Effects of Pioglitazone on Stress Reactivity and Alcohol Craving

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UTHealth
The University of Texas
Health Science Center at Houston

CONSENT TO TAKE PART IN RESEARCH

Simple Study Title:	Pio Alcohol Stress
Full Study Title:	Effects of Pioglitazone on Stress Reactivity and Alcohol Craving
Study Sponsor:	Department of Psychiatry and Behavioral Sciences
Principal Investigator:	Jin H Yoon, PhD Assistant Professor University of Texas Health Science Center Department of Psychiatry and Behavioral Sciences Center for Neurobehavioral Research on Addictions
Study Contacts:	Jin Yoon, Principal Investigator, [redacted] Sarah Jensen, Research Assistant [redacted]

The purpose of this study is to assess the effects of a study medication (pioglitazone) on stress reactivity and alcohol craving. If you choose to participate in this study, you will be asked to take the study medication, attend weekly clinic visits for 8 weeks, answer various study-related questionnaires, and complete 3 reactivity assessments. The total amount of time you will be in this study is approximately a couple of hours each week.

There are potential risks involved with this study that are described in this document. Some known risks include upper respiratory tract infections, edema (swelling in the legs), headache, sinus swelling, myalgia (muscle aches), and sore throat. More rare but potentially serious side effects are worsening of congestive heart failure, liver failure, low blood sugar, and increased ovulation. Because of this risk, individuals with congestive heart failure will not be allowed into this study. An additional significant risk that has recently been reported is increasing the risk of bladder cancer in patients who took Pioglitazone for long periods of time. However, this study will only involve taking Pioglitazone for 8 weeks. This is a short time period, and is not associated with the increased risk of bladder cancer.

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

Your decision to take part is voluntary. You may refuse to take part or choose to stop taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from Dr. Yoon and research staff with the University of Texas Health Science Center at Houston (UTHealth) or the Department of Psychiatry and Behavioral Sciences in the McGovern Medical School.

What is the purpose of this research study?

The purpose of this study is to see how well the drug pioglitazone works at help people quit drinking alcohol. This study will also test the safety pioglitazone and look at the effects of pioglitazone on stress

and/or anxiety and alcohol craving. Pioglitazone is currently approved by the Food and Drug Administration (FDA) for the treatment of diabetes and metabolic disorders. Pioglitazone will be used in an off-label manner in the current study. You have been invited to join this research study because you are interested in quitting drinking and report a history of stress and/or anxiety.

This is a local study that will be conducted at the Center for Neurobehavioral Research on Addiction in the Behavioral and Biomedical Sciences Building. The study will enroll a total of 60 people. This study is supported by funds from the National Institute on Alcohol Abuse and Alcoholism.

Who is being asked to take part in this study?

You are being asked to take part in this research study because you have reported being concerned about your alcohol use and think it may be related to your stress and/or anxiety. This study is being conducted at UTHealth. About 60 people will take part in the study worldwide/in this country/in this city including approximately (state local enrollment target) at UTHealth.

What will happen if I take part in this study?

If you agree and are able to take part in this study you will first sign the consent form before undergoing these study procedures:

- First you will be asked to sign a separate consent form to participate in an intake evaluation as part of the general screening procedures for research studies in our clinic. This intake evaluation includes a psychiatric interview, a history and physical examination, a blood draw for serum chemistry and blood count, urine sample for urinalysis and an electrocardiogram (EKG) which will monitor how well your heart is working. You will also be asked to provide a urine sample for drug testing. If you are female, you will also undergo a urine pregnancy test. The EKG, urine testing, and pregnancy testing will be repeated during the 8 weeks of the study.
- Answer a number of research questionnaires related to stress, anxiety, illicit drug use and cigarette smoking, and alcohol use and craving.
- After the initial baseline screening, attending weekly clinic visits for 8 weeks.
- You will be asked to participate in CAROMA sessions (cell-phone assisted remote observation of medication adherence) for days in which you do not have a clinic visit. These sessions will consist of you showing your face on camera as you take your medication at home and will be visually confirmed by research staff. These session help ensure study medication is taken at the same time each day throughout the study. Each CAROMA session should last no longer than 1 minute.
- Complete 3 stress reactivity assessments at the initial screening and at weeks 4 and 8. The stress reactivity assessment will involve a Cold Pressor Task, in which you place your dominant arm in an ice water bath for up to 2 minutes or until you can no longer stand it, whichever comes first. This Cold Pressor Task is known to reliably activate the body's stress response and is a common assessment in stress-related research. We will also record your facial reactions, using a video camera connected to a computer, during the Cold Pressor Task for later analysis. Finally, we will take salivary cortisol measures before and after the stress reactivity assessment. This will involve

holding a cotton swab in your mouth for approximately one minute. Heart rate and blood pressure using standard medical equipment will be measured several times over the course of the stress reactivity assessment.

