AD_____

AWARD NUMBER: W81XWH-14-1-0025

TITLE: Effect of Prazosin and Naltrexone on Alcohol Craving and Alcohol Consumption in Veterans and Servicemembers with and without PTSD

PRINCIPAL INVESTIGATOR: Tracy Simpson, PhD and Andrew Saxon, MD

RECIPIENT: Seattle Institute for Biomedical and Clinical Research

REPORT DATE: Dec 2019

TYPE OF REPORT: Annual Progress Report

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

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Effect of Prazosin and Naltrexone on Alcohol Craving and Alcohol Consumption in Veterans and Servicemembers with and without PTSD

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14. ABSTRACT

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 α1 adrenergic receptors. Given the interplay of the noradrenergic system with craving-related brain systems, blocking α1 receptors with the noradrenergic antagonist, prazosin, theoretically has the potential to modulate reward and relief craving. This study is to evaluate whether prazosin alone and/or in conjunction with naltrexone is effective at reducing reward and relief craving for alcohol. The proposed study also seeks to evaluate whether specific individual characteristics, including PTSD status, moderate medication response.

In 2019, we completed data entry, data quality assurance, and preliminary analyses. Dr. Murray Raskind presented the promising results of these analyses at the September CDMRP meeting. We were interested in expanding our study to active servicemembers in the Madigan Army Medical Center and submitted our application; however, we learned later on that the DoD was reluctant to support this work, thus we are focusing our efforts on writing and submitting a manuscript and will submit a follow-up grant next year.

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			19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	13	

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

   Recently deployed Veterans and Servicemembers 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 α1 receptors with the noradrenergic antagonist, prazosin has the potential to modulate craving. 150 Veterans and Servicemembers with an alcohol use disorder (AUD) will be randomized to receive prazosin, naltrexone, both medications, or placebo for 7 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
   Drinking Behavior
   Alcohol Craving
   Naltrexone
   Prazosin
   Adrenergic Agents
   Adrenergic Antagonists
   Adrenergic alpha-1 Receptor Antagonists
   Adrenergic alpha-Antagonists
   Antihypertensive Agents
   Cardiovascular Agents
   Central Nervous System Agents
   Molecular Mechanisms of Pharmacological Action
   Narcotic Antagonists
   Neurotransmitter Agents
   Peripheral Nervous System Agents
   Pharmacologic Actions
   Physiological Effects of Drugs
   Sensory System Agents
   Therapeutic Uses

3. **ACCOMPLISHMENTS:** The 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.

   What were the major goals of the project?
   See beneath for the study's scope of work table (rev. 10/16/2018) which lists major project goals approved in the SOW. In accordance with the revised timeline and project plan submitted June 18, 2019 and approved in award modification P0005 (June 26, 2019), the JBLM/Madigan recruitment efforts are no longer occurring and the remaining activities are data analysis and publication preparation scheduled to end February 2020. The approved timeline for remaining tasks is:

   Task 13: June-July 2019 – an SIBCR research assistant will perform quality assurance checks on the data collected to-date from the 31 completed participants.
   Task 14: August-September 2019 – PIs (Tracy Simpson and Andrew Saxon) will collaborate with Biostatistician (Jane Shofer) on data analysis.
   Task 15: Write and submit necessary reports to the DoD on the following schedule:

- July 31, 2019 – Quarterly financial report due (4/1/19-6/30/19)
- September 19, 2019 – Quarterly technical progress report due
- October 31, 2019 – Quarterly financial report due (7/1/19-9/30/19)
- January 31, 2020 – Quarterly financial report due (10/1/19-12/31/19)
- April 30, 2020 – Quarterly financial report due (1/1/20-3/31/20)
- May 28, 2020 – Final scientific, financial, and invention reports due 90 days after end date (2/29/2020)

Task 16: October-November 2019 – PIs (Tracy Simpson and Andrew Saxon) will collaborate with Biostatistician (Jane Shofer) to write up manuscripts.
December 2019-February 29, 2020 – submit manuscripts, pay publication charges

What was accomplished under these goals?

