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

CONTRACTING ORGANIZATION: Seattle Institute for Biomedical and Clinical Research

REPORT DATE: May 2020

TYPE OF REPORT: Final Report

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

REPORT DOCUMENTATION PAGE

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May-2020	Final	04-Dec-2013 to 28-Feb-2020

4. TITLE AND SUBTITLE
Effect of Prazosin and Naltrexone on Alcohol Craving and Alcohol Consumption in Veterans and Servicemembers with and without PTSD

5a. CONTRACT NUMBER

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W81XWH-14-1-0025

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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Andrew Saxon, MD

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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 South Columbian Way
SIBCR 116 MIRECC
Seattle WA 98108-1532

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

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 evaluated whether prazosin alone and/or in conjunction with naltrexone is effective at reducing drinking and reward and relief craving. The study also evaluated whether specific individual characteristics, including PTSD status, moderate medication response.

We have submitted a manuscript detailing the drinking and craving outcomes. Despite having fallen short of our recruitment goal, the study found promising results for the combination of naltrexone and prazosin relative to either medication alone. Veterans in the Naltrexone/Prazosin group began reducing drinking during the first week of medication and showed the greatest improvement on three of the four main outcomes relative to the other three groups; percent days drinking), percent heavy drinking days, and overall craving level. They did not differ appreciably on average number of drinks per drinking day. Medication side effects consistent with dizziness, lightheadedness, and fatigue were more commonly reported by those in the Naltrexone/Prazosin condition than the other conditions, but medication compliance, visit attendance, and study completion were all better for this group than for the other groups, suggesting that the side effects were not overly troubling and may have been offset by the improvements in drinking and craving.

15. SUBJECT TERMS
Alcohol Drinking, Drinking Behavior, Naltrexone, Prazosin, Adrenergic Agents, Adrenergic Antagonists, Adrenergic Alpha-1 Receptor Antagonists, Adrenergic Alpha-Antagonists, Antihypertensive Agents, Narcotic Antagonists, Mu opioid Receptor Antagonists, Opioid Receptor Antagonists, Therapeutic Uses

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	47	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

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?
   The major goal of this project was originally to randomize 150 Veterans into this study to receive prazosin, naltrexone, both medications, or placebo for 7 weeks, then measure the affect the treatment had on craving and drinking. The Aims were:

   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.

   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.

   3. To explore whether PTSD status moderates medication response.

See beneath for the study's scope of work table (rev. 10/16/2018) which lists major project goals approved in the SOW. This SOW was approved in award modification P0004 (16-Oct-2018) that would have added an additional recruitment site for Active Duty servicemembers at Joint Base Lewis McChord/Madigan Army Medical Center.

While this version remains the approved SOW, the program office later decided not to continue support of the addition of the JBLM/MAMC recruitment site. At that time, SIBCR submitted a close-out timeline and project plan (approved in award modification P0005, dated 26-Jun-2019), with the following remaining data analysis and publication preparation activities. The approved timeline for remaining tasks was:

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 The requested 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?
This SOW table shows progress made against goals by year, with Xs indicating completed tasks:

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 1S – 7S are halted, per notice from Inna Williams on May 28, 2019.								
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								
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								X
Task 15: Write and submit necessary reports to DoD	X		X	X	X	X	X	X
Task 16: Write and submit manuscripts								X

Data Cleaning, Analysis, Manuscript, and Report Milestones: Tasks 13 through 16 will be completed by the end of the grant period.							X

Target Enrollment Table (rev. 10/2018)						
Period		Dates			Target Enrollment (October 2018 SOW)	Actual Enrollment (as of 2/28/2020)
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*	*0*
	Q3	*4/1/2020*	*to*	*6/30/2020*	*0*	*0*
	Q4	*7/1/2020*	*to*	*9/30/2020*	*0*	***0***
Total					**120**	***31***

Discontinuation/Withdrawals:

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	

We have completed data analyses and have drafted a manuscript, which we plan to submit to the journal *Alcoholism: Clinical and Experimental Research* by the end of June, 2020. A copy of this manuscript is attached detailing the data that we collected and analyzed in this project. In our study, the combination of Naltrexone and Prazosin showed promising results in managing alcohol use disorders:

1. Veterans in the Naltrexone/Prazosin group began reducing drinking activity by the first week post-titration and showed the greatest improvement in three of the four main outcomes compared to the other three groups (Naltrexone/Prazosin, Naltrexone/Placebo, and Prazosin/Placebo): PDD (Percent Day Drinking), PHDD (Percent Heavy Drinking Day), and craving level.
2. Two Naltrexone/Prazosin Veterans were completely abstinent in the last week of study compared to one participant in each of the other treatment groups.

3. Veterans in the Naltrexone/Prazosin group also showed the greatest reduction in the average number of drinks per drinking day, although this achievement was also shared with Veterans in the Naltrexone/Placebo group.

Through these findings, we believe that our study contributes to the management of alcohol use disorders by demonstrating the possibility of Naltrexone and Prazosin to treat alcohol use disorders.

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?
This question is not applicable because this report is a final report.

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?
In our study, the combination of Naltrexone and Prazosin showed promising results in managing alcohol use disorders:

4. Veterans in the Naltrexone/Prazosin group began reducing drinking activity by the first week post-titration and showed the greatest improvement in three of the four main outcomes compare to the other three groups (Naltrexone/Prazosin, Naltrexone/Placebo, and Prazosin/Placebo): PDD (Percent Day Drinking), PHDD (Percent Heavy Drinking Day), and craving level.
5. Two Naltrexone/Prazosin Veterans were completely abstinent in the last week of study compared to one participant in each of the other treatment groups.
6. Veterans in the Naltrexone/Prazosin group also showed the greatest reduction in the average number of drinks per drinking day, although this achievement was also shared with Veterans in the Naltrexone/Placebo group.

Through these findings, we believe that our study contributes to the management of alcohol use disorders by demonstrating the possibility of Naltrexone and Prazosin to treat alcohol use disorders. We will pursue publication of these findings so that they can be disseminated to practitioners and other researchers.

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?
Alcohol use disorder (AUD) contributes significantly to global disease burden and excess mortality, yet treatment uptake to address AUD, including pharmacotherapy, is low. Past studies have increasingly explored the use of combinations of medications because they are postulated to have the following potential benefits: they can target more than one neurotransmitter system implicated in AUD, target different drinking behaviors, treat both AUD and comorbid psychiatric disorders, may offer additive or synergistic effects, and may improve adherence should lower doses of either or both medications be effective, thereby minimizing side effects. One medication that is most frequently combined with others to treat AUD is naltrexone, one of the medications used in our study, thus we hope that our study will contribute beyond the academic world, benefiting not only to the clinical management of AUD, but also to the society at large by reducing the social burden of AUD.

5. CHANGES/PROBLEMS:

Meeting recruitment goals was an issue throughout the life of the project. We ceased recruitment at the VA site in 2018 after consenting 62 and randomizing 31 subjects, 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 were no major problems completing the close-out 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
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. This was 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 large VA Community-Based Outpatient Clinic (CBOC) to our north setting up study recruitment and offered the location as an additional recruitment site, as they were currently 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.

We encountered a final delay in completing task 16 (writing and submitting manuscripts) due to the original study biostatistician having left the research group and the need to secure the services of another biostatistician. Nevertheless, this is now resolved and we have completed a draft of our first manuscript and plan to submit it to *Alcoholism: Clinical and Experimental Research* by the end of June, 2020.

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 was sufficient to support 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**
  We have manuscript to submit to the Alcoholism: Clinical and Experimental Research Journal. Dr. Murray Raskind presented the study preliminary results at the CDMRP meeting in September 2019.

- **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."

These are the individuals who have worked on the project in the report period from December 2013 to February 2020. There is no change in any of their involvement since the prior reports on which they appeared.

Name: *Tracy Simpson, PhD*

Project Role: *Co-PI*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *1.8 CMs/Year for 6.15 Years = 11 CMs*
Contribution to Project: *Dr. Simpson is the study PI.*
Funding Support: *Dr. Simpson's salary is supported by VAPSHCS*

Name: *Andrew Saxon, MD*
Project Role: *Co-PI*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *1.2 CMs/Year for 6.15 Years = 7 CMs*
Contribution to Project: *Dr. Saxon is co-study PI*
Funding Support: *Dr. Saxon's salary is supported by VAPSHCS*

Name: *Carol Achtmeyer, MN, ARNP*
Project Role: *Study Clinician*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *8*
Contribution to Project: *Performed in-person participant visits*

Name: *Bergetta Dietel*
Project Role: *Research Coordinator*
Nearest person month worked: *2*
Contribution: *Participant Recruitment and Regulatory Duties*

Name: *Kimberley A. Hodge*
Project Role: *Research Coordinator*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *18*
Contribution to Project: *Participant recruitment and regulatory duties*

Name: *Robert Lyons*
Project Role: *Research Coordinator*
Nearest person month worked: *20*
Contribution: *Participant Recruitment and Regulatory Duties*

Name: *Daniel Murray*
Project Role: *Research Assistant*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *2*
Contribution to Project: *Data entry and quality assurance*

Name: *Dana Tell, ARNP*
Project Role: *Study Clinician*
Nearest person month worked: *10*
Contribution: *Performed 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?
VA Puget Sound MIRECC and CESATE supported the expenses for preparing the MAMC/JBLM IRB application to conserve DoD funds to perform the trial, as well as effort of Lisa Batten, Research Health Science Specialist, during project close-out. This is not considered cost sharing because VA Puget Sound is a federal entity.

