Effects of Cannabis on Cognition and Endocannabinoid Levels in Bipolar Disorder Patients and Healthy Volunteers NCT04231643

Informed Consent Form 4/27/2023

University of California, San Diego
Consent to Act as a Research Subject

A RANDOMIZED CONTROLLED TRIAL OF CANNABIS IN BIPOLAR DISORDER PATIENTS AND HEALTHY VOLUNTEERS EVALUATING COGNITION AND ENDOCANNABINOID LEVELS

William Perry PhD, David Grelotti MD, and their colleagues are conducting a research study to find out more about cannabis and its effect on thinking in people with bipolar disorder. You have been asked to participate in this research study because you either have been diagnosed with bipolar disorder or have no psychiatric diagnosis. There will be 144 participants recruited. This research study is funded by the National Institutes of Health.

The purpose of the research study is to determine (1) the effect of Δ9-tetrahydrocannabinol (Δ9-THC)on thinking and (2) the relationship between Δ9-THC and brain neurotransmitters called endocannabinoids. Δ9-THC is a major component that makes up cannabis, also known as marijuana. Δ9-THC is often called the "psychoactive" chemical in cannabis because it is responsible for the "high" feeling people can experience when they use cannabis.

If you agree and qualify to be in this research study you will have 2 visits, upon a mutually agreeable scheduling of your visits. During visit 1 a Screening Evaluation will be done initially to see if you meet the criteria to be in the research study. If found eligible during the Screening Evaluation and if you agree, you will then come in for a 7 hour Experimental Visit. All components of the research study are research related and not part of clinical care. All visits will take place at the UCSD Medical Center at 200 West Arbor Drive, San Diego, CA 92013, in two of our laboratories: Center for Medicinal Cannabis Research (CMCR) center at 220 Dickinson St and our other laboratory nearby at 140 West Arbor Drive.

What the Research study Drug is, What the research study drug is for, and How the research study drug works

If you agree to come in for the experimental visit, you will swallow a capsule that contains either placebo or cannabis that contains Δ9-THC and complete some tests. The THC drug is also known as dronabinol. Your thinking ability will be examined using computer tests. There will also be bodily fluid collections of urine, saliva, blood, and cerebrospinal fluid (CSF). CSF is obtained via lumbar puncture (spinal tap).

If you agree to participate in this research study, the following will happen:

Screening/Baseline Visit

The following information will be obtained to find out if you can be in the research study:

- **Health Status:** A research associate will ask you about your general health status. You may not participate in this research study if you have any life threatening or significant disease or medical condition.
- **Physical exam:** You will have a brief physical examination, similar to those done for regular medical care. You will be asked to give a urine and saliva sample to detect the use of drugs, and a machine like a breathalyzer to detect use of drugs of abuse. This machine uses saliva collected by a "Q-tip" like device. The research

study requires that you have a history of cannabis use but, if you are currently using cannabis, you are not using more than 4 times a month. We also ask that you not use cannabis for the two days prior to the experimental visit (described below). It also requires that you are not currently using illegal drugs. You may be asked to provide a blood sample to test for diseases such as liver and kidney disease.

- **Pregnancy testing:** Because the drug in this research study can affect a fetus, pregnant women may not participate in this research study. If you are a female of childbearing potential, a pregnancy test will be done to make sure you are not pregnant. You may not participate in this research study if you are pregnant or lactating, or if you do not agree to prevent pregnancy.
- **Psychiatric diagnosis and mood evaluation:** You will be asked questions about your substance use, including history of cannabis use, and psychiatric history and about your current mood state (including depression).
- **Vocabulary test:** You will do a 15-minute test where you will be asked to name objects in drawings.

Experimental Visit

During the experimental visit, you will again be asked to provide a urine and saliva sample to detect use of drugs. If these tests indicate that you have recently used illegal drugs or have used cannabis in the last two days, the rest of your visit will be cancelled for the day and you will be given the option to reschedule. You will also be asked to answer questions ask you about feelings and behaviors that you may have had recently or in the past (1 hr 15 minutes).

You will then be asked to swallow a capsule that contain one of 2 drugs: a placebo (an inactive substance) or 5 mg of Δ9-THC also known as dronabinol. Neither you nor the research team will know whether you will be receiving the THC or placebo. The drug you receive will be assigned randomly, like the flip of a coin. The size of the capsule is 8 millimeters.

