

**Medical University of South Carolina
Protocol**

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Study Title: The Effects of Oxytocin on Couples' Conflict-Resolution Interactions

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1. SPECIFIC AIMS

Dyadic conflict is highly prevalent among individuals with substance use disorders. Dyadic conflict is known to precipitate and exacerbate negative health correlates such as addiction, depression, PTSD, and intimate partner violence. Most notably, dyadic conflict is a salient proximal trigger for substance use behaviors and substance use problems. Researchers have demonstrated that behavioral interventions for couples yield positive mental health and substance abuse outcomes. Indeed, conjoint couples therapies are increasingly becoming known for their capacity to effectively treat addiction (1, 2). However, an important limitation remains in the literature on couples therapy interventions. Whereas the augmenting effects of numerous pharmacological agents have been investigated in the context of individual behavioral interventions, and the existing literature overwhelmingly demonstrates that the most positive mental health outcomes are derived from the use of both pharmacological and behavioral interventions concurrently, studies investigating pharmacological augmenters for couples interventions are scant.

Oxytocin is a neuropeptide known to have prominent anxiolytic and prosocial effects. Among both animals and humans, oxytocin is known to mitigate the effects of social stress on addictive behaviors. Among normative couples, preliminary data suggests that oxytocin promotes more positive conflict resolution skills. Taken together, this literature suggests that oxytocin holds promise as a tool to modulate the effects of dyadic conflict on addictive behaviors. If evidence supporting this notion emerged, these data would support the investigation of oxytocin as a potential augmenter to couples therapies for substance abuse problems. However, the first step toward evaluating oxytocin in this role, and the primary objective of the proposed study, is to examine the extent to which oxytocin improves conflict resolution skills among couples with substance abuse. Our secondary objective is to examine the extent to which oxytocin mitigates couples' subjective, physiological, and neuroendocrine reactivity to dyadic conflict. Thirty-six couples (n=72) consisting of at least one partner with recent substance abuse will participate in the study. The study will consist of one 4-hour laboratory visit. Couples will complete a thorough psychosocial assessment interview and two 10-minute videotaped conflict resolution tasks using a well-established paradigm. Participants will be randomly assigned to self-administer either a 40 IU dose of intranasal oxytocin or placebo. We will implement a double-blind design. We will examine standardized, repeated dependent measures of change in each partner's conflict resolution skills, subjective, physiological, and neuroendocrine responses to the conflict resolution task. The following specific aims are proposed:

Specific Aim 1: Examine the effects of oxytocin on couples' conflict resolution skills.

Couples will complete a psychosocial assessment and two 10-minute videotaped conflict resolution tasks. 45 minutes prior to the second conflict resolution task, a 40-IU dose of intranasal oxytocin or saline spray will be administered to both partners. Conflict resolution skills will be coded according to a well-established system and compared from Task 1 to Task 2.

Specific Aim 2: Examine the effects of oxytocin on couples' subjective, physiological, and neuroendocrine reactivity to the conflict resolution task.

Subjective (craving, distress, feelings toward partner), physiological (heart rate, skin conductance, skin temperature), and neuroendocrine (salivary cortisol, Dehydroepiandrosterone) measures will be assessed at baseline and at 6 other time points throughout the laboratory portion of the study for both partners.

2. BACKGROUND AND SIGNIFICANCE

A. Overview

Substance use disorders (SUD) are characterized by dysregulation of the hypothalamic-pituitary axis (HPA). The neuropeptide oxytocin, commonly administered as an intranasal spray, is a drug that has prominent anxiolytic and prosocial effects on human behaviors (3-6). While the mechanisms of action facilitating the behavioral effects of oxytocin in humans is complex and many questions about this process remain, there is a consensus in the existing literature that oxytocin modulates HPA axis reactivity to stressful social stimuli (7-9). Preliminary studies suggest that oxytocin is known to reduce couple conflict among normative couples (10, 11). A more developed line of research indicates that oxytocin mitigates addictive behaviors in the context of various drugs of abuse (12-14). Given the high prevalence and severity of dyadic conflict among couples where one or both partner has substance abuse, and given the salience of dyadic conflict as a precipitant to substance use behaviors (15-17), it is critical to investigate the therapeutic effects of oxytocin among couples with substance use problems. Namely, oxytocin holds promise as a potential augmentor for conjoint couples therapies, particularly those targeting the reduction of substance use problems. However, only two studies have examined the effects of oxytocin on couples' communication behaviors. Those two studies found that couples' communication skills improved following the administration of oxytocin. It is important to extend this line of research to examine conflict resolution skills among couples with substance use problems. To date, no studies have examined the effects of oxytocin on subjective, physiological, or neuroendocrine reactivity to dyadic conflict. The present study aims to fill that gap in the literature.

B. The Effects of Oxytocin on Addictive Behaviors in the Context of Social Stress

Social stress, both generally and specifically in relation to dyadic conflict, is known to exacerbate addictive behaviors. One well-developed body of literature evidencing this connection demonstrates a strong temporal association between verbal and physical intimate partner violence and substance use behaviors (15, 18-21). Studies examining the effects of social stress on subjective, physiological, and neuroendocrine reactivity among substance-dependent individuals suggests that social stress exacerbates craving, use, and relapse (22, 23). More recently, many studies have examined the potential for oxytocin to reduce stress reactivity in the context of addiction. Research in both animal and human studies has shown that oxytocin reduces addictive behaviors (i.e. withdrawal, craving, substance self-administration) and subjective, physiological, and neuroendocrine stress reactivity (12, 14, 24, 25). However, this literature has not been extended to examine whether oxytocin mitigates substance use behaviors and stress reactivity in response to dyadic conflict among substance-abusing couples.

C. The Effects of Oxytocin on Prosocial Behavior

Oxytocin has well-established and prominent effects on prosocial human behavior (5). It promotes feelings of warmth, trust, and safety and promotes social bonding (5, 26). Some research asserts that these effects are due to oxytocin's influence on humans' capacity to read and respond to social cues and to better retain positive social memories. While some researchers caution that amplifying one's capacity to interpret social cues may not always be adaptive(27), and that one's social context and history may play an influential role in the response to oxytocin, the consensus in the existing studies on humans is that oxytocin's positive therapeutic effects are promising. Despite the abundant literature that has documented the prosocial effects of oxytocin in animals and humans, only one study to date has investigated the effects of oxytocin on human couples interactions. Ditzen and colleagues (28) found that among normative couples, oxytocin increased positive communication and decreased cortisol levels in response to a conflict resolution task. Notably, and consistent with other literature citing gender differences in response to oxytocin (citations), this study also found that female partners had reduced ANS activity in response to dyadic conflict while male partners showed increases ANS activity in response to dyadic conflict. While, as mentioned above, some researchers caution about the consistency of positive effects of oxytocin, it is important to note that in this study, the increase in ANS activity was associated with more positive conflict resolution behaviors. Thus, an increase in physiological reactivity in the context of oxytocin and dyadic conflict may indicate a positive, rather than negative response.

