Study Title: Neurosteroid Intervention for PTSD in Iraq/Afghanistan-era Veterans

NCT03799562

ICF Document Date: June 11, 2024

Participant Name:	**Date:**
Study Title: Neurosteroid Intervention for PTSD in Iraq/Afghanistan-Era Veterans	
Principal Investigator: Jennifer C. Naylor, PhD	**VAMC**: Durham

Please read this form carefully. It tells you important information about a **voluntary** research study. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. It is important that you understand the information on this form. If you would like to check that this study is approved by the Durham VAMC's Institutional Review Board, please call the research office at (919) 286-6926 or (888) 878-6890, extension 17-6926.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research is to determine if a medication called pregnenolone can improve symptoms of posttraumatic stress disorder (PTSD). We also want to learn whether pregnenolone can improve symptoms of depression and pain. Pregnenolone is a neurosteroid. A neurosteroid is a naturally occurring substance made in the brain, adrenal glands, and other places in the body. Recent research has shown that neurosteroid levels levels may be low in individuals with PTSD, depression, and pain disorders. It is possible that giving pregnenolone could improve symptoms of these disorders. Another purpose of this research is to measure blood levels of various small molecules (including neurosteroids) and proteins, which may be affected by the study drug and/or related to your symptoms. We are additionally interested in genetic differences that may affect response to the study medication. This research study will also evaluate if pregnenolone administration is safe and effective in Veterans with PTSD.

You are being asked to participate in this research study because you have experienced a traumatic event and have been diagnosed with PTSD. You may also have depression and/or pain symptoms. Please read this consent form carefully and take your time deciding if you wish to participate. Ask Dr. Naylor, the study physician, or study staff to discuss this consent form with you, and ask him/her to explain any words or information that you do not clearly understand. You are encouraged to talk with your family and friends before you decide to participate in this research study. The nature of the study, risks, discomforts, and other important information about the study are listed below. Please tell the study doctor or study staff if you are currently participating in another research study. If you decide to participate, Dr. Naylor or the study physician may be in contact with your regular health care provider via telephone or in person, if needed.

It is anticipated that about 90 Veterans will complete this study at the Durham VA Medical Center.

WHAT IS THE EXPERIMENTAL PART OF THIS RESEARCH STUDY?

If you consent to participate in this study, you will either receive the study drug (pregnenolone) or a sugar pill (placebo). Neither you nor your treating physician will know if you are receiving

pregnenolone or placebo until the study is completed. This is part of the research study clinical care (not part of your routine care).

WHAT PROCEDURES, DRUGS, OR TREATMENTS ARE INVOLVED IN THIS RESEARCH STUDY?

If you agree to participate in this research study, you will be interviewed first to be sure that you meet the entry requirements of this study. This study will require you to:

1. Give basic information about you, your military experiences, and your mental and physical health. You will be asked to fill out forms that ask your name, age, phone number(s), addresses, and emergency contact information. Forms will also ask your military position, dates of service, type of service, and if you took part in combat. You will also be asked about your mental and physical health.

2. Donate blood and urine. You will be asked to give about 3.5 tablespoons of blood on the first study visit. You will also be asked to give approximately 2.5 tablespoons of blood on Visits #2, 3, 4, 5 and 6. This is a total of approximately 16 tablespoons of blood over the 10-week study. Your blood will be tested for chemicals like neurosteroids, other small molecules, and proteins that may be related to brain function. Your blood and serum coming from your blood will be stored at the Durham VAMC. Some of your blood will be used for routine laboratory testing (for example, cholesterol and electrolyte levels, liver, kidney function, and others). You will also be asked to donate blood for genetic analysis (at Visit 1 only) to determine why some people may respond to the study medication and others may not. Urine will be collected at various visits for the purposes of urinalysis, drug screening, and pregnancy testing for females only.

Study Procedures: All study procedures are for research purposes only and would not be part of your usual care.

VISIT 1 (screening visit), Estimated Time: approximately 6 hours.

1. You will receive a routine physical examination and medical and psychiatric history will be obtained (including current medications).
2. You will be asked to provide blood for laboratory testing and urine for drug screening and urinalysis (to include a pregnancy test for females) . A blood sample for genetic testing (for the current study) will also be collected. The total amount of blood drawn during Visit #1 is about 3.5 tablespoons (52 ml).
3. You will receive an electrocardiogram (ECG) (to determine your heart function).
4. Your vital signs will be assessed (for example, blood pressure, heart rate, weight, height).
5. You will receive several mental health assessments (to determine symptoms of PTSD, depression and other mental health conditions) and physical assessment instruments.