- A urine sample will be collected at each visit to test for illicit drug use and recent alcohol use.
- Breath samples will be assessed at each visit to test for breath alcohol levels. Breath samples will also be used to assess for carbon monoxide for cigarette smokers.
- You will have about one table spoon of blood drawn from a vein in your arm during the baseline screening.

If you agree to take part in this study you will receive the study medication pioglitazone or placebo (a tablet that contains no active ingredient). It is not known whether pioglitazone will be of benefit. For this reason, some study participants may receive a placebo. This will allow a careful comparison to study the benefits and side effects of the investigational drug. Only the doctor will know if you are receiving pioglitazone or placebo.

Outline of Study-Related Assessments and Procedures

Study Week **Procedures and Assessments**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Consent and Baseline Screening									
Psychiatric interview, medical history and physical examination, blood draw for serum chemistry and blood count, EKG.	X								
Drug and alcohol use history and questionnaires	X								
General Study-Related Questionnaires and Assessments									
Alcohol Use and Craving Questionnaires	X	X	X	X	X	X	X	X	X
Stress and Anxiety Questionnaires	X	X	X	X	X	X	X	X	X
Urine Samples for Drug and Alcohol Testing	X	X	X	X	X	X	X	X	X
Breath Samples for Alcohol and Cigarette Smoking	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X
Receive Study Medication (Pioglitazone or Placebo)	X	X	X	X	X	X	X	X	
Assess Medication Compliance and Adverse Events		X	X	X	X	X	X	X	X
Stress-Reactivity Assessment									
Cold Pressor Task	X				X				X
Salivary Cortisol, Heart Rate, Blood Pressure, Alcohol Craving, Video Monitoring	X				X				X

What choices do you have other than this study?

The only alternative is not to take part in this study.

What are the risks of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

While in this study, you are at risk for side effects. The study doctor will discuss these risks with you. This study may include risks that are unknown at this time.

Medication: Pioglitazone is approved by the FDA for the treatment of diabetes. The most common side effects seen in patients treated with pioglitazone for diabetes compared with patients treated with placebo include upper respiratory tract infections, edema (swelling in the legs), headache, sinus swelling, myalgia (muscle aches), and sore throat.

More rare but potentially serious side effects have been reported with pioglitazone. In studies in patients with diabetes the most serious potential side effect is worsening of congestive heart failure. Because of this risk, individuals with congestive heart failure will not be allowed into this study.

An additional significant risk that has recently been reported is increasing the risk of bladder cancer. An increase in bladder cancer was seen in patients who took Pioglitazone for long periods of time. However, this study will only involve taking Pioglitazone for 8 weeks. This is a short time period, and is not associated with the increased risk of bladder cancer.

There have been rare reports of liver failure in people taking pioglitazone. Due to this risk, liver function tests will be performed every two weeks during the trial.

Patients treated with insulin or other anti-diabetic medication in addition to pioglitazone may be at increased risk of hypoglycemia (low blood sugar). Due to this risk subjects with diabetes will not be allowed into the study.

For female patients, pioglitazone can increase ovulation (egg cell release) in women who have not yet undergone menopause. In addition, similar medicines decrease the effectiveness of oral birth control. Because of these facts, female subjects must agree to an effective barrier method of contraception (condom).

Pregnancy: There are no known adverse events of pioglitazone during pregnancy but there are inadequate studies in humans. Animal studies using doses 10 to 40 times the maximum recommended human dose showed increased rates of miscarriage, delayed development, smaller fetuses, and delayed birth. Due to these issues, all female subjects must agree to an effective barrier method of contraception.

Blood Draws: Obtaining blood samples may cause some discomfort, feeling lightheaded, fainting, bruising, clotting, and bleeding from the site of the needle stick and, in rare cases, infection.

Cold Pressor Task. Individuals with cardiovascular disorders and neurological disorders should not participate in the cold-pressor task due to cardiovascular change induced by the testing. Because of this, individuals with cardiovascular and neurological disorders will not be allowed in this study. Due to individual variation in pain and cold sensitivity, for some subjects the cold water may become too painful to sustain immersion for the full 2 minutes. There are no lasting effects from placing the hand and wrist in ice water (~0° Celsius) for 2 minutes.

