THE GENDER-SEX HORMONE INTERFACE WITH CRAVING & STRESS-RELATED CHANGES IN SMOKING

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SPECIFIC AIMS

Despite considerable advances in treatment development, cigarette smoking remains the leading cause of preventable death in the United States, and most smokers engaged in treatment are unsuccessful in quitting. The burden of illness is disproportionately borne by female smokers, who are less responsive to cessation interventions than males. The relationships between stress, craving, and smoking behavior are recognized as key factors underlying gender differences in nicotine dependence, but must be better understood and characterized to yield avenues for interventions addressing this critical health disparity.

In prior and ongoing SCOR studies, our research team has demonstrated gender and menstrual cycle/sex hormone influences on reactivity to laboratory-presented cues. Building from these laboratory findings, we propose taking two important next steps: (1) evaluating the experience of craving in the "real world" natural environment of female and male smokers, and (2) examining the impact of a safe and novel pharmacological intervention (oxytocin) on stress reactivity in female and male smokers.

During a 2-week period, participants will use the newly developed and validated Cue Reactivity Ecological Momentary Assessment (**CREMA**) software implemented on a widely available personal digital assistant (iPhone) to provide real-time responses to stressful, smoking-related, and neutral picture cues presented multiple times daily in their natural environment. Additionally, daily saliva samples will be used to determine sex hormone (estradiol, progesterone, and testosterone) levels. These procedures will provide an unprecedented opportunity to prospectively and continuously evaluate dynamic sex hormone influences on cue-responsive craving in the "real world" natural environment of smokers.

Following the two weeks of CREMA data collection, a laboratory session will be conducted to investigate responses to acute dosing of oxytocin (versus placebo) in context of controlled evaluation of stress reactivity and smoking behavior. Prior to the session, participants will abstain from smoking for 12 hours and provide a salivary sample for measurement of stress and sex hormone (cortisol, estradiol, progesterone, and testosterone) levels. Participants will receive a double blind intranasal dose of oxytocin or placebo and will then be exposed to the Trier Social Stress Test (**TSST**). Measures collected at multiple time points during the laboratory session will include subjective craving, stress, and negative emotion as well as heart rate, blood pressure, skin conductance, and cortisol. Immediately following the TSST, participants will complete a smoking resistance task (**SRT**) in which they will receive a monetary reward for every 5-min period they can resist smoking. After completing the SRT, participants will be allowed to smoke freely during a one-hour ad libitum smoking period (**ASP**), with smoking topography assessed via a portable device.

Aim 1: Evaluate gender and sex hormone influences on reactivity to stressful and smoking-related cues presented, via CREMA, in the natural environment of smokers.

Hypothesis 1: Female smokers will be more reactive (craving ratings) than male smokers to stressful and smoking-related cues presented in the natural environment.

Hypothesis 2: Among female smokers, estrogen to progesterone ratio will be positively related to reactivity (craving ratings) to stressful and smoking-related cues presented in the natural environment.

Aim 2: Evaluate gender, sex hormone, and oxytocin administration influences on stress, craving, and smoking behavior response to a laboratory-based stressor task (TSST).

Hypothesis 1: Female smokers will evidence greater subjective stress, craving, and smoking behavior (e.g., shorter latency to smoke during the SRT and greater number of puffs during the ASP), but less neuroendocrine reactivity (cortisol), to the TSST than male smokers.

Hypothesis 2: Oxytocin, relative to placebo, will attenuate subjective stress, craving, and neuroendocrine responses to the TSST.

Hypothesis 3: Among female smokers, estrogen to progesterone ratio will be positively related to craving reactivity during the TSST.

If, as hypothesized, gender, sex hormones, and oxytocin administration influence the relationships between stress, craving, and smoking behavior, the findings could substantially address a key gender-related health disparity. Such knowledge could also inform the development of gender-specific interventions to enhance female

smokers' response to cessation treatments. Therefore, the knowledge to be gained from the proposed study may yield significant public health benefits.

RESEARCH STRATEGY

A. SIGNIFICANCE

Smoking occurs in approximately 21% of the US population, is responsible for an annual mortality rate of approximately 438,000 citizens, and has an associated healthcare economic burden of $167 billion . Although treatments have improved cessation outcome, the vast majority of individuals making quit attempts relapse within 5 to 10 days of cessation (Hughes, Keely, & Naud, 2004; Piasecki, 2006). The hypotheses to be examined in this proposal may have potentially important implications for the treatment of smoking and will, therefore, target the single greatest addiction-related public health problem.

Gender and Cessation Outcome: Epidemiological data (Giovino, 2002) indicate that smoking rates of both men and women have substantially declined from their peak levels in the 1960s but the rate of decline in women has been half that observed for men (25% vs. 50% rate reduction, respectively). Additionally, lower rates of cessation in women have been reported in studies of self-quitters (Fortmann & Killen, 1994; Husten et al., 1997; Ward, Klesges, Zbikowski, Bliss, & Garvey, 1997), smokers in large population-based treatment trials (Bjornson et al., 1995; COMMIT, 1995), and smokers in medication and nicotine replacement trials (Davis et al., 1994; Killen, Fortmann, Newman, & Varady, 1990; Perkins & Scott, 2008; Scharf & Shiffman, 2004; Wetter, Fiore, et al., 1999; Wetter, Kenford, et al., 1999). Thus, several studies of self-quitters and treatment-seekers echo the epidemiological data and collectively they suggest that women are less able to quit smoking than men, either alone or with the aid of treatment. Since the health and economic costs of smoking are so great, it is vital that the tobacco research community focus on the elucidation of factors that contribute to gender differences in cessation. Such efforts could inform the development of tailored interventions that strategically address gender-specific needs of smokers. The focus of this proposal will be to build upon our recent laboratory findings to (1) undertake the first prospective evaluation of gender and dynamic sex hormone influences on cue-responsive craving in the "real world" environment of smokers (i.e., outside the laboratory), and (2) evaluate the acute effects of a gender-relevant pharmacological intervention (oxytocin) targeting stress-induced craving and smoking behavior.

Conceptual Underpinnings of the Proposed Study: Smoking cessation is an important health outcome that is complex and multiply determined. Figure 1 depicts a conceptual model of several important causal variables that contribute to variation in smoking behavior, including cessation. The figure characterizes gender, and the sex hormones that impact gender, as a smoker attribute that provides the larger context for the operation of numerous other variables that determine cessation outcome but explicitly emphasizes the special significance of craving, stress, and sex hormones. The figure further suggests that these factors can operate both independently (non-overlapping portions of each Venn element) and collectively (overlapping portions of the Venn elements) to influence smoking behavior and the results of quit attempts. For example, cues associated with smoking can elicit craving to smoke independent of the effects of stress; however, it is well known that stress can elicit cravings (e.g., see Preliminary Studies, Section C1. below) that motivate smoking. Moreover, sex hormones (e.g., variation across the menstrual cycle) influence the experience of both stress and craving to smoke (Ferree, Kamat, & Cahill, 2011; Gray et al., 2010). The unfilled space in the gender sphere acknowledges that numerous other variables influence cessation outcome (e.g., variation in responsiveness to social support, Murray, et al., 1995; personality and demographic factors, Gilbert, 1995, etc.), while at the same time clearly establishing the importance of craving, stress, and gender/sex hormones. The proposed study is specifically designed to examine associations among these potentially important contributory causes of variation in cessation outcome.

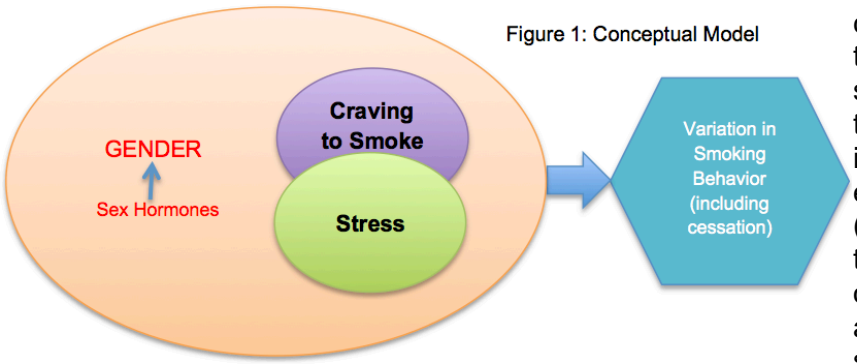


Figure 1: Conceptual Model

Interface between Craving, Stress, and Smoking, and the Importance of "Real World" Methodology: Recent research has led to a richer conceptualization of craving as a multidimensional response that is elicited by a variety of stimuli and or experiences; as noted above, craving is often elicited by stimuli (sight and smell of cigarettes) that have a prior history of being paired with nicotine ingestion. Craving is also elicited by stress-

inducing stimuli and/or situations, as has been demonstrated in several studies (Buchmann et al., 2010; Maude-Griffin & Tiffany, 1996; R. S. Niaura, Shadel, Britt, & Abrams, 2002; Payne, Schare, Levis, & Colletti, 1991; Perkins & Grobe, 1992; Tiffany & Drobes, 1990). To date, however, nearly all cue reactivity assessment has occurred in the laboratory, a "sterile" setting that, while providing experimental control, lacks the rich context of smokers' day-to-day natural environment. If cue-elicited craving has a meaningful relationship to "real world" smoking behaviors and cessation outcomes, its investigation must be translated to that same "real world." We thus propose using novel methodology (Gass, Wray, Hawk, Mahoney, & Tiffany, 2011; Warthen & Tiffany, 2009a; Wray, Godleski, & Tiffany, in press) to undertake the first investigation of gender and sex hormone influences on cue-elicited craving in the natural environment of smokers.

