A Randomized, Double-blind Placebo-controlled Multi-center Study of Identifying Neural Mechanisms of PTSD Symptom Reduction Induced by Combined Estrogen and Prolonged Exposure Therapy

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UTHealth Houston

ADULT CONSENT TO TAKE PART IN RESEARCH

Simple Study Title: Estrogen and Fear in PTSD

Full Study Title: Identifying neural mechanisms of PTSD symptom reduction induced by combined estrogen and prolonged exposure therapy.

Protocol No.: HSC-MS-23-0497

Study Sponsor: National Institutes of Health (NIH)

Principal Investigator: Mohammed Milad, Ph.D.
UTHealth Houston
[redacted]

Emergency Study Contact:
Mira Milad, MD
[redacted]

1. About volunteering for this research study

The purpose of this study is to is to determine if taking a pill of estradiol (a form of estrogen) together with prolonged exposure (PE) therapy can improve treatment outcome in women diagnosed with Post- Traumatic Stress Disorder (PTSD). If you choose to participate in this study, you will be asked to complete an assessment interview and questionnaires to determine your eligibility. If you are eligible, you will be asked to undergo experimental visits and fMRIs, Prolonged Exposure (PE) therapy sessions along with taking the study medication, and follow-up assessments. The total amount of time you will be in this study is approximately 6 months, but only a portion of this will include active participation: the study is comprised of 12 visits that will be completed in approximately 6 - 9 weeks, and then 2 follow-up visits after 3 months and 6 months.

There are potential risks involved with this study that are described in this document. Some known risks include emotional discomfort or distress to the assessments, questionnaires, or treatment sessions, discomfort during the fMRI procedures or blood draws.

You may not benefit directly from your participation in this study; however, the information gained from your participation may benefit others in the future.

There are alternatives to participating in this research study, such as other treatments or procedures outside of this study that are available to treat PTSD, such as psychotherapy (such as cognitive processing therapy or prolonged exposure) and antidepressant medications (such as paroxetine or sertraline).

Participation in this research study is voluntary. You may choose not to take part in this research study or may choose to leave the research study at any time. Your decision will not affect the clinical care you receive at the University of Texas Health Science Center at Houston (UTHealth Houston).

If you are interested in participating, please continue to read below.

2. What is the purpose of this study?

The purpose of this research study is to determine if taking a pill of estradiol (a form of estrogen) together with prolonged exposure (PE) therapy can improve this treatment outcome in women diagnosed with Post- Traumatic Stress Disorder (PTSD). PTSD is a mental health disorder that some people develop after witnessing or experiencing a traumatic event. People who have PTSD re-experience the traumatic event and feel the same fear and discomfort that they associated with the trauma long after the danger has gone.

Prolonged Exposure (PE) therapy is a validated treatment for PTSD. However, while this therapy is a first- line, evidence-based treatment for PTSD, some people with PTSD do not fully recover after receiving PE therapy and others do not benefit at all from this treatment. This has driven researchers to find ways to improve the treatment.

Based on previous findings that the hormone known as estrogen facilitates people learning not to fear things they had feared before, we want to supplement prolonged exposure therapy with an estradiol pill given before each therapy session. We expect estradiol to increase the effects of the therapy. The use of estradiol is not approved by the U.S. Food and Drug Administration to treat PTSD but experimental research like the present study is needed to test if it is beneficial.

We are asking you to take part in this study because you are woman between the ages of 18 and 45 who developed PTSD symptoms following a traumatic event. We are recruiting women who are taking oral contraceptives, or are using a vaginal birth control ring (e.g., NuvaRing) or transdermal birth control patch as well. We want to study the effects of estrogen on the brain's response during learning not to fear. This study is being paid for with NIH funds.

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.

3. How long will I be in the study? How many other people will be in the study?

Part one of the study will be completed in six to nine weeks. During this time, we will ask you to make 12 visits to our facilities at UTHealth Houston and/or Baylor College of Medicine. In the second part of the study, we will ask you to come for two follow-up visits after 3 and 6 months of completing part one of the study.

In order to have the study intervention and assessments be as complete as possible, any visit, with the exception of the pre- and post-experimental days, may be conducted remotely if needed at the discretion of the research team, such as in the circumstance of weather or a possible participant COVID-19 exposure. Remote visits will only be done if the research team has determined that the participant is able to tolerate the remote Prolonged Exposure (PE) therapy visits in a safe manner.

