

Characterization of Comorbid PTSD in Treatment-Seeking Alcohol Dependent  
Inpatients:  
Severity and Personality Trait Differences

by

Joanna R. Sells

Thesis submitted to the Faculty of the  
Medical and Clinical Psychology Graduate Program  
Uniformed Services University of the Health Sciences  
In partial fulfillment of the requirements for the degree of  
Master of Science 2016



UNIFORMED SERVICES UNIVERSITY, SCHOOL OF MEDICINE GRADUATE PROGRAMS  
 Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814



April 8, 2016

APPROVAL SHEET

Title of Thesis: **"Characterization of Comorbid PTSD in Treatment-Seeking Alcohol Dependent Inpatients: Severity and Personality Trait Differences"**

Name of Candidate: **Joanna Sells, Master of Science in Medical and Clinical Psychology,**

Date: 04/07/16

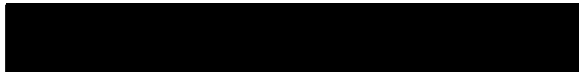
THESIS AND ABSTRACT APPROVED:



Andrew J. Waters  
 DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY  
 Committee Chairperson

DATE:

4/8/16



Marjan Holloway  
 DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY  
 Committee Member

4-8-2016



David S. Riggs  
 DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY  
 Committee Member

4-8-2016

## **ACKNOWLEDGMENTS**

Thank you to my parents, David and Diana Sells, for always supporting me in every area of life. Thank you to Dr. Vijay Ramchandani for helping me believe I could be a researcher. Thank you to Dr. Andrew Waters for teaching me how to be a successful scientist. Thank you to Dr. Patrick DeLeon for opening every door.

## COPYRIGHT STATEMENT

The author hereby certifies that the use of any copyrighted material in the thesis manuscript entitled: Characterization of Comorbid PTSD in Treatment-Seeking Alcohol Dependent Inpatients: Severity and Personality Trait Differences is appropriately acknowledged and, beyond brief excerpts, is with the permission of the copyright owner.



---

Joanna Sells

May 20, 2016

## ABSTRACT

### Characterization of Comorbid PTSD in Treatment-Seeking Alcohol Dependent Inpatients: Severity and Personality Trait Differences

Joanna Sells, BA, 2016

Thesis directed by: Andrew Waters, Associate Professor, Medical & Clinical Psychology

**Introduction:** Posttraumatic stress disorder (PTSD) and alcohol dependence (AD) are often comorbid. We examined AD treatment-seeking inpatients with and without PTSD. We hypothesized AD/ PTSD+ would have higher levels of: (1) AD severity; (2) anxious and depressive symptoms; (3) neuroticism; and (4) aggression.

**Methods:** Inpatients were monitored over 30 days at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health (NIH). Inpatients were evaluated for alcohol use and AD, withdrawal, anxiety and depression symptoms, personality, and aggression.

**Results:** Those with PTSD consumed the same amount of alcohol, but had: (1) greater AD severity; (2) more anxiety and mood symptoms during treatment; (3) greater likelihood of diagnosis of anxiety or mood disorder; and (4) higher levels of neuroticism and aggression.

**Conclusions:** AD patients with comorbid PTSD present a more severe phenotype across a range of measures including AD severity, higher self-reported depressive and anxious symptoms, neuroticism, and aggression. Individualized treatment targeting AD and PTSD should be further explored.

# TABLE OF CONTENTS

LIST OF TABLES .....	vi
LIST OF FIGURES .....	vii
CHAPTER 1: Introduction .....	8
Prevalence of Alcohol Use.....	8
Alcohol and the Central Nervous System .....	8
Alcohol Dependence .....	9
Post-Traumatic Stress Disorder .....	10
Alcohol Dependence and Post-Traumatic Stress Disorder .....	10
Alcohol and Personality .....	12
PTSD and Personality .....	13
PTSD and Aggression.....	13
Physiological Measures of PTSD and Alcohol Dependence .....	14
Treatment for Alcohol Dependence and PTSD .....	15
Rationale for the Current Study .....	16
Specific Aims and Hypotheses .....	17
CHAPTER 2: Method.....	18
Participants.....	18
Procedures .....	18
Interview Assessments.....	19
Questionnaire Assessments.....	20
Physiological Assessments .....	21
Statistical Analysis.....	21
CHAPTER 3: Results .....	22
Demographics .....	22
Alcohol Consumption and Dependence.....	23
Functioning and Comorbidity .....	23
Anxiety and Depression Symptoms.....	23
Physiological Changes Over Time.....	23
Personality.....	24
Aggression .....	24
CHAPTER 4: Discussion.....	24
Strengths .....	29
Limitations .....	29
Future Directions .....	30
Summary.....	31
REFERENCES .....	50

## LIST OF TABLES

Table 1a Review of Laboratory Studies.....	32
Table 1b Review of Epidemiological Studies.....	34
Table 1c Review Studies.....	35
Table 2: Baseline Sample Characteristics.....	36
Table 3: Comorbidity Diagnoses .....	37
Table 4: Anxiety (Brief Scale of Anxiety; BSA) and Depression Symptoms (Montgomery-Asberg Depression Rating Scale; MADRS) .....	38
Table 5: NEO Personality and Buss-Perry Aggression Questionnaire (BPAQ).....	39
Table 6: Addiction Severity Index (ASI).....	40
Table 7: Smoking .....	41

## LIST OF FIGURES

Figure 1.	Study Overview .....	19
Figure 2.	Alcohol Use and Dependence .....	42
Figure 3.	NEO Personality Scores .....	43
Figure 4.	BPAQ Aggression Questionnaire Scores .....	44
Figure 5.	Pulse Rate Week 0.....	45
Figure 6.	Diastolic Blood Pressure Week 0 .....	46
Figure 7.	Systolic Blood Pressure Week 0.....	47
Figure 8.	Depression Weeks 1-4.....	48
Figure 9.	Anxiety Weeks 1-4.....	49

## **CHAPTER 1: Introduction**

### **PREVALENCE AND EFFECTS OF ALCOHOL USE**

Alcohol consumption causes approximately 9.6% of disability-adjusted total life years lost and accounts for 44.4% of years of life lost due to mental and substance use disorders. It is the fifth leading cause of death, according to the 2010 Global Burden of Disease Study. The prevalence of alcohol dependence increased 37.6% between 1990 and 2010, fueled in part by ageing and growing populations (81). Heavy drinking can lead to the development of alcohol dependence (AD) and a host of difficulties associated with the disease, including cancer, liver cirrhosis, depressive episodes, insomnia, and suicide (50; 61).

### **ALCOHOL AND THE CENTRAL NERVOUS SYSTEM**

Alcohol is formed in the fermentation of ethanol sugars by yeast to a concentration of 15%, while distillation greatly increases this concentration (42). Distilled spirits have approximately 30-60% ethanol concentration, sherry/port and other fortified wines have 14-20%, wines have 11-14%, and beer has 4-10%. Ethanol is water-soluble and small, leading to fast action in the gastrointestinal tract within 30 minutes of ingestion (42). At a blood alcohol concentration (BAC) of 50-100mg/dL, alcohol causes sedation, the feeling of being “high,” and slower reaction times. At 100-200mg/dL, alcohol impairs motor function, slurs speech, and leads to ataxia. At 200-300mg/dL, emesis and stupor are experienced. At 300-400mg/dL the alcohol user will experience a coma, and use at more than 400mg/dL, the result of alcohol use is respiratory depression and death (42).

Ethanol (or alcohol) concentration in the brain rises quickly following ingestion as it readily crosses biologic membranes, with tissue levels containing nearly equivalent concentration of ethanol in the blood (42). Alcohol exerts its effects on the central nervous system through dopamine, norepinephrine, endogenous opioids, GABA, glutamate, and serotonin (47). Alcohol increases dopamine function in the mesolimbic system reward pathway, specifically affecting the nucleus accumbens. This accounts for the rewarding effects of alcohol use. Alcohol releases norepinephrine, which accounts for the uplifting and energizing clinical effects of alcohol use. Endogenous opioid stimulation by alcohol leads to the stress-reducing, pleasurable analgesic effects from use. Alcohol stimulates GABA receptors, provoking inhibitory effects that lead to amnesia, sedation, and anxiolytic and ataxic responses of the brain. The depressant effects of alcohol on the brain are primarily due to its blocking of glutamate or NMDA receptors, furthering amnesic effects. Finally, serotonin stimulation from alcohol use is responsible for nausea responses and may help explain the variety of alcohol user types- from aggressive to anxious (47).

### **ALCOHOL DEPENDENCE**

Chronic alcohol use may become alcohol dependence. In order to be classified as alcohol dependent, those with chronic use must exhibit three or more of the following within 12 months: tolerance, withdrawal, use in larger quantities or over longer periods of time than intended, persistent desire or unsuccessful efforts to cut down use, large amounts of time spent obtaining, using, recovering from use, reduction of important activities (social, occupational, recreational) (2). In terms of biological effects, chronic alcohol use impacts the liver as well as the nervous, gastrointestinal, cardiovascular, and

immune systems, and can lead to death. Chronic alcohol consumption deaths are typically a result of liver disease, cancer, accidents (car, falls, or otherwise), and suicide (42).

### **POST-TRAUMATIC STRESS DISORDER**

Posttraumatic stress disorder (PTSD) is a severe debilitating disorder that develops after a person is exposed to a traumatic event such as violent combat. Symptoms include persistent re-experiencing of the event through uncontrollable flashbacks, intrusive thoughts, distressing dreams or response to related cues, and physiological reactions to associated internal or external cues. Further, persistent avoidance of stimuli associated with the traumatic event and increased arousal for at least one month (including sleep problems, anger, concentration difficulties, hypervigilance, and high startle response) are part of the diagnostic criteria for PTSD (1). The intensity and breadth of symptoms of PTSD is disruptive to daily functioning. Moreover, those with PTSD have higher resting blood pressure and heart rates than their trauma exposed peers without PTSD or their no trauma peers, leading to increased risk of cardiovascular conditions (13). Increased cardiac activity in those with PTSD has been demonstrated in studies of combat veterans, with mostly male participants dating back to 1980 (13), and is indicated by increased rates of nonfatal myocardial infarction (8).

### **ALCOHOL DEPENDENCE AND POST-TRAUMATIC STRESS DISORDER**

Table 1 reviews key findings in the area of AD and PTSD. PTSD and alcohol dependence lifetime prevalence is 1.59%, compared with lifetime prevalence of alcohol dependence at 13.66% and PTSD at 4.83% (7). Despite the high prevalence of PTSD and

alcohol dependence comorbidity, little is known about this group. Clinical presentation of symptoms, the course of the disease, factors that put an individual at risk of comorbid symptomology, and treatment-seeking behavior have not been well studied (7). This comorbid group has greater complexity from an interplay between two disorders that are difficult to treat. A strong relationship between PTSD and alcohol misuse and dependence has been demonstrated by Breslau and colleagues (9), while an epidemiological review of the literature found inconsistent associations that suggest the relationship is more complicated (46). Complicating factors for the development of both disorders include type of precipitating trauma (46) and family history of alcohol misuse and dependence (7), and early life emotional or sexual trauma (31; 33). Age at trauma onset is also relevant when considering the relationship between PTSD and alcohol misuse or dependence in young adults aged 21-30 (10). Once both diseases are established, affected individuals have a higher severity of dysfunction across many indicators when compared to those with PTSD or alcohol dependence alone (7). Further, those with PTSD and a substance use disorder (including alcohol) have greater severity of PTSD (33). Due to the limitations of current treatment and with no cure on the horizon, those with PTSD are prone to self-medicate with alcohol (37). As a result, they are at a particularly high risk of developing alcohol dependence. Findings from the National Co-Morbidity Study show that individuals with PTSD are two to four times more likely to have a substance abuse disorder, including alcohol dependence, than those without PTSD (36). Studies show a positive correlation between drinking and frequency of PTSD symptoms (35; 80). Individuals with PTSD subtypes where hyper-arousal or

avoidance is the key feature are more prone to using alcohol to relieve symptoms (33; 70).

McCarthy and Petrakis's (43) review of the epidemiology and management of alcohol dependence in those with PTSD found that comorbid individuals had more severe PTSD symptoms and were more prone to alcohol use relapse. Jacobsen et al.'s (34) review also supports the strong association between AD and PTSD, as well as with depression and anxiety. Alcohol dependence and PTSD interact and produce worse outcomes than either disorder alone (6), further complicating treatment. Treating these disorders separately does not address possible common mechanisms and pathways (40; 51) leading to poorer prognosis (6). Further, McCarthy and Petrakis (43) found that psychosocial and pharmacological interventions that target the symptoms of both PTSD and AD for comorbid individuals were most effective.

