PROTOCOL TITLE: Oxytocin to Enhance Alcohol Behavioral Couple Therapy

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1.0 Objectives / Specific Aims

Identifying effective medications to treat alcohol use disorder (AUD) is a national public health priority. Combining pharmacological interventions with evidence-based behavioral treatments may help maximize and sustain AUD treatment outcomes[1-3]. Alcohol Behavioral Couples Therapy (ABCT[4]) is a manualized, evidence-based psychotherapy for the treatment of AUD[5-7] that simultaneously targets relationship functioning, which is an important mechanism in the etiology, course, and treatment of AUD[8,9]. While adaptive relationship functioning facilitates successful treatment engagement and outcomes[9-11], maladaptive relationship functioning interferes with AUD recovery[12-15] and is a precipitant of relapse[16,17]. Thus, ABCT employs cognitive behavioral techniques to (1) reduce alcohol consumption, (2) enhance partners' skills to facilitate recovery (e.g., communication, managing cravings together), and (3) enhance relationship functioning. Although ABCT is a highly efficacious treatment, there is room for improvement in outcomes, as more than half of ABCT patients report hazardous drinking episodes during treatment and a similar proportion fail to achieve abstinence[5,6,18,19].

The neuropeptide oxytocin is a promising candidate to enhance ABCT via neurobiological and behavioral pathways including its potential to restore sensitivity to natural rewards such as interpersonal relationships[20]. Neuroimaging studies indicate that dysregulation of corticolimbic brain circuitry is centrally involved in AUD pathophysiology[21,22]. Individuals with AUD demonstrate lower corticolimbic connectivity than healthy controls[23,24] and disrupted corticolimbic connectivity is associated with AUD relapse[25]. Notably, oxytocin increases corticolimbic connectivity[26-29]. Behaviorally, human and animal studies indicate that oxytocin reduces alcohol withdrawal, tolerance, craving and self-administration[30-35]. However, emerging literature emphasizes individual differences such as sex, social context, and psychosocial history that moderate the effects of oxytocin on social behavior[36-41]. Pilot data from our team revealed that among distressed couples with substance use disorders, oxytocin was associated with worse conflict behaviors among female partners, but did not affect male partners' behavior[42]. These nuanced findings may be explained by the social salience hypothesis[43], which proposes that rather than selectively enhancing prosocial behavior, oxytocin might universally amplify an individual's current social tendencies which, in the context of addiction and relationship distress and without corrective intervention, may be maladaptive [8,13,17]. ABCT has demonstrated the ability to insulate couples from maladaptive relationship behaviors that are proven antecedents to hazardous drinking and relapse by cultivating and implementing new adaptive skills that facilitate recovery [44,45]. Notably, treatment gains are greater among couples who begin ABCT with poorer relationship functioning and greater psychiatric comorbidity[5] and within-session gains predict positive ABCT outcomes [44]. Thus, a key approach to the therapeutic translation of oxytocin is to combine oxytocin with a behavioral intervention such as ABCT to reduce alcohol consumption. Doing so will ensure that oxytocin has an adaptive platform to enhance the positive gains made within ABCT sessions.

The proposed study will test the efficacy of oxytocin to enhance ABCT outcomes. We will also determine the effects of treatment on corticolimbic connectivity using blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI). In order to accomplish this, we will employ a double-blind, placebo-controlled, randomized study design and examine standardized, repeated, dependent measures of change in: (1) alcohol consumption, (2) relationship functioning, and (3) corticolimbic connectivity in response to a validated in-scanner cue paradigm. Couples (N=100) will be randomly assigned to receive oxytocin (40 IU) or placebo prior to each of 12 weekly ABCT therapy sessions. The following specific aims are proposed:

Specific Aim 1: Compare the efficacy of ABCT with oxytocin vs. placebo in reducing alcohol consumption.
Specific Aim 2: Compare the efficacy of ABCT with oxytocin vs. placebo in improving relationship functioning.
Specific Aim 3: Use neuroimaging to determine the effects of treatment on corticolimbic connectivity in response to alcohol and relationship conflict cues.

2.0 Intervention to be studied

Study Medication, Dosage, and Administration. A 40-IU dose of oxytocin or matching placebo will be self-administered 30 minutes prior to the start of each weekly ABCT session. The dose and timing of medication administration is based on past research in our group and others[46,47,82,117,118], and determined in consultation with NIAAA program staff. Study prescribers (Anjinetta Johnson, P.A. and Jennifer Jones, M.D.) will conduct the H&P exams, provide prescriptions for oxytocin, and assist with weekly assessment of adverse events. Investigational Drug Services (IDS) at MUSC or Pitt Street Pharmacy in Mt. Pleasant will compound and dispense oxytocin and matching placebo. Research staff will instruct participants on the correct method of administration to achieve the desired dose and will observe participants' self-administration. 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[45,119,120] Randomization will be carried out by a research pharmacist not involved in clinical management of participants in order to preserve the double-blind design.

Psychosocial Intervention: Alcohol Behavioral Couple Therapy (ABCT[25]). All participants will receive 12 weekly, 90-minute ABCT therapy sessions delivered by trained Masters or Doctoral-level clinicians consistent with the published manual[25]. The main goal of ABCT is to concurrently reduce AUD symptom severity and improve relationship functioning. Patients receive psychoeducation pertaining to the interconnectedness of AUD and relationship functioning. AUD-focused components of the treatment help patients identify and manage cravings, urges to drink, and thoughts about alcohol use; enhance individual problem solving and decision-making abilities; identify and plan for "high-risk" situations in which vulnerability to relapse is heightened; learn drink refusal skills; and cope with a potential relapse. ABCT also teaches couples to work together to enhance reciprocity and communication skills in the relationship, increase positive rewards of initiating and maintaining drinking reductions and abstinence, and identifying and implementing ways partners can help minimize and manage alcohol use triggers, participate in drink refusal skills, and help prevent relapse.

3.0 Study Endpoints

Primary Outcome Measures. Primary outcomes include (1) alcohol consumption (percent days abstinent and heavy drinking as measured by the TLFB) and (2) relationship functioning (DAS-7). Additional AUD outcomes include alcohol craving (PACS) and ethanol metabolites and traditional biomarkers (e.g., EtG and PEth) to corroborate participant self-reports of abstinence and alcohol use[121-123]. PEth is among the most specific biomarkers used to detect heavy drinking and monitor abstinence[124-126]. The conjugated alcohol metabolite EtG remains positive in urine for several days following cessation and is a useful biomarker of recent drinking in outpatient settings[127]. Selected assessment instruments are standardized, have good psychometric properties, are widely used, and have been used extensively by our research group.

AUD Symptom Severity

- **Time Line Follow-Back (TLFB[128]):** The TLFB, which uses a calendar to stimulate recall, will assess consumption of alcohol (e.g., number of standard drink units, percent of days drinking and abstinence, time span in which drinks were consumed), drugs, and tobacco for 60 days prior to study entry, and during the treatment and follow-up phase.

Relationship Functioning

- **Dyadic Adjustment Scale-7 (DAS-7[129]):** The self-report DAS-7 is based on the original 32-item measure[130]. It is used to assess domains relationship functioning and has demonstrated strong psychometric properties[129].

