Official Title: A randomized controlled trial to test whether oxytocin amplifies the effect of vibration to increase heat pain threshold after UVB burn

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A Randomized Controlled Trial to Test whether Oxytocin Amplifies the Effect of Vibration to Increase Heat Pain Threshold after UV-B Burn

Informed Consent Form to Participate in Research
James C. Eisenach, M.D., Principal Investigator

1. SUMMARY

You are invited to participate in a research study. The purpose of this research is to evaluate the effects oxytocin (naturally occurring hormone made in the brain that transmits messages) may have when given by an intravenous (IV) route on your threshold to sensing touch and heat in normal skin and on skin exposed to ultraviolet-B (UV-B) light to create a mild sunburn. In this study you will either receive IV oxytocin or placebo (inactive solution). You are invited to be in this study because you are a healthy subject. Your participation in this research study will involve 4-5 visits and last approximately 10-11 hours for all visits. Participation in this study will involve receiving IV administration of oxytocin, thermal heat testing, exposure to a small amount of UV- B radiation (a mild sunburn) and vibratory sensory testing.

All research studies involve some risks. Risks to this study that you should be aware of are discomfort from the thermal/sensory/UV-B testing and IV placement. Potential risks associated with receiving oxytocin are headache, facial flushing and a sensation of your heart pounding; additional risks are discussed later in this document. This is not a treatment study, therefore you are not expected to benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. This is not a treatment study and there are no additional choices. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study please contact the Principal Investigator at [redacted].

If you have any questions, suggestions, or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted].

2. INTRODUCTION

You are invited to be in a research study. Studies help researchers learn new information that may help other people in the future. You are being asked to be in this study because you are a healthy adult. Your participation is voluntary. You do not have to be a part of this study if you do not want to. Please take your time in making your decision if you would like to join. Ask the researchers to explain any words or information in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

This study will take place at Atrium Health Wake Forest Baptist Medical Center at Piedmont Plaza 2 in the Pain Research Unit and in the Clinical Research Unit (CRU) on the Main campus of Atrium Health Wake Forest Baptist Medical center in Winston Salem, NC.

3. WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to evaluate the effects oxytocin (naturally occurring hormone made in the brain that transmits messages) administered by intravenous (IV) infusion may have on thermal, vibratory and UV-B testing when compared to a placebo. Oxytocin (intravenously or intramuscularly) is commonly given to pregnant women to cause labor to start or given after the delivery of an infant to stop the mother from bleeding. In this study we will be administering a specific dose of oxytocin or placebo twice during study visit 4. Each infusion will be given over a 30-minute period. Oxytocin is being given to help researchers develop a model for evaluating the effect, if any on the response you have to thermal heat temperatures with a vibratory stimulus and in the presence of a UV-B burn.

Oxytocin has been approved by the US Food and Drug Administration (FDA) for intravenous and intramuscular administration. However, oxytocin is considered investigational in this study because it is being administered so that investigators can determine its effect, if any, on the thermal/ UVB burn model that will be used in this study.

In this study, a drug will be compared to a placebo. A placebo looks like the study drug but does not have active ingredients. It is not thought to have any effect on your disease or condition. In this study you will either receive active study medication, or placebo. Placebos are used in research studies to see if the drug being studied really does have an effect.

4. WHO IS SPONSORING THIS STUDY?

This study is being sponsored by National Institutes of Health: National Institute of Neurological Disorders and Stroke. The sponsor is providing money or other support to the researchers to help conduct this study.

5. HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 36 people will take part in this study. Some people may be screened for the study but will not be eligible to participate. In order to identify the 36 subjects needed, we may need to screen and consent up to as many as 40 because some people will not qualify to be included in the study.

6. HOW LONG WILL I BE IN THE STUDY?

Your participation in the study is planned to last until you complete all of the study visits. Typically this will take 2-4 weeks depending upon your scheduling availability.

Long-term Follow-up

Subjects will be contacted daily the week following the study visit 4 (infusion visit) and questioned about adverse events from the study.

7. WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following tests and procedures:

- Vital Signs**:** we will monitor your blood pressure, heart rate, respiratory rate and oxygen saturation (amount of oxygen in your blood).

- Laboratory Testing: female participants of child-bearing potential will provide a urine sample to determine that they are not pregnant.

- Intravenous infusion of Oxytocin: we will place an intravenous catheter and administer oxytocin or placebo.

- Thermal Heat Testing: A thermal heat probe (about the size of a penny), controlled by a computer that is programmed to deliver temperatures that range from skin temperature up to a temperature that is hot (124 ºF) and uncomfortable, but does not burn your skin will be placed on your forearm. You will be able to stop the thermal heat temperature when you feel pain.