Rigorous Stress-Reactive Smoking Laboratory Paradigm: While translation of gender/sex hormone/craving investigation to the natural environment of smokers is a key element of the proposal, we acknowledge the laboratory as the ideal setting for evaluation of acute pharmacological effects on reactivity. Of special relevance to the proposed work, a recent study by McKee and colleagues (McKee et al., 2011) employed a laboratory-based, personalized (imagery) stressor task to examine, in overnight deprived smokers, the effects of stress on (a) ability to resist smoking in exchange for monetary reward, and (b) subsequent smoking behavior as measured with a smoking topography device. They observed that stress decreased resistance to smoke, increased smoking intensity (e.g., number of puffs) and increased satisfaction and reward from smoking. Relatedly, our ongoing SCOR protocol has offered some initial insight into the association between sex hormone levels and (a) craving during a smoking cue reactivity assessment, and (b) topographical aspects of smoking behavior obtained during a 1-hour ad libitum smoking period (see Preliminary Studies, Section C1. below). These findings are consistent with a large body of research indicating that smokers perceive stress to be a major contributor to relapse episodes (Baer, Kamarck, Lichtenstein, & Ransom, 1989; Baer & Lichtenstein, 1988; Brandon, 1994; Brandon & Baker, 1991; Piper et al., 2004) and that quit rates are lower among smokers experiencing serious psychological distress (Hagman, Delnevo, Hrywna, & Williams, 2008; Sung, Prochaska, Ong, Shi, & Max, 2011). Collectively, these study findings suggest that stress may reduce resistance to smoking, potentially via augmented craving, and increase smoking behavior. The proposed study will employ a strategy similar to McKee et al but will employ the Trier Social Stressor Task (TSST) to provoke a stress response in overnight deprived smokers, providing the unprecedented opportunity to examine gender, sex hormone, and acute pharmacological effects on post-stressor measures of smoking behavior (i.e., resistance to smoke and smoking topography).

Evaluation of a Novel Candidate Pharmacotherapy: Oxytocin, a neuropeptide synthesized in the hypothalamus, plays a critical role in mating, childbirth, and lactation (Ludwig & Leng, 2006) and appears to have pro-social and anxiolytic effects (Francis, Young, Meaney, & Insel, 2002; Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005; Williams, Insel, Harbaugh, & Carter, 1994; Witt, Winslow, & Insel, 1992). Recent studies indicate that (a) oxytocin may be dysregulated in chronic substance dependence (Sivukhina, Dolzhikov, Morozov Iu, Jirikowski, & Grinevich, 2006), and (b) acute intranasal administration of oxytocin reduces subjective and neuroendocrine stress response (de Oliveira, Zuardi, Graeff, Queiroz, & Crippa, 2011; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), suggesting that administration of exogenous oxytocin may be a promising candidate intervention targeting stress-induced drug craving and drug self-administration. Pilot data obtained at our SCOR site (see Preliminary Studies, Section C1. below) revealed that cannabis dependent participants pre-treated with intranasal oxytocin exhibited reduced anxiety and cannabis craving in response to a laboratory stressor task (TSST), compared with those pre-treated with placebo. These findings, especially in light of oxytocin's well-established safety and tolerability, suggest that oxytocin is an ideal candidate for evaluation as an intervention targeting stress-induced craving and smoking behavior.

B. INNOVATION

One of the major innovative features of this protocol is the measurement approach that will be adopted. Until relatively recently, nearly all craving and cue reactivity data were collected in laboratory settings rather than in the "day-to-day" natural environments of smokers. However, Tiffany (Co-I on this application) and colleagues (Gass, et al., 2011; Warthen & Tiffany, 2009a; Wray, et al., in press) have developed a portable methodology, termed cue reactivity ecological momentary assessment or CREMA, which permits real-time cue reactivity assessment in the natural environment of smokers. This methodology, which was based on the ecological momentary assessment (EMA) procedures originally developed by Shiffman and colleagues (Shiffman et al., 2002; Shiffman et al., 1997; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Shiffman, Paty, Gwaltney, & Dang, 2004; Stone & Shiffman, 1992, 1994), utilizes a handheld personal digital assistant technology (PDA; Tungsten E2 by Palm, Inc.) to present pictures of smoking-related cues and smoking-unrelated (neutral) control cues to smokers at varied times during the day (see Preliminary Studies, Section C1. below for summary of published

findings). The CREMA technology developed by the co-investigator on this application (Stephen Tiffany, Ph.D.) is an effective methodology for assessing subjective cue-elicited craving and mood responses, across extended periods of time, in the natural environment of smokers. Accordingly, we propose to implement a refined version of the CREMA assessment methodology on the Apple iPhone platform and examine the impact of gender and sex hormones on craving and cue reactivity assessed in the natural environment.

A complementary longitudinal assessment strategy that will be employed in the present study is the collection of salivary samples for the purpose of determining daily levels of sex hormones in all participants. This "high-resolution" approach to characterizing reproductive hormone fluctuations is relatively rare in addictions research (Fox, Hong, Paliwal, Morgan, & Sinha, 2008; Fox, Wilker, Kreek, & Sinha, 2006) but is fairly commonly employed in other research domains (Chapman, McIntyre, Lipson, & Ellison, 2009; Edler, Lipson, & Keel, 2007; Gann, Giovanazzi, Van Horn, Branning, & Chatterton, 2001; Klump, Keel, Culbert, & Edler, 2008). The proposed study contains a plan to, for the first time, measure daily hormone levels and evaluate their relationship with (a) reactivity to stressful and smoking-related cues presented in the natural environment of smokers via CREMA procedures, and (b) stress-induced changes in smoking behavior assessed in a laboratory environment.

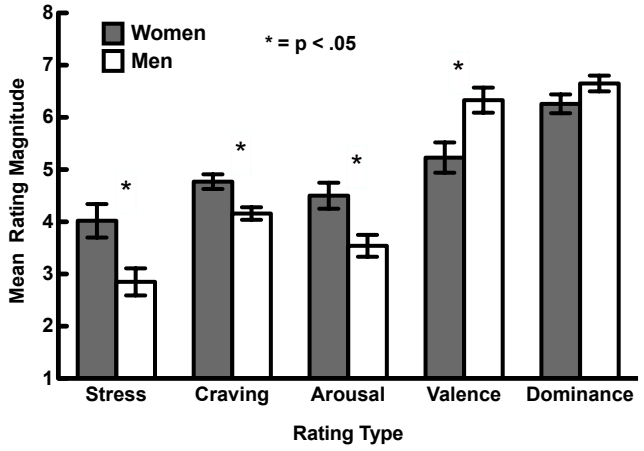
We additionally propose evaluating the acute effects of oxytocin, a safe and potentially promising pharmacotherapy, on stress-induced craving and smoking behavior in women and men within an innovative, rigorous laboratory paradigm. While oxytocin has been the subject of increasing interest in regard to social behaviors and anxiety, its investigation in the field of addictions, and specifically in nicotine dependence, is novel. The overall design of the study is especially novel in that it will integrate sophisticated laboratory procedures with naturalistic and/or longitudinal methodologies to exhaustively examine gender and sex hormone influences on smoking behaviors.

C. APPROACH

C1. Preliminary Studies

Relevant Gender Differences Experience. In one of our previous SCOR studies (Saladin et al., in press) we examined the effects of gender on craving and cue reactivity. We recruited female (n=37) and male (n=53) nicotine dependent smokers to participate in a multi-session laboratory study of craving and cue reactivity to smoking and stress/negative affect cues. The smoking cues consisted of a package of the participant's preferred brand of cigarettes, which (s)he held and manipulated for 90 sec. as instructed by research staff. The stressful/negative affect cues consisted of a detailed description of a recent life event that the participant perceived as emotionally negative and stressful. Neutral control cues for the smoking cues consisted of a similar guided manipulation of a pack of pencils and an eraser while a script of a neutral or relaxing event that the participant had recently experienced served as a control for the stressful/negative affect script. Following each cue presentation, participants provided subjective ratings of stress, craving, arousal (calm vs. aroused), valence (pleasant vs. unpleasant; lower ratings indicate more unpleasant) and dominance (feeling in control vs. feeling out-of-control/submissive; lower ratings indicate feeling more out-of-control/submissive). In addition to subjective measures, heart rate (HR) and skin conductance (SC) measures of physiological arousal were assessed at baseline and during each cue exposure. ANCOVAs were performed to assess gender differences in cue reactivity; covariates in the models were responses to neutral cues, FTND score (measure of nicotine dependence level) and order of cue presentation. Results of analyses performed on smoking cue data indicated that although women trended toward having greater stress, craving, arousal, and lower valence and dominance ratings than men, none of the differences reached significance (e.g., arousal difference, p = .09). Analyses of the HR/SC data indicated that (a) women trended towards greater heart rate than men (p = .05) but this effect was not cue specific (i.e., did not vary across smoking vs. neutral cue type), and (b) SC level was higher on smoking vs. neutral cue trials (p < .01) but this effect did not vary by gender. Figure 2 shows the stress, craving, arousal, valence and dominance ratings in response to the stressful/negative affect script. The figure clearly shows that women, relative to men, evidence greater stress, craving, arousal and negative emotion