About 40 subjects will take part in this research study at UTHealth Houston.

4. What will I be asked to do in the study?

If you choose to take part in the study, we will ask you to sign this consent form before you have any procedures with the study staff that are part of the study.

This study is a randomized study. This means, like flipping a coin, you will be assigned to one of the treatment groups and receive either the study drug or the placebo. There are no special requirements or criteria to be in either group. You will have an equal chance of getting estradiol or placebo.

This study will compare estrogen (estradiol) to a placebo. The placebo looks just like estrogen (estradiol) but contains no medicine. During this study, you may get the placebo instead of estrogen (estradiol). A placebo is used in research studies to compare the results and side effects of the drug being studied to the results and side effects of taking no medication. This allows us to see if the drug being studied works and what side effects it causes.

On the first assessment visit, we will determine your eligibility and explain to you details of the study. On the second and third visits, you will go through an emotional learning task. We will examine your physiological response (skin conductance response) during visits 2 and 3, and your brain responses using a functional Magnetic Resonance Imaging (fMRI) machine on visit 3. Following this 2-day visit, you will go through 6 therapy sessions over 3 weeks: 2 sessions per week. After that, we will repeat the experimental visits over 2-days. These visits are briefly summarized in the table below and are described in greater detail in the following paragraphs. All fMRI scans will be conducted at Baylor College of Medicine. Blood draws will be conducted at LabCorp or Quest Diagnostics (or if needed due to scheduling constraints, blood will be drawn by phlebotomist at UTHealth Houston).

Visit	Procedures	Location
Visit 1	Informed consent, psychiatric diagnostic interview, urine pregnancy and toxicology test, questionnaires examining mental health, demographics, personality, drug and medication use, medical history, and menstrual cycle	UTHealth Houston
Visit 2	Psychophysiological measurements, blood draw, urine pregnancy test, mild electric shocks	UTHealth Houston LabCorp/UTHealth/Quest Diagnostics (for blood draw, if completed on this day)
Visit 3	fMRI scan, adverse event assessment, (blood draw could occur on this day instead of Visit 2 if needed due to scheduling)	UTHealth Houston Baylor College of Medicine LabCorp/UTHealth/Quest Diagnostics (for blood draw, if completed on this day)
Visit 4	*First session of PE treatment*	UTHealth Houston
Visit 5	*Session 2 PE treatment* Psychophysiological measurements, intake of estradiol or placebo blood draw	UTHealth Houston LabCorp/UTHealth/Quest Diagnostics (for blood draw)

Visit 6	*Session 3 of PE treatment* Psychophysiological measurements, intake of estradiol or placebo	UTHealth Houston
Visit 7	*Session 4 of PE treatment* Psychophysiological measurements, intake of estradiol or placebo	UTHealth Houston
Visit 8	*Session 5 PE treatment* Psychophysiological measurements, intake of estradiol or placebo	UTHealth Houston
Visit 9	*Session 6 of PE treatment* Psychophysiological measurements, intake of estradiol or placebo blood draw	UTHealth Houston LabCorp/UTHealth/Quest Diagnostics (for blood draw)
Visit 10	Identical to Visit 2: Psychophysiological measurements, blood draw, urine pregnancy test, mild electric shocks	UTHealth Houston LabCorp/UTHealth/Quest Diagnostics (for blood draw, if completed on this day)
Visit 11	Identical to Visit 3: fMRI scan, adverse event assessment (blood draw could occur on Visit 11 instead of Visit 10 if needed due to scheduling)	UTHealth Houston Baylor College of Medicine LabCorp/UTHealth/Quest Diagnostics (for blood draw, if completed on this day)
Visits 12	Assessments, including questionnaires examining trauma symptoms	UTHealth Houston
Visits 13 and 14	3- and 6-month follow-up visits: assessments, including questionnaires examining trauma symptoms	UTHealth Houston

Visit 1:
We will explain to you the study procedures, answer any question you may have and ask you to sign this consent form. You will then undergo a diagnostic interview with a trained study staff. This interview will focus on symptoms related to PTSD. In addition, we will ask you about your mood and particularly if you are experiencing symptoms of depression. This session will be audiotaped. You will also have urine drug and pregnancy test.

We will also ask you to fill questionnaires about:

- Medical history
- Drug and medication use
- Life history, including any stressful life events that you have had.

