PROJECT DESCRIPTION

Title: Attenuation of Stress Response Using Progesterone in Individuals with Alcohol Dependence and Post-Traumatic Stress Disorder NCT02187224

1. Principal Investigator:

Elizabeth Ralevski, PhD

Authorized Prescribers: Ismene Petrakis MD, Albert Arias MD, Gihyun Yoon MD, Louis Trevisan MD

2. Purpose:

Primary Aims:
1.To test if progesterone (PROG) is more effective than placebo in reducing craving after exposure to trauma or stress cues in a laboratory paradigm among men and women with a) comorbid AUD and PTSD and b) AUD only.
We hypothesize that progesterone in comparison to placebo will significantly reduce craving for alcohol in response to trauma cues in individuals with a) comorbid AUD and PTSD and b) AUD only. Craving for alcohol will be measured using a self-report Visual Analog Scale - Craving (VASC) and the Alcohol Urge Questionnaire (AUQ).

Secondary Aims:
1. To test if progesterone attenuates stress-induced anxiety, measured by the State Trait Anxiety Inventory (STAI-6).
2: To describe PROG's subjective mood effects, we will use the Differnetial Emotion Scale (DES-R)
3: To describe PROG's effects on cognitive performance, we will assess the ability to inhibit incongruent competing conflicts using the Stroop Color/Word test (Stroop).

Exploratory Aims:
1. To test if progesterone is more effective than placebo in reducing drinking and relapse during one month following exposure to trauma cues *using the Timeline Follow Back Method (TLFB).*

2. To examine if there are gender differences in progesterone effects on stress and alcohol cue-induced craving.
We hypothesize that the effects of progesterone on stress and craving will be stronger in women than in men.

3. Background:
Alcohol use disorder (AUD) is one of the most prevalent of all psychiatric disorders(Grant et al., 2004; Kessler et al., 1994) with a considerable morbidity and mortality that is preventable(Johnson, 2008). It is also among the most costly health care problems with an estimated economic burden of $185 billion dollars per year(Harwood, 1998). Evidence shows that alcohol use and abuse is strongly correlated with psychiatric disorders associated with stressful events, notably Post Traumatic Stress Disorder (PTSD)(Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Helzer, Robins, & McEvoy, 1987; Jacobson et al., 2008; Keane & Kaloupek, 1997; Kulka et al., 1990; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993; Reynolds et al., 2005). The rates of PTSD among individuals with AUD are higher than those in the general population(Kessler et al., 1997). This comorbidity is associated with more severe clinical impairment, poorer treatment prognosis, more severe symptoms of PTSD, higher relapse rates, higher reports of family problems, and heavier drinking when compared to individuals with either AUD or PTSD alone (Brady, Killeen, Saladin, Dansky, & Becker, 1994;

Brown, Stout, & Mueller, 1999; Foa & Williams, 2010; Ouimette, Finney, & Moos, 1999; Read, Brown, & Kahler, 2004). *Currently, there are no FDA approved or effective treatments for individuals with PTSD and AUD indicating an urgent need for the development of novel pharmacologic treatments for these patients.*

Although the co-occurrence of substance use disorders and PTSD is well documented in the literature, mechanisms that perpetuate and maintain the relationship between them are not completely understood. It has been shown that stress can be a trigger for relapse and a main contributing factor to the reinforcing effects of alcohol (R. Sinha, Kimmerling, Doebrick, & Kosten, 2007; R. Sinha, Robinson, & O'Malley, 1998). *Therefore, the study of neural systems that mediate the stress response and identification of factors that can predict successful treatments are clinically relevant and of paramount importance.*

Stress reactivity and link to craving (evidence from laboratory studies): Several studies have documented the positive association between chronic stress early in life and increased likelihood of substance abuse later in life(Dembo, Dertke, Borders, Washburn, & Schmeidler, 1988; Enoch, 2011; Harrison, Fulkerson, & Beebe, 1997; Kaplan, Martin, Johnson, & Robbins, 1986; Widom, Weiler, & Cottler, 1999; Wills, McNamara, Vaccaro, & Hirky, 1996). Laboratory studies that have used cue reactivity paradigms using both stress inducing cues (fear, anxiety)(Breese et al., 2005; Childress et al., 1994; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; R. Sinha, 2009; R. Sinha et al., 2009; Stasiewicz et al., 1997), and alcohol cues (smell of alcohol)(Coffey et al., 2002; Smith-Hoerter, Stasiewicz, & Bradizza, 2004) provide evidence that both types of cues increase craving for alcohol in individuals with AUD, and stressful stimuli have been shown to be as powerful in eliciting self-reported craving for alcohol as is exposure to alcohol cues(Meisler, 1996; R. Sinha et al., 2009; R. Sinha, Garcia, Kemp, Krystal, & O'Malley, 2005). Abundant evidence shows that PTSD is associated with abnormalities in stress reactivity. For example, most but not all studies show that individuals with PTSD have increased levels of the hormones commonly associated with stress response including norepinephrine, epinephrine, and cortisol when compared to healthy controls(Bremner, Krystal, Southwick, & Charney, 1996; Lemieux & Coe, 1995; Lupien, McEwen, Gunnar, & Heim, 2009; R. Yehuda, 1998; R Yehuda, 2009). Laboratory studies using techniques to simulate stress, such as anticipating public speaking, show increased levels of cortisol(Bremner et al., 1996; Heim et al., 2000; Van der Kolk, 2004) and increases in negative affect (such as fear, sadness or anger) as well as PTSD symptoms(Calhoun, Dennis, & Beckham, 2007) in individuals with PTSD and in those who have experienced severe trauma.