#### **ALCOHOL AND PERSONALITY**

Recent research has focused on personality factors in alcohol use. Neuroticism has been defined as "the tendency to experience frequent and intense negative emotions in response to various sources of stress," with emotions including anger, fear, anxiety, depressed mood, and irritability (4). Neuroticism also includes the perception of the world as dangerous (4). Neuroticism has been associated with substance use disorders (78) and with higher relapse rates (27). For example, Valero et al. (78) evaluated personality traits and drug/alcohol dependence using a decision tree learning model. They found that neuroticism (and impulsivity) were the key traits associated with

drug/alcohol dependence. Thus, there is some evidence that neuroticism is associated with drug/alcohol dependence.

### **PTSD AND PERSONALITY**

Research has suggested that PTSD and neuroticism are associated for both men and women, even when controlling for type of trauma (19). Two theories exist about the direction of causality of neuroticism and PTSD. One is that PTSD is caused in part by pre-existing elevated neuroticism, and the other is that PTSD, possibly through common arousal symptoms, leads to increased neuroticism (23). The data are currently mixed. One study reported that individuals high in neuroticism do not have greater PTSD, depression, and somatic symptoms following exposure to adverse events once pre-trauma symptoms were controlled (24). However, in this sample of soldiers deployed to Iraq, only 4% of the sample developed PTSD five months after exposure to trauma. A recent prospective study found that baseline neuroticism significantly increased the relative risk of PTSD response to trauma exposure (11). In sum, while the causal relationship between PTSD and neuroticism is not clear, the literature suggests that individuals with PTSD tend to report higher levels of neuroticism than those without PTSD.

### **PTSD AND AGGRESSION**

In a 39 study meta-analysis of the association between anger/hostility and PTSD, Orth and Wieland (54) found a strong association that was not inflated due to overlap with anger as one diagnostic criterion for PTSD. Taft et al. found that among Vietnam combat veterans, trait anger mediated the relationship between PTSD symptoms and physical assault/psychological aggression perpetration in interpartner violence (74).

Several theories address the relationship between aggression and PTSD. Survival mode

theory hypothesizes that those with PTSD perceive threat more readily which activates a biological survival mode that includes fight or flight reactions. Further, survival mode supersedes other cognitive processing and employs biases towards threat confirmation and increased vigilance (15; 52). Another theory that addresses the link between anger and PTSD is the fear avoidance theory, which hypothesizes that those with PTSD avoid feelings of fear related to their trauma intrusions, and instead focus on anger because they perceive it as a more acceptable emotion (25; 28; 59). Moderator analyses from the Orth and Wieland meta-analysis found that initially following the index trauma occurrence, the association between anger/hostility and PTSD is small, but in the following months, it increases strongly to medium-large (54). Among type of trauma analyses, military war experience had the biggest association, while criminal victimization had the smallest effect size (54). We were not able to explore these two moderators in the current study due to the fact that these variables were not assessed.

#### **CARDIOVASCULAR FUNCTION IN PTSD AND ALCOHOL DEPENDENCE**

Heavy alcohol consumption plays a role, alongside factors such as age and sex, in many heart-related conditions such as rapid and chaotic heartbeats and hypertension (85). Reduced risk for coronary heart disease and subsequent decreased mortality have been associated with light to moderate alcohol intake in experimental (49) as well as review articles (20). Epidemiologic studies report higher blood pressure among those with a usual intake of three or more drinks per day (84). When undergoing alcohol withdrawal, individuals have elevated blood pressure (57; 58) and heart rate (58), as well as less heart rate variability (58). In a study of 15 normotensive male patients with alcoholism in drinking and abstinence states, average daily blood pressure did not differ (41).

However, when consuming alcohol, the participants had a fall in systolic blood pressure before noon and after six pm during abstinence (41). A more recent study of participants with alcoholism undergoing 12 weeks of treatment found that abstinence significantly decreased blood pressure (5). Further, the authors found that systolic and diastolic blood pressure decreased significantly from baseline to week 12, but only when participants were in total abstinence (5). When the participants were actively drinking, there was a negligible change in blood pressure (5). Therefore, there are mixed data on the effects of withdrawal from alcohol on blood pressure.

When compared to controls without PTSD, basal heart rate (13; 79) and blood pressure (13) is higher in individuals with PTSD. Those with PTSD also have reduced variability in heart rate in response to stressors (29). Further, those with chronic PTSD have the greatest increase in basal heart rate (13). Data are mixed as to whether this increased resting cardiovascular activity is due to anticipatory anxiety or emotional priming often associated with cue-reactivity paradigms, as neutral demands also elicited an increased response (13). There is evidence that suggests dysregulation of the autonomic nervous system may preface the development of PTSD, rather than be caused by it (12; 62). Little is known about the role of having comorbid AD and PTSD in heart function. However, given that those in a state of alcohol withdrawal have increased heart rate (58) and blood pressure (57; 58), PTSD symptoms may be exacerbated for those in withdrawal.

### **TREATMENT FOR ALCOHOL DEPENDENCE AND PTSD**

Treating individuals with alcohol dependence is challenging because AD is heterogeneous (32). Consequently, treatment for alcohol dependence should be

individually tailored (32). Further, alcohol treatment and corresponding research often focuses on the singular disorder (6), but, clinically, alcohol dependence rarely occurs in isolation. Post-traumatic stress disorder (PTSD) and other anxiety as well as mood disorders are often comorbid with AD. According to Wave 2 of the National Epidemiologic Survey on Alcohol and Related conditions, the rate of comorbid alcohol abuse/dependence among those with PTSD was 41.8% (56). Certain clinical treatment guidelines for individuals with AD and PTSD advise clinicians to treat each disorder as a separate specialty, even when treated concurrently (75; 76), while others suggest integrating treatment for AD and PTSD (82). According to a systematic review and meta-analysis of RCTs by Roberts et al. (60), psychological interventions that target trauma while concurrently treating SUD have small treatment effects of reducing PTSD symptom severity. However, there may be tolerability concerns for this level of treatment as evidenced by limited treatment completion rates. There was no evidence to support non-trauma focused group interventions and individual non-trauma focused interventions have insufficient data for evaluation (60).

#### **RATIONALE FOR THE CURRENT STUDY**

Although much research has examined the association between PTSD and AD, little research has examined whether the association between PTSD and alcohol use can be observed in a population of individuals with AD presenting for treatment at an inpatient facility. Although these individuals tend to have severe alcohol use behaviors, there are individual differences in use and dependence, and it would be clinically instructive to learn about the association between PTSD and alcohol use, and between PTSD and severity of dependence in this population. This would also help to determine

those characteristics that distinguish alcohol dependent patients with PTSD from alcohol dependent patients without PTSD. The ultimate goal of this study is to use the data to further precision medicine, which improves outcomes by tailoring treatments to individuals.

Our study examined 411 individuals with AD over 30 days in a closely monitored inpatient setting. The specific aims were as follows:

### **SPECIFIC AIMS AND HYPOTHESES**

Specific Aim 1: To examine differences between treatment-seeking alcohol dependent inpatients with and without comorbid PTSD.

Hypothesis 1.1: Inpatients with alcohol dependence and PTSD will have greater alcohol dependence severity than those without PTSD.

Hypothesis 1.2: Inpatients with alcohol dependence and PTSD will have greater anxious and depressive symptoms than those without PTSD.

Specific Aim 2: To explore whether inpatients with alcohol dependence and PTSD scored higher on personality measures of neuroticism and aggression than those without PTSD.

Hypothesis 2.1: Inpatients with alcohol dependence and PTSD will have greater neuroticism than those without PTSD than those without PTSD.

Hypothesis 2.2: Inpatients with alcohol dependence and PTSD will have greater aggression than those without PTSD than those without PTSD.

Specific Aim 3: To explore whether inpatients with alcohol dependence and PTSD had worse cardiovascular functioning as measured by increased blood pressure and heart rate than those without PTSD.

Hypothesis 3.1: Inpatients with alcohol dependence and PTSD will have greater blood pressure and heart rate than those without PTSD.

## **CHAPTER 2: Method**

### **PARTICIPANTS**

Participants included 411 (111 females and 300 males) civilian treatment-seeking participants who underwent detoxification and treatment at the NIAAA inpatient treatment unit at the NIH Clinical Center in Bethesda, MD, from 2005-2009 (see Table 2). Participants had a mean age of  $41.7 \pm 9.9$  years. All 411 participants met criteria for AD, and 79 (19.2%) met criteria for PTSD. Participants were recruited for a study on AD for those seeking inpatient treatment mainly via local media. Participants underwent initial screening over the telephone and were further assessed for eligibility by experienced clinicians on a supervised NIAAA inpatient unit. Participants met criteria for alcohol dependence according to criteria set forth in the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, Text-Revised (DSM-IV-TR), and were not selected for PTSD. Participants did not exhibit active psychotic symptoms or cognitive impairment. Participants were in otherwise good physical health.

### **PROCEDURES**

All study measures were taken after participants had completed a standard course of medically supervised alcohol withdrawal lasting approximately one week, with the exception of the CIWA-Ar, CPRS, and physiological assessments, which were taken weekly starting upon initial admission. Participants resided in a supervised inpatient unit and underwent standardized behavioral treatment for alcohol dependence for approximately four weeks. During the initial days of detoxification, participants were

administered standard doses of benzodiazepines (Diazepam, Lorazepam, or Oxazepam) as clinically indicated for alcohol withdrawal. The study was approved by the NIH Institutional Review Board.

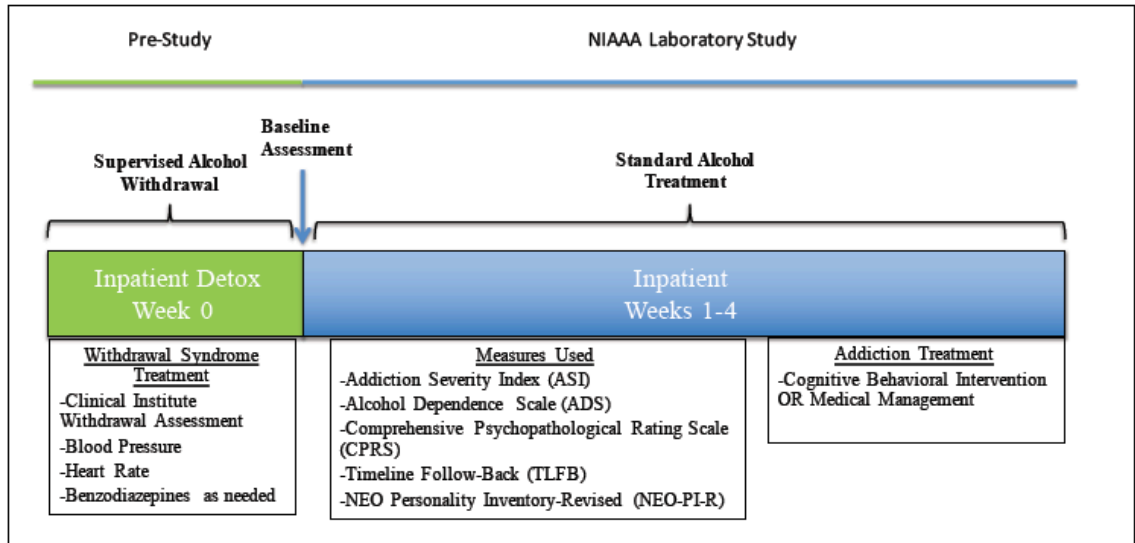


Figure 1. Study Overview

## INTERVIEW ASSESSMENTS

As data collection for this study preceded the introduction of DSM-5 (APA, 2014), The Structured Clinical Interview for DSM-IV (SCID) (26) was used for diagnostic assessment of alcohol dependence and other psychiatric conditions. The SCID has been demonstrated as a reliable method of diagnosing mental disorders.

The Alcohol Dependence Scale (ADS) (66) was used to assess alcohol dependence severity. The ADS is a 25 question semi-structured interview assessing severity of drinking that has been validated as more accurate than a measure of drinking restraint (18; 65). The 25 items assess alcohol withdrawal symptoms, impaired control over drinking, awareness of compulsion to drink, increased tolerance to alcohol, and

saliency of drink-seeking behavior over the past 12 months (minimum possible score =0, maximum possible score = 47).

The Addiction Severity Index (ASI) (48) is a 200-item interview used to identify problems in multiple dimensions of functioning, including alcohol, drug, psychiatric, legal, and family, and has been validated (39).

The Timeline Follow-Back (TLFB) (68) uses personal historical events, to identify alcohol consumption patterns. This measure has been well validated (77). In this study we used it to characterize drinking behavior for the 90 days prior to admission.

#### **QUESTIONNAIRE ASSESSMENTS**

The NEO Personality Inventory (NEO PI-R) (45) is a 240-item self-report questionnaire used to assess facets of personality. It encompasses the five major factors of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness. It also measures the six facets that define each factor. For example, the dimension of neuroticism has six facets: anxiety, hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress. Combining all five factors and thirty facets provides a comprehensive and detailed assessment of normal adult personality. This measure has been validated (44).