Tests:

Some of the tests will take place at the CMCR, where you will swallow the drug. Other tests will take place at our laboratory on Arbor Drive, which is a 10-minute walk away from the CMCR. If you are feeling dizzy, faint, or lightheaded you may be asked to sit in a wheelchair for the travel back and forth between laboratories. Research staff will always go with you.

You will fill out some questions about how you are feeling, your sleepiness level, and your mood. You will be asked to stay awake. About 2 hours after taking the drug, you will take some problem-solving tests on the computer, where you will be asked to click a mouse when certain objects appear on the computer screen, choose from decks of cards, judge periods of time as short or long, and move a joystick in a circle. These computer tests will take about 50 minutes. Later in the day you will be asked two questions about how the drug made you feel.

You will put on a strap that fits around your chest that has electrodes inside it that measure the movements of your body. Electrodes are small, round metal objects that, when placed close to your skin, can measure how your muscles work. You will be asked to wear the strap for approximately 1 hour.

During a portion of time that you are participating in the research study, your activities may be recorded with a video camera for about 15 minutes. The video recording is done to make sure

that you are safe at all times, and also to measure your activity and behavior, which tells us about how the brain solves problems. The video recording will only happen if you sign a separate consent form describing the video recording. The video recording will typically only be seen by research study personnel. The video recording might be presented at a scientific conference. The video recording of you will be altered so that your face will be blacked out or pixelated before anyone outside of study personnel can view it.

Your hearing will be measured while you listen to sounds over headphones for 5 minutes. Then, two electrodes may be placed next to each eye so that your blink reflex can be measured. You may be asked to listen to a series of tones for approximately 25 minutes. Some of the tones you hear will be so loud that you might find them annoying or uncomfortable.

Blood Pressure, Heart Rate, and Breathing Rate: You will have these measurements taken several times just to insure that they remain normal.

Lumbar Puncture/Spinal Tap (approximately 30 minutes): You will be asked to undergo a lumbar puncture (spinal tap) for examination of your spinal fluid. A lumbar puncture involves a doctor or nurse inserting a needle through the spaces between your backbone to take fluid (approximately 2 tablespoons) from the sac surrounding your spinal cord. This procedure takes about 30 minutes to complete. We will be measuring three biological markers in your spinal fluid that will inform us about the function and activity of neurotransmitter activity in your brain that could relate to your behavior.

Blood Draw Collection (approximately 10 minutes): From a needle inserted into your arm, blood will be drawn to get another measure of the biological markers. The total amount of blood that will be drawn will be 7 tablespoons.

Blood, saliva, and spinal fluid collected will be used for research and are not a part of your clinical care. These fluids will be used for research analysis and stored for future use and may also be used to isolate your DNA (the genetic material inside your cells). Fluid samples and data derived from their analysis as well as data collected in the course of the research study are banked and may be sent to other research scientists anonymously (without identifying you).

Questions about Symptoms: After the lumbar puncture and blood draw, you will be asked to answer some questions about your mood, anxiety, sadness, and sleepiness. These will take about 30 minutes.

At the conclusion of the Experimental Visit, you need to arrange for a responsible adult to drive you home or we will provide taxi service. Please be aware that you should not drive or operate heavy machinery for the remainder of the day. We ask that you remain onsite for at least 7 hours after you have taken the drug. If you cannot stay for the 7 hours, do not participate in this research study.

PARTICIPATION IN OTHER STUDIES

The samples collected and results of your interviews, exams and/or other tests will be available to other investigators conducting IRB approved research. This information may be used only to determine if you are eligible for other related studies that Drs. Perry and Grelotti or their associates are conducting. Data and samples will be provided without identifying you – only select personnel will have access to your contact information and will inform you about studies for which you may be eligible. Whether or not you choose to become involved in those studies will not affect your continued involvement in this research study. If you decide to enroll in other research studies, you will sign a separate consent form. Your data (samples, interviews, tests) from this research study will not be used as part of the other research study's data if you do not consent to the other research study. Note that if you choose to participate in other research studies conducted by Drs. Perry and Grelotti and their associates, data collected during those assessments or procedures may be shared with this research study. There is no additional compensation when data is shared among studies.

☐ YES, you would like to be considered for other studies.

☐ NO, you do not want to be considered for other studies.

METHODS FOR CONTACTING AND LOCATING YOU

You will be asked to provide information that will help us locate you in the future to follow up with you about this research study or inquire about your interest in other studies. This information may include your contact information and information about others who might be able to locate you in the future. You can choose which information to provide. We will use the information provided by you as well as publicly available methods (e.g. internet search) to locate you as needed. All contact information we collect will remain confidential.