4.0 Inclusion and Exclusion Criteria/ Study Population

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

Inclusion criteria are: 1) aged 18- 75, 2) English fluency and intellectual functioning sufficient to provide informed consent and accurately complete assessments and participate in treatment (as assessed by a criterion of $\leq$ 26 on the Mini-Mental Status Exam [MMSE][131]), , 4) married, cohabiting, or in a committed relationship for $\geq$ 6 months, 5) one partner must meet DSM-5 diagnostic criteria for current (i.e., past 12 months) alcohol use disorder (assessed via the Quick Structured Clinical Interview for DSM-5 Disorder). Couples in which both partners meet diagnostic criteria for current AUD are eligible for participation, 6) maintenance of psychotropic medications on a stable dose for at least 4 weeks before study initiation, and 5) concurrent substance use disorders (e.g., marijuana) are acceptable provided that alcohol is the participant's primary substance of choice. The inclusion of participants with substance use disorders is essential because of the marked frequency of co-occurrence among patients with AUD.

Exclusion criteria include: 1) meeting DSM-5 criteria for a history of or current psychotic or bipolar affective disorders, 2) current suicidal or homicidal ideation and intent, 3) a history of seizures and/or a seizure disorder per the judgement of the medical clinician, 4) severe, unilateral intimate partner violence in the past 6 months as defined by the Revised Conflict Tactics Scale[132], and 5) pregnancy or breastfeeding for women, 6) Acute alcohol withdrawal as indicated by CIWA-Ar scores >8, Attendance at therapeutic activities other than study sessions will be closely monitored using the Treatment Services Review, 7) any unstable or serious medical condition affecting the potential participant's ability to participate in the study, 8) Individuals with claustrophobia; tattoos above the shoulders; permanent eyeliner or permanent artificial eyebrows; cardiac pacemaker; metal fragments in eye, skin, or body, including shrapnel; heart valve replacement; brain clips; venous umbrella; current or former sheet-metal worker or welder; lifetime history of aneurysm surgery; lifetime history of seizures and/or epilepsy per the judgement of the medical clinician; intracranial bypass, renal, or aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants; joint replacements; non-removable hearing aid, neurostimulator, or insulin pump; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires; or any other MRI contraindications as determined by the MRI technician at the time of scanning will not be eligible to participate in the neuroimaging component of the study, however individuals who meet inclusion/exclusion criteria for the medication component of the study but not the MRI portion will still be eligible to reenroll in and complete the medication/treatment phase.

5.0 Number of Subjects

100 couples will be enrolled (200 total participants).

6.0 Setting

All procedures will be conducted on the MUSC campus or in VA research offices. Procedures can also be conducted via telehealth.

7.0 Recruitment Methods

Recruitment sites will include the Center for Drug and Alcohol Programs (CDAP) at MUSC, the Ralph H. Johnson VAMC Substance Treatment and Recovery (STAR) clinic, and other in state and out of state VA clinics (e.g., Savannah CBOC). CDAP, directed by Dr. Joshua Smith, is an inpatient and outpatient addictions treatment facility with approximately 398 inpatient and 880 outpatient annual admissions. There were 1,279 new CDAP admissions in 2017 (~106/month) with the majority of patients (75-80%) seeking AUD treatment. The STAR clinic is directed by Dr. Karen Hartwell and Dr. Back (Co-I) is a Staff Psychologist in STAR. Consults for treatment are made directly to the STAR intake team. In 2017, STAR delivered 1,460 unique patient visits (682 AUD patients; 56 patients/month). An additional recruitment site will be the outpatient Ralph H. Johnson VAMC Couples and Family Clinic, directed by Dr. Julian Libet. The Couples and Family Clinic received 433 and 408 unique patient intakes in 2016 and 2017, respectively. We need to enroll 2-4 couples per month to complete the study within the proposed timeline. No other studies are enrolling couples at the proposed recrutiment sites. Thus, there should be no difficulty recruiting an adequate sample. Participants will also be recruited through IRB-approved flyers posted in (a) VAMC Women's Health Clinic, Primary Care Clinic, and Emergency Department; (b) affiliated community based outpatient clinics; and (c) MUSC treatment clinics. Finally, we will place advertisements on social networking sites (e.g., Craigslist, Facebook), in local newspapers, and television. 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. Further, participants from past MUSC research studies who have consented to be contacted for future research studies will be recruited. 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. Our research team has successfully used these methods in previous and ongoing clinical trials among individuals and couples with AUD.

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.
Chart review and EPIC/VINCI lists will be used for recruitment; only individuals who have previously agreed to be contacted for research opportunities will be identified. The study team will use an IRB approved letter and script will be used to inform identified individuals about our study.

Participants will be recruited and enrolled from all 50 states. The protocol/NIH grant application was written pre-COVID 19, where we had various recruitment methods that included in-person collaboration with providers and clinics, as well as physical methods of recruitment (like flyering) from community locations (bars and clinics, etc). Since the COVID 19 pandemic, the climate of clinical trial recruitment has shifted drastically and reaching potential participants has moved almost fully virtual/digital. With the shift in recruitment methods, the market has become saturated throughout most of our social media outlets. We have also difficulty getting new methods of recruitment strategies/platforms approved by

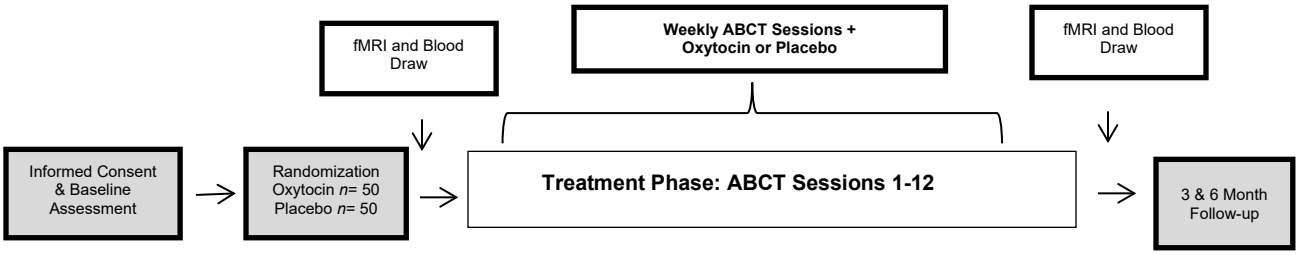
MUSC/SC purchasing restrictions. Thus, the inclusion of participants out of state increases the pool of potential participants, helping to mitigate the impacts of COVID19.
Further, the inclusion of out of state participants allows us to enroll more veterans referred through the VA system, as Savannah CBOC is part of the RHJVA.
Also, out of state recruitment allows for a more diverse study sample. Recruitment of out of state participants will be accomplished through social media advertisements targeted at out of state areas. The advertisements will include our study screener. Study staff will connect with the potential participant based on the method of contact indicated by the participant on the screener. Our study contact information will also be provided should the participant not want to provide contact information for themselves.

8.0 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. Additionally, VA participants and their partners who are recruited from the VA will only be consented by study staff who have an active WOC or VA appointment. Informed consent will take place on the MUSC campus or via telehealth, using an IRB approved platform, such as Doxy.Me or RedCap. Initial eligibility screening will be conducted by the PI, Co-Is, Coordinator, 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. 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. VA participants and their partners who are recruited from the VA will be given a VA Notice of Privacy Practices in addition to a copy of their consent.