Psychological: Items on certain questionnaires and interviews might be perceived as psychologically discomforting to some subjects. While subjects may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low.

Confidentiality: There is a possible risk of breach of confidentiality

Questionnaires: You may get tired when we are asking you questions or you are completing questionnaires. You do not have to answer any questions you do not want to answer.

What are the benefits to taking part in this study?

You may receive no direct benefit from being in the study; however, your taking part may help patients get better in the future.

Can you stop taking part in this study?

Your decision to take part is voluntary. You may decide to stop taking part in the study at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from Dr. Yoon, research staff, and Department of Psychiatry and Behavioral Sciences in the McGovern Medical School

Also, there may be instances where the PI may withdraw you from the research study. They include if you have an adverse effect from the study drugs, if you need a treatment not allowed in this study, if you are unable to keep your study-related appointments, if you do not take the study drug as instructed, if you do not later consent to future changes that are made in the study plan, if the study is stopped by the sponsor ahead of schedule, or for any other reason. Should the study be stopped, your study doctor will discuss other options for treatment. They will explain to you the procedures to allow you to stop taking part in the research study in the safest manner.

If you withdraw, information collected may still be used in the study unless you request that it not be used. To withdraw from the study, please contact Dr. Jin Yoon at [redacted]

What happens if you are injured during the study?

If you suffer an injury as a result of taking part in this research study please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, necessary facilities, emergency treatment and professional services will be available to you, just as they are to the general community. You should report any such injury to Dr. Yoon 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.

What are the costs of taking part in this study?

If you decide to take part in this research study, you will not incur any additional costs.

You will be paid for taking part in this research study. You will receive $50 for completing the baseline screen. You will receive $25 for each of the weekly visits (9 visits, $225 total). You will receive $25 for completing each of the stress reactivity assessments at screening and Study Weeks 4 and 8 ($75 total). You will receive $100 for completing the study. Additionally you can earn an additional $10 for each study week ($80) for demonstrating that you are taking your study medication. The grand total you may

receive is up to $530. Finally, you will receive a compensation for bus fare/parking for each study visit.

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

If you receive payment for taking part in this study please be informed that you will be asked to complete a copy W-9 form that will be forwarded to the accounting department as a requirement by the Internal Revenue Service. You will also be issued a 1099-Misc form from this study for tax reporting purposes.

How will privacy and confidentiality be protected?

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 The University of Texas Health Science Center at Houston to use or disclose (release) your health information that identifies you for the research study named above.
The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston for the purposes of verifying research records. The researchers may also disclose information to the following entities:

- National Institutes of Health
- Department of Psychiatry and Behavioral Sciences at McGovern Medical School
- Food and Drug Administration (FDA)
- Data Safety Monitoring Board

The University of Texas Health Science Center at Houston is required by law to protect your health information. By signing this document, you authorize The University of Texas Health Science Center at Houston to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. The University of Texas Health Science Center at Houston 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 write to the primary investigator Dr. Jin H. Yoon at [redacted]

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

NDA

This study is funded by the National Institute on Alcohol and Alcoholism (NIAAA). All studies funded by NIAAA, including this study, now submit data to the National Institute of Mental Health Data Archive (NDA) at the National Institutes of Health (NIH). NDA is a large database where deidentified study data from many NIH studies are stored and managed. Sharing your deidentified study data helps researchers learn new and important things about brain science more quickly than before.

Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. The study researchers will have to collect your personal information from you in order to make that code number. The code number cannot be used to identify you. The study researchers will never send your personal information to NDA.

It is possible that you will participate in more than one study that sends data to NDA. NDA can connect your data from different studies by matching the code number on your deidentified data from each study. This data matching helps researchers who use NDA data to count you only one time. It also helps researchers who use NDA to better understand your health and behavior without knowing who you are. Your unique, de-identified code number is generated based on your name (first, middle, last), date of birth, sex, and city/location of birth.

During and after the study, the study researchers will send deidentified study data about your health and behavior to the NDA. Other researchers across the world can then request your deidentified study data for different research projects. Every researcher (and the institution to which they belong) who requests your deidentified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about brain science and how to help others who have problems with brain science. NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to NDA. You can still participate in this research study even if you decide that you do not want your data to be added to NDA. If you know now that you do not want your data in NDA, please check the box below stating that you do not want your data in the NDA.

☐ I do not want my data to be shared with the NDA.

If you decide any time after today that you do not want your data to be added to NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, it is available on-line at http://nda.nih.gov.

Who can I contact if I have questions about the study?

If you have questions at any time about this research study, please feel free to contact the Dr. Yoon at [redacted], as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input 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].

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