In addition to the scarcity of literature investigating the effects of oxytocin on dyadic conflict, this literature is limited by the investigation of normative couples only. Given the prominence and effectiveness of couples therapies to treat substance abuse problems (1, 2), a natural extension of the existing literature is to examine the therapeutic effects of oxytocin on couples with substance abuse problems. Namely, we aim to investigate the effects of oxytocin on substance-abusing couples' conflict resolution skills and their subjective, physiological, and neuroendocrine responses to dyadic conflict.

D. Conclusion

In summary, dyadic conflict is a salient predictor of addictive behaviors. Along these lines, several evidence-based behavioral interventions for couples aimed at treating substance abuse problems have been developed: By effectively reducing couple conflict and improving conflict resolution skills, the chances of positive treatment outcomes for substance abuse problems are greatly increased and more effectively sustained.

Abundant literature also indicates that oxytocin has positive influences on humans' prosocial and addictive behaviors. Despite this literature, only one study has investigated the effects of oxytocin on couples' conflict resolution skills, and this study was conducted among normative, rather than substance-abusing couples. Thus, we aim to investigate the extent to which oxytocin improves dyadic conflict resolution skills and mitigates negative subjective, physiological, and neuroendocrine responses to dyadic conflict. Findings from this study may support the evaluation of oxytocin as an augmenter to behavioral couples interventions targeting substance abuse.

3. PRELIMINARY STUDIES

Studies conducted by Dr. Flanagan and her collaborators that demonstrate their collective experience in conducting intervention development research are outlined below. These studies also demonstrate the need to investigate oxytocin as a pharmacological augmenter to behavioral couples interventions.

Dr. Flanagan has experience in the collection of dyadic data and the precautions necessary when assessing men, women, and couples with acute and complex mental health problems, substance

abuse problems, interpersonal violence, and criminal justice system involvement. She also has extensive clinical experience in facilitating psychotherapy groups for men and women from several specialized clinical populations. Dr. Flanagan oversaw the day to day implementation of three NIH-funded clinical trials during her pregraduate work. Each of these studies aimed to assess the efficacy of alcohol interventions on the reduction of violence among individuals court mandated to batterer intervention treatment or in partial hospital substance abuse treatment. Dr. Flanagan conducted recruitment, assessment, and retention of participants as well as dissemination of data in presentation and peer review publications (29, 30).

Dr. Flanagan's program of research has focused extensively on the conduct of studies focused on improving women's health. Namely, the reduction of interpersonal violence, substance use, and mental health problems. Dr. Flanagan carried out anNIAAA-funded National Research Service Award titled "Risk Factors for Intimate Partner Violence During Pregnancy". During this time, Dr. Flanagan collaborated with a university-affiliated health clinic to recruit 180 pregnant women and conducted follow-up assessments with more than two thirds of this sample. Several studies have been published from this data (8, 31, 32). Dr. Flanagan is also trained on the laboratory procedures for collecting observational problem solving data from couples and employing the coding system outlined below (33).

Currently, Dr. Flanagan is collaborating with Dr. Back in the conduct of her NIDA-funded clinical trial investigating Concurrent Treatment with Prolonged Exposure (COPE) among Iraq and Afghanistan combat Veterans. Dr. Flanagan functions as a member of the study treatment team and will gain first-hand experience in the execution of a large scale clinical trial focusing on treating Veterans in the Charleston community. To date, we have found that approximately one third (37.7%) of the participants in the COPE study have reported aggression during the thirty days prior to baseline assessment, and approximately half (53.2%) have reported aggression during their lifetime. Drs. Flanagan and Back are in the process of presenting these findings, including an assessment of the differences in mental health, substance use, and combat exposure, between individuals who enter treatment with a recent history of aggression compared to those who do not. Dr. Flanagan has published two other manuscripts regarding the use of aggression among Veterans (6, 34).

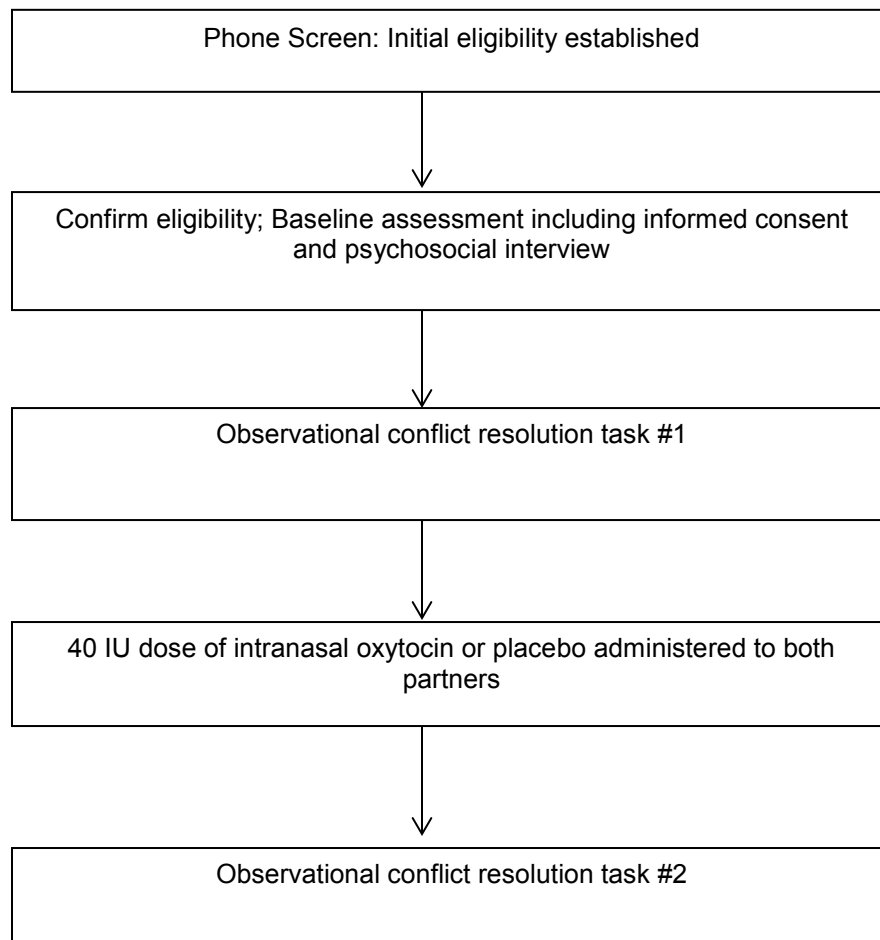
Finally, Dr. Flanagan has collected focus group data from 20 substance-abusing male Veterans and 14 civilian women partnered with Veterans to inform the development of potential treatments for couples struggling with substance abuse problems. These data suggest that anger and distrust are two primary obstacles to better relational health among these couples and participants have requested interventions to facilitate improved management of these challenging emotions. Recently, Dr. Flanagan has been collaborating with Dr. Back and other colleagues to develop her expertise in the use of laboratory-based stress induction paradigms. Dr. Flanagan has co-authored two manuscripts under review focusing the use of a social stress paradigm to examine subjective, physiological, and neuroendocrine reactivity among individuals dependent on prescription opioids. Dr. Flanagan has also led the analyses of these data to examine the influence of interpersonal trauma on stress reactivity in this sample. Finally, Dr. Flanagan is in the preliminary stages of a collaboration with other members of the CND to examine the interactive effects of oxytocin and childhood adversity on stress reactivity among cocaine-dependent individuals.