6. You will receive the placebo medication (sugar pill). At some point during study participation you will be randomized to pregnenolone or will continue on placebo. Randomization means that we will use a procedure like flipping a coin, and you will have a 1 in 2 chance of receiving an inactive substance like a sugar pill (a placebo) instead of pregnenolone. Neither you, nor your treating physician will know whether you are receiving pregnenolone or placebo after randomization.

VISITS 2, 3, 4, and 5 (Estimated Time: approximately 3.5 hours)

1. You will be asked about current medications.
2. Visit 2 Only - You will receive a routine physical examination if not completed at Visit 1.
3. You will be asked to provide blood (2.5 tablespoons) for laboratory testing and urine for drug screening and urinalysis (to include a pregnancy testing for females) .
4. Your vital signs will be assessed (for example, blood pressure, heart rate, weight, height).
5. You will receive several mental health assessments (to determine symptoms of PTSD, depression and other mental health conditions) and physical assessment instruments.
6. You will receive either pregnenolone or placebo study medication.

VISIT 6 (Estimated Time: approximately 4.0 hours)

1. You will receive a routine physical examination, and will be asked about medication changes.
2. You will be asked to provide blood (2.5 tablespoons) for laboratory testing and urine for drug screening and urinalysis (to include a pregnancy testing for females) .
3. Your vital signs will be assessed (for example, blood pressure, heart rate, weight, height).
4. You receive an electrocardiogram (ECG) (to determine your heart function).
5. You will receive several mental health assessments (to determine symptoms of PTSD, depression and other mental health conditions) and physical assessment instruments.
6. You will receive verbal and written information on how to taper from the study medication.

FOLLOW UP PHONE CALLS AND TEXT MESSAGES

1. Six (6) phone calls will be scheduled over the duration of the study. Five (5) will be "check ins" during the first 10 weeks and one (1) will be a "follow up" after the study medication has ended. During these calls, you will be asked about any changes in medications and about any side potential side effects. Each call will last approximately 10-15 minutes. Additional phone calls will be made if needed.
2. You will receive appointment reminders via text message.

Permission for Digital Recording:

We would like your permission to digitally audiotape our PTSD interviews with you. These recordings of your voice will be labeled with your study ID and will be stored on a secure VA server. A trained PTSD expert will access the secure VA server to listen to some of the recorded sessions and compare

them to the written staff evaluation of your PTSD symptoms. The written evaluation will also be coded with your subject ID number and will be scanned to the same secure VA server. This process is to ensure that our staff are rating all participants consistently throughout their involvement in the study. The recorded sessions and paper versions of the PTSD assessment will only be accessible to our study staff and to the expert reviewer. The expert reviewer will not be able to identify you. None of your information will be disclosed outside of VA.

I agree for my PTSD interviews to be audiotaped: ☐ Yes ☐ No

Study Procedure Table

	Visit 1	Phone	Visit 2	Phone	Visit 3	Phone	Visit 4	Phone	Visit 5	Phone	Visit 6	Follow up Phone
	Screening											
	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
Procedures												
Informed Consent	X											
Demographics, Medical History, Mental Health Diagnosis	X											
Medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam and ECG	X										X	
Mental and Pysical Health Assessments	X		X		X		X		X		X	
Suicide Assessment	X		X		X		X		X		X	
Blood Draw and Vital Signs	X		X		X		X		X		X	
Urine Collection (tox screen/urinalysis)	X		X		X		X		X		X	
Urine pregnancy Test (females only)	X		X		X		X		X		X	
Side Effect Scale		X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication	X		X		X		X		X			

For women of childbearing age: Since this research may have bad effects on an unborn child and should not be done during pregnancy, we will give you a pregnancy test. If you are pregnant, we will withdraw you from the study. You also agree to avoid becoming pregnant during the study by using at least two effective non-hormonal forms of birth control such as a diaphragm, or intrauterine device (IUD) during this study. However, participants in this research study cannot currently be taking oral contraceptives (birth control pills or any other type of birth control that affects hormone levels).

Because this is a new drug, we do not know all of its effects. You should contact the Investigator or a member of the study team if you have any questions.