9.0 Study Design / Methods

Figure 1 below illustrates the study design.



Overview. The proposed study is a 12-week, Stage-II, double-blind RCT examining the efficacy of combining oxytocin (40 IU) with ABCT in the treatment of AUD. A repeated measures design with two intervention arms will be used: ABCT + oxytocin compared to ABCT + placebo (Figure 1).

General Procedures. Following phone screening for preliminary eligibility, participants will complete a baseline assessment. In a private room apart from their partner, 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 are conducted. In the event of telehealth, separate appointments will be made to meet with each individual partner separately. Consent will be conducted by trained staff (PI, Co-Is, Study Coordinator, or Research Assistant). Ineligible participants will be given treatment referrals as needed. During 1-2 baseline visits, participants will complete a breathalyzer or alcohol saliva test strip (to test current BAC), pregnancy test (for women), ethyl glucuronide (EtG) and phosphatidyl ethanol (PEth) testing, a history and physical (H&P) exam, urine drug screen (UDS), a battery of standardized self-report and interview measures (Table 1).,. 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. H&P exams will include a physical and neurological examination; orthostatic blood pressure and pulse measurements; and weight and BMI calculation. In the event of telehealth baseline appointment, biological measures will not be collected. Provided full eligibility criteria are met, participants will schedule visits to complete script development needed for the fMRI sessions and a fMRI session (described in the Neuroimaging Procedures section). Participants will then enter the treatment phase, which is a 12-week, double-blind, placebo controlled RCT during which they will receive weekly ABCT therapy sessions in combination with oxytocin or placebo (see Study Interventions and Procedures Section). Intranasal oxytocin has a half-life of approximately 3-4 hours and can be stored, refrigerated, for 2-4 weeks. If a participant misses multiple appointments, a new dose may be dispensed from IDS or Pitt Street Pharmacy. Participants will complete 3- and 6-month follow-up visits. AUD symptoms, relationship functioning, associated problems (e.g., depression), UDS, EtG, and adverse events will be assessed weekly. In addition, participants will be asked to complete a breathalyzer/alcohol saliva test strip while in the same room; after which they will be taken to separate rooms until it is time for therapy. PEth will be examined at baseline, weeks 6 and 12, and at both follow-up assessments. Blood samples will be refrigerated until sent to out for assay. Therapy sessions may be videotaped, with participant consent. In order to explore secondary outcomes such as the effects of treatment on within-session behaviors, we will employ observational coding to assess frequency of positive, negative, and alcohol change talk behaviors (using the SCCIT-A[133]) in ABCT sessions 1, 4, 8, and 12.

Table 1. Assessment Instruments and Timeline

Instrument	Purpose	BSL	Weekly	Week 6	Week 12	3M F/U	6M F/U
Demographics Form	Characterize sample	X					
Mini Mental Status Exam (MMSE)[131]	Screen for cognitive deficits	PRN					
Quick Structured Clinical Interview for DSM-5 Disorders	Assess DSM-5 psychiatric disorders	X					
Concomitant Medications Form	Assess concomitant medications	X	X	X	X	X	X
Time Line Follow-Back (TLFB)[128]	**Primary outcome: AUD**	X	X	X	X	X	X
Penn Alcohol Craving Scale (PACS[135])	Assess alcohol craving	X	X	X	X	X	X
Alcohol Use Disorders Identification Test (AUDIT)[136]	Assess alcohol problems	X		X	X	X	X
Alcohol Dependence Scale (ADS)[137]	Assess domains affected by AUD	X			X	X	X
Readiness to Change Questionnaire (SOCRATES[138])	Assess readiness to change AUD	X		X	X	X	X
Clinical Institute Withdrawal Assessment of Alcohol-Revised (CIWA-Ar)[139]	Assess alcohol withdrawal	X	X			X	X
Traumatic Life Events Questionnaire (TLEQ) [140]	Assess Trauma History	X					
PTSD Checklist (PCL-C) [141]	Assess PTSD symptoms	X			X	X	X
Beck Depression Inventory-II[142]	Assess depression	X	X	X	X	X	X
Cognitive Emotion Regulation Questionnaire; CERQ-Short [143]	Assess emotion regulation	X			X	X	X

Dyadic Adjustment Scale-short form (DAS)[129]	**Primary outcome: Relationship functioning**	X	X	X	X	X	X
Infidelity Assessment [144]	Assess Infidelity	X			X	X	X
Revised Conflict Tactics Scale[132]	Assess intimate partner violence	X		X	X	X	X
Reasons for Violence Scale[145]	Assess reasons for partner violence	X			X	X	X
Treatment Services Review	Monitor service utilization		X	X	X	X	X
Helping Alliance Questionnaire, Therapist and Client Version[146]	Asses therapeutic alliance		X	X	X		
Treatment Adherence	Assess homework compliance		X	X	X		
History of Head Injuries	Assess fMRI eligibility	X			X		
Drinking goals	Assess treatment goals for alcohol	X					
Coping Questionnaire	Assess coping skills	X					
Marijuana Motives	Assess marijuana use	X					
Visual Analog Scale (VAS)	Asses alcohol craving	X			X		
Telehealth Questionnaire	Asses telehealth				X		
Psychological Stress Associated with COVID-19 Crisis Questionnaire	Assess stress related to COVID-19	X					
BSL=Baseline. F/U = Follow-Up. BP=Orthostatic Blood Pressure. BMI= Body mass index.							

Telehealth: Participants in this research study may choose to complete appointments 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 in-person sessions. Further, telehealth allows the study team to recruit and enroll participants who are located outside of the state of South Carolina (inside continental US). 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, pregnancy tests, and medication. 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 baseline 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 baseline appointment and prior to administration of any study medication.

Female participants who complete appointments via telehealth will be required to take an at-home urine pregnancy test during those visits (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.

Study medication and other study required study materials will be shipped overnight from research pharmacy to participant's designated location at the agreed upon date using overnight shipping with contracted shipping company (FedEx, UPS) and with appropriate ice packs and temperature monitoring device as well as a signature requirement at delivery. Regarding all telehealth participants (including out of

state): Research participants will be asked to retrieve the study drug from their refrigerator at the beginning of each check-in video telehealth session with study staff. Participants will self-administer the medication while in view of the study staff on screen. Once medication is administered, participant will be instructed to return drug to their refrigerator prior to continuing with the remainder of the appointment.

Optional Neuroimaging Procedures. fMRI scans will be completed with participants and conducted at the MUSC Center for Biomedical Imaging (CBI; see Facilities and Resources), which houses a Siemens 3T Prisma MRI scanner (Siemens Medical, Erlangen, Germany). Neuroimaging sessions (Figure 5) will last approximately 60 minutes each and take place at baseline and week 12. After baseline, personalized imagery scripts will be developed for alcohol and neutral cues according to the manualized procedures described by Sinha and Tuit[147], which are currently being utilized in several of our team's ongoing federally-funded pharmacological trials for AUD. Participants will also develop a relationship conflict cue consistent with our past work. The VAS will be administered prior to, during, and after scanning to track perceived craving. Participants will be screened for metal using a self-report questionnaire and a handheld metal detector. Trained staff will position participants on the scanner bed with foam padding placed around their head to prevent motion. Participants will wear headphones to listen to the audio-recorded cues. During initial scanner tuning, localizing, and structural scanning, participants will be shown "relaxing" images (i.e., 20 scenic pictures, each displayed for 30 seconds). For co-registration and normalization of functional images, a high resolution T1-weighted MPRAGE anatomical image will be acquired with the following parameters: TR = 2300 ms, TE = 2.26 ms, flip angle = 8°, field of view = 256 mm, slice thickness 1.0 mm, 192 slices. The scanning planes will be oriented parallel to the anterior commissure–posterior commissure line.

