: United States Department of Transportation, McLean VA,2015.

63. Ghosh D, Jamson SL, Baxter PD, Elliott MW. Continuous measures of driving performance on an advanced office-based driving simulator can be used to predict simulator task failure in patients with obstructive sleep apnoea syndrome. Thorax 2012;67(9):815-821.

64. Tatham AJ, Boer ER, Gracitelli CPB, Rosen PN, Medeiros FA. Relationship Between Motor Vehicle Collisions and Results of Perimetry, Useful Field of View, and Driving Simulation in Drivers With Glaucoma. Translational Vision Science & Technology 2015;4(3):5-5.

65. Strand MC, Gjerde H, Mørland J. Driving Under the Influence of Non-Alcohol Drugs -- An Update. Part II: Experimental Studies. Forensic Science Review 2016;28(2):99-101.

66. Morland J. Driving under the influence of non-alcohol drugs. Forensic Sci.Rev 2000;12:80-105.

67. Plants K, Rudisill T, Zhu M. Traffic fatalities in West Virginia and the remaining United States, 2008-2012. WV Med J 2017;113(Mar/Apr):42-47.

68. Centers for Disease Control and Prevention. Alcohol and other drug use among victims of motor vehicle crashes-West Virginia 2004-2005. MMWR Morb Mortal Wkly Rep 2006;55(48):1293-1296.

69. Norris H. The action of sedatives on brain stem oculomotor systems in man. Neuropharmacology 1971;10(21):181-91.

70. Jaeger J. Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. J Clin Psychopharmacol 2018;38(5):513-519.

71. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Stanford Sleepiness Scale (SSS). In: Shahid A, Wilkinson K, Marcu S, Shapiro CM, editors. STOP, THAT and One Hundred Other Sleep Scales. New York, NY: Springer New York; 2012. p. 369-70.

72. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology 1973;10(4):431-6.

73. House ED, Arruda JE, Andrasik F, Grazzi L. The reliability and validity of the Visual Analog Mood Scales in non-English-speaking pain patients. Pain Pract 2012;12(8):626-32.

74. Stern RA, Arruda JE, Hooper CR, Wolfner GD, Morey CE. Visual analogue mood scales to measure internal mood state in neurologically impaired patients: Description and initial validity evidence. Aphasiology 1997;11(1):59-71.

75. Luria RE. The validity and reliability of the Visual Analogue Mood Scale. Journal of Psychiatric Research 1975;12(1):51-57.

76. Rosano C, Perera S, Inzitari M, Newman AB, Longstreth WT, Studenski S. Digit Symbol Substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adults. Age and ageing 2016;45(5):688-695.

77. Wagner S, Helmreich I, Dahmen N, Lieb K, Tadic A. Reliability of three alternate forms of the trail making tests a and B. Arch Clin Neuropsychol 2011;26(4):314-21.

78. Kay GG, Logan BK. Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving. In: National HIghway Traffic Safety Administration, Washington DC; 2011.

79. Gaspar JG, Brown TL, Schwarz CW, Lee JD, Kang J, Higgins JS. Evaluating driver drowsiness countermeasures. Traffic Inj Prev 2017;18(sup1):S58-S63.

80. Owens JM, Dingus TA, Guo F, Fang Y, Perez M, McClafferty J, et al. Prevalence of drowsy driving crashes: estimates from a large-scale naturalistic driving study (research brief). In: Washington DC, editor: American Automobile Association Foundation for Traffic Safety, 2018.

81. Rudisill TM. Fueled by an epidemic: a spatial analysis of opioid-positive drivers fatally injured in motor vehicle collisions in West Virginia, 2011-2015. American Journal of Public Health Research 2017;5(4):124-129.

82. Rudisill TM, Zhu M, Abate M, Davidov D, Delagarza V, Long DL, et al. Characterization of drug and alcohol use among senior drivers fatally injured in U.S. motor vehicle collisions, 2008-2012. Traffic Inj Prev 2016;17(8):788-95.

83. Rudisill TM, Zhu M, Davidov D, Leann Long D, Sambamoorthi U, Abate M, et al. Medication use and the risk of motor vehicle collision in West Virginia drivers 65 years of age and older: a case-crossover study. BMC Res Notes 2016;9:166.

84. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review. Accid Anal Prev 2016;96:255-70.

85. Classen S, Bewernitz M, Shechtman O. Driving simulator sickness: an evidence-based review of the literature. Am J Occup Ther 2011;65(2):179-188.

