

AWARD NUMBER: W81XWH-14-1-0025

TITLE: Effect of Prazosin and Naltrexone on Script Induced Alcohol Craving in Veterans with Alcohol Use Disorders with and without Co-occurring PTSD

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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1. REPORT DATE January 2015			2. REPORT TYPE Annual		3. DATES COVERED 4 Dec 2013 - 3 Dec 2014	
4. Effect of Prazosin and Naltrexone on Script Induced Alcohol Craving in Veterans with Alcohol Use Disorders with and without Co-occurring PTSD					5a. CONTRACT NUMBER	
					5b. GRANT NUMBER W81XWH-14-1-0025	
					5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Tracy Simpson, PhD E-Mail: Tracy.Simpson@va.gov					5d. PROJECT NUMBER	
					5e. TASK NUMBER	
					5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Seattle Institute for Biomedical and Clinical Research 1660 S Columbia Way, S-151F, Seattle, WA 98108-1532					8. PERFORMING ORGANIZATION REPORT NUMBER	
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13. SUPPLEMENTARY NOTES						
14. ABSTRACT Background: Military personnel are at risk for developing hazardous drinking patterns post-deployment that can negatively impact their health and psychiatric stability. This phenomenon is compounded by the fact that despite recent gains in establishing effective pharmacological and behavioral treatments for alcohol use disorders (AUD), nonremittance and relapse remain major problems for those with AUDs. One individual factor that is strongly associated with continued problematic use and relapse is craving. Three different types of craving have been hypothesized, reward, relief, and obsessive, and each is postulated to be mediated by different neurological substrates. The neural networks postulated to subserve reward and relief craving receive afferents from and project to noradrenergic neurons in non-human primates and humans express α_1 adrenergic receptors. Given the interplay of the noradrenergic system with craving-related brain systems, blocking α_1 receptors with the noradrenergic antagonist, prazosin, theoretically has the potential to modulate reward and relief craving. Objective/Hypotheses: The overarching objective of the study is to evaluate whether prazosin alone and/or in conjunction with naltrexone is effective at reducing reward and relief craving for alcohol among veterans with an AUD in both a human laboratory context and in their day-to-day lives via daily symptom telephone monitoring using Interactive Voice Response (IVR). The proposed study also seeks to evaluate whether specific individual characteristics, including PTSD status, moderate medication response.						
15. SUBJECT TERMS Alcohol Drinking, Drinking Behavior, Naltrexone, Prazosin, Adrenergic Agents, Adrenergice Antagonists, Adrenergic alpha-1 receptor antagonists, Adrenergic alpha-antagonists, Antihypertensive agents, Narcotic antagonists, Therapeutic uses						
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC	
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	8	19b. TELEPHONE NUMBER (include area code)	
Unclassified	Unclassified	Unclassified				

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Recently deployed Veterans are at risk of developing hazardous drinking patterns post-deployment. Craving is strongly associated with continued problematic use and relapse. The noradrenergic system subserves craving-related brain systems. Blocking α_1 receptors with the noradrenergic antagonist, prazosin, has the potential to modulate craving. 120 Veterans with an alcohol use disorder (AUD) will be randomized to receive prazosin, naltrexone, both medications, or placebo for 3 weeks. The purpose of this study is to see whether the drugs prazosin and naltrexone will decrease alcohol cravings and drinking in individuals who have problems with alcohol and have used alcohol at risky levels in the past 90 days.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Alcohol Drinking	Central Nervous System Agents
Drinking Behavior	Molecular Mechanisms of Pharmacological Action
Alcohol Craving	Narcotic Antagonists
Naltrexone	Neurotransmitter Agents
Prazosin	Peripheral Nervous System Agents
Adrenergic Agents	Pharmacologic Actions
Adrenergic Antagonists	Physiological Effects of Drugs
Adrenergic alpha-1 Receptor Antagonists	Sensory System Agents
Adrenergic alpha-Antagonists	Therapeutic Uses
Antihypertensive Agents	
Cardiovascular Agents	

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**
- **What was accomplished under these goals**