Next, participants will be asked to relax and keep their eyes opened and fixed on a cross-hair while resting state data are collected across two 7-minute runs. Following this, participants will be exposed to alcohol, trauma and neutral cues. We will use a block design consisting of four 2-minute blocks. During the alcohol cue block, participants will hear an audio recording describing in detail the last time they consumed alcohol. During the trauma cue block, participants will hear an audio recording describing in detail their traumatic event. Between the alcohol cue and trauma cue blocks, participants will hear an audio recording describing something neutral, such as their typical morning routine. The same excerpt will be used for each run. To minimize potential carry-over effects, the scans will be counterbalanced so that half of the participants in each treatment arm (e.g., oxytocin or placebo) are exposed to the alcohol cue first and the remaining participants in each group are exposed to the relationship conflict cue first. This order will be preserved from pre- to post-treatment scanning for each participant. T2*-weighted gradient-echo planar images (EPI) will be acquired with the following parameters: TR = 1100 ms, TE = 30 ms, flip angle = 65º, matrix 64 x 64, field of view = 192 mm, slice thickness = 3 mm with no gap, multiband factor = 3, with 48 slices to cover the entire brain. A gradient field map with the same spatial resolution and slices as the EPI will be collected to correct for geometric distortions cause by magnetic field inhomogeneity.

Compensation. Each participant will each receive $100 for completion of the baseline assessment visit, up to $75 for completion of weekly ABCT sessions (on an escalating scale), and $100 for each follow-up visit. Participants who are eligible and choose to complete the neuroimaging component of the study will also receive $30 for the script development session and $100 each for the pre-and post-treatment neuroimaging scans. Thus, participants who complete all study components may receive $1,100 total. If obstacles of transportation prevent participation, the study team will offer bus, taxi, or mileage reimbursement as needed. Mileage reimbursement is available for individuals who travel more than 50 miles to Charleston. Reimbursement will be provided at the state-approved rate, and will be capped at 100 miles. Compensation types may include, but are not limited to: checks, cash, or gift certificates/cards.

10.0 Specimen Collection and Banking

Urine samples will be collected for pregnancy testing, urine drug screens, and ethyl glucuronide (EtG) testing. Blood samples will be collected from participants in this study for examining phosphatidyl ethanol (PEth). Blood will be drawn by trained personnel or the MUSC Research Nexus nursing staff and stored the MUSC Fast Flow Lab until ready for processing. Only approved study staff will have access to data associated with specimens.

11.0 Data Management and Statistical Analysis Plan

General. Baseline clinical and descriptive characteristics will be examined and compared between treatment groups using chi-square tests, Fisher's exact tests, t-tests, or Wilcoxon rank sum tests, as appropriate. Baseline characteristics that are significantly different between treatment groups will be included as model covariates. The primary analysis will focus on end-of-treatment (i.e., the final three weeks of the treatment phase) outcomes using an intent-to-treat framework.

Randomization. Both partners in each couple will be randomized to the same drug condition in a one-to-one manner utilizing a randomized permuted block design. In order to ensure that the treatment groups are balanced with respect to alcohol consumption (TLFB), a stratified randomization process will be used.

We plan to use REDCap and VA REDCap for data capture and management. REDCap (Research Electronic Data Capture) is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data (Harris et al., 2008; Harris et al., 2007). REDCap provides secure, web--based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The system allows the research team to create and engage respondents using a variety of notification methods.

REDCap data dictionaries can be distributed for reuse at multiple institutions. A library of data dictionaries is made available for standards--based data collection forms and validated instruments (Obeid et al., 2012). The underlying database is hosted in a secure data center at MUSC/VA, a secure environment for data systems and servers on campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including, user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption.

Power and Sample Size. This study is powered to detect moderate treatment group differences in percent days abstinent (PDA) and percent of days of heavy drinking (PDH), and relationship functioning as measured by the TLFB and DAS-7, respectively at end-of-treatment (weeks 9-12). Assuming 2-sided hypothesis testing and alpha levels of 0.05, we will have 80% power to detect treatment group differences with effect sizes of 0.6 in the presence of 30% attrition (n=70 couples) during the treatment phase. This approach is consistent with treatment group differences in PDA (d=0.59) and PDH improvements (d=0.79) in a prior ABCT trial (n=102)[26], although we recognize that that trial compared individual therapy vs. ABCT (not ABCT ± medication). In that study, PDA increased from 34.98% ± 29.17% to 80.52% ± 27.75% at the end of treatment in the ABCT group, and PDH decreased from 56.83% ± 28.87% to 10.52% ± 22.16% in the ABCT group. Incorporating an arcsine or other appropriate transformation to account for non-normality of these metrics will enable us to discern whether oxytocin enhances end of treatment PDA by an additional absolute 9% or greater (i.e., to 80.5% in the ABCT+ placebo group vs. 89.5% in the ABCT + oxytocin group) and whether oxytocin further decreases PDH by an absolute 6% or greater (i.e., to 10.5%

in the in the ABCT+ placebo group vs. 4.5% in the ABCT + oxytocin group). Another prior ABCT trial found that DAS-7 scores (21.1 ± 6.7) remain relatively constant throughout treatment[27]. We will have 80% power to detect treatment group differences of 4 units of improvement in DAS-7 scores.

Missing Data. We will examine whether participants who complete treatment differ from those who drop out on key variables, and whether variables on which they differ interact with treatment group to affect outcome measures. Because participants will be randomized to treatment condition, it is unlikely that missing data will produce biased estimates of treatment effect, as observed and unobserved covariates will theoretically be balanced across treatment groups. In addition, less than 10% missing data generally has little impact on power and does not introduce bias, regardless of the missing data mechanism. If the percent missing data are greater than 10%, multiple imputation techniques will be used to examine the influence of missing data on our study findings. If data are missing not at random, propensity score methods will be considered for data imputation. In the propensity score method, first the distribution of the missing indicator variable given the observed data is modeled to derive a propensity score. Then observations are grouped on these propensity scores and an approximate Bayesian bootstrap imputation is applied to each group.

Hypotheses and statistical approaches for testing each are described below.

Hypothesis 1: The ABCT + oxytocin group will demonstrate significantly greater reduction in alcohol consumption from baseline to end of treatment as compared to the ABCT + placebo group (PDA and PDH measured by TLFB).
Hypothesis 2: The ABCT + oxytocin group will demonstrate significantly greater improvement in relationship functioning (measured by DAS-7) from baseline to end of treatment as compared to the ABCT + placebo group.