Year:	1	2	3	4	5E	6S	7S
VA Preparatory Tasks							
Task 1: Obtain all necessary regulatory approvals (IRB, R&D, biohazard)	X						
Task 2: Hire research staff (recruit study RA; study clinician)	X						
Task 3: Purchase medication; have study medications compounded	X						
Task 4: Set up pharmacy dispensing and randomization protocol	X						
Task 5: Set up agreement with VA laboratory for blood and urine assays	X						
Task 6: Finalize case report forms	X						
Task 7: Train clinician on Clinician Administered PTSD Scale; establish reliability	X						
Task 8: Work with Data Systems Inc. to program IVR system	X						
Task 9: Set up recruitment systems	X						
Task 10: Set up participant payment and purchase order systems with SIBCR	X						
Preparatory Milestones: Tasks 1 - 10 will be completed by the end of month 6	X						
JBLM/Madigan Preparatory Tasks							
Task 1S: Adapt study protocol to fit active duty JBLM/ Madigan context					X		
Task 2S: Secure VAPS regulatory approvals for adding JBLM/Madigan site							
Task 3S: Secure regulatory approvals from JBLM/Madigan							
Task 4S: Arrange medication compounding at Madigan							
Task 5S: Set up pharmacy dispensing and randomization protocol							
Task 6S: Set up agreement with Madigan laboratory for blood and urine assays and shipment of blood to MedTox for Peth analyses							

Task 7S: Work with JBLM-based study recruiter to set up recruitment systems								
JBLM/Madigan Preparatory Milestones: Tasks 1S – 7S are halted, per notice from Inna Williams on May 28, 2019.								
VA Recruitment and Retention Tasks								
Task 11: Initiate recruitment and retention efforts		X	X					
Task 12: Recruit and retain Veterans and National Guard/Reserve Members with an AUD and recent alcohol craving.		X	X					
JBLM/Madigan Recruitment and Retention Tasks - halted, per notice from Inna Williams on May 28, 2019.								
Task 8S: Initiate recruitment and retention efforts								
Task 9S: Recruit and retain Active Duty Service Members with an AUD and recent alcohol craving.								
Combined Recruitment and Retention Milestones: *Because we are unable to meet our recruitment goals at VAPS we plan to initiate recruitment of active duty Service Members at JBLM/Madigan as soon as the work is IRB-approved*								
• 25 participants recruited (goal: Year 1-5)		X	X	X	X			
• *48 participants recruited (goal: Year 6)*								
• *52 participants recruited (goal: Year 7)*								
• *150 participants recruited (goal: Year 1-7)*								
Data Cleaning, Analysis, Manuscript, and Report Tasks Across All Recruitment Sites								
Task 13: Enter and clean study data (lab values, adverse events, self-report data, IVR data)		X	X	X	X	X	X	
Task 14: Perform analyses germane to Aims 1, 2, and 3								
Task 15: Write and submit necessary reports to DoD	X		X	X	X	X	X	
Task 16: Write and submit manuscripts – **In progress now**							o	
Data Cleaning, Analysis, Manuscript, and Report Milestones: Tasks 13 through 16 will be completed by the end of the grant period.								