<u>Urine Drug Screen</u>
During the study, we will test your urine for drugs, including illegal drugs like cocaine, marijuana, amphetamines and others. If your urine shows you have taken any of these drugs, you may not be able to participate in the study. On the days of the scans, if your urine drug test is positive for THC, the main compound in cannabis (and negative for all other substances), we will administer a saliva THC test to determine recency of THC use. If the saliva THC test is positive, the scan will be rescheduled. The results of the urine drug test will NOT become part of your medical record. These test results WILL become part of your research record.

Although it is hoped that you will answer all the questions in the interview and questionnaires, you may skip over any questions you do not want to answer. The interview and questionnaires could take about three hours. Once you have completed the interview and questionnaires, we will tell you if you are eligible to continue to take part in the study. If you are eligible, we will schedule your next visits. If you are not eligible, we will offer you appropriate referrals.

Visit 2:
This visit will start with a urine pregnancy test. If you are pregnant, you cannot take part in this study for two reasons: we do not know the risk of magnetic imaging on the developing fetus; and you cannot take an estradiol pill if you are pregnant.

Visit 2 will take place in an experiment room where you will be sitting quietly in a chair and paying attention to images displayed on a monitor about three feet away from you. Two small electrodes will be attached to two fingers. The electrodes are made of a small piece of metal that is attached to a cable. The cable is connected to a battery-powered stimulator. The electric shock feels like, to most people, an annoying tingling sensation.

In the first part of this experiment, we will find the level of current that you find is very annoying, but not painful. To do this, we will begin at a low level that you will not be able to feel. We will slowly increase the shock levels with your permission. We will ask you to tell us when you find the level of the current to be very annoying, but not painful. During the rest of the experiment, the level of current that you will experience will not be higher than this very annoying level.

The purpose of the electric shock is to create a situation in which emotional learning may occur. This means that you will learn that the shock may always follow a specific picture (see below). When we thereafter show you the picture, you may become a bit nervous because you now learned that this given picture predicts the occurrence of the shock. We will then show you a series of pictures of different rooms. You will see these pictures on a computer monitor about three feet away from you. After you see some of the pictures, you will receive a half-second electric shock to your fingers at the very annoying level that was selected earlier. You will receive no more than twelve of these electric shocks. Wires that are attached to the surface of your hands will measure your body's responses to the pictures that you see. The small stick- on pads with wires attached (electrodes) that are attached to your hands will be connected to a computer that can detect how nervous you are by measuring the amount of little sweat in the palm of your hand. This procedure may take about 1 hour.

During this visit we will take the first blood draw to measure the level of estrogens/estradiol in your body. This is important because it will let us have an idea of the level of estrogens/estradiol you have before participating in our experiment.

Visit 3:
Exactly one day after Visit 2, we will ask you to return to our facilities for another study visit. If the blood draw did not occur on Visit 2 due to scheduling, we will take the first blood draw at this visit. Then we will ask you to take part in an experiment similar to the one you did during Visit 2, however you will be in the fMRI scanner.

The fMRI machine uses a magnetic field to take pictures (images) of your brain while you are performing a task. This machine is routinely used you scientists to study the brain. This procedure does not use any radiation (x-rays). During the fMRI, you will be asked to lie quietly on a table that slides into a tunnel shaped machine. The machine is slightly wider than your body. The top and sides of the tunnel will be very close to your body. The

machine makes knocking and beeping sounds as it takes pictures of your brain. Earplugs will be provided to reduce the sound and to protect your hearing. During the scanning session, the investigators will be able to speak to you while you are in the machine. You will also be able to hear and speak to them at all times. We can stop the procedure at any time, if necessary.

We will place electrodes on your hands to measure your body responses. We will also place the electric shock electrodes on your fingers. Following that, you will be shown the same pictures of the rooms that you saw during Visit 2 on the computer monitor. During this visit, you may or may not receive electric shocks. However, if you do receive the electric shocks, you will receive no more than three of these shocks. The shocks that you may receive will be at the same annoying level that you received during Visit 2. This procedure will take about 1 hour.

Randomization:
In visits 5 to 9 and before each therapy session, one group of subjects will receive a pill of estradiol and the other group of subjects will receive a placebo. Estradiol or placebo will be given as one dose (one pill) taken by mouth. Note that all participants will receive 1 pill (either 1 placebo, or 1 x 2mg pill of estradiol). You and the study doctor cannot choose which one you get. You and the study doctor also will not know which you get, but we can find out that information if needed.

