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PROTOCOL TITLE: Effects of Oxytocin on Alcohol Craving and Intimate Partner Aggression

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1.0 Objectives / Specific Aims

Alcohol use disorders (AUD) and intimate partner aggression (IPA) frequently co-occur. AUD is commonly associated with IPA perpetration14-16 as well as victimization14,17-19. Indeed, AUD is responsible for a substantial portion of the $4 billion in health care costs that U.S. taxpayers sustain annually as a result of IPA20-24. Behavioral interventions to reduce AUD and co-occurring IPA have received moderate, but inconsistent support 25-28. Thus, there is a critical need to develop more effective interventions to reduce AUD and co-occurring IPA.

The neuropeptide oxytocin has been shown to significantly attenuate hypothalamic–pituitary–adrenal (HPA) axis dysregulation, which is a well-established correlate of both AUD and aggression29-32. Oxytocin has demonstrated the ability to reduce stress-induced craving, drug-seeking behaviors, and relapse among individuals with alcohol, marijuana, cocaine, or stimulant use disorders32-36. Notably, these are the substances most strongly and consistently linked with IPA37,38. Clinical and preclinical research also indicate that oxytocin promotes prosocial behavior and reduces negative affect and aggression39-41. Preliminary findings among normative human couples suggest that oxytocin may also reduce dyadic conflict42. Thus, oxytocin may effectively reduce alcohol craving and IPA. However, this topic has not yet been investigated.

A significant barrier to the investigation of AUD and co-occurring IPA is the scarcity of studies employing laboratory paradigms to measure IPA. Human laboratory paradigms have been used extensively to advance the study of craving and AUD29,43,44. This methodology is essential to develop interventions to reduce AUD and co-occurring IPA. The current study will address this gap in the literature by utilizing the well-validated Taylor Aggression Paradigm (TAP)2 to examine the effects of oxytocin (40 IU) or placebo on (1) alcohol craving, (2) laboratory-induced IPA, and (3) subjective, physiological, and neuroendocrine reactivity in couples with AUD and IPA. To accomplish this, we will employ a double-blind, placebo-controlled design. The sample will include 100 couples in which one or both partners meet diagnostic criteria for current AUD and report IPA within the current relationship. The following Specific Aims are proposed:

Specific Aim 1: Examine the effects of intranasal oxytocin (40 IU) vs. placebo on subjective alcohol craving and aggression in response to the Taylor Aggression Paradigm (TAP) among couples with AUD and IPA.

Specific Aim 2: Examine the effects of intranasal oxytocin (40 IU) vs. placebo on physiological (i.e., heart rate, skin conductance) and neuroendocrine (i.e., cortisol,) response to the Taylor Aggression Paradigm (TAP) among couples with AUD and IPA.

Specific Aim 3: Identify predictors of oxytocin response (e.g., gender, endogenous oxytocin, IPA severity).

We hypothesize that individuals who receive oxytocin, as compared to placebo, will demonstrate significantly lower alcohol craving and aggression, as well as lower physiological and neuroendocrine reactivity to the TAP. Furthermore, we hypothesize that oxytocin response will be greater among women as compared to men. While the existing literature examining the effects of endogenous oxytocin and potentially traumatic experiences, such as IPA, on oxytocin response is scant, we hypothesize that oxytocin response will be lower among individuals with higher endogenous oxytocin levels and greater IPA severity.

2.0 Background

AUD and IPA commonly co-occur. Alcohol use disorders (AUD) are consistently identified as both a precipitant and consequence of intimate partner aggression (IPA). In the general population, rates of IPA perpetration are 2 to 8 times higher among individuals with, as compared to without, AUD [1]. Furthermore, rates of AUD are up to 6 times greater among individuals with, as compared to without, a history of IPA victimization[2]. Among treatment-seeking populations, high rates of co-occurring AUD and IPA have also been observed[3]. A strong temporal association has been established between alcohol use and IPA perpetration[4-7] and between IPA victimization and AUD[4,8], suggesting that AUD and IPA have a bi-directional nature. As the co-occurrence of IPA in combination with AUD often reflects greater levels of aggression, severity and risk, being able to identify and treat co-occurring AUD and IPA is a significant health priority[13-15].

The health burden associated with co-occurring AUD and IPA is extensive. The annual cost of AUD alone in the U.S. is over $600 billion[9,10]. More than one-third of Americans experience IPA during their lifetime[11], costing taxpayers approximately $4 billion dollars annually in health care costs, lost time at work, and criminal justice expenses[12,13]. The high health care costs associated with IPA are known to persist even after IPA ends[14]. The health burden associated with co-occurring AUD and IPA is particularly malignant, resulting in increased risk of mortality from partner homicide and suicide, injury, physical health problems, psychiatric problems (e.g., PTSD, depression, anxiety, insomnia), HIV, and smoking[13,15-22], and poor treatment outcomes[23]. Evidence that co-occurring AUD and IPA are transmitted across generations[24] further highlights the significant and enduring societal health burden associated with this dual condition.

There is a scarcity of effective treatments for co-occurring AUD and IPA. Several evidence-based psychosocial interventions for AUD have been developed[25,26]. However, relapse rates are high and there is significant room for improvement. Because AUD is a salient proximal and distal predictor of IPA[27,28], a strong theoretical rationale exists to use AUD treatments to help reduce AUD and IPA concurrently[29,30]. While recent research has found some promising reductions in IPA following AUD treatment[31-33], findings are inconsistent and grow increasingly spurious following the end of treatment[34-36]. Thus, there remains a critical need to improve treatments for co-occurring AUD and IPA, including the exploration of pharmacological interventions.

Inadequate measurement is a critical barrier to developing effective treatments for AUD and IPA [37,38]. Researchers examining IPA rely primarily on self- or partner-report methodologies[39] which are frequently influenced by factors such as recall bias, interdependency of partners' behaviors, and non-agreement between partners' reports which limit the reliability of IPA self-report data. Whereas research integrating technological advances such as experience sampling methods, interactive voice response, and handheld devices to collect ecological momentary assessments have reduced this barrier, data indicate that these biases in the current state of data collection methodology remain[39]. Thus, developing effective treatments for co-occurring AUD and IPA remains difficult in the absence of more effective measurement strategies.

