Oxytocin reduces noradrenergic-induced opioid-like withdrawal symptoms in individuals on opioid agonist therapy

INFORMED CONSENT DOCUMENT

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BROWN UNIVERSITY
CONSENT FOR RESEARCH PARTICIPATION

Oxytocin to reduce stress-induced craving in individuals with opioid use disorder
Primary Participation
Version #8, May 4, 2022

Principal Investigator: Carolina Haass-Koffler, PharmD
Co-Investigator: Robert Swift, MD, PhD

INFORMED CONSENT FORM

1. You are invited to participate in the following research study:

Oxytocin to reduce stress-induced craving in individuals with opioid use disorder

Key Information

You are invited to take part in a Brown University research study. Your participation is voluntary.

- PURPOSE: The purpose of the study is to evaluate the safety and efficacy of oxytocin in opioid craving after a stress induced condition resulted by a single dose of yohimbine.
- PROCEDURES: You will receive both 40 IU twice a day of oxytocin and oxytocin-placebo. There are two sessions where you will receive a single dose of yohimbine and two sessions where you will receive a single oral dose of yohimbine-placebo. You will be exposed to non-invasive cues, will complete other lab assessments and will have blood drawn at multiple study sessions.
- TIME INVOLVED: There will be seven visits total over the course of 20 days.
- COMPENSATION: Total maximum possible compensation is $550.
- RISKS: Answering questions about your drug and alcohol use may cause you discomfort and/or put you at risk for loss of confidentiality. You may notify a researcher if you feel discomfort. We will also protect your information in locked filing cabinets and on password protected computers.
- BENEFITS: There are no benefits to be expected by your participation in this study.
- ALTERNATIVES TO PARTICIPATION: This is a research study and your participation is completely voluntary.

This consent form may contain words that are used in ways you may not understand. Please ask the study doctor or the study staff to explain anything that you do not clearly understand.

The goal of this study is to determine if, under stress, opioid craving is reduced using a medication.

You are being asked to take part in this study because you have stated that you are receiving *Suboxone, which is the trade name for the generic formulation of the* buprenorphine/naloxone, or methadone as opioid replacement therapy (ORT). This study is being done to determine if a drug

called oxytocin reduces your desire to use opioids while also receiving a single oral dose of yohimbine that increases your stress level.

- Oxytocin is a naturally occurring substance in your body and when administered has been shown to be well tolerated with minimal to no side effects.
- Yohimbine is an investigational drug that has been shown to increase nervous system activity. As in other similar studies, we will use yohimbine to increase stress.

During the study, you will receive either 40 IU twice a day of oxytocin (or placebo) for 7 days. Which medication that you receive will be determined by a process called randomization (a process that is similar to flipping of a coin) and gives each participant in the study an equal chance to receive either oxytocin or placebo.

To test if oxytocin reduces your desire to consume opioids under stress, we will give you yohimbine or placebo (sugar pill) to produce a stress-like condition on 2 occasions, separated by 2 days, after you have taken either oxytocin or placebo. A similar randomization procedure will be used for yohimbine, but you will receive both yohimbine and placebo, the order of which you will receive first will also be randomized. The two yohimbine periods are separated by 2 days (plus or minus 2 days to accommodate your schedule) during which there are no study procedures; we will call/email you to check how you are doing and remind you of your next visit.

This study is called a double-blind study. This means that neither you nor the study staff will know which medication (oxytocin, yohimbine or placebo) you are taking. In case of an emergency, the study staff can find out which group you are in. Neither you nor the study staff will know what you received until all the participants have completed the study. At that time, you may be told about the order of your condition and your response.

In order for you to decide whether or not you wish to be a part of this research study, you should consider the risks and benefits so that you can make an informed decision. This consent form gives you important information about the research study and a member of the research team will discuss this information with you. This discussion will go over all parts of this research: its purpose, the procedures that will be done, and possible benefits and risks. Once you understand what this study is about, you will then be asked if you wish to participate. If so, you will be asked to read and initial each page and sign the last page of this informed consent document.

2. If you decide to participate, the procedures to be followed are explained below:
This study is expected to last approximately 20 days and will consist of a total of 7 visits. You will be assigned a specific ID number for the study to protect your privacy. We will use your ID number rather than your name on all study documents. All information collected during each visit will be kept in a locked cabinet in our locked office here at Brown University. Your data will be entered and saved in password-protected computer files. All lab samples (saliva and blood) using your study ID number will be sent to an outside laboratory and will be tested for possible important clinical conditions (e.g. liver and kidney damage, altered blood analysis, etc.), which could prevent you from participation in the study.