A relatively new area of study is the relationship between stress and drug taking behavior in individuals with comorbid PTSD and AUD. As do individuals without comorbid disorders, individuals with dual diagnosis of AUD and PTSD report increased levels of stress and craving for alcohol after exposure to stress inducing cues(T.M Chaplin et al., 2010; Coffey et al., 2002; Coffey, Stasiewicz, Hughes, & Brimo, 2006). As expected, individuals exposed to stress (trauma imagery) and alcohol cues (alcoholic drink), report stronger desire for alcohol than when exposed to neutral imagery or non-alcoholic cues (T.M Chaplin et al., 2010; Coffey et al., 2002; Coffey et al., 2006). Also, craving is stronger when trauma and alcohol cues are combined as compared to craving when trauma or alcohol cues are presented alone suggesting an additive effect. Further, the data collected by our group shows that veterans diagnosed with PTSD and AUD reported significantly more craving for alcohol when exposed to trauma imagery than when exposed to stressful or neutral imagery (see pilot data). *In AUD with PTSD, stress inducing cues (trauma imagery) lead to significant increases in craving for alcohol.*

Can stress reactivity paradigms predict outcome and alcohol relapse? There is increasing evidence that laboratory paradigms evaluating stress reactivity (R. Sinha, Kimmerling, et al., 2007) are clinically relevant and may be useful in predicting outcomes and relapse in patients with alcohol dependence. For example, stress-induced craving has been shown to be associated with drinking outcomes in alcoholics followed for 90 days after discharge from an

inpatient treatment program(Breese et al., 2005). Stress induced craving has also been used as a marker for relapse; individuals with greater stress reactivity have a shorter time to relapse to their preferred substance than individuals with lesser stress reactivity (R. Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006). These findings suggest that attenuation of trauma-related distress may be effective in reducing both craving and negative affect (such as fear, sadness or anger) in individuals with AUD and PTSD. Coffey and his colleagues (Coffey et al., 2006) exposed individuals with AUD and PTSD, in the laboratory, to personalized trauma and neutral scripts followed by exposure to their favorite beverage or water in a counterbalanced fashion. After the laboratory sessions participants were assigned to either exposure therapy or relaxation therapy followed by a second laboratory session. Exposure therapy attenuated the stress response. Rates of alcohol relapse were not recorded, therefore, no conclusions can be drawn about the relationship among stress reactivity, decrease in PTSD symptoms, craving and relapse to drinking*. Our own data (see pilot data) with veterans diagnosed with AUD and PTSD shows that treatment attenuated the stress response, and stress reactivity predicted relapse; stronger stress reactivity was related to higher number of drinking days 3 months after treatment (r=0.603).*

Progesterone and its effects on stress and craving: Progesterone is a hormone produced by both males and females in gonads and adrenal glands. Progesterone is also synthesized in the brain by oligodendrocytes and neurons, and as such is considered a “neurosteroid”(Brinton et al., 2008). In premenopausal women, progesterone levels fluctuate during the menstrual cycle. In the follicular phase of the menstrual cycle, women have low progesterone levels that are comparable to those in men, < 1 ng/ml(Murphy & Allison, 2000). Women have higher progesterone levels than men during the luteal phase of the menstrual cycle (2-28 ng/ml), especially during pregnancy (9 to 200 ng/ml) (Buffet, Djakoure, Maitre, & Bouchard, 1998). Progesterone and its metabolites interact with multiple neurotransmitter receptors including GABAA, glycine, sigma1, kainate, serotonin3, and nicotinic receptors(Chesnoy-Marchais, 2009; Dar & Zinder, 1997). Several studies have successfully administered progesterone during the first 7 days of the follicular phase (Justice & De Wit, 2000; Sofuoglu, Babb, & Hatsukami, 2001, 2002; Tan, McFarlane, & Lipworth, 1997b). Also, a number of studies have examined the effects of progesterone on stress and craving in the laboratory among smokers(Sofuoglu, Mouratidis, & Mooney, 2011) and cocaine dependent men and women(Fox, Sofuoglu, Morgan, Tuit, & Sinha, 2013; R. Sinha, Fox, et al., 2007). Progesterone significantly improved cognitive performance and reduced smoking urges in smokers (Sofuoglu et al., 2011). Using the same laboratory paradigm men and women with cocaine dependence and matched for age, years of education, and drug use were given either progesterone (200mg bid) or placebo for 7 days before exposure to 5-minute personalized stress, neutral and drug cue scripts(Fox et al., 2013) Progesterone was well tolerated by both men and women. Progesterone, compared to placebo, significantly decreased cue-induced craving for cocaine and improved cognitive performance in both men and women. Also, women in comparison to men reported improved negative mood, lower blood pressure, and greater relaxation suggesting that progesterone’s efficacy may be moderated by gender. This is consistent with other findings showing that women with high progesterone levels report significantly lower stress-induced and cue-induced craving for cocaine than women with low progesterone levels(R. Sinha, Fox, et al., 2007). Gender differences in stress-related disorders(Kajantie & Phillips, 2006), physiological response to stress(Allen, Boquet, & Shelley, 1991), and emotional response to stress and craving(T. M. Chaplin, Hong, Bergquist, & Sinha, 2008; R. Sinha & Rounsaville, 2002; Taylor et al., 2006; Zahn-Waxler, 2000) have been well documented, indicating that gender may play an important role in the response to stress and craving. Currently, progesterone is being evaluated as a treatment for cocaine and tobacco addiction(Institute, 2013).

Preliminary Data: (I) *Our group has extensive experience conducting laboratory studies and working with patients with dual diagnoses. We have conducted clinical trials with over 250 participants diagnosed with AUD and PTSD.* Recent publications on this topic include: 1)

Petrakis et al. Noradrenergic vs. serotonergic antidepressant with/without naltrexone for veterans with PTSD and comorbid alcohol dependence. *Neuropsychopharmacology*, 2012; 2) Ralevski et al. Quality of life in veterans with alcohol dependence and co-occurring mental illness. *Addictive Behaviors*, 2013; 3) Fuehrlein et al. Characteristics and drinking patterns of veterans with alcohol dependence with and without post traumatic stress disorder. *Addictive Behaviors*, 2013.

(II) *Ongoing studies*: Pilot data from a study conducted by our group "Relationship between stress and craving in veterans diagnosed with PTSD and AD". Main objectives of this study are: 1) to test how an attenuation of stress response will affect alcohol craving, 2) to examine relationship between stress and craving, and 3) to determine if laboratory induced stress predicts relapse during treatment. The study has III phases. In phase I all subjects participate in a laboratory session and are exposed to neutral, stressful and trauma imagery (randomly assigned). In phase II they undergo treatment with either prazosin or placebo for 12 weeks. After at least 6 weeks of treatment they participate in a second laboratory session that is identical to the session in phase I. During the laboratory session craving, anxiety, and cardiovascular responses are measured. Eighteen veterans completed the study.