In addition, Dr. Candice Monson is serving as a co-mentor and co-investigator on the proposed project. Dr. Monson is Professor and Director of Clinical Training at Ryerson University. Dr. Monson previously served as Deputy Director of the Women's Health Sciences Division at the National Center for PTSD in Boston as has an extensive research track record including serving as PI on several VA and NIH funded treatment development research studies focusing on designing couples therapies. Dr. Monson's combination of expertise in couples therapy treatment development, women's health, and Veterans health is an ideal compliment to Dr. Flanagan's mentorship team.

4. RESEARCH DESIGN AND METHODS (including data analysis)

A. Overview

The primary objective of this study is to examine the extent to which oxytocin improves couples' conflict resolution skills and mitigates their subjective, physiological, and neuroendocrine responses to this common stressor. Couples in which one or both partners have a recent history of substance abuse will be recruited. The present study will take place over one visit. In addition to a thorough psychosocial evaluation conducted by a trained clinician, couples will complete two laboratory conflict resolution tasks. Prior to the start of the second conflict resolution task, both partners will be administered a 40 IU dose of intranasal oxytocin. The flow chart below illustrates each element of the study:



B. Subjects

Thirty-six couples (N=72 individuals total) will be recruited to participate in the proposed study. Respondents will be screened by phone and provided all pertinent information about the study. Inclusion criteria are: 1) 18-65 years of age, 2) both partners are willing to participate, and 3) at least one partner has engaged in hazardous drinking (i.e. 4 or more drinks for women, 6 or more for men) or illicit drug use during the past 60 days. Exclusion criteria are: 1) pregnancy for women, 2) current psychotic or bipolar disorders, 3) active suicidal or homicidal ideation and intent, 4) subjects who would

present a serious suicide risk, such as those with severe depression, or who are likely to require hospitalization during the course of the study, 5) severe, unilateral intimate partner violence in the past year, 6) BMI greater than 39. If both partners meet criteria for participation and independently provide informed consent, they will be scheduled to complete a baseline assessment. Participants will also be scheduled at the same time of day to control for diurnal variations in neuroendocrine function.

C. Recruitment and Eligibility Screening

Participants will be recruited through the use of flyers posted in MUSC treatment clinics. Recruitment ads will also be placed in local newspapers and on Craigslist. These strategies have been successful in the PI's mentor's ongoing and past research endeavors and among other researchers within the Department of Psychiatry and the Clinical Neurosciences Division at MUSC. Respondents will contact research staff via phone to be screened for inclusion and exclusion criteria. The PI and research staff will conduct eligibility screening by phone. Respondents will be provided a brief description of the study including study scope and time commitment, and various methods of data collection including observational, physiological, and interview and self-report methods. Respondents will also be informed that none of their study data, including reports of sensitive nature such as IPV and UDS results will be shared with any third party including one's partner. Initial screening questions can be found in the appendix section of this protocol. If respondents are eligible, they will be provided information about the purpose, nature, and duration of the study and asked if they would like to be scheduled to attend a baseline interview session with their partner. Participants will be provided with a full description of study procedures, given the opportunity to ask any questions they may have, and will be asked to read and sign an IRB-approved consent form before any study procedures take place. All participants will be consented in a private room apart from their partner to ensure confidentiality and safety of research participants.

D. **Assessment Measures.** Table 1 presents the assessment instruments included in the study.

Table 1. ASSESSMENT MEASURES	
Construct	Measure
Laboratory Task Assessments	<ul style="list-style-type: none"> • Substance craving (3 items) • Emotional distress (1 item) • Feelings toward partner (11 items) • Constructive discussion (1 item)
Physical Health Screening	<ul style="list-style-type: none"> • Health Screening Interview
Dyadic Functioning	<ul style="list-style-type: none"> • Dyadic Adjustment Scale; DAS (35) • Conflict Tactics Scale-2; CTS-2 (36) • Reasons for Violence Scale (29) • Infidelity assessment (37) • TLFB for partner violence (38) • Self-Report of Aggression & Social Behavior Measure (39, 40)

Substance Abuse	<ul style="list-style-type: none"> • Alcohol Use Disorders Test; AUDIT(41) • Drug Abuse Screening Test; DAST(42) • Fagerstrom Nicotine Dependence Test (43) • Time Line Followback; TLFB (38, 44) • Inventory of Drug-Taking Situations; IDTS (45) • Urine Drug Screen • Breathalyzer • Pregnancy test for women
Mental Health	<ul style="list-style-type: none"> • Mini International Neuropsychiatric Interview (MINI; 46) • Traumatic Life Events Questionnaire (47) • Patient Health Questionnaire; PHQ-9 (48) • Perceived Stress Scale -4; PSS-4 (49) • Interpersonal Sensitivity Measure; IPSM (50) • PTSD Checklist, Civilian Version; PCL-C(51)
Coping Factors	<ul style="list-style-type: none"> • Coping Strategies; Brief COPE (52) • Cognitive Emotion Regulation Questionnaire; CERQ-Short (53)
Demographics	<ul style="list-style-type: none"> • Age, gender, ethnicity, education, income, relationship information, military service

Laboratory Conflict Resolution Task

Couples will be asked to participate in two 10-minute video recorded problem-solving tasks while physiological measures are recorded for both partners. Using the procedure employed by McNulty and colleagues (33, 54), each partner will identify a topic of relationship difficulty, and a coin flip will determine the topic of the discussion. The couple will be asked to work towards a resolution or agreement on that topic. The conflict resolution skills of each partner will be estimated by coding each speaking turn using the Rapid Marital Interaction Coding Scheme (RMICS; 55). Each participant's speaking turn is coded as being characterized by one of the following domains: psychological abuse, distress-maintaining attributions, dysphoric affect, withdrawal, relationship-enhancing attributions, acceptance, self-disclosure, humor, constructive problem discussion, other. An additional option is to calculate a total proportion of negative behavior and a total proportion of positive behavior exhibited by each participant by dividing the number of codes for a participant in a given conversation by the total number of speaking turns for that participant in that conversation.