No information from this study will become part of any permanent medical record.

You can stop your participation in this part of the study at any time. If the blood, saliva and urine samples have not yet been analyzed, we will destroy them upon your request. However, if we have already analyzed the samples, you can tell us whether we may keep the information about the results or if you would like us to destroy them.

STUDY PLAN

In order to determine if you are eligible to participate in the study, you must have a breath alcohol content of =0.00% at each visit when you arrive to our office. If able to become pregnant, we will perform a pregnancy test at each visit and it must be negative to participate.

Below is a Table that briefly describes what will occur at each visit and compensation.

Visit		Procedures and Estimated Time	Compensation
1	Screening	Physical exam, three small tubes of blood will be drawn for screening tests (once), for (buprenorphine/naloxone or methadone) levels (once), and for hormones levels (once). Saliva tests (by spitting three different times in a tube), urine (drug screen) and urine pregnancy test (if applicable). Medical and psychiatric history, ECG, vital signs and questionnaires (3 hours)	$40
2	Randomization (day 1)	We will give you 5 days of the study medication (oxytocin or placebo) and will explain how to take the medication. Vital signs and questionnaires, urine pregnancy test (if applicable) (1 hour)	$40
3	Lab Session I (day 5)	You will fill out questionnaires, a small tube of blood will be drawn to test for hormones levels (once), saliva tests (by spitting three different times in a tube), urine test (drug screen), and urine pregnancy test (if applicable). We will measure your vital signs, give you the yohimbine or placebo dose and will start the cue-reactivity for opioid craving (3 hours)	$100
Days 6-7		No study procedures are scheduled; we will call to check how you are doing and to remind you of your next visit	
4	Lab Session II (day 7)	The procedures are identical to those described for Visit #3 above but with the opposite condition for yohimbine or placebo (3 hours)	$100
Days 8-9		There will be a two day wash out period where no study procedures are scheduled. We will call to check in how you are doing. On day 10, you will begin taking the next dose of oxytocin or oxytocin-matched placebo.	
5	Lab session III (day 14)	The procedures are identical to those described for Visit #3 above. You will take yohimbine or placebo.	$100
Days 15-16		No study procedures are scheduled; we will call to check how you are doing and to remind you of your next visit.	
6	Lab session IV (day 17)	The procedures are identical to those described for Visit #3 above. You will take yohimbine or placebo.	$100
Days 18-19		No study procedures are scheduled; we will call to check how you are doing and to remind you of your final visit.	
7	Follow up (day 20)	Questionnaires, urine (drug screen), urine pregnancy test (if applicable) and vital signs (2 hours) END of STUDY	$20 + $50 bonus = $70

A urine drug screen on the first and follow-up visits will be performed at Brown University.

Initials _____

You will be also reimbursed for travel via parking validation or public transportation.

Please note that blood will be drawn at five visits: Visits 1, 3, 4, 5 and 6

NOTE: In the event that research staff are unable to give cash, you will be compensated the full amount via a ClinCard, or via an Amazon e-giftcard, emailed to the email address of your choice.

ClinCard Information

We will mail you the card. You will be given one card for the entire time of your participation and this card may be used to pay you in any future Brown University studies that uses ClinCard. You will also get information about how to use this card and whom to call if you have any questions. Be sure to read this information, including the cardholder agreement from Greenphire.

Money will be added to your card based on the study's payment schedule. You may use this card online or at any store that accepts Mastercard. Please read the FAQ information sheet from your study coordinator for details about the ways you can use the card, some of which may involve fees that will reduce the amount of money on the card. This card is administered by an outside company called Greenphire. Greenphire will be given your name, address, and date of birth. They will use this information only as part of the payment system, and it will not be given or sold to any other company. Greenphire will not receive any information about your health status or the study in which you are participating. If your card is lost or stolen, please call the study coordinator for a free replacement card. If you request a replacement card from Greenphire directly, you may be charged a fee.