Figure 2



(lower valence ratings) in response to the script cues. Overall, the findings of this and eight other studies (Colamussi, Bovbjerg, & Erblich, 2007; Field & Duka, 2004; Heishman, Lee, Taylor, & Singleton, 2010; Knott, Cosgrove, et al., 2008; Knott, Naccache, et al., 2008; R. Niaura et al., 1998; Rohsenow et al., 2007; Tong, Bovbjerg, & Erblich, 2007) reporting on gender differences in cue reactivity suggest two general conclusions: (1) the two studies examining gender differences in stress/negative affect cue reactivity have clearly demonstrated that women vs. men experience greater craving to smoke, higher arousal/stress and greater negative emotion in response to stress/negative affect cues, and (2) five of eight studies examining gender differences in reactivity to smoking cues found women to be more craving responsive. Thus, the available evidence appears to suggest that women tend to be more responsive to both cue types, albeit less definitively in the case of smoking cues. Of note, laboratory-measured neuroendocrine (e.g., cortisol) reactivity may not follow the same gender pattern, as prior studies suggest that men exhibit more cortisol reactivity to psychological stressors than women (Back et al., 2008; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kirschbaum, Wust, & Hellhammer, 1992; Kudielka & Kirschbaum, 2005), a finding that may be accentuated among smokers in light of gender-imbalanced dampening of neuroendocrine response over chronic nicotine administration (Back et al., 2008).

Relevant Experience Examining Menstrual Cycle/Ovarian Hormone Effects on Craving/Smoking Behavior. Our initial efforts to understand the role of sex hormones in smoking focused on menstrual cycle phase effects on smoking-related craving and cue reactivity (Gray, et al., 2010). In this study, female smokers (n=37) received a smoking cue reactivity assessment during each of four biologically verified phases of the menstrual cycle: early- and mid-follicular and mid- and late-luteal. Stimuli presented during the cue reactivity assessments were in vivo smoking cues, which consisted of manual handling of the participant's preferred brand of cigarettes, and scripted stressful/negative affect cues, which consisted of an personalized imagery script of a stressful event in the participants recent past. Control cues for the smoking and stress/negative affect cues consisted of the handling of pencils & eraser and a relaxing imagery script, respectively. Results indicated significant variation across the cycle, with craving to smoking cues elevated in the follicular phases, relative to the luteal phases ($p = .02$). Heart rate reactivity to stressful/negative affect cues ($p = .01$) and skin conductance reactivity to smoking cues ($p = .05$) varied across cycle phases as well, with maximum reactivity occurring during the mid-follicular phase. These findings, taken together, demonstrated elevated reactivity during at least part of the follicular phase, but it remained unclear what underlying ovarian hormone fluctuations might be contributory. While other studies (Sofuoglu, Babb, & Hatsukami, 2001; Sofuoglu, Mouratidis, & Mooney, 2011) have suggested that progesterone, which is present in higher levels during the luteal phase relative to the follicular phase, may have a protective effect against craving, it remained unclear whether progesterone effects may be static versus dynamic (i.e., related to absolute level at a given time point versus change in level over time), or whether estradiol might also contribute.

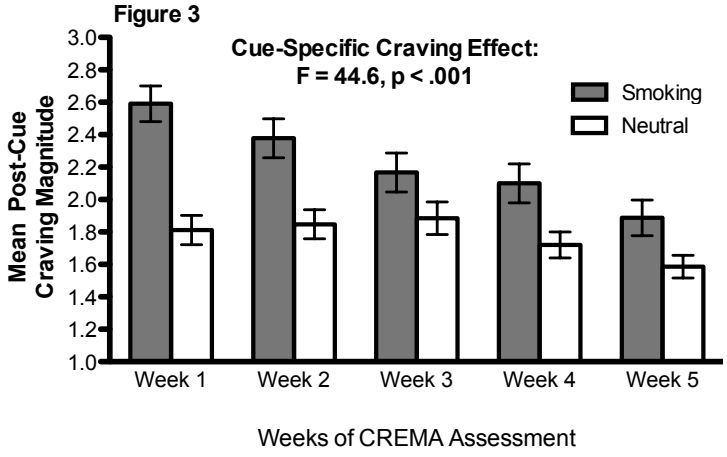
A goal of our ongoing SCOR study is to more directly investigate the relationship between ovarian hormones and smoking behavior. Within this study, we examined the predictive relationship between static and dynamic plasma levels of estradiol and progesterone and (a) craving elicited in a human laboratory cue reactivity procedure, and (b) smoking behavior during a subsequent 1-hour ad libitum smoking session. Briefly, 93 female smokers received an initial assessment to determine study eligibility, nicotine dependence severity, etc. Approximately one week later, participants were administered a standardized cue reactivity assessment where the Questionnaire of Smoking Urges–Brief (QSU-B) was used to measure craving prior to and after exposure to smoking-related cues (i.e., preferred brand of cigarette & lighter). An ad libitum smoking session followed, with measurement of smoking behavior via a topography device. Estradiol and progesterone levels were derived from plasma samples collected at the time of the initial assessment (T1) and the laboratory cue reactivity assessment (T2). The primary predictor variables were absolute levels of estradiol and progesterone at T2, % change in estradiol and progesterone between T2 and T1; primary craving reactivity outcomes were QSU-B factor and total scores (difference score = postcue - precue craving) and primary ad libitum smoking outcomes were number of puffs and weight of cigarettes smoked.

Cue reactivity analyses indicated that the ratio of estradiol to progesterone correlated positively ($p < .05$) with QSU craving. While not significant in magnitude within the preliminary sample, the direction of association was positive for estradiol (T2 level and % change between T1 and T2) and negative for progesterone measures (T2 level and % change between T1 and T2). Ad libitum smoking analyses revealed a similar pattern of findings. While directional trends existed in static and dynamic hormone associations with smoking variables, only the ratio of progesterone to estradiol significantly predicted number of puffs ($p < .01$) and weight of cigarettes ($p < .05$) smoked. These findings are among the first to suggest that the smoking behavior of women may be

influenced by the relationship between estradiol and progesterone rather than by the effects of progesterone alone, as suggested by at least two previous laboratory studies (Sofuoglu, et al., 2001; Sofuoglu, et al., 2011).

Absent from these and other human investigations of sex hormone effects on craving and smoking behavior is the role of testosterone in males. Testosterone levels vary temporally in men, and these variations are associated with behavioral changes (Kempenaers, Peters, & Foerster, 2008; Rowe et al., 1974; Stanton, Mullette-Gillman, & Huettel, 2011). Acute administration of testosterone decreases cocaine self-administration in rhesus monkeys, a parallel to the acute effects of progesterone administration (Mello, Knudson, Kelly, Fivel, & Mendelson, 2011). In the context of research involving gender and sex hormone effects on craving and smoking behavior, testosterone thus appears to be an important, albeit exploratory, variable for investigation. Since daily testosterone levels will be assessed in the male participants of this study, an opportunity will provided to explore, for the first time, the association between testosterone levels and (a) cue-elicited craving measured daily for two weeks in the natural environment, and (b) stress reactivity to the TSST and subsequent smoking behavior (as measured during the smoking resistance task and the ad libitum smoking period).

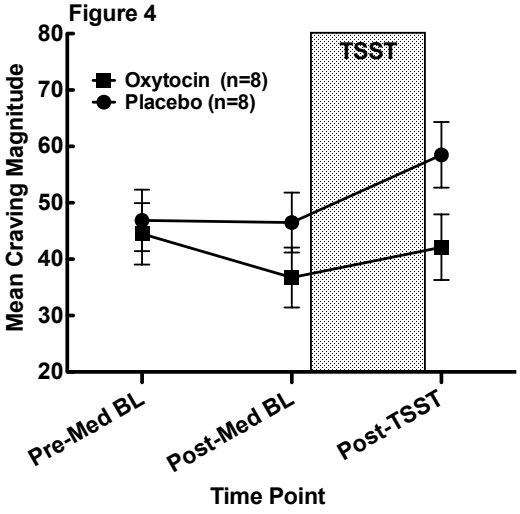
Relevant CREMA Experience. As noted above, Dr. Stephen Tiffany (Co-Investigator) and colleagues have developed a PDA-based technology (Palm Tungsten E2, Palm Inc.) called cue reactivity ecological momentary assessment or CREMA, which they have successfully used to administer experimental cue reactivity sessions in the natural settings of smokers and to gather real-time measurement of craving, mood, smoking behavior, temporal data and contextual variables. In the first of two published studies (Warthen & Tiffany, 2009a) using this technology, 43 non-treatment seeking, heavy smokers were trained to use PDAs that administered 4 cue reactivity (CR) sessions each day for 8 days. The daily CR session occurred randomly over the course of a 12-hour period (determined by the participant at the outset of the study) and consisted of one cue type from four categories: (1) smoking picture, (2) smoking imagery script, (3) neutral picture, and (4) neutral imagery script. Participants also provided data on the timing of their smoking during the course of the day. Additionally, laboratory-based CR sessions were performed with the PDA prior to and following the 8-day CREMA assessment period. Results indicated that the smoking pictures and smoking imagery cues elicited significantly greater craving, negative mood and lower positive mood than either of the corresponding neutral cues in both the CREMA sessions and the laboratory-based CR assessments. A second study by Tiffany and colleagues (Wray, et al., in press), which employed a similar 8-day CREMA assessment design, found smoking pictures to be more effective than in vivo smoking cues (i.e., handling a real cigarette) at eliciting cue specific craving and negative emotion. This observation held regardless of whether the picture and in vivo cues were presented in the participant's natural environment or in a laboratory setting. Finally, Figure 3 depicts smoking vs. neutral picture cue-elicited craving (error bars are SEM) from 60 treatment-seeking smokers who participated in a third study involving a 5-week CREMA assessment period that preceded a target quit date. Since one of the goals of this study was to determine whether varenicline dampened cue-elicited craving, half of the participants received varenicline during weeks 2, 3 & 4 and the other half received placebo (double-blinded). The figure shows that CREMA procedures can be used to assess cue-elicited craving over an extended period of time (effects sizes- partial eta^2 - ranged from .62 at week 1 to .19 at week 5). Collectively, these three CREMA studies indicate that (1) smoking picture cues presented on a PDA are equal to, or better than, both imagery and in vivo cues at eliciting craving and negative mood, (2) these differential cue reactivity effects are as (if not more) robust when measured in the natural environment vs. laboratory setting, (3) CREMA procedures can be used over extended periods of time to reliably measure cue specific craving, mood, smoking behavior, temporal data and contextual variables. Accordingly, **the proposed study will employ an enhanced version of CREMA methodology (implemented on the popular Apple iPhone platform) to measure cue-elicited craving, mood and other responses to stressful, smoking-related, and neutral picture cues**. These data, together with the sex hormone levels measured daily over the same two-week period will permit the assessment of the association between estradiol, progesterone and



