Clinical Trials Cover Sheet

Study Title: Impact of Lofexidine on Stress, Craving and Opioid use

IND Number: 141345

Drug Name: Lucemyra (lofexidine)

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A. Significance

A.1. Opioid Epidemic in Women. Opioid use disorder (OUDs) are increasing at alarming rates in the United States and the prevalence in women is substantial. While the number of opioid-dependent men in the US remains larger than the number of opioid-dependent women, there are some disturbing trends. Between 1999 and 2015, overdose deaths from prescription pain drugs increased 471 percent in women compared to an increase of 218 percent in men (CDC, 2018). Although nonmedical use of prescription opioids among women has generally been decreasing since 2010 (Jones, 2016), heroin use among women increased faster in women than men and between 2002 and 2013, heroin use among women increased 100% compared to an increase of 50% among men (Cicero et al., 2014). Disturbingly, there has been an enormous increase in the rates of synthetic opioid-related deaths, with an 850 percent increase in deaths for women between 1999 and 2015 (CDC, 2018).

A.2. Gender Differences in Substance Use Disorders (SUDs). There is growing recognition that biological and psychosocial differences between men and women influence the prevalence, presentation, comorbidity and treatment of SUDs. For example, women tend to use smaller amounts of drugs or alcohol for a shorter amount of time before seeking treatment, a phenomenon known as "telescoping" (Brady and Randal, 2007). A similar trend is seen in OUDs; an analysis of data from a multisite clinical trial demonstrated that women progressed to opioid dependence more quickly and experienced more craving as compared to men (Back et al., 2011). Women with SUDs are also more likely to have comorbid depression and anxiety disorders (Brady et al., 1993; Brady and Randall, 1999) and are more likely to attribute use and relapse to negative emotional states and interpersonal conflict (Connors et al., 1998; Back et al., 2011) as compared to men. There is also evidence of gender differences in neurocognitive and brain responses in drug-dependent individuals. An fMRI study examining gender differences in neural correlates of stress- and drug cue exposure found greater corticostriatal-limbic reactivity in cocaine-dependent women during stress exposure, but higher reactivity in these regions during drug cue exposure in cocaine-dependent men suggesting greater neural stress sensitization in women (Potenza et al., 2012). Another study found psychological and emotional distress were identified as risk factors for hazardous prescription opioid use among women, but not men (Back et al., 2011).

A.3. Stress and Relapse: Sex and Gender Differences. Etiologic theories of SUDs suggest that stress plays an important role in vulnerability and motivation to abuse addictive substances (Higgins and Marlatt, 1975; Koob and LeMoal, 2001; Russell and Mehrabian, 1975). Animal studies demonstrate that exposure to stress facilitates both initiation and reinstatement of drug use after a period of abstinence (Koob et al., 2004; Stewart, 2000). The brain circuitry (including amygdala and hippocampus) underlying cognitive processing of stress is sexually dimorphic in humans and animals (Kudielka and Kirschbaum, 2005). In addition, hormonal regulation contributes to sexual dimorphism in stress response (Patchev and Almeida, 1998), with estrogen and progesterone acting as modulators of stress regulation (Windle et al., 2006). Corticotropin-releasing factor (CRF), an important mediator of the stress response through the hypothalamic-pituitary-adrenal (HPA) axis and extra-hypothalamic systems, has been implicated in the pathophysiology of stress-induced relapse (Koob et al., 2014). Preclinical studies have demonstrated significant sex differences in CRF systems. For example, female rodents have higher basal levels of CRF in the hypothalamus (Viau et al., 2005; Dunko et al., 2001) and significantly greater adrenocorticotropin hormone (response) to CRF (Kuhn and Francis, 1997).

One focus of our previous SCOR work was the neural circuitry and mechanistic connection between stress and vulnerability to relapse in cocaine dependence. Preclinical studies by our group and others demonstrated that CRF agonists can initiate reinstatement of cocaine-seeking in rodent models (Shaham et al., 2003; Lu et al., 2003). Our SCOR group was the first to demonstrate that female rats are more sensitive to the impact of CRF on cocaine reinstatement compared to male rats (Buffalari et al., 2012). In our human laboratory studies, we found higher subjective stress response and greater HPA axis disruption in cocaine-dependent women compared to men (Brady et al., 2009). Of interest, high stress and craving following CRF administration was associated with higher relapse rates in the month following laboratory testing (Back et al., 2010).

In this same study, the heart rate response following CRF was also more robust and prolonged in women (Brady et al., 2009), suggesting greater noradrenergic activity. Interactions between the brain's noradrenergic and CRF systems are critical to the stress response (Koob et al., 2014; McRae et al., 2017). The noradrenergic system is comprised of two main projections distributed throughout the brain: the dorsal noradrenergic bundle (DNB) originating in the locus coeruleus (LC) and the ventral noradrenergic bundle (VNB) in the brain stem. The noradrenergic receptor system is made up of alpha1, alpha2, and beta receptor subtypes (Berridge and Waterhouse, 2003). Alpha-2 adrenergic agonists, such as clonidine, guanficine and lofexidine, stimulate

inhibitory presynaptic alpha-2 receptors and decrease norepinephrine (NE) cell firing and release centrally (Aghajanian, 1982). Preclinical studies indicate significant sex differences in the LC-NE system, including increased numbers of LC neurons and differences in dendritic structure, so female rats receive more CRF-containing afferents from limbic regions (Bangasser et al., 2016). In addition, estrogen can increase NE in LC target regions by enhancing NE synthesis and reducing degradation (Bangasser et al., 2106). Finally, one study found that CRF was 10–30 times more potent in activating LC neurons in female versus male rats (Curtis et al., 2006).

A.4. Sex and gender differences in response to noradrenergic agents. Preclinical evidence suggests that increased NE activity is a mediator of stress-induced reinstatement. Yohimbine, an alpha-2 receptor antagonist that increases NE release, facilitates reinstatement of cocaine (Feltenstein and See, 2006; Lee et al., 2004), methamphetamine (Shepard et al., 2004), and alcohol (Le et al., 2005) seeking. Our SCOR group was the first to demonstrate that female rats were more sensitive to the impact of yohimbine on cocaine-reinstatement than males, with females in proestrus demonstrating the greatest response to yohimbine (Feltenstein et al., 2011). Our SCOR group also demonstrated gender specific sensitivity to noradrenergic dysregulation in cocaine dependence using a human laboratory paradigm. In a double-blind placebo-controlled cross-over study of yohimbine prior to cocaine cue exposure, women reported greater anxiety and craving with yohimbine compared to men (Moran-Santa Maria et al., 2014), suggesting that noradrenergic-mediated stress increased the salience of drug cues for women more than men.

Of interest, alpha-2 agonists selectively block reinstatement of heroin, cocaine, alcohol and nicotine-seeking in animal models (Erb et al., 2000; Shaham et al., 2000; Highfield et al., 2001; Yamada and Bruijnzeel, 2011; Le et al., 2005). Several human laboratory studies have also demonstrated that alpha-2 agonists decrease both stress and cue-induced craving in cocaine- and nicotine-dependent individuals (Jobes et al., 2011; Fox et al., 2012; Fox et al, 2014). One investigation of the impact of guanfacine on stress and cue-induced response in cocaine-dependent men and women found that guanfacine significantly attenuated cocaine and alcohol craving, anxiety, and negative emotion in women but not in men (Fox et al., 2014). A Cochrane review found that clonidine treatment for smoking cessation was more effective in women than in men (Gourlay et al., 2004). In a meta-analysis (n = 813) of clonidine studies for smoking cessation, end-of-treatment quit rates in women were 70% for clonidine versus 18% for placebo, whereas men did not demonstrate a medication effect (Glassman et al., 1988). McKee and colleagues (2015) found that guanfacine significantly and equally reduced the number of cigarettes per day following a quit attempt for men and women over a 4-week treatment period. However, guanfacine decreased smoking lapse, cigarettes smoked, and tobacco craving following stress in women but not in men. Although preliminary, these findings suggest that interventions that decrease noradrenergic activity may be more efficacious in reducing substance use in women as compared to men due to sex differences in stress-related sensitization.

A.5. Opioids, HPA Axis and Noradrenergic Systems. In opioid dependence, stress system dysregulation is of major significance because of the complex relationships between stress-related neuropeptides (i.e. CRF), the endogenous opioids, and the LC-NE system. The LC–NE system is reciprocally regulated by endogenous opioids and CRF (Curtis et al., 2001; Kawara et al., 2000; Valentino and Van Bockstaele 2001; 2013). Preclinical studies demonstrate that chronic morphine sensitizes the LC-NE system to CRF expressed as increased sensitivity of the neurons to stress, providing a potential mechanism to link opioid use with stress-sensitive disorders (Xu et al., 2004). As detailed above, there is substantial pre-clinical evidence indicating sex differences in these systems, but these differences have not been specifically explored with regard to opioids.

There is some lack of consistency in studies of HPA axis function in opioid dependence. As expected because opioid receptors exert inhibitory control over CRF and HPA axis output, ACTH and cortisol are reduced during heroin exposure and early studies demonstrated normalization of HPA axis function during methadone maintenance (Kreek et al., 2002; Kreek et al., 1983). More recent studies have demonstrated some persistent alterations in HPA axis activity in methadone-maintained individuals, including increased sensitivity to high dose CRH administration (Schulger et al., 2003) and decreased cortisol and CRF levels (Zhang et al., 2009), suggesting suppressed HPA axis function. Although the impact of buprenorphine maintenance on HPA axis function has not been as thoroughly explored, one study using a metyrapone challenge suggested suppressed HPA axis function in individuals on buprenorphine maintenance (Kakko et al., 2008). It is clear, however, that opioid withdrawal engages CRF and other stress-systems, including noradrenergic pathways, and is associated with anxiety and dysphoria (Schulger et al., 2003). Several studies have demonstrated that increased cortisol during opioid withdrawal is positively correlated with opioid craving (Nava et al., 2008; Shi et al., 2009).

A.6. Apha-2 Agonists in Opioid Dependence. Clonidine was the first alpha-2 agonist shown to ameliorate some signs and symptoms of opioid withdrawal (Gold et al., 1978) and is now used in opioid detoxification. Although clonidine is traditionally used only for opioid detoxification, Kowalczyk and colleagues (2015) conducted a randomized double-blind, placebo-controlled relapse prevention trial of adjunctive clonidine treatment in 118 OUD men and women on buprenorphine. The rationale for the trial was based on preclinical reinstatement studies cited above (Erb et al., 2000; Shaham et al., 2000; Highfield et al., 2001). To preserve consistency with the preclinical models, a relapse prevention model requiring a period of abstinence before entering the medication treatment portion of the trial was used as preclinical data suggests that cessation of on-going drug use is mediated by different neural mechanisms than those involved in prevention of relapse (Shalev et al, 2002; Kalivas and Volkow, 2005). Ecologic momentary assessment (EMA) was used during the 14-week trial to query participants about daily life stress and craving. The clonidine-treated group had a significantly longer duration of abstinence as compared to the placebo group. EMA assessment demonstrated that daily life stress was partly decoupled from opioid craving in the clonidine group, supporting the hypothesis that clonidine exerted its beneficial effects by muting the stress response. The number of women in the sample was not large enough to support gender-specific data analysis. Of interest, in studies using a preclinical model of polysubstance abuse, methadone blocked cocaine and heroin-induced reinstatement, but not stress-induced reinstatement (Leri et al., 2004; Sorge et al., 2005).