Human laboratory paradigms have been useful in enhancing treatments for AUD[40], but have not yet been applied to IPA. Laboratory paradigms utilized by Dr. Back (Primary Mentor) and others have successfully predicted craving[41-45], relapse propensity[46-48], and self-initiated abstinence[49]. Laboratory paradigms such as those used by Dr. Becker (Co-Mentor)[50-52] have also facilitated the study of pharmacological interventions for AUD[53]. Human laboratory paradigms have been applied to the measurement of aggression[54,55]. However, IPA specifically has not yet been examined in the laboratory among AUD populations. Applying well-controlled laboratory paradigms to the study of AUD and co-occurring IPA will: (a) allow for the identification

of neurobiological risk and protective factors contributing to AUD and aggression, (b) more precisely elucidate associations between risk factors and IPA compared to existing daily diary and experience sampling methods[5,39], (c) examine aggression among both partners simultaneously, and (d) inform effective treatment development for AUD and IPA.

Oxytocin may help reduce craving and aggression. Accumulating evidence suggests that oxytocin may help reduce the effects of social stress on alcohol use behaviors[49,56]. Few studies, however, have investigated the effects of oxytocin on human aggression. Oxytocin may help reduce IPA by reducing its known precipitating factors such as alcohol use, stress reactivity, and negative affect and by enhancing positive affect. No studies to date have examined the effects of oxytocin among individuals with AUD and co-occurring IPA. Further, accumulating evidence suggests that individual and contextual differences may influence concentrations of endogenous oxytocin and its effects on human behavior[57]. The proposed study will address critical gaps in the literature by utilizing a well-controlled human laboratory paradigm (Taylor Aggression Paradigm) to examine the ability of oxytocin to reduce craving and aggression among couples with AUD and co-occurring IPA. We will compare subjective, physiological and neuroendocrine responses to the laboratory test within-subjects before and after they receive oxytocin or placebo, and between-subjects who receive either oxytocin or placebo. We will also examine individual, dyadic, and contextual factors that may influence oxytocin's effects on craving and aggression, which will help inform future translational research focused on the use of oxytocin among AUD and IPA populations.

3.0 Intervention to be studied

Oxytocin is a hypothalamic nonaneuropeptide that initiates physiologic events necessary for parturition and lactation[58,59]. Intravenous infusions of oxytocin are commonly administered among women during childbirth to facilitate labor and lactation and has FDA approval for this purpose. Scientific inquiry of intranasal oxytocin is growing at a rapid rate in the field of psychiatry. Current perspectives on the effects of oxytocin support its role in mitigating addictive behaviors[49,60-64] and enhancing adaptive social behavior and cognition such as interpersonal trust[65], recognition[66], empathy[67,68], generosity[69]. Preliminary findings indicate that oxytocin can enhance positive conflict resolution behaviors among couples[70]. Recent studies also suggest that individual and contextual factors such as gender and psychosocial history may inform the behavioral effects of oxytocin[71-77].

Oxytocin and placebo (saline) will be compounded by MUSC's Investigational Drug Services (IDS) or Pitt Street Pharmacy in Mt. Pleasant. IDS will conduct randomization and keep a record of the blind. Once study fully transitions to use of Pitt Street Pharmacy, Anjinetta Johnson, the study Physician's Assistant, will hold the blind. Participants will blow their nose, exhale through their nose, then spray into one nostril while inhaling, alternating nostrils until the 40 IU dose is achieved. A 40 IU dose has demonstrated extensive safety and efficacy, is within the normal dosing range, and one of the most common concentrations utilized in human research[78-80]. Dr. Moran-Santa Maria (Co-I) has an FDA IND to utilize oxytocin.

4.0 Study Endpoints

Outcome measures include 1) alcohol craving, 2) aggression as measured by the Taylor Aggression Paradigm, 3) physiological (e.g. heart rate, skin conductance) and neuroendocrine reactivity(e.g., salivary cortisol)

5.0 Inclusion and Exclusion Criteria/ Study Population

All participants will be at least 18 years of age or older. Women and members of minority groups will be eligible for participation.

Inclusion criteria indicate that participants must (a) aged 18-75, (b) fluent in English, (c) endorse at least one instance of mild or moderate physical IPA with their partner as defined by the Revised Conflict Tactics Scale (CTS-2)[97], (d) both partners must be willing to participate and (e) one or both partners must meet DSM-V diagnostic criteria for an alcohol use disorder (AUD). Concurrent substance use disorders (e.g., marijuana) is acceptable provided alcohol is the participant's primary substance of choice.

Exclusion criteria include (a) pregnancy or breastfeeding, (b) current or history of psychiatric or medical condition that could interfere with neuroendocrine function (e.g., hematological, endocrine, renal, or pulmonary disease; synthetic glucocorticoid or exogenous steroid therapy; psychotic, bipolar, eating disorders), (c) both partners with a BMI ≥ 39, (d) current suicidal ideation and intent, (e) severe physical or sexual IPA in the past as defined by the CTS-2[97], (f) initiation of psychotropic medication in the past 4 weeks, (g) acute alcohol withdrawal as indicated by a score of 8 or greater on the CIWA-Ar[98], (h) a current or past diagnosis of epilepsy or history of seizures.

6.0 Number of Subjects

A total of 200 participants comprised of 100 couples will participate in this study.

7.0 Setting

All procedures will be conducted on the MUSC campus. Procedures can also be conducted via telehealth.