Coding will be conducted by Dr. Richard Heyman's team at The RMICS Coding Center within the Translational Couples Research Laboratory at New York University. Dr. Heyman's team provides fee-based coding, 25% reliability checking, reliability estimates at both system and code level, and SPSS output of the data. The RMICS is a widely used coding system providing dyadic coding services to investigators nationwide. Dr. Heyman's team will be provided access to the secure network server used to store video coding materials in Dr. Back's laboratory.

Data Collection Procedures

The extant couples literature emphasizes the utility of collecting physiological data in addition to self-report and observational data to examine dyadic synchronicity in physiological responses, gender differences in physiological arousal during the problem solving task, and to relate physiological data to self-report ratings of mental health, dyadic functioning, and substance abuse (56). Physiological measures to be collected in this study include skin conductance, skin temperature, heart rate, salivary cortisol and dehydroepiandrosterone (DHEA). All physiological measures will be collected using the ProComp Infiniti biofeedback acquisition tool (Thought Technology, Ltd.). Heart rate and skin conductance will be collected using electrodes on the participant's right clavicle and on their ankle. Skin temperature will be measured using a self-adhering sensor placed on the participant's index finger of the non-dominant hand. Cortisol and DHEA will be measured via participants' saliva samples. Participants will be asked to avoid drinking coffee and smoking in the hours prior to their appointment to

avoid interference with physiological measures. Participants will also be assessed at the same time of day to control for diurnal variations in neuroendocrine function.

Following informed consent, couples will complete self-report and interview measures in separate rooms. When finished, couples will be escorted into a room together asked to relax for a 15 minute period in this room to acclimate to their surroundings. Following this relaxation period, finger sensors will be placed and baseline measures of all physiological data will be collected. DHEA and cortisol will be collected at 8 time points in all: baseline, immediately following the first conflict-resolution task, 15 minutes after the first conflict resolution task, immediately prior to the second conflict resolution task, immediately after the second conflict resolution task, and 15, 30, and 60 minutes after the conflict resolution task. Skin temperature, skin conductance, and heart rate will be measured continuously from baseline through the end of the laboratory task. Subjective measures will be administered at baseline, immediately before and after both conflict resolution tasks. Following completion of the first conflict resolution task and its associated post-test measurements, couples will self-administer either oxytocin or placebo spray and 45 minutes later will begin the second conflict resolution task. A timeline for completion of the laboratory task is outlined below:

Laboratory Task Timeline

TIME	PROCEDURE	MEASUREMENT
8:00am	Informed consent and questionnaires at Charleston Center	Informed consent; pregnancy test; breathalyzer; UDS; Interview and self-report assessment measures
9:00am	Couple escorted to CTTC; Relaxation period begins	
9:20am	Finger sensors placed; Begin baseline measurement	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; feelings toward partner
9:30am	Begin conflict resolution task #1	
9:40am	End conflict resolution task #1	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; relationship satisfaction; aggression
9:50am	Oxytocin or placebo self-administered	
10:30am	Finger sensors replaced; Begin second baseline measurement	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; feelings toward partner
10:40am	Begin conflict resolution task #2	
10:50am	End conflict resolution task #2	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; feelings toward partner
11:05am	15-minute post task assessment	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; feelings toward partner

11:20am	30-minute post task assessment	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; feelings toward partner
11:50am	60-minute post task assessment	Neuroendocrine: Salivary cortisol; DHEA Physiological: Skin temperature; skin conductance; heart rate Subjective: craving; distress; mood; feelings toward partner

Oxytocin administration and Neuroendocrine Assays

A 40-IU dose of intranasal oxytocin will be self-administered. Dr. Brady will provide prescriptions for oxytocin for research participants assigned to the oxytocin condition to research pharmacy services on the MUSC campus, who will compound the oxytocin doses and inform investigators as to the proper number of nasal sprays necessary to achieve the intended dose.

Unstimulated salivary samples will be collected at the previously noted time points by CTRC medical staff to measure cortisol and DHEA. Passive drool will be collected in polypropylene vials and iced immediately. Samples will be aliquoted into 1.8 mL nunc tubes and frozen at -70°C until assayed. Samples will be assayed twice using a high sensitivity salivary cortisol enzyme immunoassay system with an intra-assay precision (coefficient of variation, CV) of 3.35% - 3.65% with a sensitivity of <0.003 ug/dL (Salimetrics LLC). Samples will be analyzed using a PowerWave HT Microplate Spectrophotometer in conjunction with a Precision Series Automated Liquid Handling System (BioTek Instruments, Inc.).

E. Compensation

Participants will be remunerated for their time in cash. Each participant will be paid \$100 upon completion of the study. In the event that participants complete only part of the study, they will be remunerated \$15 for completing self-report and interview measures, \$15 for the first conflict resolution task, and \$70 for taking the oxytocin dose and completing the second conflict resolution task.

F. Maximizing Engagement and Retention

The proposed study targets a population facing considerable challenges that may influence the research team's ability to recruit participants through the duration of the study. The PI will recruit adequate research staff to assist in the recruitment, assessment, and scheduling appointments. All study staff will be trained in available techniques that the PI and Dr. Back have used in previous studies to minimize participant burden and facilitate participants' access to study staff and their attendance at study appointments. Study staff will provide appointment reminder cards, will call or text the day prior to each appointment to remind participants of study appointments, and will contact participants immediately by phone and/or email if appointments are missed.

G. Data Analysis

General. Data analysis will be conducted using SPSS v. 21 and Mplus™ software version 5.2 or higher (57). All analyses will be tested using significance level <0.05. Preliminary analyses will include determining the characteristics of the sample including demographic variables and descriptive statistics for all variables of interest included in the study. Reliability of assessment measures will be calculated prior to beginning main study analyses. We will also compare individuals who were eligible but declined

participation following screening and/or informed consent with those who chose to participate. We will also compare participants who withdrew or dropped out of the study following baseline assessment with study completers on demographic variables and main variables of interest. Subsequent analyses will be theory-driven and informed by the primary research questions of this study. Bivariate associations between variables will be examined via correlation. Demographic variables with significant bivariate associations with main outcome variables will be employed as covariates in subsequent analyses. The PI will conduct these preliminary analyses in consultation with Dr. Back and biostatistics consultation provided through SCTR at MUSC.

Missing Data. Given the multi-modal assessment strategy employed in the proposed study, it is expected that only a small proportion of missing data will appear. However, in the event that more than 10% of data on a key variable is missing, we will attempt to reduce bias and maximise statistical power by choosing and employing a method for imputing data. This method will be chosen in collaboration with Dr. Back and biostatistics consultation available through SCTR resources.

Preliminary Analysis. All study variables will be examined to assess normality, distributions, and outliers. Non-normal data will be transformed using log-10 or natural log transformation in an attempt to achieve greater normality of distributions. If appropriate normality cannot be achieved on key variables of interest, non-parametric statistical analyses will be employed.