Visit 4:
Visit 4 is the first prolonged exposure (PE) therapy session. During this visit, the therapist will provide an overview of the PE treatment along with the proposed mechanism of action of estradiol on the exposure process. The therapist will ask you about the trauma you suffered from and about history of previous trauma. The therapist will tell you about PTSD and discuss with you common reactions to trauma and the rationale for treatment. In addition, the therapist will construct the treatment plan with you and explain to you the different techniques employed in PE. This session is about two hours long. Before leaving this session, you will be given 5 pills (either Estradiol or placebo) to take home with you, and take one pill prior to each of the following 5-9 visits. A non-invasive skin conductance monitor will be used during all PE sessions to measure skin conductance, which is a measure of the level of electrical conductance from your skin. Electrodes will be used for measurements only and will be placed on your fingers at the beginning of each PE session and taken off at the end. This session will be videotaped.

Visits 5-9:
Each of these sessions will last for about 60 minutes. Each will consist of imaginal exposure. Specifically, you will be instructed to revisit in imagination the trauma and recount it aloud for about 25-30 minutes. In the following 15 minutes, you will process your reactions to revisiting the traumatic event by discussing related thoughts and feelings. Each session will end with in vivo exposure homework to be completed that same day as the session. Visit 9: in this last session, imaginal exposure is conducted one last time for the same duration as previous sessions. The therapist and you will review treatment progress and discuss applications of treatment principles to daily life. We will ask you to take one pill 4-6 hours before you come in for the therapy session (we will send you a text reminder or give you a call to tell you the exact time to take the pill). These sessions will be videotaped.

You will be asked to complete some questionnaires assessing your symptoms and your mood at each session, and skin conductance will be measured throughout the imaginal exposure sessions. During the fifth and ninth visit, we will take the second and third blood draw to measure the level of estrogens/estradiol in your body. These blood draws are important to see the effect of the pill (either estradiol or placebo) on the total level of estrogens/estradiol in your body. It will show us if the pill increased estrogens/estradiol up to a level that we have previously shown to help women have better extinction.

Visits 10 and 11:
These visits will be identical to Visits 2 and 3 described above in this consent form. The fourth blood draw will occur on Visit 11, or Visit 12 if needed due to scheduling.

Visit 12:
This visit can take place on the same day as Visit 11 or can be completed sometime within the week following completion of PE therapy session 9. During this visit, you will undergo the same diagnostic interview you completed in Visit 1 with a trained study staff. This interview will focus on symptoms related to PTSD. In addition, we will ask you about your mood and particularly if you are experiencing symptoms of depression, as well as ask you to complete a few of the same questionnaires that you completed in Visit 1. This session will be audiotaped.

Visit 13 and 14 (3- and 6-month follow-up):
During these visits, we will ask you about your mood as well as the symptoms that you have experienced recently with regards to the traumatic experience that you have had. You will also be asked to fill out some questionnaires. In some situations, additional PE sessions might be offered to some participants. These sessions will be audiotaped.

Audio/Video Recording:
Your assessments will be digitally audio-recorded and your PE therapy sessions will be digitally video- recorded. This will allow us to monitor that assessments/therapy sessions are being done accurately by our clinical staff working on the study. Making an audio/video recording of each clinician assessment/PE therapy session is part of this study Your consent to be audio/video recorded may be withdrawn at any time and the recordings can be erased either during or after the session. However, if you withdraw your consent to be audio or video recorded, you will not be eligible to continue to receive study treatment.

People who will listen to and/or view the recordings include your study therapist and their study-approved supervisors at UTHealth Houston and/or The University of Pennsylvania, the two collaborating study centers. Other study clinicians and/or people who are learning the study protocol may also hear/view some segments of the audio/video recordings. Approved rating trainers or therapists at UTHealth Houston and The University of Pennsylvania (UPENN) will listen to/view selected audio/video recordings in order to evaluate whether the assessments/PE therapy sessions are being done according to study guidelines.

Audio/video recordings may be shared electronically with approved investigators working on this study. Transmissions will be done only through secure channels that give access for listening/viewing within the UTHealth Houston firewall. The audio/video files will be labeled with a code and will not be labeled with any information that could be used to identify you, such as your name or your date of birth. We plan to keep these recordings on an electronically secure, password protected hard drive in a locked room for no longer than 5 years after the primary study is completed (approximately 10 years total) to allow enough time for the study investigators to complete approved study of the recordings.

Any identifiable private information or specimen collected or used for the purposes of this research will not be used or distributed for future research studies.

