Department of Veterans Affairs

RESEARCH CONSENT FORM

VA Connecticut Healthcare System

Subject Name: _____ Date:_____

Title of Study: _Effects of allopregnanolone on stress-induced craving

Principal Investigator: __Elizabeth Ralevski, PhD_____ Version Date: _03/09/2022_

NCT04015869 Protocol ID: 2000021601

RESEARCH SUMMARY

You are invited to take part in a research study because you are between 21 and 65 years of age, have alcohol use disorder (AUD), and are not seeking treatment. This study is sponsored by Yale University. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This initial summary is to give you key information to help you decide whether to participate. Detailed information follows this brief summary. Ask the research team questions. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

We are asking you to choose whether or not to volunteer for a research study about the effects of allopregnanolone (ALLO) on the subjective effects of alcohol. ALLO is a product of the hormone progesterone and is found naturally in your body. This initial summary is to give you key information to help you decide whether to participate. We have included detailed information after this brief summary. Taking part in this study is completely voluntary.

Your participation in this research will last about two months.

If you decide to participate in this research study, you will be asked to complete a screening visit, script writing session, one test day, and 2 telephone follow-ups, one approximately one business day after the test day, and another follow up one month later. On the test day, you will be given either an intravenous ALLO infusion or placebo (saline). You will have a 1 in 2 chance of being administered ALLO, much like the probability of flipping a coin. Everyone who participates in the test day will receive an intravenous infusion of alcohol. Other study assessments include blood draws, urine drug and pregnancy tests, EKG, physical examination, interviews, questionnaires, and assessments.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You have been invited because you are between 21 and 65 years of age, have an alcohol use disorder (AUD), and are not seeking treatment. Although this study is not designed to benefit you personally, your participation may lead to knowledge that may help others.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

Administration of ALLO in humans is very novel with only a few studies being conducted to date and none in this population. The dose of ALLO selected for this study is similar to the levels found in women in their third trimester of pregnancy. Similar doses have been safely given to healthy participants in a small number of studies with minimal and transient side effects.
You may experience side effects associated with alcohol/ALLO/placebo, including sedation, alcohol-like intoxication, blurred vision, headaches, lightheadedness, mild nausea, vomiting, and

flushing. Less common side effects associated with neurosteroids, such as progesterone, and reported after long-term use include depression, anxiety, blockage of blood vessels, and increased risk for heart attack or stroke. However, since this will be the first-time alcohol/ALLO/ placebo will be given together you may experience other side effects that have not been listed but a physician and/or a nurse will be present during the laboratory session at all times to continuously monitor you.

The script development session will require you to discuss stressful experiences. These procedures are expected to cause a moderate degree of anxiety, psychological discomfort, and alcohol craving. However, it is possible that you may experience a more intense reaction. Should you experience any unpleasant symptoms; clinically-trained research staff will guide you through relaxation techniques. One of the study physicians will be prepared to provide physical and medical assistance, and will be available for further evaluation, treatment, and follow-up. If necessary, you may be referred for further evaluation and/or treatment. For a complete descriptions of risks, refer to the Research Details.

You should not participate in this study if you are pregnant or currently breastfeeding.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

RESEARCH DETAILS

WHAT IS THE PURPOSE OF THIS STUDY?

With this research we hope to learn how ALLO, compared to placebo, influences how people experience the effects of alcohol, including craving, anxiety, and stimulant/sedative effects. ALLO is not approved by the FDA as a treatment for AUD.

HOW LONG WILL YOU BE IN THE STUDY?

This research study is expected to take approximately 2 years. Your individual participation in the project will take approximately 2 months. Approximately 30 men and 30 women will complete the study.

WHAT WILL HAPPEN IF YOU TAKE PART IN THE STUDY?