To test hypotheses 1 and 2, a general linear modeling (GLM) framework will be used, treating end-of-treatment (weeks 9-12) PDA, PDH, and DAS-7 scores as dependent variables (in separate models), and treating treatment group (ABCT + oxytocin vs. ABCT + placebo) as the primary independent variable. Baseline values for PDA, PDH, and DAS-7 will be included as covariates, along with other potentially significant baseline characteristics. Since PDA and PDH may exhibit non-Gaussian distributional forms and/or zero-inflation, alternative modeling strategies (e.g., arcsine or Box-Cox transformations, two-part Hurdle models) may need to be explored. Model fit will be compared by examination of Likelihood Ratio chi-square values. If transformations are necessary, back-transformations will be used in conveying the model results. Similar modeling strategies will be used for secondary exploratory outcomes (described below).

Hypothesis 3a: PFC-AMY functional connectivity after treatment will be greater in participants who receive ABCT+ oxytocin compared to those who receive ABCT + placebo.
Hypothesis 3b: Baseline PFC-AMY functional connectivity in response to alcohol vs. neutral cues will predict the magnitude of change in alcohol use (PDA and PDH measured by TLFB in the final 3 weeks of treatment).
Hypothesis 3c: Baseline PFC-AMY functional connectivity in response to relationship conflict vs. neutral cues will predict amount of change in relationship functioning (IP DAS-7 scores in the final 3 weeks of treatment).

For hypothesis 3, preprocessing and analysis of fMRI data will use FSL v 5.0[148]. Preprocessing includes rigid-body head motion correction of EPI images within a run, high-pass temporal filtering (sigma = 150 seconds), geometric distortion correction, slice timing correction, spatial filtering (FWHM = 6 mm) and registration to the MNI standard brain template. 'fsl_motion_outliers' will be used to determine head motion outliers which will be used a covariate of no interest in statistical analysis (together with the 6 rigid-body

translation and rotation head motion parameters). The primary analysis of fMRI data will use psychophysiological interaction (PPI) modeling[149] with a seed region defined in the right AMY region from the Harvard–Oxford probabilistic structural atlas thresholded at 50%. Time series will be extracted from each participant's right AMY using 'fslmeants" after warping the AMY mask into each participant's EPI space. This time series will serve as the physiological regressor for each run. The primary psychological regressors are based on the alcohol cue blocks in the alcohol run or the conflict cue blocks in the conflict run. The interaction between the primary psychological regressor for each run and the physiological regressor is the primary variable of interest.

fMRI analysis: To assess whether corticolimbic connectivity is modulated by oxytocin, the parameter estimate from the PPI interaction term will be extracted in the right and left inferior frontal cortex, opercular portion (IFC; -47, 18, 6) in each participant. The IFC regions-of-interest (ROI) are based on our preliminary study where the right AMY was functionally connected to the left IFC for the conflict cue, especially in women. In addition, the right IFC is strongly implicated in behavioral inhibition[150] and may not be activated to the same degree in participants with AUD[151]. The parameter estimates from the left and right IFC regions in each IP at pre- and post-treatment will be used in statistical analyses testing hypotheses 1 and 2 (described above). Because the hypothesized ROI may not yield the most robust response, we will also conduct a whole-brain, voxel-wise PPI analysis to identify PFC regions that show the greatest change in right AMY connectivity as a function of treatment. The voxel-wise PPI analysis will be conducted separately for each run (alcohol, conflict) but pre- and post-treatment sessions will be treated as a repeated measure. Group-level analyses will be carried out using FLAME 1 (FMRIB's Local Analysis of Mixed Effects) to generate z statistical images for each interaction term in each run. The final statistical maps will be cluster thresholded at $Z=2.33$, $p = .05$) and will indicate which regions show the greatest change in connectivity with the right AMY as a function of treatment group.

Exploratory Hypothesis 4: The ABCT + oxytocin group will demonstrate significantly greater improvement in frequency of within-session behaviors (i.e., positive, negative, and alcohol change-talk behaviors measured by the SSCIT-A[133] at sessions 1, 4, 8, and 12) as compared to the ABCT + placebo group.

To test exploratory hypotheses, a nonlinear mixed effects modeling framework will be used, where nonlinearity is likely to arise when participants transition from the treatment to follow-up phase. Separate models will be constructed for IPs and their partners. Time-specific outcome data will serve as dependent variables (in separate models, with treatment group being the primary independent variable of interest. Baseline values for PDA, PDH, DAS-7 and sex will be included as covariates, along with other potentially significant baseline characteristics. Models will include linear (and possibly non-linear) effects for time through the 6-month follow-up, allowing for changes in time effects to occur at end-of-treatment (i.e., using a regression 'join-point'). Random subject effects will be incorporated to account for the fact that within-subject measurements over time are correlated with each other. Autoregressive covariance structures along with other structures (e.g., compound symmetry, spatial power) will be investigated, with final models based on Akaike Information Criterion. When examining outcomes involving counts (i.e., positive, negative, and alcohol change-talk behaviors), we will assume these variables follow Poisson and/or negative binomial distributions, accompanied by log-link functions within a generalized linear mixed models framework.

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

Summary of the Protocol. The proposed Stage II study will examine the efficacy of oxytocin in combination with a behavioral intervention (ABCT) in reducing alcohol use disorder (AUD) severity and improving relationship functioning among couples. We will also examine the ability of oxytocin to modify corticolimbic connectivity from pre- to post-treatment. Primary outcomes include AUD symptom severity

and intimate partner relationship functioning. Between-group changes in corticolimbic connectivity will also be evaluated.

Trial Management. Dr. Flanagan (PI) will be responsible for monitoring the trial. 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.

Responsible Party. Dr. Flanagan (PI) and Dr. Brady (Co-I and Study Physician) will be responsible for distinguishing between serious (SAEs) and non-serious adverse events (AEs), and determining study relatedness.

DSM Board. 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 AUD (Lindsay Squeglia, Ph.D. and Kevin Gray, M.D.) and a biostatistician (Amy Wahlquist). 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. Confidentiality will be maintained during all phases of the study.

Adverse Events. 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 to the local Institutional Review Board (IRB) 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 will be reviewed weekly by the PI, and annually by the Data and Safety Monitoring Board (DSMB), MUSC IRB, and VA Research and Development. 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.

AE/ Unanticipated Problem Follow-up. Unanticipated problems, potential AEs and SAEs will be identified during the study via self-report data, as well as weekly 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 and Study Physician at the weekly study team meeting.

Risks of Study Participation. Risks of participation related to oxytocin safety, pregnancy, neuroimaging, and confidentiality are outlined in the Human Subjects Section. Well-established strategies to protect participants from risks are also outlined.

Safety Reporting. All unexpected 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. SAEs will be reported within 48 hours of knowledge of the SAE. In accordance with the MUSC IRB, any deaths that occur during the study or 30 days post termination from the study will be reported within 24 hours, regardless of whether it is expected or unrelated. Follow-up of all unexpected and serious AEs will also be reported to the appropriate agencies. All AEs are reviewed

weekly by the PI, and annually by the DSMB and IRB. Any significant actions taken by the local IRB and protocol changes will be reported to NIAAA. An annual report summarizing all AEs will be provided to the NIAAA project officer. This report will include 1) confirmation of adherence to the DSMP, 2) a summary of any data and safety monitoring issues that have arisen since the previous report, 3) a description of any changes in the study protocol or DSMP that might possibly affect risk, and 4) all new and continuing IRB approvals.