testosterone and cue-elicited responses to smoking and neutral picture cues presented during the same two-week period.

Relevant Oxytocin Experience. Members of MUSC's SCOR research team (McRae, Brady) recently completed a pilot study examining the effects of intranasal oxytocin vs. placebo on the subjective craving and anxiety responses of marijuana-dependent individuals before and after administration of the Trier Social Stressor Task (TSST). Figure 4 depicts the mean craving responses of the oxytocin vs. placebo treated groups prior to receiving oxytocin/placebo (Pre-Med BL), after receiving oxytocin/placebo but prior to the TSST (Post-Med BL) and immediately following the TSST (Post-TSST). The data indicate that while the groups exhibited similar levels of craving prior to medication administration, oxytocin appears to have a dampening effect on craving both before ($p = .06$) and after ($p = .03$) the TSST is administered. Parallel finding were observed for subjective anxiety (not shown). Thus, these preliminary findings suggest that oxytocin may have potential as therapeutic adjunct for managing both basal and stress-elicited craving and anxiety in substance dependent individuals. The proposed project will employ a similar research strategy with nicotine dependent smoker to examine whether oxytocin (vs. placebo) (a) reduces stress and craving reactivity to the TSST, and (b) enhances smoking resistance and attenuates smoking behavior/topography. Since the sex hormone levels of a substantial number of male and female smokers will be quantified in the two-week period preceding the laboratory stress procedures, the proposed research design will permit an exploratory analysis of the association between sex hormone levels and oxytocin's impact on laboratory measures of stress reactivity/smoking behavior and also the interaction between medication condition and gender.

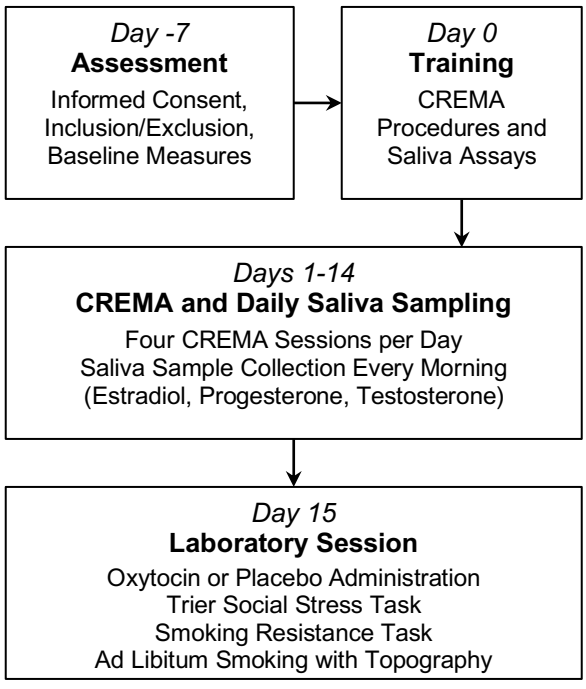
Figure 4



C2. Research Team

Dr. Saladin (PI) and Dr. Gray (Lead Co-I), have a long history of collaboration inclusive of their roles on the ongoing SCOR nicotine component study. They possess complementary skills critical to the completion of the proposed study, and have assembled and trained a research staff adept with the skills necessary for day-to-day study management. Dr. Saladin is a clinical psychologist with expertise in craving, cue reactivity, and the interface between stress and substance use disorders. Dr. Gray is a psychiatrist with expertise in assessment and clinical management of nicotine dependence. Dr. Tiffany, Co-I, is an internationally recognized addictions researcher with special interest in craving and cue reactivity in nicotine dependent smokers. He has conducted numerous NIH-funded laboratory studies with smokers and has published extensively on the relationship between craving, stress and negative emotion. His most recent work has examined smoking cue reactivity in the natural environment of smokers using picture cues administered via a hand-held PDA (referred to as cue reactivity ecological momentary assessment or CREMA), a critical component of the proposed study.

Figure 5



C3. Design and Methods

C3a. Overview.

The proposed project incorporates naturalistic and laboratory procedures to comprehensively evaluate gender and reproductive hormone effects on stress reactivity and smoking behavior (see Figure 5). Cue reactivity ecological momentary assessment (CREMA), involving the assessment of reactivity to stressful and smoking-related cues, will be conducted four times daily for two-weeks in the natural environment of female and male nicotine dependent smokers, while daily salivary sampling will be used to track changes in reproductive hormones (estradiol and progesterone in females and

testosterone in males). On the last day of the second week, following a 12-hour period of smoking abstinence, a laboratory session will be conducted. At the beginning of this session, participants will receive nasal administration of either oxytocin (OXY) or placebo (PBO) prior to the administration of the Trier Social Stress Test (TSST). Random assignment and double-blinding procedures will be employed to ensure that (a) each participant will have an equal probability of receiving OXY or PBO, (b) approximately half of the female and male smokers will receive OXY while the remaining half will receive PBO, and (c) neither the participant nor the research staff will know whether the participant received OXY or PBO. Established self-report, physiological, and laboratory measures of stress/cue reactivity will be administered at regular intervals prior to, during and following the TSST. To assess the acute effects of stress on smoking behavior, the TSST will be followed by a smoking resistance task (SRT) and an ad libitum smoking period (ASP) using smoking topography assessment technology.

We considered several potential alternative designs, including options that would involve only naturalistic or laboratory assessments/procedures (rather than both). The naturalistic (CREMA) approach holds appeal in terms of innovation, and allows for an analytically strategic pairing of cue reactivity and smoking behavior measurement (multiple sessions daily) with serial reproductive hormone measurement over the course of two weeks. The laboratory approach provides assessment of reactivity in a highly structured and controlled environment, and allows for detailed assessment of the acute effects of a standardized stressor on smoking behavior, as assessed with the SRT and ASP. It also permits the assessment of the effects of a very novel pharmacological agent, oxytocin, on stress reactivity and smoking behavior. Therefore, we concluded that the proposed design offers a mutually complementary integration of naturalistic and laboratory-based methodologies that balance internal and external validity and maximize the opportunity to comprehensively assess the role of gender and sex hormones in stress induced alterations in smoking behavior.

C3b. Participants and Recruitment.

A total of 250 smokers , between the ages of 18-45, will be recruited over a 51-month period. The oversampling of female participants was necessary to achieve adequate power to test hypotheses involving ovarian hormone measures. The sample size determination was based on statistical power necessary to test primary hypotheses as outlined in the Sample Size Determination, Section C3i, below.

Participants will be recruited from the general community through media advertising (radio, print, online and television). Advertisements will target smokers interested in participating in a study examining the relationship between stress and smoking. This media-based recruitment strategy has generated large numbers of participants for both cessation and non-cessation studies. To illustrate, we have an ongoing cessation study for women smokers that attracted 400 screening calls and netted 46 study enrollees over a 12-month recruitment period. Respondent-Driven Sampling (RDS) will also be used to enhance recruitment of the sample. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample “snowballs”. Each eligible participant who is randomized into the study, and agrees to take part in this recruitment assistance, will be given business cards to pass on to other potential participants. The business cards will have a unique code linked to the person who passes them out. A referral will be instructed to call the site offices for screening and, if eligible, an appointment for further evaluation. If a referral completes the screening process and is eligible for the study, the participant who referred the person can redeem the business card for $20.

Since the proposed study targets both female and male smokers who are not currently interested in quitting, we anticipate successfully recruiting at least 2-3 female and 1-2 male smokers per month using our aggressive recruitment strategies. This rate of recruitment will allow us to achieve our target sample over the 51-month recruitment period. Inclusion/exclusion criteria for the study are located in the Protection of Human Subjects section of this application.

C3c. Intake and Comprehensive Assessment.