Target Enrollment Table (rev. 10/2018)						
Period		Dates			Target Enrollment (October 2018 SOW)	Actual Enrollment (as of 12/3/19)
Year 1	Q1	12/4/2013	to	3/3/2014	0	0
	Q2	3/4/2014	to	6/3/2014	0	0
	Q3	6/4/2014	to	9/3/2014	10	0
	Q4	9/4/2014	to	12/3/2014	10	0
Year 2	Q1	12/4/2014	to	3/3/2015	10	0
	Q2	3/4/2015	to	6/3/2015	10	3
	Q3	6/4/2015	to	9/3/2015	10	4
	Q4	9/4/2015	to	12/3/2015	10	2
Year 3	Q1	12/4/2015	to	3/3/2016	10	1
	Q2	3/4/2016	to	6/3/2016	10	3
	Q3	6/4/2016	to	9/3/2016	10	2
	Q4	9/4/2016	to	12/3/2016	10	1
Year 4	Q1	12/4/2016	to	3/3/2017	10	0
	Q2	3/4/2017	to	6/3/2017	10	4
	Q3	6/4/2017	to	9/3/2017	0	1
	Q4	9/4/2017	to	12/3/2017	0	3
Year 5 (No cost extension)	Q1	12/4/2017	to	3/3/2018	0	3
	Q2	3/4/2018	to	6/3/2018	0	1
	Q3	6/4/2018	to	9/3/2018	0	3
	Q4	9/4/2018	to	12/3/2018	0	0
Subtotal					**120**	**31**
Period		Dates			Target Enrollment (application)	
Year 6	*Q1*	*10/1/2018*	*to*	*12/31/2018*	*0*	***0***
	Q2	*1/1/2019*	*to*	*3/31/2019*	*0*	***0***
	Q3	*4/1/2019*	*to*	*6/30/2019*	*0*	***0***
	Q4	*7/1/2019*	*to*	*9/30/2019*	*0*	*0*
Year 7	*Q1*	*10/1/2019*	*to*	*12/31/2019*	*0*	*0*
	Q2	*1/1/2020*	*to*	*3/31/2020*	*0*	
	Q3	*4/1/2020*	*to*	*6/30/2020*	*0*	
	Q4	*7/1/2020*	*to*	*9/30/2020*	*0*	
Total					**120**	***31***

Discontinuation/Withdrawals: No changes since prior annual report

Period	Consented	Randomized	Discontinued/ Withdrawn	Reason for Discontinuation/ Withdrawal
4 Dec 2016 3 Dec 2017	15	8	3	- 1 withdrew from study due to a lack of weekly availability - 1 withdrew from study in order to request a prescription for one of the study meds from their GP. - 1 withdrawn from the study at Visit 2 due to an SI endorsement on PHQ-9.
4 Dec 2017 3 Dec 2018	12	7	1	- 1 withdrew from study due to a lack of funds for transportation
4 Dec 2018 3 Dec 2019	0	0	0	N/A
4 Dec 2013 3 Dec 2019	62	31	6	- 1 withdrawn from study at Visit 2 due to an SI endorsement on PHQ-9. - 1 withdrew from study in order to request a prescription for one of the study meds from their GP. - 1 withdrew from study due to a spouse requesting that they not participate in the study. - 2 withdrew from study due to a lack of weekly availability with a new schedule. - 1 withdrew from study due to a lack of funds for transportation
Overall Total	62	31	6	

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?
We have completed data analyses and are in the process of writing with plans to submit at least one manuscript early next year.

4. **IMPACT:** 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:**
   Meeting recruitment goals was an issue through the life of the project. We ceased recruitment at the VA site in 2018 to preserve the budget for recruitment of Active Duty servicemembers at the Madigan/JBLM site. However, that project extension was cancelled and we did not commence subject recruitment at Madigan/JBLM. There are no current problems with the remaining Tasks 13-16.

   Changes in approach and reasons for change
   Although it became moot, we removed the lab-based craving induction portion of the study due to concerns on the part of Madigan/JBLM leadership regarding potential untoward effects on Active Duty personnel should anyone leave the assessment session and engage in drinking. We planned to retain the close monitoring of craving and alcohol use via different forms of frequently collected self-report measures throughout the trial and would have still been able to address the central questions of the project pertaining to medication effects on craving.

   Actual or anticipated problems or delays and actions or plans to resolve them
   There are actual or anticipated delays with the remaining Tasks 13-16. Throughout the project, despite employing a variety of active recruitment efforts, we continued to face challenges in bringing ample numbers of veterans into the study largely because a majority of patients seen at our facility with an active alcohol use disorder are already on one or the other study medication or are medically or psychiatrically too unstable to be admitted into the study. In order to address this fundamental issue, we worked with the American Lake VA Puget Sound campus and one of our large CBOCs to our North setting up study recruitment and offering the location as an additional recruitment site, as the CBOC were unable to meet all the needs of their patients with alcohol use disorders and wanted the option of referring to the study. Despite our best efforts, we were only able to recruit two people from that CBOC. Our recruitment efforts at the VA Puget Sound American Lake facility similarly only yielded minor improvements in our recruiting numbers.