8.0 Recruitment Methods

Recruitment will be conducted at the Center for Drug and Alcohol Problems (CDAP) at MUSC and in VA treatment clinics. There are approximately 436 inpatient and 822 outpatient annual admissions to CDAP. In 2014, there were 1,258 admissions to the program with the majority of patients seeking AUD treatment. The Charleston VAMC Substance Abuse Treatment Center (SATC) received 1,253 new admissions in 2014. Approximately 70-80% of weekly referrals meet criteria for AUD. The Charleston VAMC Couples and Family Clinic treats approximately 130 new unique couples each year. The study team will use a list provided by the VAMC to mail IRB approved recruitment letters. In addition, we will post IRB and R&D-approved recruitment flyers in other MUSC and VA treatment clinics and catchment areas. Advertisements will be placed on the internet (e.g., Craigslist and SCresearch.org). Participants who refer others to the study will be compensated $10 per randomized referral, allowing us to reach a wider pool of potential participating couples including couples from the community with IPV and AUD, in addition to treatment-seeking couples with IPV and AUD. Further, participants from past MUSC research studies who have consented to be contacted for future research studies will be recruited via telephone screening and/or e-mails. These individuals will be referred to us via other MUSC researchers, or they may have indicated consent to be contacted about future research studies within their MUSC medical records. The research team has used these methods successfully to recruit patients to clinical and laboratory studies. If recruitment is delayed during the first year, we will run advertisements in local newspapers and radio stations to ensure the target sample is achieved.

EPIC will be used for recruitment. The study team will use an IRB approved letter and script to inform identified individuals about our study.

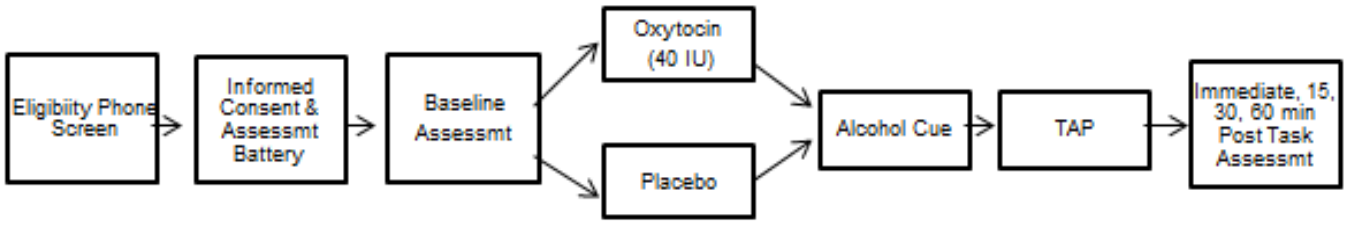
College students ages 18-75 enrolled at area colleges and universities will be contacted from respective registrar lists (no participants will be recruited until an interinstitutional agreement is signed by the respective institution, submitted as an amendment to the MUSC IRB, and approved by the MUSC IRB). Potential participants will be sent a recruitment email that includes details about the study (e.g., time requirement, basic inclusion criteria, compensation), a link to the IRB approved screener, and contact information for the research team will be included in the email. Potential participants will also be contacted via phone.

9.0 Consent Process

Potential participants will be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form before any study procedures or assessments are conducted. Individuals who were recruited from the VA will also be required to read and sign a VA R&D –approved consent. Informed consent will take place on the MUSC campus or via telehealth, using an IRB approved platform. Individuals who were recruited through the VA can be screened and assessed at the VA clinic site. Initial eligibility screening will be conducted by the PI or a trained research assistant by telephone or in person. If preliminary inclusion and exclusion criteria are met, staff will schedule an assessment appointment for the couple. In a private room apart from their partner, participants will be provided with a description of the nature and requirements of study participation, and asked to read and sign an IRB-approved consent form prior to beginning any study procedures. In the event of eConsent, the informed consent process will still take place privately. If couples do not have the ability to each have a private room for eConsent (within their residence(s), separate appointments may be arranged to maintain privacy and to meet with each individual partner separately. REDCap will be utilized for re-consents when coming to the office would place undue burden on the participant. In the case of a VA consent, a VA consent document will either be mailed or emailed to the participant. PI/study team will use government furnished equipment to video call with the participant and go over the document. Once the document is signed, the participant will be asked to hold it up to the screen and a screenshot will be taken and saved for records

10.0 Study Design / Methods

Figure 1 below illustrates the study design.



Telehealth: Participants in this research study may choose to complete the assessment appointment via home-based telehealth (HBT) care (i.e., service delivery to patients in their homes using consumer-friendly, video-conferencing technology) which may likely enhance retention by directly circumventing financial and transportation barriers associated with traveling to MUSC/VA for an in-person session. HBT sessions will be delivered via standard desk, laptop

computer, tablet, or smartphone running MUSC/VA approved applications. Participants who choose telehealth will be required to have their own computer, tablet, or smartphone; however, webcams will be provided to participants for these visits as needed. Participants will be mailed required materials such as alcohol saliva test strips and pregnancy tests. Separate appointments will be made with each partner for instances where study team needs to meet with each individual separately or privately.
Biological samples will not be collected for individuals participating in HBT care, however prior to the assessment appointment the study team will mail pregnancy tests and alcohol saliva strips to test for pregnancy and recent alcohol use. The alcohol saliva strip must read white (indicative of 0.00 BAC to validate the consent and prior to completing any study procedures. Further, prior to proceeding, females will be asked to take a pregnancy test and must provide verbal confirmation of a negative pregnancy test prior to proceeding with the assessment appointment.

Female participants who complete the assessment appointment via telehealth will be required to take an at-home urine pregnancy test during that visit (provided by study team) and confirm a negative result (verbally and with photo of dipstick). The pregnancy tests used in this study are designed for at-home use, come with clear and simple instructions. In very rare and highly unlikely circumstances where the participant is unfamiliar with how to provide a urine sample or take an at-home pregnancy test, study staff can provide further instructions on how to provide a urine sample, how use the dipstick to test, and to differentiate between a positive and negative result. Ability and willingness to perform an at-home pregnancy test is required for telehealth female participants.

Required study supplies for telehealth participants will be shipped overnight via trackable UPS.