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 AE reporting will receive training including identification, evaluation, 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, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

When a reportable SAE is identified, research staff will initiate an SAE form, and the following individuals will be notified within 48 hours of knowledge of the SAE: study co-investigators, the MUSC Institutional Review Board (IRB), the NIAAA project officer, and members of the Data Safety Monitoring Board. If complete information is not available when the initial 48-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 project officer as appropriate. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NIAAA Medical Safety Officer within two weeks of the initial SAE report.

Inclusion/Exclusion Criteria.

Inclusion criteria

1) Male or female; any race or ethnicity; aged 18-75 years.
2) Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of the assessment instruments (> 26 on the Mini-Mental State Exam).
3) Married, cohabiting, or in a committed relationship for ≥ 6 months.
4) Identified Patients (IPs) must meet DSM-5 diagnostic criteria for current (i.e., past 12 months) alcohol use disorder (assessed via the MINI). Couples in which both partners meet diagnostic criteria for current AUD are eligible for participation.
5) Concurrent substance use disorders (e.g., marijuana) are acceptable provided that alcohol is the IP's primary substance of choice.
6) Participants taking psychotropic medications will be required to be maintained on a stable dose for at least four weeks before study initiation. This is because initiation or change of psychotropic medications during the course of the trial may interfere with interpretation of results.

Exclusion criteria

1) Meeting DSM-5 criteria for a history of or current psychotic or bipolar affective disorders, or with current suicidal or homicidal ideation and intent. Those individuals will be referred clinically for treatment.
2) Participants who present a serious suicide risk or are likely to require hospitalization during the study.
3) Participants on psychotropic medications which have been initiated during the past 4 weeks. They may be re-assessed after at least four weeks on a stable dose.

4) Acute alcohol withdrawal as indicated by CIWA-Ar scores >8. They may be re-assessed once they are no longer in withdrawal. Those individuals will be referred for medically supervised detoxification.
5) Severe unilateral intimate partner violence in the past 6 months as defined by the CTS-2.
6) Pregnancy or breastfeeding for women.
7) Individuals with implanted metal devices above the waist will be eligible to enroll in the clinical trial but will not be eligible to participate in the neuroimaging component of the study.

Study Safety. Dr. Flanagan (PI) or Dr. Back (Co-I) will be present or on call at the time of all study visits. The proposed study does not involve alcohol or drug administration. Females who are pregnant or breastfeeding are ineligible to participate due to the known effects of the study drug (oxytocin) on parturition and lactation. Couples must agree to use a reliable method of birth control and female participants will complete pregnancy tests each week during the treatment phase (for telehealth participants, pregnancy tests will be provided and study staff will require a verbal confirmation of negative pregnancy test prior to medication administration). If one of the participants becomes pregnant during the trial (despite the requirement to use an approved method of contraception), the study staff will continue to follow the participant through the course of the pregnancy. Further, since this is an intent-to-treat trial, participants will be allowed to continue in engage in therapy offered as part of standard of care in this trial. Participants who become pregnant will no longer be allowed to engage in the experimental portion of the trial and the study medication will no longer be administered. Additionally, they will not be asked questions or administered surveys regarding illegal substance use. Participants who become pregnant will also be excluded from completing urine drug screens. Since ABCT is the standard of care for couples where one individual meets AUD criteria, continuing to allow both participants to participate in the standard of care portion of the trial holds the prospect of direct benefit to the participant and is in the best interest of the participant. Protocols for reported AEs and SAEs are outlined above. All unexpected AEs 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 Dr. Flanagan. All requests by participant's physicians and other medical providers will be referred directly to the applicant.

Follow-Up Phase. All participants will be provided with a list of community resources upon study completion. Individuals presenting at any time with serious mental or physical health symptoms including acute alcohol withdrawal will be referred clinically for treatment. All AEs occurring during the follow-up phase will be reported to MUSC IRB and NIAAA. SAEs occurring during the follow-up phase will be reported to MUSC IRB and NIAAA within 48 hours. Any participant demonstrating clinical deterioration will be referred clinically consistent with the procedures outlined in the Human Subjects section. In the event that emergency evaluation or intervention is necessary, the participant will be escorted by a study staff member to the psychiatric walk-in clinic or emergency room. Psychiatric hospitalization is available for emergencies at any point in the study.

Data Management and Analysis. A data analytic plan (including power calculation) is outlined in the Data Analysis section. This study is powered to examine the efficacy of oxytocin versus placebo on the primary outcomes of interest. The main outcome variables include the severity of AUD, relationship functioning, and corticolimbic connectivity determined via neuroimaging procedures. Analyses will be guided by the specific hypotheses of the study and conducted by the study biostatistician, Dr. Paul Nietert. Post-hoc exploratory analyses will be conducted with two-tailed tests and more conservative statistical procedures which guard against Type I error (e.g., Tukey tests). All primary hypotheses will be tested at level of

significance α=0.05. We will also estimate the effect sizes of interest and provide 95% confidence intervals. Please see the Statistical Analysis and Power section for more details.

Quality Assurance and Confidentiality. Data quality will be monitored by random inspection of the completed forms by research staff and any irregularities or problems detected will be discussed with the PI. Project therapists will receive standardized training from the PI and Co-Is (Drs. Flanagan, Back, and McCrady). Dr. McCrady developed the ABCT intervention which will be utilized in the proposed study and is currently being tested in several federally-funded trials to examine various adaptations of ABCT. Adherence to the manual will be monitored using videotapes and weekly supervision. If therapy drift is observed the therapists will be re-trained. Booster sessions will be held annually.

DSM Plan Administration. The PI will be primarily responsible for monitoring the study. The PI and a statistician will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSMB report will be filed with the IRB on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs and SAEs. We will report main outcome results at the end of the trial. An annual report of all AEs will be submitted to the NIAAA project officer. In addition, all AEs will be reviewed weekly by Dr. Flanagan, and annually by the DSMB, local IRB and VA Research and Development. Any significant actions taken by the local IRB and protocol changes will be reported to NIAAA.

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 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 Dr. Flanagan 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.

Stopping Rules for Clinical Trials. The trial will be stopped under any of the following conditions: 1) there is clear evidence of harm; 2) there is no likelihood of demonstrating treatment benefit, or 3) there is overwhelming evidence of the benefit of treatment.

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.

13.0 Withdrawal of Subjects

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.

14.0 Risks to Subjects

Oxytocin Safety: Oxytocin is a neuropeptide commonly administered intravenously among women during childbirth. 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 participants protection methods. Our group has administered intranasal oxytocin at this dose to over 300 research participants to date, including distressed couples with AUD and intimate partner violence, without a single adverse event reported. Participants will be informed about the potential side effects of oxytocin and will be closely monitored by the research team. Oxytocin self-administration will occur only in the context of the study visit with clear instruction from the study staff, who are equipped with ready access to clinicians and emergency care if necessary. All participants will be given clear instructions on when and where to administer the study medication (only during the study visit, while study staff are monitoring). The study medication will be stored in under refrigeration before and after medication administration (either at the participant's home or at the study site).
All telehealth participants complete a participant locator form with study staff, that allows the study team to identify local emergency care facilities and contact information. Specifically, for out of state or remote participants, the study staff will compile a list of referrals and emergency contacts to provide to study participants ahead of enrollment.

Blood Draw: Participants may experience pain or discomfort, faintness, bruising, or bleeding at the location where the blood is drawn. There is also a slight chance of infection as a result of having blood drawn.