Since ALLO is not an FDA approved treatment for AUD, this is an experimental study. If you decide to participate in this research study, you will be asked to participate in the following:

- Screening visit: 2-3-hour visit involving interviews, questionnaires, physical exam, EKG, blood and urine tests

- Script writing session: 2-hour visit to complete a questionnaire and discuss the most stressful event you have experienced, creation of audio tape
- Test day: 6-8-hour visit involving blood and urine tests, questionnaires, assessments, IV infusion of ALLO or placebo, tape session, IV infusion of alcohol
- Telephone follow-up 1: 10-minute follow up phone call
- Telephone follow up 2: 30-60-minute visit scheduled approximately 1-month after the test day to answer questions and a follow up survey.

WHAT IS EXPECTED OF YOU IF YOU TAKE PART IN THIS STUDY?

Screening and clinical assessments:

During the screening visit, a detailed assessment will be completed to assess your current health. You will be asked specifically about alcohol and drug use, and you will also be asked about any traumatic experiences that you may have had. In addition, we will gather information from your medical history and complete a physical assessment. As part of the physical assessment, an electrocardiogram (EKG), blood work, and drug test will be completed. Your urine will be tested for drugs of abuse (cocaine, marijuana, benzodiazepines, etc.); if you are female, a blood pregnancy test will also be performed. If your urine is positive for drugs, except marijuana, or if you are pregnant, you will not be allowed to participate in the study. All lab results will become part of your medical record at the VA. The screening will last approximately 2-3 hours and it may take one week before we receive all the test results. You will not be charged for these tests. At this point the physician in charge of the study will determine if you are eligible to participate.

At any time during the screening evaluation, or study days, your participation may be terminated without your consent if we determine that you do not meet the entry criteria, or if the study physician feels it would be harmful for you to continue participating.

You will have the option to complete part of this screening visit remotely using a VA approved telephone or video platform. If you choose this option a member of the research team will contact you to set up an appointment to go over this consent with you. If you would still like to participate in the study after reviewing the consent, we will obtain verbal consent to continue and this will be documented in your medical record. You will need to sign written consent at your first in-person study visit.

For female subjects of childbearing potential:
If you are a female subject you will have a blood pregnancy test done at screening, and you will have a urine pregnancy test when you come in for the test day. Because alcohol and ALLO both have adverse effects on the fetus, you will not be able to participate in this study if you are pregnant or breastfeeding. To your knowledge, you are not pregnant at this time. You also agree to avoid becoming pregnant. If you change your mind about becoming pregnant we ask that you tell us.

Script Development Session: During the script development session, you will be asked to recall the most stressful event that you have experienced. A questionnaire will be completed to gather specific information about this event. Stressful experiences related to substance use will not be considered. An audiotape of the event lasting approximately five minutes will then be created. We will also develop a neutral script, but this will be based on previously developed neutral scripts that will consist of a relaxed beach scene commonly experienced by most individuals but personalized for you. This appointment will take approximately 2 hours and can be done in person or by a VA approved telephone or video platform.

Since levels of ALLO fluctuate in women we will ask all female participants to call our lab when their menses start. If you are a woman, you will be scheduled for your laboratory test session within the first 4-7 days of your menstrual cycle.

Test Day: If you are eligible for the study on the basis of the screening and other clinical assessments, a member of the research team will contact you to schedule your test day, if you decide to participate.

You will be required to have a negative COVID test within 3 days of the test session. If you show proof that you are fully vaccinated you will not be required to have a COVID test prior to the test day, unless local guidelines (e.g., Yale University, VACT, the state of CT) require it at the time of your participation in the study.

For the test day, you will come to the Neurobiological Studies Unit (known as Biostudies), also located at the West Haven VA (Building 1, 9th floor) for testing. The test day will start at approximately 7:30am and will last for 6 to 8 hours. You will be asked to **arrive with no alcohol or illicit drugs (except marijuana) in your system**. Since we will provide you with a light meal, we ask that you **do not eat anything after midnight before coming in for the test day**. You can drink water before the test day. If you smoke cigarettes you can smoke cigarettes as you normally do, until you come in for the test day; you will not be able to smoke cigarettes during the test day.