Lofexidine, also an alpha-2 agonist, has been licensed for opioid detoxification in England since 1992. Three studies and a Cochran review comparing the efficacy and tolerability of lofexidine to clonidine suggest comparable efficacy in reducing withdrawal, with a better risk-benefit profile for lofexidine including better tolerability and less hypotension (Kahn et al., 1997; Lin et al.,1997; Carnwath and Hardman, 1998; Gowling et al, 2016). In a study of 18 opioid-dependent individuals stabilized on naltrexone (NTX), treatment with lofexidine versus placebo was tested (Sinha et al., 2007). During the 4-week treatment period, the lofexidine-NTX patients had higher abstinence rates and improved relapse outcomes as compared to the placebo–NTX group. Ten subjects participated in a human laboratory stress/drug cue exposure paradigm. The lofexidine–NTX patients had significantly lower heart rate and attenuated stress and drug cue response as compared to the placebo–NTX group. The sample size did not support a gender-specific analysis in this study. As in the study by Kowalczyk and colleagues (2015), participants were stabilized on NTX before initiation of study medications, making this a relapse prevention study. Following these two positive clinical studies and based on the preclinical data, we will use a relapse prevention model in this study requiring a period of abstinence before the medication treatment period.

In sum, alterations in the stress response and noradrenergic system are important in pathophysiology of OUD. Alpha-2 agents, which decrease noradrenergic activity, may be helpful in decreasing the stress response in OUD individuals. In cocaine and nicotine dependence, alpha-2 agents have a more robust impact in women as compared to men, however gender differences in OUD individuals have not been explored. The primary objective of this study is to explore gender differences in the impact of an alpha-2 agonist, lofexidine, on the relationship between stress, craving and drug use in individuals with OUDs.

A.7. Conclusions. OUDs are increasing at alarming rates in women. Stress and dysregulation in biologic stress response systems appear to play an important role in drug use and the connection between stress and drug use may be particularly important for women. Alterations in CRF, the HPA axis and noradrenergic system are important in the pathophysiology of OUDs and there is evidence that agents that decrease noradrenergic activity may help to prevent relapse and stress reactivity in individuals with OUDs, but gender differences in these effects have not been systematically explored. The primary objective of this study is to explore gender differences in the impact of an alpha-2 agonist, lofexidine, on the relationship between stress, craving and drug use in individuals with OUDs.

B. INNOVATION

The proposed study will test truly novel hypotheses using innovative methodology. Specifically, it will build on our previous SCOR work investigating sex and gender differences in the stress-relapse connection, while expanding the focus to opioid dependence, a problem of epidemic proportions in the United States. Several studies suggest alpha-2 agonists may be useful in reducing stress-induced craving and relapse in OUDs and studies in cocaine and nicotine dependence suggest that women may be more responsive to these agents as compared to men. However, to our knowledge, there are no previous or ongoing studies investigating gender differences in the impact of alpha-2 agonists in decreasing stress-induced craving or relapse in OUDs. In addition, we will use a novel alpha-2 agent, lofexidine. While lofexidine has been approved for use in England,

it is now being evaluated by the FDA for use in the United States. Studies suggest that lofexidine is better tolerated than clonidine, the alpha-2 agent most commonly used in the United States for opioid detoxification (Gowing et al., 2009). We will utilize a novel dual-level approach by examining the impact of lofexidine on stress and drug cues presented in a laboratory paradigm and on ambient stress, craving and stress cues occurring over the course of a clinical trial. In the latter case, we will use innovative mobile technology to allow for assessment of craving, stress and stress-cue reactivity in the "day to day" natural environment before, during and after treatment in individuals with OUD. We will also assess medication compliance using an innovative video capture procedure. These approaches represent a highly innovative "next step" in the development of personalized, gender-specific treatment for individuals with OUD.

C. APPROACH

C.1. Preliminary Studies

C.1.a. Capacity of Research Team. The proposed research requires experience in: 1.) recruitment, retention, and assessment of OUD individuals, 2.) human laboratory stress induction procedures, 3.) collection and interpretation of neuroendocrine and physiologic measurements, 4.) ambulatory assessments, and 5.) clinical trial conduct and follow-up of individuals with SUDs. As detailed below, the multidisciplinary research team has the requisite expertise to successfully conduct the proposed work and a proven track-record. The proposed project will be co-directed by Drs. Kathleen Brady and Connie Guille. Dr. Brady is a Distinguished University Professor with a 30-year history of successful conduct of clinical trials and human laboratory studies in individuals with SUDs. Dr. Connie Guille's research focus is perinatal OUD, incuding the ultization of EMA to identify predictors of opioid use. Drs. Brady and Guille have been collaborators for the past decade. Dr. Kelly Barth is a board-certified Addiction Psychiatrist with specific interests in chronic pain management, the interface of pain and addictions, and gender differences in OUDs. Dr. Jenna McCauley is a licensed clinical psychologist with experience in assessment of early life trauma and opioid research, as well as clinical trial conduct and follow-up of individuals with SUDs. Importantly, these investigators have been working closely together over the past 2 years leading state-wide efforts to address the opioid epidemic in South Carolina. As such, they are a cohesive team with a history of successful collaboration.

C.1.b. Experience with Recruitment, Retention, and Assessment OUDs. Dr. Brady has been conducting clinical trials in close connection with local treatment programs over the past 20 years as part of the NIDA-funded clinical trials network (DA013727). The Charleston Center is a public treatment program located 1 block from the MUSC campus. In 2017, Charleston Center treated 356 men and 224 women with primary OUDs. In 2017, the MUSC addiction treatment service treated over 250 patients with OUDs, including approximately 100 individuals on buprenorphine, the target population for this proposal. Dr. Brady and colleagues recruited 126 men and women with OUDs from these settings over a two-year period. A subset of these individuals participated in a human laboratory study similar to the proposed project (described below). In addition, this team is currently leading a multi-pronged statewide effort focused on the opioid epidemic which includes a component focused on providing buprenorphine and rapid access to treatment for OUD patients presenting in emergency rooms (ERs). In the MUSC ER, they have identified 56 individuals with OUD in the last 6 months and facilitated treatment at the Charleston Center and MUSC addiction treatment services.Shoreline Behavioral Health in Conway, SC works closes with DAODAS to provide medication-assisted treatment to residents of Horry County. With these multiple recruitment sites, we anticipate no difficulties meeting recruitment goals for the proposed study.

C.1.c. Stress Induction Procedures and Neuroendocrine/Physiologic Measurement. Dr. Brady has conducted a number of human laboratory studies involving stress induction and drug cue exposure in alcohol, cocaine and nicotine dependence (Brady et al., 2009; Moran et al., 2014; Hartwell et al., 2011; Brady et al., 2006). Of direct relevance, Drs. Brady and colleagues completed a pilot study involving a human laboratory stress task in 39 (N=19 women; 20 men) individuals with OUD. Subjects were randomly assigned to either the Trier Social Stress Test (TSST; n=19) or no-stress control (no stress; n=20) followed by opioid cue exposure. Distress tolerance, Inventory of Drug Taking Situations and Time-line Follow-back were completed at baseline. Self-reported visual analog scale ratings of stress and craving, as well as heart rate and salivary cortisol were assessed immediately before and at multiple time points for 60 minutes following the TSST/drug cue exposure. Individuals were followed for one month after the laboratory session to assess opioid use (Time-line Follow-Back) and daily stress. Significant group (TSST vs. no stress) differences emerged in self-reported stress [$F(1,35)=41.77$, $p<.001$], anger [$F(1,35)=13.00$, $p<.001$], sadness [$F(1,35)=4.78$, $p<.05$], cortisol and heart rate

(HR) [F(1,35)=5.28, p<.05], with the TSST group exhibiting more reactivity. Women demonstrated significantly greater self-reported stress [F(1,35)=11.24, p<.01], (Figure 1); however, they exhibited significantly less cortisol response following the TSST as compared to men. Data (Figure 2) are shown as log 10 transformed model-

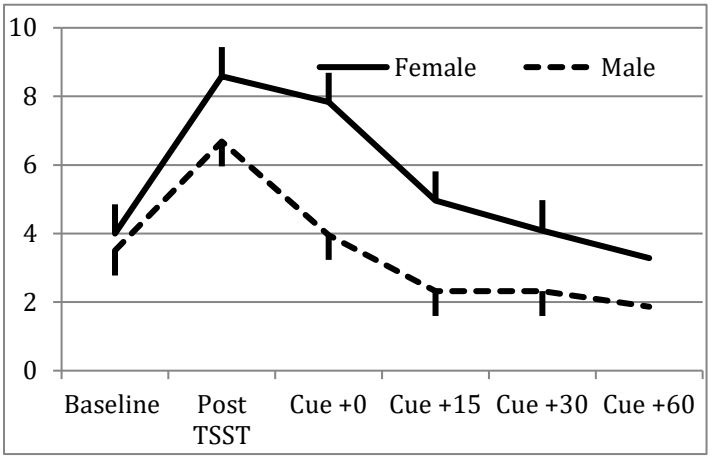


Figure 1: Stress Response

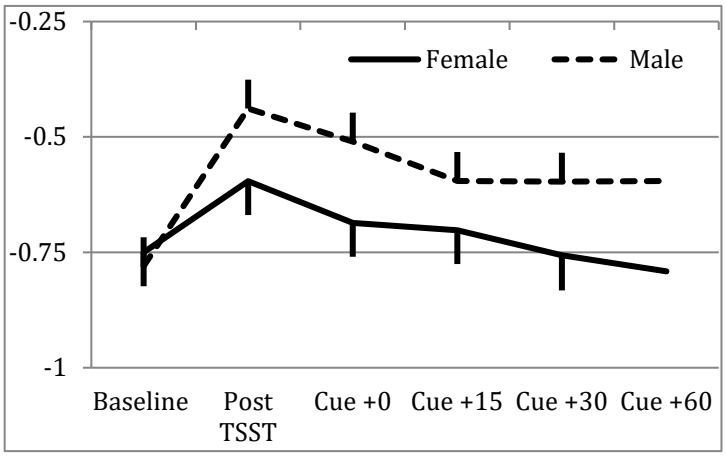


Figure 2: Cortisol Response

based means and standard errors adjusted for baseline cortisol. Of interest, women also exhibited a significantly protracted HR response following the TSST compared to men; it had not returned to baseline by the end of the 1 hour follow-up period (Figure 3) suggesting greater noradrenergic stimulation in women. This finding is similar to the gender-specific pattern of response seen in cocaine-dependent individuals in an earlier SCOR study (Brady et al., 2009). Women in this study reported significantly more daily hassles and used opioids on a higher percentage of days in the one-month follow-up period as compared to men (Table 1). In addition, lower distress tolerance, measured at baseline, was significantly associated with a higher percentage of opioid use days for women (b=17.01, p=.013), but not for men. In summary, these data suggest that OUD women demonstrate greater subjective and noradrenergic stress response than OUD men. The pattern of low cortisol and high subjective response to stress exhibited by women in this study has been associated with higher relapse in studies in cocaine dependence (Back et al., 2010). Furthermore, women reported lower distress tolerance, higher experience of daily hassles and a robust relationship between low distress tolerance and drug use. Taken together, these preliminary findings suggest that an intervention targeting stress vulnerability, particularly through blockade of noradrenergic activation, may be particularly effective in relapse prevention for opioid-dependent women.