VISIT#1 Screening

- Before starting any study procedure, a breath alcohol test will be performed and must be 0.00%. Breath alcohol is measured by blowing into a machine called a breathalyzer. If your breath alcohol is 0.00%**,** the study will be discussed with you, and you will have an opportunity to ask questions about the study.
- If your breath alcohol is above 0.00% you may wait until it is 0.00% or return another day.
- If you agree to participate, you will be asked to sign this consent form. You will receive a copy of the signed consent form.
- You will be asked to provide your contact information.
- You will have a physical exam and your blood pressure, pulse, weight, height, and temperature will be recorded. You will also have an electrocardiogram (ECG) that measures the electrical activity of your heart.
- You will be asked about any medications that you are taking. For your safety, it is IMPORTANT to discuss all medications that you are taking with the study staff. This includes over the counter medications and vitamins. Drug interactions are serious and could cause harm.
- There are no known drug-drug interactions between Suboxone (buprenorphine/naloxone) and or methadone and yohimbine. To protect you against any risk of additional drug-drug interactions, we will ask you of any prescriptions or over-the-counter medications to ensure that there are no interaction with oxytocin and yohimbine.
- We will be collecting blood samples to conduct screening tests (approximately 2 teaspoons, one tube) and to test for hormones levels (less than 1 teaspoon, small vial). Saliva tests are done by spitting three different times into a tube. We will collect saliva three times total: upon arrival, after the dose of yohimbine 45 minutes later, and at the end of the session. You will be asked to provide urine samples for drug screening and routine analysis.
- You will be examined to determine if you are having any opioid withdrawal symptoms.

- You will complete a number of questionnaires asking you about your drug use, family history of drug use, mood, urge and craving for drugs.
- If applicable, you will be asked about your periods or menopausal status and will be tested for pregnancy at each visit.
- You will be asked about your medical history as well as about your traumatic and psychiatric history, including past use of any substances of abuse. If answering these questions makes you uncomfortable, you can decide not to answer these questions and this does not affect your participation in the study.

VISIT#2 (Randomization) - Day 1. Upon your arrival, a breath alcohol test will be performed and must be 0.00%. After medical clearance, you will be randomized to either oxytocin or the oxytocin matched placebo group that will be dispensed as a nasal spray and the session will include a 30 minute discussion of the proper administration of the nasal spray, the potential side effects and drug-drug interactions. Those who are able to become pregnant will provide a urine sample for a pregnancy test.

In the event that we determine (based upon a case by case basis) that study session 2 can safely and effectively be conducted remotely, we will set up a time for a study session phone call and ask you the paper assessments typically filled out by you in lab over the telephone. If a remote session occurs, you will not be asked to come into the lab, and all procedures will be conducted over the telephone.

Visit 3 (Laboratory Session I) – Day 5. Upon your arrival, a breath alcohol test will be performed and must be 0.00% and you will provide a urine sample for drug toxicology screening (which will be kept confidential and not shared with your Suboxone (buprenorphine/naloxone) prescriber). A pregnancy test will be conducted (if applicable). Blood will be collected to test for hormone levels (one small tube), and the first sample of salivary cortisol (small tube) will be collected. You will then complete a series of assessments and receive a single oral dose of yohimbine or yohimbine-matched placebo. Fifteen minutes later, we will administer a dose of oxytocin or oxytocin-matched placebo (40 IU, 4 sprays per nostril), and the cue-reactivity will begin. The Cue-Reactivity (CR) Task will be administered with cues selected based on your drug experience. To measure cue-induced opioid craving, you will a view images of neutral stimuli and then images of opioid drug use. You will rate your craving, then the second sample of salivary cortisol will be collected (30 min later). Vital signs will be monitored during the entire procedure. Finally, you will complete post-Cue measures, will have your vital signs measured, and the last sample of salivary cortisol will be collected (for a total of 3 samples of saliva for the visit).

During Study **Days 6-7** there are no study procedures, but we will call you to check how you are doing. We will also contact you either by phone or email to remind you of your next visit.

Visit 4 (Laboratory Session II) – Day 7 You will come back after two days. The procedure will be identical to Visit 3, but you will receive the opposite condition (yohimbine or yohimbine-matched placebo).

There will be a two day wash out period where there will be no study visits. We will mail you the next intranasal medication (i.e. oxytocin or placebo) which you will take for one week. Whichever you did not take the first week, you will take the second week.

Initials _____

Visit 5 (Laboratory Session III) – Day 14 You will come back for the third lab visit after taking the second round of medication for 5 days. The procedure will be identical to Visits #3-4, and you will receive yohimbine or placebo.

Visit 6 (Laboratory Session IV) – Day 17 You will come back for the fourth and final lab visit two days after the third lab visit. The procedure will be identical to Visits #3-5, and you will receive yohimbine or placebo.