   Changes that had a significant impact on expenditures

The removal of the JBLM/Madigan component of this study resulted in award modification P0005, which relinquished the initial $300,000 supplement for this work and revised the total costs awarded back to $802,000. VA Puget Sound MIRECC and CESATE supported the expenses for preparing the MAMC/JBLM IRB application to conserve DoD funds to perform the trial, so this change did not have a significant impact on actual expenditures, just anticipated ones. The remaining balance of the original $802,000 awarded should be sufficient to support the remaining work on Tasks 13-16.

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. If there is nothing to report under a particular item, state "Nothing to Report."

- **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). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	*Tracy Simpson, PhD (no change)*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	*None*
Nearest person month worked:	*1.8*
Contribution to Project:	*Dr. Simpson is the study PI.*
Funding Support:	*Dr. Simpson's salary is supported by VAPSHCS*
Name:	*Andrew Saxon, MD (no change)*

Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	*None*
Nearest person month worked:	*1.2*
Contribution to Project:	*Dr. Saxon is co-study PI*
Funding Support:	*Dr. Saxon's salary is supported by VAPSHCS*

Name:	*Daniel Murray*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*None*
Nearest person month worked:	*1.5*
Contribution to Project:	*Data entry and quality assurance*
Funding Support:	*Effort on this project supported by this budget.*

Name:	*Jane Shofer*
Project Role:	*Biostatistician*
Researcher Identifier (e.g. ORCID ID):	*None*
Nearest person month worked:	*0.8*
Contribution to Project:	*Statistical analysis of Veteran study participants data*
Funding Support:	*Effort on this project supported by this budget.*

Name:	*Lisa Batten*
Project Role:	*Research Health Science Specialist*
Researcher Identifier (e.g. ORCID ID):	*None*
Nearest person month worked:	*0.5*
Contribution to Project:	*Data management and regulatory compliance activities, as well as progress reporting*
Funding Support:	*The remainder of Ms. Batten's effort is supported by VAPSHCS.*

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

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. **APPENDICES:** See attached Quad Chart and DSM Cover Letter.

Effect of Prazosin and Naltrexone on Alcohol Craving and Alcohol Consumption in Veterans and Service Members 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 α1 receptors with the noradrenergic antagonist, prazosin, has the potential to modulate craving.

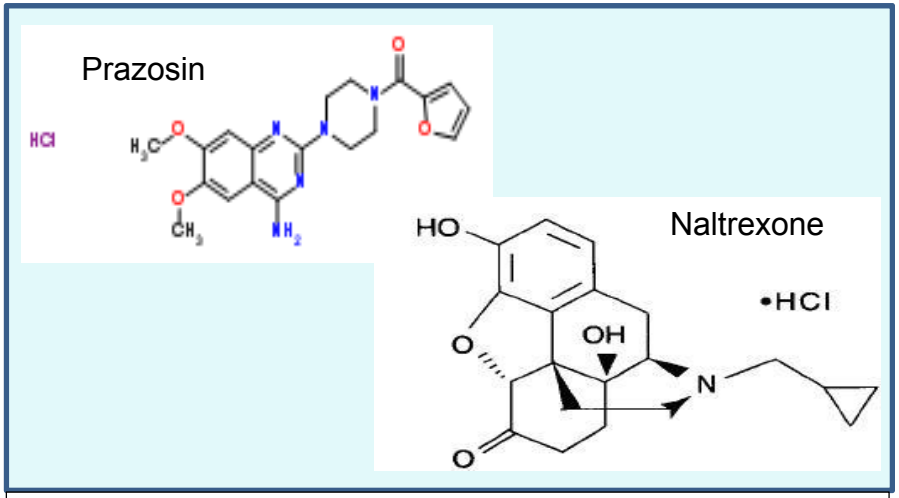
150 Veterans and Service Members will be randomized to receive prazosin, naltrexone, both medications, or placebo for 3 weeks. Craving will be assessed through daily monitoring and a laboratory based craving induction paradigm.