86. Fitten L, Perryman KM, Wilkinson CJ, et al. Alzheimer and vascular dementias and driving: A prospective road and laboratory study. JAMA 1995;273(17):1360-1365.

87. Tuokko H, Tallman K, Beattie BL, Cooper P, Weir J. An examination of driving records in a dementia clinic. J Gerontol B Psychol Sci Soc Sci 1995;50(3):S173-81.

88. Beaussart M, Beaussart-Defaye J, Lamiaux JM, Grubar JC. Epileptic drivers - A study of 1,089 patients. Medicine and Law 1997;16(2):295-306.

89. Classen S, Brumback B, Monahan M, Malaty, II, Rodriguez RL, Okun MS, et al. Driving errors in Parkinson's disease: moving closer to predicting on-road outcomes. Am J Occup Ther 2014;68(1):77-85.

90. Cox DJ, Quillian WC, Thorndike FP, Kovatchev BP, Hanna G. Evaluating driving performance of outpatients with Alzheimer disease. Journal of the American Board of Family Practice 1998;11(4):264-271.

91. Duchek JM, Carr DB, Hunt L, Rose CM, Chengjie X, Shah K, et al. Longitudinal Driving Performance in Early-Stage Dementia of the Alzheimer Type. Journal of the American Geriatrics Society 2003;51(10):1342.

92. Eby DW, Silverstein NM, Molnar LJ, LeBlanc D, Adler G. Driving behaviors in early stage dementia: A study using in-vehicle technology. Accid Anal Prev 2012;49(0):330-337.

93. Frittelli C, Borghetti D, Iudice G, Bonanni E, Maestri M, Tognoni G, et al. Effects of Alzheimer's disease and mild cognitive impairment on driving ability: A controlled clinical study by simulated driving test. International Journal of Geriatric Psychiatry 2009;24(3):232-238.

94. George CFP, Boudreau AC, Smiley A. Simulated driving performance in patients with obstructive sleep apnea. American Journal of Respiratory and Critical Care Medicine 1996;154(1):175-181.

95. George CFP, Boudreau AC, Smiley A. Comparison of simulated driving performance in narcolepsy and sleep apnea patients. Sleep: Journal of Sleep Research & Sleep Medicine 1996;19(9):711-717.

96. Gieteling EW, Bakker MS, Hoekema A, Maurits NM, Brouwer WH, van der Hoeven JH. Impaired driving simulation in patients with Periodic Limb Movement Disorder and patients with Obstructive Sleep Apnea Syndrome. Sleep Medicine 2012;13(5):517-523.

97. Gresset J, Meyer F. Risk of Automobile Accidents Among Elderly Drivers with Impairments or Chronic Diseases. Canadian Journal of Public Health / Revue Canadienne de Sante'e Publique 1994;85(4):282-285.

98. Guibert R, Duarte-Franco E, Ciampi A, Potvin L, Loiselle J, Philibert L. Medical conditions and the risk of motor vehicle crashes in men. Arch Fam Med 1998;7(6):554-8.

99. Hansotia P, Broste SK. The effect of epilepsy or diabetes mellitus on the risk of automobile accidents. N Engl J Med 1991;324(1):22-6.

100. Haymes SA, Leblanc RP, Nicolela MT, Chiasson LA, Chauhan BC. Risk of falls and motor vehicle collisions in glaucoma. Invest Ophthalmol Vis Sci 2007;48(3):1149-55.

101. Hours M, Fort E, Charnay P, Bernard M, Martin JL, Boisson D, et al. Diseases, consumption of medicines and responsibility for a road crash: a case-control study. Accid Anal Prev 2008;40(5):1789-96.

102. Karakontaki F, Gennimata S-A, Palamidas AF, Anagnostakos T, Kosmas EN, Stalikas A, et al. Driving-Related Neuropsychological Performance in Stable COPD Patients. Pulmonary Medicine 2013:1-10.

103. Koepsell TD, Wolf ME, McCloskey L, Buchner DM, Louie D. Medical conditions and motor vehicle collision injuries in older adults. Journal of the American Geriatrics Society 1994;42(7):695-700.

104. Lings S, Dupont E. Driving with Parkinson's disease. A controlled laboratory investigation. Acta Neurologica Scandinavica 1992;86(1):33-39.