Assessment Procedures. Following informed consent, eligible participants will complete a breathalyzer or saliva alcohol test, urine drug screen, blood draw, and pregnancy test (for women). Participants will have the option to participate in genomic research by providing an extra 7 milliliters of blood during the study blood draw. Participants will complete a psychosocial and medical history assessment (see Table 2). Note that for telehealth participants, biological specimens will not be collected, however, female participants will be required to take a pregnancy test (provided by study staff) and will be required to verbally confirm a negative result prior to continuing with any procedures. Provided that all inclusion and exclusion criteria are met, participants will be scheduled to complete the laboratory testing portion of the study. Participants will be instructed to abstain from caffeine, nicotine, alcohol or other substances of abuse prior to the laboratory testing procedure. Smokers will be asked to abstain from smoking during study procedures and offered a nicotine patch prior to participation. Nicotine patch dosage will be determined by the number of cigarettes participants smoke daily (≥20 cigarettes/day=21mg; 10–19 cigarettes/day = 14 mg patch; 5–9 cigarettes/day =7 mg patch).

Human Laboratory Procedure. Participants will complete an alcohol cue reactivity task and the TAP procedure approximately 45 minutes after receiving a 40 IU intranasal dose of oxytocin or placebo (i.e., saline). In a recent review of oxytocin studies, 40 IU is within the normal dosing range for humans and is one of the most common single dose concentrations utilized in human research[78]. This literature indicates that a 40 IU dose is safe and effective in eliciting effects on HPA axis reactivity among participants with AUD[78,79].

Alcohol Cue Procedure. Consistent with the procedure developed by Monti and colleagues[81], participants will spend 3 minutes holding and smelling a control beverage (water), and reactivity (e.g., craving, urge to use) will be assessed. Following a 3-minute rest period, participants' preferred alcoholic beverage will be presented and poured into an appropriate glass

and they will spend 3 minutes holding and smelling the beverage. Subjective and physiological reactivity will be measured again.

TABLE 2. ASSESSMENT MEASURES	
Construct	**Measure**
Eligibility	•Phone Screen Questionnaire •Demographics •Health History Interview & Concomitant Medications •Breathalyzer and Urine Drug Screen •Pregnancy (women only) •Mini International Neuropsychiatric Interview[82] •Revised Conflict Tactics Scale; CTS-2[83] •Patient Health Questionnaire; PHQ-9[99]
Dyadic Functioning	•Dyadic Adjustment Scale; DAS[87] •Emotional & Physical Infidelity[88]
Substance Use	•Revised Clinical Institute Withdrawal Assessment; CIWA-Ar[89] •Time Line Follow back; TLFB [90,91] •Alcohol Use Disorders Test;AUDIT[92] •Drug Abuse Screening Test; DAST[93] •Fagerstrom Nicotine Dependence Test[94] ·Marijuana Motives Questionnaire
Mental Health	•Traumatic Life Events Questionnaire; TLEQ[96] •PTSD Check List; PCL-5[97] •Childhood Trauma Questionnaire; CTQ[98] •Patient Health Questionnaire; PHQ-9[99] • Cognitive Emotion Regulation Questionnaire; CERQ-Short [101] • Perceived Stress Scale -4; PSS-4 [102] • Interpersonal Sensitivity Measure;IPSM [103]Impulsive Behavior Scale; UPPS
Neuroendocrine	•Endogenous Oxytocin (blood) Note: Collected unless staff learn of contraindications. •Cortisol (saliva) Note: Collected unless staff learn of contraindications.
Physiological	•Heart Rate (HR) •Blood Pressure (BP)
Subjective	•Visual Analogue Scale (VAS)

TAP Procedure. In the couple-specific TAP utilized in Dr. Parrott's (Consultant) is his ongoing NIAAA-sponsored trial, participants engage in a fictitious reaction time competition with their partner. Participants are led to believe that their partner chooses whether or not they receive a shock and its intensity. Participants have the option to administer a shock to their partner and its intensity in response to a "winning" trial. In reality, participants receive electric shocks in response to a "losing" trial at intervals randomly generated by the TAP software[104]. IPA is operationalized as the number of shocks administered, intensity of the first "unprovoked" shock, proportion of maximum shocks selected, and average shock intensity. Each participant will receive the same number of shocks. Electric shocks are brief in duration (1 second), range in intensity from 25-250 mV, and are administered to two fingertips of the participant's non-dominant hand. The TAP task entails 30 trials for a total duration of 12-14 minutes.

At the outset of the TAP procedure, the words "Get Ready" appear on the computer screen in front of the participant. Then the words "Press the Spacebar" appear on the screen. Participants press and hold the space bar until the words "Release the Spacebar" appear on the screen, at which time the participant will release the spacebar as quickly as possible. A "win" is indicated to the participant with the words "You Won. You May Give a Shock" appearing on the screen.

Following a winning trial, participants choose whether or not to shock their opponent and its intensity on a level ranging from 1 (very mild shock, definitely not painful) through 10 (intense shock, definitely painful). A "loss" is indicated with the words "You Lost. You Will Get a Shock" appearing on the screen. The shock intensity received by the participant is randomly selected by the computer software within the calibrated range specified for each participant.

Calibration: The finger stimulator apparatus (Colbourn Instruments, Whitehall, PA) is calibrated for each participant, controlling for individual differences in pain threshold that may influence shock selection. Two electrodes are attached to the participant's middle and index finger on the non-dominant hand. Each participant is administered 1-second shocks that increase stepwise beginning with the lowest possible intensity. Participants are instructed to inform the researcher when the shocks are first detectable and then again when they experience a shock as painful. During the actual TAP procedure, shock levels range from 1 to 10 and correspond to the participant's 55% through 100% pain threshold.