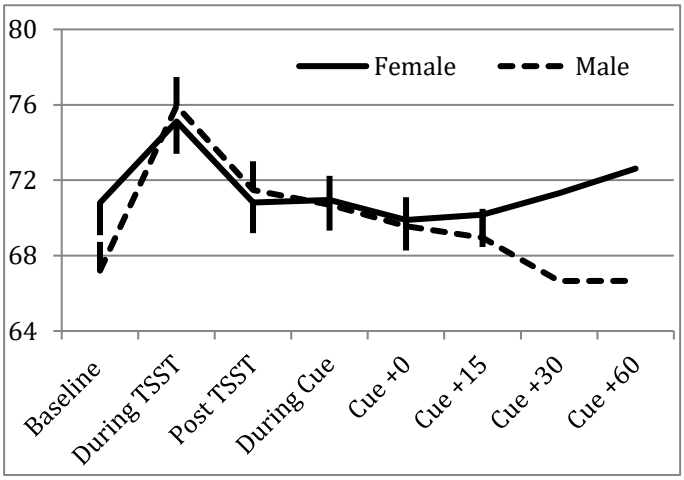


Figure 3: Heart Rate Response

TABLE 1: MONTH AFTER TESTING

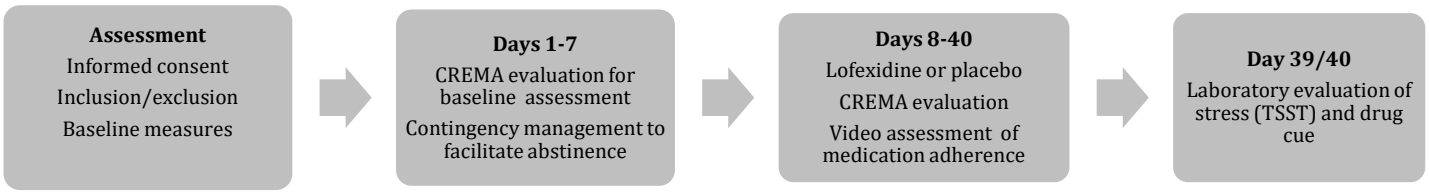
	Men (n=21)	Women (n=18)	Stats
% days using	30.4	55.3	p = 0.107
Daily Hassles Score			
One Week	46.3	105.4	p = 0.018
One Month	41.6	87.5	p = 0.058

C.1.d. Experience with Ambulatory Assessments. During the last funding period, the MUSC SCOR research group developed ambulatory assessment tools to assess stress reactivity and drug craving, collect data on drug use and withdrawal symptoms, validate abstinence, and measure/encourage medication adherence. The Cue Reactivity Ecological Momentary Assessment (CREMA) paradigm was modified to assess cue- and stress-related nicotine craving (Wray et al., 2015). Over 80% of CREMA sessions were successfully completed (Tomko et al., 2017), supporting the feasibility of remote collection of this type of data. We also capitalized on the capabilities of the REDCap data system to remotely collect self-report of drug use and video confirmation of medication adherence (Tomko et al., in press). In a smoking cessation trial, there was high compliance with video (73.8%) and self-report (74.8%) completion. All

participants agreed that the surveys and videos were easy to use, and the majority of participants preferred the REDCap assessments to traditional, paper measures. In an ongoing pharmacotherapy trial for cannabis use disorder (UG3DA04323), we have observed high compliance with video uploads for medication adherence, with a median of 80% of medication doses verified.

C.2. Research Design and Methods. This project is a double-blind, placebo-controlled trial to assess gender differences in the impact of lofexidine, an alpha-2 agonist, on stress-related opioid craving in men and women with OUD on stable buprenorphine or methadone maintenance. Following this period, participants will be randomized to receive either lofexidine or placebo for a 5-week period during which cue reactivity ecological momentary assessment (CREMA) will be used to assess stress levels, craving and drug use and video confirmation of medication adherence will be employed. Naturalistically collected stress and drug cue reactivity data will be complemented by administration of a validated laboratory stress (the Trier Social Stress Task) and drug cue exposure procedure at the end of the 5-week treatment period while participants are still taking study medications. A schematic of study procedures is shown below.

C.2.a. Participants. A total of 136 participants (68 men and 68 women) with OUD who have been on a stable dose of buprenorphine or methadone for at least 2 weeks, aged 18 to 65 years of age, will be recruited over a 54-



month period. Additional inclusion criteria are consent to random assignment, ability to read and provide informed consent and willingness to remain abstinent from illicit opioids during the 1-week baseline assessment period. Contingency management procedures (described below) will be used to facilitate the maintenance of abstinence during this period. Exclusion criteria are women who are pregnant, nursing, or planning to become pregnant during the course of the study; having a history of or current major psychiatric or medical disorder; hypotension or QTc prolongation on EKG; and meeting criteria for moderate or severe use disorder for another substance with the exception of nicotine. A detailed list of inclusion/exclusion criteria can be found below.

C.2.b. Recruitment. MUSC staff will recruit participants from the Charleston Center,, MUSC and community addiction treatment programs, Shoreline Behavioral Health, and through media advertisements As noted in C.1.b., we have a long and successful track record of recruiting from these programs for clinical trials, and the numbers of patients on buprenorphine or methadone maintenance at both sites are more than adequate for recruitment of the required four participants per month to meet the study timeline.

C.2.c. Procedures

C.2.c.1. Ensuring a Robust and Unbiased Approach: Rigor and Transparency. The proposed study will achieve robust and unbiased results via several design features including: explicit inclusion/exclusion criteria; randomization of treatment condition; placebo control; blinding; use of validated laboratory and interview/self-report measures and methods; explicit hypotheses and planned statistical analyses; power estimates; management of retention/attrition and missing data; and careful consideration of potential confounds. All experimental details are reported in a detailed and fully transparent manner to support replication.

C.2.c.2. Screening and Eligibility Assessment. Individuals interested in participating will be screened by an MUSC research study intake coordinator on site at the Charleston Center, MUSC/community treatment program, Shoreline Behavioral Health or over the phone A quick screen, focused on inclusion/exclusion diagnoses, medical status, medication regimen, and ability/willingness to complete assessments and study procedures, will be used to initially determine study eligibility. Potential participants will be given a full description of study procedures and asked to read and sign an IRB-approved Informed Consent Form if they choose to participate. Inclusion/exclusion criteria are detailed below.

Inclusion Criteria: 1.) Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of assessment instruments. 2.) Meet DSM-5 criteria for OUD (within the past three months); while individuals may also meet criteria for another substance use disorder, they must not meet criteria for moderate or severe use of any other substance (except tobacco or marijuana) within the last 60 days. 3.) On a

stable dose of buprenorphine or methadone for 4 weeks. 4.) Age 18-60. 5.) Women of childbearing potential must agree to utilize an effective means of birth control. 6.) Must consent to random assignment.
Exclusion Criteria: 1.) Women who are pregnant, nursing or of childbearing potential and not practicing an effective means of birth control. 2.) Evidence or history of major medical illnesses, including liver or renal diseases, abnormal vaginal bleeding, suspected or known malignancy, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, insulin-dependent diabetes, history of stroke or other medical conditions that the investigator deems as contraindicated for the individual to be in the study. 3.) History of or current psychotic disorder or bipolar I affective disorder. 4.) Current suicidal or homicidal risk. 5.) Taking any medications known to act on the adrenergic system (B-blockers, alpha agonists or antagonsits). 6.) Hypotensive individuals with a sitting blood pressure of < 90/50 mmHg 7). QTc interval of > 440 in males and > 460 in females as the combination of lofexidine and methadone may increase QTc interval. For males with a QTc of greater than >440, but less than 470 AND absence of any history of CV disease AND absence of family history of CV death, they are eligible for enrollment. For females with a QTc of greater than >460, but less than 490 AND absence of any history of CV disease AND absence of family history of CV death, they are eligible for enrollment. 8.) Known allergy to lofexidine.
C.2.c3. Screening and Diagnostic Instruments. Quick Screen: The instrument is designed to assess for substance dependence and obvious psychiatric, medical, and logistic exclusions. **Mini-International Neuropsychiatric Interview (M.I.N.I)** is a brief structured interview designed to assess DSM-5 diagnoses using a series of questions in dichotomous format (yes/no). The M.I.N.I. is similar in sensitivity, specificity, and inter-rater reliability to other lengthier diagnostic interviews, such as the SCID-I/P (Sheehan & Lecrubier, 2003; Sheehan et al., 1998). The alcohol and drug use disorder modules will be used to thoroughly assess current and lifetime diagnostic status for abuse and dependence. It has excellent inter-rater and test-retest reliability (First et al., 2002). **Menstrual History Diary** will be used for female participants to estimate the timing of their cycle for the 90-days prior to study entry and track during study participation. **Perceived Stress Scale (PSS)** is a 10-item assessment of daily stress (Cohen et al., 1983) that has previously been used in substance use research (Fox et al., 2009; Hyman et al., 2007). **Adverse Childhood Experiences (ACE) Questionnaire** assesses childhood maltreatment and exposure to household dysfunction. It has been utilized to examine the relationship between adverse childhood experiences and health risk behavior in adulthood (Felitti et al., 1998). The **Life Stressor Checklist-Revised** (LSC-R; Wolfe & Kimerling, 1997) will be used to assess for the number of exposures to various potentially traumatic life events including accidents, interpersonal violence, and death of a relative. Participants will answer yes or no for 30 potential life events. *In addition to providing data to assess the impact of daily stress and early childhood trauma on opioid use, utilization of the PSS and ACE will likely allow for potential cross-SCORE collaborations as these scales have been previously recommended as components of the core assessment battery utilized across centers.* **Coronavirus Impact Scale:** 12 item questionnaire assesses life changes that have occurred as a result of the coronavirus (Stoddard & Kaufman, 2020). We will also ask how substance use has been impacted.

Substance-Related Instruments. Time Line Follow-back (TLFB; Sobell & Sobell, 1992) is a calendar-based instrument designed to assess daily substance consumption. Opioid use will be recorded in times used per day as well as quantity, type of opioid and route of administration. **Urine Drug Screening:** Urine samples will be collected and analyzed for prescribed and illicit drugs at baseline and at each study visit. All urine specimens will be analyzed using drug test cups with temperature-controlled monitoring. Drug test cups with immunoassay drug screen cards will be used to identify the following substances: oxycodone, buprenorphine, methadone, tramadol, benzodiazepines, Opiate 300 group analytes (morphine, heroin, and codeine), THC, cocaine, amphetamine, methamphetamine, ethyl glucuronide, fentanyl, K2, and MDMA. Other drugs may be detected by these analytes at high concentrations. For example, hydrocodone may be detected under the oxycodone test at high concentration levels. The cups also include adulterant testing for creatinine, nitrite, pH, bleach and specific gravity. **Saliva drug screening:** Saliva drug screens will be obtained from Forensic Fluids and will test for THC, cocaine, opiates, benzodiazepines, methadone, oxycodone, buprenorphine, and fentanyl. Patients will collect and store samples which will be returned to the clinic and sent to Forensic Fluids in batches. Samples will be de-identified. **Inventory of Drug-Taking Situations (IDTS)** (Annis et al., 1997) measures typical drug using situations based on Marlatt and Gordon's (1985) eight category taxonomy. This instrument will be used at baseline and contains eight subscales mapping frequency of use in distinct types of situations including use during negative situations (unpleasant emotions) and positive situations (social situations). Although initially developed for alcohol use, it has been modified for other SUDs and has demonstrated sensitivity to gender

differences (Ross et al., 1994). **Brief Pain Inventory (BPI)** (Cleeland & Ryan, 1994). Assesses severity of pain and impact on functioning. This measure will be completed at screening and at the end of treatment.