105. Lundqvist A, Gerdle B, Rönnberg J. Neuropsychological aspects of driving after a stroke—in the simulator and on the road. Applied Cognitive Psychology 2000;14(2):135-150.

106. McGwin G, Jr., Sims RV, Pulley L, Roseman JM. Diabetes and automobile crashes in the elderly. A population-based case-control study. Diabetes Care 1999;22(2):220-7.

107. Mulgrew AT, Nasvadi G, Butt A, Cheema R, Fox N, Fleetham JA, et al. Risk and severity of motor vehicle crashes in patients with obstructive sleep apnoea/hypopnoea. Thorax 2008;63(6):536-541.

108. Owsley C, McGwin Jr G, Sloane M, Wells J, Stalvey BT, Gauthreaux S. Impact of cataract surgery on motor vehicle crash involvement by older adults. Journal of the American Medical Association 2002;288(7):841-849.

109. Owsley C, Stalvey B, Wells J, Sloane ME. Older Drivers and Cataract: Driving Habits and Crash Risk. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 1999;54(4):M203-M211.

110. Redelmeier DA, Kenshole AB, Ray JG. Motor vehicle crashes in diabetic patients with tight glycemic control: A population-based case control analysis. PLoS Medicine 2009;6(12).

111. Redelmeier DA, Zung JD, Thiruchelvam D, Tibshirani RJ. Fibromyalgia and the Risk of a Subsequent Motor Vehicle Crash. The Journal of Rheumatology 2015;42(8):1502-1510.

112. Sagberg F. Driver health and crash involvement: a case-control study. Accid Anal Prev 2006;38(1):28-34.

113. Signorovitch JE, Macaulay D, Diener M, Yan Y, Wu EQ, Gruenberger JB, et al. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. Diabetes Obes Metab 2013;15(4):335-41.

114. Stewart RB, Moore MT, Marks RG, May FE, Hale WE. Driving accidents in the elderly: an analysis of symptoms, diseases, and medications. Journal of Geriatric Drug Therapy 1993;8(2):31-44.

115. Wingen M, Ramaekers JG, Schmitt JAJ. Driving impairment in depressed patients receiving long-term antidepressant treatment. Psychopharmacology 2006;188(1):84-91.

116. Innes KE, Selfe TK, Khalsa DS, Kandati S. Meditation and Music Improve Memory and Cognitive Function in Adults with Subjective Cognitive Decline: A Pilot Randomized Controlled Trial. J Alzheimers Dis. 2017; 56:899-916.

117. Jongen S, Vuurman EF, Ramaekers JG, Vermeeren A. The sensitivity of laboratory tests assessing driving related skills to dose-related impairment of alcohol: A literature review. Accid Anal Prev 2016;89:31-48.

118. Brunet JF, Dagenais D, Therrien M, Gartenberg D, Forest G. Validation of sleep-2-Peak: A smartphone application that can detect fatigue-related changes in reaction times during sleep deprivation. Behav Res Methods 2017;49(4):1460-1469.

119. Deary IJ, Liewald D, Nissan J. A free, easy-to-use, computer-based simple and four-choice reaction time programme: the Deary-Liewald reaction time task. Behav Res Methods 2011;43(1):258-268.

120. Vickers AJ. How to randomize. J Soc Integr Oncol. 2006; 4:194-8.

121. Bhattacharyya S, Wilson R, Appiah-Kusi E, O'Neill A, Brammer M, Perez J, et al. Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. JAMA Psychiatry. 2018; 75:1107-17.

122. Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacol. 2018; 235:1923-32.

123. Hundal H, Lister R, Evans N, Antley A, Englund A, Murray RM, et al. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. J Psychopharmacol. 2018; 32:276-82.

124. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42(4):327-360.

125. Klüver M, Herrigel C, Preuß S, Schoener H-P, Hecht H. Comparing the Incidence of Simulator Sickness in Five Different Driving Simulators. Presented at Max Planck Institute for Biological Cybernetics, Tübingen, Germany; Sep 2015.

126. Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials. 2000; 21:167-89.

127. Nielsen SF. Proper and improper multiple imputation. Int Stat Rev. 2003; 71:593-607.

128. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clin Trials. 2004; 1:368-76.

129. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: how to analyze and what to report. CMAJ. 2014; 186:1153-7.

130. Vickers AJ. Parametric versus non-parametric statistics in the analysis of randomized trials with non-normally distributed data. BMC Med Res Methodol. 2005; 5:35.

131. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007; 39:175-91.