TABLE 3. LABORATORY TESTING

Duration	Procedure
Screening portion	
2-2.5 hours	Informed consent and assessment battery
30 minutes	Blood draw from nurse from Research Nexus
Laboratory portion	
Minute 0	Baseline measurement #1 (VAS, HR, BP, cortisol)
Minute 5	Baseline measurement #2 (VAS, HR, BP, cortisol)
Minute 10	Oxytocin or placebo administered
Minute 40	Post-medication assessment (VAS, HR, BP, cortisol)
Minute 45	Alcohol Cue
Minute 50	Post-Cue assessment (VAS, HR, BP, cortisol)
Minute 65	TAP
Minute 70	Immediate post-task assessment (VAS, HR, BP, cortisol)
Minute 85	15-minute post-task assessment (VAS, HR, BP, cortisol)
Minute 100	30-minute post-task assessment (VAS, HR, BP, cortisol)
Minute 130	60-minute post-task assessment (VAS, HR, BP, cortisol)
Minute 135	Participant debriefed, compensated and discharged

Manipulation Check: To maintain the façade of the experiment, participants are informed that the purpose of the study is to assess reaction time performance among intimate partners. Following the TAP, participants will be asked a series of questions to assess the experiment's validity.

Laboratory Testing. Table 3 includes the laboratory testing procedures. A modification of the Within Session Rating Scale[105] will be used to assess subjective ratings including craving, stress, and anger. This 100 mm Visual Analogue Scale (VAS) is anchored from 0 (none) to 10 (extreme). Heart rate and blood pressure will be collected with a BP Tru Heart Rate and Blood Pressure machine. Cortisol will be measured using Salimetrics Passive Drool enzyme immunoassay kit, which has a 0.91 correlation with serum samples and a sensitivity of <0.007 ug/dL. Saliva samples will be collected and immediately placed in storage at -20°C until assay. One blood draw will be completed to assess endogenous oxytocin. Blood will be centrifuged at 1500 rpm at 4˚C and stored at −70˚C. Commercial ELISA kits (Enzo Life Sciences) will determine oxytocin levels. Intra-assay coefficients of variation for oxytocin average 3-5% and inter-assay variation is <10%.

Debriefing. Existing literature indicates that distress resulting from the TAP is manageable[54,106,107]. Debriefing will include full disclosure of the study's purpose and the necessity of deception. Participants reporting ≥5 on any VAS subscale will be asked to remain in

our waiting room until the rating subsides. Participants will be re-assessed in the waiting room every 5-10 minutes, and contacted by phone later that day by the PI to check-in.

Debriefing Procedure. Because this study involves an element of deception, it is important that participants receive a debriefing as soon as the experiment is concluded. We do not want participants believing for any extended period of time that they shocked their intimate partner or received shocks from their intimate partner. Dr. Parrott's extensive experience conducting TAP research among individuals and couples is that participants are well able to understand the nature and necessity of the deception employed in the TAP procedure. In the debriefing, participants will be told that their intimate partner was not actually engaged in the experimental tasks, that at no time during the procedure did they actually administer an electric shock to their partner, and that their responses were "normal" and consistent with those of others in the study. They will also be informed that they were not told, at the beginning of the study, that the TAP measures aggression because many people artificially alter their responses if they are aware of this information. Dr. Parrott has used these debriefing procedures in prior research projects that used a variety of interpersonal provocations without incident. To mitigate the likelihood that participants may feel intellectually inadequate because they were deceived by any manipulations, they will be told that 90-95% of the participants in comparable projects are similarly deceived (this is a conservative average deception rate of similar laboratory aggression studies in Dr. Parrott's laboratory) and that being deceived is completely "normal." Questions and concerns will then be addressed by the PI.

Participant Compensation. Participants will receive $25 for the baseline assessment and $125 for the laboratory portion of the study, totaling $150 per participant. Each participant will receive an additional $25 if they arrive on time to their original appointment.

Participants who have obstacles to participation due to transportation will be offered taxi, bus pass, or mileage compensation.

3.0 Specimen Collection and Banking

Blood and saliva samples will be collected from participants in this study for the purpose of examining cortisol and endogenous oxytocin. Saliva will not be collected from participants with a BMI of ≥39 or from participants with an appointment start time later than 10:00am. Blood will be drawn by MUSC Research Nexus nursing staff, processed, and stored at the MUSC Research Nexus until ready for assay. Saliva will be collected by trained research staff only and transported to the MUSC Research Nexus for processing, storage, and assay. Only approved study staff will have access to data associated with specimens.
Note that saliva and/or blood samples may not be collected if the study team determines a contraindication exists that might affect study results (including recent consumption of caffeine or food, medications that affect oxytocin (e.g., androdgel, levothyroxine, etc.) or other factors).

12.0 Data Management and Statistical Analysis Plan

Descriptive statistics will be used to characterize participants at each time point. Because the units of randomizations are dyads (i.e., couples), all analyses will account for potential within-dyad correlation (e.g., intraclass correlation [ICC]). Generalized linear mixed models (GLMMs) with random couple effects will be used to assess group differences in baseline characteristics. These can be operationalized using SAS Proc Mixed and Proc GLIMMIX. Should any variables

exhibit significant departures from normality, variable transformations (e.g., logarithmic) or non-parametric approaches will be used, as appropriate. GLMMs are ideal for handling analyses involving correlated measures[108], and they will allow us to estimate both the between- and within-couple variation. GLMMs are also useful for modeling longitudinal (repeated) outcomes on individual subjects, and the models can be adapted with appropriate link functions for continuous, binary, and count outcomes. GLMMs will be constructed for analyses involving group (or subgroup) comparisons over time. The models will also control for relevant covariates, including baseline outcome levels and number of standard drinks during the 60 days prior to participation. Various covariance structures (e.g., compound symmetry, autoregressive, etc.) will be tested, with final model selection based on fit statistics such as Akaike Information Criterion[109]. Analyses will be conducted using SAS v9.4 (Cary, NC).

Hypothesis 1: Participants who receive oxytocin, as compared to placebo, will demonstrate significantly lower craving, aggression, physiological (HR, BP), and neuroendocrine (cortisol) reactivity to the TAP. To test this hypothesis, GLMMs with identity link functions (for continuous measures) and log link functions (for count data) will be used to model the between-group differences. Random couple effects will be used to account for within-couple correlation.

Hypothesis 2: Oxytocin response will be greater among women as compared to men. To test this hypothesis, GLMMs will be used to assess serially measured time points following medication administration (15, 30, and 60 minutes post task). The effects of gender, time, and their interaction will be assessed. Primary outcomes include alcohol craving, aggression, and cortisol.