Risks of pregnancy: Because this study involves a 50% chance of a study subject receiving active medication (i.e., oxytocin) and the effects of oxytocin on pregnancy outcome are well known, pregnant and lactating females will be excluded from the trial. We will instruct female participants to use appropriate forms of contraception, and participants are required to complete pregnancy tests at baseline and weekly during treatment.

Risks related to neuroimaging: Participants will be asked to complete two optional neuroimaging scans (functional magnetic resonance imaging; fMRI), which will be conducted at the MUSC Center for Biomedical Imaging (CBI), which is located on the MUSC campus. There are very few potential risks from fMRI itself. There is no exposure to ionizing radiation and the machine and scanning sequences and gradients are approved by the Food and Drug Administration (FDA) for routine clinical use. Individuals who are claustrophobic may experience some anxiety during the scanning procedures. Participants may experience some loud noises during the scanning procedure and there is a mild risk of hearing damage if patients are not given hearing protection. All participants in the study will be given hearing protection. Participants may experience psychological discomfort from undergoing the scanning procedure, such as boredom and fatigue. Ferrous objects in the body that are undetected could move during scans. This could lead to tissue damage and hemorrhage. These risks are outlined in the informed consent document. In our past and ongoing studies utilizing fMRI, we have been able to safely complete imaging procedures without undue distress or negative outcomes. This includes research with civilians and Veterans who have current AUD.

Confidentiality: All possible efforts to protect participants' privacy and confidentially will be made throughout the course of the study. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures.

Adequacy of Protection against Risks

Recruitment and Informed Consent Procedures. All personnel will be trained in the responsible conduct of research. Participants will be recruited from MUSC and VAMC treatment clinics, community settings, and ads placed on Craigslist and social media to reach participants in South Carolina and in other states inside the continental United States. The screening measure contains questions directly pertaining to the study's inclusion and exclusion criteria. Participants who meet eligibility criteria will be scheduled with research staff for a baseline assessment session. In a private room, 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. Informed consent will be collected by the Study Coordinator, trained research assistants, PI, or Co-Is. All study personnel will read and attend training sessions in the study protocol conducted by the PI and in coordination with the Co-Is. These trainings will include 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.

Participants will also be informed that they are not required to make a 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 and confidentiality and to minimize coercion, all participants will have the opportunity to discuss participation with their partner prior to providing informed consent. Participants who are eligible to participate and choose to do so will be encouraged to ask any questions they might have about the study. Both the participant and research staff member will sign the form.

The informed consent document will outline 1) the sponsorship of the study; 2) the nature, purpose and procedures of the research study; 3) the voluntary nature of participation (i.e., participation is not required and can be discontinued at any time; 4) duration of the study; 5) potential risks and discomforts and potential benefits of participating; 6) that all information will be kept confidential subject to the provisions of state and federal law; 7) compensation; 8) alternative treatments; and 9) telehealth procedures and limitations. Participants will be informed that they can discontinue participation in the study at any time and that this decision will not influence the care they receive at any MUSC or VAMC clinic.

Assessment Procedures. Some participants may experience distress in response to self-report and interview measures pertaining to AUD symptoms or associated areas of functioning such as relationship problems or depression. Participants may also experience physical or psychological discomfort during the neuroimaging procedures or medication self-administration. However, based on the research team's past experience and available literature the risks involved in the proposed project are minimal and manageable. Nevertheless, we have a specific protocol in place to manage participant distress in the event that it arises. This protocol is discussed in more detail below. Additionally, all participants will receive an evidence-based behavioral intervention (e.g., ABCT) that includes techniques to help reduce distress and anxiety, and improve mood (e.g., communication skills, cognitive restructuring). We will also inform participants during the informed consent process that they may terminate any assessments, study procedures, or therapy sessions at any point. Our past and ongoing research suggests that the measures and methods proposed in this study can be implemented without undue psychological distress or exacerbation of symptoms. This experience includes numerous federally-funded projects with civilians and Veterans with AUD.

In the event that a participant becomes distressed secondary to participation, they will be encouraged to contact the PI. In addition, they will have access to urgent care services at MUSC and VAMC treatment clinics, as well as the VA Crisis Line. Telehealth participants not located in Charleston will be provided with urgent care contact information local to them. Any adverse effects noted by any project personnel will be immediately reported to the PIs, who will then report these adverse effects in writing to the IRB and NIH per protocol (see the Data and Safety Monitoring Plan at the end of this section for more details). The research team includes several licensed clinical psychologists and psychiatrists who are equipped to help

participants manage distress and to evaluate conditions in which participants need additional assistance. In the event that a participant becomes significantly distressed, the PI 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. If called by participants, the PI will attempt to address all participant concerns and set up an alternate referral for counseling for those who desire it from outside the project.
Every attempt will be made to engage participants for the duration of the 12-session treatment phase. Participants will be considered drop-outs from the treatment phase if they fail to attend therapy sessions for four consecutive weeks, in spite of attempts by phone, email and mail to engage the participant in treatment. All telehealth participants complete a participant locator form prior to each visit, that allows the study team to identify local emergency care facilities and contact information. Specifically, for out of state or remote participants, the study staff will compile a list of referrals and emergency contacts to provide to study participants ahead of enrollment. Participants will be provided with contact information for their local mental health clinicians, urgent care, and national suicide prevention lifeline for their use should suicidal ideation occur outside of weekly therapy sessions. Should a suicide safety plan be needed based on participant's BDI during either baseline or weekly visits, participants will meet with study therapist to complete the suicide safety plan together which will also include resources which are local to the participant.
A note on VA Crisis Line: the VA Crisis Line can be reached at any time from any location. Study teams have been trained on how to connect a veteran with the VA Crisis Line via three-way teleconferencing. Once the VA Crisis Line is contacted, they will dispatch necessary care to the veteran in crisis anywhere in the United States, and provide follow up services.

Study Physician. Kathleen Brady, M.D., Ph.D. will serve as the Study Physician on this project. Dr. Brady has extensive experience with NIH-sponsored clinical trials involving individuals with AUD and other substance use disorders, as well as comorbid psychiatric conditions. She has ample experience monitoring and treating individuals with acute substance-related withdrawal. She will review all adverse events, unanticipated problems involving risk to participants or others, serious adverse events, and any participant deaths associated with the protocol and provide an unbiased written report of the event within 10 calendar days. In addition, the investigative team includes psychologists with ample addiction expertise (Drs. Flanagan, Back, Bottonari) who will closely monitor study participants. If at any point a participant necessitates medical management, psychiatric consultation or psychiatric hospitalization, they will be evaluated and referral to treatment will be provided accordingly. If a participant becomes suicidal, emergency psychiatric assessment will be arranged. The participant will be closely monitored until they are no longer suicidal or an appropriate care plan is in place.

Alcohol Withdrawal. 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.

Military Personnel. Because some participants may be U.S. military personnel, absolute confidentiality of research records cannot be guaranteed. However, 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 are additional resources available to study staff and research participants. Risks of participation will be outlined in the informed

consent and reviewed during the informed consent procedure. In similar past and ongoing studies, these resources have been sufficient to manage problems or distress related to participation.

