A Randomized Trial of Pioglitazone for the Treatment of Alcohol Use Disorder

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Title of Study: A Randomized Trial of Pioglitazone for the Treatment of Alcohol Use Disorder
Principal Investigator: Eric Dieperink, MD **VAMC:** Minneapolis - 618

INTRODUCTION

It is important that you read and understand the following explanation of the proposed research study before you agree to participate. This consent form describes:

- The purpose,
- The description of the study,
- The benefits,
- The risks and/or discomforts (including any potential for pain),
- Steps taken to decrease or eliminate the risks, discomforts, or possible pain,
- Any other treatments that may be available, and
- Confidentiality and use of research results.

Whether you decide to participate or not, treatment at the VA for which you are eligible will not be affected.

This consent form may contain words you do not understand. Please ask the study doctor or the study staff to explain any words or information unclear to you.

PURPOSE OF THE STUDY

You are being asked to voluntarily participate in a research study to find out whether the drug pioglitazone, a medication typically used for the treatment of diabetes, is a safe and effective treatment for Alcohol Use Disorder. You have been asked to participate in this study because you are drinking alcohol and have an Alcohol Use Disorder. Your participation is expected to last 16 weeks and approximately100 people will be in the study at this site.

DESCRIPTION OF STUDY

The following information describes what will happen while you participate in the study. Qualifying/baseline and week 4 and 14 visits will be done in person, all other visits will take place by phone or may be done in person if needed.

Qualifying/Screening Assessment (45 minutes): At the first visit, the study procedures will be explained to you and you will be given the opportunity to ask questions. You will be asked to provide written consent by signing this consent form. If you agree to participate, you will be given a breathalyzer test. The test result must be below 0.05 in order to proceed with the qualifying assessment and to sign the informed consent.

Next you will complete a structured interview about your alcohol and drug use history and answer questions about your alcohol and drug use over the past 90 days. Women of childbearing potential will be given a pregnancy test. After completing the qualifying assessment, you will be notified within 7 days of your eligibility. In some cases, you will be notified immediately following the screening visit. Both eligible and ineligible participants will be compensated for

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completing the screening visit. You should not enroll in this study if you have diabetes or congestive heart failure.

Randomization: If, after completing these tests and questionnaires, you are eligible to enroll in this study, you will then be randomly assigned (like by the flip of a coin, with a 50-50 chance of either outcome) to the experimental group and receive the drug pioglitazone or to the control group and receive a placebo. A placebo, sometimes called a "sugar pill," is a pill that tastes, looks, and smells like the study drug but has no real medicine in it. You and the research team will be unaware (blinded) to which group you are assigned; only the clinical research pharmacist will know what group you are assigned to. You will be given a wallet card with the research pharmacy's number. If a medical professional needs to know whether you are taking the study drug, the medical professional can call the pharmacy to obtain any necessary information. Please ask the study doctor for more information if you have any questions at all about this type of study.

Baseline Visit (Week 0, 30 minutes): During this visit, you will be asked to complete surveys about your mental health, alcohol and drug use, depression, anxiety and posttraumatic stress disorder symptoms. You will also receive a brief counseling (15 minutes) to emphasize the importance of taking your assigned medication. These surveys and the counseling are for research purposes only and will not be completed if you decide not to take part in this study. All the information collected for this study will remain strictly confidential. The following blood tests will also be obtained: GGTP, ALT, AST as markers of alcohol use, BNP a marker of possible heart failure, creatine kinase (CK) a marker of muscle damage and C-Reactive Protein (CRP) and other inflammatory markers. A urine sample will also be obtained for a drug test as a marker of substance use, and EtG and EtS as markers of alcohol use.

Follow-Up Visits, weeks 1, 2, 3, 4, 6, 8, 10, 12, 14 and 16 (30 minutes each):

1. Breathalyzer for alcohol – week 4 and 14
2. Surveys
3. Brief counseling
4. Urine Sample for EtG and EtS Test– **Weeks 4, and14**
   Collected to determine alcohol use
5. Blood Draw for GGTP, ALT, AST– **Weeks 4, and 14**
   Collected as markers of alcohol use (GGTP, ALT and AST)
6. BNP will be assessed from blood draws **Weeks 4, 14**. BNP is a marker of possible heart failure. CK will be assessed from blood draws at **Weeks 4 and 14**. CK is a marker of possible muscle injury.