Key Information for:
The effects of cannabidiol (CBD) on the driving ability of healthy adults

You are being asked to participate in the research described below. This page provides key information that may help you to make this decision; more detailed information can be found after this section.

Why is this research being done and what is involved?

The purpose of this study is to determine whether cannabidiol (CBD) impacts the driving ability, cognition, and drowsiness of healthy adults' aged 18-30 years. You will be asked to answer several questions about your current health and provide a urine sample which will be analyzed immediately on site for any drugs which may influence your performance. If you meet the study criteria and your urine sample is negative, you will then be asked to complete a practice drive on a driving simulator for about 10 minutes. The driving simulator is set up to mimic a car—it has breaks, an accelerator, controls, and steering wheel, along with a computer screen. You will be asked to drive a course on the simulator and follow the rules of the road (i.e., follow speed limits, use turn signals, obey traffic control devices, etc.). You will then complete a brief survey inquiring about your driving habits and health history including body mass index where you may need to be weighed. You will then complete 5 brief cognitive tests using a computer tablet and pen/paper. You will then be randomized to receive either CBD or placebo and given food and a beverage to drink. You will then wait 120 minutes where you are free to relax, read, play on the internet, etc. You will then complete a longer driving simulation (~25-35 minutes). After the second simulation, you will retake the 5 computer or pen/paper tests and an end of study survey. These activities will take approximately 4-4.5 hours of your time.

Do I have to participate and what are the risks involved?

Participation in this research study is completely voluntary and you are free to withdraw from the research at any time. If you do not wish to participate, please discuss alternatives with the researcher or refer to the "Alternatives" section in the consent form. You may or may not directly benefit from participating in this research.

Risks from participation in this study include side effects from the CBD which could include liver injury, gastrointestinal changes, mood disturbances (i.e. drowsiness, sedation, anger, agitation), sleep disturbances, hypersensitivity reactions, and male reproductive toxicity. You could also potentially experience mild nausea or dizziness from the driving simulator. Also, we will be collecting health and driving information, which some may find invasive.

Who can I talk to if I have questions or concerns?

If you have any questions or concerns about this research or would want to withdrawal from the study, you can contact Dr. Toni Marie Rudisill at 717-817-3028 from the Dept. of Epidemiology at West Virginia University.

For more information, please see the Informed Consent Form

Informed Consent for Research | Minimal Risk

Principal Investigator (PI) | Toni Marie Rudisill, MS, PhD

Department | Epidemiology

Co-Investigator(s) | Drs. Gordon Smith, Karen (Kim) Innes, Sijin Wen, Treah Haggerty

Sponsor or Funding Source | West Virginia Clinical and Translational Science Institute

WVU IRB Protocol # | 2007073792

Study Title | The effects of cannabidiol (CBD) on the driving ability of healthy adults: a clinical trial

Introduction

You, _____, have been asked to participate in this research study, which has been explained to you by _____. This study is being conducted by Dr. Toni Marie Rudisill, MS, PhD in the Department of Epidemiology at West Virginia University, along with Drs. Gordon Smith, MB ChB, MPH, Karen (Kim) Innes, PhD, MSPH, Sijin Wen MA, MS, PhD, and Treah Haggerty, MD, MS. Funding for this research is provided by the West Virginia Clinical and Translational Science Institute.

Purpose

The purpose of this study is to determine whether CBD impacts healthy adults' aged 18-30 years ability to drive and whether CBD impacts their cognition and/or makes them drowsy. WVU expects to enroll approximately 40 subjects at the WVU campus. A total of approximately 40 subjects, at all sites, are expected to participate in this study.

Description of Procedures

This study involves a urine drug screen, 3 brief surveys, 5 cognitive tests (to be taken twice), and two short drives on the driving simulator (~10 and 25-35 minutes) and will take approximately 4-4.5 hours of time in one visit in total to complete.

First, you will be asked to answer several questions about your current health status (i.e., first survey). This is done to ensure you meet the study requirements. You are able to see these questions prior to signing the consent form. You do not need to answer each question.

Second, you will provide a urine sample which will be analyzed immediately on site for drugs that may impair driving performance and/or cognition. This is done to ensure that any drugs you may have taken will not influence your performance on the activities you are asked to perform.