Individuals interested in the study will receive a brief telephone screening to determine if they may be eligible to participate. They will then be scheduled for an initial assessment session, consisting of an informed consent procedure, followed by completion of medical history, physical exam, self-report questionnaires, and semi-structured interviews to determine study eligibility. If volunteers complete the informed consent process and are eligible for participation, they will be enrolled in the study. A comprehensive battery of instruments will be administered to characterize participants’ smoking, stressor exposure history (past and current), and general psychiatric functioning (see Instruments/Measures, Section C3g.). The research team will use several methods of contact to keep in touch with participants. We will ask them to provide us with phone numbers, e-mail

addresses, current home and work addresses, and contact information of family and friends who may know how best to reach them. We will also have a Facebook account that we may use to contact participants. The research team will only use private messages to contact participants through Facebook

We considered incorporating luteinizing hormone home testing kits to randomize female participants to start study procedures at the outset of the follicular or luteal menstrual cycle phase, but opted not to for multiple reasons. First, we noted in our initial SCOR study that the associated lag in initiation of study procedures for some women was associated with relatively high dropout rates. Additionally, the proposed study will enroll both men and women and we wanted to avoid using any menstrual phasing procedures that would result in substantially different treatment of male and female participants (i.e., long delays before the occurrence of study procedures for some females but no delays for other females and all males). Second, we noted in our subsequent SCOR study that enrolling a similarly sized sample of women resulted in an even distribution of enrollees across the menstrual cycle (while also resulting in improved participant retention rates). We also felt it important to progress from a "follicular versus luteal" phase approach to a continuous measurement approach involving the direct assessment of hormone levels. Therefore, we elected to use a participant enrollment approach that will allow women to enroll at any time/stage of the menstrual cycle.

C3d. Training Procedures.

Enrolled participants will return for a training visit, during which they will gain mastery of saliva sample collection and storage, personal digital assistant (PDA; iPhone) operation, and CREMA procedures.

C3e. Natural Environment Procedures.

CREMA Assessment. Participants will carry a PDA for two weeks (Days 1-14). They will be instructed to keep the PDA with them at all times. Auditory alarms will alert participants to complete four, randomly scheduled cue-reactivity/CREMA sessions per day (session duration = 3-4 min.). Alarms will be distributed over a 12-hour period, divided into four, 3-hr blocks with a minimum time of 30 minutes between alarms/CREMA sessions. Each CREMA session will contain two trials and each trial will consist of one picture cue presentation. There will be three types of picture cues that differ based on content: stressful (e.g., stress-inducing images from the standardized International Affective Picture System [IAPS; Libkuman et al., 2007; Rehme et al., 2009]), smoking (e.g., lit cigarettes, people smoking, etc.) and neutral (e.g., pencils, scissors, etc.). Thus, each of the four daily CREMA sessions will contain two picture cues from one or a combination of these three categories.

At the start of each CREMA session, participants will be asked to finish their cigarette if they were smoking, then provide craving and mood ratings, and answer questions about distractibility, etc. (see Section C3g. Instruments/Measures). Next, a photograph will be presented and the participant will be instructed to look at it carefully. Each picture cue will appear only once during the study. An alarm will sound at the end of each trial, after which participants will complete a post-cue assessment consisting of the Craving Questionnaire, mood items, and ratings of how carefully they looked at the photograph and their distraction level during each trial. CREMA sessions will present the pictures for 10 seconds.

Participants will be prompted for four CREMA sessions per day on Days 1-14, and will thus complete a maximum of 56 CREMA sessions. To encourage CREMA session completion, participants will be compensated $1.25 for each completed session (see Participant Compensation, Section C3h). Previous studies employing this incentive strategy have reported 90% CREMA completion rates (Gass, et al., 2011; Warthen & Tiffany, 2009a; Wray, et al., in press).

Saliva Sample Collection. Participants will, via established procedures reviewed during the training visit, collect saliva samples a half hour after awakening. Samples will be dispensed into containers supplied by study staff, and stored in participants' home freezers until bringing the samples to a subsequent study visit. The laboratory will analyze samples for levels of estradiol & progesterone (females only) and testosterone (males only). These daily home collection and storage procedures have been used in numerous previous studies with excellent participant adherence and sample quality (Edler, et al., 2007; Klump, et al., 2008).

C3f. Laboratory Procedures.

An overview of the laboratory session procedures is presented in the Laboratory Procedure Timeline table. Participants will receive the following instructions to prepare for their laboratory session: they are to 1) abstain from smoking for 12 hours; generally, this will mean not smoking overnight before the laboratory session, 2) abstain from alcohol/other drug use for a minimum of two days prior to the laboratory session, 3) perform saliva collection the morning of the laboratory session and bring it, as well as the samples collected during the previous week, to the appointment, and 4) arrive at MUSC's Clinical Neurosciences Division office between 9:00 and 9:30

AM the day of their scheduled laboratory session. Upon arrival at the office, participants will provide research staff with the saliva samples they collected over the previous 8 days; in the event that a participant fails to collect a saliva sample the morning of the laboratory session, (s)he will be requested by research staff to provide a sample on site. Smoking abstinence will be confirmed via carbon monoxide assessment and abstinence from alcohol/other drug use will be assessed via breathalyzer and urine drug screen (UDS). Participants who fail any of the abstinence assessments will have their laboratory session re-scheduled at the earliest possible date. Individuals who must reschedule their laboratory session will be asked to continue to collect saliva samples daily upon awakening until the day of their laboratory session. Next, sensors for the measurement of heart rate and skin conductance will be affixed to the participant and a blood pressure cuff fastened to the non-dominant arm. Participants will complete baseline assessments (salivary cortisol, craving, stress, mood, etc.) and then receive a lunch snack. Participants will sit quietly for approximately 20-30 minutes after finishing their snack and then will receive nasal administration of either oxytocin or placebo (described in more detail below) at 12:00 noon. Approximately 30 minutes following medication administration, a second set of baseline measures will be obtained, after which the participant will sit comfortably until the Trier Social Stress Test/TSST (Kirschbaum, Pirke, & Hellhammer, 1993) begins.

The TSST procedure is widely recognized as the gold standard for evoking stress response in the laboratory (Dickerson & Kemeny, 2004). It begins when the participant is told that (s)he will soon have to perform both a speech and arithmetic task in front of an audience. They are told that the topic of the speech is why (s)he should be hired for a particular job (the participant's "dream job"). The participant will deliver the speech as though speaking to a group of hiring managers. The experimenter then tells the participant that (s)he has 5 min to prepare the speech, and starts the countdown clock (placed in view of the participant). The experimenter leaves the room to allow the participant to prepare. Five minutes later, three individuals unfamiliar to the participant (the audience) enter the room and are seated; the participant is instructed by one audience member (the spokesperson) to stand and begin his/her prepared speech (without notes). The speech is delivered for 5 min; if the participant pauses, (s)he is instructed by the spokesperson to continue. At the end of the speech task, the participant is instructed to serially subtract 13 from 1,022 as quickly and accurately as possible. The mental math recitation continues for 5 min, and at its conclusion, the spokesperson instructs the participant to stop and be seated, and the audience leaves the room. The total time for the TSST procedure is approximately 15 min.

Laboratory Procedure Timeline

<table>
<tr><th>TIME</th><th>PROCEDURE(S)</th><th colspan="2">MEASUREMENT(S)</th></tr>
<tr><td>10-10:55 AM</td><td>General Assessment & Preparation</td><td colspan="2">CO Assessment; Breathalyzer; UDS; Saliva collection (if not done at home); NWSC; STAI, Mood Form; DDT.</td></tr>
<tr><td>11:00-11:30 AM</td><td>Placement of HR & SC sensors & BP cuff; Baseline 1 Measurements; Snack.</td><td colspan="2">CQ; CREMA Mood & Stress Assessment; NWSC; HR, SC & BP; Cortisol.</td></tr>
<tr><td>12:00 Noon</td><td>Intranasal Administration of Oxytocin or Placebo</td><td colspan="2"></td></tr>
<tr><td>12:30 PM</td><td>Baseline 2 Measurements</td><td colspan="2">CQ; CREMA Mood & Stress Assessment; NWSC; HR, SC & BP; Cortisol</td></tr>
<tr><td>12:45-1:00 PM</td><td>Trier Social Stressor Task (TSST)</td><td colspan="2"></td></tr>
<tr><td>1:00 PM</td><td>Immediate post-TSST assessment; SRT begins.</td><td colspan="2">CQ; CREMA Mood & Stress Assessment; NWSC; HR, SC & BP; Cortisol; DDT</td></tr>
<tr><td>1:20 PM</td><td>20-minute, post-TSST assessment</td><td rowspan="4">*Cortisol & subjective stress (verbal report) will be assessed 20, 40 & 60 min. post-TSST.</td><td rowspan="4">*CQ, CREMA Mood & Stress Assessment, NWSC, HR, SC & BP will be assessed when each participant ends SRT and during ASP at 30 and 60 min.</td></tr>
<tr><td>1:40 PM</td><td>40-minute, post-TSST assessment</td></tr>
<tr><td>1:50 PM</td><td>Maximum duration of SRT reached. Latest time that ASP begins.</td></tr>
<tr><td>2:00 PM</td><td>60-minute, post-TSST assessment</td></tr>
<tr><td>2:50 PM</td><td>ASP Ends.</td><td colspan="2"></td></tr>
<tr><td>2:50-3:20 PM</td><td>Sensors removed; participant debriefing and compensation.</td><td colspan="2"></td></tr>
</table>

Table Key: **UDS**=Urine Drug Screen; **CO**= Carbon Monoxide; **NWSC**=Nicotine Withdrawal Symptom Checklist; **STAI**=State-Trait Anxiety Inventory; DDT = Delay Discounting Task; **CQ**=Craving Questionnaire; **CREMA**=Cue Reactivity Ecological Momentary Assessment; **HR**=Heart Rate; **SC**=Skin Conductance; **BP**=Blood Pressure; **SRT**=Smoking Resistance Task; **ASP**=Ad libitum Smoking Period.