Longitudinal Analysis. Linear regression analyses, structural equation modeling, and hierarchical linear modeling (HLM) will be employed to test study hypotheses. These approaches, HLM in particular, are ideally suited to analyze non-independent data reported by dyads (58). Multilevel models will be estimated, where the statistical non-independence of each partner's data is controlled by estimating each partner's parameters simultaneously through a procedure described in greater detail by Raudenbush and colleagues (59).

Hypothesis 1: Couples will demonstrate improved conflict resolution skills from the first observational conflict resolution task to the second following the administration of oxytocin.

Hypothesis 2: Couples will demonstrate lessened subjective, physiological, and neuroendocrine reactivity to the second conflict resolution task following the administration of oxytocin.

First, average levels of each of the outcome variables will be estimated through the use of a level-1 equation of a multilevel model. This approach will allow us to examine the average estimates of change in each of the outcome variables over the multiple time points assessed. Chi-square analyses and effect sizes will also be estimated to examine the between-subjects variance in each variable of interest. Chi-square analyses will indicate whether changes on each variable differed significantly across either or both partners. We will also examine the within-subject relationships between mental health and substance abuse variables over time for both partners.

H. Strengths of the Research Design

Expertise of Research Team. The PI, her mentor, co-mentor, and consulting staff at MUSC were assembled for the specific purpose of the proposed study. Each investigator taking part in this project has expertise in the treatment of PTSD, SUDs, and interpersonal violence. Dr. Flanagan also has expertise in the assessment and treatment of couples and the administration of behavioral interventions for couples in a variety of treatment settings.

Use of multi-modal, longitudinal assessments. The combined use of self-report, interview, observational, physiological, and dyadic data will provide rich and highly informative data. The repeated measures design of this study (assessing the same constructs over multiple assessment time points) will allow the research team maximize construct validity and evaluate a wide range of potential outcome variables in order to derive the most information possible from these data.

Assessment of novel treatment approach. Oxytocin has demonstrated tremendous promise in the fields of addiction. The present study is one of the first to investigate the effects of oxytocin on couples conflict resolution skills. It is the first to examine its effect on dyadic conflict resolution among couples with substance abuse problems, and the first to examine its effects on subjective, physiological, and neuroendocrine correlates dyadic conflict.

I. Limitations of study design

Use of retrospective self-report data. Recall bias may be a factor that limits the validity and generalizability of the proposed study. The use of multi-model assessment approaches may minimize the limitations incurred by this design element.

Absence of control group. A more rigorous design may include a control group receiving placebo with which to compare a treatment group. However, the goal of this preliminary study is to evaluate the feasibility and preliminary efficacy of oxytocin on the above mentioned factors and to provide information that will facilitate its revision and improvement.

J. Project timeline

During the first 3 months of this project, 2-3 couples will be recruited to pilot the study procedures. Also during this time, the study database will be created and data entry will be ongoing. Following the completion of this pilot phase, recruitment and assessment of couples will continue. Data cleaning and maintenance will also begin in month 4 and will continue through the duration of the study. Dissemination of data including presentation of preliminary pilot data at national conferences will begin in the second year of the project.

K. Study personnel

Principal Investigator: Julianne C. Flanagan, Ph.D. is an Assistant Professor within the Department of Psychiatry and the Division of Clinical Neurosciences at MUSC. Dr. Flanagan is a clinical psychologist with 10 years of specialized training in the treatment of trauma, substance abuse, and interpersonal violence. Dr. Flanagan received her Ph.D. from the University of Tennessee, completed her internship at the VAMC Puget Sound, Seattle, and a postdoctoral fellowship in the NIDA-funded T32 training program within the Department of Psychiatry at Yale University School of Medicine. She was the PI of a NIAAA-funded NRSA entitled Risk Factors for Intimate Partner Violence During Pregnancy. She is currently serving as Co-Investigator on a NIDA-funded study aimed at evaluating the efficacy of an integrated treatment for PTSD and substance abuse among OIF/OEF Veterans (PI; Back). She also has extensive experience working with diverse and vulnerable populations (e.g., pregnant women, incarcerated and court-mandated individuals, individuals with substance use disorders). Across various studies, she has taken a lead role in developing and implementing recruitment protocols; hiring, training and supervising research staff; designing and maintaining stringent human subjects protection plans; conducting statistical analyses; and preparing data for conference presentation and submission to peer-reviewed journals. She has expertise in mental health treatment, including dyadic interventions among civilian and military populations to address PTSD and co-occurring problems such as substance abuse and interpersonal violence.

Co-Investigator: Sudie E. Back, Ph.D. is an Associate Professor in the Department of Psychiatry at the Medical University of South Carolina (MUSC), and a clinical psychologist specializing in substance use disorders (SUDs) and the integrative treatment of co-occurring PTSD. She is a Staff

Psychologist at the Charleston VAMC's Substance Abuse Treatment Clinic (SATC). Dr. Back has been involved in the treatment of comorbid SUD/PTSD patients for the past 15 years. She served as a therapist on the original Stage Ia, NIDA-funded trial of COPE, was a Co-I on the RCT of COPE in Australia, a Therapist Trainer on a NIDA-funded study (PI: Hien) comparing COPE with relapse prevention among civilians with SUDs and PTSD, and was a therapist trainer for a STRONG STAR study (PI: Roache) examining the pharmacologic treatment of co-occurring alcohol dependence and PTSD in OEF/OIF Veterans. She is first author on the COPE manual, which is currently in press with Oxford University Press. She is the past PI of a 4-year NIDA-funded National Research Service Award that investigated cocaine dependence and PTSD. In addition, Dr. Back was involved with the Clinical Trials Network (CTN) and served as a therapist and a therapist trainer. She will serve as PI on this study. She will work closely with Dr. Flanagan to ensure that the project is successfully implemented.

Co-Investigator: Kathleen Brady, M.D., Ph.D. is a Professor in the Department of Psychiatry at the MUSC and a staff psychiatrist at the Ralph H. Johnston VAMC in Charleston. She is a board-certified psychiatrist specializing in addiction psychiatry who has been actively involved in clinical research in the drug abuse area for the past 18 years. Dr. Brady received her Ph.D. in Pharmacology from Virginia Commonwealth University and her M.D. degree from the Medical University of South Carolina (MUSC), where she completed a residency in psychiatry and completed an Addiction Psychiatry fellowship. As a Professor of Psychiatry at MUSC, Dr. Brady is Director of the Clinical Neuroscience Division, Director of the Women's Research Center, Director of the General Clinical Research Center (GCRC), and Associate Dean for Clinical and Translational Research. She has also served as the PI for the Southeastern Node of the NIDA Clinical Trials Network (CTN) since 2000. She will assist with implementation of the project and dissemination activities and will provide oxytocin prescriptions to research pharmacy services in this study.