Hypothesis 3: Oxytocin response will be lower among individuals with higher endogenous oxytocin levels and greater IPA severity. To test this hypothesis, alcohol craving, aggression, and cortisol levels will be examined as repeated measures variables using the strategies described above. Separate models will be conducted for endogenous oxytocin levels and IPA severity.

Randomization. Participants will be randomized to oxytocin or placebo. Because the extant literature suggests that the frequency and intensity of aggression in the TAP may be higher in men, on average, than women, a stratified randomization scheme will be used to ensure that groups are balanced by gender.

Sample Size Justification. Given the preliminary nature of this investigation, we aim to detect between-group differences in aggression measured by the TAP (oxytocin vs. placebo). Prior work[110-112] suggests that mean baseline aggression as measured within the TAP ranges from 2 to 4, with a standard deviation of 1.1 and with men having higher scores, on average, than women. With 50 couples (n=100) per group (and assuming alpha=0.05 and 2-sided hypothesis testing), we will have 80% power to detect moderate within-group changes (around 0.4 units [±10%-20%] on the TAP shock intensity scale), consistent with our study hypotheses. We will have 80% power to detect moderate between-group differences (0.4 units) but with a larger alpha level (0.25), which is consistent with our pilot study framework.

Confidentiality and Data Security. All research personnel will attend a required in-service training conducted by Dr. Flanagan and Dr. Back 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. Standard operating procedures (SOPs) for the management of any participant or study-related emergency will be established and research staff will be trained on these protocols. All participant assessments will be scheduled during normal working hours beginning at 8am on the MUSC campus to ensure the presence of clinical staff and 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 de-identified 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.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Data and Safety Monitoring Plan. This section is based on the recommendations in NIAAA's "Data and Safety Monitoring Guidelines": http://www.niaaa.nih.gov/ResearchInformation/ExtramuralResearch/ResourcesAppGrantees/guidelines.htm.

Summary of the Protocol. The proposed study will examine the ability of oxytocin to reduce alcohol craving and aggression among individuals with a substance use disorder and co-occurring intimate partner aggression (IPA), and identify predictors of oxytocin response (e.g., gender, endogenous oxytocin, IPA severity). The primary outcomes in this study include a reduction in (1) alcohol craving, (2) aggression, and (3) subjective, physiological, and neuroendocrine reactivity to a laboratory task (i.e., modified Taylor Aggression Paradigm).

Trial Management. Dr. Flanagan (PI) will be responsible for monitoring the study. The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC), College of Medicine, Charleston, SC.

Regulatory Issues.

(1) The DSM plan must designate an experienced, qualified professional (usually the PI) who can distinguish a serious adverse event (SAE) from a non-serious adverse event (AE) and an unanticipated problem.

Drs. Flanagan (PI) and Back (primary mentor) will be responsible for distinguishing between serious (SAEs) and non-serious adverse events (AEs), and determining study relatedness. Potential AEs and SAEs will be identified during the study via self-report data, as well as assessments and interviews. All unexpected AEs and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff and reviewed by the PI at the weekly study team meeting.

An Adverse Event (AE) is defined as any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the study that may or may not be related to study participation. 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. All AEs are reviewed weekly by the PI, and annually by the Data and Safety Monitoring Board (DSMB), MUSC IRB, and VA R&D. 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.

(2) This experienced, qualified professional may be the PI, an independent investigator, or a team of experts.

Dr. Flanagan (PI) will consult with Dr. Back (Primary Mentor) to identify and determine AE severity.

(3) The DSM plan must indicate that serious adverse events and unanticipated problems will be reported to the local IRB, VA R&D, and to the NIAAA project officer within 48 hours.

AEs and SAEs occurring during the course of the trial will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. Adverse Events (AEs) that meet criteria for reportable AEs will be reported to all regulatory entities including the local IRB, VA R&D, and NIAAA project officer within 48 hours. SAEs will be reported within 24 hours. All research staff involved with adverse event reporting will receive training including identification, evaluation, and documentation and reporting.

(4) The DSM plan must indicate that an annual report will be submitted to the NIAAA Project Officer summarizing all adverse events.

An annual report of all adverse events will be submitted annual to the NIAAA Project Officer. In addition, AEs will be reviewed weekly by Drs. Flanagan and Back, and annually by the Data Safety Monitoring Board (DSMB) and local IRB. Any significant actions taken by the local IRB, VA R&D, and protocol changes will be reported to NIAAA.

(5) The DSM plan must specify that female subjects who are pregnant, nursing, or not using effective methods of birth control will be excluded from studies involving the administration of alcohol and/or drugs.

The proposed study does not involve alcohol or drug administration. However, women who are pregnant or breastfeeding are not eligible to participate in the proposed study due to the known effects of the study drug (oxytocin) on parturition and lactation.

(6) The DSM plan must indicate that trained personnel will be present or on call when human laboratory studies of alcohol or other drug intake are conducted.

Dr. Flanagan (PI) and/or Dr. Back (primary mentor) will be present or on call at the time of all study visits including the human laboratory visit.

(7) The DSM plan must indicate the follow up plans for serious adverse events and unanticipated problems.

For any SAE, the appropriate SAE protocol specific reporting forms will be completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. If complete information is not available when the initial 24-hours that the 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 Drs. Flanagan and Back and for forwarding to the NIAAA Program Officer. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NIAAA Medical Safety Officer within 2 weeks of the initial SAE report. Follow-up of all unexpected and serious AEs will be reported to all regulatory entities including the local IRB, DSMB, and NIAAA. 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.

(8) For studies in which alcohol is administered, the DSM plan must indicate that NIAAA guidelines for the administration of alcohol will be followed. These guidelines can be found at the following web address: http://www.niaaa.nih.gov/research/guidelines-and-resources/administering-alcohol-human-studies.

The proposed study does not involve alcohol administration.

(9) If the study has a follow-up phase, there must be a specific plan for referral to treatment during follow-up of any patient requiring additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms.