- Vibratory Testing: a mechanical device will be used to vibrate the skin near the heat testing probe or in your hand during heat testing.

- Sensory Testing: a mechanical von Frey filament (similar to a paintbrush bristle) in will be used to touch your skin and you will report when you feel the filament and when the touch becomes painful.

- UV-B Testing: we will expose areas of your skin to a light that will give you a mild sunburn in small areas (about the size of a dime).

Visit	**During this visit, you will**	**How long is this visit?**	**Reminders**
Visit 1 (Screening)	• Review and sign this consent form first • Provide a detailed medical history • Females a urine pregnancy test (if required) • Have your blood pressure, heart rate, respiratory rate and pulse oximetry measured	2 hours	This visit will occur at Piedmont Plaza 2

	• Thermal heat/vibratory training(threshold) • Touch and pain threshold testing with von Frey filament • Controlled UV-B exposure to your lower leg		
Visit 2 (24 hours after Visit 1) Option to combine Visit 3 with this visit	• Evaluation of UV-B exposure to determine the area that shows the least amount of redness	10 minutes Visit 2 and 3: 30 minutes	This visit will occur at Piedmont Plaza 2
Visit 3	• Receive 3 times the UV-B exposure that was determined from Visit 2 on your forearm	20 minutes	This visit will occur at Piedmont Plaza 2. Do not take and non-steroidal medications such as aspirin, ibuprofen, Motrin or Aleve.
Visit 4 (24 hours after Visit 3)	• Vital signs: baseline and 5, 10, 30, 60, 90 and 120 minutes after oxytocin infusion • Touch and pain threshold at the UV-B site and on the opposite arm using von Frey filament • Thermal heat pain threshold testing alone and with vibration at the UV-B site and on the opposite arm • Placement of IV catheter	4.5 hours	This visit will occur at Atrium Health Wake Forest Baptist Medical Center in the Clinical Research Unit. Please do not eat or drink anything other than water for 8 hours prior to this visit.

	• Oxytocin or placebo infusion over 30 minutes repeat X 1 • Thermal heat pain threshold testing alone and with vibration at the UV-B site and on the opposite arm • Touch and pain threshold at the UV-B site and on the opposite arm using von Frey filament		
Visit 5 (approximately 24 hours after visit 4)	• Touch and pain threshold at the UV-B site and on the opposite arm using von Frey filament • Thermal heat pain threshold testing alone and with vibration at the UV-B site and on the opposite arm • Touch and pain threshold at the UV-B site and on the opposite arm using von Frey filament	1.5 hours	This visit will occur at Piedmont Plaza 2

You will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have a 50% chance of being in either group.

Group 1: oxytocin
Group 2: placebo

Neither you nor the researcher will know which part of the study you have been assigned to. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

8. WILL I RECEIVE THE RESULTS OF THE STUDY?

Research results that are not clinically relevant will not be disclosed to you.

9. WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk/inconvenience to you. You should discuss the risk of being in this study with the study staff. These can be physical, emotional, financial, or social. Many side effects go away, but sometimes they can be serious, long-lasting, or may never go away. There may be other side effects that we do not know about yet, so be sure to tell the study doctor about any unusual symptoms.

Risks and side effects that we know about related to the thermal heat, UV testing, intravenous catheter placement and oxytocin administration include:

Heat Probe	You may experience brief pain during the thermal heat testing.
Vibratory Testing	You may experience a mild vibration in your forearms.
UV-B	UV-B radiation causes mild sunburn, and may blister or hurt for a few days. The sunburned skin will almost always tan in normal individuals, and may tan more darkly than the surrounding skin for several weeks to several months. It is possible that the darker patches of skin may be present on your legs for up to a year. Long-term darkening (discoloration) or scarring is possible, but rare in people with healthy skin and a history of normal tanning.
Intravenous catheter placement	You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions.
Oxytocin	The dose of oxytocin we are using in this study and the route of administration are approved by the Food and Drug Administration (FDA). However, the

	indication we are using oxytocin for in this study is not approved by the FDA. We will monitor you for many potential problems such as changes in your blood pressure, how fast your heart is beating, and your urge to breathe. We will treat any side effects that you may experience if the changes are enough to concern us. There is the possibility of a feeling of being flushed (warm feeling), headache and increased heart rate with no significant change in blood pressure during or immediately after the infusion. These events have been reported by previous participants but were short lived, lasting approximately 12-15 minutes. Additionally, the following events have been reported as associated with the administration of oxytocin in the laboring female population: Anaphylactic reaction (a severe, life-threatening allergic reaction) Postpartum hemorrhage (heavy bleeding after giving birth) Cardiac arrhythmia (irregular heartbeat) Fatal afibrinogenemia (a very rare, severe and life threatening blood disorder in which the blood does not clot normally) Nausea Vomiting Premature ventricular contractions (irregular heartbeats) Pelvic hematoma (bleeding in the pelvic area) Water intoxication (having more water in your body than you need) Subarachnoid hemorrhage (bleeding in the area between your brain and the thin tissues that cover and protect it) Hypertensive episode (sudden increase in blood pressure) Uterine rupture (the rare event of the uterus tearing during childbirth) Additional precautions are used in the presence of specific anesthetic medications; we are not administering any of these