COMPENSATION

You will receive compensation at each visit based on the following schedule:

Screening Visit $40

Experimental Visit..... $100

* If you are unable to complete the entire Experimental Visit, we will prorate your compensation at $20 per hour.

Lumbar Puncture……..$100

In addition, you have the chance to earn an extra $5 depending on how much you complete one of the computer tests.

There is no cost to you for participation in this research study.

RISKS AND DISCOMFORTS

If you take part in this research study, you may have some added risks or discomfort. These include:

Likely

- difficulties with your balance
- increased heart rate
- possible low blood pressure
- reversible problems with your appetite

Less Likely

- some change in your mood (good or bad)
- loss of memory
- decreased ability to concentrate or think properly

Rare But Serious

- dizziness
- head and chest pressure
- disorientation
- agitation
- combativeness
- incoherence
- visual hallucinations
- panic attacks

1. **Physical harm:**
   Blood Draw- There may be some discomfort when blood samples are taken, and there is a small risk of bruising, infection, or inflammation, bleeding, faintness at the site at which the needle is inserted.
   Lumbar Puncture- There is a risk of pain, bruising, bleeding, infection, fainting or headache from the lumbar puncture. To minimize these risks, you may be asked to lie flat briefly following the procedure, with your feet slightly elevated, and to drink plenty of liquids. Some participants may experience nausea or lightheadedness. If you should develop a headache, you may be prescribed mild pain killers. Headaches are uncommon and bleeding and infection are extremely rare. Occasionally headaches may be prolonged for more than 2-3 days and require a procedure called a blood patch. A blood patch involves injection of your own blood into the same area as the lumbar puncture to stop the leaking of spinal fluid. It is the loss of this fluid that causes the lumbar puncture headache. Injury to nerves is a possible, though rare, complication of lumbar puncture. Nerve injury can cause problems such as pain, muscle weakness, or loss of sensation. The research clinicians performing the procedure have been trained to take precautions to avoid injuring your nerves. If you think that you may be experiencing symptoms of nerve injury, you should call the research clinicians, who will evaluate your condition and arrange any necessary care.
2. **Psychological harm:** Mental and/or emotional distress may result from questions asked during assessment or as a result of the time taken in the assessment process. Additionally, some tests may require concentrated effort and may be frustrating for you to complete. We are required to inform you (by the Research Advisory Panel of California) that there is a small risk of abuse and dependence (addiction) from using cannabis.
3. **Legal harm:** We will be asking sensitive questions about use of marijuana. Access to such material for legitimate research purposes is generally acceptable, as long as the researcher protects the confidentiality of that information. We will use all available

methods to ensure confidentiality, including a Certificate of Confidentiality from the National Institute of Drug Abuse.

4. **Social harm:** Invasions of privacy and breaches of confidentiality may result in embarrassment within one's business or social group. Every effort will be made to maintain confidentiality of your participation to lessen this type of risk.
5. **Economic harm:** Eligibility for insurance, political campaigns, and standing in the community are problems may result from loss of confidentiality. Consuming marijuana may hinder application for future employment, if drug screening is a condition of employment. It is likely that detectable traces of marijuana will remain in your hair or blood for a minimum of six weeks after using marijuana. If applicable, a letter will be written to your employer explaining your participation in this research study and the dates of your participation.
6. **Reproductive risks:** The procedures in this research are known to harm a fetus in the following ways: poor educational attainment. You should not become pregnant or father a baby while on this research study because the drugs in this research study can affect an unborn baby. Women should not breastfeed a baby while on this research study. It is important to understand that you should prevent pregnancy while on this research study.
7. **Unknown Risks:** The experimental tests may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the research study.

BENEFITS

You will not receive any direct benefit from participating in this research study. The new knowledge gained may help others in the future. The new scientific knowledge gained may help others in society in the future.

UNFORESEEABLE RISKS

There may be some risks that are not currently known. If the research study doctor learns of any new risks during the course of this research study, you will be notified immediately.

WHAT IF YOU ARE INJURED AS A DIRECT RESULT OF BEING IN THIS RESEARCH STUDY?

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

ALTERNATIVE TO PARTICIPATING IN THIS RESEARCH STUDY

The alternative to participating in this research study is to choose not to participate.

NEW FINDINGS

You will be told of any new, relevant information that comes out while you are in this research study that might lead you to change your mind about staying in the research study. At the end

of the research study, you will be told when research study results may be available and how you can find out about them.