The proposed study takes place during one study visit and does not include a follow-up phase. All participants will be provided with a list of community resources upon study completion. Ineligible individuals presenting with serious mental or physical health symptoms including acute alcohol withdrawal will be referred clinically.

(10) The DSM plan must indicate that all adverse events and unanticipated problems during *follow-up* will be reported (SAEs within 48 hours) to the IRB and NIAAA.

Not applicable, as the proposed study does not include a follow-up phase.

(11) The DSM plan must briefly describe the procedures for data quality assurance and confidentiality.

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 alcohol craving, aggression, and subjective, physiological, and neuroendocrine reactivity to the laboratory procedure. Outcome data will be analyzed using chi-square, ANCOVA, and Poisson regression models. The alpha level for statistical significance will be set at .05.

Data quality will be monitored by random inspection of completed assessment forms by research staff. Dr. Flanagan and a statistician will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. Any problems with the assessment process, data collection, or data entry will be discussed between Drs. Flanagan and Back. Study procedures will follow the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Confidentiality will be maintained during all phases of the study. Any outside requests for information or any breaches in confidentiality will be reported to Dr. Flanagan. All requests by subject's physicians and other medical providers will be referred directly to applicant. No names or other identifying information will be included on any source documents. Only a subject identification number will be used on source documents. All data will be kept securely in a locked cabinet in a locked office.

(12) Phase III clinical trials must have an independent data and safety monitoring board. Phase I and II studies that have multiple clinical sites, are blinded or employ particularly high risk interventions or vulnerable subjects may require a DSMB at the discretion of NIAAA.

The proposed study meets the definition of a phase II clinical trial in that (a) oxytocin has an established dosing range, (b) it will be conducted among 100-300 individuals, and (c) examines efficacy of oxytocin for a specific purpose (e.g., to reduce alcohol craving and IPA). We will create a DSMB to monitor 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 alcohol use disorders and IPA and a statistician. The board may be called at any point if needed for unexpected AEs, etc. Modifications will be made in the procedures and/or the protocol if necessary based on the recommendations of the board. A DSMB 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. Results will be reported at the end of the trial.

ClinicalTrials.gov Requirements: In accordance with Public Law 110-85, the proposed trial will be registered with ClinicalTrials.gov. Applicable requirements regarding results reporting will be adhered to.

14.0 Withdrawal of Subjects

This is a cross-sectional study. All participants will be screened thoroughly for eligibility following informed consent. The PI may discontinue participation at any time if a participant demonstrates or reports significant distress, presents a risk of harm to self or others, or is otherwise unable to complete the study. Participants may withdraw from participation at any time during the study procedure. Clinical referrals to community resources will be provided to all study participants.

15.0 Risks to Subjects

Potential Risks. Risks associated with this study include discomfort associated with (1) TAP participation (e.g. psychological and physical discomfort), (2) oxytocin self-administration, (3) alcohol cue procedures, (4) discomfort from being deceived, and (5) risk of aggression during and after completion of study procedures. Procedures using the TAP may result in psychological or physical distress. Participants may experience distress related to reporting IPA or engaging in the laboratory aggression task. Based on the research team's past experience and available literature the risks involved in the proposed project are minimal and manageable[7,131]. Dr. Parrott (consultant) has tested approximately 2,000 participants (sober and intoxicated) using the TAP without a single adverse event to date. With respect to the receipt and ostensible administration of mild electric shocks during the TAP, it is important to note that this task has been shown to be a safe measure of aggression in over 100 studies[83,132-134].

Risks associated with oxytocin administration have been noted among women given intravenous, but not intranasal, oxytocin for its FDA-approved purpose to induce labor and facilitate lactation[135,136]. 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[99]. However, preliminary studies

conducted by our group and others 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. Our group has administered intranasal oxytocin at this dose to over 200 research participants to date without a single adverse event reported.

Participants will be screened for acute alcohol withdrawal at the outset of the study. Participants reporting CIWA-Ar scores ≥8 will be excluded from participation and referred clinically. All possible efforts to minimize participant burden and distress will be made. All possible efforts will 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. The Mobile Crisis Unit of Charleston County and urgent care services on the MUSC campus and at the Charleston VAMC are additional resources available to study staff and research participants. Dr. Flanagan and her mentor (Dr. Back) are licensed clinical psychologists equipped to help participants manage distress and to evaluate conditions in which participants need additional assistance. In the event that a participant becomes distressed during or following an assessment, I will contact the participant later that day to check-in and the following day to ensure they have received necessary resources, and to assess their safety and welfare. In the event that any serious adverse event occurs resulting from study participation, that event will be reported in writing to the MUSC IRB and NIH within 24 hours. In similar past and ongoing studies, these resources have been sufficient to manage problems or distress related to participation.

Furthermore, it is possible that participants will experience psychological discomfort as a result of being deceived. Deception will be used in the proposed study in relation to the TAP. Participants cannot be told that the true purpose of the study is to measure aggression toward an intimate partner. Informing participants of this fact may elicit artificial socially desirable (non-aggressive) responses. Instead, participants will be told that they will be competing in a reaction-time task against their intimate partner in a nearby room. In actuality, there is no opponent (and therefore no competition). This deception exists to create the impression of an adversarial interpersonal interaction and is required to increase the ecological validity of the study.

It is possible that participation in this study may "prime" some participants to behave aggressively toward an intimate partner or another person after leaving the laboratory. Given that the long-term goal of this research project is to inform interventions designed to prevent IPA, it is essential that participants (a) not experience an increased risk for IPA as a function of participating in this project, and (b) be afforded all available protections and services to reduce this risk. Although we do not anticipate increases in the risk of physical safety of male or female partners due to participation in this study, we have nonetheless included procedures to mitigate these risks and to help ensure their safety. In order to reduce the already minimal probability of aggression between intimate partners *in the laboratory* following the conclusion of the TAP, researchers will conduct individual debriefing sessions separately for the participant and the partner. Thus, when the couple reunites at the conclusion of study procedures, participants will be aware that it was not actually the partner against which they were playing during the TAP, and the partner will be aware that the participant was led to believe that he/she was the opponent during the game. If, for any reason, the partner expresses any fear or concern about reuniting with the participant, all necessary and practical steps for intervention will be taken. Towards this end, we will conduct all screenings and consent discussions without partners present, thus reducing the likelihood that

participants are coerced into participating. In addition, we have created multiple measures to maintain the confidentiality of partner responses, including not sharing any partner information with the male/female index participant. Also, we will further manage this risk by excluding couples that report acts of severe IPA (as defined by the CTS-2) during screening.