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 manuscript.

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.

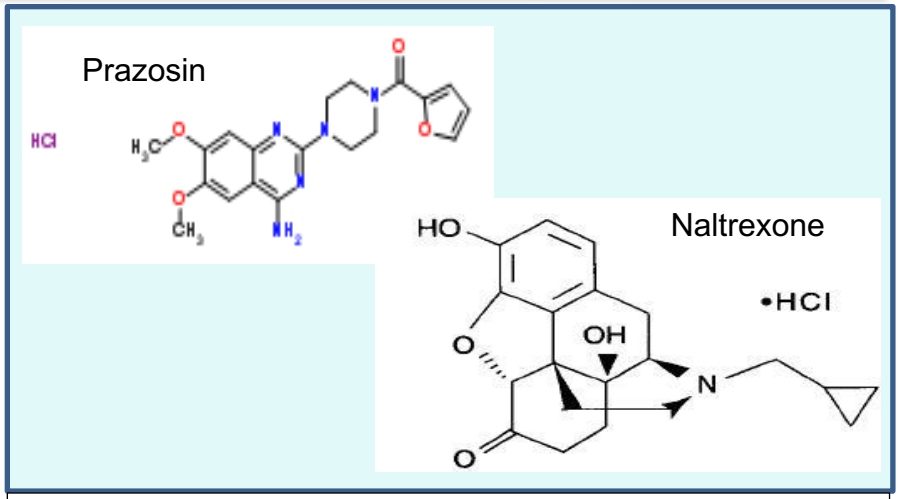
150 Veterans and Service Members will be randomized to receive prazosin, naltrexone, both medications, or placebo for 3 weeks. Craving will be assessed through daily monitoring and a laboratory based craving induction paradigm.

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: $802,000.00
Exps. through end: $791,859.78

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.
- ☑ Write and submit manuscripts [Submission pending]

Comments/Challenges/Issues/Concerns

Thank you for the opportunity to pursue this important line of research.

Updated: 5/28/2020

REPORT OF INVENTIONS AND SUBCONTRACTS

(Pursuant to "Patent Rights" Contract Clause) (See Instructions on back)

Form Approved
OMB No. 9000-0095
Expires Jan 31, 2008

PLEASE DO NOT RETURN YOUR COMPLETED FORM TO THE ABOVE ORGANIZATION. RETURN COMPLETED FORM TO THE CONTRACTING OFFICER.

1.a. NAME OF CONTRACTOR/SUBCONTRACTOR	c. CONTRACT NUMBER	2.a. NAME OF GOVERNMENT PRIME CONTRACTOR	c. CONTRACT NUMBER	3. TYPE OF REPORT *(X one)*
See 2.a	See 2.c	Seattle Institute for Biomedical & Clinical R	W81XWH-14-1-0025	a. INTERIM [ ] b. FINAL [X]

b. ADDRESS *(Include ZIP Code)*	d. AWARD DATE *(YYYYMMDD)*	b. ADDRESS *(Include ZIP Code)*	d. AWARD DATE *(YYYYMMDD)*	4. REPORTING PERIOD *(YYYYMMDD)*
See 2.b		1660 S. Columbian Way, Seattle WA 98108	20131203	a. FROM 20131204 b. TO 20200228

SECTION I - SUBJECT INVENTIONS

5. "SUBJECT INVENTIONS" REQUIRED TO BE REPORTED BY CONTRACTOR/SUBCONTRACTOR *(If "None," so state)*

NAME(S) OF INVENTOR(S) *(Last, First, Middle Initial)* a.	TITLE OF INVENTION(S) b.	DISCLOSURE NUMBER, PATENT APPLICATION SERIAL NUMBER OR PATENT NUMBER c.	ELECTION TO FILE PATENT APPLICATIONS *(X)* d.				CONFIRMATORY INSTRUMENT OR ASSIGNMENT FORWARDED TO CONTRACTING OFFICER *(X)* e.	
			(1) UNITED STATES		(2) FOREIGN			
			(a) YES	(b) NO	(a) YES	(b) NO	(a) YES	(b) NO
	None to report							

f. EMPLOYER OF INVENTOR(S) NOT EMPLOYED BY CONTRACTOR/SUBCONTRACTOR		g. ELECTED FOREIGN COUNTRIES IN WHICH A PATENT APPLICATION WILL BE FILED	
(1) (a) NAME OF INVENTOR *(Last, First, Middle Initial)*	(2) (a) NAME OF INVENTOR *(Last, First, Middle Initial)*	(1) TITLE OF INVENTION	(2) FOREIGN COUNTRIES OF PATENT APPLICATION
(b) NAME OF EMPLOYER	(b) NAME OF EMPLOYER		
(c) ADDRESS OF EMPLOYER *(Include ZIP Code)*	(c) ADDRESS OF EMPLOYER *(Include ZIP Code)*		

SECTION II - SUBCONTRACTS *(Containing a "Patent Rights" clause)*

6. SUBCONTRACTS AWARDED BY CONTRACTOR/SUBCONTRACTOR *(If "None," so state)*

NAME OF SUBCONTRACTOR(S) a.	ADDRESS *(Include ZIP Code)* b.	SUBCONTRACT NUMBER(S) c.	FAR "PATENT RIGHTS" d.		DESCRIPTION OF WORK TO BE PERFORMED UNDER SUBCONTRACT(S) e.	SUBCONTRACT DATES *(YYYYMMDD)* f.	
			(1) CLAUSE NUMBER	(2) DATE *(YYYYMM)*		(1) AWARD	(2) ESTIMATED COMPLETION

SECTION III - CERTIFICATION

7. CERTIFICATION OF REPORT BY CONTRACTOR/SUBCONTRACTOR *(Not required if: (X as appropriate))* [ ] SMALL BUSINESS or [X] NONPROFIT ORGANIZATION

I certify that the reporting party has procedures for prompt identification and timely disclosure of "Subject Inventions," that such procedures have been followed and that all "Subject Inventions" have been reported.

a. NAME OF AUTHORIZED CONTRACTOR/SUBCONTRACTOR OFFICIAL *(Last, First, Middle Initial)*	b. TITLE	c. SIGNATURE	d. DATE SIGNED

DD FORM 882 INSTRUCTIONS

GENERAL

This form is for use in submitting INTERIM and FINAL invention reports to the Contracting Officer and for use in reporting the award of subcontracts containing a "Patent Rights" clause. If the form does not afford sufficient space, multiple forms may be used or plain sheets of paper with proper identification of information by item number may be attached.

An INTERIM report is due at least every 12 months from the date of contract award and shall include (a) a listing of "Subject Inventions" during the reporting period, (b) a certification of compliance with required invention identification and disclosure procedures together with a certification of reporting of all "Subject Inventions," and (c) any required information not previously reported on subcontracts containing a "Patent Rights" clause.

A FINAL report is due within 6 months if contractor is a small business firm or domestic nonprofit organization and within 3 months for all others after completion of the contract work and shall include (a) a listing of all "Subject Inventions" required by the contract to be reported, and (b) any required information not previously reported on subcontracts awarded during the course of or under the contract and containing a "Patent Rights" clause.

While the form may be used for simultaneously reporting inventions and subcontracts, it may also be used for reporting, promptly after award, subcontracts containing a "Patent Rights" clause.

Dates shall be entered where indicated in certain items on this form and shall be entered in six or eight digit numbers in the order of year and month (YYYYMM) or year, month and day (YYYYMMDD). Example: April 2005 should be entered as 200504 and April 15, 2005 should be entered as 20050415.

1.a. Self-explanatory.

1.b. Self-explanatory.

1.c. If "same" as Item 2.c., so state.

1.d. Self-explanatory.

2.a. If "same" as Item 1.a., so state.

2.b. Self-explanatory.

2.c. Procurement Instrument Identification (PII) number of contract (DFARS 204.7003).

2.d. through 5.e. Self-explanatory.

5.f. The name and address of the employer of each inventor not employed by the contractor or subcontractor is needed because the Government's rights in a reported invention may not be determined solely by the terms of the "Patent Rights" clause in the contract.

Example 1: If an invention is made by a Government employee assigned to work with a contractor, the Government rights in such an invention will be determined under Executive Order 10096.

Example 2: If an invention is made under a contract by joint inventors and one of the inventors is a Government employee, the Government's rights in such an inventor's interest in the invention will also be determined under Executive Order 10096, except where the contractor is a small business or nonprofit organization, in which case the provisions of 35 U.S.C. 202(e) will apply.

5.g.(1) Self-explanatory.

5.g.(2) Self-explanatory with the exception that the contractor or subcontractor shall indicate, if known at the time of this report, whether applications will be filed under either the Patent Cooperation Treaty (PCT) or the European Patent Convention (EPC). If such is known, the letters PCT or EPC shall be entered after each listed country.

6.a. Self-explanatory.

6.b. Self-explanatory.

6.c. Self-explanatory.

6.d. Patent Rights Clauses are located in FAR 52.227.

6.e. Self-explanatory.

6.f. Self-explanatory.