Figure 1. Means and Standard Errors for Alcohol Craving Following Exposure to Neutral, Stress, and Trauma Imagery Before and After Treatment

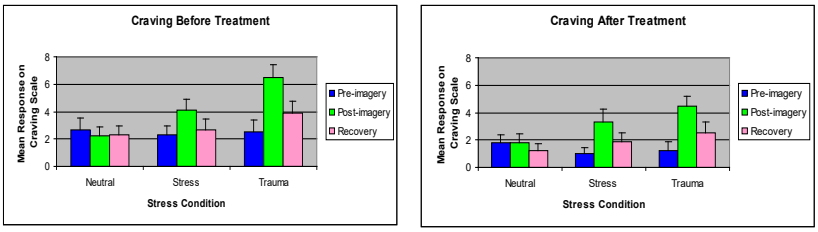


Figure 2. Change in Drinking Days in High and Low Stress Responders and those on Prazosin or Placebo

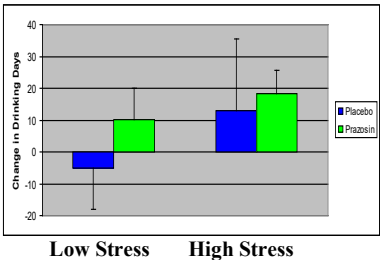
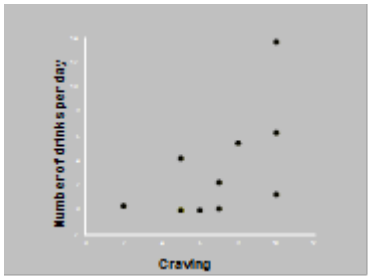


Figure 3. Relationship between Stress Reactivity and Drinking at Follow up



Results: Dually diagnosed veterans reported significantly more craving for alcohol when exposed to trauma imagery than when exposed to stressful or neutral imagery ($p<0.001$) (Figure 1). The stress response decreased with treatment, and those with high stress response on prazosin reported greater, but not statistically significant, change in their drinking at the end of treatment (Figure 2). Also, there was a significant relationship ($r=0.603$) (Figure 3) between craving and the number of drinking days at follow up.

Conclusions: The preliminary findings show that veterans with dual diagnosis report strong craving after exposure to trauma related imagery. **Based on this result we eliminated the stress condition for the present study.** The trauma-induced response predicted drinking at the end of treatment and at follow up.

- *These finding support the notion that reactivity to stress may increase the susceptibility for relapse.*
- *This study demonstrates that we have experience with this paradigm.*
- *It validates the ability of our research team to recruit individuals with AUD and PTSD.*

4. Significance:

To our knowledge, this study is the first to examine the ability of progesterone to reduce trauma or stress-induced craving in individuals diagnosed with a) comorbid AUD and PTSD and b) AUD only. Positive findings from this study will: 1) provide evidence that progesterone is important in mediating stress and alcohol craving, 2) provide insight into the underlying mechanisms of stress and alcohol craving, 3) help identify a potential marker that will distinguish who may be at

higher risk for alcohol relapse, and 4) provide a platform for other exploratory studies that can include the use of progesterone as treatment options for AUD and PTSD.

5. Research Plan:

Participants: Participants (N=72 completers) will be eligible for the study if they fullfill the following criteria:

Inclusion criteria:

a) men (n=36) and women (n=36) age 21 to 60;
b) have current diagnosis of *either*:
    1. AUD and comorbid PTSD
    OR
    2. AUD

    AUD will be determined by Structured Clinical Interview for DSM-5 (SCID-5) (First, Spitzer, Gibbon, & Williams, 2015). PTSD will be determined by Clinician Administered PTSD scale (CAPS-5)(Weathers et al., 2013) and by SCID-5);
c) drink regularly (determined by TLFB and recorded 90 days prior to the interview);
d) are not in an active phase of alcohol withdrawal;
e) are not at risk for suicide; if on medication, they must be on a stable dose for at least 2 weeks;
f) for women, have regular menses every 25-35 days.

Exclusion Criteria:

a) current SCID diagnosis of any psychotic disorder; substance use disorder (other than alcohol, nicotine, and marijuana) in the past 30 days;
b) current unstable medical condition; positive test results at more than one baseline appointment on urine drug screens conducted for opiates, cocaine, benzodiazepines, and barbiturates (marijuana is allowed);
c) for women, amenorrhea, use of oral contraceptives;
d) known allergy to progesterone or peanuts (vehicle for micronized progesterone);
e) history of thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, or history of stroke.

Methods: All participants will complete 1 test day. In order to control for gender differences in progesterone levels we will test women in the follicular phase of the menstrual cycle. This experiment is a between-subject design. Before the test day every participant will receive either progesterone (200 mg. bid) or placebo in identical looking capsules for three days. In previous studies with addicted individuals, this dosing schedule of progesterone attenuated stress-induced craving and improved cognitive function(Fox et al., 2013; Sofuoglu et al., 2011). On the fourth day they will attend the laboratory session. The study will consist of four phases. 1) We will first recruit participants, obtain informed consent, and evaluate eligibility for the study. 2) Following completion of intake assessments, participants will receive a full physical examination to further determine eligibility. 3) If eligible they will be randomized to start pre-treatment with either progesterone or placebo and scheduled for the laboratory session. 4) Follow-up: Participants will be contacted approximately 1 day after completing the stress lab to see how they are doing and to answer questions about their drinking.They will also be asked to come for one follow up session 1 month later to determine their drinking habits following the lab session. Initial Assessments: Participants will be interviewed with the SCID and CAPS for diagnostic evaluation. The TLFB(Sobell & Sobell, 1992) will be used to document the degree of daily alcohol consumption in the three months prior to study entry. Participants will have a psychiatric and medical examination by one of the investigators. Study data will be collected and managed using REDCap electronic data capture tools hosted at VA CT Healthcare System. REDCap

(Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (Harris et al 2009).

Screening and Baseline: Each participant will sign an informed consent. The study will be conducted with the approval of the VA Connecticut Human Subject Subcommittee. As part of the screening procedure detailed clinical assessment (to determine diagnosis), and medical assessments (physical exam, medical history, blood work and electrocardiogram) will be conducted. Those participants who fulfill all the inclusion and exclusion criteria will be enrolled in the study. On the first visit participants will be asked to come for a script development session. Also, women will be instructed to call the clinic when their menses starts and begin taking the study medication within the first 4 days of their menstrual cycle. The procedure is implemented in order to give some flexibility to female subjects and to ensure that they can finish the study during the early follicular phase (within the first seven days of the menstrual cycle).

Script Development Session: Scripts will be developed during a visit prior to the first laboratory session. Two scripts will be developed for each participant based on a procedure developed by our group. Participants with AUD and comorbid PTSD will develop one trauma related script and one neutral script. Participants with AUD only will develop one stress related script (since they have not experienced trauma) and one neutral script.