If you meet the study criteria and your urine sample is negative for potentially impairing drugs, you will then be asked to complete a practice drive on the driving simulator for approximately 10 minutes. People who are prone to motion sickness sometimes experience brief mild nausea or dizziness when operating a driving simulator, which is known as simulator sickness. This practice drive helps ensure that you do not experience simulator sickness and can complete the study requirements. The practice drive will also familiarize you with the equipment. The driving simulator is set up to mimic a car—it has breaks, an accelerator, controls, and steering wheel, along with a computer

screen. You will be asked to drive a course on the simulator and follow the rules of the road (i.e., follow speed limits, use turn signals, obey traffic control devices, etc.).

If you do not experience simulator sickness on the practice drive, you will then complete a brief survey inquiring about your driving habits and health history (second survey). This survey will also ask you about your height and weight so you may need to be weighed. You are able to see these questions prior to signing the consent form. You do not need to answer each question.

You will then complete 5 cognitive tests using a computer tablet and pen/paper: the Sanford Sleepiness Scale (SSS), the Visual Analog Mood Scale (VAMS), Digital Symbol Substitution Test (DSST), Trail Making Test (TMT), Simple Reaction Time (SRT), and Psychomotor Vigilance Test (PVT). These are done to gather your baseline cognitive function. The first test is the SSS, which is one multiple choice question regarding your current level of sleepiness. The second test is the VAMS which assesses mood, mental and physical sedation; this test is 16 multiple choice questions in length. The DSST and TMT are tests administered by paper and pencil. The DSST measures psychomotor speed, attention and working memory by requiring participants to translate numbers into symbols; the test is scored by the degree of completion and accuracy over a timed 90 second period. The TMT measures executive function and consists of two parts; the first part requires participants to connect numbers in ascending order, while the second part requires individuals to connect numbers and letters in sequence. The test is scored by the time it takes to accurately complete each test. Increases in time correlate with greater impairment. The SRT will be administered on a computer tablet and it measures reaction time, general alertness, and motor speed through delivery of a stimulus. During the test, a specific object will randomly appear on the tablet screen and a participant will have to select a button to acknowledge their response. The program will record response time to the stimulus, correct responses, as well as errors of omission. The PVT will be administered on a computer tablet and it will assess alertness and vigilance. The participants will have to respond to an object on the screen as quickly and accurately as possible. The program will record response time to the stimulus, correct responses, errors of omission, and false starts.

After completing the cognitive testing, you will be randomized to receive CBD oil or placebo. You will then be given food and a beverage to drink. You will then wait 120 minutes where you are free to relax, read, play on the internet, etc. This will allow the CBD to be absorbed in your system and/or take effect.

You will then complete a longer driving simulation (25-35 minutes). This time frame includes a practice drive and brake reaction time assessment. The second driving simulation will be similar to the first, but will be longer in length. You will be asked to drive a course on the simulator and follow the rules of the road (i.e., follow speed limits, use turn signals, obey traffic control devices, etc.), avoid objects, and pass slower vehicles/objects. The second simulation is scored and will assess your driving performance.

After the second simulation, you will retake the 5 computer or pen/paper tests (i.e., SSS, VAMS, DSST, PVT, SRT, TMT). This is to assess your cognitive function after you may have received CBD.

Finally, you will complete a brief end of study survey (third survey). This is to gauge you thoughts on the study and see if you can identify what study drug you received (i.e., placebo or CBD). You are able to see these questions prior to signing the consent form. You do not need to answer each question.

All these activities, in total, will take approximately 4-4.5 hours of your time and will be completed in one day.

For patient safety purposes, Dr. Treah Haggerty, MD, MS (Co-Investigator) is a licensed family medicine physician in WV and will be available during testing and up to 24 hours post testing for study participants to consult with should they have any medical questions or health concerns regarding this research study. You must first call Dr. Toni Marie Rudisill at 717-817-3028 who will then connect you with Dr. Haggerty. While CBD has a half-life of 17 hours, we ask that you refrain from driving for 24 hours post-testing. We also require that you have an

individual take you home after the testing is completed. If you do not have an individual available, you will be taken home by study personnel.