When you arrive, the research nurse will take your blood pressure, pulse, and breath alcohol level and collect a urine sample that will be tested for illicit drugs. If you are a female, we will also do a urine pregnancy test. If these tests indicate that you have recently used drugs (other than marijuana) or alcohol, or that you are pregnant, you may be discharged from the study. If the study physician determines that it is unsafe for you to leave the hospital, you may be taken to the Psychiatric Emergency Room.

A thin plastic tube called an IV line will be inserted into a vein in each of your arms. Both IV lines are to permit administration of study drugs and for blood drawing. Blood will be drawn several times during the test day. Both you and the research staff will not know if you were administered ALLO or a placebo (saline) for the duration of the time that you are involved in the study. We will also take your blood pressure, and your pulse will be monitored continuously.

After the IV lines are placed, you will be asked some questions regarding the way you feel and think. You will be asked similar questions throughout the study. You will also be asked to take a computer test which involves watching a screen and pressing a button according to the instructions given to you. After completing the initial questions, administration of either ALLO or a placebo (saline) will begin.

You will then be presented with a tape that describes your most stressful event or decribes a pleasant, neutral event. You will hear the stress tape 1 time and the neutral tape 1 time in a random order. You will then be asked to complete a variety of questionnaires and computer tasks, including ones asking about your alcohol craving, anxiety, mood, and cognitive functioning.

If you experience unpleasant symptoms a few hours following tape presentation, a clinically-trained staff member will guide you through relaxation techniques. If urges to drink or emotional distress persist after an hour of relaxation training, you will then receive an individual counseling session with a psychologist who is experienced in psychotherapy. If urges to drink or emotional distress persist after the psychotherapy session, you will be escorted to the Psychiatric Emergency Department and treated by the on-call psychiatrist.

Following the tape session, you will receive alcohol (breath alcohol concentration target of 40mg %- about what is associated with approximately 2-12 oz. cans of beer in an hour for a man or 1-2 12oz cans of beer for a woman) over a 50-minute period. The alcohol will be administered through one of the IV lines that will be placed in your arm. Your breath alcohol concentration will be maintained by using a small pump that will regulate the flow of a solution containing alcohol into a vein in your arm. The infusion pump rate will be adjusted every few minutes, based on the results of the breathalyzer tests. On the test day, your breath alcohol concentration may be as high as 40mg% (Breathalyzer value of 0.04). At several points during the alcohol administration you will complete a variety of questionnaires and computer tasks, including ones asking about your alcohol craving, anxiety, mood, and cognitive functioning. You will also be asked to do these questionnaires several times after the alcohol administration is completed, until you are cleared to go home.

After the test day is completed, you will be asked to remain on the Biostudies Unit to make sure that there are no after effects of the alcohol or ALLO. A physician will examine you before you are permitted to go home. After the test day, you will be encouraged to make arrangements to be driven home. If you are driving yourself home, you will not be permitted to leave until your breathalyzer is at or below (≤) 0.02 and prior to discharge a physician will evaluate you to detect any signs of intoxication that would impair your driving ability. The option to drive yourself home is available only if there are no other methods of transportation available (e.g. public transportation, Yale shuttle, friends etc.). This must also be approved by the Principal Investigator (Elizabeth Ralevski, PhD). If you are deemed unsafe to leave due to intoxication, you may be kept against your will.

Follow-up: After your test day is complete, you will be contacted approximately 1 business day and 1 month after your last test session for a telephone interview. During the first telephone

interview you will be asked about how you have been doing since the test day. The phone interview will last approximately 10 minutes. About four weeks after your test day is completed, you will be contacted again for a 30-60-minute follow-up interview, where you will be asked questions about your drinking and how you have been doing since the test day.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF YOU TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Effects of Alcohol/ALLO/placebo: Administration of alcohol/ALLO/placebo may cause alcohol-like intoxication, blurred vision, sedation, headaches, lightheadedness, mild nausea, vomiting, and flushing. Less common side effects associated with neurosteroids, such as progesterone, and reported after long-term use include depression, anxiety, blockage of blood vessels, and increased risk for heart attack or stroke. However, since this will be the first-time alcohol/ALLO/ placebo will be given together you may experience other side effects that have not been listed but a physician and/or a nurse will be present during the laboratory session at all times to continuously monitor you.

