Title: CAP: Doxazosin in the Treatment of Co-Occurring PTSD and Alcohol Use Disorders
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Subject's Name: **Date:**

Principal Investigator: Sudie Back, PhD

Study Title: Doxazosin in the Treatment of Co-Occurring PTSD and Alcohol Use Disorders

A. PURPOSE AND BACKGROUND:

You are being asked to volunteer for a research study. This study is being sponsored by the national Consortium to Alleviate Posttraumatic Stress Disorder (CAP), the Department of Veterans Affairs (VA) and the Department of Defense (DoD). The purpose of this study is to evaluate the effects of a medication (doxazosin) on reducing symptoms of posttraumatic stress disorder (PTSD) and alcohol and drug use in military Veterans. We will also look at the effects of doxazosin on brain activity. Doxazosin is approved by the Food and Drug Administration (FDA) to treat high blood pressure or to improve urination in men with an enlarged prostate. In the current study, doxazosin is considered "investigational use", which means the FDA has not approved it for treating symptoms of PTSD or reducing alcohol or drug use in individuals with alcohol use disorders, substance use disorders, and PTSD. You are being asked to participate in this study because you are a Veteran and may have an alcohol or substance use disorder as well as PTSD.

The investigator in charge of this study is Dr. Sudie Back. All study procedures will take place at the Ralph H. Johnson Veterans Affairs Medical Center (VAMC) and affiliated Community-Based Outpatient Clinics (CBOCs), as well as the Medical University of South Carolina (MUSC), in Charleston, SC or Savannah, GA, or by telephone when necessary. You will be asked to sign an MUSC informed consent for the imaging component of the study if you are interested in participating in the imaging component. You can participate in the medication trial without participating in the imaging component. The study will involve approximately 144 volunteers. Please read this consent form carefully because it explains what to expect with this study. Feel free to ask any questions now, or at any time during this study.

B. PROCEDURES:

If you agree to be in this study, the following will happen:

1. The study will include two screening visits followed by a 12-week medication phase. During the medication phase you may be asked to come into the clinic up to 2 visits per week. We may also ask you to come back to the clinic for a follow-up visit about six weeks after the medication phase. A urine sample will be collected at baseline, and may be collected monthly during treatment and at follow-up to test for drugs of abuse (e.g., cocaine, benzodiazepines, amphetamines, opiates, marijuana) and to track medication adherence. A breathalyzer test will

be collected from you each time you come into the clinic to test for recent use of alcohol. If you are a female you will be asked to complete a urine pregnancy test at baseline, week 4, and week 8. If your pregnancy test is positive, your participation in the study will end and no further testing will be done. If your test is negative study procedures will continue.

2. At the screening visits you will be evaluated to see if you meet the study requirements. Research personnel will ask you questions about your psychiatric, substance use, and medical history. You will have a physical exam and have your vital signs (blood pressure and heart rate) measured. You will have blood drawn (approximately two teaspoons) to assess your health. You will have an electrocardiogram (ECG) performed. This painless procedure will require electrodes to be placed at different locations on your chest to measure the activity of your heart. You will also be asked about the presence of metal in your body. Prior medications will also be recorded and you will be asked to complete a series of questionnaires.
3. If you are eligible to participate in the study, you will be randomly assigned to either receive doxazosin or placebo (an inactive substance). You will have a 50/50 chance (like flipping a coin) of receiving either doxazosin or placebo. If you are not eligible for the study, you will be given local referrals for treatment.
4. If you are eligible and choose to participate in the Magnetic Resonance Imaging (MRI) phase of the study, you will be asked to come into the office and work with research staff to develop brief imagery scripts related to your experiences with alcohol or drugs, your trauma, and your most relaxing experience (e.g., walking on the beach). You will be asked to recount a traumatic event, a time when you used alcohol or drugs and a relaxing activity you engage in. These scripts will be developed by research staff and played back to you during the MRI visits.
5. You will be asked to take your medication for 12 weeks. If you are in the doxazosin group you will begin with a dose of 1 mg/day and then titrate up to 16 mg/day as tolerated. Each medication (placebo and doxazosin) contains 25 mg of riboflavin (a vitamin), which will allow us to assess medication compliance. If you would like, we can provide you with a multivitamin that does not contain riboflavin.
6. During the 12-week medication phase you may be asked to come to the clinic up to 2 times per week. If you are unable to come into the clinic in person, procedures may be conducted via telephone. As noted above, breathalyzer tests will be performed at each time you come into the clinic. In addition, your urine will be tested at baseline for illicit drugs and may also be collected monthly during treatment for drugs and the presence of riboflavin. At each of these

visits we will record your vital signs and ask you about any symptoms that may have occurred during the previous week. You will also be asked to complete a series of assessments about your mood, sleep, PTSD symptoms and substance use. At the 6-week and 12-week study visits you will be asked to complete additional assessments of PTSD symptoms, health questionnaires, and alcohol use.