7. Certification not required by small business firms and domestic nonprofit organizations.

7.a. through 7.d. Self-explanatory.

Naltrexone and Prazosin for Alcohol Use Disorder: Results from a Randomized Controlled Double-Blind, Double-Dummy Pilot Study

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Manuscript DRAFT attached to DoD Final Report

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Although not widely used in clinical practice (see Williams, Matson, & Harris, 2019), there are three FDA approved medications for the treatment of alcohol use disorder (AUD); disulfiram (Antabuse), naltrexone (including the injectable form, Vivitrol) and acamprosate. Disulfiram, which inhibits mitochondrial aldehyde dehydrogenase, was the first such medication to receive FDA approval for AUD. In open-label, but not masked randomized clinical trials (RCTs), disulfiram is associated with reduced alcohol consumption (Akbar et al., 2018; Skinner, Lahmek, Pham, & Aubin, 2014), though adequate compliance is generally less than 20% in voluntary samples (Jorgenson, Pedersen, & Tonnesen, 2014), markedly limiting its utility. Naltrexone is a mu-opioid receptor antagonist, and a meta-analysis of pharmacotherapy for AUD (Jonas et al., 2014) found that across double-blind RCTs the number needed to treat (NNT) with naltrexone (using the standard 50 mg dose) to prevent one patient's return to any drinking was 20 (k = 16 studies), while the NNT to prevent return to heavy drinking was 12 (k = 19 studies). Acamprosate, which enhances function at N-Methyl D-aspartate subtype of glutamate receptors (Akbar et al., 2018), was found to have an NNT of 12 for return to any drinking (k = 16; Jonas et al., 2014). Although additional, off-label medications for AUD hold some promise (e.g., topirimate, nalmefene (see Jonas et al., 2014), varenicline (Litten et al., 2013), and prazosin (Simpson et al., 2018); see Ray et al., 2019 for an overview), trial results have been modest. Moreover, no AUD medication has been found to reliably reduce both drinking and craving (Haass-Koffler et al., 2018), the latter being important because it is both subjectively distressing and puts people at risk for return to use that is outside their treatment goals (Sinha, 2011).

In light of the modest efficacy of the FDA approved medications and the heretofore modest performances of off-label medications, the field has increasingly explored the use of combinations of medications. As noted by Lee and Leggio (2014), medication combinations

could have the following potential benefits: they can target more than one neurotransmitter system implicated in AUD, target different drinking behaviors, treat both AUD and comorbid psychiatric disorders, may offer additive or synergistic effects (see also Frohlich et al., 2013), and may improve adherence should lower doses of either or both medications be effective, thereby minimizing side effects.

The medication most frequently paired with others in combination studies is naltrexone, likely because it is FDA approved, may be successfully and safely administered in the context of double-blind RCTs, and in the US, is the most widely prescribed medication for AUD (see Ehrie, Hartwell, Morris, Mark, & Kranzler, 2020). Two studies have found support for experimental medication combinations involving naltrexone when compared with the two single medications paired with placebo (Anton et al., 2011; Pettinati et al., 2010). Anton and colleagues (2011) found initial support for the combination of naltrexone and gabapentin such that it outperformed either medication alone, but no other trials evaluating this particular pair of medications have appeared in the literature so its utility is not yet known. Pettianati and colleagues (2010) found that the combination of naltrexone and sertraline was more efficacious than either single medication in alcohol dependent individuals with DSM-IV major depression. However, two other studies evaluating the latter combination in general samples of people with AUD (i.e., a diagnosis of major depression was not required) did not find support for it relative to naltrexone alone or sertraline alone (Farren et al., 2009; O'Malley et al., 2008). Additionally, a recent review of this literature (Naglich, Lin, Wakhlu, & Adinoff, 2018) concluded that there was little evidence that any of the combinations involving naltrexone yielded better outcomes than either medication paired with placebo, and studies testing combinations not including naltrexone were similarly disappointing.

While this unfortunate pattern of results pertaining to medication combinations for AUD was accumulating in the human clinical literature, animal researchers were simultaneously testing other combinations and finding promising signals. One such promising combination, which has been subjected to testing by different research groups and using several different animal addiction paradigms, is naltrexone and prazosin (Froehlich, Hausauer, & Rasmussen, 2013; Rasmussen, Kincaid, & Froehlich, 2015; Verplaetse & Czachowski, 2015). The mu-opioid system has long been a target for pharmacologic intervention in the setting of AUD with naltrexone consistently showing modest efficacy in reducing drinking via reductions in the reinforcing or euphoria-inducing aspects of alcohol consumption (Setiawan, Pihl, Benkelfat, & Leyton, 2012; Setiawan et al., 2011). The noradrenergic system is also implicated in regulating drinking, particularly in response to stress (Koob, 2009; Turnstall, Carmack, Koob, & Vendruscolo 2017). Animal studies have consistently found that prazosin, an alpha-1 noradrenergic medication, is associated with decreased alcohol consumption (see Rasmussen et al., 2015 for an overview), and there is preliminary evidence supporting prazosin's use in humans with AUD (Fox et al., 2012; Simpson et al., 2018). A combination of medications that can successfully address these two complementary brain systems implicated in addiction would be a boon to individuals who drink for a variety of reasons (e.g., to feel intoxicated, to enhance positives, to cope with negative affect and stress, etc.). The fact that all three of the extant animal studies evaluating the combination of naltrexone and prazosin found that it outperforms either medication alone (Froehlich et al., 2013; Rasmussen et al., 2015; Verplaetse & Czachowski, 2015), suggests that it is a promising combination to evaluate in humans with AUD.

To this end, we conducted a double-blind, double-dummy pilot RCT comparing the combination of naltrexone and prazosin relative to each medication combined with placebo and double placebo in veterans with AUD who were actively drinking, reported at least moderate craving for alcohol, and wished to abstain or moderate their alcohol consumption. Our primary drinking outcomes were changes in percent days drinking (PDD) and percent days heavy drinking (PHDD; calibrated by sex) during the baseline period relative to drinking during the six weeks of study medication. Our primary craving outcome was the change in craving strength from the week prior to initiating study medication to the final week of study medication. We hypothesized that those assigned to the combined medication condition would report significantly greater decreases in percent drinking days and heavy drinking days as well as significantly greater reduction in craving from pre to post-treatment than those assigned to either single medication arm and the double-placebo arm.

Materials and Methods

Study Design, Initial Power Calculations and Sample Size

This Department of Defense funded study recruited US military veterans with active AUD and alcohol-related craving with and without PTSD and was designed as a four-arm double-blind, double-dummy RCT with equal allocation to the following treatment conditions: Naltrexone + Prazosin (Nal/Praz); Naltrexone + Placebo (Nal/Pl); Prazosin + Placebo (Praz/Pl), and double placebo (Pl/Pl). Because participants were either in active VA addiction treatment or were referred to care, there was not a specific behavioral platform beyond standard supportive encouragement and problem-solving regarding medication adherence.

The study was originally conceived of as a 4-week test of the medication conditions on craving following two weeks of prazosin titration (naltrexone was dosed consistently throughout)

and two weeks of stable medication, but we opted to extend the stable medication phase by two weeks to obtain preliminary information on drinking outcomes. In accord with the original focus on craving, the a priori power calculations used craving as the dependent variable of interest and determined that 30 participants per cell, or 120 participants total, were needed to detect an overall difference in craving between the four groups for a two-sided, Type I error of 5% with an effect size of 0.50 (defined as the outcome standard deviation for the study sample) and power of 90%.

Recruitment fell well short of the target. We randomized only 31 participants, largely because so many veterans in the population of interest were already receiving one of these medications clinically.

Study Participants

We conducted 200 telephone screens. Ninety-seven individuals were eligible to participate in an in-person screening assessment (see Figure 1 for the CONSORT diagram). Of these, 61 attended the assessment visit and provided written informed consent. Thirty-one met study inclusion criteria and were randomized.

Study inclusion criteria were as follows: 1) veteran of the U.S. military or National Guard Reserve; 2) current AUD by DSM-5 criteria; 3) heavy drinking (>14 drinks per week for females; > 21 drinks per week for males) for at least 2 weeks in the last 3 months **and** some drinking during the past two weeks OR binge drinking for at least 3 days in the last month (4+ drinks for females; 5+ drinks for males); 4) at least mild alcohol craving as assessed by the Pennsylvania Alcohol Craving Scale (PACS; score $\geq$ 10; Flannery, Volpicelli, & Petinatti, 1999) at baseline; 5) age 18-80; 6) English fluency and literacy; 7) trying or planning to try to cut down

on or abstain from alcohol; 8) good general medical health, and 9) capable of giving informed consent.