Co-Investigator: Dr. Margaret Moran-Santa Maria, Ph.D. is an Assistant Professor in the Department of Psychiatry at the Medical University of South Carolina. She has 17 years of preclinical research experience and training in rodent models of stress including addiction. She has seven years of clinical research experience and training in substance use disorders and trauma, including extensive experience administering oxytocin in human trials. She has extensive experience with recruiting, retaining, assessing, and evaluating outcomes substance-dependent individuals and healthy resilient controls. She has collaborated with Drs. Back and Flanagan on multiple projects and publications that are directly related to this project. Dr. Moran-Santa Maria will be a Co-I on the study.

Study Physician: Bryan K. Tolliver, M.D., Ph.D. is an Assistant Professor in the Department of Psychiatry at MUSC and a licensed addictions psychiatrist with extensive experience working with adults who have experienced significant life stressors and substance use disorders.

Consultant: Michael E. Saladin, Ph.D. is a clinical psychologist and Professor in the Department of Health Sciences and Research at MUSC. Dr. Flanagan seeks to advance her training under the proposed award by collecting physiological data such as skin conductance and heart rate of Veterans and their intimate partners during an observational problem-solving task. Dr. Flanagan is particularly interested in examining the synchronicity of intimate partners' physiological responses during an observational problem solving task. He has both clinical and research expertise in examining and treating PTSD and substance abuse, as well as in implementing laboratory-based, experimental psychopathology protocols that involve the measurement of physiological responses to stress cues. Additionally, as Co-PI on a clinical research component of the SCOR P50 (Brady PI), he has over 12 years of experience examining gender differences in reactivity to both substance and stress cues/tasks. Dr. Saladin's role in this study is to assist the PI by providing consultation related to the collection and analysis of physiological data. He will guide Dr. Flanagan through the setup of the necessary data collection equipment and computer software, provide feedback regarding the design of her data collection protocol, and provide consultation regarding appropriate methods to reduce and analyze the data. Finally, I will be available to consult with Dr. Flanagan during the project period and will assist with the implementation of her training plan as needed.

Consultant: Peter Tuerk, Ph.D. is an Assistant Professor in the Department of Psychiatry and Behavioral Science at MUSC and Associate Director of the PCT at the Ralph H. Johnson VAMC, where he specializes in treating OEF/OIF Veterans. He also serves as Director of Research Training (DRT) for the APA-accredited psychology internship. Dr. Tuerk specializes in exposure therapy for PTSD and currently works with Dr. Edna Foa (founder of PE) as a trainer of PE therapy for the national VA PE dissemination effort. In that role, he works closely with Dr. Foa in providing clinical supervision and instruction to VA therapists across the country. Dr. Tuerk also has expertise in the area of physiological data collection. For the proposed project, Dr. Tuerk will assist the PI in the collection and analysis of dyadic physiological data.

Study Prescriber: Anjinetta Johnson, P.A. is a physician assistant who has worked with our group on a variety of past studies. Ms. Johnson will contribute to screening participants for eligibility, conducting clinical interviews, history and physical exams and venipuncture when necessary. She will also be able to write prescriptions for study medications.

Research Assistant: Alexandra Snead, B.A. is currently a first year graduate student at the Citadel working towards her Masters degree in psychology. Ms. Snead will be responsible for data entry and will participate in participant recruitment and assessment activities.

6. PROTECTION OF HUMAN SUBJECTS

Risks to the subjects. The PI and co-investigators located at MUSC have completed the mandatory University of Miami CITI Human Subjects Research Education Course online. All research activities will be reviewed by MUSC's IRB on a yearly basis. The research staff will ensure that all information needed for the continuing review is at the IRB in accordance with IRB requirements.

Human Subjects Involvement and Characteristics. A total of 30 couples (60 individuals) who meet inclusion criteria will be enrolled in the proposed study over a 2 year period. Women and men of all racial and ethnic groups are eligible for participation in the proposed study. Charleston's population is 64% Caucasian, 34% African American and 2% identifying a racial background other than those previously listed. Therefore we anticipate a similar racial spectrum for the proposed study. Individuals under the age of 18 will not be included in the study. Inclusion criteria dictate that all participants must be 18-65 years of age, both partners must be willing to participate, at least one partner in the couple must endorse substance abuse in the past 60 days. Exclusion criteria include pregnancy for women, current psychotic or bipolar disorders, active suicidal or homicidal ideation and intent, subjects who would present a serious suicide risk, such as those with severe depression, or who are likely to require hospitalization during the course of the study, severe unilateral IPV in the past year, or BMI greater than 39. If both partners meet criteria for participation and independently provide informed consent, they will be scheduled to complete a baseline assessment.

Targeted/Planned Enrollment Table

Total Planned Enrollment: 40

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	0	0
Not Hispanic or Latino	36	36	72
Ethnic Category: Total of All Subjects*	72		

Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	24	24	48
White	12	12	24
Racial Categories: Total of All Subjects*	36	36	72

**The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects”.*

Sources of Materials. All data collection described in this protocol is collected specifically for the purposes of the proposed research project. All data will be collected on the MUSC campus. Self-report, observational, physiological, and interview data will be collected. Data will be used to evaluate the efficacy of oxytocin to improve conflict resolution skills among couples with recent substance abuse. Observational problem-solving tasks will be recorded for data analytic purposes and will be kept on the secure, password protected CND network. Participants will also provide breathalyzer and UDS samples analyses prior to the beginning of each interview and group treatment session. To maintain standards of confidentiality set forth by the American Psychological Association, all digital and paper data collected will be numerically coded, kept in locked filing cabinets and password-protected computers within MUSC’s encrypted data server. No parties shall have access to these data aside from the PI and necessary research staff. A master list of participant names, ID number, and contact information will be kept in a location separate from study materials within MUSC’s encrypted data server. Video recorded problem solving tasks will be kept in the same manner as the other PHI collected in this study: secured on the password protected CND server.

Potential Risks. Research participation may result in psychological distress as a result of the conflict resolution task, from disclosing personal or sensitive information about their health, their history, or their relationship within the self-report or interview portions of data collection. Loss of confidentiality is a risk of participation. Risks associated with intranasal oxytocin have been noted among women given intravenous, rather than intranasal, oxytocin for its FDA-approved purpose, to induce labor. These risks include seizures, mental disturbances, nausea, vomiting, irregular heartbeat, high blood pressure, and unexpected bleeding or contraction of the uterus and have been observed in a small number of women. However, preliminary studies conducted by the PI, Dr. Back, and senior researchers in our department and others conducting clinical trials in this area indicate that risks of intranasal oxytocin administration at the planned dose of 40 IU is minimal and manageable through the proposed human subjects protection methods described below. All possible efforts to minimize participant burden and distress will be made. All possible efforts will also be made to protect the confidentiality of participants’ data, except in the event of imminent risk to self or others, or in the event of disclosure of child or elder abuse. In the event that confidentiality must be broken to protect the safety of participants or others, only the data essential to make an adequate report to authorities will be disclosed. All participants will review the IRB-approved informed consent document with research staff in a private room separate from their partner. Through this process, research staff will inform all research participants of the risks of participation, including emotional distress. In the event that a participant experiences substantial distress or reports risk of harm to oneself or others, they will be asked to complete a safety plan and if necessary, call 911. The Mobile Crisis Unit of Charleston County and urgent care services on the MUSC campus are additional resources available to study staff and research participants. Drs. Flanagan and Back are licensed clinical psychologists equipped to help participants effectively manage their distress and to evaluate conditions in which participants may need additional assistance. In the event that a participant becomes distressed during or following an assessment, the PI will also contact the participant the following day to ensure they have received resources necessary, and to assess their

safety and welfare. In the event that any adverse event occurs resulting from study participation, that event will be reported in writing to the MUSC IRB and NIH within 24 hours. In past and ongoing studies conducted at MUSC, these resources have been sufficient to manage problems or distress related to participation in studies on similar topics.