The participant will then complete the Smoking Resistance Task (SRT), which is a empirically validated laboratory model of smoking lapse behavior (McKee, 2009; McKee, Krishnan-Sarin, Shi, Mase, & O'Malley, 2006; McKee, et al., 2011). The task involves testing the ability of overnight abstinent smokers to resist smoking in a situation where they are free to smoke but continued abstinence is reinforced with money. In the present case, a participant's preferred brand of cigarettes and a lighter will be presented on a tray. The experimenter will explain that the participant may begin smoking at any time, but the participant will be eligible to earn $1.50 for every 5 minutes the participant is able to "resist" smoking (up to a total of 50 minutes or $15). Once (s)he elects to smoke, the participant will begin the Ad libitum Smoking Period (ASP), in which (s)he is permitted to smoke as much as desired over the next hour in the laboratory. Topographical features of smoking behavior will be measured using the CReSS Pocket (CReSS, Borgwaldt KC, Inc., Richmond, VA), a self-contained, battery-operated device. In addition, the experimenter will record the number of cigarettes smoked.

Oxytocin/Placebo Administration: As noted above, participants will be administered 40 IUs of oxytocin or matching placebo nasal spray at approximately 12:00 noon. This dose and timing of administration was selected based on previous studies that have used similar doses of oxytocin (Ditzen et al., 2009; Heinrichs, et al., 2003; Macdonald et al., 2011), as well as our own previous pilot work (see Preliminary Data). Intranasal oxytocin and matching placebo will be compounded by MUSC Investigational Drug Service (IDS). The concentration of oxytocin will be 40 IUs/ml. Randomization will be done by the MUSC Investigational Drug Service, who will keep a record of the blind and be available should unblinding be necessary.

C3g. Instruments/Measures.

The diagnostic instruments/assessments employed in this investigation are widely cited, standardized instruments that have strong psychometric properties. This project has several instruments in common with Projects 1 in an attempt to foster assessment synergy between clinical projects. A brief description of each measure is as follows (where possible, instruments are grouped according to purpose and/or timing of use):

i. Initial General/Diagnostic Assessments: Demographic and Medical Information Assessment Form will be used to assess standard demographic information at baseline (using the NIH race/ethnicity categories) and medical history; Mini-International Neuropsychiatric Interview or MINI (Sheehan et al., 2003; Sheehan et al., 1998) will be used to assess general psychiatric functioning and DSM-IV diagnostic status, including alcohol and other drug abuse and dependence; Structured Clinical Interview for DSM-IV (SCID-I/P) is a structured diagnostic interview that assesses each of the criteria for DSM-IV diagnoses. The substance use disorder modules from the SCID are used as an alternative for these modules in the MINI. The SCID has proven to have excellent inter-rater and test-retest reliability (First et al., 2002); Daily Hassles Scale (DeLongis, Folkman, & Lazarus, 1988) consists of a list of irritating, frustrating or distressing events that characterize everyday interactions with the environment (participants rate both frequency and intensity of events for the past month); Adverse Childhood Experiences Questionnaire and ACE Brief (ACE; Felitti et al., 1998) assess childhood maltreatment and exposure to household dysfunction (employing the ACE will allow for potential cross-SCOR collaborations as it also being employed by the UCLA SCOR); Toronto Alexithymia Scale (TAS-20, Bagby, Parker & Taylor, 1994) is a scale which measures alexithymia, a condition in which people have trouble identifying and describing feelings. Items are rated using a 5-point Likert scale whereby 1 = strongly disagree and 5 = strongly agree. Both the original, 1985 version and the revised, 1992 version will be administered at the assessment visit; Modified Cigarette Evaluation Questionnaire (mCEQ, Rose, Behm, & Westman, 1998; Brauer, Behm, Westman, Perkins, & Rose, 2001) is a 12-item questionnaire assessing the reinforcing effects of smoking and contains 5 subscales (smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief, aversion) that will be given at screening, Day 7, and during the laboratory session post-cigarette during the ASP; The Distress Tolerance Scale (DTS, Simmons & Gaher, 2005) is a validated self-report which measures tolerance, appraisal, absorption, and regulation of emotional distress; Timeline Follow-Back (TLFB; Sobell & Sobell, 1992) is a calendar-based instrument with specific probes to obtain detailed information about substance use (including smoking) that will be used to assess smoking and other substance use in the three months prior to study involvement; Smoking History Form will be used to assess current smoking patterns, smoking environment, and previous smoking quit history; Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) will be used to assess degree of nicotine dependence; Menstrual History Diary

will be used to assess the timing of the menstrual cycle of female participants for the 90-days prior to study entry and to track their cycle during study participation. The Pittsburg Sleep Quality Index will be used to assess sleep patterns (Buysse, et al., 1989). Anxiety and depression symptoms will be assessed through The Quick Inventory of Depressive Symptoms (Rush, et al., 2003) and from the PROMIS© item bank (US DHHS). Daily stress will be obtained using the 10-item Perceived Stress Scale (PSS; Cohen et al., 1983). The Life Events Occurrence Scale (Maciejewski,, et al.) will be used to inventory adult trauma. A brief survey from the National Health and Nutrition Examination Survey (CDC, 2000) will be used to rate quality of life. A body map will be used to rate areas of pain (Cleeland et al., 1989).

Genetic Testing

Consenting participants will have blood drawn for genetic testing. This will typically occur during the assessment unless circumstances do not permit. We plan to examine genes associated with stress and cigarette smoking. Our group has previously collaborated with Dr. Ananda Amstadter at Virginia Commonwealth University (VCU), whose research group is actively investigating genetic variations associated with stress and nicotine use. Samples will be collected and stored at the MUSC Clinical Neurobiology Lab and periodically shipped to Dr. Ananda Amstadter's Laboratory at VCU for analysis.

ii. Daily (Longitudinal) Assessments: Craving Questionnaire/CQ (Carter & Tiffany, 2001) is a 4-item self-report questionnaire that assesses urge to smoke in all CREMA sessions. CREMA Stress/Mood Assessment (Warthen & Tiffany, 2009a; Wray, et al., in press) will assess stress, negative mood ("I am stressed, depressed, angry, worried, or frustrated") and positive mood ("I am happy, joyful, or pleased") during CREMA sessions. CREMA validity scales (Warthen & Tiffany, 2009a; Wray, et al., in press) assess distractibility and attentiveness during CREMA sessions using 5-point rating scales (strong disagreement=1; strong agreement=5). As noted above, saliva samples will be collected on a daily basis in order to determine levels of estradiol (females only), progesterone (females only) and testosterone (males only). Qualified laboratory technicians at MUSC's Clinical and Translational Research Center (CTRC) will perform all assays using commercially available immunoassay kits provided by Salimetrics^{tm}.

iii. Laboratory Session Assessments: As above, the Craving Questionnaire (CQ) and the CREMA Mood/Stress Assessment will be used to assess craving/urge to smoke and stress/mood at multiple time points during the laboratory session, respectively; State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) will be administered at the beginning of the laboratory session to assess state anxiety levels; Mood Form is a 9-item form (Diener & Emmons, 1984) that will be administered at the beginning of the laboratory session and will provide an immediate, corroborative assessment of current positive and negative mood states; Nicotine Withdrawal Symptom Checklist/NWSC (Hughes, Hatsukami, & Skoog, 1986) will be used to assess several withdrawal symptoms (i.e., craving, irritability/anger, anxiety/tension, difficulty concentrating, restlessness, etc.) from 0 to 4 (0 = not present, 4 = severe) at the laboratory visit; Delay Discounting Task is a 27 item form that will be measured before and after TSST and provides estimates of impulsivity and the degree to which participants discount future rewards; Heart rate and skin conductance (indices of physiological arousal) will be measured repeatedly over the course of the laboratory session. Heart rate (HR) will be collected via two electrodes along the bottom of the participant's ribcage, rather than on the participant's forearm, to minimize movement artifacts while skin conductance (SC) will be recorded using Ag/AgCl electrodes attached to the second phalanx of the first and third fingers of the non-dominant hand (HR and SC signals will be amplified using the ECG 100c and GSR 100c Modules of the Biopac MP100 data acquisition system); Blood pressure (BP) will be measured repeatedly via a non-invasive arm cuff; Cortisol levels will be determined via salivary samples collected at regular time intervals over the course of the laboratory session (they will be processed at the CTRC as described ii. above); Penetration of the Blind Questionnaire will be used to assess patient's opinion regarding whether they were administered the study medication or placebo; Adverse Events (AE) form will be used to document any participant-reported adverse events, whether related or unrelated to session procedures, including intranasal oxytocin or placebo administration.

C3h. Participant Compensation.