Visit 7 (follow-up) – Day 20 After three days, you will come to the lab for the final assessments. **END of STUDY**

3. Risks and Discomforts:

The following complications or risks have been reported, are known, or may occur:
Please take your time with this section and feel free to discuss any words you may not understand with the research staff.

Answering questions about your drug use may cause you discomfort and/or put you at risk for loss of confidentiality. You may notify a researcher if you feel discomfort. We will also protect your information in locked filing cabinets and on password-protected computers.

Both oxytocin and yohimbine have been given to many research participants, including healthy individuals, individuals affected by chronic or serious medical conditions (i.e. obesity, gastric surgery, chronic heart failure, diabetes, malnutrition, digestive disorders, cancer, and others), and individuals affected by mental illness (i.e. psychotic major depression, Post-traumatic Stress Disorder). Also, both drugs have been used in studies with individuals with alcohol and opioid use disorders.

Some discomfort may occur during the blood draw.

Oxytocin: there are usually no side effects in individuals that administer intranasal oxytocin spray at the dose provided in this proposed project. Common side effects include: relaxation, irritability and stomach cramps. Less common side effects that are reported at higher doses include: mild dizziness, dry mouth, nausea, vomiting, nasal irritation, runny nose, or tearing of the eyes. These are common with medications given by nasal spray.

You will be instructed on how to properly administer the nasal spray with an empty spray bottle and you will administer the first dose while at the laboratory to ensure correct administration.

With your copy of the informed consent, you are given a list of mental health resources that are available in the State of Rhode Island. Some participants may have suicidal thoughts or actions. Should you have thoughts of suicide for any reason before you are randomized, the study physician will be notified and he will assess the best course of action to take, including coming here to talk with you or referring you to receive appropriate medical or psychiatric interventions. For your safety we will monitor your mood or any thoughts of suicide closely during the entire course of the study. Between visits, however, if you feel a change in your mood or if you feel depressed or feel you may harm yourself, please contact us, or one of the resources provided to you. The principal investigator,

the study physician, and the nurse will be monitoring your mood and behavior as a way to measure your risk of suicide and to measure depression. Should you develop any medical or psychiatric problems that require clinical attention, the study physician will refer you to receive appropriate medical or psychiatric interventions. However, there is no provision for any medical or monetary compensation in the event of physical or psychological injury resulting from these research procedures. Brown University does not routinely provide any compensation for these events.

4. **The benefits, which can be expected, have been described as:** There are no benefits to be expected by your participation in this study. You will have the chance to contribute to research that may prove beneficial to you or to others in the future.

5. **Financial Considerations:** There will be no cost(s) to participate in this study. The study medications and all procedures that are required for the study will be provided to you. If eligible for the study, you will be compensated for your time and travel costs. The amounts of compensation that can be received are described in the study table on pages 2-3. The maximum amount of compensation that can be received if you complete all study procedures is **$350**. However this amount can vary depending upon missed appointments.

6. De-identified data will be kept and used for future research. This includes your biospecimens. We may share your de-identified data and biospecimens with researchers at Brown or other institutions. It is unlikely but possible that biospecimens may be used to generate discoveries or other applications for commercial profit. You will not share in any profit arising from such uses.

7. We may learn things about your health as part of the research. If this happens this information will be provided to you. For example, if you become pregnant or if your blood test results or ECG reveal any abnormalities. You may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions.

8. Should any problems arise or you experience any side effects during the study, you can contact our lab at (401) 863-6624 during normal business hours. After hours, you may call (401) 273-7100 and ask to have the study physician paged.

9. **Your confidentiality will be maintained as follows:**

- This study will ask potentially sensitive information about your alcohol and drug use. Every attempt will be made to keep this information confidential. All reasonable efforts will be made to protect the confidentiality of your participation in the study. However, it is possible that your confidentiality may be violated.

- In order to protect your confidentiality, all your records collected during the study will be kept in a locked file under a code number rather than your name. None of the information, including this consent form, will become part of your medical record. Your name will not be publicly disclosed at any time, and the records will be strictly maintained according to current legal requirements. However, please note that state law mandates reporting of any incidents of child or elder abuse (age 60 or older).

- If you give us your permission by signing this document, information (including biospecimens) which does not identify you by name, may be used for medical and scientific purposes including

teaching and/or publication. No one at Brown University who is unaffiliated with this research project will have access to information that identifies you.