Communicating with the Research Team:
Researchers may need to communicate with you about information relevant to the research study. The

research team will usually contact you for these purposes by phone, but if you have given the researchers your email address and mobile/cell phone number and permission to send a text message, the research team may contact you that way. When the research team sends email messages that include identifiable health information, they will use encrypted messaging (e.g., SendSafe). When the research team uses texting over mobile/cell phones there is no way to encrypt the message. This means that information you send or receive by text message is unencrypted and could be intercepted or viewed by an unintended recipient, or by your mobile/cell phone provider or carrier. Therefore, text messages carry security and privacy risks.

Below are some important points about texting in this research study.

- Text messages are not encrypted, and therefore are unsecure and may result in a breach of your confidentiality.
- You will be responsible for all fees charged by your carrier's service plan for text messaging. This research study and UTHealth Houston will not cover the cost related to any increased charges, data usage against plan limits or changes to data fees from the research texts.
- Text messages will only be read during regular business hours. However, if you have a scheduled visit outside of business hours, you may receive a text in relation to this visit outside of regular business hours.
- Text messaging should not be used in case of an emergency. If you experience a medical emergency, call 911 or go to the nearest hospital emergency department.
- You may decide to not send or receive text messages with staff associated with this research study at any time. You can do this in person or by sending the research number a text message that says "Stop Research Text."
- Your agreement applies to this research study only. Agreeing to other texts from UTHealth Houston, for example appointment reminders, is a separate process. Opting out of other texts from UTHealth Houston is a separate process as well.

Please make sure to keep the research team updated if your mobile/cell phone number changes during the study.

☐ Yes, I agree to receive texts from this research group. Initial here_____

Cellphone#: _____

Cell carrier/provider: _____

☐ No, I do not agree to receive texts from this research group. Initial here_____

5. What are the possible risks or discomforts?

Risk of Study Drug

Taking estrogen (estradiol) may cause you to have one or more of the side effects listed below. Because this is a research study about estrogen (estradiol), not all side effects are known. There may be rare and unknown side effects. Some of these side effects may be bad enough to cause death.

It is important for you to tell the study staff and study doctor about any changes you feel after you begin taking the study drug. You can tell the study staff at your scheduled visits or by calling the staff and telling them how you

might feel different. If you are not honest with the study staff during this study, it may not be safe for you to stay in the study.

Below is a list of the most common side effect of chronic administration of estrogen (estradiol):

- Headache
- breast pain
- nausea

Below is a list of less common side effects of chronic administration of estrogen (estradiol):

- irregular vaginal bleeding
- stomach cramps
- hair loss

Below is a list of rare side effects of chronic administration of estrogen (estradiol):

- increased risk of endometrial cancer (a type of cancer that begins in the uterus)

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away at the phone number at the top of page 1 of this consent form. If you are having trouble breathing, call 911 immediately.

If you have or had breast cancer or any estrogen sensitive cancer, because of risks with estrogen you will not be allowed to participate in the study. These risks are similar to those of oral contraceptives, vaginal birth control rings (e.g., NuvaRing), or the transdermal birth control patch containing estrogen. All study participants will be those already taking specific types of oral contraceptives containing up to 35 mcg of estrogen called monophasic first, second, third or fourth generation oral contraceptives, or vaginal birth control rings (e.g., NuvaRing) or transdermal patch.

Taking benzodiazepines is not allowed and exclusionary for the study. Other psychiatric medications if stable for at least 3 months prior to starting are allowed, but those already planning to start a new psychiatric medication during the study period are not eligible.

NOTE: Since the research involves a placebo, there is a chance you will not actually be taking medicine that will treat your condition. In this case, your condition might not improve or could get worse. You could miss the benefits or harms (if any) of the study medication.

Risks of Psychotherapy

During assessment, you may experience some discomfort or anxiety from discussion of personal information. You may feel uncomfortable about having treatment sessions audiotaped and reviewed by others. You may also experience some interference with daily activities due to scheduling of treatment and assessment sessions.

The assessment and treatment of PTSD involves discussion of the trauma and trauma symptoms. These discussions may temporarily increase distress and other symptoms of PTSD (for example, vivid memories of the trauma, feelings of unreality, or feelings of fear for PTSD) in individuals suffering from this disorder. This distress potentially experienced during the treatment of PTSD is balanced by clinical improvement when patients receive effective treatment. You may also feel uncomfortable about having your sessions audiotaped and reviewed by others.