The trauma related scripts will be based on the "most traumatic" experience the participant could recall. The ***stress imagery script*** will be based on subjects' description of a recent personal stressful event (e.g. breakup with significant other, a verbal argument with a significant other or family member or unemployment-related stress, such as being fired or laid off from work). Subjects will be acclimated to the procedures, warned of the risks, and trained on relaxation techniques. The neutral script will be based on previously developed neutral scripts that will consist of a relaxed beach scene commonly experienced by most individuals but personalized for each participant. Any trauma, stressful, or neutral experience related to substance use will not be considered in order to avoid eliciting internal cues related to substance use. Individual scripts will be developed using scene construction questionnaires (Rajita Sinha & Tuit, 2012). In order to maximize the differences in stress reaction between conditions among those with AUD and PTSD we eliminated the stress imagery since trauma imagery elicited stronger stress reaction when compared to neutral (see preliminary data). The questionnaires elicit details regarding the event and individuals involved, including physical sensations, thoughts, emotions, and cues related to the event described. Each scene will be audiotaped for presentation during each laboratory session. Each tape will be 5 min. long.

Relaxation Technique: Subjects will be introduced to all self-report measures and instructed how to complete them. In order to minimize baseline imagery variability participant will be given relaxation and imagery training, as described in the imagery training procedures manual (Rajita Sinha & Tuit, 2012). Relaxation training will be approximately 10 minutes and will consist of progressive muscle relaxation technique. The imagery training will consist of two types of visualizations. First, participants will be asked to visualize an unemotional scene, such as reading a magazine. Second, they will be presented with an unemotional but physically arousing scene, such as exercising in a gym. Here, the emphasis will be placed on assuring that participants are aware of physiological changes, increased heart rate, or breathing. Subjects will be given instructions throughout the imagery exercises regarding the process of imagining the scenes and maintaining the visualization for an extended period of time.

Medication: All participants will be asked to take progesterone or placebo for three days leading up to the laboratory test day. They will be asked to take the first dose of medication

(progesterone or placebo) at night to minimize possible sedation from progesterone treatment. The following morning they will come to the clinic to take the second dose in the morning and will be given three additional doses (one to take at night the same day and two doses – morning and night for the following day). On the fourth day they will come in the morning for the laboratory session and will take one last dose in the lab. For women, the treatment will be initiated within the first 4 days of the menstrual cycle, day one being the first day of menses, and will be completed within the early follicular phase.

Laboratory sessions: Laboratory sessions will be conducted on the Biological Studies Unit at the West Haven VA with trained personnel, and a psychologist or MD will be on call during the laboratory session. Additionally, all participants will be cleared by a study doctor prior to leaving the lab at the end of the imagery session (see Table 1 for details). Participants will be asked to arrive around 10:00 am. On arrival there will be a urine and breath alcohol concentration (BrAC) check. If clear to start an IV line will be placed. Those who test positive for any substance (other than marijuana) will be discharged. Blood pressure and pulse will be monitored continuously. Subjective measures of craving for alcohol, anxiety, affect, and cognitive functioning will be administered shortly after the set up. Prior to the presentation of the 1st and 2nd tapes, the relaxation technique will be used. Two conditions will be administered in a counterbalanced order: Trauma/Stress script and Neutral script. Subjective measures of craving, anxiety, affect, and cognitive functioning will be presented:1) prior to presentation of the scripts, b) immediately after presentation of each script, and c) following a 5 minute recovery period. After the last recovery period and assessments subjects will be encouraged to use the relaxation techniques. Craving and emotional distress will be evaluated throughout the session and subjects must return to baseline levels prior to being discharged from the unit. Subjects will wear an ambulatory physiological monitor (APM) (Eqivital EQ02, Vivonoetics, San Diego, CA) that collects continuous ECG, respiration, and activity for 20 minutes while at quiet rest at baseline, and throuout the stress challenge procuedure. After completion of the scheduled portion of a session, any subject that reports residual craving or distress will participate in guided relaxation procedures with a clinically-trained psychologist for up to one additional hour. Relaxation has also been shown to reduce PTSD symptoms(Hamid & Neissi, 2009). If craving or emotional distress persists after an hour of relaxation training, the subject will receive an individual counseling session with a psychologist who is experienced in psychotherapy for PTSD. If craving or emotional distress persists after the psychotherapy session, the subject will be escorted to the Emergency Department and treated by the on-call psychiatrist.

Table 1. Summary of procedures and measures during the test day
(Note: all times are approximate)

Condition		Event	Measures		
	Time		Biochemical	Physiologic	Subjective
Baseline	10:00 am	Baseline measures Study medication administration	Urine, BrAC, Blood collection for: progesterone, ALLO, and estradiol (women)	HR/BP APM	SEQ, VASC, AUQ, VASA, STAI, DES-R, Stroop, TLFB
	11:30 am	Meal			
Tape 1	11:50 am	Relaxation period			
	12:00 pm	Measures before presentation of 1st tape		HR/BP APM	VASC, AUQ, VASA, STAI, DES-R, Stroo

	12:20 pm	Presentation of 1st tape		HR/BP APM	
	12:25 pm	Measures after 1st tape		HR/BP APM	VASC, AUQ, VASA, STAI, DES-R, Stroo
	12:45 pm	Recovery		HR/BP APM	
	12:50 pm	Measures after recovery		HR/BP APM	VASC, AUQ, VASA, STAI, DES-R, Stroo
	1:10 pm	5 minute break			
	1:15 pm	Relaxation period			
	1:25 pm	Measures before presentation of 2nd tape		HR/BP APM	VASC, AUQ, VASA, STAI, DES-R, Stroo
Tape 2	1:45 pm	Presentation of 2nd tape		HR/BP APM	
	1:50 pm	Measures after 2nd tape		HR/BP APM	VASC, AUQ, VASA, STAI, DES-R, Stroo
	2:10 pm	Recovery		HR/BP APM	
	2:15 pm	Measures after recovery	Blood ALLO	HR/BP APM	VASC, AUQ, VASA, STAI, DES-R, Stroo

Progesterone:

Progesterone, a natural hormone, is safe and well-tolerated by women. The safety, tolerability and efficacy of micronized progesterone is well established and it is FDA approved for hormone replacement therapy (HRT), absence of menstrual periods (amenorrhea), and infertility treatment. The recommended dose of progesterone for hormone replacement treatment is 200 to 400 mg/day, given as a single evening dose. After oral administration, micronized progesterone reaches its peak plasma levels in two to three hours and has an elimination half-life of three to four hours (McAuley *et al*, 1996). Because of its short half-life progesterone will be given twice daily to maintain stable plasma levels. Progesterone doses higher than 400 mg/day will not be used since they are more likely to cause sedation. The safety and tolerability of micronized progesterone are well established. Others have used micronized progesterone in several previous studies with male and female smokers and cocaine users (Sofuoglu *et al*, 2001; Sofuoglu *et al*, 2009; Sofuoglu *et al*, 2011). Progesterone was well-tolerated and there were no serious adverse events. The most common adverse effect is mild sedation. Other less common adverse effects include menstrual irregularity, spotting or breakthrough bleeding, dizziness, cramps, nausea, fatigue, headache, an allergic reaction, and breast tenderness. Other side effects attributed to synthetic progestin, including depression, fluid retention, pruritus, jaundice, rash and thrombotic disorders have not been observed with natural progesterone. Women will be warned to use caution when driving a motor vehicle or operating machinery while undergoing study treatment.