An EKG and physical exam including orthostatic hypotension testing will be conducted by a licensed medical provider. Serum will be collected for baseline labs and a UDS will be collected. If the participant is female, a pregnancy test will be done prior the urine drug screen. Females who are pregnant will not be allowed to participate. Participants at Shoreline will have labs drawn by Mako Medical Lab at the Shoreline site.

C2.c4.. Remote screening visit:. Patients may also complete the initial visit remotely if warranted. In this case, subjects will be electronically consented using Doxy.me or RedCap or a combination. The informed consent will be emailed to the participant prior to the video call. The patient will have the opportunity to ask questions on the call and will electronically sign the document. A signed copy will be emailed to the participant. The M.I.N.I interview and medical history then be conducted, also via Doxy.me Patients will be advised to find a private location during these procedures to protect privacy and confidentiality. Patients will be sent survey links to complete self-report questionnaires.The blood draw, EKG and orthostatic BP will be done at Baseline. A physical exam may be done if it is warranted based on medical history. Urine drug screening and pregnancy testing will not be done until baseline for participants who screen remotely.

C.2.c.5. Phase 1: Baseline and Medication Trial

a. Initial Study Visit. Participants will be trained to use CREMA and the one-week naturalistic baseline data collection period will begin following screening procedures. If it is determined that patient is ineligible based on labwork, they will be excluded and baseline procedures will end.

b. Baseline Assessment (Study days 1-7). Throughout this study period, participants will come to the clinic for UDS collection. To facilitate opioid abstinence during the baseline period, we will use a standard contingency-management procedure. Participants will earn payments of $10 for the first negative UDS and $20 for the second. Two consecutive UDSs during the baseline week must be negative for illicit opioids in order for the subject to enter the medication treatment part of the trial. During the baseline assessment period, participants will be asked to use CREMA (described below). Subjects may have up to 10 days to provide the negative UDSs.

c. CREMA Assessment. Cue Reactivity Ecological Momentary Assessment (CREMA; Warthen & Tiffany, 2009; Wray, Godleski, & Tiffany, 2011; Wray et al., 2015) can collect subjective ratings of stress, craving, etc. either without provocation or using photos from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) presented on a mobile electronic device (iPhone). If an individual does not have an iPhone or does not wish to use his/her own for the study, a phone will be provided. Participants will be instructed to keep their phone with them at all times.Participants will complete a daily survey about substance use and stressful life events over the previous 24 hours. Auditory alarms will alert participants to complete one randomly scheduled session per day to rate stress, craving and mood. This visual analog scale is anchored with adjectival modifiers (“not at all, mildly, moderately, and extremely”). The scale includes items assessing anxiety, stress, irritability, and craving. Participants will also be alerted to daily random CREMA sessions including IAPS pictures; session will randomly include neutral IAPS pictures or stressful IAPS pictures (described below). Iindividuals be presented one of two types of picture cues that differ based on content: stress-related (i.e., a child in distress) or neutral (i.e., sunglasses). Each picture will appear only once during the study. Participants will be instructed to look at the photo carefully for 10 seconds. An alarm will sound at the end of the trial, and participants will complete a post-cue rating scale assessment, ratings of how carefully they looked at the photographs and their distraction level. Using this strategy, we can assess ambient emotional state and craving as well as “evoked” response to stressful cues. To encourage CREMA session completions, participants will be compensated $10.00 for each day they complete all sessions. Previous studies employing this incentive strategy have reported 85-90% completion rates (Gass et al., 2011; Warthen et al., 2009), including in our previous SCOR work (Wray et al., 2015).

d. Lofexidine/Placebo Titration Procedures (Days 8-17). After two consecutive negative drugs screens have been obtained, participants will be randomly assigned to study medication (lofexidine or matching placebo). For the Shoreline site, medication will be dispensed by IDS and delivered to MUSC staff at that site. At the randomization visit, females will provide saliva samples for estradiol and progesterone testing. Trained study personnel will evaluate heart rate, orthostatic blood pressure, and pre-syncope and syncope signs and symptoms prior to the initiation of Lofexidine. Lofexidine will not be dispensed if the participant is found to have

one of the following on physical exam: 1) clinically significant bradycardia as determined by study physician; 2) orthostatic hypotension defined as a systolic blood pressure decrease of at least 20mm Hg or a diastolic blood pressure decrease of at least 10mm Hg within three minutes of standing; 3) participant endorsement of pre-syncope symptoms such as lightheadedness, muscular weakness, blurred vision, or feeling faint during the evaluation of orthostatic blood pressure; or 4) syncope (fainting) during the evaluation of orthostatic blood pressure. Participants with bradycardia, orthostatic hypotension, pre-syncope or syncope would be terminated from the study and study staff will facilitate appropriate follow-up medical care. To minimize risks of hypotension, lofexidine will be titrated over a 10-day period with 0.36 mg QDfor days 1 and 2; 0.36 mg BID for days 3 and 4; 0.36 mg TID for days 5 and 6; 0.36 mg BID and 0.72 QD days 7 and 8; 0.37 QD and 0.72 BID for days 9 and 10, and 0.72 mg TID on day 11 and throughout the rest of the study (see **Table 2)**. This is the dose recommended by the regulatory agencies in England and the titration schedule is consistent with lofexidine titration in 8 published studies (Gish et al., 2010).

Table 2

Days	AM Dose (mg)	PM Dose (mg)	QHS Dose (mg
Days 1 and 2 (Study days 8 and 9)			**0.36**
Days 3 and 4 (Study days 10 and 11)	**0.36**		**0.36**
Days 5 and 6 (Study days 12 and 13)	**0.36**	**0.36**	**0.36**
Days 7 and 8 (Study days 14 and 15)	**0.36**	**0.36**	**0.72**
Days 9 and 10 (Study days 16 and 17)	**0.36**	**0.72**	**0.72**
Days 11-40 (Study days 18-40)	**0.72**	**0.72**	**0.72**

Trained study personnel will evaluate heart rate, orthostatic blood pressure, pre-syncope and syncope signs and symptoms at all study visits during the titration period. If the study participant does not have bradycardia, orthostatic hypotension, or pre-syncope or syncope signs or symptoms as defined above, the dose of Lofexidine will be increased according to the titration schedule (**Table 2**). If bradycardia, orthostatic hypotension, or signs/symptoms of pre-syncope or syncope are identified at any point, the dose of Lofexidine will be lowered to the prior tolerated Lofexidine dose and the participant will remain at that dose for the duration of the study. At the beginning of the study, participants will be given a rescue pack of 36 tablets in case visits are missed. This will cover 3 days at the full dose.

The medical provider will inform the participant, verbally and with a take-home hand-out, of common side effects of lofexidine (dizziness, somnolence, dry mouth) and precautions to minimize risks associated with blood pressure (BP) decreases (hydration, standing up slowly). Participants will attend study visits three times a week during the induction period and throughout the study during which a UDS will be collected. The MUSC Investigational Drug Service will be responsible for randomization, will keep a record of the blind and will be available should unblinding be required. In the event that WorldMeds is unable to supply matching placebo. lofexidine tablets (supplied by US WorldMeds) will be encapsulated along with matching placebo capsules by Pitt Street Pharmacy, a specialty compounding pharmacy. Randomization will be stratified on presence/absence of other substance use as well as the presence/absence of significant childhood trauma (ACE>4).

e. Medication maintenance and adherence monitoring (Days 18-40). Trained study personnel will evaluate heart rate, orthostatic blood pressure, pre-syncope and syncope signs and symptoms once per week following the Lofexidine titration. If bradycardia, orthostatic hypotension, or signs/symptoms of pre-syncope or syncope are identified at any point, the dose of Lofexidine will be lowered to the prior tolerated Lofexidine dose and the participant will remain at that dose for the duration of the study.Participants will record themselves taking their medications A survey link will be sent to the participant's cell phone via app alert two to three times daily, depending on where they are in the medication schedule. Video capture will occur through the CREMA app. The research coordinator will review the subjects' videos before each study visit. As discussed, we have used this

technology successfully for medication adherence monitoring. To encourage compliance, participants will receive $10 for each day that they complete their medication adherence videos.

f. Intervention phase (Study Days 18-40). During the 5-week medication phase, study participants will come in three times per week for UDSs. Blood pressure and pulse will be assessed at each visit. If the SBP < 90 mmHg and > 20% below screening value and/or DBP is < 50 mmHg and >20% below screening value, or the individual is complaining of symptoms of hypotension, the medication dosage will be reduced. If these symptoms do not resolve, the individual will be removed from the study and followed until vital signs normalize. EKG's will be performed at Weeks 4 and 6 to monitor QT intervals. A contingency-management procedure will be implemented to facilitate study visit adherence. The payments will start at $4 and increase by $4 for each consecutive visit.

g. **Virtual monitoring**: In order to reduce face-to-face visits when necessary, remote monitoring may be done during the medication phase. At the randomization visit, patients will be given a wrist blood pressure cuff for at home monitoring, and they will be trained in testing orthostatic blood pressure. Patients will come to the clinic once a week for a UDS, to meet with staff/medical personnel and have ave orthostatic testing done, and receive medication refills. Two weekly visits will be conducted via Telehealth. Patients will be observed doing a saliva drug screen and doing orthostatic blood pressure testing. If patients are symptomatic or having difficulty with telehealth procedures, they may be asked to attend the clinic more frequently. Participants who are not comfortable with telehealth procedures may choose to attend clinic visits instead.

C.2.c.5. Phase Two: Scripted Opioid Imagery and Laboratory Stress Induction Session (Days 39 and 40). At the end of the five-week period of lofexidine or placebo administration, participants will return to complete a scripted opioid imagery taksk and a laboratory stress task (Trier Social Stress Test, TSST). Tasks will be counterbalanced. Subjects will remain on study medications for the test days. Subjects who miss their scheduled visits may be re-scheduled for up to one week.