The Buss-Perry Aggression Questionnaire (BPAQ) (14) is a 29-item self-report used to assess factors of aggression. It has been validated (22).

The Clinical Institute Withdrawal Assessment- Alcohol revised (CIWA-Ar) (71) is a 10-item subset of the 30-item Clinical Institute Withdrawal Assessment-Alcohol scale, a well-studied and commonly used scale for assessing alcohol withdrawal

symptoms and severity. This scale has been validated (71). The CIWA was assessed multiple times per day until symptoms remitted.

The Comprehensive Psychopathological Rating Scale (3), the CPRS (73), an 18-item scale, was used to assess symptoms of anxiety and depression. The CPRS has been validated (38; 55). Within the CPRS, the Brief Scale of Anxiety (BSA) and the Montgomery-Asberg Depression Rating Scale (MADRS) were used to measure anxiety and mood symptoms respectively. The CPRS was administered on days 2, 9, 16, 23, and 30. Due to early discharge, many participants did not complete the day 30 assessment.

#### **PHYSIOLOGICAL ASSESSMENTS**

Blood pressure and heart rate were monitored using Philips SureSigns VS3 vital signs monitors by trained nurses at least once daily during the first 9 days of inpatient treatment. Data presented are the first assessment of each day.

#### **STATISTICAL ANALYSIS**

Summary statistics are presented as Means  $\pm$ SD. Chi-square analyses (categorical variables) and t-tests (continuous variables) were conducted to examine possible differences in background characteristics of the PTSD and No PTSD groups. Consistent with previous data (36), PTSD was associated with sex (see Table 2), and therefore sex was included as a covariate in all analyses. PTSD was marginally associated with Age (see Table 2), and Age was also included as a covariate in all analyses.

To examine differences between the groups on continuous and dichotomous outcome variables, we used ANCOVA and multiple logistic regression respectively. To examine the effect of Group on withdrawal symptoms and physiological measures that were assessed repeatedly over time, we used linear mixed models (LMMs). LMM takes

into account the dependence between participant observations and allows for different numbers of observations across participants. We used a random (subject-specific) intercept and an autoregressive model of order 1 for the residuals within subjects. Time was entered as a continuous variable in all models, and slopes were allowed to vary. For all analyses, SPSS (version 22) was used, alpha was set to 0.05, and all tests were 2-tailed. Two tailed tests are generally recommended by statisticians in that they permit rejection of the null hypothesis when differences occur in either direction (30). As Howell notes, not infrequently study results are opposite to the direction hypothesized by researchers (30). In addition, for some hypotheses in the current study (e.g., cardiovascular variables) the previous data do not clearly indicate the direction of an effect.

## **CHAPTER 3: Results**

### **DEMOGRAPHICS**

Of the 411 recruited participants (mean age:  $41.7 \pm 9.9$  years; 111 females), 79 met diagnostic criteria for PTSD (35 females, 44 males). As shown in Table 2, the PTSD group was marginally younger than the No PTSD group, and the PTSD group contained a significantly higher proportion of females ( $\chi^2(1) = 14.8, p < .001, OR = 2.68$ ). There was no difference in ethnicity, smoking behavior, or benzodiazepine administration during withdrawal between the PTSD and No PTSD groups (Table 2; see also Table 7 for smoking variables). There was no between-group difference in peak CIWA scores,  $F(1, 279) = 0.07, p = 0.80$ , or CIWA scores on days 1 and 2 ( $p > 0.57$ ) (not shown in table).

## **ALCOHOL CONSUMPTION AND DEPENDENCE**

Participants reported drinking approximately 14 drinks per drinking day in the 90 days preceding admission. The two groups did not differ on number of drinks, drinking days, or drinks per drinking day. However, participants with PTSD had a greater severity of alcohol dependence, with a moderate effect size (Table 2 and Figure 2).

## **FUNCTIONING AND COMORBIDITY**

The PTSD group had worse functioning as measured by ASI psychiatric status (Table 6). There were no significant differences between the groups on the other ASI domains. The PTSD group had a greater odds for having a diagnosis of anxiety disorders other than PTSD (Table 3), and with mood disorder (Table 3). The two groups did not differ on diagnosis of substance abuse other than alcohol (Table 3).

## **ANXIETY AND DEPRESSION SYMPTOMS**

As expected, there was a significant effect of PTSD group on BSA (Anxiety),  $F(1, 587) = 26.82, p < .001$ , and MADRS (Depression),  $F(1, 587) = 50.52, p < .001$  (Table 4 and Figures 8 and 9). For both Anxiety and Depression, the main effect of PTSD group was robust at all time-points except day 30 (Table 4), when the sample sizes were much smaller. The PTSD group by Day interaction did not approach significance for either measure ( $p > .43$ ). There was a robust effect of Day for both measures ( $p < .001$ ), with Anxiety and Depression scores becoming lower over time.

## **PHYSIOLOGICAL CHANGES OVER TIME**

There was no effect of PTSD group on Diastolic blood pressure,  $F(1, 2805)=1.68, p=.20$  (Figure 6), Systolic blood pressure,  $F(1, 2806)=2.33, p=.13$  (Figure 7), or Heart

Rate,  $F(1, 2802)=0.50, p=.48$  (Figure 5). There was a robust effect of day for all three measures ( $p < .001$ ), indicating that blood pressure and heart rate decreased significantly over the nine days of assessment. The PTSD group by Day interaction did not approach significance for any measure ( $p > .20$ ).

### **PERSONALITY**

The PTSD group had significantly higher scores on the NEO domain of neuroticism, but not on other NEO personality domains (Table 5 and Figure 3). Within the six facets of neuroticism, participants with PTSD had higher scores of anxiety, angry hostility, depression, self-consciousness, and vulnerability to stress. There was no significant difference on impulsiveness.

### **AGGRESSION**

The PTSD group had higher BPAQ scores on verbal aggression, anger, hostility, and aggression (Table 5 and Figure 4). There was no difference on physical aggression.

## **CHAPTER 4: Discussion**

This study compared drinkers with AD and PTSD with those with AD and no PTSD on drinking characteristics, alcohol withdrawal, anxiety and depression symptoms, psychiatric diagnoses, personality, and cardiac and overall functioning. The main findings were as follows. First, alcohol dependent patients with PTSD did not report heavier alcohol consumption than alcohol dependent patients without PTSD in the ninety days before the study, nor did they report higher scores on the alcohol withdrawal scale. Interestingly, however, they did report higher level of dependence, with a moderate effect

size. Second, alcohol dependent patients with PTSD reported consistently higher levels of anxiety and depressive symptoms across the first 30 days of treatment. As expected, they were also more likely to be diagnosed with another anxiety disorder and mood disorder, and to report worse functioning on the ASI psychiatric domain score. Last, alcohol dependent patients with PTSD reported higher levels of neuroticism and aggression than alcohol dependent patients without PTSD.

The main finding was that alcohol dependent patients with PTSD did not report heavier alcohol consumption than alcohol dependent patients without PTSD in the ninety days before the study, but that they did report higher level of dependence on the ADS, with a moderate effect size. The ADS is a unidimensional assessment of severity of dependence incorporating alcohol withdrawal symptoms, impaired control over drinking, awareness of compulsion to drink, increased tolerance to alcohol, and salience of drink-seeking behavior over the past 12 months (65). It is noteworthy that although both groups consumed the same amount of alcohol, those with PTSD had more difficult functioning with regards to their higher level of dependence. The drinking patterns and measures were high overall with both groups reporting averages between 13 and 14 drinks per drinking day. The absence of an association between PTSD and drinking in our data may be due to a ceiling effect. Our individuals without PTSD may be drinking at such a high rate that further increases are unlikely as a result of PTSD.

We also found no differences in withdrawal severity between alcohol dependent patients with PTSD and alcohol dependent patients without PTSD, and there were no significant group differences in heart rate or blood pressure. Notably, blood pressure decreased in both AD and AD and PTSD groups during withdrawal. Findings on the

effects of withdrawal on blood pressure are mixed. Little research has examined the association between PTSD and alcohol withdrawal symptoms. However, individuals with PTSD did report higher levels of anxiety and depressive symptoms over the 30-day assessment period. This suggests that the psychological distress of those with PTSD was greater, despite this group not experiencing more physiological signs of distress when compared to the group without PTSD.

The observation that individuals with PTSD experienced significant anxiety and depressive symptoms during treatment underscores the importance of treating mood and anxiety related disorders in this population. If these symptoms are not treated, they may be exacerbated in the future, particularly when the patient experiences their PTSD triggers. The re-experiencing of PTSD triggers and related mood and anxiety symptoms may lead an individual to return to using substances in an effort to self-medicate. Anxiety and depression symptoms declined over time in both groups. A study examining PTSD symptomatology during acute and protracted alcohol abstinence in patients with a history of victimization likewise found that anxiety and depression symptoms declined over a 28-day period (17).

As expected we found that alcohol dependent patients with PTSD were more likely to have mood and anxiety disorders. Consistent with Driessen et al (21), we also found that PTSD was associated with higher ASI scores in psychiatric dysfunction. Previous studies have found that alcohol dependent patients with PTSD are more likely to have comorbidity with other psychiatric disorders. Kessler et al (36) found that those with PTSD were more likely to have mood disorders such as major depressive episodes, dysthymia, and mania. They also found those with PTSD had more incidences of general

anxiety disorder, panic disorder, and certain types of phobias. Breslau et al. found that while those with PTSD have high rates of major depression and alcohol abuse/dependence, there is a stronger association between PTSD and anxiety or mood disorders than with alcohol abuse/dependence (9). While comorbidity is often found with substance use disorders, Chen et al (16) found that alcohol dependence had a higher occurrence with PTSD than cocaine and heroin dependence, further supporting a possible common mechanism underlying AD and PTSD.

We found that comorbid individuals with PTSD had higher levels of neuroticism, especially in sub-traits of anxiety, angry hostility, depression, self-consciousness, and vulnerability to stress. The International Classification of Disease, Injuries, and Causes of Death classifies posttraumatic stress disorder in the neurotic, stress-related and somatoform disorder section (83). A wealth of other data suggests that PTSD and neuroticism are closely related. For example, Cox et al (19) found that after controlling for a lifetime history of mood and anxiety disorders, which all have neuroticism as a common mechanism, PTSD and neuroticism were still associated. Further, PTSD arousal symptoms, which include neuroticism-like symptoms such as trouble sleeping and irritability, rather than re-experiencing or avoidance and numbing symptoms, have been particularly strongly linked to neuroticism (23). Barlow et al (4) have suggested that neuroticism should be a target of treatment for anxiety and mood disorders, which, consistent with our study, may include PTSD.

As noted in the introduction, the nature of the relationship between neuroticism and PTSD is not currently clear. A prospective study of pregnant mothers found that neuroticism did not rise following trauma (23). Engelhard et al. suggested that PTSD and

neuroticism have significant overlap in symptoms but are not causally related. In a prospective study of infantry troops, Engelhard et al. found that those with higher pre-trauma levels of neuroticism did not have an increase of PTSD symptoms post-trauma event, lending further support that neuroticism does not cause PTSD (24).

Studies have also found that those with substance use disorders such as AD score higher on the NEO-PI R domain of neuroticism, and that neuroticism is related to relapse (27). However, the nature of the relationship between neuroticism and AD is also not currently clear. Some argue that neuroticism is a risk factor for AD (63). However, other data argue against the idea that neuroticism can lead to AD (67). Sutherland (72) argued that AD may increase neuroticism. If further research shows that neuroticism is indeed a causal risk factor for AD, then it can be a target for intervention. A review by Soskin et al (69) outlines serotonergic drug agents that have been effective in addressing temperament issues consistent with neuroticism.

In our sample, alcohol dependent patients with PTSD had higher levels of aggression than alcohol dependent patients without PTSD. Alcohol dependent patients with PTSD had higher scores on verbal aggression, anger, hostility, and general aggression, but not on physical aggression. This could be due to behavior associated with PTSD such as irritability and outbursts of anger as well as re-experiencing trauma. These behaviors are also associated with neuroticism and should be included in treatment planning tailored to individuals with AD and PTSD. Orth and Wieland (54) completed a meta-analysis of the association between anger/hostility and PTSD symptom severity and found a stronger correlation between PTSD and anger directed inward (inhibition, nondisclosure of anger, and rumination) than between PTSD and anger directed outward

(expressive style of anger) (64). This is consistent with our finding that those with AD and PTSD had greater aggression with the exception of physical, which accounts for most of anger outward behavior. Anger directed inward, which may be associated with neuroticism, can be difficult to assess initially, but it should also be included in treatment planning for those with AD and PTSD. It is worth noting that several studies have explored anger as a function of diagnostic criteria for PTSD and found that PTSD tends to lead to anger, not the other way around (52; 53).