Safety and Monitoring Plan. Every possible effort will be made to protect the safety and confidentiality of research participants. In the event that any participant in this study reports or demonstrates the need for more substantial mental health, substance abuse, or other intervention including hospitalization, referral for treatment will be made by the research staff. Participants who report suicidality will be closely monitored by the research staff, will be engaged in safety planning, and if necessary, will be referred for psychiatric treatment/hospitalization. The PI and her mentor are licensed clinical psychologists and are equipped to monitor study participants for improvements and deterioration in mental health/substance use symptoms. Drs. Flanagan and Back have extensive experience working with acute populations and populations at-risk for severe mental health problems and substance abuse problems.

The PI, in collaboration with her team of co-investigators, will follow MUSC's well-established protocol for referring participants for emergency hospitalization, crisis management, management of suicidal/homicidal ideation, and acutely severely mentally ill individuals. In the event that research staff establishes the need for any of these services, research staff will page the on-call psychiatrist to consult about the participant's presentation and treatment needs. Research staff will also have the option to escort the participant to the psychiatric walk-in clinic or hospital emergency room.

Suicide Risk Reduction Plan. A specific protocol to address suicidal ideation among study participants has been developed. All investigators are highly trained doctoral-level psychologists or medical doctors with extensive experience in assessing and managing suicidality and self-harm behaviors, particularly among Veterans and their families. The baseline assessment includes specific assessments (on the PHQ-9) of suicidal ideation. Research assistants hired to conduct recruitment and have contact with study participants will be trained in the assessment of suicide risk and the protocol in place to facilitate access to care for those in need. Participants who report acute suicidal ideation, intent, and plan will be excluded from further participation in the study and will be immediately referred for psychiatric evaluation/care at one of the 24 hour care clinics on the MUSC campus or in the VAMC psychiatric emergency room. If research staff other than the PI conduct an assessment where acute suicidal ideation/intent is identified, the PI will contact that participant for further assessment of mental health treatment needs.

B. ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent

Initial respondents will contact research staff by phone to be screened for eligibility. This brief screening measure contains questions directly pertaining to the study's inclusion and exclusion criteria. Participants who meet eligibility criteria and are interested in participating will be scheduled with research staff for an in-person assessment session with their partner. In a private room apart from their partner, potential subjects will be provided with a full description of the nature and requirements of study participation, and asked to read and sign an IRB-approved consent form.

Informed consent will be collected by the PI and trained research assistants. Dr. Flanagan is a licensed clinical psychologist with extensive experience working with couples. Dr. Flanagan will train research staff in the study protocol, and the essential elements of ethical conduct of research so that each member of the research staff is well-equipped to provide participants with adequate information prior to their agreeing to participate in the study.

Informed consent will be collected in a private room, separately for each member of the dyad. Research staff will provide information related to any questions participants may have. Participants will

also be informed that they are not required to make an immediate decision about whether or not they choose to participate on that day. Although participants will complete the informed consent procedure apart from their partner to ensure each partner's safety, confidentiality, and to minimize the potential for coercion by partners, all participants will have the opportunity to privately discuss their decision to participate with their partner prior to beginning any study procedures.

Protection against Risk

All research personnel will attend a required in-service training conducted by the PI, where the screening, informed consent, and assessment protocols will be described. The study protocol and safety plan will be printed and kept in a central location within the research space for easy access for all research staff. Protocols for the management of any participant or study-related emergency will be established and research staff will be trained on these protocols. Drs. Flanagan will be aware of the scheduling of all participant assessments. Dr. Flanagan will conduct many assessments. All participant assessments will be scheduled during normal working hours in the Charleston Center on MUSC campus in order to ensure the presence of clinical staff and to ensure the safety of participants and research staff.

To protect participant confidentiality, all data will be stored in locked filing cabinets within a locked office and on MUSC's encrypted computers and data servers. All participants will be assigned a numerical study identifier to minimize the potential to link identifying information with study data. One master list of study participants will be kept separate from all other study data. Access to data will be restricted to research staff. Data will be maintained in a manner consistent with IRB-approved protocol. Only deidentified data will be used to present findings in presentations or publications. All research staff have or will complete the University of Miami CITI training course in the responsible conduct of research.

Drs. Flanagan and Back are clinical psychologists with extensive experience working in research and clinical settings with high-risk populations. They are intimately familiar with the safety needs of Veterans and their families and methods for optimizing participant safety. Drs. Flanagan and Back have received specialty training to safely manage crises and are equipped to train research staff to effectively do the same. Drs. Flanagan and Back will oversee the training of research staff in IPV safety planning. Dr. Flanagan has run more than one hundred couples through experimental protocols and recently published a first-authored manuscript describing the best practices for maintaining the highest level of participant safety in research including an IPV component (60), which directly impacted the methodology chosen in the proposed study. Both investigators are practicing clinicians and will be available to manage safety issues presented by research participants. In order to further ensure participant safety and minimize risk outside of working hours, each participant will be provided with a list of referral information to 24-hour acute care facilities, community counseling and mental health centers, suicide prevention hotlines and crisis management facilities, and substance abuse programs at the VA and in the surrounding community. Participants in the proposed study may experience emotional distress during the course of the treatment as they discuss problematic issues in their lives and relationships. However, based on the research team's past experience and available literature the risks involved in the proposed project are minimal and manageable (60, 61). In the event that a participant is excluded from the study due to reports by one or both partners of safety concerns or coercion, research staff will immediately provide the participant with community resources and invite them to complete a safety plan. In the event that a participant arrives to an assessment session intoxicated, the study visit will be rescheduled and safe transportation home will be arranged for that participant. Dr. Flanagan will also call that participant the following day to follow-up, provide any necessary resources, referrals, or support, and encourage that participant to continue participation in treatment. Participants will be informed during the informed consent procedure that the fact of their participation and their responses are completely confidential and will not be shared with their partner, their health care providers, or any other third party. They will also be informed of the standard limitations of confidentiality set forth by the American Psychological Association such as imminent risk

of harm to self or others, or child or elder abuse. Participants will be informed that they can decide not to answer any questions and, should they become distressed or are uncomfortable with continuing to participate, they may discontinue participation at any time without penalty. The compensation schedule will be stated verbally and in writing in the initial study description and the informed consent procedure. The participant's copy of the consent form will provide contact phone numbers and email for each member of the research team should a participant have any questions, comments, or concerns about their participation. Participants will have the opportunity to have a copy of the consent form mailed to them at any time.