	TABLE 3: LAB TESTING TIMELINE	
Test Day 1	8:15am	UDS, Saliva
	8:35 am	Relaxation
	8:55am	Baseline 1 Subjective, physiologic, endocrine measurement
	9:00am - 9:15am	TSST/Imagery
	9:15am	Subjective, physiologic, endocrine measurement
	9:20am	Subjective, physiologic, endocrine measurement
	9:45am	Subjective, physiologic, endocrine measurement
	10:15am	Subjective, physiologic, endocrine measurement
Test Day 2	815am	UDS, Saliva
	8:35am	Relaxation
	8:55am	Baseline 1: Subjective, physiologic, endocrine measurement
	9:00am	Opioid imagery/TSST
	9:05am	Subjective, physiologic, endocrine measurement
	9:10am	Subjective, physiologic, endocrine measurement
	9:35am	Subjective, physiologic, endocrine measurement
	10:05 am	Subjective, physiologic, endocrine measurement

a.Session Preparation. Participants will be instructed to arrive at 8:00am on the test days, and to avoid caffeinated beverages since caffeine can introduce variability in heart rate response. If the individual is nicotine-dependent, (s)he will be provided with a nicotine patch throughout their study visit. Upon arrival, the participant will be breathalyzed and will provide a urine sample to be tested for drugs of abuse. For women, a pregnancy test will be done prior to the urine drug screen, and saliva will be collected for estrogen and progesterone measurement.

b.Progesterone and Estrogen. As there is significant individual variability in progesterone and estrogen levels across the menstrual cycle, measurement of progesterone and estrogen at the time of testing in combination with the menstrual cycle history will allow us to approximate the menstrual cycle phase as well as to utilize all participants' data with absolute progesterone and estrogen levels as continuous measures.

c. Design timing. Subjects will first undergo a progressive relaxation task. Baseline assessments of subjective, hormonal (cortisol), and physiologic measures (blood pressure and heart rate) will be collected following relaxation, 5 minutes before the stressor or imagery; TSST takes 15 minutes, and the imagery takes 5 minutes. At the end of the stressor of drug cue, a salivary sample will be collected to assay cortisol and physiological (blood pressure and heart rate) and subjective measures (Mood Rating Scale, Opioid Craving Questionnaire, STAI) will be obtained. Measurements will also be obtained at 5- 30-, and 60-minutes post-task.

d. Trier Social Stress Task (TSST) is a standardized psychological stress challenge which has been used extensively in research studies. A meta-analysis supports its utility for evoking a HPA axis stress response in a laboratory setting (Dickerson & Kemeny, 2004). It has induced a robust and reliable physiological stress

response in cocaine, alcohol, and cannabis-dependent individuals in our previous studies (McRae et al., 2006; McRae-Clark et al., 2011; Waldrop et al., 2010). At test initiation, the participant is told that (s)he will give a speech and perform an arithmetic task. The topic of the speech will be why (s)he should be hired for a particular job (the individual's "dream job"). The participant will deliver the speech as though speaking to a group of potential employers. The experimenter then tells the participant that (s)he has 5 minutes to prepare the speech and starts the countdown clock (placed in view of the individual). The experimenter leaves the room and five minutes later, three individuals unfamiliar to the participant (the audience) enter the room; the individual is instructed by one audience member to stand and begin his/her prepared speech (without notes). The speech will be delivered for 5 minutes. If the individual pauses, (s)he will be instructed to continue. At the end of the speech task, the individual will be instructed to serially subtract 13 from 1,022 as quickly and accurately as possible. The mental math recitation will continue for 5 minutes, at the end of which time, the spokesperson will instruct the individual to stop and be seated, and the audience leaves the room.

e. Opioid imagery script. We are using a scripted imagery paradigm developed by Sinha and Tuit (2012). A script will be developed based on staff interviews with subjects about a time they craved and used opioids. The 5-minute script will be audio-recorded and played back to the subject during the task. Subjects will be asked to listen and imagine the task as if they are there.

f. Assessments. Self-Report Measures. *Mood Rating Scale*: As described above and used with the CREMA sessions, to allow for cross-task comparisons. *State-Trait Inventory (STAI):* The STAI is a 20-item self-report scale (Spielberger, 1983) employing a Likert-scale format with four responses per item (1-4). Ten of the STAI items measure feelings of stress and anxiety, while the remaining ten items measure feelings of relaxation. The STAI has good psychometric properties. Opioid craving will also be measured using a Likert scale format. We have had good success with this in prior studies in OUDs (Back et al., 2014) Physiological Measures. Heart rate and blood pressure will be measured using an intermittently inflatable cuff as indices of physiological arousal during the test session. Hormonal Measures. *Cortisol:* Cortisol will be measured in unstimulated passive saliva using the Salimetrics expanded range, high sensitivity salivary cortisol enzyme immunoassay kit. This kit has a lower sensitivity level of <0.003 μg/dL. The correlation between salivary and serum cortisol has been shown to be high ($r=0.91$, $p<0.0001$). Cortisol is commonly measured as an indication of stress response in human laboratory studies.

Modifications may be made to lab day procedures if necessary for patient and staff safety, ie fewer confederates, remote procedures.

g. Discharge. Following assessments, participants will be given instructions to taper their lofexidine over the next five days. A member of the research staff will be available to discuss management of any craving or urges to use any substance if craving remains elevated at the end of study procedures.

C.2.c.6. Follow-up Assessment (Days 41-47). During a one-week follow-up period, lofexidine will be tapered... They will come to the two times during the taper for BP monitoring (0.72 BID for two days, 0.36 mg BID for 2 days, 0.36 QD for 1 day). After five days, participants will return to the clinic and return clinic-provided phones, complete a questionnaire regarding their experience with the CREMA and REDCap surveys, and be provided referrals to treatment if interested.

Participant Compensation: Participants will be compensated $40 for completing the screening visit, and an additional $20 for completing the screening the first time they are scheduled. They will receive $20 for the CREMA training and a $25 bonus if they come to their first baseline visit as scheduled..They will receive $10.00 for each day that all CREMA sessions are completed. During the opioid abstinence period, participants can earn a total of $30 for completing drug testing (2 negative UDS compenstated at $10 and $20). During the medication period, subjects can receive up to $10 for each day they complete medication videos and $364 ($4+$8+$12+$16+$20+$24+$28+$32+$36+$40+$44+$48+ $52) for completing study visits with UDS. Participants will be compensated $10 for each blood pressure check during the tapering phase. Participants will also be compensated $50 for completion of each human laboratory session, a $50 bonus for completing both as scheduled,and $100 for the follow-up. follow-up visit, for a total potential compensation of $819 per participant plus earnings from CREMA and medication videos. Participants will be asked to complete a W-9. This document may be completed in person or via Doxy.me.

Confidentiality: Confidentiality of all research data will be maintained by keeping all data in a locked file, limiting access to the computer database to only study personnel, and by using patient code numbers as opposed to names on all paperwork.

C.2.d. Statistical Analysis and Data Management

Data Management and Reduction: All paper-based assessments (other than laboratory reports) will be entered into REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides an intuitive interface for data entry (with data validation), audit trails for tracking data manipulation, and automated export procedures for data downloading to statistical packages such as SPSS and SAS. Quarterly database management and data integrity audits will be conducted and reports submitted.

Statistics and Data Analysis (complete statistical/data analysis plan in Biostatistics Resource Core):

Aim 1: Using a human laboratory paradigm, determine the impact of lofexidine on stress and drug cue-induced craving in women and men with OUDs: The primary study outcome of interest in Aim 1 is the differential craving, stress and anxiety response to a human laboratory paradigms containing both a stressor (TSST) and an opioid specific cue between participants randomized to lofexidine and placebo in addition to buprenorphine/methadone maintenance. *Hypothesis 1: Lofexidine will attenuate drug craving and subjective stress response to a stress task in opioid-dependent individuals compared to individuals receiving placebo. Hypothesis 2: Lofexidine will attenuate drug craving and subjective stress response to a drug-related cue in opioid-dependent individuals. Hypothesis 3: The ameliorative effects of lofexidine on stress and cue-reactivity will be more pronounced in females than male subjects.* To assess the hypothesis that lofexidine will attenuate drug craving and subjective stress response to the stressor and the opioid-related cue task, multilevel longitudinal GLMMs will be developed using all post-stressor and post-cue data. Initial models will control for study design aspects such as order (stressor or cue first), treatment assignment, and baseline craving and stress (task level). Covariate adjusted models will additionally include baseline characteristics determined to be correlated with study outcomes or those determined to be significant effect modifiers. To examine the differential effects of lofexidine on stress and cue-reactivity across female and male subjects, the models will have additional parameters added to include an indicator of participant gender and the interaction between gender and randomized treatment assignment. Relevant interactions will be assessed in all models. Least square means and associated standard errors will be assessed to compare craving and subjective stress response between treatment assignments at all time points.

Aim 2: To evaluate the impact of lofexidine on opioid craving and subjective experience of daily stressors in men and women with OUDs: The primary measures of interest for Aim 2 are craving and stress ratings in response to stress-related cues using *Cue Reactivity Ecological Momentary Assessment* (CREMA) as well as subjective experiences of daily life stressors *Hypothesis 1: Lofexidine will decrease craving and decrease the subjective experience of daily stressors in opioid-dependent men and women. Exploratory Hypothesis 2: Lofexidine will be more efficacious in decreasing stress-related craving in opioid-dependent women as compared to men.* To assess this hypothesis a multilevel generalized linear mixed effects models with repeated measures (GLMMs) will be developed using CREMA session response data from the 5-week period during study medication administration. Pre-cue stress and craving rating will be centered and used as a time varying covariate in all analysis. Additionally, CREMA cue response data during the 7 day baseline assessment period will be used as a time naïve covariate in all analyses. Least squares means and associated standard errors will be used for post-hoc comparisons of craving and stress response between women and men over time. Models developed to address hypothesis 2 will be utilized to examine the impact of gender on opioid use and stress-related craving during study treatment. All other relevant interactions will be assessed in all models.

Exploratory Aim 3: To evaluate the impact of lofexidine on illicit drug use in men and women with OUDs: Daily use data will be collected through morning reports via EMA and verified by urine drug screens (3 times weekly). *Hypothesis 1: Lofexidine will increase the number of consecutive days abstinent as compared to placebo. Hypothesis 2: Lofexidine will be more efficacious in increasing consecutive days abstinent in women as compared to men.* Time to relapse will be calculated as the days between the start of study medication (following titration; day 14) and the first day of lapse to opioid use or the laboratory stress induction day (day 40). Additionally, daily use data will be examined to determine the maximum number of consecutive days abstinent during follow up. Kaplan-Meier estimates and log-rank tests will be used to assess initial relationships between study treatment assignment and relapse while Cox proportional hazards models will be developed to assess the differential time to return to use across gender (using and appropriate interaction term). A significant interaction indicates that treatment may impact return to use time differently in women and men. Proportionality of hazards will be assessed using log-log plots and log-time interactions.