Other Risks

Magnetic Field Risk

MRI uses a strong magnetic field to create images of the body. Because of the strong magnetic field, there are risks. One possible risk is burns to the skin. There is an increased risk of burns from devices that conduct electrical energy. These devices can include metallic objects, pulse oximeters, EKG leads, or skin tattoos. These devices can be either in or on the patient in order for a skin burn to occur. The FDA has found that 70% of all reported injuries from MRIs were burns to the skin. To reduce this risk, all patients who are scanned in this study must complete thorough screening to ensure that no conductive materials are present in or on the patient's body. Additionally, the power limits of the magnet will be adjusted as necessary.

Another possible risk is that a metal object could be pulled into the scanner and hit you. You could be physically injured as a result. To reduce this risk, everyone near the magnet will remove all metal from their clothing or pockets when in the scanning environment. The door to the scan room will remain closed during the exam for your safety.

There are no known risks or adverse effects resulting directly from exposure to MRI. However, subjects who have a pacemaker or metal objects in their body such as shrapnel or metal in the eye should not have the scan performed. If you have any question about metal implants or metal fragments in the body, you should inform the technologist or investigators before entering the magnet room.

Fear of Confined Spaces: Some people may feel confined and experience anxiety in the MR scanner. If you are unable to tolerate being in the scanner, we can stop the scan immediately at any time.

Noise Levels: The MR scanner produces tapping sounds during operation, which may reach very loud levels. To minimize any discomfort from this noise, you will be given disposable earplugs to reduce the noise levels but will still allow voice communication with the scanner operator.

MRI system failure (quench): In extremely rare cases, a magnet can lose its magnetism, in which case cooling fluids may be released noisily through escape valves and may collect in gas form in the scan room. The gas is not harmful in itself as long as fresh air is available. In this very remote event, you will immediately be brought out of the magnet room.

Neurostimulation and heating: Some subjects may experience muscle twitches or tingling sensations and/or a slight increase in body temperature during some types of scan activity. These are very unlikely under current MR guidelines.

Metallic Foreign Fragments/Flying Object Clause – The known risks associated with this study are minimal. Implanted medical devices and metallic foreign fragments inside your body may pose a risk if you were to enter the MRI magnet room. Therefore, questions regarding medical and work history will be asked prior to your exam.

The greatest risk is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.

Incidental Findings Clause – This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you of the results if necessary. A copy of the original radiology report will also be provided to you and you will be encouraged to follow up on the discovery with your treating physician. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

Electric Shocks
The electric shocks that you will receive will be uncomfortable, but it should not be painful or dangerous. If you find it necessary, you may stop the electric shocks at any time.

Fear Conditioning and Extinction Paradigm
The association between the electric shocks and the pictures to be presented during the fear conditioning and extinction paradigm might induce some anxiety when viewing the pictures in anticipation of the shock.

Blood Drawing
Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. You may also experience a decrease in hemoglobin and hematocrit (red blood cell number, called anemia) from having blood drawn frequently. Approximately 6 ounces of blood (12 tablespoons) per participant will be drawn for research purposes during this research study.

Side Effect of Having Blood Taken: Fainting or feeling faint. Tell the study staff right away if you feel faint. Redness, pain, bruising, bleeding or infection at the needle site.

Questionnaires and Interview
There is a risk of a negative emotional reaction to the recruitment, structured interviews, and questionnaires. You could develop mild to moderate emotional discomfort or frustration associated with psychiatric interviewing or filling out questionnaires. You may experience subjective distress during treatment. You may feel uncomfortable or you may become upset when answering some of the questions in the questionnaires or during the interview. You may skip any questions you don't want to answer.

One of our trained staff members will interview you and ask questions about your mood, mental health and substance use history, diagnoses, and suicidality. As detailed in the "Confidentiality" section, the information we collect cannot be disclosed to anyone who is not connected with this study without your consent. However, disclosure, without your consent, is still necessary in situations where federal, state, or local law requires disclosure (such as to report child abuse or imminent risk/harm to others). Our trained staff members will monitor and assess your discomfort—if you are in danger of harming yourself or others, trained staff members will consult with our study PIs and clinicians, as needed, and will further evaluate your distress and respond with the appropriate interventions or referrals.

Unforeseeable Risks
There may be other risks and side effects that are not known at this time.