<p>Specific Aim 1: To compare the effects of prazosin only, naltrexone only, and their combination to placebo control on reward oriented and relief oriented alcohol craving elicited by personalized imaginal scripts in a human laboratory setting.</p> <p>Specific Aim 2: To determine the effect of the four medication conditions on day-to-day reports of alcohol craving and drinking motives via daily telephone IVR.</p> <p>Specific Aim 3: Explore whether PTSD status moderates medication response.</p>	
<p>Year 1 Goals <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/></p> <p><input checked="" type="checkbox"/> Obtain all necessary regulatory approvals</p> <p><input checked="" type="checkbox"/> Prepare staff; compound meds; set up lab and IVR</p> <p><input checked="" type="checkbox"/> Initiate recruitment and retention efforts</p> <p><input type="checkbox"/> 20 Veterans recruited by the end of year 1</p> <p>Year 2 Goals</p> <p><input type="checkbox"/> 60 Veterans recruited by the end of year 2</p>	<p><i>Comments</i></p>

Enter and clean study data

Year 3 Goals

100 Veterans recruited by the end of year 3

Enter and clean study data

Year 4 Goals

120 Veterans recruited by half way through year 4

Perform data analyses for Aims 1, 2, and 3.

Write and submit manuscripts

Comments continued: In order receive full approval to start recruitment we obtained VAPSHCS and DoD approval of our second protocol modification. This modification included changes required by DoD. The protocol modification was submitted within 3 days of receipt of DoD recommendations to the VAPSHCS IRB on 8/18/14. It was approved by VAPSHCS IRB on 10/16/14.

• **What opportunities for training and professional development has the project provided?**

Nothing to report

• **How were the results disseminated to communities of interest?**

Nothing to report

• **What do you plan to do during the next reporting period to accomplish the goals?**

Recruit 20 veterans is the only goal that we were unable to meet for year 1. This is due to the fact that we gained full approval to start recruiting participants on 10/16/14—right before the start of the holidays. In the next reporting period we plan to increase available recruitment strategies by advertising via flyers in the community and completing a data access request. The data access request will allow us to identify veterans with current alcohol use disorders, positive AUDIT scores (≥ 4 for women, ≥ 5 for men), while filtering patients with exclusionary medical conditions. Upon identifying these veterans via medical records we will contact them, and offer them the chance to phone screen for an in person screening visit.

4. **IMPACT:** This component is used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period. Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

• **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report

• **What was the impact on other disciplines?**

Nothing to report

- **What was the impact on technology transfer?**

Nothing to report

- **What was the impact on society beyond science and technology?**

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

- **Changes in approach and reasons for change**

Nothing to report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

We received human subject approval from DoD contingent upon a protocol modification on 8/18/14. We submitted a protocol revision to VAPSHCS within three days of receipt of our sponsor's message. We received final VAPSHCS IRB approval for DoD required changes, nearly two months after submission, on 10/16/14. This gave us only two months for recruitment in 2014, during the holiday season. In order to resolve issues in recruitment we plan to increase advertising within VAPSHCS via TV monitor ads, American Lake campus advertising, placing flyers in the community surrounding the VA and through a data access request (detailed in 3. Accomplishments).

- **Changes that had a significant impact on expenditures**

The unanticipated waiting period for human subject approval leaves us well under our projected expenditures for the first year of study activity.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report

6. **PRODUCTS:** List any products resulting from the project during the reporting period. Examples of products include:

- **Publications, conference papers, and presentations**

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Provide the following information for: (1) PDs/Pis; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

- Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project and with what funding support. If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Individuals Working on this Project

Name:	Tracy Simpson, PhD
Project Role:	PI
Nearest person month worked:	1.8

Contribution:	PI
Name:	Andrew Saxon, MD
Project Role:	Co-PI
Nearest person month worked:	1.2
Contribution:	PI
Name:	Robert Lyons
Project Role:	Research Coordinator
Nearest person month worked:	4
Contribution:	Participant Recruitment and Regulatory Duties
Name:	Dana Tell, ARNP
Project Role:	Study Clinician
Nearest person month worked:	2
Contribution:	Performs in-person participant visits

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report

- **What other organizations were involved as partners?**

Nothing to report

8. **SPECIAL REPORTING REQUIREMENTS:** See included quad chart

Effect of Prazosin and Naltrexone on Script Induced Alcohol Craving in Veterans with Alcohol Use Disorders with and without Co-occurring PTSD

11152009 / W81XWH-14-1-0025



PI: Tracy Simpson, PhD / Andrew Saxon, MD

Org: Seattle Institute for Biomedical and Clinical Research

Award Amount: \$802,000

Approach

Recently deployed Veterans are at risk of developing hazardous drinking patterns post-deployment. Craving is strongly associated with continued problematic use and relapse. The noradrenergic system subserves craving-related brain systems. Blocking α_1 receptors with the noradrenergic antagonist, prazosin, has the potential to modulate craving.