Power and Sample Size (complete sample size justification available in Biostatistics Resource Core):
The current study is powered on the primary Aims 1 and 2. In the proposed study, response to a laboratory stressor, CREMA cue response and daily use data will be tested using GLMMs (assuming a Gaussian distribution) and the study will be powered to sufficiently address the least of the study treatment effect sizes determined to be clinically meaningful for the study hypothesis. Aim 1: Sinha and colleagues (Sinha, et al 2007), in a small pilot sample, demonstrated that lofexidine in combination with naltrexone attenuated craving and anger in response to laboratory drug and stress cues as compared to naltrexone alone. Results indicate a larger change in opioid craving scores in response to drug-related and stress cues occurs in placebo participants than lofexidine treated participants [Drug related cue response Δ=2.2; SD_P=2.6; between group Cohen's *d*=0.85, p<0.05 and stress cues response Δ=2.1; SD_P=2.4; between group Cohen's *d*=0.88, p<0.05]. Moreover, Fox and colleagues (2014) conducted a trial of guanfacine in cocaine-dependent individuals and noted stress and craving response to stress and drug-related imagery. They noted significant gender differences across treatment assignment for craving and stress response to drug-related imagery [Craving Δ=3.0; SD_P=3.8; Treatment x Sex Intx Cohen's *d*=0.79, p<0.05; Negative Emotion Δ=3.0; SD_P=2.9; Treatment x Sex Intx Cohen's *d*=1.0, p<0.05]. Sample sizes in both the Sinha and Fox studies were somewhat small. Smaller but still clinically relevant effect sizes in an adequately powered study are anticipated. Therefore, a 20% reduction in craving and stress response from the previous studies is anticipated in the current design (Cohen's *d*=0.64 for the sex x treatment interaction on craving response). Aim 2: Kowalczyk and colleagues (2015), showed that daily life craving reports as measured by EMA were significantly reduced in opioid using participants randomized to clonidine as compared to placebo [6.3% (95% CI=5.6-7.1) vs. 11.8% (10.9-13.0); between group Cohen's *d*=1.6]. To assess the least of the differences anticipated in project 2, a sample size of 39 participants randomized to each female and males across active lofexidine and placebo groups would provide 80% power with a type 1 error rate of 5% to detect the treatment x sex interaction in craving and stress response to laboratory drug based cues (total n=156; 78 per group). We anticipate 25% attrition between randomization and the end of the 5-week active treatment period. Thus, inflating the necessary sample size to 68 participants randomized per treatment group with a total of n=136 randomized participants will provide adequate power.

C.2.e. Operational Plan and Research Timetable. Funding for five years is requested. The first three months will be spent hiring and training personnel and preparing for study initiation. We have established standard operating procedures, so we anticipate rapid study start-up. 54 months will be needed for participant recruitment and data collection. The final three months will be used for participant follow-up, data analysis and manuscript preparation.

D. Conclusions
The prevalence of OUDs in the US is alarming and women appear to be at particular risk for overdose death. In spite of this, little is known about gender-specific treatment for opioid dependence. Evidence from a number of sources demonstrate that drug-dependent women show a greater response to stress-inducing stimuli and greater noradrenergic sensitivity as compared to men. Moreover, several studies suggest that alpha-2 agonists, which decrease noradrenergic activity, may be useful in stress-induced craving and relapse in OUDs and studies in cocaine and nicotine dependence suggest that women are more responsive to these agents compared to men. In addition, we have promising preliminary data suggesting that interventions targeting stress vulnerability may be particularly effective in relapse prevention for opioid-dependent women. However, to our knowledge, there are no previous or ongoing studies investigating gender differences in the impact of alpha-2 agonists in decreasing stress-induced craving or relapse in OUDs. We have assembled a multidisciplinary team which includes experienced senior investigators as well as promising and productive junior investigators who will solidify their interest and increase their expertise in sex- and gender-based research through working on this important project. This project will provide important information about a novel treatment strategy which may demonstrate preferential efficacy in the treatment of women with OUD.

PROTECTION OF HUMAN SUBJECTS
1. RISKS TO THE SUBJECTS
a. Human Subjects Involvement and Characteristics136
Admission into the study is open to men and women and to all racial and ethnic groups, age 18-60. individuals with opioid use disorders (68 men and 68 women) will be recruited primarily through local substance use treatment facilities. Inclusion/exclusion criteria that apply to all participants are listed below:

General Inclusion / Exclusion Criteria

Inclusion Criteria

1. Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments.
2. Meet DSM-5 criteria for opioid use disorder (within the past three months). While individuals may also meet criteria for mild use disorders of other substances, they must identify opioids as their primary substance of abuse and must not meet criteria for any other moderate or severe substance use disorder (except tobacco, caffeine, or marijuana) within the last 60 days.
3. On a stable dose of daily buprenorphine or methadone for at least 2 weeks.
4. Age 18-65.
5. Women of childbearing potential must agree to use an effective means of birth control.
6. Consent to remain abstinent from opioids during the 1-week baseline assessment period.
7. Must consent to random assignment.

Exclusion Criteria

1. Women who are pregnant, nursing or of childbearing potential and not practicing an effective means of birth control.
2. Evidence or history of major medical illnesses, including liver diseases, abnormal vaginal bleeding, suspected or known malignancy, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, insulin-dependent diabetes, history of stroke or other medical conditions that the investigator deems as contraindicated for the individual to be in the study.
3. History of or current psychotic disorder or bipolar I affective disorder.
4. Current suicidal or homicidal ideation/risk.
5. Taking medications known to act on adrenergic systems (B-blockers; alpha agonists or antagonists)
6. Hypotensive individuals with a sitting blood pressure of < 90/50
7. QTc interval of >440 in males and > 460 in females as the combination of lofexidine plus methadone may increase the QTc interval. For males with a QTc of greater than >440, but less than 470 AND absence of any history of CV disease AND absence of family history of CV death, they are eligible for enrollment. For females with a QTc of greater than >460, but less than 490 AND absence of any history of CV disease AND absence of family history of CV death, they are eligible for enrollment.
8. Known allergy to lofexidine
9. Unable to comply with study procedures or pose threat to study staff.

b. Sources of Materials

Research material obtained from individual participants includes questionnaires and interviews with study personnel, ambulatory assessment data, and blood, saliva and urine samples. To ensure confidentiality, all participant data will be letter/number coded, and only the investigators will have access to the master lists of codes. The research material will be obtained specifically for research purposes. Written research material obtained will be stored in the Addiction Sciences Division or at Shoreline Behavioral Health, in an office that is locked when not in use. Saliva samples will be stored and processed in the Medical University of South Carolina Research Nexus Laboratory. MUSC staff at Shoreline will collect saliva samples, freeze and store them on site, and then send to MUSC for processing.

c. Potential Risks

1. Risks due to lofexidine: A Cochrane review provides a comprehensive overview of adverse events associated with lofexidine and other alpha-adrenergic agents (Gowing et al., 2009). Adverse events associated with lofexidine are primarily related to its alpha-adrenergic agonist effects. Hypotension has been reported (Yu et al., 2008; Gowing et al., 2009; Khan et al., 1997), but generally this was mild and studies comparing lofexidine with other alpha-agonists found that hypotension was seen less frequently with lofexidine. Rebound increase in blood pressure after lofexidine discontinuation has also been reported (Yu et al., 2008), but was not severe enough to require intervention. Sedation, dizziness and dry mouth have also been reported with lofexidine at higher rates than placebo, but lower when compared to other alpha-agonists (Khan et al., 1997; Gowing et al., 2009). A case report (Schmitter et al., 2004) and a dose escalation study (Schmitter et al., 2009) report QTc interval prolongation in individuals with lofexidine added to methadone, but there have been no reports of QTc prolongation with lofexidine monotherapy.

2. Risks due to study procedures: Participants will be asked not to use illicit opioids for 7 days, however all will be stabilized on buprenorphine or methadone so there should be no risk of opioid withdrawal symptoms.

3. Potential risks of rating scales and questionnaires: These are all non-invasive, should add no risk, and have been used without difficulty or any adverse events in our previous studies. The only minor inconvenience could be the time taken to complete them. Some participants may feel uncomfortable disclosing personal thoughts and feelings.

4. Risks of stress induction procedures: There is a small risk of increased stress or opioid craving as a result of the CREMA procedures; however, it will likely not differ substantially from the reactivity elicited by stimuli commonly encountered in the day-to-day environment of study participants. Participants that report sustained significant stress or craving after the laboratory session will be provided a debriefing to address symptoms.

5. Risks of loss of confidentiality: Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only participants' code numbers will be recorded on the forms themselves to protect confidentiality. Phones provided by study staff to participants will be password protected to limit access to study assessments and pictures; participants utilizing their own phones will be asked to password protect their device for the duration of the study.

2. ADEQUACY OF PROTECTION AGAINSTS RISKS

a. Recruitment and Informed Consent

Potential study participants will primarily be recruited through local treatment settings. Medical records will not be reviewed to identify potential study participants. The study PI, a Co-I, or other qualified study staff will obtain informed consent. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to participants in easy-to-understand language, and subjects will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent.

b. Protections Against Risks

All study participants will be closely monitored for psychiatric and medical stability. All sessions will be conducted under the supervision of experienced personnel. If crisis intervention is necessary, senior staff will be available to evaluate the subject and provide an intervention or referral. If hospitalization is indicated, the patient will be hospitalized through the Center for Drug and Alcohol Programs at MUSC or an appropriate referral will be made. All participants will be fully informed that they may withdraw from the study at any time without penalty.

Lofexidine will be titrated over ten days when it is initiated. Participants will be seen by a medical provider on three times a week uring dosage escalation and orthostatic hypotension testing will be done. The medical provider will inform the participant, verbally and with a hand-out to take home, concerning common side effects of lofexidine (dizziness, somnolence, dry mouth) and precautions to minimize risks associated with blood pressure decreases (hydration, standing up slowly). The target dose of lofexidine is 2.16 mg per day, but if hypotension or other troublesome side effects develop, the medical provider may slow the titration for that individual. At the end of the study, medications will be tapered over a five-day period. Participants will be seen every other day during medication taper and blood pressure will be monitored.

To ensure confidentiality, all participant data will be coded by letters and/or numbers, and only the investigators will have access to the master lists of codes. All participant records will be kept in a locked cabinet in an office that will be locked at times when not in use. Participants who screen remotely and have virtual medication monitoring visits will be instructed to find a private location to conduc these visits. The research staff understands the importance of maintaining confidentiality, and this method of maintaining confidentiality has been used for several years by our research group and has been effective. All electronic databases are stored on HIPAA-compliant servers with restricted access. All co-investigators and study personnel have completed (or will complete upon hiring) training in Good Clinical Practices as mandated by NIH and the MUSC IRB.

Participants will be taught about potential side effects of lofexidine, and will be closely followed by psychiatrists, a PharmD, and other members of the research team. Pregnancy tests will be performed prior to lofexidine administration. Adverse events will be monitored throughout the study. A member of the research staff will be available to discuss management of any craving urges if craving remains elevated at the end of any study procedures.

3. DATA SAFETY AND MONITORING PLAN

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html). A detailed DSMP will be developed and approved by NIH program staff prior to study initiation.

1. Summary of the Protocol.
This application proposes to investigate the effects of lofexidine on stress-induced craving and relapse. The primary outcome of interest is stress reactivity. Inclusion/exclusion criteria are outlined above. Power calculations and sample sizes are in the Data Analysis Plan section above.

2. Trial Management.
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. The target population is described above in the inclusion/exclusion criteria.

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

4. Quality Assurance.
Quarterly data audits will be conducted. Confidentiality protections are outlined above.

5. Regulatory Issues.
Potential conflicts of interest will be reported using the upcoming NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. A research assistant will identify any potential adverse events during the course of the study from participant self-report and administration of the visit assessments and procedures. The research assistant will provide information to a study physician, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. Any significant actions taken by the local IRB and protocol changes will be relayed to ORWH/NIDA.