Participants will receive $100.00 for completing the comprehensive assessment. They will also receive $50 for attending the training visit and each interim visit (at Day 7); to incentivize compliance with the salivary data collection procedures, participants will be paid $5.00 per each day's useable saliva sample delivered at the

interim visit. In the interest of incentivizing attendance at the laboratory session and in recognition of the fact that this session involves exposure to a stressor and a significant time commitment, participants will be paid $100.00. Since participants will be delivering their saliva samples (obtained over the previous week) when they attend the laboratory sessions, they will be paid an additional $5.00 for each useable daily sample they provide. Given that the laboratory session will involve the administration of the smoking resistance task (SRT), it will be possible for participants to earn up to $15.00 if they successfully resist smoking for the entire 50 min. resistance period. As noted above, the completion of CREMA sessions will be incentivized by paying participants $1.25 for each session with complete data. Participant travel expenses up to $50 are allowable on an as needed basis. Thus, maximum remuneration for study participation is $510.

C3i. Sample Size Determination.

This study is powered to test the hypothesis that non-cigarette-deprived females will be more reactive to smoking cues than males, as measured in the natural environment of smokers via CREMA technology. However, the sample size obtained for this is adequate to test all the four hypotheses with at least 80% power. The justifications for the power calculations are as follows. A recent study (Heishman, et al., 2010) found that non-cigarette-deprived females responded to smoking cues with 10% greater craving than males (i.e., 10-unit difference on a 100-mm VAS), with this difference corresponding to an effect size of d = 0.7. Since the proposed design intends to assess gender differences in a non-laboratory setting, we have reduced the expected effect size by 30% to 0.50. Based on the four-item subscale of the QSU (cf., Warthen & Tiffany, 2009b) to be used in the proposed study, a comparable detectable gender difference would be 0.45 (sd=0.9). Accounting for the multiple correlated measures within each participant (i.e., reactivity will be measured multiple times daily for 14 days using CREMA) through a between-observation correlation (autocorrelation) of 0.70, a sample of 96 females and 48 males is necessary to achieve 90% power (with a two sided type I error rate of 0.05) to detect the minimum relevant effect size of d=0.50. It is estimated that up to 20% of the participants may be lost before completion of the study.

Assuming 144 participants complete all study procedures (accounting for 20% dropout), we will also have 80% power with a type I error of 0.05 to detect a minimum effect size of d=0.50 between females and males in stress and craving response to the TSST and similarly between the oxytocin and placebo groups.

C3j. Data Management & Statistical Analysis.

Data Management

All paper-based assessments will be entered into SPSS databases using dual data entry methods for 20% of cases. Semi-annual database management and data integrity audits will be conducted. Hormone and cortisol data will be obtained from MUSC's CTRC in pre-formatted data files. HR and SC data will be acquired via specialized software and hardware (Biopac Systems, Inc.) interfaced with a computer. Standardized file formats will facilitate the rapid determination of summary values to be used for analysis purposes. The CREMA data will be automatically uploaded to a server on a daily basis and will be stored in a standard file format (to be determined in collaboration with Dr. Metts (Founder of Slicker Interactive & CREMA software developer). All data will be de-identified using participant ID number.

Statistical Analysis

Univariate descriptive statistics and frequency distributions will be calculated for all variables. Departures from distributional assumptions for the proposed parametric methods will be identified and appropriate transformations of the data will be applied or alternative procedures (semi/non parametric methods) will be employed. Baseline values for demographic, clinical, and other prognostic variables will be compared for imbalance across gender and treatment groups. These analyses will identify potential confounding variables to be used as covariates in subsequent analysis.

Aim 1: Hypothesis 1 - To test the overall hypothesis that females will be more reactive than males to stressful and smoking-related cues presented in the natural environment, a linear mixed effects model will be employed. The dependent variable will be craving and the primary independent variable will be gender. In the modeling process, within-subjects factors of stimulus type (active and neutral cues) and presentation order will also be included.

Hypothesis 2 - To test the hypothesis that the estradiol to progesterone ratio will be positively related to cue-elicited craving in the natural environment, salivary hormone levels and craving in response to the CREMA picture cues will be assessed over 14 days. Hormone curves do not behave in a linear fashion, but may, in the example of progesterone, behave in a quadratic fashion preceding menses and a linear fashion following

menses. Linear models may thus be inappropriate. Traditional analyses group the hormone curves based on the estimated phases of women's menstrual cycle (follicular and luteal) for the analyses. In addition to performing the data analyses using the same method, analysis will be extended to incorporate the non-linear patterns of an individual's hormone profile. This method will be based on a non-linear regression model that has two to three segments, each one of which may be either quadratic or linear (Marrie, Dawson, & Garland, 2009). The 'joint-points' at which the segments meet, which are referred to as knots, will also be treated as unknown and determined through the modeling process. After identifying the segments, regression models assessing hormone measures against the outcome (e.g., cue-elicited craving) in each segment will be assessed and the results interpreted accordingly.

Aim 2: Hypotheses 1 and 2 - To test for gender and medication (oxytocin versus placebo) effects on reactivity profiles to the TSST during the laboratory session, a linear mixed effects model in which the dependent variables of interest are craving, stress and neuroendocrine (cortisol) response, and the primary independent fixed effects are gender, treatment group, and a random subject effect will be utilized. To account for the repeated measures, a covariance pattern for the error structure (such as an AR(1)) will be considered. The primary goal of this analysis will be to determine if the response to TSST is significantly different between females and males and/or significantly different between those who received oxytocin versus placebo (main effects of gender and medication). Additionally, as a secondary analysis, the interaction between gender and medication condition will be explored.

To test the hypothesis that females will have a shorter latency to return to smoking than males, a discrete analog to the Cox proportional hazards model will be used. A complementary log-log model for interval censored survival times will be employed (Allison, 1982; Prentice & Gloeckler, 1978) that will take into account the interval nature of the time frame within which the return to smoking occurs. Also considered will be standard Cox proportional hazards models to compare time to begin smoking. Puff intensity, flow rate, and number of puffs will be assessed using a topography device as participants smoke freely for 1 hour following the smoking resistance task. Longitudinal data analytic methods will be applied to the craving, stress and cortisol data obtained during the laboratory session for all time points before and after the TSST.

Hypothesis 3 - To test the association between the estrogen to progesterone ratio and laboratory stress reactivity in women, a linear model will be developed to assess the relationship between hormones and subsequent stress reactivity. The dependent variables of interest will be the craving, stress and neuroendocrine (cortisol) response to the TSST while the independent variables will include the change in the hormone ratio over the week preceding the lab visit as well as the hormone ratio on the day of the visit. Assumptions such as linearity of the relationship between the hormones and reactivity measures, homoscedasticity, and normality of the error distribution will be assessed and variables will be transformed as necessary.

C3k. Operational Plan and Research Timetable.

Organizational meetings to plan the structure/content of the CREMA software application and to establish milestones will begin immediately upon notice of award. Dr. Metts (Slicker Interactive) will deliver a demo application at 3-months and pilot work will be conducted. The final product will be delivered/operational within the first 5 months of the grant tenure period. Because we already have ongoing cue/stress reactivity studies with smokers, trained personnel, an active recruitment strategy, and the TSST procedures well established, we anticipate that no more than 6 months startup will be necessary before recruitment can commence. At a rate of 3-4 participants per month, we should have no difficulty completing study recruitment during the expected 51-month recruitment period. This will allow 3 months for data reduction, management, analysis and manuscript preparation. A follow-up proposal will be planned and prepared in tandem with manuscripts.

Human Subjects Research.

Protection of Human Subjects.

1. Risks to the participants.

Drs. Saladin and Gray and their research team have completed the University of Miami computer-based training course CITI Human Subjects Research Education Course. All research activity, informed consents and continuing reviews will be reviewed by MUSC's IRB in compliance with 45CFR46 before the research is started and continuing review will occur annually. Drs. Saladin and Gray will ensure that all information needed for the continuing review is at the IRB in accordance with IRB requirements.

1.1 Human Subjects Involvement and Characteristics.

A total of 120 female and 60 male nicotine dependent smokers, between the ages of 18-45, will be recruited over a 51-month period. The sample size was determined based on statistical power analysis (details provided in Data Analysis Section). The inclusion/exclusion criteria are as follows:

Inclusion criteria:

a) Females and males age 18 – 45 who smoke at least an average of 5 cigarettes per day for at least past 6 months
b) Females must be post menarche and pre menopausal, have a regular menstrual cycle between 25 and 35 days, and, if recently pregnant, be at least three months post delivery/breast feeding
c) Participants must submit a carbon monoxide sample of ≥ 5 ppm at their screening visit

Exclusion criteria:

a) Any serious or unstable medical or psychiatric disorder that may, in the judgment of the study physician, interfere with study completion
b) Participant meet criteria for PTSD
c) Any medication (e.g., propranolol) that may interfere with psychophysiological (e.g., heart rate) monitoring
d) Current substance dependence other than nicotine and caffeine use, in the past month
e) Use of other tobacco products
f) Females that are pregnant, breast feeding, status post hysterectomy or bilateral oophorectomy, or taking birth control or hormone replacement medication that would affect the menstrual cycle
g) Males that are status post orchiectomy

1.2 Sources of Research Material.

Research material obtained from the individual subjects include physical and psychiatric examination results, drug (including nicotine) use assessment results, expired air breathalyzer alcohol and CO tests, saliva samples (for progesterone, estradiol, testosterone, cortisol, and cotinine), heart rate, skin conductance, and subjective ratings (e.g., craving). Urine samples for the urine drug screen, pregnancy assessment and cotinine analysis will also be obtained. Research data will be obtained specifically for research purposes. We will not use existing specimens, records or data.