### **STRENGTHS**

A major strength of our study was that it examined the association between PTSD and alcohol use/dependence in the context of a highly controlled unique environment - a research-oriented hospital inpatient unit located on a large suburban campus. The patients in this study are difficult to assess in outpatients contexts, where services may not be regularly provided and regular attendance is difficult. Our findings provide new data on clinical populations of alcohol dependent patients, and suggest that individuals with PTSD may represent a particularly problematic subgroup of AD.

### **LIMITATIONS**

The limitations of the study largely pertain to the limitations of the data used for secondary analysis, which limited the scope of our hypotheses. For examples, because this study was not focused on PTSD, we were limited in our knowledge of the origin of their PTSD and the subtypes of symptoms of the patients. We could have benefitted from a higher proportion of individuals with PTSD. The study could also have benefitted from additional assessment of trauma including severity and previous treatment. Additionally, most of our inpatients reside in the Northeastern United States, and many of them are

from the greater Washington D.C. area. The generalizability of the findings to the broader population is therefore not clear.

The study also had methodological limitations. Due to the study design, we were unable to determine the causal relationships between PTSD and alcohol dependence. In addition, we do not have follow-up data on this sample after discharge from our program. There were also limitations with assessment. For example, only one blood pressure measurement was available each day, which may have affected variability over time (41) and between groups. CIWA measurements were not standardized by time of day, limiting data interpretation. Finally, the presence of substantial missing data on a number of assessments (e.g., the BPAQ) reduced power for some analyses, and complicates comparisons of findings across measures.

#### **FUTURE DIRECTIONS**

Further studies could examine a similar population using a prospective design to examine the causal relationships between PTSD and alcohol use/dependence. Childhood and/or adult trauma or maltreatment could be explored as common risk factors for both disorders (31). Additionally, having non-alcohol dependent groups with and without PTSD would help clarify the relationship between AD and PTSD.

Stewart et al (70) found that alcohol dependence symptoms are strongly associated with PTSD arousal symptoms. Further research should investigate how symptoms of PTSD, including avoiding and arousal symptoms, are associated with AD, with particular attention to potential common mechanisms including neuroticism. Examination of genes and biomarkers such as carbohydrate-deficient transferrin and gamma-glutamyl transpeptidase (5) may also help explain variability within patients with

AD and between those with AD and PTSD. A greater understanding of sources of variation, environmental and non-environmental, in the etiology of both AD and comorbidity with PTSD would provide a greater understanding of the mechanisms risk and potential treatment targets and outcomes. Additionally, exploration of special populations, such as veterans and active duty military members could provide data for a greater understanding of the role of trauma type, support, resources, and standardized treatment protocols among other variables.

#### **SUMMARY**

This study examined differences between alcohol dependent individuals with and without PTSD in a rarely studied in-patient treatment-seeking population. The data suggests that despite the same rate of drinking, those with AD and PTSD have more severe dependence, psychiatric functioning, mood and anxiety symptoms, aggression, and neuroticism. A better understanding of these differences can contribute to clinical treatment for individuals with AD and PTSD. Neuroticism, as a possible common mechanism for both disorders, may be a promising treatment target.

Table 1a Review of Laboratory Studies

Author	Population	Variables/Analysis	Main Findings	Notes
Valero et al., 2014	N = 336 AUD/SUD seeking outpatient treatment n = 486 control	IV: AUD/SUD y/n DV: Personality trait profiles *hierarchical model	-Neuroticism associated with AUD/SUD -Neuroticism high level then impulsivity also linked to AUD/SUD	
Huang et al., 2012	N = 196 alcohol dependent inpatients (62 females); n=43 PTSD (22 females)	IV: Type of childhood trauma  DV: PTS	-Emotional abuse (p<.05), sexual abuse (p<.001) correlated with PTSD (logistic regression)	-Same laboratory as this study, similar dataset
Breslau et al., 1991	Random sample of 1007 21-30 year olds from HMO in Detroit, MI; overall sample PTSD 9.2%	IV: PTSD y/n  DV: Alcohol & drug abuse or dependence; neuroticism as risk factor for PTSD  Logistic regression	<b>-PTSD vs. no PTSD prevalence Odds Ratio was alcohol abuse and dependence 2.23 (1.36-3.63)</b>  -Neuroticism as risk factor for PTSD: 1.20	-PTSD: stronger association with anxiety & mood disorder than with substance abuse or dependence  -Neuroticism, preexisting anxiety or depression, family history of anxiety, all risk factors for PTSD following exposure to trauma event
Tull et al., 2010	N=48 30 day residential treatment  n=18 Alcohol dependence n= 26 Cocaine Dependence n = 12 Heroin dependence	IV: PTSD y/n  DV: Substance dependence y/n and type  Hierarchical logistic regression	<b>-Post-traumatic stress symptoms severity not uniquely associated w/ alcohol</b>	-Post-traumatic stress, not PTSD  -Similar treatment protocol to this study

Driessen et al., 2008	N = 459 n = 337 inpatient n = 45 day clinic n = 77 outpatient n = 305 Alcohol dependence n = 182 Alcohol dependence only	IV: Substance use disorder subgroups (PTSD, sub-PTSD) DV: Substance use disorder severity, craving, psychiatric symptoms  Chi-square, ANOVA, ANCOVA, GLM	<b>-PTSD group Addiction Severity Index scores vs. three other groups (p&lt;.001)</b>  <b>-PTSD vs. exposure and non-exposure on BPRS (p&lt;.001)</b>  <b>-PTSD is an independent risk factor for unfavorable outcome of substance use disorder</b>	-PTSD vs. exposure: d = 0.72 PTSD vs. no exposure: d = 0.86  -Faster drug use relapse in PTSD vs. trauma exposed (p = .002) and no exposure (p = 0.01)  -PTSD & substance use disorder interaction effect, highest score in drug dependence and PTSD (p = .008)
Waldrop et al., 2007	N = 72 (38 women), Alcohol dependence only (n = 18) AD + PTSD (n = 16) Cocaine dependence only (n = 15) Cocaine dependence + PTSD (n = 23)	IV: PTSD y/n, alcohol or cocaine use disorder y/n  DV: Situation type and triggers for use  ANCOVA	-Those with PTSD used more substances in negative situations (p<.05), with unpleasant emotions (p<.01), and physical discomfort (p<.05)	
Reynolds et al., 2005	N = 52 (n = 20 PTSD) Trauma exposed adults in UK	IV: PTSD y/n  DV: Addiction severity & psychiatric symptoms  Cross-sectional	PTSD and addiction severity index scores worse in medical (p<.02), trend in psychiatric trend (p<.06)	-Substance use relative to trauma (before & after)

Table 1b Review of Epidemiological Studies

Author	Population	Variables/Analysis	Main Findings	Notes
Boschloo et al., 2013	N = 2248 Netherlanders	IV: Depressive and/or anxiety disorder and/or AD DV: Personality traits (neuroticism etc...)	-Depressive/anxiety disorders predict the onset of AD and vice versa -Data suggests etiological overlap between these disorders which should be explored -Neuroticism and impulsivity were correlated to the IVs	-Doesn't specifically speak to PTSD, but does speak to DSM-IV anxiety disorders (GAD, social phobia, panic disorder)
McFarlane, 1998	N = 2,501 Australians	IV: PTSD y/n  DV: Alcohol use	-No uniform association between substance abuse & psychological comorbidity -Causal relationship between traumatic stress, PTSD, and alcohol abuse -Alcohol abuse can traumatization, violence & accidents	- Alcohol has possible self-medication benefits, can also hide association by modifying the symptoms of associated PTSD
Chilcoat & Brelau, 2008	N = 955 n = 237 PTSD  HMO patients, 21-30 yrs followed for 5 yrs	IV: PTSD y/n  DV: Drug Abuse Dependence, exposure to trauma y/n  PTSD for survival analysis	-PTSD and drug abuse or dependence strong association (p<.001) -Risk of trauma same for drug alcohol or dependence or none -Pre-existing PTSD increased risk of subsequent drug abuse or dependence -Adjustment for history alcohol abuse or dependence had no impact on results	<b>-Evidence for self-medication hypothesis for drugs</b>  <b>*does not speak to alcohol specifically</b>
Breslau et al., 2003	N = 1200 10 yr prospective data from HMO 21-30 yrs old in SE Michigan	IV: PTSD y/n, trauma exposure y/n DV: Drug/alcohol dependence Longitudinal, Logistic Regression, Cox Survival Analysis	-Increased risk for onset of nicotine dependence and drug abuse or dependence in people with PTSD <b>-Exposure to trauma in both presence/absence of PTSD did not predict alcohol abuse or dependence</b>	-No increased risk or a significantly lower risk in persons exposed to trauma in absence of PTSD

Table 1c Review Studies

Author	General Terms	Overall Findings
Stewart et al., 1998	PTSD + SUD	<ul style="list-style-type: none"> <li>-High comorbidity of PTSD and substance use disorders</li> <li><b>-Trauma symptoms/PTSD precedes substance use disorders</b></li> <li><b>-PTSD Arousal symptoms key to developing alcohol or substance use disorders</b></li> <li>-Same relationship, but with other drugs, is unclear (possibly because all other drugs are grouped together in research, or difficulty separating numbing &amp; avoidance symptoms)</li> </ul>
Jacobsen et al., 2001	PTSD + AA/AD /SUD	<ul style="list-style-type: none"> <li>-High rates of comorbidity are functionally related</li> <li><b>-In men with PTSD alcohol abuse or dependence are most common, then depression, anxiety</b></li> <li><b>-In women with PTSD comorbid depression and anxiety are most common, then alcohol abuse and dependence</b></li> <li>-PTSD and substance use disorder leads to high rates Axis I disorders, psychosocial &amp; medical problems, substance or alcohol related inpatient admissions, relapse</li> <li>-PTSD and SUD leads to more severe PTSD symptoms</li> <li>-PTSD and substance use disorder at 6 months post-treatment follow-up had remitted PTSD symptoms and significantly less substance use compared to unremitted PTSD</li> <li>-Patients report alcohol improves PTSD symptoms</li> </ul>
Brady & Back, 2013	Early life trauma + AD	<ul style="list-style-type: none"> <li>-Early life trauma may lead to alcohol dependence</li> <li>-Could be mechanistic: neurobiological effects of early trauma could lead to increased vulnerability to alcohol or substance use disorders</li> </ul>
Orth & Wieland, 2006	Trauma exposed adults	<ul style="list-style-type: none"> <li>-Weighed mean effect size anger-hostility with PTSD is <math>r=.48</math></li> </ul>
McCarthy & Petrakis, 2010	PTSD + AD	<ul style="list-style-type: none"> <li>-Co-morbid PTSD and alcohol dependence associated with worse outcomes compared to single diagnosis</li> </ul>
Roberts et al., 2015	PTSD + AUD/SUD	<ul style="list-style-type: none"> <li>-Treating PTSD and SUD concurrently can reduce PTSD symptom severity</li> <li>-This type of treatment, includes exposure or CBT, may be less tolerated/completed</li> <li>-Non-trauma focused group interventions did not alleviate symptoms of PTSD, did improve SUD/AUD symptoms initially but not at follow-up</li> <li>-Individual non-trauma focused interventions have insufficient data</li> </ul>

Table 2: Baseline Sample Characteristics

Variable ↓	No PTSD ( <i>n</i> = 332)	PTSD ( <i>n</i> = 79)	All ( <i>N</i> = 411)	<i>t</i> / $\chi^2$	<i>df</i>	<i>p</i> -value	Effect Size	<i>F</i> -value ANCOVA	<i>p</i> -value ANCOVA
Age	42.12 (10.05)	40.04 (9.37)	41.72 (9.95)	1.67	409	.09	0.21 <sup>b</sup>	n/a	n/a
Gender (%)				14.84	1	.001	.19 <sup>c</sup>	n/a	n/a
Male	77.11	55.70	73.00						
Female	22.89	44.30	27.00						
Ethnicity (%)				4.57	2	.10	.11 <sup>d</sup>	n/a	n/a
Caucasian	62.35	56.96	61.31						
AA	30.12	27.85	29.68						
Others <sup>a</sup>	7.53	15.19	9.00						
Smokers (%)	73.58%	75.00%	73.87%	0.056	1	.81	.01 <sup>c</sup>	n/a	n/a
Benzodiazepines (yes/no)	31.63%	32.91%	31.87%	0.049	1	.82	.01 <sup>c</sup>	n/a	n/a
90 Day Total Drinks	1021.56 (726.81)	913.15 (674.39)	1000.50 (717.35)	-1.17	379	.284	0.15 <sup>b</sup>	0.20	.65
90 Drinking Days	68.44 (25.11)	62.77 (24.37)	67.34 (25.04)	-1.75	372	.101	0.23 <sup>b</sup>	1.65	.20
90 Day Drinks per Day	14.35 (8.59)	13.61 (7.56)	14.21 (8.40)	-0.68	372	.609	0.09 <sup>b</sup>	0.00	.97
Alcohol Dependence Severity	21.21 (8.18)	24.79 (8.28)	21.89 (8.30)	3.32	377	.001	0.44 <sup>b</sup>	8.62	.004

Note. Data are Mean (*SD*) unless otherwise noted. <sup>a</sup> “Others” includes: American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, More Than One Race, and Unknown. Effect sizes are Cohen’s *d* (continuous outcomes),<sup>b</sup> Phi (dichotomous outcomes),<sup>c</sup> and Cramer’s *V* (nominal outcome variables).<sup>d</sup> ANCOVA includes Age and Sex as covariates. Denominator *df* for ANCOVA are *df* – 2.