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect OR
- Requires intervention to prevent one of the above outcomes.

7. Documentation and Reporting.

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. When a reportable SAE is identified, the research staff will notify the MUSC Institutional Review Board (IRB) within 24 hours and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 165 Cannon Street, Rm. 501, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting. A report will also be sent to the NIH program officer assigned to the project.

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

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

8. Trial Safety.

The potential risks and benefits and methods to minimize these risks are outlined above. The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. 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. Brady.

9. Trial Efficacy.

An interim analysis is not planned at this time; however, an analysis will be performed if requested by ORWH/ NIDA or the DSMB.

10. DSM Plan Administration.

Drs. Brady and Guille will be responsible for monitoring the study, and will participate in weekly study meetings. A DSM report will be filed with the IRB and ORWH/NIDA on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. Outcomes will be reported at the end of the trial.

11. DSM Board.

A Data Safety and Monitoring Board will be formed to monitor both the rate and severity of adverse events. This panel will include 3 clinicians with expertise in substance use disorders and a statistician.

12. Risk Benefit Ratio.

The assessments and questionnaires are non-invasive and have inherently minimal risks. Potential risks of concern are loss of confidentiality and adverse events to lofexidine and stress induction procedures. As discussed above, our research team will attempt to minimize these risks. Knowledge gained by the proposed study would help fill an important void in development of a potential gender-specific treatment for opioid use disorders.

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4. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECT AND OTHERS

Possible risks to study participants include adverse reactions to lofexidine administration or stress induction procedures. Potential benefits include detailed assessment of substance use and referral for treatment. Participants in the lofexidine condition may experience a reduction in stress-related drug craving. The minimal risks are reasonable in relation to the potential benefits to be gained from the study.

5. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information that can improve treatment for future patients with opioid and other drug use disorders. The moderate risks of the investigation are considered reasonable in relation to the expected knowledge to be gained.

6. CLINICALTRIALS.GOV REQUIREMENTS

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

Impact of lofexidine on stress, craving and opioid use

Concise Summary

You are being asked to volunteer for a research study. Research studies are voluntary and include only people who choose to take part. The purpose of this study is to see if the medication lofexidine, taken together with buprenorphine or methadone, is more effective at reducing opioid craving, opioid use and/or stress response compared to buprenorphine or methadone alone, We are also looking to see if these effects are different for men and women. Lofexidine is FDA approved to treat physical symptoms of opioid withdrawal. In this study, we are looking to see if it also reduces stress response, opioid craving and opioid use.

Participants will complete a screening visit to determine study eligibility. During the first week, participants will be asked to abstain from opioid use other than buprenorphine or methadone. Participants will come to the clinic that week for urine drug testing. After 2 tests are negative, participants will be randomly assigned to take either lofexidine or placebo (inactive medication) two to three times a day for about 5 weeks. During this time, participants will upload videos of themselves taking their medication. They will come to the clinic 3 times a week for urine drug screens and to have their vital signs measured. They will also participate in "CREMA" sessions (Cue Reactivity Ecologic Momentary Assessment). Twice a day these sessions will ask about substance use, craving and stress. An additional session each day will include looking at stressful or neutral pictures and rating stress and craving. At the end of five weeks, participants will return to the clinic on two consecutive days to participate in a stress task and an opioid related imagery task. For the next five days, participants will taper their medication dose. During this time they will continue to come to clinic to have their vital signs measured and complete a follow-up visit.

There may be no direct benefit to you for participating in this study. Study medication risks are detailed below; the most common side effects are low blood pressure, tiredness, dizziness and dry mouth.

If you are interested in learning more about this study, please continue to read below.

You are being asked to volunteer for a research study. The research is sponsored by the National Institute on Drug Abuse. The purpose of this study is to determine if the medication lofexidine, taken together with buprenorphine or methadone, is more effective at reducing opiate craving, use and stress response than buprenorphine or methadone alone, and to see if this effect is different for men and women. Lofexidine is FDA approved to treat opioid withdrawal. This study also involves a cue presentation app known as "CREMA" (Cue Reactivity Ecologic Momentary Assessment) which delivers pictures and surveys to you on an iPhone during your everyday routine (more information below). You are being asked to participate in this study because you are between the ages of 18 and 65, have opioid use disorder, and are currently prescribed buprenorphine or methadone. The investigators in charge of this study are Kathleen Brady, M.D., Ph.D., and Connie Guille, M.D. The study is being conducted at the MUSC Addiction Sciences Division and Shoreline Behavioral Health and will involve 136 volunteers.

B. PROCEDURES:

Screening: If you agree to be in this study, you will first be evaluated and the results of the evaluation must meet

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entrance requirements. This first evaluation will include psychiatric interviews, an assessment of your alcohol and drug use, and a physical exam including an EKG. During the physical exam you will have blood drawn (about 2 teaspoons) to assess your general health. You will also be asked to provide a urine sample to test for drugs of abuse. If you are female and of child-bearing potential, you will have a pregnancy test prior to urine drug screening. If you are pregnant, you will not be allowed to participate. You will be asked to fill out several forms dealing with how often and why you use opiates, your mood symptoms, pain, stressful events, and the impact Covid-19 has had in your life.
Remote screening: The initial visit may also be done remotely. In that case, the consent will be emailed to you prior to the screening appointment. You will be asked to find a private location to have a video call with study staff. On the call, study staff will obtain informed consent and do the initial interview. You will also speak with study medical staff to review your medical history. If you are eligible, you will be sent survey links to complete questionnaires. You will have an EKG and blood draw at your baseline visit. If you complete screening remotely, you will not provide urine for pregnancy and/or drug screening until the baseline visit. You may be asked to meet with medical staff for a physical exam if they think it is necessary based on your history. If you meet all entrance requirements, you will be trained on how to use CREMA on an iPhone. If necessary, you will be scheduled to return to complete urine samples over the next week. Two consecutive urine samples must be negative for opioids other than buprenorphine or methadone in order to continue to the next phase of the study.

CREMA: Cue Reactivity Ecologic Momentary Assessment (CREMA) is an app that allows you to complete study procedures without having to come in to the lab and provides information about your response to different types of cues in a real-world setting. You will complete three CREMA sessions a day during the study. In one session that will occur at the same time each day, you will be asked about substance use and stress over the previous 24 hours. One session will occur randomly and you will be asked about your current stress, craving and mood. During one session you will be shown either neutral pictures or stressful pictures and asked to rate levels of stress, craving, and mood.

Medication phase: After completing the baseline week assessments and testing negative for opioids (other than buprenorphine or methadone) at two visits, you will receive study medication, either lofexidine or placebo (a capsule that does not contain any active medication). Neither you nor the study staff will know which medication you are taking as both lofexidine and placebo will be given as capsules identical in appearance. You will be randomly assigned to receive either lofexidine or placebo. This means that you have a 50/50 chance (like flipping a coin) of being in either group. Neither the researchers nor you will make the choice regarding your group assignment. The medication will be started at a low dose and increased according to the following schedule: 0.36 mg on the first two evenings, 0.36 mg in the morning and evening on days 3 and 4; 0.36 mg in the morning, afternoon, and at bedtime on days 5 and 6; 0.36 mg in the morning and afternoon and 0.72 mg at bedtime on days 7 and 8; 0.36 mg in the morning and 0.72 mg in the afternoon and at bedtime on days 9 and 10, and 0.72 mg in the morning, afternoon and at bedtime on Day 11 and throughout the rest of the study.

Days	AM Dose (mg)	Afternoon Dose (mg)	PM Dose (mg
Days 1 and 2			0.36 (2 pills)
Days 3 and 4	0.36 (2 pills)		0.36 (2 pills)
Days 5 and 6	0.36 (2 pills)	0.36 (2 pills)	0.36 (2 pills)
Days 7 and 8	0.36 (2 pills)	0.36 (2 pills)	0.72 (4 pills)
Days 9 and 10	0.36 (2 pills)	0.72 (4 pills)	0.72 (4 pills)
Days 11-33	0.72 (4 pills)	0.72 (4 pills)	0.72 (4 pills)

You will be required to take your medication two times daily during titration, and three times daily for the remainder of the medication phase. You are asked to take your medication each morning, afternoon, and evening. Doses must be 6 hours apart. To assist in monitoring your medication dosing the CREMA app will send you reminders with a link to upload a video of yourself taking the medication. You will be trained on how to do this

at your randomization visit. If you do not have an iPhone or do not wish to use your own, we will provide one to you for the duration of the study. Study phones will be de-activated at the end of the study, and lost or stolen phones will be reported to the federal funding agency.

You will have study visits three times a week for five weeks. At these visits, your blood pressure and pulse will be measured, and your urine will be tested for drugs of abuse. At one of these visits, you will have an interview with a staff member to discuss a time you were craving opioids. At Weeks 4 and 6 you will have an EKG performed.

Remote monitoring: If it is necessary to limit clinic visits, medication monitoring may be done remotely. For remote monitoring, you will have one clinic visit a week and two virtual visits. At your first medication visit, you will receive a blood pressure cuff that fits on your wrist and you will be trained on how to measure orthostatic blood pressure. This process involves lying down for 3-5 minutes, then taking your blood pressure. Next you will sit up for 30 seconds, then stand up and measure your blood pressure again. You will have video calls with staff twice a week to complete these procedures. Once you are on a stable dose, you will only need to do regular blood pressure checks on these calls. You will also be provided with saliva drug screens that can be done at home, and you will do these on the video calls as well. The saliva drug screen involves collecting saliva with a swab kit that will be provided to you.

Stress task: After five weeks of study medication, you will return to the clinic on two consecutive days to complete a stress task and an opioid imagery task. You will be asked to arrive at 8:00 am each day and to avoid caffeinated beverages. If you smoke cigarettes, you may be provided with a nicotine patch. Your urine will be tested for drugs of abuse. If you are female, you will provide a saliva sample so we can measure your hormone levels, and your urine will be tested for pregnancy prior to your drug screen. Approximately thirty minutes after you arrive, a blood pressure cuff will be placed on your arm. Throughout the procedures, you will provide saliva samples for hormone measurement, rate your mood and level of opiate craving, and your heart rate and blood pressure will be measured.

Stress task: You will complete a progressive relaxation task, and then you will be asked to deliver a speech and perform a math problem out loud in front of a group of strangers.

Opioid imagery task: You will complete a progressive relaxation task, and then you will listen to a recording based on your interview about craving opioids.

You will be randomly assigned to complete either the stress or opioid imagery task first.

Medication taper and follow-up: After the second visit, you will reduce your study medication dose over the next week. You will be asked to come into the clinic after each dose reduction to have your blood pressure and pulse measured. This will total two visits. After your final dose reduction, you will come to the clinic to provide a urine drug screen, have vital signs collected, and complete surveys about the study and a questionnaire about pain.

Participation in this study is totally voluntary, and you may choose not to participate. You may also withdraw your consent and discontinue participation at any time. Discontinuation will in no way jeopardize your ability to receive treatment at this Institution now or in the future. You may be withdrawn from the study without your consent if the researchers believe it is in your best interest.