By signing this document you give Dr. Haass-Koffler permission to share your de-identified data collected (including biospecimens) during this study.
The results of the study will be analyzed, and the results of this study may be used for other research purposes, including:

- o reviewing the safety or effectiveness of the study drug and other products or therapies;
- o developing a better understanding of disease; o improving the design of future clinical trials

Because this research involves articles regulated by the Food and Drug Administration (FDA), the FDA may choose to inspect and copy medical or research records that identify individual research subjects.

10. <u>Certificate of Confidentiality from the National Institutes of Health (NIH)</u>

This research is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by NIH which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of child or elder abuse and neglect, or harm to self or others.

11. **If you have questions about your rights as a research subject** or otherwise, please contact the Brown University Human Research Protection Program at (401) 863-3050 or toll-free at 1-866- 309-2095 (for use within the Continental United States and Canada).

12. **You are making a decision whether or not to participate in this study.**

Your participation in this study is voluntary. Your decision whether or not to participate will not hurt your future relationship with Brown University. If you decide to participate, you are free to withdraw your consent and to discontinue your participation without prejudice. If you choose not to participate or if you withdraw from this study, it will not adversely affect your relationship with the doctors and

staff at Brown University. If you so choose you may also withdraw your permission for Dr. Haass-Koffler to use and share your collected research data.

If you start the study and then cancel your permission, you will not be able to continue to participate in the study. This is because the study staff and/or the study doctor would not be able to collect the information needed to evaluate the goals of the study.
If you wish to withdraw, it is important to notify the study physician because this may involve a visit to the clinic for an exit assessment.

13. You understand that you do not have to participate in this study.

If it is in your best interest medically, or if you do not follow the study procedures required of the study, the study doctors, the PI, and her staff can stop your participation in the study without your consent. This could be because you have had an unexpected reaction, or have not followed instructions, or because the entire study has been stopped. Regardless of whether you choose to withdraw or if your participation in the study is terminated, certain procedures must be followed in ending your participation in the study in order to protect your safety. You may be asked questions about any reactions you may have had during this study and may be asked to cooperate in certain tests such as physical examination and laboratory testing.

You have read and understand the preceding information describing this medical research study. It has been explained you in detail by the study doctor or the study staff and all of your questions have been answered to your satisfaction. You voluntarily consent to participate in this study. You have read this informed consent and agree to participate in the study. You will receive a copy of this consent form.

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

14. May we contact you for future studies?

Yes No Initial_____

15. May we store your de-identified blood and saliva samples (biospecimens) for future studies?

Yes No Initial_____

THIS EVIDENCE OF INFORMED CONSENT MUST BE SIGNED BY THE SUBJECT.

PARTICIPANT AGREES TO HAVING HIS/HER BLOOD SAMPLES STORED FOR TESTING ADDITIONAL HORMONAL LEVEL FOR FUTURE STUDIES:__YES__NO

PARTICIPANT (printed name):_____ DATE: _____ TIME: _____

I have explained this study to the participant.

PERSON EXPLAINING THE STUDY:_____ DATE: _____ TIME:_____

PARTICIPANT SIGNATURE: _____ DATE: _____ TIME: _____

Attachment #1

Substance Use & Mental Health

- Services for Adults: BH Link at (401) 414-LINK (5465)
- Services for children: Kids Link at (855) 543-5465
- RI's Hope & Recovery Support Line: (401) 942-STOP (7867)
- National Suicide Prevention Lifeline: (800) 273-TALK (8255)
- The Disaster Distress Helpline: 800-985-5990 or text TalkWithUs to 66746

Employment Related Issues

- The Rhode Island Department of Labor and Training COVID-19 Assistance Line and email address (401-462-2020; dlt.covid19@dlt.ri.gov) to provide support regarding employment issues. The phone line is staffed Monday to Friday during business hours.

Resources for Food Access

- Rhode Islanders seeking food assistance may locate their local food pantry online through the RI Community Food Bank or call (401) 942-6325 for a pantry near you.

Resources for People Experiencing Homelessness

- For those in our community experiencing homelessness, you can call the Rhode Island Coalition for the Homeless coordinated entry system hotline at (401) 277-4316.

Domestic Violence

- The Rhode Island Coalition Against Domestic Violence and all of its member agencies are open, as are domestic violence shelters. Rhode Islanders seeking help can call 1-800-494-8100.

Health Insurance Information

- If you have lost your employer-sponsored coverage due to job loss, or if you have experienced another qualifying life-changing event, you may qualify to sign up for coverage through HealthSource RI. You must sign up within 60 days of your qualifying life event. Please call 1-855-840-4774 for assistance.