There is black-box warning for progesterone regarding the risk for cardiovascular disorders and breast cancer. The black box warning mentions the Women's Health Initiative (WHI) study in which treatment of postmenopausal women (50 to 79 years of age) with daily oral conjugated estrogens combined with medroxyprogesterone acetate (MPA), relative to placebo, reported increased risks of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction (Hammond, 2005). The pharmacological effects of MPA, a progestin, differ significantly from those of progesterone. MPA, but not progesterone, has well-characterized androgenic, glucocorticoid and anabolic effects and have been associated with unfavorable side effects including fluid retention, androgenic effects, alterations in lipid profile, increase risk for breast cancer (Fournier *et al*, 2008; Fournier *et al*, 2005), and cardiovascular events (Hermsmeyer *et al*, 2008). In contrast to MPA, progesterone is not known to cause these adverse events (Fournier *et al*, 2008; Fournier *et al*, 2005; Hermsmeyer *et al*, 2008). However, as a safety measure for these serious adverse events, we will exclude subjects with history of thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, or history of stroke, breast cancer or other cancers. Subjects will be

warned about these side effects and the physician will be alerted to the earliest manifestations of thrombotic disorders including thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis. If any of these occur or be suspected, the study medication will be discontinued immediately. In previous studies conducted in the VA CT Healthcare System, micronized progesterone was well tolerated by both male and female cigarette smokers and cocaine users. Subjects will complete a questionnaire to note any important side-effects using the Side Effects Questionnaire (SEQ) prior to randomization (baseline), at the medication visit, and prior to the start of the laboratory session.

Progesterone effects in men: In contrast to the cyclic changes in progesterone levels in normally menstruating women, men have steady levels of plasma progesterone. The physiological levels of plasma progesterone in men are similar to the follicular phase progesterone levels found in women (Zumoff et al., 1990).

In a number of previous studies, progesterone treatment has been given to men mainly for the treatment of hypertension, COPD, or benzodiazepine withdrawal (Dolly & Block, 1983; Friess, Tagaya, Trachsel, Holsboer, & Rupprecht, 1997; Gron, Friess, Herpers, & Rupprecht, 1997; Pinet, Tessonnier, Ravel, & Orehek, 2001; Rylance et al., 1985; Schweizer, Case, Garcia-Espana, Greenblatt, & Rickels, 1995; Tan, McFarlane, & Lipworth, 1997a; Zwillich, Natalino, Sutton, & Weil, 1978). The duration of progesterone treatment in these trials ranged from weeks to months with a daily dose ranging from 200 mg to over 1, 500 mg. In men, progesterone treatment has been well tolerated with sedation as the main side effect in higher doses (Schweizer et al., 1995).

Subjective Outcome Measures: Craving for alcohol will be assessed using a Visual Analogue Scale - Craving (VASC) and the Alcohol Urge Questionnaire (AUQ) (Bohn, Krahn, & Staehler, 1995). Participants will be asked to rate their degree of craving for alcohol, “how much do you crave alcohol at that particular moment”. On the VASC their responses can range from 0= “not at all”, to 10= “extremely high”. On the AUQ the responses will be measured on an unodimentional Likert-type scale. Anxiety will be assessed using a Visual Analogue Scale - Anxiety (VASA) and the State Trait Anxiety Inventory (STAI) (Julian, 2011). Participants will be asked to rate their level of anxiety, for example, how “anxious, tense and/or jittery” they feel at that particular moment. On the VASA their responses can range from 0= “not at all” to 10= “extremely high”. On the STAI their responses can range from 1 “not al all” to 4 “very much so”. Affect will be measured using the Differential Emotions Scale-Revised (DES-R)(Izard, 1972). Participants rate on a 5-point scale the extent to which each word describes how they feel at the present moment from 1= “not at all” to 5= “extremely”. *Cognitive Measures:* Stroop color/Ward Test (Golden, 1976). The Stroop test has been used to measure the ability to inhibit incongruent competing conflicts. The number of raw items read for each trial is recorded and converted to standardized T scores. The Timeline Follow-Back (TLFB) method(Sobell & Sobell, 1992) will be used to document the degree of daily alcohol consumption for 90 days at screening, at the laboratory session, and at the 1 month following the lab session.

Cardiovascular and Hormone Outcome Measures: Blood pressure and pulse will be assessed using an SD-700 monitor. To assure greater accuracy for the initial time points (baseline and time 0) four measures of blood pressure and pulse will be taken, and their average will constitute the single blood pressure and pulse measure. A single reading will be used for the other time points during testing. During the laboratory sessions we will also collect blood samples to examine the levels of allopregnanolone (ALLO) - the active metabolite of progesterone – and markers of inflammation to explore the relationship between these biomarkers and behavioral effects (urges for alcohol, anxiety, mood, cognitive functioning) of progesterone and alcohol. ECG RR intervals will be edited to remove artifact and ectopy using CarioEdit software. High and low frequency HRV will be calculated using CardioBatch software (Mind/Body Institute, U Ill Chicago).

Subject Payments: Participants will be paid $70 for screening and diagnostic evaluation, $80 for scripting, $25 for each medication visit (2), $250 for the laboratory session, and $50 for the follow up session. Therefore, participants could earn up to $500.

Power Analysis: Sample size estimates were determined using craving from our preliminary data. Assuming a large effect size for the within-subject comparison between progesterone and placebo (d'=0.50)(Cohen, 1988), α=.05 and two-sided test, we have 80% power to detect such an effect size as statistically significant with n=30 subjects. Assuming 20% dropout rate we need to recruit 36 subjects in order to have complete data on 30 subjects per group.

Method for data collection and analyses: Prior to performing statistical analyses, we will calculate descriptive statistics and will assess whether the distributions of all measures conform to normality. We will apply transformation or use nonparametric methods as necessary. We will estimate effect sizes in order to inform the design of potential future definitive studies. For the primary hypotheses we will use mixed effects models to assess change in stress reactivity after administration of progesterone vs. placebo. Study medication (progesterone and placebo), and gender will be a between subject factors, condition (trauma vs nutral) and time (pre, post and recovery following script presentation) will be used as within-subject factors. The primary stress reactivity variables will be craving. We will first compute descriptive statistics for each variable and will assess data distributions. All tests will be two-sided at 0.05 level of significance. We will use the Schwartz-Bayesian criterion (BIC) to select the best-fitting correlation structure within subject.