Study exclusion criteria were as follows: 1) uncontrolled psychiatric disorder with psychotic symptoms or cognitive impairment; 2) *if* taking psychiatric medication, **NOT** on a stable dose for at least 30 days prior to randomization; 3) any suicidal ideation in the past 7 days, plan or intent past 6 months, or any suicide attempt past year; 4) homicidal ideation with plan and intent in the past 30 days; 5) Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001) endorsement of hopelessness or self-harm/SI and/or sum scale score ≥ 19; 6) any use of prazosin or naltrexone past 30 days; 7) currently taking disulfiram or acamprosate *OR* planning to take any of these medications (including prazosin or naltrexone) during the 8 weeks of the study; 8) current moderate or severe substance use disorder (past 30 days) on any psychoactive substance other than alcohol, nicotine, or cannabis, *OR* current diagnosis of any opioid or amphetamine use disorder, *OR* use of any amphetamine or opioid-containing medications during the previous 30 days; 9) urine drug screen positive for amphetamine, opioids; 10) significant acute or chronic medical illness; 11) preexisting hypotension (sys <100) or orthostatic hypotension (sys drop of > 20 mmHg; after two minutes of standing, or any drop w/dizziness 12) allergy or previous adverse reaction to naltrexone, prazosin, quinazolines, or other α-1 adrenergic blockers or use of other α -1 adrenergic blocker; 13) women who are pregnant, breastfeeding, or of childbearing potential and not using a contraceptive method judged by the investigator to be effective; 14) legal involvement that could interfere with study participation including being court ordered for treatment; 15) signs or symptoms of withdrawal at time of initial consent, or 15) any participation in an experimental drug study or any addiction study past 30 days.

Procedure

Recruitment. The VA Puget Sound Health Care System and the Department of Defense Human Research Protection Official oversight body both provided human subjects approval for this study. Recruitment was primarily through letters sent to those whose electronic medical records indicated they likely had an active AUD and had not been prescribed either of the study medications through the VA. We also posted flyers throughout the medical center and made regular announcements regarding the study opportunity during clinical team meetings. The study is registered through ClinicalTrials.gov (NCT02322047). Recruitment began on 12/3/14 and the last patient visit occurred on10/10/18.

Consent and Screening. Interested callers who seemed to meet basic inclusion/exclusion criteria were scheduled for an in-person consent and screening visit. At the outset of the consent/screening visit (Visit 1) the Study Clinician (SC) reviewed the informed consent form and study participants provided written informed consent. To ascertain study eligibility the SC administered the substance use disorders section of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 2006). The MINI was adapted to conform to DSM-5 and used to confirm AUD and to assess for other potential substance use disorder diagnoses, as well as psychotic disorders, suicidality and risk of harm to others (the latter two sections were modified to fit our study inclusion/exclusion criteria). The MINI AUD assessment determined whether participants met drinking inclusion requirements. Presence of craving was assessed via the PACS. Participants underwent a complete medical history and physical examination. Participants who did not meet medical or drinking exclusions were evaluated for PTSD. Among those who endorsed a lifetime traumatic event via the 17-item Life Events Checklist (LEC; Blake et al., 1995), PTSD diagnostic status was initially ascertained using the PTSD Symptom Severity-

Interview (PSS-I; Foa et al. 2016) though mid-way through the trial the funding agency requested we shift to the 30-item CAPS-5 structured interview (Weathers et al., 2013). Participants also completed a self-report demographic questionnaire that included a forced choice item regarding their goals for their alcohol use over the next month (i.e., no change, reduce or cut down on amount of drinking, abstain completely).

Those found to be initially eligible were asked to complete a short battery of self-report measures regarding craving and PTSD symptom severity.

Women with childbearing potential provided urine for a pregnancy test at screening (as well as at the mid-point and final visit). As a further health screen, all participants provided blood samples that were evaluated regarding CBC, routine liver function tests, and routine serum chemistries.

Those who met inclusion/exclusion criteria were invited to continue study participation.

Randomization. Participants were randomized to one of four study conditions: Nal/Praz; Nal/Pl; Praz/Pl, and Pl/Pl. Randomization was blocked by gender, PTSD status, and alcohol consumption goal (abstention vs. reduction). After participants were determined to meet the initial study entry criteria, random assignment to study condition was conducted by the VA Puget Sound Research Pharmacist with randomization tables supplied by the study PIs. The Research Pharmacist had no contact with participants.

Study Visits and Calls. One week after the screening visit each participant was informed as to whether they fit the initial study inclusion criteria and those who were eligible were invited to an appointment that included further assessment and medication receipt. At this visit, blood pressure and suicidality were rescreened along with craving as final checks on study eligibility (note: although participants were randomized after it was determined they met study

inclusion/exclusion criteria so as to have study medications on hand during the second study visit but for safety reasons, those who failed the additional screening measures were disenrolled from the study and not included in the analyses). Participants completed the Form-90 (Miller & del Boca, 1994) to evaluate their drinking for the last three months as well as involvement in health care and mental health treatment. Study medications were dispensed at the end of this visit to those who passed the additional safety criteria remained eligible.

Participants were oriented to the medication regimen and provided a two-week medication supply in a Mediset along with written instructions with visuals (i.e., pictures of the capsules) regarding dosing. Prazosin was titrated over a two-week period to a maximum dose of 4mg in the morning, 4mg in the afternoon, and 8mg at bedtime. Naltrexone does not require a titration period; participants took a single 50mg capsule once daily.

Five brief subsequent study visits were scheduled to assure that participants were tolerating the study medications and to provide medication refills. These visits included blood pressure and heart rate checks as well as assessment of adverse events (AEs). AEs that included a 20 mmHg drop or more in systolic BP accompanied by dizziness, lightheadedness or syncope at time of measurement or systolic BP reading <100 with reported dizziness, lightheadedness or syncope at the time of measurement or between visits were considered unacceptable, and the prazosin titration was slowed or decreased to the last tolerated dosage or all medication was discontinued.

Three brief telephone calls to check AEs were interspersed with the in-person safety visits during the initial three weeks of study medication receipt.

Participants were asked to bring their medi-sets with them to each study visit and for pill counts. If a participant either failed to attend a study visit or failed to bring their medi-set, they were counted as non-adherent with medication for that visit.

Six weeks after initiating study medications, participants were asked to return for a final study visit that included evaluation of AEs, completion of the Form-90, CAPS, PACS, a brief physical examination, and a blood draw to again assess CBC, routine liver function tests, and routine serum chemistries.

Statistical Methods

Statistical analysis was focused on three primary outcomes (percent days drinking, percent heavy days drinking, and PACS craving scores) and two secondary outcomes (average drinks per drinking day and PEth). The Form-90 (Miller & del Boca, 1994) was used to gather drinking data for the three months prior to receipt of study medication as well as the six-weeks of study medication. This information was used to compute the number of drinks per drinking day, percent drinking days (PDD) and heavy drinking days (PHDD) in both time periods. Here, heavy drinking was defined as 5 or more drinks or 4 or more drinks in a day for men and women, respectively (Centers for Disease Control, 2015).

Differences in outcome measures from pre-treatment through the study medication phase were estimated using linear mixed effects regression of outcome (the dependent variable) on treatment by study visit interaction (the independent fixed effects). Study visit was modeled as categorical (post- vs. pre-treatment). Study participant was modeled as a random effect. Model results were summarized with estimated marginal means at pre- and post-treatment for each treatment group, and within-group mean change from pre-treatment. Hypothesis testing for the overall difference in change in outcome by treatment was carried out using the likelihood ratio

test for the significance of the study visit by treatment interaction term. All means are accompanied by standard errors, and all mean differences are also presented with 95% confidence intervals (CIs), which were adjusted for the four sets of differences estimated corresponding to the four treatment groups using the single-step method (Hothorn, Bretz, & Westfall, 2008).

Exploratory analyses were carried out to separate the effect of the treatment from the effect of the pre-treatment levels of each outcome on the estimates of post-treatment change in outcomes by adding a pre-treatment outcome by visit interaction term to the model. Descriptive analyses were carried out to summarize clinical outcomes at the last week of study. Lower risk drinking was defined using NIAAA guidelines; for men this meant exceeding neither 14 drinks per week nor 4 drinks per day and for women this meant exceeding neither 7 drinks per week nor 3 drinks per day (Centers for Disease Control, 2015). The number of abstinent drinking days and the number of participants who were completely abstinent during the last week were also computed. Additionally, both the raw mean PDDs and PHDDs were computed for each week of study medication and plotted by group to illustrate changes over time in these outcomes. Type 1 error was set at .05 for each outcome. Analyses were carried out using R 3.6.2 (R Core Team, 2019), and the packages lme4, emmeans and tidyverse.

Descriptive information pertaining to study visit attendance, medication adherence, participant safety, adverse events, and medication adjustments is provided by medication treatment condition.

Results

Among those randomized, the mean age was 52.5 (sd 9.5) and 90.3% were male; 67.7% were non-Hispanic white, 16.1% were African American, 6.5% were Native American/American

Indian, and 3.2% were Asian/Pacific Islander. One participant preferred not to provide information on her race and one participant was multiracial (African American and Native American). Less than half were married/partnered (41.9%) or employed (48.4%), most were stably housed (87%) and had completed at least some college (77.4%). Only four had current PTSD diagnoses (13%).

Drinking and Craving Outcomes

While there were no significant differences in post- vs. pre-treatment change in outcomes by group (treatment by study visit interaction $p \geq .11$), some patterns were present (see Table 1 and Figure 2). For all outcomes except average number of drinks per drinking day, the Nal/Praz group showed the greatest improvement. There was a mean reduction in the PDD of 37% (95% CI: 10, 63) for this combined medication group, compared to a mean 15% reduction or less for the other medication groups. Similarly, the Nal/Praz group had a mean reduction in PHDD of 38% (95% CI: -7, 83) compared to 13% or less in the other groups. PACS scores for the Nal/Praz group improved by over 10 points (95% CI: 4, 17) compared to 4.6 points or less for the other groups. Exploratory analyses adjusting for effect of baseline outcome levels on treatment differences produced similar findings to those presented in Table 1(data not shown).