GENETIC INFORMATION

DNA, the genetic information inside your cells, is part of the blood and saliva in this research study. Your DNA, or the information from it, will be kept indefinitely, and may be used for additional research in future studies. Drs. Perry and Grelotti and their co-investigators and successors at the University of California will be responsible for deciding how your DNA and/or the information from it will be used. This DNA and/or information may have significant therapeutic or commercial value. You consent to such uses.

There will be no direct benefit to you from these tests, since you will not be provided with results or information regarding any genetic testing that might be performed.

If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to Dr. Perry or Grelotti, who will use his best efforts to stop any additional studies. However, in some cases it may be impossible to locate and stop such future research once the materials have been widely shared with other researchers.

WITHDRAWAL/ REMOVAL FROM THE RESEARCH STUDY

Participation in this research study is entirely voluntary. You may refuse or withdraw participation in this research study at any time without affecting your medical care at this institution or loss of benefits to which you are otherwise entitled. Likewise, your participation may be discontinued without your consent, if the research study is cancelled by the investigators or the sponsor, or if, in the investigator's clinical judgment, discontinuance is in your best interest.

You may be withdrawn from the research study if you fail to comply with research study procedures or do not follow the instructions given you by the research study personnel. This would include:

1. not attending research study visits
2. Urine, blood, or saliva tests indicate that you have recently used drugs including cannabis
3. not being able to swallow capsules.

There may be other reasons for declining to have you to continue to participate that have to do with your best interests in terms of your health, both medical and psychological. You might not be informed of the specific reason why your participation has been discontinued.

Drs. Perry and Grelotti should be notified of your desire to withdraw. You may also tell the research study staff of your desire to withdraw.

If you are taken off this research study for any reason, you will be notified and you will not be scheduled for any additional visits.

CONFIDENTIALITY

We will do everything we can to keep others from learning about your participation in the research. Despite careful safeguards, information regarding your history, drug use or medical

diagnosis may become known outside of the research setting. Although such an event is very unlikely, accidental disclosure of your history or medical information could be potentially damaging to your insurability, employability, and/or ability to travel.

To further help protect your privacy, a Confidentiality Certificate has been issued from the Department of Health and Human Services (DHHS).

With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of the State of California, the DHHS, the Research Advisory Panel of California, and the UCSD Human Research Protections Program for the purpose of audit or evaluation.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer, employer or other outside party, learns about your participation, and obtains your or your legal guardian's consent to receive research information, then Drs. Perry and Grelotti may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

Drs. Perry, Grelotti and the research study personnel are not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. If Drs. Perry, Grelotti, or the research study personnel determine that reporting to authorities is necessary because of imminent serious danger to yourself or others, then he would only disclose information in your records to the extent necessary to prevent such imminent danger.

Information from this research study is available only to research study investigators and authorized personnel, including the UCSD Institutional Review Board. The UCSD IRB will have access to review the research study records. 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.

To guard your privacy, only a special code number will appear on laboratory samples, questionnaires, and all records, forms, and information will be kept in locked file rooms and cabinets. Each sample is labeled with a unique sample specific ID. The data linking these sample IDs to their corresponding non-identifiable research study ID is stored in a segregated secure database. All stored samples are accessible only to the HNRP-CMCR laboratory personnel and the appropriate research study members. Samples are stored under the coded identifiers in freezers equipped with locks. In addition these freezers are located behind locked doors that require ID scan entry. The video recording of you will be altered so that your face will be blacked out or pixelated before anyone outside of study personnel can view it.

Federal and State laws, including the Genetic Information Nondiscrimination Act (GINA), generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: a) Health insurance companies and group health plans may not request your genetic information that we get from this research. b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. c) Employers with 5 or more employees may

not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

CONSENT

Dr. Perry, Dr. Grelotti and/or _____has explained the research study to you and answered all of your questions. If you have any other questions, or if you wish to report a research-related problem, you may call Drs. Perry and/or Grelotti or their associates at (619) 543-2827, or email them at cmcr@ucsd.edu or send a postal letter to them at the UC Center for Medicinal Cannabis Research, University of California, San Diego, 220 Dickinson Street, Suite B, San Diego, CA 92103.

You have received a copy of this consent form and a copy of 'The Experimental Subject's Bill of Rights' to keep. I have read this information, which is printed in English. This is a language that I read and understand.
You agree to participate.

_____
Subject's Name (Printed)

_____ _____
Subject's Signature Date