We cannot guarantee that you will be able to continue receiving this study drug after this study is over.

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Permission to Re-Contact for Future Research Studies

We would like permission to re-contact you for future research. If you answer "YES", should another study or studies become(s) available that we feel may be of interest to you, we will send you a letter in the mail about it. After a week, will contact you by phone. If you answer 'NO' below, then you will not be contacted for future research studies. Your choice to give permission to be re-contacted or not to give permission to be re-contacted will not affect your enrollment in the current study, nor your access to care at the Durham VAMC.

I agree to be re-contacted: ☐ Yes ☐ No

WHAT GENETIC TESTING IS DONE IN THIS STUDY, AND WHAT IS THE RISK?

Cells in the human body contain genes composed of deoxyribonucleic acid (DNA). The genes contain key instructions for cell function and help determine the characteristics of each individual. This information will be obtained from your blood to help researchers better understand how different individuals respond to the study drug. In order to conduct these analyses, a small portion of your blood will be moved to Duke for the analysis only. Any unused blood will be destroyed or returned to the Durham VAMC.

Potential Risks:

1. Social risks: Although unlikely, genetic testing could possibly result in genetic discrimination by employers or insurance companies (making it difficult to be employed or insured) if you have a gene mutation that causes or increases the risk of an inherited disorder. Also, any breach of confidentiality could affect reproduction plans, family relationships, immigration status, paternity suits, or stigmatization. To protect you from the possibility of discrimination, your research records will be kept confidential to the extent allowed by law. Federal Privacy Regulations provide safeguards for the privacy, security, and authorized access. VA has no policies that would deny benefits based on genetic information.

2. Psychological risks: If genetic findings are disclosed to you, psychological effects may result from learning the results of a test, learning that no effective therapy exists, or disclosing results to family members.

3. Physical risks: The risks associated with drawing your blood include the following: Pain, bruising, and rarely, fainting or infection.

4. Unknown risks: There may be unknown risks. In addition, there may be future ramifications to patients/participants or their family members that are currently unclear/unknown.

I agree to genetic testing for the current study: ☐ Yes ☐ No

CAN I REFUSE TO BE IN THIS RESEARCH STUDY OR WITHDRAW AT A LATER TIME?

Absolutely. You do not have to join this or any other research study. If you do join and later change your mind, you may quit at any time. If you withdraw from the study, no new data about you will be collected for study purposes. If you refuse to join or if you withdraw from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled. This will not affect your relationship with, or treatment by, the Veterans Health Administration (VHA) or your rights as a VHA patient. You will still receive all the medical care and benefits for which you are otherwise eligible. Please tell Dr. Naylor or the study staff if you are thinking about stopping your participation in the study or decide to stop. The study staff will tell you how to stop safely. The study staff can evaluate any risks from the study drug. Another reason to tell the study staff that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. It may be necessary for you to return for a study visit for a follow up physical examination and/or laboratory bloodwork.

WHAT OTHER OPTIONS DO I HAVE?

Taking part in this study is your choice. You have the option not to participate. If you choose not to take part in this study, your other choices may include:

- Getting no treatment
- Getting treatment without being in a study
- Getting a different experimental treatment/taking part in a different study

HOW LONG WILL I BE IN THIS RESEARCH STUDY?

The study will last 10 weeks and will also include one follow up phone call a week after the final study visit. The study will take approximately 25 hours of your time.

WHAT ARE THE RISKS AND DISCOMFORTS OF PARTICIPATING IN THIS RESEARCH STUDY?

The risks associated with drawing your blood include the following: Pain, bruising, and rarely, fainting or infection. To minimize these risks, only a qualified, experienced health professional will draw your blood.

There is a risk that some questions on questionnaires or interviews might upset you or cause psychological distress. To minimize this risk, only a trained, mental health professional will administer these questionnaires and you may refuse to answer any questions that may be upsetting for you.

There are no known severe risks that have been associated with taking pregnenolone. In prior studies, pregnenolone was very well-tolerated with few side effects. There have been rare reports of

stomach upset, headache, difficulty sleeping, irregular heartbeat, hair loss (in women), acne, and rash. The exact likelihood of your experiencing one of these side effects is currently unknown. Not all side effects of pregnenolone are known.