With regard to the average drinks per drinking day, both the Nal/Praz group and the Nal/Pl groups reduced by 5 drinks (95% CI: 0.3, 9.7) compared to an average reduction of under 4 drinks for the other two groups. Exploratory analysis adjusting for differences in average drinks prior to treatment by treatment group found reductions of almost 6 drinks for the Nal/Praz and Nal/Pl groups vs. 2.5 drinks or less for the other two groups.

Two-thirds of the six Nal/Praz participants who took any study medications engaged in low risk drinking behavior in the last week of study compared to half in the Nal/Pl, one-third in

the Praz/Pl, and 29% in the Pl/Pl group. Two Nal/Praz participants were completely abstinent the last week of study compared to one participant in each of the other treatment groups. The average number of abstinent days during the last week of study was 4.5 for the Nal/Praz group, 3.3 for the Nal/Pl group and 2.6 and 2.2 for the Pl/Pl and Praz/Pl groups respectively. While there was variability in post-treatment weekly PDD and PHDD across study participants, those in the Nal/Praz group, on average, decreased their percent days drinking shortly after the prazosin was fully titrated while most participants in that condition completely refrained from heavy drinking starting the first week of medication and persisting through the end of the study (see Supplemental Figures 1 and 2).

Safety, Medication Side Effects and Medication Titrations, and Blood Pressure Changes

There were no Serious Adverse Events. As may be seen in Table 2, two-thirds of participants assigned to Nal/Praz reported dizziness and lightheadedness while half reported nausea and a third reported drowsiness; other types of side effects were rarely reported by those assigned to this condition. For all but one participant, side effects abated mid-way through the medication phase of the study and side effects that were "probably" or "definitely" related to study medications, all were rated as "mild." Participants in the other three conditions generally did not report side effects; those side effects that were reported were varied and among those that were determined to "probably" or "definitely" be related to study medication(s), most were rated as "moderate" or "severe" (as opposed to "mild"). Of note, participants in the Pl/Pl condition largely did not begin reporting side effects until the latter half of the medication phase of the study.

One participant assigned to Nal/Praz discontinued medication after less than a week following the onset of dizziness and weakness rated as "severe" and "probably" attributed to the

study medication(s). This individual continued to participate in the study as ITT. Additionally, although it did not appear to be related to the study medications, one participant in the Praz/Pl condition discontinued study medications and was shifted to ITT after reporting two episodes of SI midway through the medication phase. One Pl/Pl participant reported loss of appetite and weight loss towards the end of the medication period and discontinued medications three days before the final visit. One participant in the Praz/Pl condition was maintained on 1mg of prazosin three times per day for the duration of the study, while the "prazosin" dose was reduced for one participant in the Pl/Pl condition who developed nausea shortly after full titration was achieved. Medication continuation and titration status did not appear to vary as a function of either gender or PTSD diagnostic status.

On average, both diastolic and systolic blood pressure dropped from baseline to the final visit for all four study conditions with the greatest drops in diastolic BP for the Nal/Praz and Pl/Pl groups, drops that were not markedly different from each other, while the Nal/Praz group showed the smallest drop in systolic BP of the four groups (see Table 3).

Study Involvement, Visit Completion, and Medication Adherence

Three participants (two in the Nal/Praz condition and one on the Pl/Pl condition) were randomized after meeting the initial screening criteria, but did not receive study medications. Two of the three did not complete the baseline assessment either because they reported clinically concerning suicidal ideation (Nal/Praz) or because they changed their mind and opted not to continue in the study (Pl/Pl). The third person (Nal/Praz) completed the baseline assessment and took study medications home but returned them all at the next visit reporting that his wife did not want him to take any medications. While all three had no further involvement with the study, the

second Nal/Praz participant was included in the ITT analyses because he had the opportunity to take study medications.

One additional participant withdrew from the study (Praz/Pl) due to side effects and two others were lost to follow-up (Nal/Pl and Pl/Pl). All six of those assigned to Nal/Praz who took study medications completed the study (i.e., attended the final scheduled study visit) while all but one in each of the other three conditions did so. Visit attendance during the medication phase was strong across the conditions ranging from 85.4% (Pl/Pl) to 100% (Nal/Praz); information by condition is in Figure 1.

Medication adherence was variable across the four conditions with those assigned to the Nal/Praz showing markedly better compliance (86% across all study visits) than the other three conditions (71%, 69%, and 46% for Praz/Pl, Nal/Pl, and Pl/Pl, respectively). When participants failed to bring their medi-set to a study visit, this was counted as medication non-adherence.

Discussion

We present the findings of this study as hypothesis generating as we did not expect to detect significant differences in the mean change in outcomes due to the small study sample. Still, we believe we found patterns warranting further study in a fully powered trial. Specifically, the finding that those assigned to the Nal/Praz condition, on average, reported 37% and 38% reductions in their percent days drinking and percent days heavy drinking, respectively, while those assigned to the other three groups reported, at best, 13% or 15% reductions on these indices, respectively. It is also noteworthy that those who received the experimental medication combination reported that their craving for alcohol was markedly diminished over the duration of the study while those in the other three groups reported only minimal reductions in craving.

Two-thirds of veterans assigned to Nal/Praz reported side effects consistent with receipt of prazosin (primarily dizziness, lightheadedness) shortly after starting study medications and all rated these side effects as "mild." Although proportionately more of those assigned to the combined medication condition reported side effects than across the other three groups, this group had markedly better medication adherence as measured by pill counts than the other three groups. This group also completed all study visits. Thus, it appears that for all but the individual who shifted to ITT after less than a week on study medications, the mild early side effects experienced by those in the Nal/Praz condition were perceived to be manageable. Moreover, as may be seen in the Supplemental Figure 2, most of the participants in the Nal/Praz condition stopped engaging in heavy drinking during their first week on medications and continued to refrain from heavy drinking throughout their study involvement, suggesting that the medications were helpful enough early on that they were worth taking despite the associated side effects.

Although the pattern of results suggests that the combination of naltrexone and prazosin has promise and appears likely to be more beneficial than either medication alone, the study is underpowered and no conclusions may be drawn at this point. The study was also limited by a brief medication duration of only six weeks, the absence of a post-medication follow-up period, inclusion of few women and few individuals with PTSD, and having changed the measure of PTSD mid-trial. The inclusion of the PEth biomarker and participants' consistent visit attendance across all four conditions were noteworthy study strengths that we hope to build on with a fully powered future trial.

Table 1. Drinking Outcomes (n = 29).

	Nal /Praz n=7	Praz/Pl n=7	Nal/Pl n=7	Pl/Pl n=8	p-value*
% Drinking days					
Baseline	73 ± 11	88 ± 11	64 ± 11	76 ± 11	
Final Visit	36 ± 12	79 ± 12	50 ± 12	61 ± 11	
Final - Baseline	-37 ± 10	-9 ± 10	-14 ± 10	-15 ± 9	.15
	(-63, -10)	(-35, 17)	(-40, 13)	(-39, 10)	
% Heavy drinking days					
Baseline	55 ± 14	78 ± 14	48 ± 14	66 ± 13	
Final Visit	17 ± 15	70 ± 15	40 ± 15	53 ± 14	
Final - Baseline	-38 ± 17	-8 ± 17	-7 ± 17	-13 ± 16	.47
	(-83, 7)	(-53, 38)	(-53, 38)	(-55, 29)	
Adjusted for pre-treatment levels	-43 ± 15	1 ± 15	-17 ± 15	-11 ± 13	
	(-81, -6)	(-38, 39)	(-55, 21)	(-46, 24)	
Mean drinks per day of drinking					
Baseline	8.2 ± 2.5	11.9 ± 2.5	8.4 ± 2.5	13.9 ± 2.3	
Final Visit	3.1 ± 2.6	9.7 ± 2.6	3.4 ± 2.6	10.2 ± 2.4	
Final - Baseline	-5.1 ± 1.7	-2.2 ± 1.7	-5.0 ± 1.7	-3.7 ± 1.6	.55
	(-9.7, -0.3)	(-6.8, 2.5)	(-9.7, -0.3)	(-8.1, 0.6)	
Adjusted for pre-treatment levels	-5.9 ± 1.4	-2.0 ± 1.4	-5.7 ± 1.4	-2.5 ± 1.3	
	(-9.4, -2.3)	(-5.5, 1.5)	(-9.3, -2.2)	(-5.9, 0.8)	
PACS					
Baseline	18.5 ± 2.2	20.3 ± 2.3	16.7 ± 2.3	16.9 ± 2.3	
Final Visit	8.0 ± 2.4	15.7 ± 2.5	12.4 ± 2.5	13.4 ± 2.5	
Final - Baseline	-10.5 ± 2.4	-4.6 ± 2.4	-4.3 ± 2.4	-3.5 ± 2.4	.11
	(-16.9, -4.0)	(-11.1, 1.9)	(-10.8, 2.2)	(-10.0, 3.0)	
Adjusted for pre-treatment levels	-10.0 ± 2.1	-3.7 ± 2.2	-4.6 ± 2.2	-3.9 ± 2.2	
	(-15.5 -4.5)	(-9.5, 2.1)	(-10.3, 1.1)	(-9.6, 1.8)	

