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TITLE: Prazosin for Treatment of Patients With PTSD and Comorbid Alcohol Dependence

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14. ABSTRACT

Background: There is a high rate of comorbidity with alcohol dependence (AD) and post traumatic stress disorder (PTSD). The rates of PTSD among individuals with AD are at least twice as high as those in the general population. In addition, alcohol dependence is the most common comorbid condition in men with PTSD. Despite this, little is known about how to best treat individuals with comorbid AD and PTSD. The use of an alpha-1 adrenergic receptor antagonist represents a novel approach to treatment that may target symptoms of both AD and PTSD. There is evidence of common neurobiological mechanisms that underlie both AD and PTSD. Prazosin is an alpha-1 adrenergic receptor antagonist that has been used successfully in the treatment of trauma nightmares and sleep disturbance in combat veterans with PTSD, and alcohol dependence.

Objective: The objective of this study is to evaluate the efficacy of prazosis (16mg) versus placebo in reducing alcohol consumption and decreasing symptoms of PTSD in patients with comorbid AD and PTSD. **Methods**: One hundred and twenty participants with a current diagnosis of AD and PTSD will be enrolled in a 13-week trial. They will be assigned, in a double-blind fashion, to either prazosin or placebo. **Findings**: No findings are yet available for this study. **Significance:** This project will be the first to compare prazosin to placebo as effective treatments for reducing alcohol consumption and PTSD symptoms in patients with both AD and PTSD.

15. SUBJECT TERMS

PTSD, alcohol dependence, treatment, Prazosin

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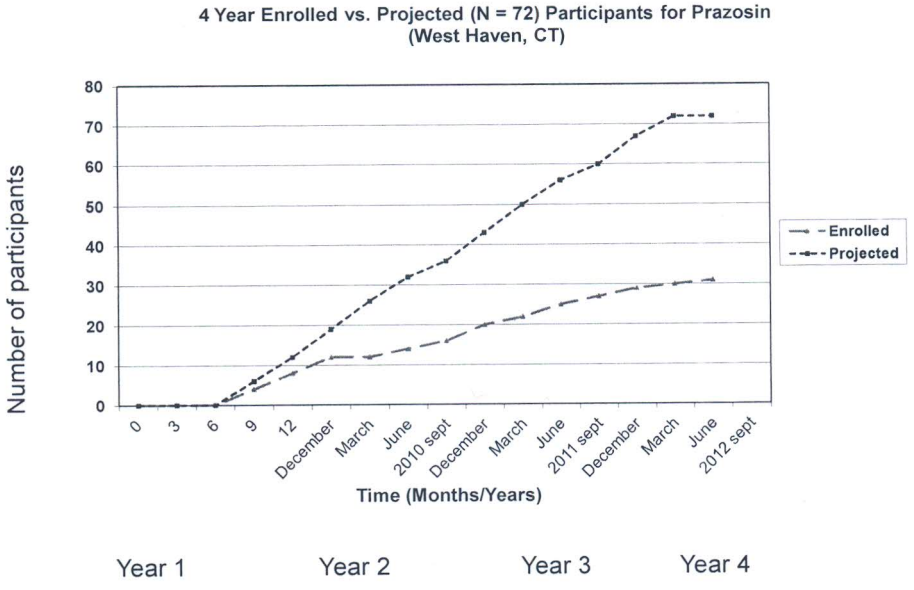
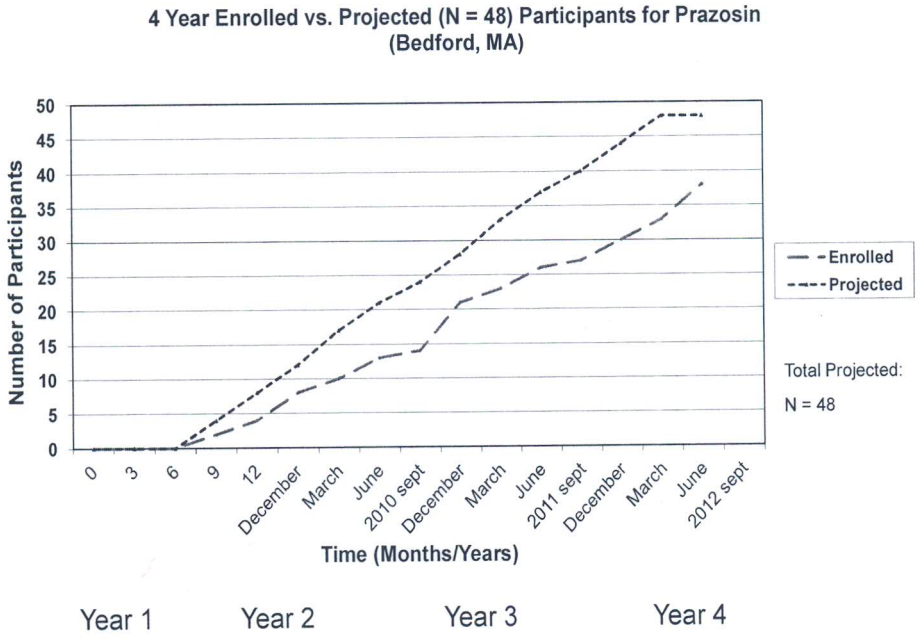
INTRODUCTION: The objective of this research is to evaluate the efficacy of Prazosin 16mg versus placebo in reducing alcohol consumption and decreasing symptoms of PTSD in patients with comorbid AD and PTSD. We hypothesize that Prazosin will significantly reduce the number of drinking days and reduce the symptoms of PTSD compared to placebo in patients with AD and PTSD. This is a double-blind, multi-site, randomized, 13-week, treatment trial. The recruitment for this study is planned for 4 years and a 1 year no cost extension (NCE) has now been approved.