To minimize possible injury as a result of alcohol consumption, you will be kept on the Biostudies Unit until your blood alcohol level is at a very low level (Breathalyzer at or below (≤) 0.02). For your protection, we encourage you to make arrangements to be driven home after the test day. If you do not feel comfortable and don't want to continue or the research staff feels that you are at risk the test day will be discontinued.

Stress induction: The script development session will require you to discuss stressful experiences. These procedures are expected to cause a moderate degree of anxiety, psychological discomfort, and alcohol craving. However, it is possible that you may experience a more intense reaction. Should you experience any unpleasant symptoms; clinically-trained research staff will guide you through relaxation techniques. One of the study physicians will be prepared to provide physical and medical assistance, and will be available for further evaluation, treatment, and follow-up. If necessary, you may be referred for further evaluation and/or treatment.

The Intravenous Lines and Blood Drawing: Blood drawing may cause pain, bruising, and rarely fainting or infection. There is a chance of inflammation (swelling), bruising or a blood clot forming at the site of blood sampling. Antiseptic technique will be used to minimize the risk of infection. Your blood will be drawn at your screening appointment and on your test day to provide information about your blood alcohol levels as well as other blood levels. You will have approximately 140 ml (5oz) of blood drawn over the course of this study and should refrain from blood donations eight weeks before and after testing.

Study procedures: During the test day, you may not leave the test room. At the end of the test day, you will remain in the Biostudies Unit until we are satisfied that you are in good health and your Breathalyzer is at or below (≤) 0.02. During the study, you will be asked questions related to your mental health and drug use history which may make you feel uncomfortable, sad or bored. If you feel the questions are too stressful and would like to stop the screening or test day, you may do so at any time and your participation will be terminated. In addition, you may be discontinued from the research study at any time if the study physician feels it is in your best interest to do so or if you are found to not be compliant with the study requirements (for example, if you tested positive for illicit drugs while enrolled in this study; if it becomes medically unsafe for you to participate; or, if the HSS withdraws approval).
Alcohol and ALLO both have adverse effects on the fetus, so you should not participate in this study if you are pregnant or breastfeeding.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect. Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of your usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

Taking part in this study is not designed to benefit you personally, but your participation may lead to knowledge that may help others.

HOW WILL YOUR PRIVATE INFORMATION BE PROTECTED?

Storage and Future Use of Data or Specimens:

Your information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Confidentiality of Information: Participation in research may involve a loss of privacy. Your research records will be kept as confidential as possible. Only a code number will identify your research records. The code number will not be based on any information that could be used to

identify you (for example, social security number, initials, birth date, etc.). The master list linking names to code numbers will be kept separately from the research data.

All research information will be secured in locked files. Your identity will not be revealed in any reports or publications resulting from this study. Only authorized persons will have access to the information gathered in this study. Authorized persons may include regulatory agencies such as the Food and Drug Administration, (FDA), the Government Accountability Office (GAO), the Office for Human Research Protections (OHRP), Office of Research Oversight (ORO), VA Connecticut Healthcare System Research Office, and the Yale University Human Investigation Committee (HIC). Yale Accounts Payable will have limited access to your information (printed name and signature on your cash payment receipt).

The Department of Veterans Affairs (VA) requires some information to be recorded in the VA electronic medical record for veteran and non-veteran research subjects. Therefore, if you participate in this study, a medical record will be created if you do not already have one. Notes from your visits, procedures, and laboratory tests will be included in this record. In addition to the research team, and the VA staff who provide clinical services, other researchers may be granted approval to access this information in the future. Federal laws and regulation that protect privacy of medical records will apply to your VA record.

There are exceptions to the promise of confidentiality. For example, if we see or are told that a child is being abused or neglected, or that there is a risk of harm to you or others, we will disclose this information to the proper authorities.

Certificate of Confidentiality:
We have obtained a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. The Certificate of Confidentiality will not be used to prevent disclosures to local authorities of child abuse or neglect, or harm to self or others. The Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

Medical Record
We will include information about your study participation in your medical record.