Note: Summary statistics (mean ± SE, and 95% CI for mean differences) for % drinking days, % heavy drinking days, and average drinks based on the FORM90 by treatment group and study week. Estimates from linear mixed effects regression on treatment by study visit week interaction

* Significance of treatment by study visit interaction

Table 2. Adverse Events by Study Condition

Adverse Events[1]	Nal/Praz n = 6[2] n (%)	Praz/PL n = 7 n (%)	Nal/PL n = 7 n (%)	PL/PL n = 8[2] n (%)
Dizziness	4 (66)	0	1 (14)	2 (25)
Lightheadedness	4 (66)	2 (29)	2 (29)	1 (12.5)
Drowsiness	2 (33)	1 (14)	1 (14)	1 (12.5)
Lack of energy	1 (17)	1 (14)	1 (14)	1 (12.5)
Weakness	1 (17)	0	0	0
Palpitations	1 (17)	0	0	0
Nausea	3 (50)	0	1 (14)	1 (12.5)
Change in urination	1 (17)	1 (14)	0	0
Diarrhea	0	1 (14)	0	1 (12.5)
Abdominal symptoms (cramps, etc.)	0	1 (14)	0	1 (12.5)
Decreased appetite	0	0	0	2 (25)
Vivid dreams, nightmares	0	0	1 (14)	0
Metallic taste in mouth	0	1 (14)	0	0
Flushed	0	1 (14)	0	0
Extreme energy, mania	0	0	1 (14)	0
Insomnia, sleep disturbance	0	0	1 (14)	0

1. Adverse events were included if they were reported to be probably or definitely related to the study medications.
2. The total number of participants include withdrawal/withdrawn and ITT participants. It excludes 3 participants who never took study medications (2 Nal/Praz and 1 Pl/Pl).

Table 3. Cardiovascular indicators at baseline, final visit, and the difference.

	Praz/Nal n=7	Praz/Pl n=7	Nal/Pl n=7	Pl/Pl n=8
Baseline				
Diastolic BP	82.86 ± 12.59	81.43 ± 4.93	80.57 ± 9.69	82.75 ± 8.08
Systolic BP	131.86 ± 14.59	137.0 ± 14.31	133.86 ± 21.02	135.38 ± 19.14
Heart Rate	71.86 ± 10.40	80.43 ± 15.87	68.29 ± 11.66	71.0 ± 11.40
Final Visit				
Diastolic BP	78.67 ± 11.50	78.17 ± 5.57	78.50 ± 3.56	77.71 ± 8.86
Systolic BP	128.83 ± 16.65	121.83 ± 8.16	126.17 ± 4.62	125.14 ± 16.43
Heart Rate	70.17 ± 7.81	73.83 ± 17.82	78.50 ± 14.03	65.57 ± 15.99
Final - Baseline				
Diastolic BP	-5.17 ± 11.44	-2.67 ± 5.61	-3.33 ± 10.52	-4.57 ± 6.95
Systolic BP	-3.83 ± 13.67	-15.50 ± 9.18	-11.17 ± 18.67	-11.14 ± 13.26
Heart Rate	0 ± 10.43	-4.50 ± 10.95	8.83 ± 10.30	-4.71 ± 17.63

Figure 1. CONSORT Diagram

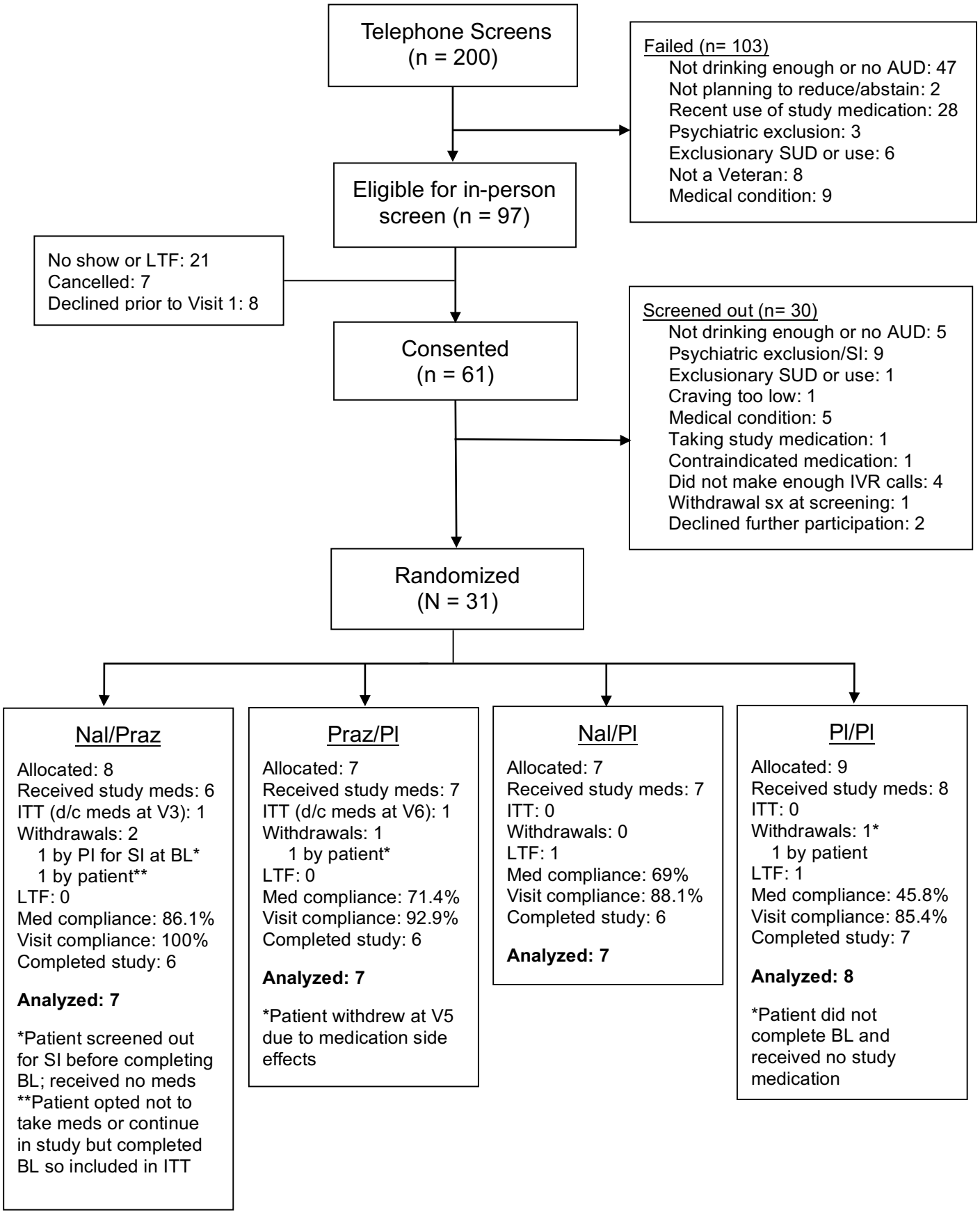
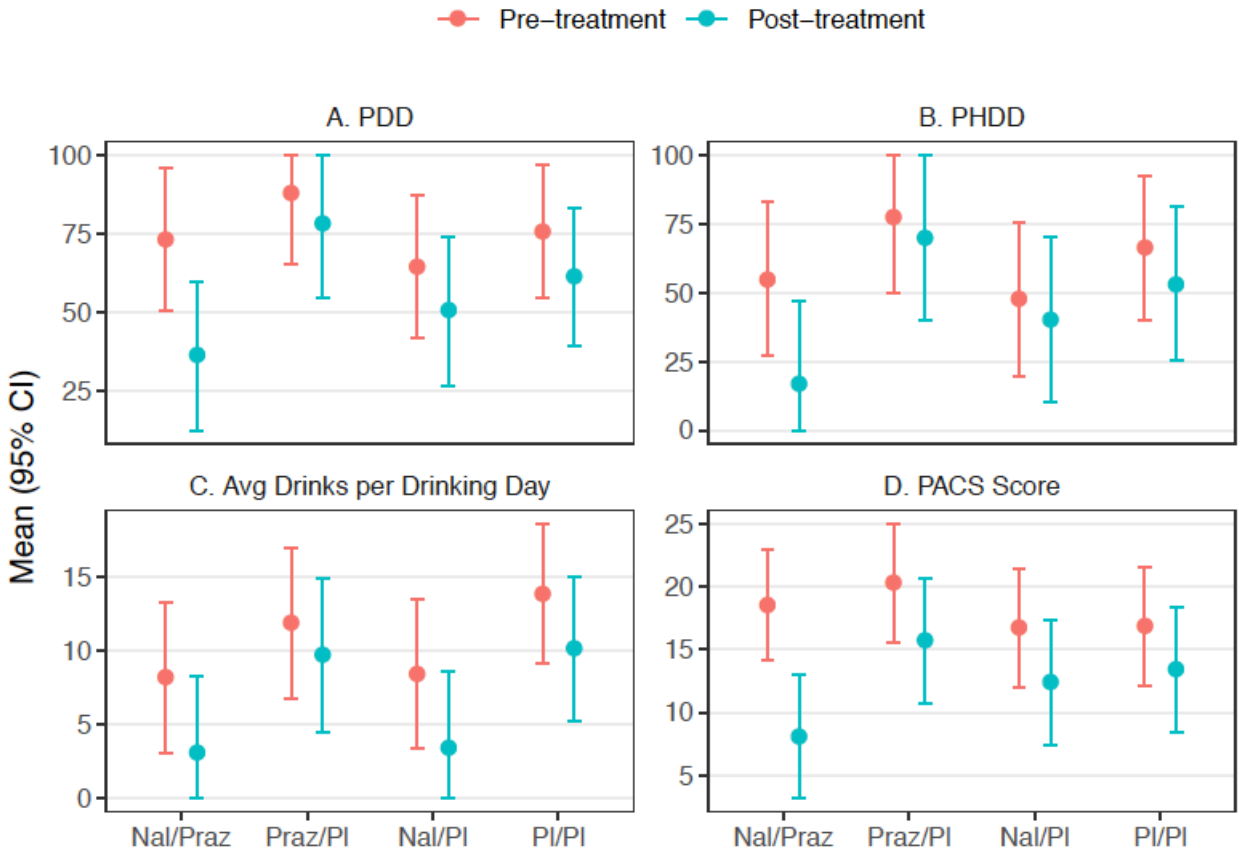
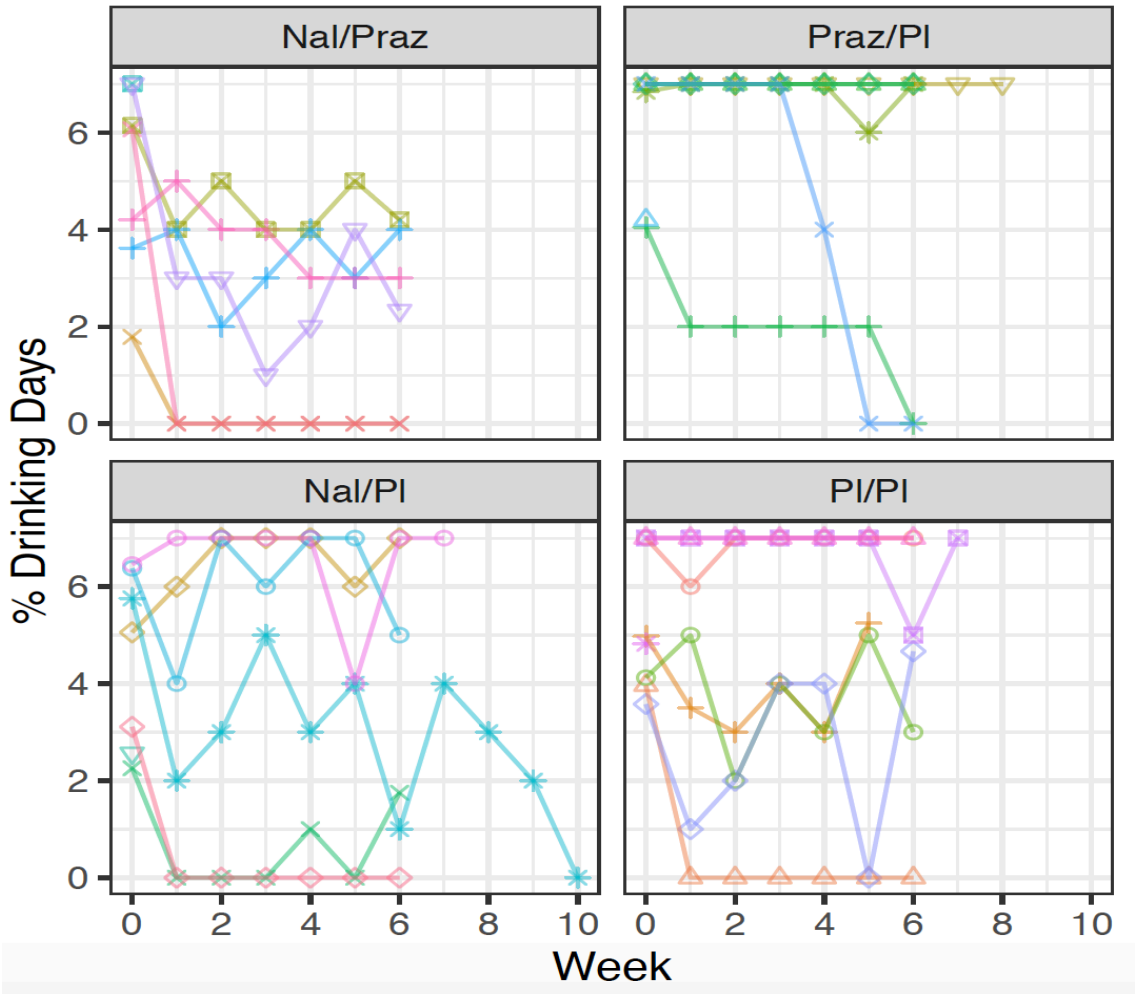