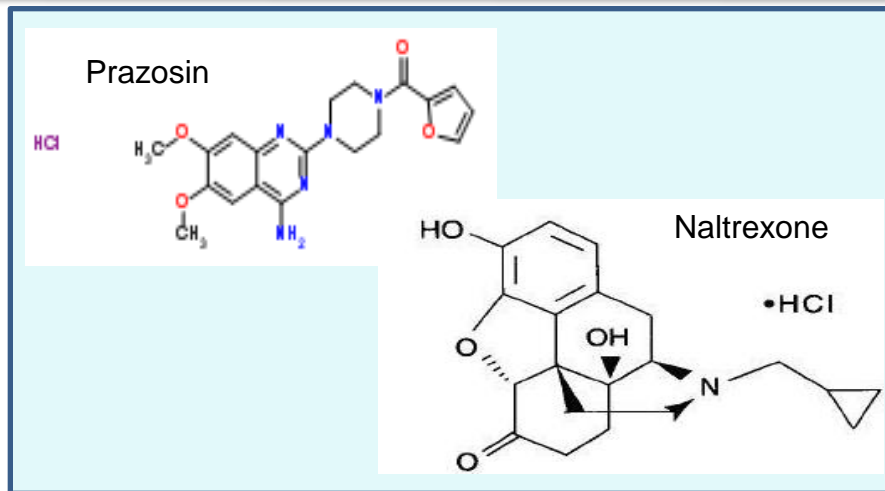
120 Veterans with an alcohol use disorder (AUD) will be randomized to receive prazosin, naltrexone, both medications, or placebo for 3 weeks. Craving will be assessed through daily monitoring and a laboratory based craving induction paradigm.

Study Aims

Specific Aim 1: To compare the effects of prazosin only, naltrexone only, and their combination to placebo control on reward oriented and relief oriented alcohol craving elicited in a human laboratory setting.

Specific Aim 2: To determine the effect of the four medication conditions on day-to-day reports of alcohol craving and drinking motives.

Specific Aim 3: To explore whether PTSD status moderates medication response.



Accomplishments: Obtained local IRB and R&D approvals; undergoing DoD IRB review; research staff hired; daily monitoring system constructed; pharmacy & lab interfaces established; compounding pharmacy interface established.

Timeline and Cost

Activities	CY 13	14	15	16	17
Preparatory Tasks		■			
Recruitment/Retention	■		■	■	■
Enter and clean study data			■	■	■
Analyze data for Aims 1, 2 & 3; write and submit manuscripts					■
Estimated Budget (\$K)		\$139k	\$207k	\$212k	\$244

Budget Expenditure to Date: Projected Expenditure: \$138,374
Actual Expenditure: \$16,631

Goals/Milestones

☑☑☑ ☐☐☐

- CY14 Goals**
- ☑ Obtain all necessary regulatory approvals
 - ☑ Prepare staff; compound meds; set up lab and IVR.
 - ☑ Initiate recruitment and retention efforts
 - ☐ 20 Veterans recruited by the end of year 1
- CY15 Goals**
- ☐ 60 Veterans recruited by the end of year 2
 - ☐ Enter and clean study data
- CY16 Goals**
- ☐ 100 Veterans recruited by the end of year 3
 - ☐ Enter and clean study data
- CY17 Goals**
- ☐ 120 Veterans recruited by half way through year 4
 - ☐ Perform date analyses for Aims 1, 2, and 3.
 - ☐ Write and submit manuscripts

Comments/Challenges/Issues/Concerns

- We experienced delays with our IRB in securing final approval for changes requested by DoD, which delayed recruitment.
- The above mentioned delays also resulted in our being below projected expenditure.

Updated: (N/A)