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7. C-Reactive protein (CRP)/inflammation blood test at **Weeks 4 and 14** . CRP is a measure of inflammation.
8. Inflammatory markers (Interleukins, Tumor necrosis factor alpha and others) will be collected for research purposes and at Weeks 4, 8 and 14.

	Qualifying	Baseline Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
Breathalyzer	x	x				x					x	
Surveys*	x	x	x	x	x	x	x	x	x	x	x	x
Brief Counseling		x	x	x	x	x	x	x	x	x	x	x
Urine Sample		x				x					x	
Blood Sample		x				x					x	

*Baseline survey includes collecting demographic information and medical history, TLFB (Time Line Follow-back), and SCID-5 (Structured Clinical Interview for DSM-5). All the following visits include the BSI (Brief Symptom inventory), BDI-II (Beck Depression Inventory-second edition) , OCDS (obsessive-compulsive drinking scale), PTSD Checklist for DSM-5 (PCL-5) and TLFB.

Medication doses: At week 0, you will be started on 15mg of medication by mouth to take each day. At the week 1 visit the dose will be increased to 30mg per day and at week 2 the dose will be increased to 45mg per day. You will take 45 mg of the medication each day until week 14 then the medication will be stopped. You should bring in all of the medication that you have left with you to each visit.

Attending Appointments while Legally Intoxicated or Visibly Impaired: If your breathalyzer reading is greater than 0.05 or you are visibly affected by alcohol when you arrive for your study appointments, the research staff will complete an evaluation and determine appropriate steps to ensure your safety and the safety of others. Such steps may include requesting that you remain in the clinic for observation until your blood alcohol level drops, requesting that you contact someone (relative or friend) who can pick you up, or escorting you to Urgent Care for further evaluation. If you choose not to cooperate with the recommendation of the nurse, the VA Police may be called in order to ensure your safety and the safety of others. If your alcohol level is over the legal limit of .08, VA police are obligated to prevent you from driving. That may include

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"booting" the car, calling a friend or relative to come drive you, sending you home in a taxicab, or, if serious, seeking emergency hospitalization or detoxification.

RISKS AND/OR DISCOMFORTS

The procedures in this study may cause all, some, or none of the risks listed. Rare, unknown or unexpected risks may also occur.

A. Study Medication: There are known risks and side effects associated with Pioglitazone. You should not take Pioglitazone if you have severe heart failure (Class 3 or 4 New York Heart Association classification) or if you are allergic to pioglitazone hydrochloride.

- **Common Risks (more than 10 out of 100 people):**
  - Edema (swelling of the ankles)
  - Cold-like symptoms (upper respiratory tract infection)
- **Less Common Risks (1-10 out of 100 people)**
  - Headache
  - Bone fractures in females
  - Muscle pain
  - Cough, sinus and throat inflammation
  - Weight gain or weight loss
- **Rare but Serious Risks (less than 1 out of 100 people)**
  - Decreased serum triglycerides, increased HDL-cholesterol, weight gain, weight loss
  - Decreased hematocrit (anemia), decreased hemoglobin (reduced red blood cells)
  - Bladder Cancer: If you have active bladder cancer or a history of bladder cancer, it is not recommended to take Pioglitazone. There may be an increased risk of bladder cancer in patients taking Pioglitazone.
  - blurred vision, decreased visual acuity, shortness of breath (associated with weight gain and/or edema), hepatic failure (very rare), hepatitis, increased serum transaminases, macular edema (vision changes)

B. Interviews and Questionnaires: The interviews and questionnaires that you will be asked to complete include questions about your use of drugs and alcohol and psychological symptoms that you may find uncomfortable or embarrassing. You need not answer any questions that upsets you. These questionnaires will ask about your current mood, any psychological symptoms

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you might be having, current alcohol/drug use, and aspects of alcohol craving. If you become upset by any question you may skip it. As a result of participation in this study, you may learn information about your drinking or psychological status that could be upsetting to you. If you are upset about the results learned during the course of this research study, Dr. Dieperink may refer you to a counselor.