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

WHAT ARE THE COSTS TO YOU IF YOU TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

IS THERE PAYMENT TO YOU IF YOU TAKE PART IN THIS STUDY?

You will receive $30 for the screening session, $30 for the script development session, and $150 for attending the test session. Thus, the total amount that you could receive during the study is $210. This payment is for the time and effort associated with study assessments and procedures. You will not be paid if a test day is cancelled or if you test positive for alcohol or illicit drugs. Payments will be given in the form of cash at the time of your participation. If you participate in a virtual screening and are not eligible to come for the in-person visits you can choose to come in to pick up your cash payment, or be mailed a gift card or check. If you choose to receive payment by gift card or check you may need to complete a tax form.

WHAT WILL HAPPEN IF YOU ARE INJURED BECAUSE OF YOUR BEING IN THE STUDY?

If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury is due to non-compliance by a study subject with study procedures. Emergency and ongoing medical treatment will be provided as needed.

There are no plans to provide compensation for disability or other losses occurring over the long term or if an injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation.

If you have questions you can contact:

DURING THE DAY:

The VA Connecticut Research Coordinator at 203-937-3830, OR

Dr. Ralevski at 203-932-5711 x4282 and

AFTER HOURS:

The research pharmacist on call at 203-932-5711._____

Emergency and ongoing medical treatment will be provided as needed.

WHO ELSE MAY YOU CONTACT IF YOU HAVE QUESTIONS?

If you have questions about your rights as a study subject, or you want to make sure this is a valid VA study, you may contact the Chairman of the Human Studies Subcommittee at 203-932-5711 x3350.

If you have questions, complaints or concerns about the study or if you would like to obtain information or offer input you may call Dr. Ralevski at 203-932-5711 x4282.

DO YOU HAVE TO TAKE PART IN THE STUDY?

Participation in this study is voluntary. You may withdraw from this study at any time. Refusal to take part in the study, or withdrawing from the study, will involve no penalty or loss of benefits to which you are otherwise entitled.

If you are a VA employee or student, the refusal to take part in the study will in no way influence your employment, ratings, subsequent recommendations, or academic progress as applicable. You may discontinue taking part at any time without any penalty or loss of benefits.

RIGHT OF INVESTIGATOR TO TERMINATE YOUR PARTICIPATION

You may be withdrawn from the study at the discretion of the investigators if you fail to follow instruction, do not meet entry criteria, or if the study physician feels it would be harmful for you to continue participating. If you test positive for pregnancy, alcohol or illicit drugs you may be withdrawn from the study. Blood pressure and heart rate are monitored frequently during the lab session and if they exceed the safety parameters you will be terminated from the study. The investigator may continue to review the data already collected for the study (prior to your withdrawal) but cannot collect further information, except from public records, such as survival data. We do not anticipate any adverse effects on your health or welfare as a result of early termination.

WILL YOU BE TOLD NEW INFORMATION ABOUT THIS STUDY?

You and your physician will be informed of any important discoveries made during this study which may affect you, your condition, or your willingness to participate in this study. If suicidal intent or other major clinical findings are detected during clinical or research assessments, the study physician will be notified immediately. You may be held against your will until you are judged to no longer be considered a threat to yourself or to others.

RE-CONTACT

We will re-contact after the original project is complete if you are interested in the findings of this study.

Department of Veterans Affairs

RESEARCH CONSENT FORM

VA Connecticut Healthcare System

Subject Name: _____ Date:_____

Title of Study: _Effects of allopregnanolone on stress-induced craving

Principal Investigator: __Elizabeth Ralevski, PhD_____ Version Date: _03/09/2022

If you are willing to be contacted for future research by our group, please specify:

YES _____ **No**_____

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

The research staff has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study You also confirm that you have read this consent document, or it has been read to you. You will receive a copy of this consent document after you sign it.

I agree to participate in this research study as it has been explained in this document.		
_____ Subject's Name	_____ Subject's Signature	_____ Date

_____ Person Obtaining Consent	_____ Person Obtaining: Signature	_____ Date