Study Duration: Two years**.**

6. References:

Allen, M. T., Boquet, A. J., Jr., & Shelley, K. S. (1991). Cluster analyses of cardiovascular responsivity to three laboratory stressors. *Psychosomatic Medicine, 53*(3), 272-288.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Klauminzer, G., Charney, D. S., & Keane, T. M. (1990). A clinician rating scale for assessing current and lifetime PTSD: The CAPS-1. *Behavior Therapy, 13*, 187-188.

Bohn, M. J., Krahn, D. D., & Staehler, B. A. (1995). Development and initial validation of a measure of drinking urges in abstinent alcoholics. *Alcoholism, Clinical and Experimental Research, 19*(3), 600-606.

Brady, K. T., Killeen, T., Saladin, M. E., Dansky, B., & Becker, S. (1994). Comorbid Substance-Abuse and Posttraumatic-Stress-Disorder - Characteristics of Women in Treatment. *American Journal on Addictions, 3*(2), 160-164.

Breese, G. R., Chu, K., Dayas, C. V., Funk, D., Knapp, D. J., Koob, G. F., . . . Weiss, F. (2005). Stress enhancement of craving during sobriety: a risk for relapse. *Alcoholism, Clinical and Experimental Research, 29*(2), 185-195.

Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1996). Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse, 23*(1), 39-51. doi: 10.1002/(SICI)1098-2396(199605)23:1<39::AID-SYN5>3.0.CO;2-I

Brinton, R. D., Thompson, R. F., Foy, M. R., Baudry, M., Wang, J., Finch, C. E., . . . Nilsen, J. (2008). Progesterone receptors: form and function in brain. *Frontiers in Neuroendocrinology, 29*(2), 313-339. doi: 10.1016/j.yfrne.2008.02.001

Brown, P. J., Stout, R. L., & Mueller, T. (1999). Substance use disorder and posttraumatic stress disorder comorbidity: Addiction and psychiatric treatment rates. *Psychology of Addictive Behaviors, 13*(2), 115-122. doi: Doi 10.1037//0893-164x.13.2.115

Buffet, N. C., Djakoure, C., Maitre, S. C., & Bouchard, P. (1998). Regulation of the human menstrual cycle. *Frontiers in Neuroendocrinology, 19*(3), 151-186. doi: DOI 10.1006/frne.1998.0167

Calhoun, P. S., Dennis, M. F., & Beckham, J. C. (2007). Emotional reactivity to trauma stimuli and duration of past smoking cessation attempts in smokers with posttraumatic stress disorder. *Experimental and Clinical Psychopharmacology, 15*(3), 256-263. doi: 10.1037/1064-1297.15.3.256

Chaplin, T. M., Hong, K., Bergquist, K., & Sinha, R. (2008). Gender differences in response to emotional stress: an assessment across subjective, behavioral, and physiological domains and relations to alcohol craving. *Alcoholism, Clinical and Experimental Research, 32*(7), 1242-1250. doi: 10.1111/j.1530-0277.2008.00679.x

Chaplin, T. M., Hong, K., Fox, H. C., Siedlarz, K. M., Bergquist, K., & Sinha, R. (2010). Behavioral arousal in response to stress and drug cue in alcohol and cocained addicted individuals versus healthy controls. *Hum Psychopharmacol Clin Exp, 25*, 368 - 376.

Chesnoy-Marchais, D. (2009). Progesterone and allopregnanolone enhance the miniature synaptic release of glycine in the rat hypoglossal nucleus. *European Journal of Neuroscience, 30*(11), 2100-2111. doi: 10.1111/j.1460-9568.2009.07013.x

Childress, A. R., Ehrman, R., McLellan, A. T., MacRae, J., Natale, M., & O'Brien, C. P. (1994). Can induced moods trigger drug-related responses in opiate abuse patients? *Journal of Substance Abuse Treatment, 11*(1), 17-23.

Coffey, S. F., Saladin, M. E., Drobes, D. J., Brady, K. T., Dansky, B. S., & Kilpatrick, D. G. (2002). Trauma and substance cue reactivity in individuals with comorbid posttraumatic stress disorder and cocaine or alcohol dependence. *Drug and Alcohol Dependence, 65*(2), 115-127.

Coffey, S. F., Stasiewicz, P. R., Hughes, P. M., & Brimo, M. L. (2006). Trauma-focused imaginal exposure for individuals with comorbid posttraumatic stress disorder and alcohol dependence: revealing mechanisms of alcohol craving in a cue reactivity paradigm. *Psychology of Addictive Behaviors, 20*(4), 425-435. doi: 10.1037/0893-164X.20.4.425

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (second ed.). Hillsdale, NJ: Lawrence Earlbaum Assoc.

Cooney, N. L., Litt, M. D., Morse, P. A., Bauer, L. O., & Gaupp, L. (1997). Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. *Journal of Abnormal Psychology, 106*(2), 243-250.

Cottler, L. B., Compton, W. M., 3rd, Mager, D., Spitznagel, E. L., & Janca, A. (1992). Posttraumatic stress disorder among substance users from the general population.[see comment]. *American Journal of Psychiatry, 149*(5), 664-670.

Dar, D. E., & Zinder, O. (1997). Short term effect of steroids on catecholamine secretion from bovine adrenal medulla chromaffin cells. *Neuropharmacology, 36*(11-12), 1783-1788. doi: Doi 10.1016/S0028-3908(97)00150-0

Dembo, R., Dertke, M., Borders, S., Washburn, M., & Schmeidler, J. (1988). The Relationship between Physical and Sexual Abuse and Tobacco, Alcohol, and Illicit Drug-Use among Youths in a Juvenile Detention Center. *International Journal of the Addictions, 23*(4), 351-378.

Dolly, F. R., & Block, A. J. (1983). Medroxyprogesterone acetate and COPD. Effect on breathing and oxygenation in sleeping and awake patients. *Chest, 84*(4), 394-398.

Enoch, M. A. (2011). The role of early life stress as a predictor for alcohol and drug dependence. *Psychopharmacology (Berl), 214*(1), 17-31. doi: 10.1007/s00213-010-1916-6

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2015). Structured Clinical Interview for DSM-5 Disorders, Clinician Version. Arlington, VA.: American Psychaitric Association.