	medications during this research study.
Pregnancy (women)	Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, OrthoEvra patch, NuvaRing, intrauterine devices (IUD), Nexplanon implant, DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a diaphragm with spermicide with Plan B used for any noticed condom or diaphragm failures. We encourage you to discuss this issue further with your physicians if you have any questions.
Minimal Risk	The risk of harm or discomfort that may happen because of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests. You should discuss the risk of being in this study with the study staff.
Confidentiality and privacy	Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

10. ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are not expected to receive any direct benefit from being in this study. We hope the results of this study will help other people in the future.

11. WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study. This is not a treatment study. Your alternative is to not participate in this study.

12. What Are the Costs?

Study costs, including any study products or procedures that would only be done as part of the study will be paid for by the study sponsor. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

13. Will You Be Paid for Participating?

You will be paid $500 if you complete all the scheduled study visits. If you withdraw for any reason from the study before completion you will be paid according to the schedule below for each completed study visit.

To receive payment, you must provide your social security number, name, and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study, but you will not be paid.

Completion of study visit 1: including heat, touch, and von Frey pain training: $100
Study visit 2 (assess MED): $25
Study visit 3 (for UVB exposure): $25
Study visit 4 (24 hr after UVB exposure): placement of IV $25, IV infusions and thermal testing/von Frey testing $125
Study visit 5: (24 hr after infusion visit): $100 thermal testing/von Frey testing

Completion of all study related procedures: $100

If an IV cannot be placed on Study visit 4: subject will be compensated $150 and subject replaced

14. Will Your Research Records be Confidential?

Your participation in this research and any study records created about your participation will be kept as confidential as possible. The overall results of this study may be presented at scientific or medical meetings or published in scientific journals. Your identity will not be shared unless you give your permission or is required by law to protect you or others.

Your information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity.

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 Web site at any time.

TEXT MESSAGE COMMUNICATION. I give permission to Atrium Health - Wake Forest University School of Medicine, and their respective affiliated entities and representatives (including third-party agents if applicable) to contact me by text message at the number I provided to send information, reminders, and to communicate with me about the research study.

I understand that I am responsible for the standard text message rate of my carrier. I also understand that text messaging is not a secure form of communication and I accept the risk that individuals not involved in the research study may be able to access the text messages. I also understand that texting is not to be used for emergency situations.

EMAIL COMMUNICATION. By providing my email address, I give permission for Atrium Health, Wake Forest University School of Medicine, and their respective affiliated entities and representatives (including third-party agents if applicable) to send me information, reminders, and messages about the research study by email. I understand that these email messages may not be encrypted, and I understand and accept the risks that individuals not involved in the research study may be able to access unencrypted email messages. I also understand that email is not to be used for emergency situations.

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.

15. WHAT IF I AM HARMED FROM BEING IN THE STUDY?

If you get hurt or sick from being in this study, you should seek medical care. Be sure to tell the researcher as soon as possible. You may receive care at Atrium Health. There is no plan to pay for lost income or any non-medical costs that might result from the illness or injury.

Atrium Health - Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for treatment of injuries or illnesses. To the extent research insurance coverage is available under this policy, the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. To the extent research coverage is not available, you or your insurance company may be charged for the costs of medical care. You may receive care at Wake Forest University Baptist Medical

Center and/or Atrium Health.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

16. WHO WILL SEE MY PROTECTED HEALTH INFORMATION?

Who may have access to my information:	*Purpose:*
Any sponsor, including future sponsors, of the study and anyone working on behalf of a sponsor or future sponsor	To oversee the study and make sure the information is correct.
Consultants and employees of Atrium Health – Wake Forest University School of Medicine, including IRB members.	To protect the rights and safety of subjects and make sure the study information is correct.
Organizations that regulate research (such as the FDA, Office for Human Research Protections (OHRP), or similar government agencies in the US and other countries).	To make sure applicable laws are being followed.
Organizations that grant accreditation to hospitals and research programs.	For Atrium Health – Wake Forest School of Medicine to remain accredited.
Monitors, auditors, IRB or other regulatory agencies may be granted direct access to your medical record.	To verify clinical trial procedures or data.