Risks and Discomforts

There are some potential risks and discomforts that you could experience if you choose to participate in this study. The first concern may be the small risk of a data breach. However, this should be minimal as participants will be assigned a study identification number. All other data will be stored on a secure virtual environment maintained by WVU's Information Technology department that only study personnel will have access to. A second minimal concern is momentary motion sickness from the driving simulator (e.g., simulator sickness); some individuals who are prone to motion sickness may report feeling brief nausea or dizziness from the simulator. It generally clears when the simulation is stopped. If participants experience this, the trial will stop immediately. The third risk involves the CBD itself. CBD comes from the *Cannabis Sativa* plant that must have <0.3% delta-9-tetrahydrocannabinol (THC) by federal law. THC is the psychoactive component of Cannabis. Thus, the CBD oil can contain very trace amounts of THC; thus, it is theoretically possible that an individual could test positive for THC/marijuana on an administered drug test. The CBD oil obtained for this study was obtained from Zatural, a CBD manufacturer from Eden, Idaho. Zatural does attempt to remove THC from their product. The CBD oil has been tested by Botanacor Laboratories (Denver, CO) for microbials, potency, heavy metals, trace THC, pesticides, and residual solvents to ensure purity, label accuracy, compliance, and safety. Testing of the product has shown that it is free of microbials, heavy metals, pesticides, and residual solvents. Potency tests have shown that the concentration of CBD is accurate and that THC and THCa (a chemical precursor of THC) were not detected by this test's level of quantitation. Trace THC tests, which have a very low level of quantitation (i.e., 0.001%), detected no THCa, and 0.006% THC, which is well below acceptable limits (legal limit is 0.3%). Copies of laboratory reports are available for your review. There are additional minimal risks with the CBD itself. Very little research exists on the effects of CBD even though it is a legal product. CBD may increase ocular pressure; thus, you will be excluded from the study if you have glaucoma. The CBD used in this study is a nutraceutical and it is not regulated by the United States Food and Drug Administration. The United States Food and Drug Administration does regulate Epidiolex, which is the prescription version of CBD oil prescribed to treat seizure disorders. According to the package insert for Epidiolex (available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf) and the United States Food and Drug Administration website (available at: https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis), several side effects of prescription CBD oil have been noted and could potentially harm participants. Prescription CBD oil can cause liver injury/hepatic dysfunction by elevating liver enzymes such as alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). Prescription CBD oil can interact with other drugs or alcohol the participant may be taking potentially resulting in serious side effects. Mainly, using CBD oil with alcohol or other drugs, especially those used to treat anxiety, panic, stress, or sleep disorders, could slow brain activity, and increase the risk of sedation and/or drowsiness, which could lead to injury. Prescription CBD oil has also been shown to impact the gastrointestinal tract with side effects such as decreased appetite, diarrhea, weight loss, gastroenteritis, and abdominal pain/discomfort. Prescription CBD oil has also been shown to affect the nervous system and cause somnolence (drowsiness or sleepiness), lethargy, fatigue, malaise, insomnia, poor sleep quality, irritability, agitation, aggression, anger, drooling, or gait disturbances. Anti-epileptic drugs, such as prescription CBD oil, have been associated with suicidal behavior and/or suicide ideation. Prescription CBD oil has also caused hypersensitivity reactions, rashes, hypoxia, respiratory failure, and infection. Studies in animals exposed to CBD oil have also shown male reproductive toxicity, or damage to fertility in males or male off-spring of women who have been exposed to CBD oil. For this study, we are using 300 mg of CBD which is a relatively small dose. This dosage was chosen as it has been used in other studies consisting of both healthy and clinical populations and is generally well-tolerated with no major adverse events; most studies use 150-600 mg, while some have used >1,200

mg. We strongly advise that you do not operate a motor vehicle/drive for 24 hours after your participation in this study. Lastly, we will also be asking you about your driving and health history such as whether you have any chronic illnesses, number of motor vehicle collisions, number of speeding tickets, whether you use seat belts when you drive, etc. While most participants will find these questions non-invasive, should you need counseling as a result, we encourage you to contact the WVU Carruth Center at 304-293-4431.

In addition, there is always the risk of uncommon or previously unknown side effect(s) or event.

Alternatives

You do not have to participate in this study.

Benefits

You may or may not directly benefit from participating in this research. The knowledge gained from this study may eventually benefit others.

Financial Considerations

You will be paid a $50 gift card for completing this study. You can earn up to $50.

Your information may be provided to the appropriate parties for billing and/or payment purposes. Please be advised that any compensation received for participation in a research study, including a gift card, is considered taxable income, and must be reported to the Internal Revenue Service (IRS).

If you are a WVU employee or a WVU student-employee, you are required to report the total amount of compensation received for your participation in a research study to the WVU Tax Services Office upon receipt of payment.