Potential benefits of the proposed research to the subjects and others

Benefits of participation in the proposed study include a thorough psychological and substance use assessment, referral and access to appropriate treatment services and community resources if desired, and remuneration for one's time and effort. While these benefits may be considered minimal, we believe that they outweigh the minimal risk and burden incurred by participants. Participation in the proposed study may facilitate improvement in relationship functioning and access to treatment services for some participants. Participants will also be participating in a study that has the potential to guide and provide treatment for similar members of the community.

Importance of the knowledge to be gained

The proposed study presents the potential for important knowledge to be gained. Preclinical and preliminary human data suggest that oxytocin has great potential to influence treatment in the field of addictions. Individuals with addictions experience considerable mental health and relational challenges, yet research investigating pharmacological augmentations to improve conjoint therapies to treat these issues is scant. The present study is the first study to our knowledge to investigate the utility of oxytocin to improve conflict resolution skills and mitigate subjective, physiological, and neuroendocrine reactivity to this common stressor. The use of oxytocin as an augmentor to behavioral interventions, particularly those that employ conjoint dyadic modalities, present the potential for a highly efficient and cost-effective way to meet the treatment needs of couples across settings nationwide.

Risk to Benefit Ratio

The experienced research staff conducting this study will make every possible effort to maintain the safety of our research participants, to minimize the risks and burden they incur as a result of participation, and to maximize potential benefits. The knowledge we may gain from the proposed study will address a crucial need for studies to develop and evaluate treatments to improve the health of couples. In the event that new information regarding the risk to benefit ratio becomes available during the course of the study, research participants will be notified. Further, the PI and her mentor will consult with our research team and DSMB to make any necessary study modifications.

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/dsmb/sop.html).

Summary of the Protocol. The proposed study aims to develop and conduct initial feasibility and efficacy testing of oxytocin for the improvement of couples' conflict resolution skills. The primary outcome in this study includes an improvement in conflict resolution skills and a reduction in subjective, physiological, and neuroendocrine reactivity to dyadic conflict.

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.

Data Management and Analysis. A data analytic plan is outlined in the Data Analysis section. Because this study is a preliminary test of a new medication, we are interested in examining a broad range of outcome variables. The main outcome variables include the frequency and severity of negative conflict resolution skills and the frequency and intensity of positive conflict resolution skills as well as

subjective, physiological, and neuroendocrine reactivity to dyadic conflict. Outcome data will be analyzed using regression analyses, structural equation modeling, and hierarchical linear modeling. The alpha level for statistical significance will be set at .05.

Quality Assurance. Data quality will be monitored by random inspection of completed assessment forms by research staff. Any problems with the assessment process, data collection, or data entry will be discussed with the PI and Dr. Back.

Regulatory Issues. All Adverse Events (AEs) that meet criteria for reportable AEs will be reported to the MUSC IRB and NIH within 10 working days. AEs are reportable if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. 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. Serious AEs (SAEs) will be reported within 24-hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies. All AEs are reviewed weekly by the PI, and annually by the Data Safety Monitoring Board (DSMB) and IRB. Any significant actions taken by the local IRB and protocol changes will be reported to NIDA. AEs and SAEs occurring during the course of 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 training including identification, evaluation, and documentation and reporting. All research staff will identify any potential AEs during the course of the study from self-report data and administration of assessments and interviews. This information will be provided to the PI and Co-Investigators, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

Definition of AE and SAE

Anticipated Risk - Mild to moderate discomfort when completing the laboratory assessment is anticipated and is not considered an adverse event for this study. Potential for relapse of alcohol and or drug use is anticipated and relapse is not considered an adverse event for this study. Potential for inpatient detoxification following a relapse is not unexpected among some subjects, particularly subjects with a prior history of medically supervised detoxification, and is not considered an adverse event for this study.

Adverse Event- An untoward medical event among randomized subjects occurring during a clinical study that can represent a new symptom experienced by a study subject or an exacerbation or worsening of an existing condition.

Serious Adverse Event- Any untoward medical event or adverse drug experience occurring at any dose that results in any of the following outcomes:

- 1) Death.
- 2) A life threatening event.
- 3) Requires or prolongs inpatient hospitalization
- 4) Persistent or significant disability/incapacity.
- 5) A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Documentation and Reporting:

Any clinical study event that is judged to be an AE will be recorded on the AE Form during the course of the study. The PI ensures this information is captured during every study subject visit. If the AE is not serious, the information is recorded, managed medically as appropriate, and the event is followed until resolution. AEs are reportable 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 a reportable AE. 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. SAEs are also recorded on the AE Form, managed medically as appropriate, and the event is followed until resolution. In addition, the PI reviews all completed AE forms for determination of SAE that require reports to the Sponsor. The PI informs the Sponsor immediately of knowledge of a SAE. As additional information becomes available on the SAE, it will be forwarded to the Sponsor. All SAE reports shall be sent to the IRB and NIH within 24 hours of learning of event occurrence.

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. Additional relevant AE information if available will 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 subject 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 within 24 hours of the site's initial notification of the SAE:

- i. Study Co-Investigators.
- ii. The MUSC institutional review board (IRB). Committee meets monthly. Communication with the IRB is through email, memos, official IRB forms, and online reporting.
- iii. The NIH program officer.
- iv. The data safety monitoring board members.

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 the PI and for forwarding to the NIH program officer as appropriate. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NICHD Medical Safety Officer within two weeks of the initial SAE report.

Study Safety. The potential risks and benefits and methods to minimize these risks are outlined above. Protocols for reported AEs and SAEs are outlined above. All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration.

Study procedures will follow the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to the PI. All requests by subject's physicians and other medical providers will be referred directly to PI.

DSM Plan Administration. The PI will be responsible for monitoring the study. The PI and statistician will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSM report will be filed with the IRB on a yearly basis, unless greater than expected problems occur. The report will include subject characteristics, retention and disposition of

study subjects, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report results at the end of the trial.

DSM Board. We will create a DSMB to monitor the overall participant safety, the rate and severity of adverse events, and the validity and integrity of the data. The panel includes 2 researchers with experience in treating patients with SUDs and PTSD (Kathleen Brady, M.D., Ph.D.; Therese Killeen, Ph.D) and a statistician (Dr. Amy Wahlquist). The DSMB will also include Dr. Erin McClure, Ph.D., an additional investigator in the field of addictions and oxytocin. The board may be called at any point if needed for unexpected AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the recommendations of the board. Confidentiality will be maintained during all phases of the study.

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