7. Throughout the 12-week medication phase, you will have the option to receive weekly structured cognitive behavioral therapy with a study therapist. This will be individual therapy and will include skills on, for example, drink refusal, coping strategies, anger management and relaxation.
8. You may be asked to return to the clinic 6 weeks after completing the medication phase. If you are unable to come into the clinic in person, procedures may be conducted via telephone. During this visit we will record your vital signs. You may be asked to perform a urine drug screen and a breathalyzer test. We will ask you questions about your PTSD symptoms and alcohol and drug use since your last visit. You will also be asked to fill-out questionnaires regarding substance use, PTSD and other mental and behavioral problems (depression, anxiety and sleep).

C. DURATION:

The total time in the study for each participant will be approximately 20 weeks consisting of:

The screening phase: These visits will occur prior to the medication phase of the study. It may take between 1-2 weeks to complete these visits depending on how long it takes to collect the required information about your health and drug/alcohol use. The screening visits should last about 4 hours total.

The script development phase: If you are eligible and interested in the neuroimaging phase, the script visit will last approximately 2 hours.

The medication phase lasts for 12 weeks: During this phase you may be asked to come to the clinic up to 2 times per week. Each weekly visit should last about 30 minutes. Visits during week 6 and week 12 will take about 2 hours because of the additional questionnaires.

The follow-up phase: This visit occurs 6 weeks after you complete the medication phase. You will be asked to fill-out questionnaires and may be asked to provide a urine sample. We will also record vital signs. This visit should last about 90 minutes.

D. RISKS/DISCOMFORTS:

a. You may experience distress by questions pertaining to your substance use history, trauma or your emotional functioning. You may terminate study participation at any point.
b. Legal risks arise if you are homicidal or suicidal and make these intentions known to project staff, who may then be required to notify authorities and the target of homicidal intent.
c. All medications have potential side effects. Side effects that have occurred in clinical trials with doxazosin include dizziness/fainting, fatigue, headache, shortness of breath, diarrhea, abdominal pain, edema (medical term for swelling), priapism (persistent and painful erection of the penis), and hypotension (abnormally low blood pressure). Doxazosin can cause floppy iris syndrome during cataract surgery. You will be monitored weekly by a study clinician for any side effects.
d. Because you are U.S. military personnel, absolute confidentiality of research records cannot be guaranteed. We will, however, make all possible efforts to protect your privacy and confidentially.
e. If you are a female of childbearing potential, you will receive pregnancy tests, and if pregnant, you will not be allowed to participate in the study as the effects of doxazosin on fetuses are unknown. If you are capable of becoming pregnant, you must be using a medically approved method of birth control (such as abstinence, surgical sterilization, diaphragms, or other forms of barrier contraceptives) and you must continue to do so during the course of the study.
f. The risks of drawing blood include temporary discomfort from the needle stick and bruising, fainting could occur.
g. Unknown risks: Participation in the study may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

h. Placebo: There is a 50/50 chance you will receive placebo, which is an inactive substance, and your condition may worsen while on placebo. We will monitor your symptoms closely each week.
i. Women participants in South Carolina only: If you are or become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or possibly be jailed.

Confidentiality:
We will take careful precautions to maintain your confidentiality, using procedures that we have successfully employed in similar previous as well as ongoing studies with Veterans. All study data related to psychological outcomes (i.e., the responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be a master list of participants (again, not linked to any participant responses) which will be kept locked separate from all data and will be available only to Dr. Back and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or Research Assistant's research office). Access to research records (paper and computerized) will be restricted to the project staff.

Your research records located at the Ralph H. Johnson Veterans Affairs Medical Center (VAMC) and affiliated CBOCs may be looked at by staff from the Medical University of South Carolina (MUSC) Institutional Review Board (IRB), the Ralph H. Johnson Veterans Affairs Medical Center (VAMC) Research and Development Office, the University of Texas Health Sciences Center at San Antonio (UTHSCSA), and/or other groups that have the responsibility of monitoring research, the Food and Drug Administration (FDA), the U.S. Army Medical Research and Material Command and representatives of the Department of Defense (DoD), and/or other government agencies as allowed by law and as part of their duties. The reason for this is to make sure that research participants are protected.

The investigators reserve the right to discontinue study participation for any individual who is determined to be a threat to self, staff, other study participants, or who is unable to complete the study assessments or provide informed consent.

E. BENEFITS:

There may be no benefits to you for participating in this study. The potential benefits include participation in cognitive behavioral therapy, receiving psychiatric assessment of your mental health conditions, and if you are assigned to the active treatment it may be more effective than placebo or other available treatments, although this cannot be guaranteed. This study will provide specific clinically relevant information for researchers regarding PTSD and alcohol use treatments. The knowledge gained will help providers make treatment decisions as well as help patients understand how treatment works. This knowledge may serve to improve the care of other military service members, Veterans, and non-Veterans with PTSD and alcohol use problems.