Figure 2. Drinking and Craving Outcomes by Condition

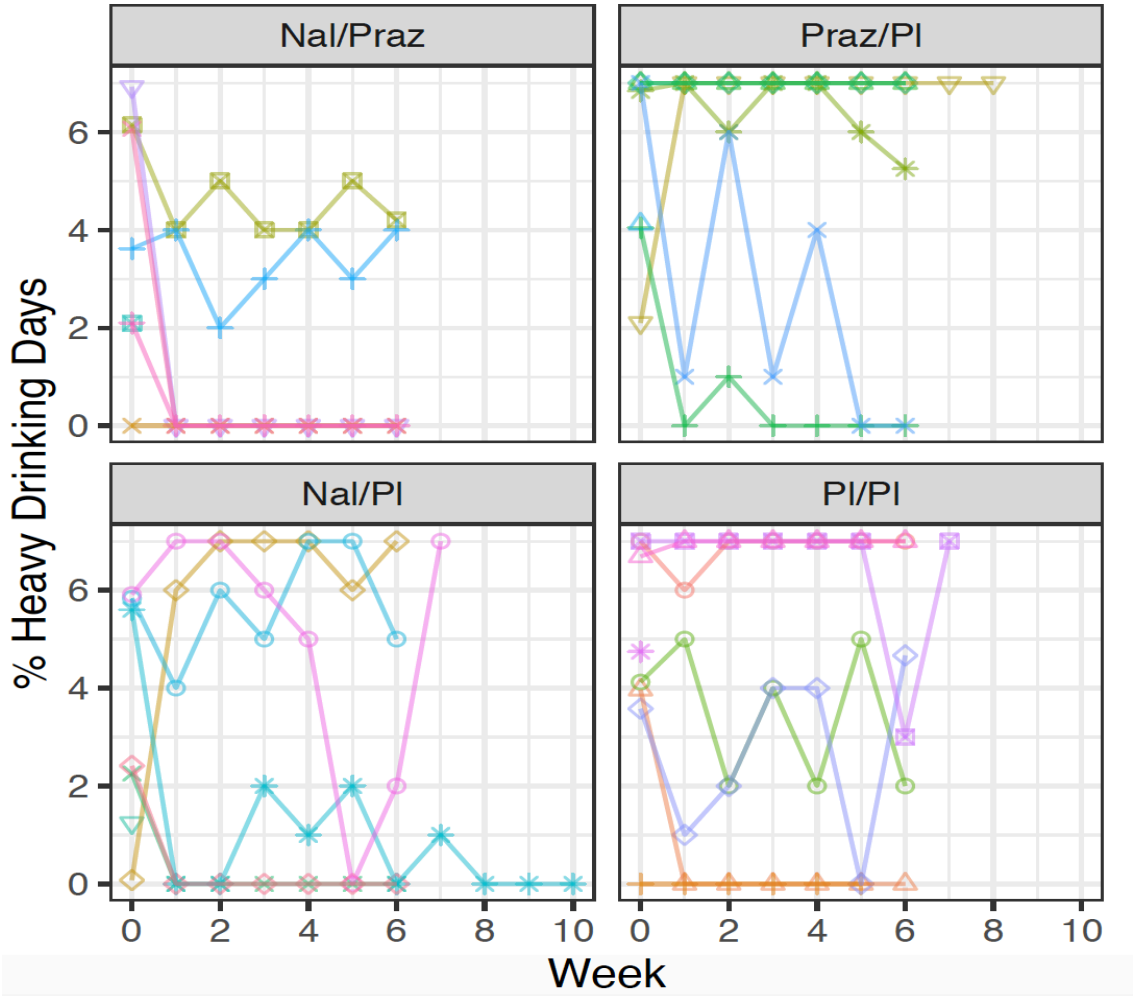


Estimated means and 95% CIs for study outcomes by treatment and study visit obtained from linear mixed effects regression of outcome on treatment by study visit interaction with study participant as a random effect.

Supplemental Figure 1. Weekly raw trajectories of PDD during the study medication phase by group.



Supplemental Figure 2. Weekly raw trajectories of PHDD during the study medication phase by group.