Managing Participant Safety and Risk. Risks of participation will be outlined in the informed consent and reviewed during the informed consent procedure. If severe forms of IPA are reported, the PI will discuss the situation with participants privately and will engage in safety planning and offer referrals to shelters and additional counseling as appropriate. Severe physical and sexual violence is defined as endorsing any of the following items from the Severe Violence subscale on the CTS-2[97]: used a knife or gun, punched or hit with something that could hurt, choked, slammed against a wall, beat up, burned or scalded on purpose, kicked, used force or threats to make my partner have oral or anal sex, used force or threats to make my partner have sexual intercourse. The PI will follow up with participants if other forms of severe violence are disclosed during interviews with research assistants or study personnel. As in all of our studies, we will vigilantly monitor these issues to protect the safety of study participants.

The laboratory procedure may induce some psychological or physical discomfort. However, it is unlikely that participants will incur any additional risk above that experienced in their daily lives. Prior to the aggression testing, participants will be told that if they feel that the TAP shocks are too high, they can either ask the PI to reduce the intensity (through an intercom) or quit the study at no penalty and receive partial payment. Dr. Parrott (consultant) and colleagues surveyed over 400 men immediately after completing the TAP and one week later. He found that an extremely small proportion (1.8%) of participants reported an increased likelihood of behaving aggressively as a result of participation. These participants denied any specific plans of action and reported one-week later that these feelings did not persist. No participant or partner reported that involvement in the research led to any increased tendencies towards aggression, and no adverse events were reported. Because interview and self-report assessment measures cover topics of a sensitive nature, participants will have the option to decline answering any questions they prefer not to answer. Participants will be informed during the informed consent procedure that no third party, including their partner, will have access to assessment responses with the standard exceptions in the event of suspected or reported child or elder abuse, or risk of harm to self or others. All couples will be debriefed by the study team following the experimental procedure including full disclosure of the study's purposes and procedures. Dr. Flanagan will follow up with any distressed participants later that day via phone and will provide clinical referrals as necessary.

Participants will be informed about the potential side effects of intranasal oxytocin and will be closely monitored by the research team. Oxytocin administration will occur in a fully-staffed clinical environment equipped with ready access to clinicians and emergency care if necessary.

Participants may also experience elevated craving following the laboratory procedure. If a participant experiences elevated craving as a result of participation in the proposed study, they will be encouraged to meet with Dr. Flanagan or her primary mentor, who are licensed clinical psychologists with extensive experience working in research and clinical settings with high-risk populations. The study procedure includes monitoring subjective craving ratings at regular intervals (15, 30, and 60 minutes) post-task. Thus, we are well equipped to detect persistent elevations in craving or other negative affect. Any subject reporting a $\geq$5 on the craving scale will be asked to sit in the waiting room and look at magazines. Their craving and distress level will be re-assessed by research staff every 5-10 minutes during this time. Subjects will be asked to remain in the waiting room until their craving is <5. Dr. Flanagan will also call the subject later that day to check-in. Finally, clinical referrals to local treatment centers

will be provided to all subjects. Participants will also have access to emergency psychiatric services at MUSC. Dr. Flanagan and her team of mentors have implemented these methods successfully in previous and ongoing studies conducted by Dr. Back and other faculty at MUSC involving subjects with AUD and co-occurring problems. In addition, previous studies at MUSC that involve stress or craving induction among individuals with AUD suggest that participation is associated with decreased, not increased, substance use in the month after completing the laboratory stress and cue tasks[11,12].

Dr. Flanagan and her primary mentor will meet weekly to review study procedures and progress and any clinical issues arising with participants. Dr. Flanagan will implement a Data and Safety Monitoring Board (DSMB) which will meet annually to review any adverse events associated with study participation. Dr. Flanagan has completed formal training in the responsible conduct of research and will continue to maintain institutional compliance requirements.

16.0 Potential Benefits to Subjects or Others

Alcohol is a significant contributing cause of IPA, and extant literature strongly indicates the need to (1) develop clear and testable models of IPA etiology and maintenance, and (2) elucidate possible mechanisms through which this social malady can be prevented or reduced. Preclinical and preliminary human data suggest that oxytocin has potential to influence treatment in the field of AUD and human aggression. The health burden associated with AUD and IPA, both individually and collectively, is tremendous in the U.S. and globally. Despite the limited treatment response to behavioral intervention for these commonly co-occurring problems, research investigating pharmacological interventions to improve intervention is scant. The present study is the first to investigate the utility of oxytocin to reduce alcohol craving, aggression, and subjective, physiological, and neuroendocrine reactivity to a well-controlled aggression paradigm. The use of oxytocin as a supplement to behavioral interventions, particularly those addressing AUD and commonly co-occurring problems such as IPA, present the potential for a highly efficient and cost-effective way to meet the treatment needs of individuals and couples nationwide.

17.0 Sharing of Results with Subjects

Study data will not be shared with participants to maintain confidentiality.

18.0 Drugs or Devices

The IND for oxytocin's use in this study is held by Dr. Flanagan. Oxytocin will be compounded, stored, and dispensed by Investigational Drug Services (IDS) on the MUSC campus or Pitt Street Pharmacy in Mt. Pleasant, SC. Pitt Street Pharmacy is a compounding pharmacy used by many other MUSC clinical trials, including others within our group. Pitt Street Pharmacy is also a member of The International Academy of Compounding Pharmacists (IACP). IACP is an international, non-profit association protecting and promoting the art and skill of pharmaceutical compounding.

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