Neuroimaging. All project study staff will be required to complete the CBI's MRI safety training class. The course is taught by an American Registry of Radiologic Technologists registered technician. The staff will be trained about safety in the MRI environment, and how to screen oneself and others. The staff will also have knowledge of safety procedures for entering the scanner facility, safely removing participants from the scanner, when and how to quench the magnet and basic emergency procedures including emergency contact information. Standard operating procedures for emergency situations are located on-site. The MRI technician and Dr. Joseph (Co-I) are authorized to operate the equipment and will be present throughout the scanning sessions. Although there are no known risks of MRI scanning to a developing fetus at 3.0 T, the possibility that risks could be discovered in the future cannot be ignored. Therefore, urine pregnancy tests will be used to exclude pregnant women from study participation. A careful metal screening history will be taken from each participant to assess the possibility of metal devices/implants and will be reviewed by the PI, MRI technician and/or clinical staff who have had extensive training and experience with MRI safety. If the screening yields information that raises a question of safety, the participant will be asked to provide the appropriate documentation (i.e., film) before they are allowed to participate. In addition, participants will be asked to empty their pockets and will be screened with a hand-held ferromagnetic-detector wand. Participants will wear earplugs and sound-dampening headphones to decrease the intensity of the scanner noise. Prior exposure to pictures of the scanner, getting into the scanner, and seeing others in the scanner, often reduces psychological discomfort or identifies people for whom scanning is not appropriate.

Safety and Monitoring Plan. A procedure for clinical deterioration has been established based upon our experience with previous and ongoing NIH-funded clinical trials. Therapists (who will be trained Master's or Doctoral level clinicians) will be instructed to use their best clinical judgment regarding emergencies and inform the PI as soon as possible. In addition to relying on clinical judgment on the part of the treating therapists who are experienced with this population, we will also monitor alcohol and drug use, depression, and relationship functioning weekly using standardized measures (TLFB, BDI-II, DAS-7, breathalyzer/saliva alcohol tests) in order to detect any symptom worsening requiring further evaluation. Additionally, participants will be advised to observe any signs of worsening alcohol use, depression symptoms, or relationship functioning including intimate partner violence, and to discuss these challenges with their therapist.

Participants will be withdrawn from the study and referred for more intensive treatment if: (1) there are increases in alcohol use leading to the need for a more intensive level of care (i.e., medical detoxification, inpatient or partial hospitalization); (2) there is active suicidal or homicidal ideation and/or intent; (3) there is an inability to manage the participant psychiatrically within the inclusion/exclusion criteria of the study (i.e., need for the initiation of psychotropic medications; development of psychosis); or (4) there is an inability to complete ABCT therapy appointments due to incarceration or hospitalization.

There is a well-established protocol at MUSC for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed participants. Immediately on detection of these needs, the assessor/therapist will page a psychiatrist to review the participant's situation. If appropriate, the psychiatrist will personally evaluate the participant. Alternatively, during weekdays, the participant will be escorted by a study staff member to the psychiatric walk-in clinic or emergency room. Psychiatric hospitalization is available for emergencies.

Participants will be informed during informed consent procedures of the standard limitations of confidentiality 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 the PI 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.

Suicide Specific Risk Identification and Response Plan. Specific precautions will be taken to prevent harm to participants and potential participants. Project therapists will be trained Masters or Doctorate level clinicians and will be supervised by Dr. Flanagan (PI) and Dr. Back (Co-I), who are licensed clinical psychologists. All project therapists and staff will be specifically trained to assess suicide risk, including ideation, plan, and intent as well as history of ideation or attempts, and they will be trained to develop a safety plan with participants. In initial screening procedures, participants identified by clinical interview with both suicidal ideation and acute intent will be excluded from the study, but will be offered emergency psychiatric care immediately. This care is available 24 hours per day at MUSC and the Charleston VAMC, as indicated above. Moreover, during the course of the study, any participant scoring above 25 on the BDI-II (administered weekly) or answering a 1 or above to question 9 will be specifically queried about suicidal ideation and intent. In any instance where ideation or intent is identified, the PI will be immediately notified and will contact the participant for further evaluation. If both ideation and intent are present, the aforementioned hospital intervention will be provided. Thus, all assessment points represent suicide risk identification, assessment, and intervention opportunities. Study therapists and staff will be specifically trained regarding the increased risk of suicide in Veterans with chronic pain and substance use disorders, and will receive specific instruction of suicide risk assessment during the initial training workshop. In the case of acutely suicidal or distressed veterans participating via telehealth and located outside of our immediate geographical location (and the state of South Carolina),the study team will initiate a three-way call with the VA Veteran Crisis Line who has the ability to locate the veteran and send emergency help to the veteran.

Study Implementation and Data Security. We will take careful precautions to maintain confidentiality for all participants, using procedures we have used with similar previous studies: All research personnel will attend a required in-service training conducted by PI where the screening, informed consent, and assessment protocols will be described. All members of the research team will sign a confidentiality agreement that no identifying information of specific individuals will appear in any external documents (e.g., peer-reviewed publications, presentations) or in any internal reports.

All study data related to psychological outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached in any way. 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. The master list will be destroyed upon study completion; it will be kept separate from all data and will be available only to the PI, Study Coordinator, and research assistants. To protect participant confidentiality, all data will be maintained in a manner consistent with IRB-approved protocol. Data will be stored in locked filing cabinets within a locked office and on MUSC's encrypted computers and data servers. Access to de-identified study data will be limited to named project investigators, the Study Coordinator, NIH audit personnel, MUSC IRB audit personnel, and the VAMC Office of Research & Development (R&D) personnel. Data will be maintained per an IRB-approved protocol.

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. At least two members of the study team will be present during all participant appointments in order to ensure the safety of participants and research staff. Appointments will be scheduled primarily during normal working hours, however accommodations will be made to fit participants' schedules.

All research staff has completed or will complete the University of Miami CITI training course in the responsible conduct of research. Necessary certifications in the responsible conduct of research and the protection of human research participants will be completed on an annual basis, in compliance with MUSC institutional and NIH regulations.

15.0 Potential Benefits to Subjects or Others

While there is no guarantee of specific benefit to participants in this study, the potential benefits include a thorough psychological and substance use assessment, referral to appropriate treatment services and community resources, and remuneration. Participants may also benefit from receiving access to an evidence-based behavioral treatment which may result in a reduction in aversive AUD symptom severity, improvement in relationship functioning and symptoms of other mental health problems (e.g., depression) and improvements in other areas of functioning (e.g., sleep, quality of life). Other study benefits include regular contact with research staff, access to assessment information pertaining to mental health, substance abuse, etc., and referral to treatments for associated problems such as smoking. While these benefits may be considered minimal, we believe that they outweigh the minimal risk and burden incurred by participants. Participants will also enroll in a study that has the potential to enhance treatment for other patients and families with AUD.

16.0 Sharing of Results with Subjects

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

17.0 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.

Anjinetta Johnson, PA or Jennifer Jones, MD will send participants' prescriptions to the Pitt Street Pharmacy each week. Pitt Street Pharmacy will assign participants to one of the treatment groups (oxytocin or placebo), but this information will remain blinded to the research staff and to the participants. Research staff will pick up the weekly prescriptions from Pitt Street Pharmacy and transport the study drug to the research site (using a cooler bag with an ice pack to maintain refrigeration). Research staff will administer the study drug to participants in our Charleston Center offices. Research staff will select the prescribed medication for each individual participant, will confirm the identity of the participant, and will instruct participants on the correct method of administration to achieve the desired dose and will observe participants' self-administration. 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.

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