Foa, E. B., & Williams, M. T. (2010). Methodology of a randomized double-blind clinical trial for comorbid posttraumatic stress disorder and alcohol dependence. *Ment Health Subst Use, 3*(2), 131-147. doi: 10.1080/17523281003738661

Fox, H. C., Sofuoglu, M., Morgan, P. T., Tuit, K. L., & Sinha, R. (2013). The effects of exogenous progesterone on drug craving and stress arousal in cocaine dependence: impact of gender and cue type. *Psychoneuroendocrinology, 38*(9), 1532-1544. doi: 10.1016/j.psyneuen.2012.12.022

Friess, E., Tagaya, H., Trachsel, L., Holsboer, F., & Rupprecht, R. (1997). Progesterone-induced changes in sleep in male subjects. *Am J Physiol, 272*(5 Pt 1), E885-891.

Golden, C.J. (1976). Identification of brain disorders by the Stroop Color and Word Test. *Journal of Clinical Psychology*, 32, 654-658

Grant, B. F., Dawson, D. A., Stinson, F. S., Chou, S. P., Dufour, M. C., & Pickering, R. P. (2004). The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug and Alcohol Dependence, 74*(3), 223-234. doi: 10.1016/j.drugalcdep.2004.02.004

Gron, G., Friess, E., Herpers, M., & Rupprecht, R. (1997). Assessment of cognitive performance after progesterone administration in healthy male volunteers. *Neuropsychobiology, 35*(3), 147-151.

Hamid, N., & Neissi, A. (2009). Comparing the effects of three relaxation methods on treatment of PTSD in Iran-Iraq war veterans. *Journal Of Education And Psychology, 3*(2), 1 - 12.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data

capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42:377-381

Harrison, P. A., Fulkerson, J. A., & Beebe, T. J. (1997). Multiple substance use among adolescent physical and sexual abuse victims. *Child Abuse and Neglect, 21*(6), 529-539. doi: Doi 10.1016/S0145-2134(97)00013-6

Harwood, H. (1998). 10th Special Repot to the US Congress on Alcohol and Health: US Department of Health and Human Services.

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood.[see comment]. *JAMA, 284*(5), 592-597.

Helzer, J. E., Robins, L. N., & McEvoy, L. (1987). Post-traumatic stress disorder in the general population. Findings of the epidemiologic catchment area survey. *New England Journal of Medicine, 317*(26), 1630-1634. doi: 10.1056/NEJM198712243172604

Institute, U. o. M.-C. a. T. S. (2013). Progesterone and Atomoxetine for Cocaine Cessation. *ClinicalTrials.gov*. doi: NCT01741376

Izard, C. E. (1972). *Patterns of emotions: a new analysis of anxiety and depression*: Academic Press.

Jacobson, I. G., Ryan, M. A., Hooper, T. I., Smith, T. C., Amoroso, P. J., Boyko, E. J., . . . Bell, N. S. (2008). Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA, 300*(6), 663-675. doi: 10.1001/jama.300.6.663

Johnson, S. D. (2008). Substance use, post-traumatic stress disorder and violence. *Curr Opin Psychiatry, 21*, 242 - 246.

Julian, L. J. (2011). Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken), 63 Suppl 11*, S467-472. doi: 10.1002/acr.20561

Justice, A. J., & De Wit, H. (2000). Acute effects of d-amphetamine during the early and late follicular phases of the menstrual cycle in women. *Pharmacology, Biochemistry and Behavior, 66*(3), 509-515.

Kajantie, E., & Phillips, D. I. (2006). The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology, 31*(2), 151-178. doi: 10.1016/j.psyneuen.2005.07.002

Kaplan, H. B., Martin, S. S., Johnson, R. J., & Robbins, C. A. (1986). Escalation of Marijuana Use - Application of a General-Theory of Deviant-Behavior. *Journal of Health and Social Behavior, 27*(1), 44-61. doi: Doi 10.2307/2136502

Keane, T. M., & Kaloupek, D. G. (1997). Comorbid psychiatric disorders in PTSD. Implications for research. *Ann N Y Acad Sci, 821*, 24-34.

Kessler, R. C., Crum, R. M., Warner, L. A., Nelson, C. B., Schulenberg, J., & Anthony, J. C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry, 54*(4), 313-321.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry, 51*(1), 8-19.

Kulka, R. A., Schlenger, W. E., Fairbank, J. A., Hough, R. L., Jordan, B. K., Marmar, C. R., & Weiss, D. S. (1990). Trauma and the Vietnam war generation: Report of findings from the national vietnam veterans readjustment study. In Brunner/Mazel (Ed.). New York.

Lemieux, A. M., & Coe, C. L. (1995). Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. *Psychosomatic Medicine, 57*(2), 105-115.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews: Neuroscience, 10*(6), 434-445. doi: 10.1038/nrn2639

Meisler, A. W. (1996). *PTSD and substance abuse in Vietnam*. Paper presented at the International Society Of Traumatic Stress Studies, San Francisco, CA.

Murphy, B. E. P., & Allison, C. M. (2000). Determination of progesterone and some of its neuroactive ring A-reduced metabolites in human serum. *Journal of Steroid Biochemistry and Molecular Biology, 74*(3), 137-142.

Ouimette, P. C., Finney, J. W., & Moos, R. H. (1999). Two-year posttreatment functioning and coping of substance abuse patients with posttraumatic stress disorder. *Psychology of Addictive Behaviors, 13*(2), 105-114. doi: Doi 10.1037//0893-164x.13.2.105

Pinet, C., Tessonnier, F., Ravel, T., & Orehek, J. (2001). Association of oral almitrine and medroxyprogesterone acetate: effect on arterial blood gases in chronic obstructive pulmonary disease. *Respir Med, 95*(7), 602-605.

Read, J. P., Brown, P. J., & Kahler, C. W. (2004). Substance use and posttraumatic stress disorders: Symptom interplay and effects on outcome. *Addictive Behaviors, 29*(8), 1665-1672. doi: DOI 10.1016/j.addbeh.2004.02.061

Resnick, H. S., Kilpatrick, D. G., Dansky, B. S., Saunders, B. E., & Best, C. L. (1993). Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *Journal of Consulting and Clinical Psychology, 61*(6), 984-991.

Reynolds, M., Mezey, G., Chapman, M., Wheeler, M., Drummond, C., & Baldacchino, A. (2005). Co-morbid post-traumatic stress disorder in a substance misusing clinical population. *Drug and Alcohol Dependence, 77*(3), 251-258. doi: 10.1016/j.drugalcdep.2004.08.017

Rylance, P. B., Brincat, M., Lafferty, K., De Trafford, J. C., Brincat, S., Parsons, V., & Studd, J. W. (1985). Natural progesterone and antihypertensive action. *Br Med J (Clin Res Ed), 290*(6461), 13-14.