By signing this form, you are giving the researchers permission to use and share your personally identifiable health information. This includes direct access to your medical records.

Please note that the study doctor or study staff may also share personal information about you if required by law (for example, if the study doctor or study staff suspects that you are going to harm someone or yourself, reporting of communicable disease (HIV, hepatitis, tuberculosis, etc.). If you have questions about this, please ask the study doctor.

How will my information be used for this study?
You must authorize the use and sharing of your information by signing this form or you cannot be in the study.

The study principal investigator and study staff will collect, use, and share identifiable health information about you for the following reasons:

- to conduct this research study.
- to review the study, and to check the safety and results of the study.
- to seek government approval of an investigational study drug, vaccine, device or product if such was involved in the trial.
- to assist a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions.

Information used and shared may include:

- information from your medical records related to the research or your routine medical care.
- information collected about you during the research and any follow-up related to study visits, tests, procedures, outcomes, etc.

The collected information may contain your name, address, telephone number, health plan number, date of birth, medical record numbers, dates relating to various medical procedures, and/or other identifying information.

How will my information be kept confidential?

We will keep your personal health information as confidential as possible. Your identity will be protected as required by law and according to any policies described in the study consent form. Researchers may share your information with representatives and agents of the sponsor(s) for the purposes of managing and overseeing the study. Usually, the health information sent to sponsors does not directly identify participants (for example, by name or address). Instead initials and a code number are used. Some personal information, such as date of birth, will usually be included but will not be used to identify you.

Once your information leaves the organization we cannot control how it is used, and the law may not require other groups to protect the privacy of your information.

To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally will have access to your health information.

If this study is designed so that you are intentionally not told what treatment or study intervention you are receiving (called a blinded study), you will not have access to health information in your medical record that was collected as part of this study until those who run the study determine it is no longer necessary to keep you blinded. This usually occurs after everyone in the study has completed study treatment or intervention but can sometimes last until all study data is collected and analyzed.

How do I cancel my authorization?

You can cancel your authorization to use and share your information at any time by writing a letter to the study doctor. If you cancel your authorization, you will not be able to continue in the study. If some aspects of the study were optional, you may cancel your authorization for the optional part(s) of the study and still remain in the main study.

James C. Eisenach, M.D.

[redacted]

If you cancel your authorization, no new information will be collected without your permission. The study doctor and study staff will still be able to use and share your information that has already been collected to maintain the integrity of the study.

When will my authorization expire?

The authorization to use and share your information has no end date.

If study information is used for scientific publications or educational purposes, all identifying information will be removed.

17. What Are My Rights as a Research Study Participant?

Taking part in this study is voluntary. You may choose not to take part, or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped.
Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.
Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

You may be asked to complete a survey about your experiences participating in a research study.

18. Whom do I call if I have questions or problems?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. James Eisenach at [redacted] or after hours you should call the study coordinator by calling [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact [redacted].

19. Signatures

Subject name: _____

- I have read this form and the research study has been explained to me.

- I have had ample time to consider participation in the study and have been given the chance to ask questions, and my questions have been answered. I have been told who to call if I have more questions.
- I understand the research study and voluntarily agree to be in the research study described above.
- I will receive a copy of this consent form after I sign it. A copy will be put in my medical record and/or study record.
- I am not giving up any of my legal rights by signing this form.
- I agree to follow the investigator's instructions.
- I understand and agree that representatives from the sponsor, regulatory authorities and the institutional review board will be granted direct access to my medical records.
- I understand that I may decide to refuse participation or stop participating at any time without penalty and without affecting the quality of my health care or the relationship with the study doctor.
- I understand that there may be consequences to my withdrawal from the study as noted within this document.
- I understand and agree that personal information about me will be collected in this study and from my medical records, and used and processed (manually and by computer) for the purposes of the study by the manufacturer of a medical device used in my treatment or any other designated party that is involved in the study (e.g. hospital, study doctor, regulatory authorities, ethics committees).
- If I so choose, I have provided the name of a person to be contacted by the principal investigator in case I cannot be reached for follow-up.

		AM /PM
Participant signature	Date	Time

For Site Use only:

My signature below certifies the following:

- The subject has been given enough time and an adequate place to read and review this form.
- All elements of the study, as contained in this document, were explained, and discussed with the subject **before** research-related procedures began.
- The subject has had a chance to ask questions and receive answers about this study.
- The subject expressed understanding of the study.
- The subject will receive a copy of the signed and dated consent form/authorization.

Name of person obtaining informed consent (print)

Signature of person obtaining informed consent Date Time AM /PM