Table 3: Comorbidity Diagnoses

<b>Diagnosis</b>	<b>No PTSD (n = 332)</b>	<b>PTSD (n = 79)</b>	<b>All (N = 411)</b>	<b>Wald Statistic</b>	<b>p-value</b>	<b>OR (unadjusted)</b>	<b>95% CIs (unadjusted)</b>	<b>OR (adjusted)</b>	<b>95% CIs (adjusted)</b>
Anxiety Disorder	79 (23.80%)	42 (53.16%)	121 (29.44%)	24.70	.000	3.64	2.19-6.05	3.29	1.96-5.54
Mood Disorder	41 (12.35%)	32 (40.51%)	73 (17.76%)	30.89	.000	4.83	2.77-8.42	4.29	2.41-7.53
Substance Dependence	246 (74.10%)	65 (82.28%)	311 (75.67%)	2.29	.130	1.62	0.87-3.04	1.73	0.90-3.34

*Note.* Adjusted ORs derived from models that include age and gender as covariates.

Table 4: Anxiety (Brief Scale of Anxiety; BSA) and Depression Symptoms (Montgomery-Asberg Depression Rating Scale; MADRS)

Measure↓	Day	No PTSD ( <i>n</i> = 227)	PTSD ( <i>n</i> = 54)	All ( <i>N</i> = 281)	<i>t</i>	<i>df</i>	<i>p-value</i>	<i>d</i>	<i>F-value</i> <i>ANCOVA</i>	<i>p-value</i> <i>ANCOVA</i>
BSA	2	10.16 (6.03)	13.72 (7.07)	10.86 (6.39)	3.76	275	<.001	0.57	11.80	<.001
BSA	9	6.18 (4.92)	8.29 (6.29)	6.57 (5.26)	2.64	277	.009	0.41	5.92	.02
BSA	16	4.98 (4.23)	9.20 (6.10)	5.77 (4.91)	5.85	269	<.001	0.91	30.98	<.001
BSA	23	4.59 (4.25)	7.37 (5.40)	5.14 (4.62)	3.87	249	<.001	0.62	13.44	<.001
BSA	30	4.70 (4.85)	6.35 (6.17)	5.08 (5.19)	1.25	84	.214	0.32	1.84	.18
MADRS	2	13.93 (8.19)	18.83 (9.61)	14.88 (8.69)	3.81	275	<.001	0.58	12.69	<.001
MADRS	9	6.67 (5.62)	9.92 (6.99)	7.28 (6.02)	3.58	277	<.001	0.55	9.60	.002
MADRS	16	5.82 (5.38)	11.59 (8.15)	6.91 (6.39)	6.19	269	<.001	0.96	36.41	<.001
MADRS	23	4.95 (5.12)	8.37 (6.52)	5.62 (5.58)	3.96	249	<.001	0.63	13.90	<.001
MADRS	30	5.42 (5.46)	7.60 (8.91)	5.93 (6.43)	1.33	84	.187	0.35	2.04	.16

Note. ANCOVA includes Age and Sex as covariates. *df* (denominator) for ANCOVA are *df* - 2. *d* = Cohen's *d*.

Table 5: NEO Personality and Buss-Perry Aggression Questionnaire (BPAQ)

Variable ↓	No PTSD ( <i>n</i> = 283)	PTSD ( <i>n</i> = 65)	All ( <i>N</i> = 348)	<i>t</i>	<i>df</i>	<i>p-value</i>	<i>d</i>	<i>F-value</i> <i>ANCOVA</i>	<i>p-value</i> <i>ANCOVA</i>
NEO Neuroticism Factor	55.76 (10.36)	62.82 (11.48)	57.08 (10.92)	4.86	346	<0.001	0.67	20.94	<.001
Anxiety	53.97 (10.10)	57.18 (9.71)	54.57 (10.09)	2.33	346	.021	0.32	5.29	.02
Angry Hostility	53.73 (11.17)	59.04 (11.96)	54.72 (11.49)	3.42	346	.001	0.47	8.70	.003
Depression	58.43 (10.94)	64.79 (10.69)	59.62 (11.16)	4.25	346	.000	0.58	16.18	<.001
Self-consciousness	53.84 (10.32)	58.23 (11.23)	54.66 (10.62)	3.05	346	.002	0.42	6.83	.009
Impulsiveness	55.25 (9.32)	57.01 (7.49)	55.58 (9.03)	1.42	346	.156	0.20	1.78	.18
Vulnerability	56.30 (12.29)	62.42 (12.94)	57.44 (12.63)	3.59	346	.000	0.49	10.32	.001
NEO Extraversion Factor	53.64 (10.05)	51.96 (10.06)	53.33 (10.06)	-1.22	346	.225	-0.17	2.12	.15
NEO Openness Factor	51.56 (10.22)	53.31 (9.95)	51.89 (10.18)	1.26	346	.210	0.17	0.92	.34
NEO Agreeableness Factor	47.07 (11.20)	45.10 (9.53)	46.70 (10.92)	-1.31	346	.191	-0.18	0.71	.40
NEO Conscientiousness Factor	43.22 (11.39)	42.74 (10.60)	43.13 (11.24)	-0.31	346	.756	-0.04	0.01	.91
BPAQ Physical Aggression	20.36 (7.59)	22.94 (9.05)	20.78 (7.86)	1.28	107	.204	0.33	1.34	.25
BPAQ Verbal Aggression	13.71 (3.83)	16.22 (4.57)	14.13 (4.05)	2.46	107	.016	0.63	6.78	.01
BPAQ Anger	15.15 (5.89)	18.94 (6.69)	15.78 (6.16)	2.44	107	.016	0.63	3.97	.05
BPAQ Hostility	43.31 (5.62)	50.22 (6.09)	44.45 (6.22)	4.71	107	.000	1.21	20.11	<.001
BPAQ Aggression	92.54 (18.89)	108.33 (22.18)	95.15 (20.24)	3.15	107	.002	0.81	9.09	.003

*Note.* ANCOVA includes Age and Sex as covariates. *df* (denominator) for ANCOVA are *df* - 2. *d* = Cohen's *d*. \*For the BPAQ, No PTSD group (*n* = 91), PTSD (*n* = 18).

Table 6: Addiction Severity Index (ASI)

<i>Indices Composite Score</i>	<i>No PTSD (n = 297*)</i>	<i>PTSD (n = 70*)</i>	<i>All (N = 367*)</i>	<i>df</i>	<i>t</i>	<i>p-value</i>	<i>d</i>	<i>F-value ANCOVA</i>	<i>p-value ANCOVA</i>
Medical	0.22 (0.31)	0.31 (0.38)	0.23 (0.32)	325	1.98	.049	0.26	2.77	.097
Employment	0.55 (0.30)	0.62 (0.34)	0.56 (0.31)	362	1.77	.078	0.22	2.23	.136
Alcohol	0.73 (0.18)	0.71 (0.20)	0.73 (0.18)	364	-0.86	.392	0.11	0.47	.493
Drug	0.10 (0.13)	0.13 (0.14)	0.11 (0.13)	326	1.79	.075	0.22	1.28	.260
Legal	0.13 (0.20)	0.17 (0.23)	0.14 (0.21)	318	1.27	.204	0.19	2.07	.151
Family	0.23 (0.22)	0.31 (0.25)	0.25 (0.22)	322	2.58	.010	0.34	2.26	.134
Psychiatric	0.25 (0.23)	0.38 (0.22)	0.28 (0.23)	353	4.13	< .001	0.58	13.39	< .001

*Note.* Data are Mean (*SD*) unless otherwise noted. ANCOVA includes Age and Sex as covariates. *df* (denominator) for ANCOVA are *df* - 2. *d* = Cohen's *d*.

Table 7: Smoking

	<i>No PTSD</i>	<i>PTSD</i>	<i>All</i>	<i>df</i>	<i>t</i>	<i>p-value</i>	<i>d</i>	<i>F value ANCOVA</i>	<i>p value ANCOVA</i>
FTQ	3.20 (2.82)	3.41 (2.80)	3.24 (2.82)	240	-.89	.375	0.07	1.49	.223
Cigarettes per day	15.72 (10.65)	15.82 (10.24)	15.74 (10.55)	244	-.07	.948	0.01	0.24	.622
Cigarettes per week	111.98 (90.47)	106.59 (82.43)	110.86 (88.72)	243	.39	.700	0.06	0.00	.957
Years smoked	19.42 (10.45)	20.77 (11.0)	19.70 (10.56)	243	-.81	.420	0.13	3.39	.067

*Note.* Data are mean (*SD*). Measures were administered to smokers only. No PTSD Cigarettes per day is  $n = 195$  (PTSD is  $n = 51$ ), No PTSD Cigarettes per week is  $n = 194$  (PTSD is  $n = 51$ ), No PTSD Years smoked is  $n = 194$  (PTSD is  $n = 51$ ). All Cigarettes per day is  $N = 246$ , Cigarettes per week is  $N = 245$ , Years smoked is  $n = 245$ . ANCOVA includes Age and Sex as covariates. *df* (denominator) for ANCOVA are  $df - 2$ . *d* = Cohen's *d*.