Risks of Breach of Confidentiality of Study Information
There is a possibility that if your study information were to become generally known, this knowledge of your study information could potentially impact you. It may impact your future insurability, employability, reproduction plans, or have a negative impact on family relationships and/or result in shame or embarrassment.

Similarly, although every effort is being made to assure your confidentiality including the use of study codes instead of names and secure servers for audiotape storage and transfer, it is possible someone could without permission gain access to study related audiotapes during the time they are being used or stored for study supervision, to evaluate whether PE is carried out according to the study guidelines, and for examination of results.

Other Risks
There is also a risk of the study doctors detecting an earlier unrecognized medical or psychiatric problem. If this happens, you will be referred for appropriate treatment based on your needs and desires.

Incidental Findings
The investigators for this project are not trained to perform radiological diagnosis, and the MRI scans performed in this study are not designed to find abnormalities and are being conducted only for research purposes. If the investigators notice a finding on an MRI scan that seems abnormal, the scan will be shared with a licensed radiologist for further evaluation. Should this occur, a neuroradiologist would be consulted and the MRI scan will be sent to Baylor College of Medicine and/or UTHealth Houston. If the neuroradiologist thinks that further investigation of the finding is called for, you will be contacted about the finding and next steps. You will also receive a copy of the radiology report for your records. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The images collected in this study do not comprise a proper clinical MRI study these images will not be made available for diagnostic purposes.

6. Can I be in the study if I am pregnant or breastfeeding?

Because taking part in this study might harm an embryo, fetus, or breastfeeding baby, you should not become pregnant or breastfeed a baby while participating in this study.

If you are pregnant, you cannot take part in this study for two reasons: the first is that we do not know the risk of magnetic imaging on the developing fetus and the second is that you cannot take an estradiol pill if you are pregnant. You should not become pregnant while you are participating in this study. You will be required to take oral contraceptives, or be using a vaginal birth control ring (e.g., NuvaRing) or transdermal patch while in this study.

If you become or you think you have become pregnant during the study, you must tell the principal investigator right away and must tell your obstetrician or other health care provider caring for you during your pregnancy that you took part in this study. If you become pregnant, you will have to stop taking part in the study for safety reasons. The principal investigator may ask you to provide information about the outcome of your pregnancy and the health of your baby.

7. What if new information becomes available?

During the course of this study we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

8. What are the possible benefits of the study?

You may not benefit from taking part in this study. There is no guarantee that your symptoms will improve. You may benefit from the screening procedures that include a careful examination of your mental health condition. You may also benefit from the ongoing close mental health evaluation during the course of the study. You may benefit from receiving therapy that helps many people with PTSD. Since there is a potential benefit to society, you

may also benefit from knowing that you have contributed to the scientific understanding of the role of estrogen in augmenting existing treatments for PTSD and that this may help other women with similar problems.

9. What other choices do I have if I do not participate?

You do not have to take part in this research study to be treated for PTSD. Prolonged exposure therapy is also available outside of this study. If you decide not to participate, your decision will not interfere with your future care, payment for your health care or your eligibility for health care benefits. Other treatments or procedures that are available to treat PTSD include:

- Psychotherapy, such as cognitive processing therapy or prolonged exposure
- Antidepressant medications, such as paroxetine or sertraline

10. Will I be paid for being in this study?

You will receive a total of $560 for completing all study visits and to defray costs of time and travel. See the table below for the timing of payments. If you do not complete the entire study, you will be paid for the visits/procedures you have completed.

VISIT	COMPENSATION
visit 1:	$60
visit 2:	$20
visit 3:	$15
visit 4:	$15
visit 5:	$20
visit 6:	$15
visit 7:	$15
visit 8:	$15
visit 9:	$15
visit 10:	$20
visit 11:	$15
visit 12:	$235
visit 13:	$50
visit 14:	$50
Total (if complete all study procedures)	**$560**

11. Will I have to pay for anything?

Study funds will pay for the assessments, the 6 therapy sessions, the study drug, and the fMRI studies that are done only for research.

Although study funds will pay for certain study-related items and services, we may bill your health insurer for, among other things, routine items and services you have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you need to be hospitalized due to a worsening of your PTSD symptoms, you or your insurance provider will be billed for the costs associated with this hospital stay.

If you receive a bill that you believe is related to your taking part in this research study, please contact Mohammed Milad, PhD, or research staff at [redacted] with any questions.