BODY: This report covers the period of the fourth year of funding. Our goals for the fourth year were to: continue subject recruitment, develop and implement new avenue for recruitment, create new liaisons for recruitment, and follow patients already recruited in the study. The goals for this year have been accomplished regarding continuous recruitment as well as initiation and implementation of new recruitment strategies. However, our goal to recruit a total of 120 subjects has not been reached. Below we provide graphical representation of our recruitment to date in relationship to the goals we outlined in our statement of work. Our recruitment is progressing, and we have developed and implemented a number of strategies to increase recruitment in the past year. At the West Haven site, we have allocated resources for newspaper advertisement, and we created new liaisons in the community. Our recruitment has improved but in order to reach our recruitment goal we need to recruit more subjects into the study.

The recruitment at West Haven has been slower than predicted and what we are experiencing at our Bedford site. We believe that the differences in site explain, in part, the differences in recruitment. For example, Bedford has a residential program that allows for more stable patients to be in the potential subject pool. West Haven is a more acute setting so while a great number of patients have signed consent (n=36), we have only randomized 6 particpants. Nevertheless we are trying to address this shortage. In the past few months we have implemented a number of new strategies to increase recruitment: 1) one stuff member is actively recruiting participants from the Newington VA (an affiliate of West Haven VA). Those participants can be seen at Newington or since there is a scheduled daily shuttle several times per day between the two VAs study visits can be arranged at West Haven VA as well; 2) we have implemented daily recruitment to our Emergency Room to identify potential subjects; 3) we most recently have begun to evaluate all patients who are seen by our Integrated Psychiatric Care clinic (psychiatric care embedded in a primary care setting).. Those new strategies seemed to be effective and we are presently awaiting randomization of 3 new subjects.





Included in this report is a table that outlines our recruitment success – at both sites - to date.

Site	# Ss that have signed consent	# Ss enrolled	Ratio of Ss to target
West Haven	103	31	31/72
Bedford	61	38	38/48

KEY RESEARCH ACCOMPLISHMENTS: This study is ongoing and the sample size is not large enough for statistical analysis of the data at this time.

REPORTABLE OUTCOMES: The PI gave a presentation at the American Psychiatric Association Annual meeting on the comorbidity of PTSD and alcohol dependence in 2009. An abstract was also submitted for the Military Health Research Forum. A poster was presented at the Research Society of Alcoholism meeting in Atlanta, GA (June, 2011) comparing demographic characteristics of patients with dual diagnosis of AD and PTSD (from this study) and patients with only AD diagnosis (who had enrolled in another pharmacotherapy study). Analysis of the data for this poster revealed that the two groups were very similar in terms of their demographic characteristics. There were no differences in age, gender, marital status, education, employment status, or yearly income. There were significant differences in ethnicity ($p=0.017$); larger sample of those with AD alone considered themselves "White" while a larger sample of those with PTSD and AD considered themselves "Puerto Rican". Also all participants (100%) with PTSD and AD were veterans while the sample of participants with AD alone consisted of 68% veteran population.

There were significant differences in personality measures based on the NE, where the comorbid group had higher levels of impulsivity and neuroticism than the non-comorbid group. Also the comorbid sample had higher rates of psychiatric symptoms and psychiatric distress than the non-comorbid sample. Interestingly, the comorbid group had different alcohol consumption patterns. They reported lower levels of drinking as measured by drinking days and heavy drinking days but reported higher levels of consequences from their alcohol use based on the ADS.

At a symposium at the Research Society of Alcoholism meeting in San Francisco, CA (June, 2012) some preliminary data was presented evaluating the relationship between stress and drinking. The data come from a laboratory study designed as a companion to this treatment trial. The laboratory study design consists of II phases. *In Phase* I, all subjects participate in a **laboratory session I** to determine their reactivity to stress. Stress reactivity in the laboratory is generated using: a personalized trauma-related stressor, a personalized non-trauma related stressor and a neutral stressor, presented randomly. Outcome measures include self-reported measures of alcohol craving and anxiety. *Subjects are subsequently randomized into the clinical trial within a week of the*

laboratory session. In Phase II, subjects participate in **laboratory session II, a repeat of session I**. This second session occurs after at least 6 weeks of medication treatment and while participants are still receiving prazosin or placebo. The main outcome measures for the laboratory study include measures of alcohol craving and anxiety.

The findings to date indicate that: **A)** Subjective levels of craving and anxiety significantly increase after the trauma and stress session, but not the neutral session; there was a significantly higher level of craving and anxiety reported after the trauma imagery when compared to both stress and neutral imagery. **B)** Changes in peak stress response was significantly correlated with changes in heavy drinking – the bigger the change in stress response the bigger the change in heavy drinking. **C)** Individuals were characterized as high stress responders (HSR) vs. low stress responders (LSR). HSR's had an overall smaller change in their drinking behavior compared to LSR's and this change was mediated by medication treatment. Specifically, a prazosin effect on alcohol drinking was the strongest in the LSR group.

CONCLUSION: To date, our sample size does not permit statistical analysis of the data. We can only report that to date, medication has been well tolerated. During this reporting period there was one serious and unexpected adverse event occurring at our Bedford site. The patient was admitted to the inpatient unit after showing signs of agitation, inability to follow simple directions, and psychotic thought processes. He was not taking medication for 5 days when the symptoms occurred. The event is under review at the Bedford IRB. In the opinion of the local PI the event is not related to study participation.

REFERENCES: None, to date.

APPENDICES: None, to date.