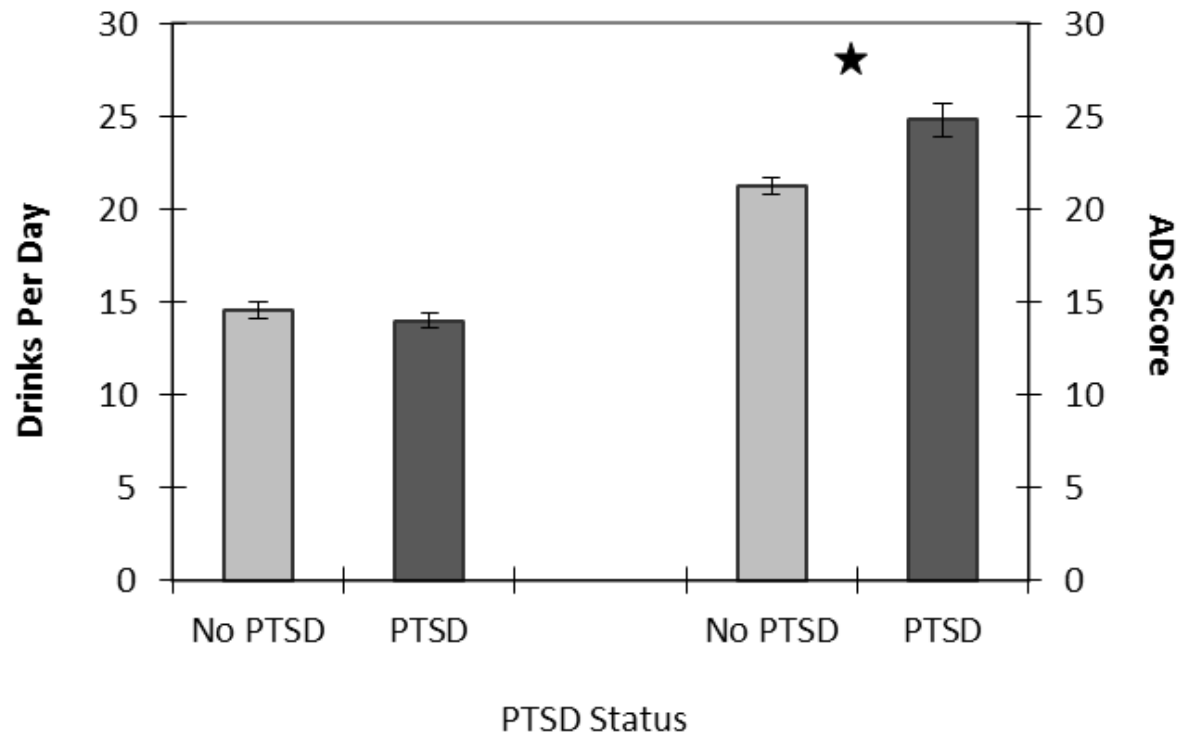


Figure 2. Alcohol Use and Dependence by PTSD status. \* $p < .05$

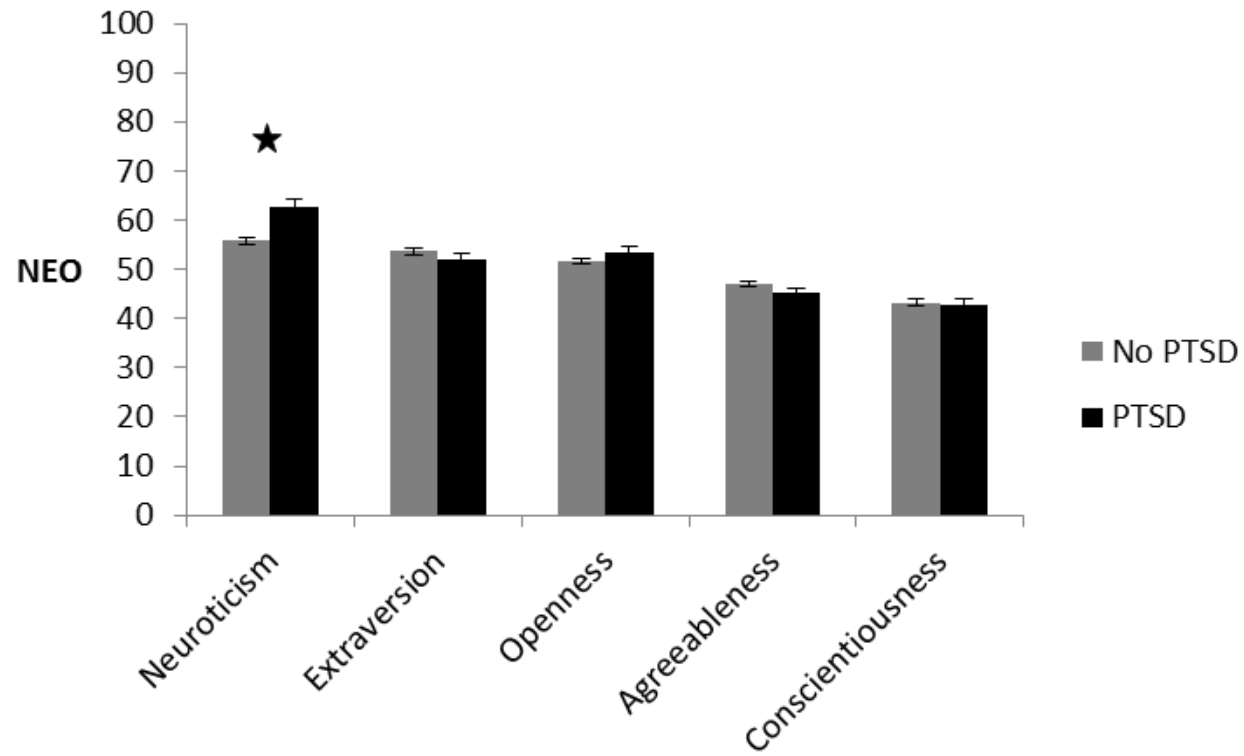


Figure 3. NEO Personality Scores by PTSD status.  $*p < .05$

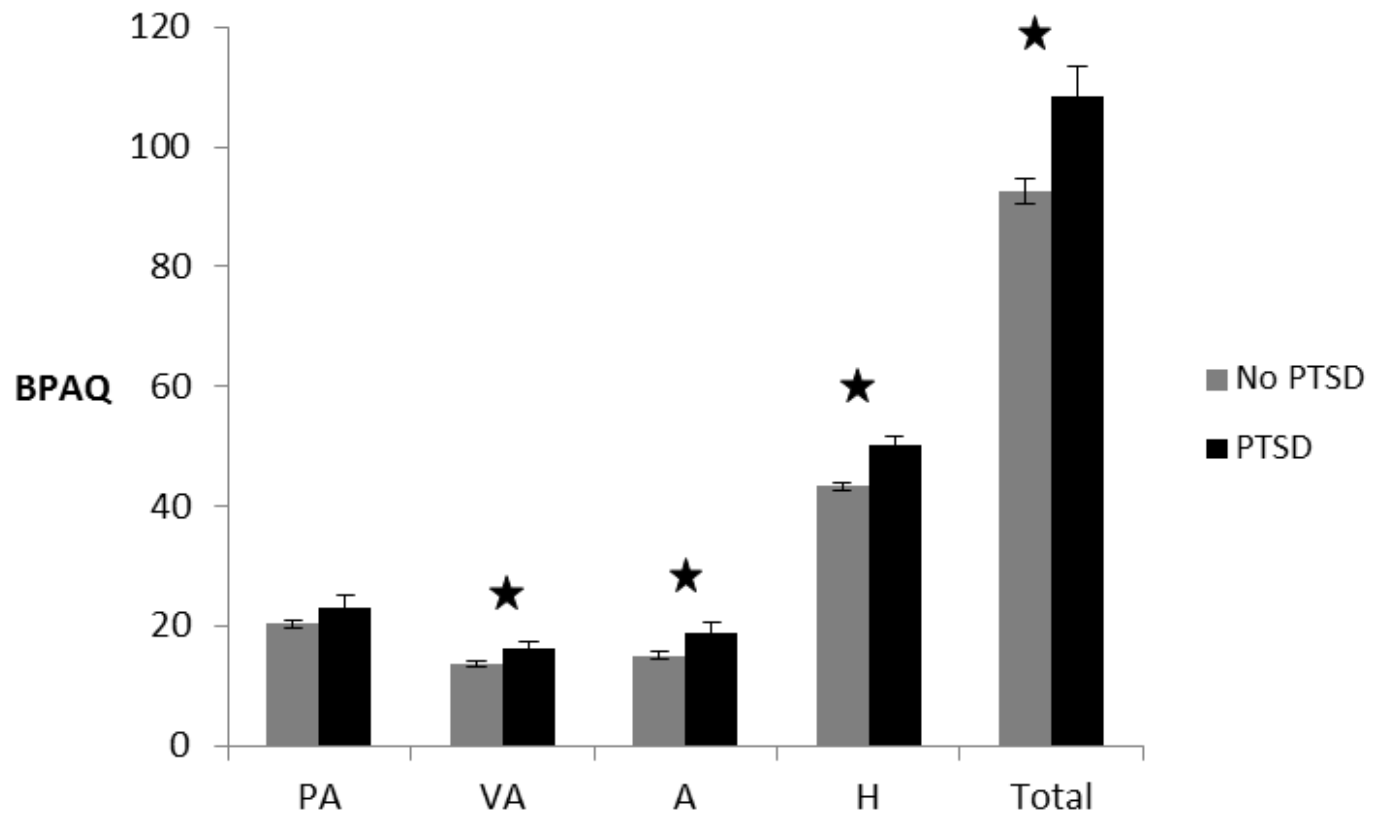


Figure 4. BPAQ Aggression Questionnaire Scores by PTSD status.  $*p < .05$

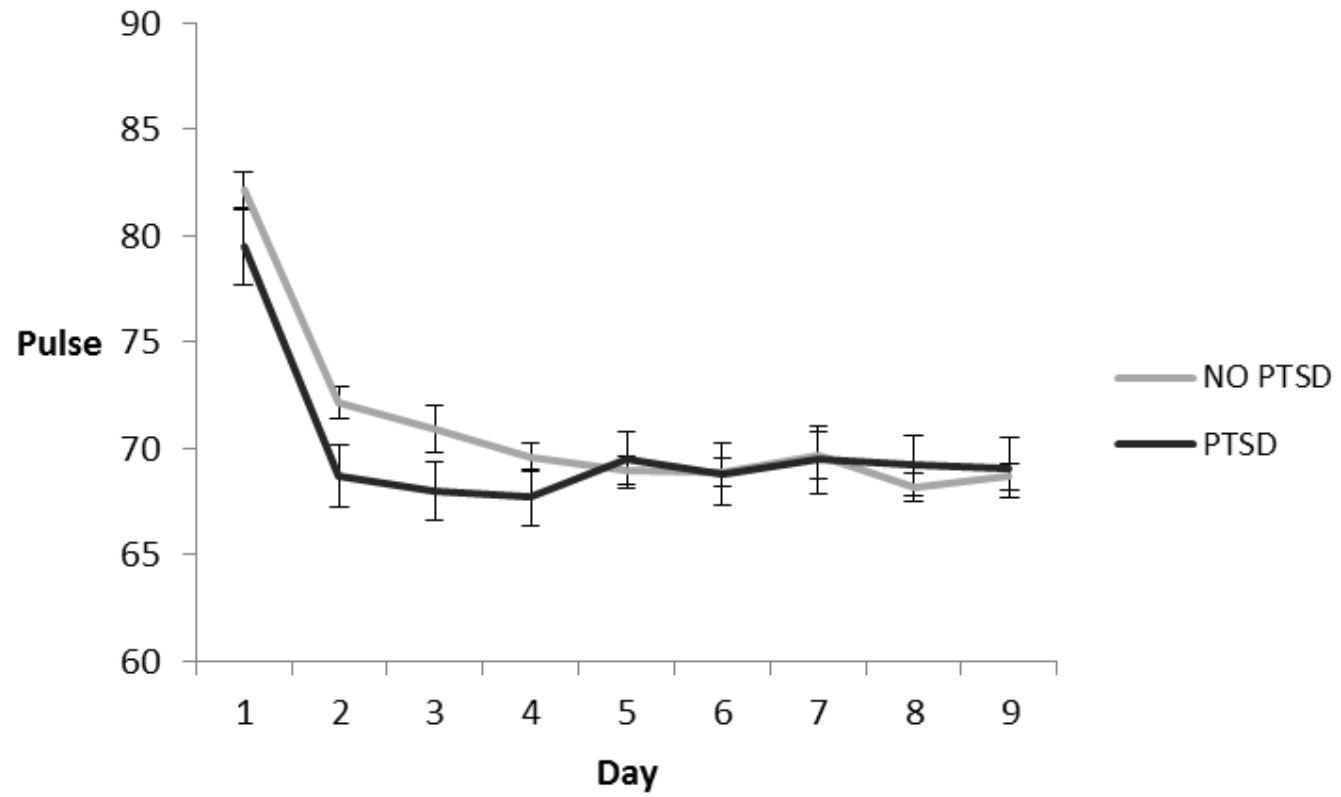


Figure 5. Pulse Rate by PTSD status during Week 0

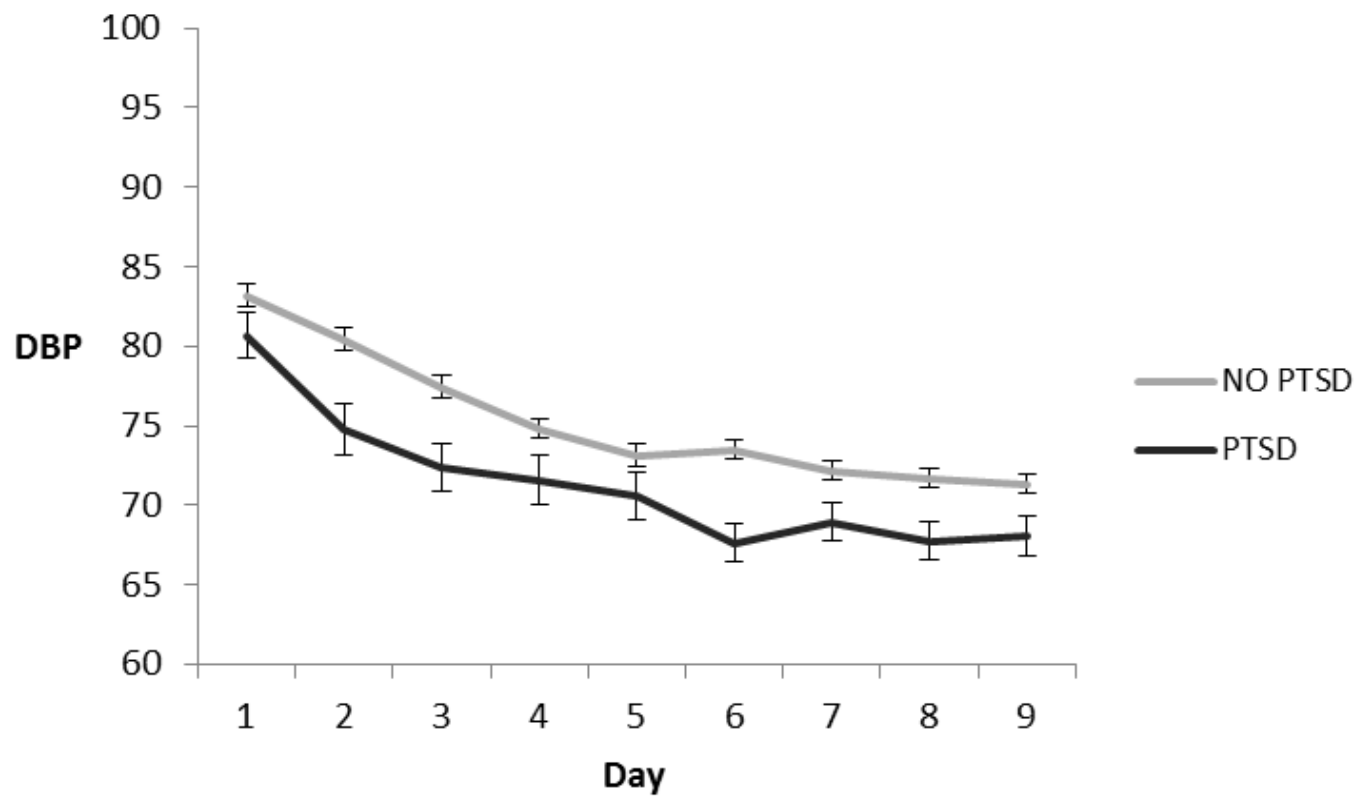


Figure 6. Diastolic Blood Pressure (DBP) by PTSD status during Week 0

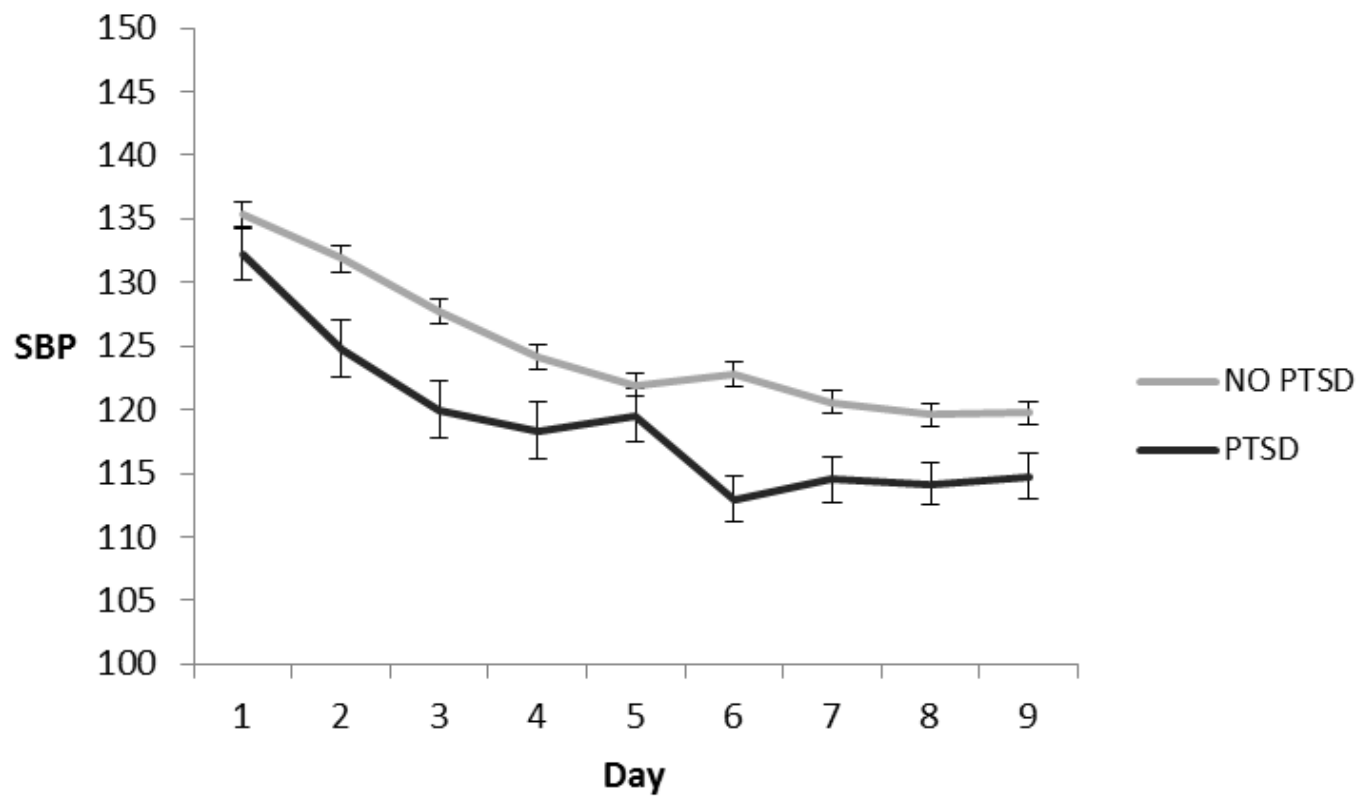


Figure 7. Systolic Blood Pressure (SBP) by PTSD status Week 0

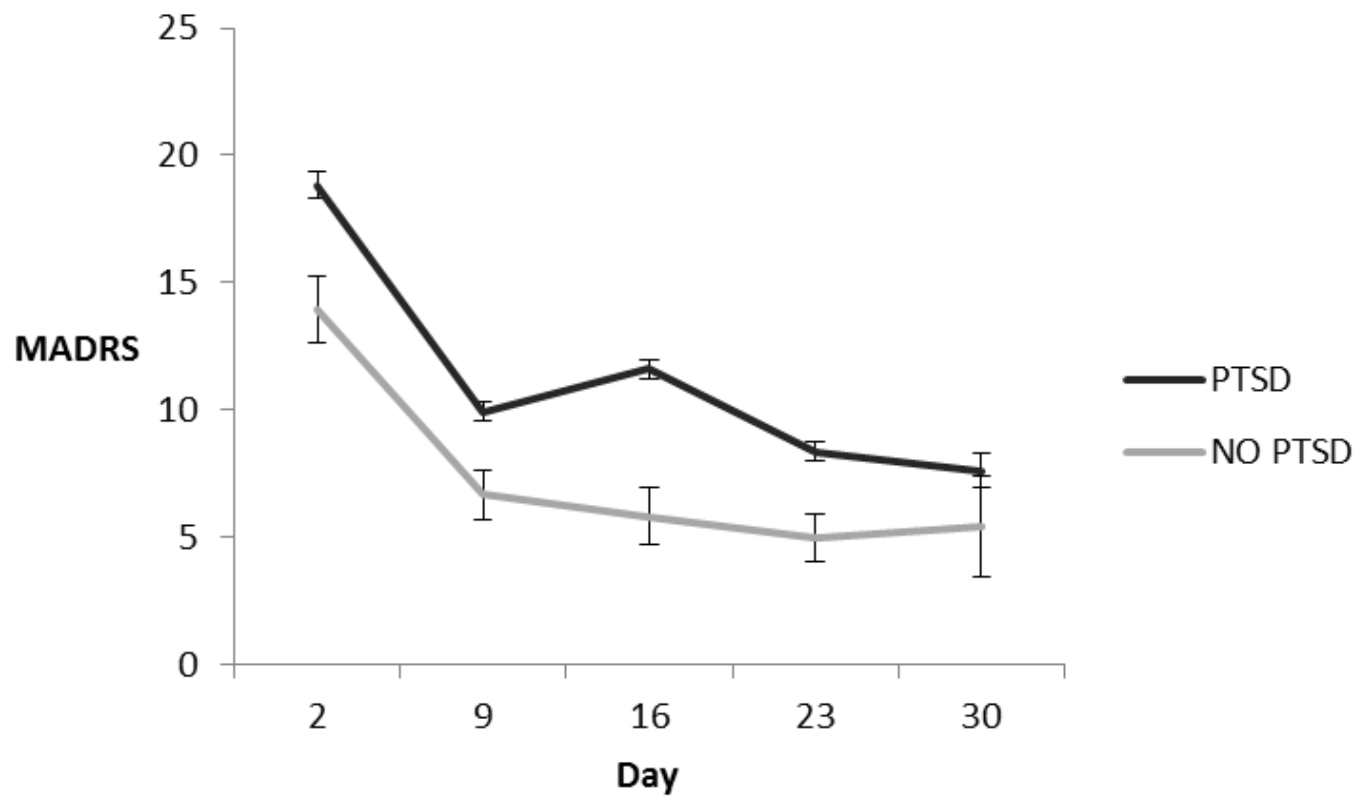


Figure 8. Depression Weeks 1-4 by PTSD status (see Table 4 for *p* values)

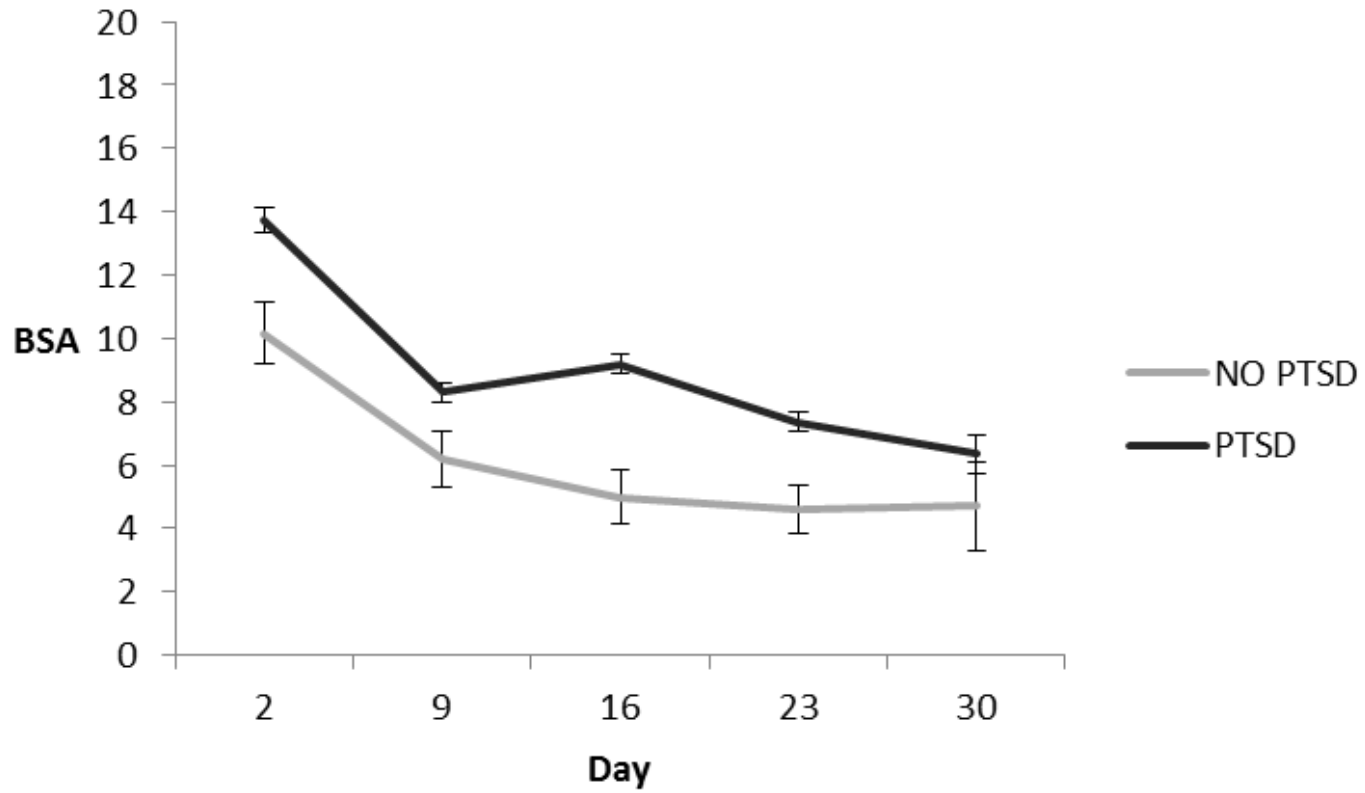


Figure 9. Anxiety Weeks 1-4 by PTSD status (see Table 4 for *p* values)

## REFERENCES

1. American Psychiatric Association. 2000. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR, Text Revision*. Arlington, VA
2. American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders 5th edition*. Washington, DC
3. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. 1978. A comprehensive psychopathological rating scale. *Acta Psychiatr. Scand. Suppl.*:5-27
4. Barlow DH, Sauer-Zavala S, Carl JR, Bullis JR, Ellard KK. 2014. The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science* 2:344-65
5. Baros AM, Wright TM, Latham PK, Miller PM, Anton RF. 2008. Alcohol consumption, %CDT, GGT and blood pressure change during alcohol treatment. *Alcohol Alcohol.* 43:192-7