F. COSTS:

You will not be required to pay for medical care or services received as a participant in a VA research project except as follows: Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

G. COMPENSATION:

In return for your time, effort, and travel time to participate in this study, you will be compensated in cash, gift cards, or an electronic funds transfer (EFT). You will receive $40 for the baseline visit. If you arrive to all baseline appointments on-time and as scheduled, you may receive a $25 bonus. You will receive up to $560 for completion of up to twice weekly visits during the 12-week treatment phase. You will receive $100 for the 6-week follow-up visit. Thus, the total amount you may receive for all medication phase visits is $725. For the imaging phase, you will be compensated $25 for the script generation visit and $70 for each scanning visit, for a potential total of $165. The total amount you may receive for all visits (medication phase plus imaging phase) is $890. You will be compensated for the portions of the study that you complete.

If you are eligible and interested in participating in the imaging phase and you currently live more than 60 miles away from Charleston, SC, you may be compensated an additional $325 per scanning visit for

time and travel. With this additional $650, the total amount you may receive for all visits (medication phase plus imaging phase) is $1540.

Referrals
You are invited to participate in the recruitment of other subjects for this study. If you choose to participate, we will provide you with cards that you may give to other veterans (e.g. friends, acquaintances) who you think would be eligible and interested in this study. These individuals will not be identified unless they contact the study staff themselves. If any of the cards results in successful study recruitment, you will receive $10 for each referred individual who enrolls in the study. Participation in the recruitment process is completely voluntary and if you elect not to participate, your participation in this study will not be affected in any way.

The Internal Revenue Service (IRS) requires a tax form be filed if your compensation exceeds $600/year. However, if the payment for participation will be made through Austin Financial Service Center, it may generate IRS Form 1099 automatically, regardless of amount.

H. ALTERNATIVES:

If you choose not to participate in this study, you could receive other treatments for your condition. The standard therapy for your condition is individual or group therapy in the form of supportive counseling, or treatment by antidepressant or other medications. You may receive this care at the Ralph H. Johnson VAMC or affiliated clinics in the community. If you choose not to participate, it will not affect your relationship with any current treatment providers you may have or your right to health care or any other services to which you are otherwise entitled.

Withdrawal from the Study
Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should talk with the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled. The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions. If your participation is ended for medical reasons, you will be

referred to a doctor or other health professional for care. You will be responsible for the cost of these services.

I. DISCLOSURE OF RESULTS:

You may request to receive a report of the aggregate results following completion of the study.

J. NEW INFORMATION:

If there are significant new findings during the course of the study, you will be notified.

K. RELEASE OF MEDICAL RECORDS TO ANY ONE OTHER THAN THE INVESTIGATORS:

You will be asked to sign a separate release for the release of your medical records.

L. STUDENT PARTICIPATION:

Your participation or discontinuance will not constitute an element of your academic performance nor will it be part of your academic record at this Institution.

M. EMPLOYEE PARTICIPATION:

Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be part of your personnel records at this Institution.

N. INVITATION TO PARTICIPATE IN FUTURE STUDIES:

In the future, the VAMC and/or MUSC may be conducting other related studies. Please let us know your interest in being re-contacted in the future by telephone, mail or email about other studies that you may qualify for.

□ Yes, I am interested in being contacted about future studies.
□ No, I am not interested in being contacted about future studies.

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O. PERMISSION TO RECORD SOME VISITS:

For the medication phase, we would like to record some of the first screening visit during which you receive a diagnostic assessment. We will always tell you ahead of time when we are going to record. These recordings will be uploaded to the STRONGSTAR website for diagnostic reliability purposes. For the imaging phase, we would like to have a staff member create an audio recording of the imagery scripts you and the research staff develop. This will allow us to measure brain activity while you listen to the recorded scripts. These could pose a risk to confidentiality and although we will take every step possible to ensure that all recordings are stored securely and any risks minimized, there is a risk that you could be identified. To minimize risk, all recording will be kept on a secure and encrypted server and only the project staff and supervisors will have access to the recordings. They will be destroyed after the study has been completed. Would that be acceptable to you?

I permit these recordings for the purposes of the study.
□ Yes □ No Initial _____

P. CLINICAL TRIAL REGISTRY DATABANK:

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

CONSENT

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

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The VA will provide necessary medical treatment to a research subject injured by participation in a research project. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by this VA Medical Center. Financial compensation is not available for such things a lost wages, disability or discomfort due to an injury.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

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Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, or if I have comments, concerns or complaints, I may contact: Dr. Sudie Back at (843.792.9383). I may contact the VA Medical Center's Medical Director (843.789.7200) concerning medical treatment.

If I have questions, comments, concerns or wish to voice a complaint, I may contact the VA Research Compliance Officer at (843.789.7399).

If I have any questions about my rights as a research subject in this study I may contact the Medical University of SC Institutional Review Board for Human Research at (843.792.4148).

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date