If you have any questions about costs to you that may result from taking part in the research please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

12. What happens if I am injured from being in the study?

In the event of injury resulting from this research, UTHealth Houston are not able to offer financial compensation nor to absorb the costs of medical treatment. However, necessary facilities, emergency treatment, and professional services will be available to you, just as they are to the general community. You or your insurance company will be billed for any treatment.

You should report any such injury to PI Mohammed Milad, PhD at [redacted] and to the Committee for the Protection of Human Subjects at [redacted] You will not give up any of your legal rights by signing this consent form.

13. When is the study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped or your participation ended at any time by your physician, the study sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The study sponsor, the principal investigator, the Food and Drug Administration (FDA) or other body responsible for monitoring the safety of the study has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Leaving the study will not interfere with your future care, payment for your health care or your eligibility for health care benefits.

14. How will you protect my confidentiality?

Your medical information is protected health information, or "PHI", and is protected by federal and state laws, such as the Health Insurance Portability and Accountability Act, or HIPAA. This includes information in your research record as well as information in your medical record at UTHealth Houston. In compliance with UTHealth Houston policies and procedures and with HIPAA, only those individuals with a job purpose can access this information.

If you sign this document, you give permission to UTHealth Houston to use and disclose (release) your health information.

Medical information created by this research study may become part of your medical record. We may include your research information in your medical record for several reasons, including for the billing of services provided in connection with the study, to securely document any medical services you receive, and so that other members of the UTHealth Houston community who may treat you have access to important information about your health.

You have a right to access information in your medical record. As it is necessary to protect the integrity of the research, you will not have access to any study-related information relating to the study while the study is in

progress, including your blood test results which may be entered in the medical record, but you will have the right to see and copy the information once the study is over in accordance with UTHealth Houston policies and applicable law.

The Certificate of Confidentiality cannot be used to refuse a request for information from appropriate government agencies responsible for project oversight. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your involvement in this research, including for your medical treatment. Federal regulations may also allow for the use or sharing of information for other scientific research.

15. HIPAA Authorization

Your privacy is important and your participation in this study will be kept confidential. However, absolute confidentiality cannot be guaranteed.

If you sign this document, you give permission to UTHealth Houston to use and disclose (release) your health information. The health information that we may use or disclose for this research includes all information in a medical record, results of physical examinations, medical history, lab tests, or certain health information indicating or relating to your post traumatic stress disorder. Please understand that health information used and disclosed may include information relating to HIV infection, drug abuse, alcohol abuse, behavioral health, and psychiatric care.

All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the private information (data) and biospecimens (samples) collected in this study. After we remove all identifiers, the data may be used for future research or shared with other researchers without your additional informed consent.

If you are not comfortable with the use of your data or specimens in future research, you may not want to participate in this study.
Representatives of the organizations listed below will see your name and other personal identifiers when they review your research records and medical records for the purposes of verifying study data:

The following individuals may use, share, or receive your information for this research study:

- Representatives of UTHealth Houston
- Representatives from the U.S. Food and Drug Administration (FDA)
- Representatives of the National Institutes of Health, sponsor of this research including contract research organizations
- University of Pennsylvania
- Members of Data and Safety Monitoring Boards (an independent group of experts that reviews this study's data to make sure participants are safe and the research data is reliable)
- Companies engaged with the UTHealth Houston for the commercialization of the results of the research study

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. UTHealth Houston and/or Memorial Hermann Health System and/or Harris Health System may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about you as

necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must contact PI Dr. Mohammed Milad in writing at UTHealth Houston, [redacted]

This Authorization will expire 15 years after the end of the study.

Certificate of Confidentiality
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state, or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information

16. Who can I call with questions, or if I'm concerned about my rights as a research subject?
If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on top of the page 1 of this consent form. You can contact the study team to discuss problems, report injuries, voice concerns, obtain information in addition to asking questions about the research.

The Committee for Protection of Human Subjects at the University of Texas Health Science Center has reviewed this research study. You may contact them for any questions about your rights as a research subject, and to discuss any concerns, comments, or complaints about taking part in a research study at [redacted]

Are you interested in being contacted for future research studies?
Please check the appropriate box to indicate your preference. If you are interested in participating in future studies, the research team will retain information that will identify you, such as your name, phone number, mailing address, and/or email address.

⎦ Yes, I am interested in being contacted for future research studies.

⎦ No, I am not interested in being contact for future research studies.

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to take part in this research study. Make sure that all your questions have been answered. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of Subject	Signature of Subject	Date	Time
Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date	Time