Schweizer, E., Case, W. G., Garcia-Espana, F., Greenblatt, D. J., & Rickels, K. (1995). Progesterone co-administration in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and taper outcome. *Psychopharmacology (Berl), 117*(4), 424-429.

Sinha, R. (2009). Modeling stress and drug craving in the laboratory: implications for addiction treatment development. *Addiction Biology, 14*(1), 84-98. doi: 10.1111/j.1369-1600.2008.00134.x

Sinha, R., Fox, H., Hong, K. I., Sofuoglu, M., Morgan, P. T., & Bergquist, K. T. (2007). Sex steroid hormones, stress response, and drug craving in cocaine-dependent women: implications for relapse susceptibility. *Experimental and Clinical Psychopharmacology, 15*(5), 445-452. doi: 10.1037/1064-1297.15.5.445

Sinha, R., Fox, H. C., Hong, K. A., Bergquist, K., Bhagwagar, Z., & Siedlarz, K. M. (2009). Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. *Neuropsychopharmacology, 34*(5), 1198-1208. doi: 10.1038/npp.2008.78

Sinha, R., Garcia, M., Kemp, K., Krystal, J. H., & O'Malley, S. S. (2005). Alcohol craving and subjective emotional state during stress and alcohol cue exposure in alcoholics and social drinkers. *Alcoholism: Clinical & Experimental Research, 29*(5), 150A.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M. J., & Rounsaville, B. J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry, 63*(3), 324-331. doi: 10.1001/archpsyc.63.3.324

Sinha, R., Kimmerling, A., Doebrick, C., & Kosten, T. R. (2007). Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. *Psychopharmacology (Berl), 190*(4), 569-574. doi: 10.1007/s00213-006-0640-8

Sinha, R., Robinson, J., & O'Malley, S. (1998). Stress response dampening: effects of gender and family history of alcoholism and anxiety disorders. *Psychopharmacology (Berl), 137*(4), 311-320.

Sinha, R., & Rounsaville, B. J. (2002). Sex differences in depressed substance abusers. *J Clin Psychiatry, 63*(7), 616-627.

Sinha, R., & Tuit, K. (2012). *Imagery Script Development Procedures Manual*: CreateSpace.

Smith-Hoerter, K., Stasiewicz, P. R., & Bradizza, C. M. (2004). Subjective reactions to alcohol cue exposure: a qualitative analysis of patients' self-reports. *Psychology of Addictive Behaviors, 18*(4), 402-406. doi: 10.1037/0893-164X.18.4.402

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In R. Z. Litten & J. Allen (Eds.), *Measuring Alcohol Consumption: Psychosoical And Biological Methods* (pp. 41-72). Totowa, NJ: Humana Press.

Sofuoglu, M., Babb, D. A., & Hatsukami, D. K. (2001). Progesterone treatment during the early follicular phase of the menstrual cycle: effects on smoking behavior in women. *Pharmacology, Biochemistry and Behavior, 69*(1-2), 299-304.

Sofuoglu, M., Babb, D. A., & Hatsukami, D. K. (2002). Effects of progesterone treatment on smoked cocaine response in women. *Pharmacology, Biochemistry and Behavior, 72*(1-2), 431-435.

Sofuoglu, M., Mouratidis, M., & Mooney, M. (2011). Progesterone improves cognitive performance and attenuates smoking urges in abstinent smokers. *Psychoneuroendocrinology, 36*(1), 123-132. doi: 10.1016/j.psyneuen.2010.07.005

Stasiewicz, P. R., Gulliver, S. B., Bradizza, C. M., Rohsenow, D. J., Torrisi, R., & Monti, P. M. (1997). Exposure to negative emotional cues and alcohol cue reactivity with alcoholics: a preliminary investigation. *Behaviour Research and Therapy, 35*(12), 1143-1149.

Tan, K. S., McFarlane, L. C., & Lipworth, B. J. (1997a). Effect of exogenous female sex-steroid hormones on beta 2-adrenoceptors in healthy males. *Eur J Clin Pharmacol, 52*(4), 281-283.

Tan, K. S., McFarlane, L. C., & Lipworth, B. J. (1997b). Paradoxical down-regulation and desensitization of beta2-adrenoceptors by exogenous progesterone in female asthmatics. *Chest, 111*(4), 847-851.

Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry, 60*(7), 671-676. doi: 10.1016/j.biopsych.2006.04.019

Van der Kolk, B. (2004). Psychobiology of posttraumatic stress disorder. In J. Panksepp (Ed.), *Textbook Of Biological Psychiatry* (pp. 319-344). New York: Wiley-Liss.

Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G, Marx, B.P., & Keane, T.M. (2013). *The Clinician Administered PTSD Scale for DSM-5 (CAPS-5)*. Interview available from the National Center for PTSD at www.ptsd.va.gov.

Widom, C. S., Weiler, B. L., & Cottler, L. B. (1999). Childhood victimization and drug abuse: a comparison of prospective and retrospective findings. *Journal of Consulting and Clinical Psychology, 67*(6), 867-880.

Wills, T. A., McNamara, G., Vaccaro, D., & Hirky, A. E. (1996). Escalated substance use: A longitudinal grouping analysis from early to middle adolescence. *Journal of Abnormal Psychology, 105*(2), 166-180. doi: Doi 10.1037/0021-843x.105.2.166

Yehuda, R. (1998). Psychoneuroendocrinology of post-traumatic stress disorder. *Psychiatric Clinics of North America, 21*(2), 359-379.
Yehuda, R. (2009). *Post-Traumatic Stress Disorder: Basic Science and Clinical Practice* (1 ed.). New York (NY): Humana Press.
Zahn-Waxler, C. (2000). The development of empathy, guilt, and internalization of distress: Implications for gender differences in internalizing and externalizing problems. *Anxiety, Depression, and Emotion*, 222-265.
Zumoff, B., Miller, L., Levin, J., Levit, C. D., Miller, E. H., Heinz, U., . . . Rosenfeld, R. S. (1990). Follicular-phase serum progesterone levels of nonsmoking women do not differ from the levels of nonsmoking men. *Steroids, 55*(12), 557-559.
Zwillich, C. W., Natalino, M. R., Sutton, F. D., & Weil, J. V. (1978). Effects of progesterone on chemosensitivity in normal men. *J Lab Clin Med, 92*(2), 262-269.