Your data, health information, research results, specimens, or any and all other information related to this research study used in this research study may contribute to a new discovery or treatment. In some instances, your data, your health information, your research results, your specimens, these discoveries or treatments, or any other information related to this research study, even if identifiers are removed, may be of commercial value and may be sold, patented, or licensed by the investigators and West Virginia University for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money or commercial profit that the investigators, West Virginia University, or their agents may realize.

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or federal regulatory authorities, including the Food and Drug Administration (FDA), without your additional consent.

In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases, mandatory reporting of information about behavior that is imminently dangerous to you or to others, such as suicide, child abuse, etc.

In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent.

Participant's information or biospecimen collected as part of the research, even if identifiers are removed, will not be used, or distributed for future research studies.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

HIPAA Authorization

We know that information about your health is private. We are dedicated to protecting the privacy of that information. Because of this promise, we must get your written authorization (permission) before we may use or disclose your protected health information or share it with others.

You can decide to sign or not to sign this authorization section. However, if you choose not to sign this authorization, you will not be able to take part in the research study. Whatever choice you make about this research study will not have an effect on your access to medical care.

Persons/Organizations Providing the Information

Patient /West Virginia University Hospitals/ WVU Medicine

Persons/Organizations Receiving the Information

- The research site(s) carrying out this study. This includes UHA or UHA Affiliates, WVU, WVU Hospitals, West Virginia University Health System (WVUHS). It also includes each site's research and medical staff.
- Health care providers who provide services to you as part of this research study.
- Laboratories and other people and groups that look into your health information as part of this study in agreement with the study protocol.
- The members and staff of any institutional review board that oversees this research study.
- The West Virginia University Office of Human Research Protection and the West Virginia University Office of Sponsored Programs.

The Following Information Will Be Used

Information from your existing medical records, and new information about you that is created or collected during this study, such as: laboratory results, demographic data, and study forms.

The Information is Being Disclosed for the Following Reasons

- Review of your data for quality assurance purposes
- Publication of study results (without identifying you)
- Other research purposes such as reviewing the safety or effectiveness of the study drug and other products or therapies; conducting performance reviews of the study drug; evaluating other products or therapies for patients; developing a better understanding of disease; improving the design of future clinical trials.

You may Cancel this Authorization at Any Time by Writing to the Principal Investigator

Dr. Toni Marie Rudisill
West Virginia University School of Public Health
PO BOX 9190
Morgantown, WV 26506

If you cancel this authorization, any information that was collected already for this study cannot be withdrawn. Once information is disclosed, according to this authorization, the recipient may re-disclose it and then the information may no longer be protected by federal regulations.

This authorization will expire at the end of the study unless you cancel it before that time.

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time. If you choose to withdraw your participation from the study, the data collected on you up until that time remains a part of the study database and may not be removed. No additional information will be added to the study database after your withdrawal.

Refusal to participate or withdraw will not affect your class standing or grades and will involve no penalty to you. Refusal to participate or withdraw will not affect your employee status at West Virginia University. Refusal to participate or withdraw will not affect your future care or status at West Virginia University.

In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation. Individual research results will not be disclosed to subjects.

Contact Persons

If you have any questions, concerns, or complaints about this research, you can contact Dr. Toni Marie Rudisill at 717-817-3028.

If you are hurt from being in this research, you should contact Dr. Toni Marie Rudisill at 717-817-3028. If injury occurs outside of business hours and is related to your participation in this research, please contact Dr. Toni Marie Rudisill at 717-817-3028.

For information regarding your rights as a participant in research or to talk about the research, contact the WVU Office of Human Research Protection (OHRP) at (304) 293-7073 or by email at IRB@mail.wvu.edu.

Future Contact

Future research may be conducted for which you are eligible. If you are interested in being contacted for future research, please indicate so by completing this section.

☐ Yes, I want to be contacted if future research studies, for which I am qualified, become available.

☐ No, I **do not** want to be contacted if future research studies, for which I am qualified.

Signatures and Authorization

You have been given the opportunity to ask questions about the research and your authorization of HIPAA, and you have received answers concerning areas you did not understand. Upon signing this form, you will receive a copy.

Participant Signature

I willingly consent to participate in this research.

Signature of Subject or Subject's Legal Representative

Printed Name Date

Consenting Individual Signature

The participant has had the opportunity to have questions addressed. The participant willingly agrees to be in the study.

Signature of Person Obtaining Informed Consent

Printed Name Date