6. Berenz EC, Coffey SF. 2012. Treatment of co-occurring posttraumatic stress disorder and substance use disorders. *Curr Psychiatry Rep* 14:469-77
7. Blanco C, Xu Y, Brady K, Perez-Fuentes G, Okuda M, Wang S. 2013. Comorbidity of posttraumatic stress disorder with alcohol dependence among US adults: results from National Epidemiological Survey on Alcohol and Related Conditions. *Drug Alcohol Depend.* 132:630-8
8. Boscarino JA, Chang J. 1999. Electrocardiogram abnormalities among men with stress-related psychiatric disorders: Implications for coronary heart disease and clinical research. *Ann. Behav. Med.* 21:227-34
9. Breslau N, Davis GC, Andreski P, Peterson E. 1991. Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch. Gen. Psychiatry* 48:216-22
10. Breslau N, Davis GC, Schultz LR. 2003. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. *Arch. Gen. Psychiatry* 60:289-94
11. Breslau N, Schultz L. 2013. Neuroticism and post-traumatic stress disorder: a prospective investigation. *Psychol. Med.* 43:1697-702
12. Bryant RA, Harvey AG, Guthrie RM, Moulds ML. 2000. A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. *J. Abnorm. Psychol.* 109:341-4
13. Buckley TC, Kaloupek DG. 2001. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosom. Med.* 63:585-94
14. Buss AH, Perry M. 1992. The aggression questionnaire. *J Pers Soc Psychol* 63:452-9
15. Chemtob CM, Roitblatt HL, Hamada RS, Carlson JG, Twentyman CT. 1988. A cognitive action theory of post-traumatic stress disorder. *J. Anxiety Disord.* 2:253-75
16. Chen KW, Banducci AN, Guller L, Macatee RJ, Lavelle A, et al. 2011. An examination of psychiatric comorbidities as a function of gender and substance