C. Confidentiality: As with all personal information that is collected, there is a risk of some of the information collected as a part of this study being accessed by those not permitted to view it. This risk is slight, and we take many precautions to prevent this from happening. We keep a file with your name and identifying information in a separate folder from your research data and have a code that helps us keep track of it. We lock all paper files in file cabinets in locked offices to protect your privacy. Any computerized data will be stored on servers that are password protected and only accessible by research staff for this study. We don't discuss our participants in places where we can be overheard. We treat your research data in exactly the same way that we would treat your medical data. A breach in confidentiality and a resulting loss of privacy could result in monetary loss due to identity theft or carry other risks affecting your ability to get insurance, current or future job status, plans to have a family, relations with your family, immigration status, parental rights or responsibilities, credit history, status in the community, or could result in embarrassment. However, the research team will make every effort to protect your private health information and to guard against any loss of privacy.

D. Blood Drawing: Approximately 1 tablespoon of blood will be drawn from your arm at the baseline visit and at weeks 4, 8, 12, 14 and 16. Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of the puncture. There is also a slight possibility of infection. Your samples will only be stored long enough to analyze and then will be discarded.

E. Female Participation: It is unknown if Pioglitazone is safe to an unborn baby. Pioglitazone may also induce ovulation and may increase your chances of becoming pregnant. To reduce the risk of an unintended pregnancy, women of childbearing potential need to use a barrier method of birth control during their participation. You will not be allowed to participate in the study if you plan to become pregnant during your participation time. You should not take Pioglitazone if you breastfeed your baby.

F. Contraindications
There are several drugs (prescription and non-prescription) that may cause problems when taken with the study drug. The investigators will carefully review all of the drugs you are taking before

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giving you the study drug. If any other health care provider prescribes any new drug(s) for you while you are in this study, please tell Dr. Dieperink before you take the new drug(s). You could also have your provider talk to Dr. Dieperink before prescribing the new drug(s). Do not take any new over-the-counter drugs or herbal or dietary supplements while you are in this study unless you first check with the investigator.

EMPLOYEES AS RESEARCH SUBJECTS

If you are a VA employee you are considered a special class of research subject who deserves special protections: 1) Your decision to participate in this study should be free from pressure or coercion to participate. 2) The VA research team will work to secure your information according to VA data security and privacy policies and every effort will be made to keep your information from your supervisor and co-workers. However, accidental disclosure or release of your private information could occur during the conduct of this study.

BENEFITS

You may not personally benefit from being in this study. By serving as a subject, you may help us learn how to provide better care to Veterans with alcohol problems.

ALTERNATIVES (OTHER AVAILABLE TREATMENTS)

You do not have to participate in this research study. There are alternative courses of treatment available for treating AUD, including other medications. For further information on available treatments, please consult with your provider.

COMPENSATION

You will receive $20 for your baseline visit and $20 for each completed follow up visit. You will receive your payment after each completed visit. You will be compensated using direct deposit to your bank account.

CONFIDENTIALITY AND USE OF RESEARCH RESULTS

The results of this study may be published or presented but your identity and records will not be revealed unless required by Federal Law. A Federal Law allows the U.S. Food and Drug Administration, Office for Human Research Protections, Government Accountability Office and other Federal agencies, the Research and Development Committee and/or the Institutional Review Board (IRB)/Human Studies Subcommittee of the VA Medical Center to review records. By participating in this research, you have also agreed to allow the sponsor or sponsors of the

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research project to review your medical records. Because of the need for these inspections, absolute confidentiality cannot be guaranteed.

COSTS TO YOU FOR PARTICIPATING

There is no cost to you for taking part in this study. All the study costs, including any study medications provided by the sponsor and procedures related directly to the study, will be paid for by the VA Medical Center. **Veterans who must make a co-payment for their usual medications or treatments will continue to be required to make such a co-payment for non-study related drugs**. There should be no additional medical costs to you for taking part in this study. However, frequent clinic visits may result in transportation costs and possible wages lost due to time missed from work.