References

Akbar, M., Egli, M., Cho, Y. E., Song, B. J., & Noronha, A. (2018). Medications for alcohol use disorders: An overview. *Pharmacology & Therapeutics*, 185, pp.64–85. https://doi.org/10.1016/j.pharmthera.2017.11.007

Anton, R. F., Myrick, H., Wright, T. M., Latham, P. K., Baros, A. M., Waid, L. R., & Randall, P. K. (2011). Gabapentin combined with naltrexone for the treatment of alcohol dependence. *The American Journal of Psychiatry*, 168(7), pp.709–717. https://doi.org/10.1176/appi.ajp.2011.10101436

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress*, 8(1), pp.75-90. https://doi.org/10.1007/BF02105408

Centers for Disease Control. (2015) *Alcohol Use and Your Health Fact Sheet* [Online]. Available at: https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm (Accessed: March 30, 2020)

Ehrie, J., Hartwell, E. E., Morris, P. E., Mark, T. L., & Kranzler, H. R. (2020). Survey of Addiction Specialists' Use of Medications to Treat Alcohol Use Disorder. *Frontiers in Psychiatry*, 11, 47.

Farren, C. K., Scimeca, M., Wu, R., & Malley, S. O. (2009). A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. *Drug and Alcohol Dependence*, 99(1-3), pp.317–321. https://doi.org/10.1016/j.drugalcdep.2008.06.006

Flannery, B.A., Volpicelli, J.R., Pettinati, H.M. (1999). Psychometric Properties of the Penn Alcohol Craving Scale. *Alcoholism, Clinical and Experimental Research*, 23(8), pp1289-1295. https://doi.org/10.1111/j.1530-0277.1999.tb04349.x

Foa, E. B., McLean, C. P., Zang, Y., Zhong, J., Rauch, S., Porter, K., Knowles, K., Powers, M. B., & Kauffman, B. Y. (2016). Psychometric properties of the Posttraumatic Stress Disorder Symptom Scale Interview for DSM-5 (PSSI-5). *Psychological Assessment*, 28(10), pp.1159–1165. https://doi.org/10.1037/pas0000259

Fox, H. C., Anderson, G. M., Tuit, K., Hansen, J., Kimmerling, A., Siedlarz, K. M., Morgan, P. T., & Sinha, R. (2012). Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. *Alcoholism, Clinical and Experimental Research*, 36(2), pp.351–360. https://doi.org/10.1111/j.1530-0277.2011.01628.x

Froehlich, J. C., Hausauer, B. J., & Rasmussen, D. D. (2013). Combining naltrexone and prazosin in a single oral medication decreases alcohol drinking more effectively than does either drug alone. *Alcoholism, Clinical and Experimental Research*, 37(10), pp.1763–1770. https://doi.org/10.1111/acer.12148

Haass-Koffler, C. L., Swift, R. M., and Leggio, L. (2018). Noradrenergic targets for the treatment of alcohol use disorder. *Psychopharmacology (Berl)*, 235(6), pp.1625-1634. https://doi.org/10.1007/s00213-018-4843-6

Hothorn, T., Bretz, F., & Westfall, P. (2008). Simultaneous Inference in General Parametric Models. *Biometrical Journal 50*(3):346-363.

Jonas, D. E., Amick, H. R., Feltner, C., Bobashev, G., Thomas, K., Wines, R., Kim, M. M., Shanahan, E., Gass, C. E., Rowe, C. J., & Garbutt, J. C. (2014). Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*, 311(18), pp.1889–1900. https://doi.org/10.1001/jama.2014.3628

Jørgensen, C. H., Pedersen, B., and Tønnesen, H. (2011). The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcoholism, Clinical and Experimental Research*, 35(10), pp.1749–1758. https://doi.org/10.1111/j.1530-0277.2011.01523.x

Koob, G.F. (2009). Brain stress systems in the amygdala and addiction. *Brain Research*, 1293, pp.61-75. https://doi.org/10.1016/j.brainres.2009.03.038

Kroenke, K., Spitzer, R.L., Williams, B.W. (2001). The PHQ-9 validity of a brief depression severity measure. *Journal of General Internal Medicine*, 16(9), pp.606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Lee, M. R., & Leggio, L. (2014). Combined pharmacotherapies for the management of alcoholism: rationale and evidence to date. *CNS Drugs*, *28*(2), pp.107–119. https://doi.org/10.1007/s40263-013-0137-z

Litten, R. Z., Ryan, M. L., Fertig, J. B., Falk, D. E., Johnson, B., Dunn, K. E., Green, A. I., Pettinati, H. M., Ciraulo, D. A., Sarid-Segal, O., Kampman, K., Brunette, M. F., Strain, E. C., Tiouririne, N. A., Ransom, J., Scott, C., Stout, R., & NCIG (National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group) Study Group. (2013). A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *Journal of Addiction Medicine*, 7(4), pp.277–286. https://doi.org/10.1097/ADM.0b013e31829623f4

Miller, W.R., Del Boca, F.K. (1994). Measurement of drinking behavior using the Form 90 family of instruments. *Journal of Studies on Alcohol and Drugs,* Suppl 12, pp. 112-118. https://doi.org/10.15288/jsas.1994.s12.112

Naglich, A. C., Lin, A., Wakhlu, S., & Adinoff, B. H. (2018). Systematic review of combined pharmacotherapy for the treatment of alcohol use disorder in patients without comorbid conditions. *CNS Drugs*, 32(1), pp.13–31. https://doi.org/10.1007/s40263-017-0484-2

O'Malley, S. S., Robin, R. W., Levenson, A. L., GreyWolf, I., Chance, L. E., Hodgkinson, C. A., Romano, D., Robinson, J., Meandzija, B., Stillner, V., Wu, R., & Goldman, D. (2008). Naltrexone alone and with sertraline for the treatment of alcohol dependence in Alaska natives

and non-natives residing in rural settings: a randomized controlled trial. *Alcoholism, Clinical and Experimental Research*, 32(7), pp.1271–1283. https://doi.org/10.1111/j.1530-0277.2008.00682.x

Pettinati HM, Oslin DW, Kampman KM, Dundon, W. D., Xie, H., Gallis, T. L., Dackis, C. A., & O'Brien, C. P. (2010). A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *American Journal of Psychiatry*, 167(6), pp.668- 675. https://doi.org/10.1176/appi.ajp.2009.08060852

R Core Team. (2019) *R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria* [Online]. Available at: https://www.R-project.org/ (Accessed: July 2019)

Rasmussen, D. D., Kincaid, C. L., & Froehlich, J. C. (2015). Prazosin + naltrexone decreases alcohol drinking more effectively than does either drug alone in P rats with a protracted history of extensive voluntary alcohol drinking, dependence, and multiple withdrawals. *Alcoholism, Clinical and Experimental Research*, 39(9), pp.1832–1841. https://doi.org/10.1111/acer.12828

Setiawan, E., Pihl, R.O., Cox, S. M., Gianoulakis, C., Palmour, R. M., Benkelfat, C., & Leyton, M. (2011). The effect of naltrexone on alcohol's stimulant properties and self-administration behavior in social drinkers: influence of gender and genotype. *Alcoholism, Clinical and Experimental Research*, 35(6):1134-41. https://doi.org/10.1111/j.1530-0277.2011.01446.x

Setiawan, E., Pihl, R.O., Benkelfat, C., Leyton, M. (2012). Influence of the OPRM1 A118G polymorphism on alcohol-induced euphoria, risk for alcoholism and the clinical efficacy of naltrexone. *Pharmacogenomics*, 13(10), pp.1161-1172. https://doi.org/10.2217/pgs.12.99

Sheehan D, Janavs J, Baker R, et al. *M.I.N.I.: Mini International Neuropsychiatric Interview: English Version 5.0.0.* Tampa, FL: Author; 2006

Simpson, T. L., Saxon, A. J., Stappenbeck, C., Malte, C. A., Lyons, R., Tell, D., Millard, S. P., & Raskind, M. (2018). Double-blind randomized clinical trial of prazosin for alcohol use disorder. *The American Journal of Psychiatry*, 175(12), pp.1216–1224. https://doi.org/10.1176/appi.ajp.2018.17080913

Sinha, R. (2011). New findings on biological factors predicting addiction relapse vulnerability. *Current Psychiatry Reports* 13(5), pp.398-405. https://doi.org/10.1007/s11920-011-0224-0

Skinner, M. D., Lahmek, P., Pham, H., & Aubin, H. J. (2014). Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. *PloS One*, *9*(2). https://doi.org/10.1371/journal.pone.0087366

Tunstall, B.J., Carmack, S.A., Koob, G.F., Vendruscolo, L.F. (2017). Dysregulation of Brain Stress Systems Mediates Compulsive Alcohol Drinking. *Current Opinion in Behavioral Sciences*, 13, pp.85-90. https://doi.org/ 10.1016/j.cobeha.2016.10.006

Verplaetse, T. L., & Czachowski, C. L. (2015). Low-dose prazosin alone and in combination with propranolol or naltrexone: effects on ethanol and sucrose seeking and self-administration in the P rat. *Psychopharmacology*, 232(15), pp.2647–2657. https://doi.org/10.1007/s00213-015-3896-z

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2018). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, 30(3), 383–395. https://doi.org/10.1037/pas0000486

Williams, E.C., Matson, T.E., and Harris, A.H.S. (2019). Strategies to increase implementation of pharmacotherapy for alcohol use disorders: a structured review of care delivery and implementation interventions. *Addiction Science & Clinical Practice*, 14(6), pp.1-19. https://doi.org/10.1186/s13722-019-0134-8