1.3 Potential Risks.

Questionnaires and interviews are all non-invasive and, as such involve minimal physical risk to the participants. Potential risks incurred by participants include:

a) Loss of confidentiality: There is a risk of loss of confidentiality regarding the information obtained during study participation.
b) Craving and stress induction: There is a risk of increased stress and craving for cigarettes as a result of the cue-reactivity procedures.
c) Oxytocin: Participants will be given a single intranasal administration of oxytocin or placebo (double blind) during the laboratory session. There is potential for adverse effects associated with intranasal oxytocin, though a recent review of controlled human studies revealed minimal adverse effects, with rates equivalent to placebo (Macdonald et al., 2011). The most frequent adverse effects included (1) lightheadedness, drowsiness, and/or headache (in 6% of participants), (2) increased calmness/euphoria, feeling more comfortable or having more energy (in 5% of participants), and (3) nasal irritation and/or dry mouth/throat (in 3% of participants).
d) Venipuncture: The risks of drawing blood include temporary discomfort from the needle stick and bruising.
e) Adverse events unrelated to study participation may occur during the course of study participation.

There are no alternative methods of obtaining this information.

2. Adequacy of protection against risks.

2.1 Recruitment and Informed Consent Procedures.

Recruitment of the subjects will be from the community by media advertising, word of mouth, flyers, broadcast emails, media articles, and clinical referrals. Medical University of South Carolina IRB approved Informed

Consent (IC) will be obtained prior to the initial assessment. The consent will be explained orally and in written form, and will be documented by the signature of the participant on the IC.

Absence of Coercion: Participation in the study is voluntary. Participants will be compensated up to $460 if completing all study procedures, an amount commensurate with the necessary commitment of time and effort. The informed consent agreement that will be read to each person prior to his or her enrollment in the study explains the following:

a) Compensation will be provided for assessment and various study procedures and visits.
b) Participants may discontinue participation in the study at any point.
c) Withdrawing from the study will not result in any adverse consequences to the participants.

2.2 Protection Against Risks.

The research staff will closely supervise all participants entering into the study. Every effort will be made to protect study participants from harm. MUSC abides by federal regulations governing the protection of special populations including women and children. Potential risks associated with participation in this study are:

a) Loss of confidentiality: The research materials will become a part of the modern record keeping facility of the Institute of Psychiatry (IOP), which will minimize risks to the privacy of the subjects. In addition, we will obtain a Certificate of Confidentiality from the NIH to protect participants' information to the extent of the law.
b) Craving induction: While there is a small risk of increased stress and craving for cigarettes as a result of the cue-reactivity procedures, it does not appear to differ substantially from the reactivity elicited by stimuli commonly encountered in the day-to-day environment of the study participants. Participants that report significant stress or craving after the laboratory session will be provided a debriefing session to address symptoms.
c) Oxytocin: Given the benign safety profile of single-dose intranasal oxytocin (MacDonald et al., 2011), we anticipate minimal adverse effects. Nonetheless, the study medical clinician will monitor, record, and address any adverse effects experienced by participants.
d) Venipuncture: The optional blood draw for genetic testing will be conducted by an experienced phlebotomist with all required training and certification. Any concerns or issues related to the blood draw will be addressed as needed.
e) Serious adverse events will be reported to the NIDA project officer, in addition to the local IRB and FDA as appropriate.

3. Potential Benefits of the Proposed Research to the Participant and Others.

A potential benefit is that research participants may learn about the types of cues that trigger their smoking cravings and this may be useful in helping them to avoid and/or cope with smoking triggers in their day-to-day life. Other benefits of study participation include access to assessment information pertaining to physical and mental health and wellness, substance use/misuse, etc. Also, regular contact with and monitoring by research staff may serve to assist participants in future attempts to abstain from cigarette use. Overall, given the potential benefits, it would appear that exposure to the risks associated with study participation are well justified. The risk/benefit ratio appears to favor the study participant.

4. Importance of the Knowledge to be Gained.

The knowledge gained from this study may serve to inform the clinical treatment of smoking by elucidating gender and sex hormone influences on stress, craving, and smoking behavior. Additionally, the study will allow for exploration of oxytocin as a potential pharmacotherapy targeting stress-related craving and smoking behavior. This information could then be used to guide investigation of gender-optimized smoking cessation interventions. Additionally, the proposed study will involve the collection of subjective and physiological reactions to stress and smoking cues, yielding important information about how gender and sex hormones influence these reactions.

5. Data and Safety Monitoring Plan.

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html).

5.1 Summary of the Protocol.

This application proposes a combined naturalistic and laboratory approach to investigate gender, sex hormone, and oxytocin influences on cue-responsive craving and smoking behavior. Inclusion/exclusion criteria are outlined above.

5.2 Trial Management.

The study will be managed from the Division of Clinical Neuroscience within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. The target population is described above in the inclusion/exclusion criteria.

5.3 Data Management and Analysis.

Data will be entered by research assistants directly into a computer using standard database software. The data analysis plan is outlined in the Data Management & Statistical Analysis section.

5.4 Quality Assurance.

Dr. Saladin (PI) and Dr. Gray (Lead Co-I), will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores, and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality protections are outlined above.

5.5 Regulatory Issues.

Prior to the start of the study, the protocol will be registered in the Clinical Trials Registry. We will notify FDA to assess the need for an IND. All unexpected AEs will be reported to the MUSC Committee on Human Research and NIDA within 48 business hours. Serious AEs will be reported within 24 business hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies. All AEs will be reviewed weekly by Dr. Gray and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to NIDA. Potential conflicts of interest will be reported using standard rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the study will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. A research assistant will identify any potential adverse events during the course of the study from participant self-report and administration of the visit assessments and procedures. The research assistant will provide information to a study medical practitioner, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

5.6 Definition of AE and SAE.

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect.

OR

- Requires intervention to prevent one of the above outcomes.

5.7 Documentation and Reporting.

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information

if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol.

When a reportable SAE is identified, the research assistant will initiate an SAE form, and the following individuals will be notified by facsimile transmission within 24 hours of the site's initial notification of the SAE:

a) The Principal Investigator(s) and the study safety officer at the site will provide oversight, consultation, assessment and documentation as appropriate of the SAE.
b) The research staff will notify the MUSC institutional review board (IRB) and complete the AE report form in conjunction with a study medical practitioner. The MUSC IRB meets monthly and is located at 19 Hagood Avenue, Suite 601, MSC857, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting.
c) The NIH program officer.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by a study medical practitioner for forwarding to the NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, a study medical practitioner will provide a signed, dated SAE summary report, which will be sent to the NIDA Medical Safety Officer within two weeks of the initial SAE report.

We will report adverse events to the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) online as soon as possible, but no later than 10 working days after the investigator first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

5.8 Trial Safety.

The potential risks and benefits and methods to minimize these risks are outlined above, and the methods of collecting AEs are described in the research design. The research staff will report any unexpected AEs or any scores of "severe" on the side-effect symptom rating form or any FDA-defined serious AEs to a study medical practitioner within 24 hours so that they can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. AEs will be coded on a weekly basis using the FDA's COSTART rules (Center for Drug Evaluation and Research, 1993) and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, including their severity, presumed relation to drug intake, and whether they caused a dropout or required treatment. A study medical practitioner will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), research assistants will report any premonitory symptoms of emergence of a mental disorder such as depression or alcohol dependence.

Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp) plus we have found using Spilker's comprehensive text on conducting clinical trials useful (Spilker, 2000). We will encourage participants to notify their physician that they are in a research study and that the physician should contact the study medical practitioner directly if he/she has any questions.

The research assistants will be instructed not to reveal whether a person is a participant in the study and will report to a study medical practitioner any outside requests for information about a participant or any breaches in confidentiality. All requests by participant's physicians and other medical providers will be referred directly to a study physician.

5.9 Trial Efficacy.

Final analyses, inclusive of fully unblinded oxytocin versus placebo effects on stress reactivity and craving, will occur after all participants have completed the study.

5.10 DSM Plan Administration.

The PI and Lead Co-I will be responsible for monitoring the trial. The statistician will examine (monthly) the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSM report will be filed with the IRB and NIDA on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs, and serious AEs. We will report main outcomes, including effects of oxytocin versus placebo on stress-reactive craving, at the end of the trial.

5.11 DSM Board.

We will seek guidance during discussion with the program officer on the potential necessity of convening a data and safety monitoring board for this project.

5.12 Risk Benefit Ratio.

The assessments and questionnaires are non-invasive and have inherently minimal risks. Potential risks of concern are loss of confidentiality, increased stress and craving associated with cue reactivity procedures, and adverse events associated with oxytocin. As discussed above, our research team will attempt to minimize these risks. The relationships between stress, craving, and smoking behavior, and the underlying influences of gender and sex hormones, are poorly understood. Investigation in this area will be critical in addressing gender-related health disparities in smoking, the leading cause of preventable death in the US. Knowledge gained by the proposed study will help fill an important void in research on treatments for nicotine dependence.

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