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.

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: Maintained local IRB and R&D approvals and DoD IRB approval; completed IRB submission to initiate active duty service member recruitment.

Timeline and Cost

Activities	CY 13	14	15	16	17-18	19	20
Preparatory Tasks							
Recruitment/Retention							
Enter and clean study data							
Analyze data for Aims 1, 2 & 3; write and submit manuscripts							
Estimated Budget ($K)		**$139**	**$207**	**$212**	**$244**		

Budget Expenditure to Date: Project Budget: $802,000
Exps. through 12/3/19: $791,405

Goals/Milestones

CY13-18 Goals
- ☑ Obtain necessary VA regulatory approvals
- ☑ Prepare staff; compound meds; set up lab and IVR.
- ☑ Initiate recruitment and retention efforts
- ☑ 25 Veterans recruited by the end of year 5
- ☑ Enter and clean study data
- ~~☐ Obtain necessary JBLM/MAMC regulatory approvals~~
- ~~☐ JBLM/MAMC study initiation~~

CY19 Goals
- ~~☐ 48 Vets/Service Members recruited in year 6~~
- ☑ Enter and clean study data

~~CY20 Goals~~
- ~~☐ 52 Vets/Service Members recruited in yearr 7~~
- ~~☐ Enter and clean study data~~
- ~~☐ 150 Vets/Service Members recruited years 1-7~~
- ☐ Perform data analyses for Aims 1, 2, and 3. [Begun]
- ☐ Write and submit manuscripts [In progress]

Comments/Challenges/Issues/Concerns

In the next 3 months, we will continue final data analyses and prepare a manuscript. We do not anticipate delays in these remaining tasks.

Updated: 12/19/19

PaN Study Safety Monitoring Cover Sheet

General Study Info

Date Range: 08/01/18 - 07/31/19

This is the PaN study's sixth safety monitoring report. Since our last data safety report on 7/30/18, four participants have been consented. Of these four, two failed the in-person screening and were found to be ineligible and two were enrolled and randomized. One participant (P029) who was consented at the end of the previous monitoring period was also enrolled and randomized in this monitoring period. All 31 participants have completed the study. The last participant completed the study on 10/10/2018. **There are no SAEs to report for this monitoring period.**

Summary data are provided for each participant regarding AEs, blood pressure, SI, visit completion and IVR data at baseline, titration, and maintenance period to the final visit. AE forms, safety call information, and lab results are provided as well.

Summary of Protocol Revisions/Amendments Affecting Safety Monitoring

No PRAF affecting safety monitoring was submitted in this period.

Report of Other Problems

There was no problem affecting safety monitoring in this period.

List of protocol deviations

08/23/2018 – A pregnancy test for participant 029 was completed at V4 instead of V5 due to a change in study clinician at V5 and PI's request to keep the ordering of study labs completed by the same study clinician.

08/31/2018 – Clinicians were unavailable to make third med safety call (TC3) to patient #030 and RC was unable to make first safety call (TC1) to 1522. Study clinician followed up with 1522 at a later time.

09/05/2018 –RC was unable to make first safety call (TC1) to patient 1520 due to the holiday weekend and RC's work schedule. Study clinician followed up with participant on 9/05/18.

09/20/2018 – Lab at Mt Vernon CBOC VA was closed during #029's V8. PI authorized that participant come back on a different day to have labs drawn & for study clinician to request labs through #029's medical record in order for labs to be completed at a later date. No MedTox specimen shipping to analyze the participant's PEth level will happen for this participant.

09/24/2018 – RC was delayed in disenrollment of #029 by a few days due to being out sick and then the weekend.

07/12/2019 – Disenrollment note of #031 was entered into CPRS 9 months after the participant had completed the study. The reason is unknown because the previous RC is no longer with the VA.