- type within an inpatient substance use treatment program. *Drug Alcohol Depend.* 118:92-9
17. Coffey SF, Schumacher JA, Brady KT, Cotton BD. 2007. Changes in PTSD symptomatology during acute and protracted alcohol and cocaine abstinence. *Drug Alcohol Depend.* 87:241-8
  18. Connor JP, Young RM, Williams RJ, Ricciardelli LA. 2000. Drinking restraint versus alcohol expectancies: which is the better indicator of alcohol problems? *J. Stud. Alcohol* 61:352-9
  19. Cox BJ, MacPherson PS, Enns MW, McWilliams LA. 2004. Neuroticism and self-criticism associated with posttraumatic stress disorder in a nationally representative sample. *Behav. Res. Ther.* 42:105-14
  20. Di Castelnuovo A, Costanzo S, Donati MB, Iacoviello L, de Gaetano G. 2010. Prevention of cardiovascular risk by moderate alcohol consumption: epidemiologic evidence and plausible mechanisms. *Intern. Emerg. Med.* 5:291-7
  21. Driessen M, Schulte S, Luedecke C, Schaefer I, Sutmann F, et al. 2008. Trauma and PTSD in patients with alcohol, drug, or dual dependence: a multi-center study. *Alcohol. Clin. Exp. Res.* 32:481-8
  22. Eckhardt C, Norlander, B., Deffenbacher, J.,. 2004. The assessment of anger and hostility: a critical review. *Aggression and Violent Behavior* 9:17-43
  23. Engelhard IM, van den Hout MA, Kindt M. 2003. The relationship between neuroticism, pre-traumatic stress, and post-traumatic stress: a prospective study. *Pers. Individ. Dif.* 35:381-8
  24. Engelhard IM, van den Hout MA, Lommen MJ. 2009. Individuals high in neuroticism are not more reactive to adverse events. *Pers. Individ. Dif.* 47:697-700
  25. Feeny NC, Zoellner LA, Foa EB. 2000. Anger, dissociation, and posttraumatic stress disorder among female assault victims. *J. Trauma. Stress* 13:89-100
  26. First M, Spitzer R, Gibbon M, Williams J. 1995. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient edition. (SCID-I/P)*. New York: Biometrics Research, New York Psychiatric Institute
  27. Fisher LA, Elias JW, Ritz K. 1998. Predicting relapse to substance abuse as a function of personality dimensions. *Alcohol. Clin. Exp. Res.* 22:1041-7
  28. Foa EB, Riggs DS, Masie ED, Yarczower M. 1995. The impact of fear activation and anger on the efficacy of exposure treatment for posttraumatic stress disorder. *Behavioral Therapy* 26:487-99
  29. Hauschildt M, Peters MJ, Moritz S, Jelinek L. 2011. Heart rate variability in response to affective scenes in posttraumatic stress disorder. *Biol. Psychol.* 88:215-22
  30. Howell DC. 2012. *Statistical Methods for Psychology*. Belmont, California: Wadsworth
  31. Huang MC, Schwandt ML, Ramchandani VA, George DT, Heilig M. 2012. Impact of multiple types of childhood trauma exposure on risk of psychiatric comorbidity among alcoholic inpatients. *Alcohol. Clin. Exp. Res.* 36:1099-107
  32. Institute of Medicine. 1990. Broadening the base of treatment for alcohol problems, Washington, DC

33. Jacobsen LK, Southwick SM, Kosten TR. 2001. Substance Use Disorders in Patients With Posttraumatic Stress Disorder: A Review of the Literature *Am. J. Psychiatry* 158:1184-90
34. Jacobsen LK, Southwick SM, Kosten TR. 2001. Substance Use Disorders in Patients With Posttraumatic Stress Disorder: A Review of the Literature. *Am. J. Psychiatry* 158:1184-90
35. Jacobsen LK, Southwick SM, Kosten TR. 2001. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. *Am. J. Psychiatry* 158:1184-90
36. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. 1995. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch. Gen. Psychiatry* 52:1048-60
37. Leeies M, Pagura J, Sareen J, Bolton JM. 2010. The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. *Depress. Anxiety* 27:731-6
38. Lemperiere T, Guelfi JD, Waintraub L. 1985. [The C.P.R.S.: comparison with other general evaluation scales in psychopathology]. *Ann. Med. Psychol. (Paris)* 143:915-24
39. Leonhard C, Mulvey K, Gastfriend DR, Shwartz M. 2000. The Addiction Severity Index: a field study of internal consistency and validity. *J. Subst. Abuse Treat.* 18:129-35
40. Logrip ML, Zorrilla EP, Koob GF. 2012. Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder. *Neuropharmacology* 62:552-64
41. Maiorano G, Bartolomucci F, Contursi V, Saracino E, Agostinacchio E. 1995. Effect of alcohol consumption versus abstinence on 24-h blood pressure profile in normotensive alcoholic patients. *Am. J. Hypertens.* 8:80-1
42. Masters SB. 2012. *The Alcohols*. McGraw-Hill Companies, Inc
43. McCarthy E, Petrakis I. 2010. Epidemiology and management of alcohol dependence in individuals with post-traumatic stress disorder. *CNS Drugs* 24:997-1007
44. McCrae RR, Costa PT, Jr. 1989. The structure of interpersonal traits: Wiggins's circumplex and the five-factor model. *J Pers Soc Psychol* 56:586-95
45. McCrae RR, John OP. 1992. An introduction to the five-factor model and its applications. *J. Pers.* 60:175-215
46. McFarlane AC. 1998. Epidemiological evidence about the relationship between PTSD and alcohol abuse: The nature of the association. *Addict. Behav.* 23:813-25
47. McIntosh C, Chick J. 2004. Alcohol and the nervous system. *J. Neurol. Neurosurg. Psychiatry* 75 Suppl 3:iii16-21
48. McLellan AT, Luborsky L, Woody GE, O'Brien CP. 1980. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *J. Nerv. Ment. Dis.* 168:26-33
49. Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA, Jr., Stampfer MJ, et al. 2003. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N. Engl. J. Med.* 348:109-18

50. National Institute on Alcohol Abuse and Alcoholism. 2012. *Rethinking drinking alcohol and your health*.  
<http://rethinkingdrinking.niaaa.nih.gov/Strategies/TipsToTry.asp>
51. Norman SB, Myers US, Wilkins KC, Goldsmith AA, Hristova V, et al. 2012. Review of biological mechanisms and pharmacological treatments of comorbid PTSD and substance use disorder. *Neuropharmacology* 62:542-51
52. Novaco RW, Chemtob CM. 2002. Anger and combat-related posttraumatic stress disorder. *J. Trauma. Stress* 15:123-32
53. Orth U, Cahill SP, Foa EB, Maercker A. 2008. Anger and posttraumatic stress disorder symptoms in crime victims: A longitudinal analysis. *J. Consult. Clin. Psychol.* 76
54. Orth U, Wieland E. 2006. Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis. *J. Consult. Clin. Psychol.* 74:698-706
55. Perris C. 1979. Reliability and validity studies of the comprehensive Psychopathological Rating Scale (CPRS). *Prog. Neuropsychopharmacol.* 3:413-21
56. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. 2011. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *J. Anxiety Disord.* 25:456-65
57. Potter JF, Bannan LT, Saunders JB, Ingram MC, Beevers DG. 1983. Blood pressure and pressor mechanisms during alcohol withdrawal. *J. Hypertens. Suppl.* 1:97-9
58. Rechlin T, Orbes I, Weis M, Kaschka WP. 1996. Autonomic cardiac abnormalities in alcohol-dependent patients admitted to a psychiatric department. *Clin. Auton. Res.* 6:119-22
59. Riggs DS, Dancu CV, Gershuny BS, Greenberg D, Foa EB. 1992. Anger and post-traumatic stress disorder in female crime victims. *J. Trauma. Stress* 5:613-25
60. Roberts NP, Roberts PA, Jones N, Bisson JI. 2015. Psychological interventions for post-traumatic stress disorder and comorbid substance use disorder: A systematic review and meta-analysis. *Clin. Psychol. Rev.* 38:25-38
61. Schuckit MA. 2009. Alcohol-use disorders. *Lancet* 373:492-501
62. Shalev AY, Sahar T, Freedman S, Peri T, Glick N, et al. 1998. A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder. *Arch. Gen. Psychiatry* 55:553-9
63. Sher KJ, Grekin ER, Williams NA. 2005. The development of alcohol use disorders. *Annu. Rev. Clin. Psychol.* 1:493-523
64. Siegel JM. 1986. The Multidimensional Anger Inventory. *J Pers Soc Psychol* 51:191-200
65. Skinner HA, Allen BA. 1982. Alcohol dependence syndrome: measurement and validation. *J. Abnorm. Psychol.* 91:199-209
66. Skinner HA, Horn JL. 1984. Alcohol Dependence Scale: User's Guide. Toronto, Canada: Addiction Research Foundation. Number of.
67. Slutske WS, Heath AC, Madden PA, Bucholz KK, Statham DJ, Martin NG. 2002. Personality and the genetic risk for alcohol dependence. *J. Abnorm. Psychol.* 111:124-33

68. Sobell LC, Maisto SA, Sobell MB, Cooper AM. 1979. Reliability of alcohol abusers' self-reports of drinking behavior. *Behav. Res. Ther.* 17:157-60
69. Soskin DP, Carl JR, Alpert J, Fava M. 2012. Antidepressant effects on emotional temperament: toward a biobehavioral research paradigm for major depressive disorder. *CNS Neurosci. Ther.* 18:441-51
70. Stewart SH, Pihl RO, Conrod PJ, Dongier M. 1998. Functional associations among trauma, PTSD, and substance-related disorders. *Addict. Behav.* 23:797-812
71. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. 1989. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br. J. Addict.* 84:1353-7
72. Sutherland I. 1997. The development and application of a questionnaire to assess the changing personalities of substance addicts during the first year of recovery. *J. Clin. Psychol.* 53:253-62
73. Svanborg P, Asberg M. 1994. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr. Scand.* 89:21-8
74. Taft CT, Street AE, Marshall AD, Dowdall DJ, Riggs DS. 2007. Posttraumatic stress disorder, anger, and partner abuse among Vietnam combat veterans. *J. Fam. Psychol.* 21:270-7
75. The Management of Post-Traumatic Stress Disorder Working Group. 2010. VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress.
76. The Management of Substance Use Disorders Working Group. 2009. VA/DoD Clinical Practice Guideline for Management of Substance Use Disorders (SUD).
77. Vakili S, Sobell LC, Sobell MB, Simco ER, Agrawal S. 2008. Using the Timeline Followback to determine time windows representative of annual alcohol consumption with problem drinkers. *Addict. Behav.* 33:1123-30
78. Valero S, Daigre C, Rodriguez-Cintas L, Barral C, Goma IFM, et al. 2014. Neuroticism and impulsivity: their hierarchical organization in the personality characterization of drug-dependent patients from a decision tree learning perspective. *Compr. Psychiatry* 55:1227-33
79. Veazey CH, Blanchard EB, Hickling EJ, Buckley TC. 2004. Physiological responsiveness of motor vehicle accident survivors with chronic posttraumatic stress disorder. *Appl. Psychophysiol. Biofeedback* 29:51-62
80. Waldrop AE, Ana EJ, Saladin ME, McRae AL, Brady KT. 2007. Differences in early onset alcohol use and heavy drinking among persons with childhood and adulthood trauma. *Am. J. Addict.* 16:439-42
81. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, et al. 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 382:1575-86
82. Work Group on Substance Use Disorders American Psychiatric Association. 2006. Practice Guideline for the Treatment of Patients with Substance Use Disorders, Second Edition.
83. World Health Organization. 2015. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines Version: 2015. Geneva: World Health Organization

84. World Hypertension League. 1991. Alcohol and hypertension- Implications for management: A consensus statement by the World Hypertension League. *J. Hum. Hypertens.* 5:227-32
85. Zakhari S. 1997. Alcohol and the cardiovascular system: molecular mechanisms for beneficial and harmful action. *Alcohol Health Res. World* 21:21-9