MEDICAL CARE IF YOU ARE INJURED

In case you are injured from this research study, treatment will be available, including first aid, emergency treatment and follow-up care, as needed, by the VA Medical Center. In the event you cannot reach a VA facility, the VA will pay for necessary medical care for any injury or illness directly related to your participation in this research study. If you receive this type of medical care, you must contact the Research Investigator for this study. You can find contact information in the section of this consent titled "Compensation for Any Injuries".

COMPENSATION FOR ANY INJURIES

You have not released the VA Medical Center from liability by signing this form. This includes but is not limited to: 1) free medical care other than as described in this consent form, 2) payment of lost wages, or 3) compensation for pain and suffering. Compensation for those items from the VA may be available under applicable Federal Law. You should immediately report any injuries resulting from your participation in this study to Dr. E. Dieperink at (612) 467-4675 during the day and during the evenings or weekends, by calling the VA operator at (612) 725-2000 and ask to have the psychiatrist on call paged. Tell the operator you are in a research study. If you do not live in the metropolitan area, you may call the toll-free number: 1-866-414-5058.

NEW INFORMATION

You will be given any new significant information which is discovered during the course of this study which may influence your willingness to continue the study.

OTHER INFORMATION A description of this clinical trial will be available on https://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.

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Your participation in this research study may be ended without your consent for the following reasons:

- If the study doctor believes, for any reason, that it is within your best interest.
- If you develop side effects that are considered dangerous.
- If you refuse to take the study medications, or fail to return for follow-up as recommended by your study doctor or fail to follow the study doctor's instructions.
- If you require treatment with drugs that are not allowed in this study.
- If you become pregnant.
- If other causes prevent continuation of this research study.

Participation in this study is voluntary and you may refuse to participate without penalty or loss of benefits to which you are otherwise entitled. The study staff will answer any questions you may have about the study. You are free to withdraw your consent and stop participation at any time. If you decide to withdraw from this study, you should contact Dr. Dieperink to discuss termination of your participation. It is important that you do this so that Dr. Dieperink can withdraw you safely. Stopping will in no way change the quality of care you receive now or in the future at this institution or your right to participate in other studies. You will not receive compensation for study visits you do not complete.
Since pioglitazone is not commonly used to treat Alcohol Use Disorder, it may not be prescribed to you at the end of the study. If you feel you benefitted from taking the study drug, talk with your physician about the possibility of continuing to take it. At any time during and after the study you may talk to your clinicians about other treatments for Alcohol Use Disorders.

RESEARCH SUBJECT'S RIGHTS: I have read or have had read to me all of the above. _____ *(Name of person obtaining consent)* has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available.

I understand that I do not have to take part in this study and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published but my identity and records will not be revealed unless required by law.

I authorize the use of my bodily fluids and substances, or tissues.

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I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect research identifying me as a subject of this investigation.

In case there are medical problems or questions, concerns, or complaints, I have been told I can call Eric Dieperink at (612) 467-4675 during the day and the VA operator at (612) 725-2000 after hours and ask to have the psychiatrist on call paged. I will tell the operator I am in a research study. If I do not live in the metropolitan area, I may call the toll-free number: 1-866-414-5058.

If any medical problems occur in connection with this study the VA will provide emergency care.
If I have any questions about the rights of a research subject, or would like to:

- obtain information
- discuss problems or concerns, or have questions about this study
- offer input regarding this research study

and would like to speak to an individual who is not part of the research team of this study, I may contact the Patient Representative at (612) 725-2106. If I wish to verify the validity of the study and its authorized contacts, I may call the patient representative or contact the IRB office at (612) 629-7387.

My questions have been answered and I voluntarily consent to participate in this study. By signing this form, I have not given away any of my legal rights, which I have as a subject of this research study. I will receive a signed copy of this consent form.

_____ _____
Subject's Signature Date

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

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