If you should experience any adverse effects from the study medication, you should contact Dr. Naylor at (919) 286-0411 Extension [redacted] during the day or [redacted] after hours. You may also contact Dr. Marx at (919) 286-0411 Extension [redacted] during the day or [redacted] after hours. There is the risk of a breach of your confidential information. To protect against this risk, all study records will identify you by a code corresponding to your name. Research records and will be kept locked in separate files, which will only be accessible by Dr. Naylor and the study team. The research code key containing names and codes will be stored on a VA, password protected computer, behind the VA firewall which will only be accessible by Dr. Naylor and her study team.

If you experience discomfort that you think may be related to the research, you can call the study team.

WILL I BENEFIT FROM TAKING PART IN THIS RESEARCH STUDY?

You may not personally be helped by taking part in this study, but your participation may lead to knowledge that will help others. You may experience reduced symptoms associated with PTSD and/or depression and pain. A more general benefit of the study is potentially helping us understand how to more effectively treat symptoms associated with PTSD, depression and pain.

DOES PARTICIPATION IN THIS RESEARCH STUDY COST ANYTHING?

There will be no costs to you for any of the research treatment or research testing done as part of this research study. Some Veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

WILL I RECEIVE ANY COMPENSATION (MONEY OR OTHER) FOR TAKING PART IN THIS RESEARCH STUDY?

You will be compensated for taking part in this study. You will receive $125 for each study visit you attend (6 visits for study completion) plus travel costs per visit. If you attend all 6 study visits, you would receive a total of $750 in compensation, plus travel. Payment will be based upon the number of visits completed. For example, if you attend only 2 study visits, you would receive a total of $250 plus travel. There will be no compensation for telephone calls. You will get an allowance for travel that depends on how far you live from the Durham VAMC. The amount you get is figured using the table below. The table shows the travel allowance for some typical cities in North Carolina:

One Way Distance (miles)	Total Allowance	Typical towns and cities
0-25	$10	Raleigh, Durham, Cary, Chapel Hill
25-50	$20	Henderson, Wake Forest, Burlington
50-100	$40	Greensboro, Fayetteville, Goldsboro
100-150	$60	Salisbury, Greenville, Rocky Mount
150-200	$80	Wilmington, Charlotte, Hickory

If you are traveling to the Durham VA from a distance of 70 miles or more, and your research study appointment is at 10am or earlier, you may also qualify for overnight lodging (for each trip you make for study participation). The study team will determine if you qualify. If you do, we will provide a flat rate reimbursement of $150 (matching the government rate for overnight accommodation at a local hotel, meals, and parking). You will be asked to provide the study team with a receipt for lodging prior to receiving reimbursement.

Money that you receive for participating in research is considered taxable income per Internal Revenue Service (IRS) regulations. The money may be reported to the IRS and you may receive an IRS Form 1099.

How will I be compensated?

You will be paid for each study visit by electronic fund transfer (direct deposit) or you will receive a signed form during the study visit which you can exchange for cash from the Agent Cashier's Office at the Durham VAMC.

Are there reasons that my research participation may end early?

Dr. Naylor and her study team may take you out of the study without your consent for one or more of the following reasons:

1. If you have an adverse reaction to the study medication.
2. If you do not take your study medication for 3 days (6 doses) or longer in between study visits or if you do not come to your visit appointments for two weeks in a row.
3. If you do not meet eligibility criteria (including if you report positive benefit from the placebo medication during the placebo-lead in period).
4. If you experience a worsening of mental or physical health symptoms.
5. If you undergo medical hospitalizations for more than 24 hours.
6. If you experience a seizure or a stroke.

7. If you develop a rash (consistent with a drug reaction on the trunk).
8. If you become pregnant.
9. By physician or PI recommendation, or if it's not in your best interest to continue.

If you are withdrawn from the study for any reason, you will be asked to schedule a follow-up visit within 14-28 days of study withdrawal.

WHAT WILL HAPPEN IF I AM INJURED WHILE PARTICIPATING IN THE RESEARCH STUDY?

The VA will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the Durham VAMC or arrangements may be made for contracted care at another facility. Every reasonable safety measure will be taken to protect your well-being. You have not released this institution from liability for negligence. In case of research related injury resulting from this study, you should contact your study team. If you have questions about compensation and medical treatment for any study related injuries, you can call the medical administration service at this VA Medical Center at 919-286-6957.

WILL MY CLINICAL OR OTHER RESEARCH TEST RESULTS BE SHARED WITH ME?

We will let you know of any important discoveries made during this study which may affect you, your condition, or your willingness to participate in this study.

WILL THE RESULTS OF THIS RESEARCH STUDY BE SHARED WITH ME?

Your individual results will not be shared with you. However, once the data are analyzed (after completion of the entire study), you may request to see the results of your data. It is not the purpose of this study to look for or provide you with any medical information or diagnoses about your present condition or other illness. Your participation in this study is not a substitute for your regular medical care or check-ups.

DO ANY OF THE RESEARCHERS HAVE A FINANCIAL INTEREST RELATED TO THIS RESEARCH STUDY?

This project is funded by VA Clinical Science Research and Development. A portion of the salaries of Dr. Naylor's research staff are being paid by the sponsors of this research.

HOW WILL MY RESEARCH DATA BE PROTECTED AND SECURED?

There is the risk of a breach of your confidential information. To protect against this risk, all research records (paper forms and blood and serum samples) will identify you by a unique numerical code (study identification number). Both the research records and the code key containing names and codes will be kept locked in separate files, which will only be accessible by Dr. Naylor and the study

team. Coded paper forms (study assessment data) will be stored in a locked filing cabinet, within a locked room. Information from these paper forms will be entered into a database and stored on a separate, secure, password protected database within the Durham VAMC. Coded blood and serum samples will be stored at the Durham VAMC in a locked freezer room. Only Dr. Naylor and her study staff will have access to these data. No protected health information (PHI) will be used for data analysis, only coded data. Coded data will be sent to Duke University for analysis. Your research records will be maintained and destroyed according to VHA records retention requirements.

WILL ANYONE ELSE HAVE ACCESS TO MY RESEARCH DATA?

If results of this study are reported to others, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent.

Your research records may be reviewed by Durham VA staff who are responsible for the safe conduct of this research. We may also provide your research records to federal agencies such as the Office for Human Research Protections (OHRP), the VA Office of the Inspector General (OIG), and the Office of Research Oversight (ORO), or other government agencies, the Durham VAMC Institutional Review Board (IRB), and/or local Research Compliance Officers. The Food and Drug Administration (FDA) may choose to inspect research records that include your medical records. We will not share any information with these groups outside the VHA unless they agree to keep the information confidential and use it only for the purposes related to the study. Any information shared with these outside groups may no longer be protected under federal law. These groups may disclose your information to other groups. If the sponsor receives identified information, it is then the sponsor, and not the VA, who is responsible for the security of the information.

The VA research pharmacist will have access to information about whether you are taking the study drug or placebo. In addition, the pharmacist will have access to your name, address and social security number for purposes of dispensing the study drug and disclosing this information to the study physician or other study staff.

ARE THERE ANY LIMITS TO THE PRIVACY AND CONFIDENTIALITY OF MY RESEARCH INFORMATION?

If during the study any information reveals suicidal intent, depression, or other major clinical findings, your primary physician or psychiatrist will be notified. In addition, if you reveal current intent to harm yourself or someone else, we may be required to escort you or have you escorted to this hospital's emergency room to be seen by staff in the Psychiatric Emergency Clinic (PEC) or contact emergency medical services (911). If during the course of the study you discuss or mention anything that gives us cause to suspect abuse or neglect of any child, elderly adult, or person with a disability,

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we are required by federal law to report the suspected abuse to your local Department of Social Services.

WHERE CAN I FIND OTHER INFORMATION ABOUT THIS RESEARCH STUDY?

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 website at any time.

WHO DO I CONTACT IF I HAVE QUESTIONS OR CONCERNS ABOUT THE RESEARCH STUDY?

If you have questions about the research or need to talk to the study team, you can contact Dr. Naylor at (919) 286-0411 ext [redacted] during the day or at [redacted] at night/weekends. If you have questions about the research or your rights as a research participant, would like to obtain information, offer input, or have other concerns or complaints, you may contact the administrative officer of the research service at (919) 286-0411, extension [redacted]

AFFIRMATION FROM PARTICIPANT

My rights as a research participant have been explained to me, and I voluntarily consent to participate in this study. I have received an explanation of what the study is about and how and why it is being done. I authorize the use and disclosure of my identifiable information as described in this form. I will receive a signed copy of this consent form.

Participant's Signature	**Date**
Signature of Person Obtaining Consent	**Date**