C. DURATION:
Participation in this study involves up to 23 visits over a period of approximately two months. The initial screening visit will take about 3 hours and the CREMA training visit will take about 30 minutes. The weekly visits, medication tapering visits and follow-up visits will take approximately 30 minutes. The visit with the opioid interview will take

about an hour and a half. The stress/imagery visits will take approximately 3 hours. You will spend approximately 20 minutes a day completing the CREMA sessions at home.

D. RISKS/DISCOMFORTS:
Participation in this study may involve risks.

Medication: Side effects that were reported by more than 10% of patients treated with lofexidine, and more often than placebo, include trouble sleeping, low blood pressure when standing up, slow heart rate, low blood pressure, dizziness, drowsiness, sedation and dry mouth. Rebound high blood pressure has also been observed when people abruptly stop taking lofexidine, however your dose will be tapered off gradually to prevent this increase, and your blood pressure and pulse will be monitored regularly throughout the study.

Opioid abstinence: You will be asked to abstain from opioids other than buprenorphine or methadone for 7 days, however you should not experience withdrawal symptoms since you are already stabilized on buprenorphine/methadone.

Treatment assignment: You will be assigned to treatment by chance. The treatment you receive may prove to be less effective or to have more side effects than the other study treatment or other available treatment. You may be in the group that receives placebo and does not receive active medication.

Stress task: Participation in the speech and math task may cause some anxiety and feelings of stress. Some of the CREMA sessions may also cause anxiety, but should be no more stressful than events encountered in everyday life.

Scripted opioid imagery: The interview and scripted imagery task may produce some craving for opioids or other discomfort. However, this discomfort is usually brief and you will be in the safety of an opioid-free laboratory environment. A member of the research team will be available to discuss your cravings with you prior to leaving the research facility.

Blood draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and infection. Fainting could occur.

Interviews: The interviews and questionnaires that you will receive during the course of the study involve no specific risks or discomforts beyond those of a standard clinical interview situation, such as feeling upset at the review of your psychiatric status, boredom, or fatigue. If a question makes you feel uncomfortable you may refuse to answer it.

Urine drug screening: If you are a female of childbearing potential, you will receive a pregnancy test, and if pregnant, you will not be allowed to participate in the study. If you are capable of becoming pregnant, you must be using a medically approved method of birth control (such as contraceptive pills, diaphragms, or other forms of barrier contraceptives) and you must continue to do so during the course of the study. Should you become pregnant during the study you must immediately contact your study doctor and discontinue treatment since the risk to your baby due to lofexidine is unknown.

Your urine will be screened for the presence of opioids and other potentially abused or illegal drugs. These results will not be part of your medical record but will be kept in research records maintained by the investigator. Every effort will be made to protect the confidential nature of this information. However, there may be circumstances under which the investigator may release this information. If you are pregnant or become pregnant and test positive for illegal drugs, the SC Department of Social Services (DSS) may be notified. You could be at risk of going to jail or losing custody of your children.

Unknown Risks: The experimental treatments may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

Confidentiality: There is a risk of a loss of confidentiality as a result of participation in this study. Information about you, as well as your image will be kept in password-protected databases and computers and will only be accessible by the principal investigator and the research staff. Video clips will only be viewed by approved research staff. Those video clips will be deleted when the study has ended and data analysis is complete. In order to ensure confidentiality, all participant information (questionnaires and identifying information) will be identified only by your initials and/or a code number and kept under lock and key and in password-protected databases.

E. MEDICAL RECORDS AND CERTIFICATE OF CONFIDENTIALITY:
This research is covered by a Certificate of Confidentiality from the Federal government. This means that the researchers may not disclose information or biospecimens that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, nor can the information or biospecimens be used as evidence, unless you have consented to this disclosure. Information or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

A Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you are an MUSC patient you have an MUSC medical record. If you have never been an MUSC patient, a MUSC medical record will be created for the purposes of this study. All information within your medical record can be viewed by individuals authorized to access the record. We will make every effort to keep confidential all research information in the medical record that identify you to the extent allowed by law; however, there is the possibility that your research information will be disclosed.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law. Examples of required disclosure include: child abuse and neglect, or harm to self or others
Finally, a Certificate may not be used to withhold information from the Federal government needed for auditing or evaluating Federally funded projects or information needed by the FDA.

F. BENEFITS:
You may receive a medication that may be effective in reducing your opioid use. Of course, this cannot be guaranteed or promised, and you may experience no direct benefit. The results of this study may also benefit other patients who might later be treated with the same medicine.

G. COSTS:
If you choose to use your own smartphone to upload your daily medication videos, any cellular data and usage rates assessed by your carrier will apply.

H. PAYMENT TO PARTICIPANTS:
In return for your time and effort, you will receive $40 for completing the screening visit ($20 for the interview and $20 for the physical), plus an additional $20 for completing the visit the first time you're scheduled. You will receive a $25 bonus for attending the baseline visit as scheduled. You will receive $20 for downloading the app and being trained on CREMA, $50 for the opioid imagery visit, $50 for the stress task visit, a $50 bonus for completing both visits as scheduled, and $100 for the follow-up visit. During the week of baseline, you will receive $30 for negative

urine drug screens ($10 for the first and $20 for the second). You will receive $10 for each day that you complete all CREMA sessions. During the medication phase, you will receive $10 for each day you complete all medication video uploads. You may earn up to $364 for completing study visits during the medication phase (schedule below). You will receive $10 for each blood pressure check during the medication tapering phase for a total of $20. The total possible compensation for study visits is $769. The completing CREMA sessions will depend on how many days are completed. Payments will be made using a pre-paid debit card called a ClinCard. It works like a bank debit card and you may use the card to purchase goods or services everywhere Debit MasterCard is accepted. You will be given a ClinCard at the beginning of the study. Each time you receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule below. Details of the debit card system are explained on an additional sheet. If you screen remotely and are not eligible, a ClinCard will be mailed to you.

Study Visits

Screening	$40
Screening attendance bonus	$20
Crema training	$20
Baseline attendance bonus	$25
Baseline week urine drug screens (Days 1-7)	$10 + $20 = $30
Scripted Imagery/TSST(Day 39)	$50
Stress task visit /Scripted Imagery (Day 40)	$50
Task completion bonus	$50
Tapering blood pressure checks	$10 x 2 = $20
Follow-up	$100
Total	**$405**

Weekly Medication Visits

Week 1- Visits 1, 2 and 3	$4 + $8 + $12 = $24
Week 2 – Visits 4, 5, and 6	$16 + $20 + $24 = $60
Week 3- Visits 7,8, and 9	$28 + $32 + $36 = $96
Week 4- Visits 10, 11 and 12	$40 + $44 + $48 = $132
Week 5- Visit 13	$52
Total	**$364**

At - home tasks

Crema sessions	$10 per day
Medication videos	$10 per day

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

I. RECRUITMENT OF SUBJECTS:

You are invited to participate in the recruitment of other subjects for this study. If you choose to participate, we will provide you with coupons that you may give to other people (e.g., peers, acquaintances) who you think would be eligible and interested in this study. You may choose to tell people to whom you give these coupons to call the study office if they are interested in participating in the study. These individuals will not be identified unless they

contact the study office themselves. If any of your coupons result in successful study recruitment, you will receive $20 for each one. Participation in the recruitment process is completely voluntary, and if you elect not to participate your participation in this study will not be affected in any way.

J. ALTERNATIVES:
There are alternative treatments for opioid use. These include special counseling and other therapies (such as twelve step groups and classes on relapse prevention) aimed at decreasing drug use. You may also choose not to participate.

K. DATA SHARING:
Information about you (including your identifiable private information and/or any identifiable biospecimens) may have all of your identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

L. DISCLOSURE OF RESULTS:
Results of the research will not be shared with you. However, any clinically relevant information that is discovered will be discussed with you.

M. AUTHORIZATION TO USE AND DISCLOSE (RELEASE) MEDICAL INFORMATION:
As part of this research study, your study doctor and his/her research team will keep records of your participation in this study. The health information MUSC may use or disclose (release) for this research study includes information in your medical record, results of physical exams, medical history, lab tests or certain health information indicating or relating to your condition.

Your study doctor and his/her research team will use and disclose (release) your health information to conduct this study. The health information listed above may be used by and/or disclosed (released) to the following, as applicable:

- The sponsor of the study including its agents such as data repositories or contract research organizations monitoring the study;
- Other institutions and investigators participating in the study;
- Other investigators in the Addiction Science Division conducting similar research;
- Shoreline staff;
- Pitt St. Pharmacy pharmacists and technicians;
- Data Safety Monitoring Boards;
- Accrediting agencies;
- Clinical staff not involved in the study whom may become involved if it is relevant;
- Parents of minor children if less than 16 years old. Parents of children 16 years old or older require authorization from the child; or
- Health insurer or payer in order to secure payment for covered treatment;
- Federal and state agencies and MUSC committees having authority over the study such as:

    - The Institutional Review Board (IRB) overseeing this study; Committees with quality improvement responsibilities; Office of Human Research Protections; Food and Drug

Administration; National Institutes of Health or Other governmental offices, such as a public health agency or as required by law.

Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You do not have to sign this consent form. If you choose not to sign, it will not affect your treatment, payment or enrollment in any health plan or affect your eligibility for benefits. However, you will not be allowed to be a participant in this research study.

You will be given a copy of this consent form. Your authorization will expire at the conclusion of this study or, if you are participating in a study designed for the development of a drug or device, your authorization will remain in effect until the drug or device is approved by the FDA or until the company's application to study the drug/device is withdrawn. You have the right to withdraw your agreement at any time. You can do this by giving written notice to your study doctor. If you withdraw your agreement, you will not be allowed to continue participation in this research study. However, the information that has already been collected will still be used and released as described above. You have the right to review your health information that is created during your participation in this study. After the study is completed, you may request this information.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and for conducting public health surveillance, investigations or interventions. No publication or public presentation about the research study will reveal your identity without another signed authorization from you.

If you have questions or concerns about this Authorization or your privacy rights, please contact MUSC's Privacy Officer at (843) 792-8740.

Regulations require that you be given a copy of the MUSC Notice of Privacy Practices (NPP) describing the practices of MUSC regarding your health information. One can be found at the end of this form.

N. FUTURE CONTACT: The researcher in charge of this study might like to contact you in the future about other research opportunities. Please initial by your choice below for paper consents,or scroll down to the bottom of the screen and select your choice electronically.

____Yes, I agree to be contacted

_____No, I do not agree to be contacted

O. SIGNIFICANT NEW FINDINGS: If there are significant new finding during the course of the study, you will be notified.

P. CLINCIALTRIALS.GOV A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will

remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that you are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact Dr. Brady at (843) 792-5205 or Dr. Connie Guille at (843) 792-6489. I may contact the Medical University of SC Patient and Family Care Liaison (843) 792-5555 concerning medical treatment.
If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB
Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.
I agree to participate in this study. I have been given a copy of this form for my own records. Please sign below for paper consents or scroll to the bottom of the screen to provide an electronic signature.

_____ _____

Signature of Person Obtaining Consent Date

_____ _____

Signature of Participant Date *Name of Participant

MUSC
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Changing What's Possible

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

NOTICE OF PRIVACY PRACTICES

MUSC Organized Health Care Arrangement (OHCA)

THIS NOTICE DESCRIBES HOW MEDICAL INFORMATION ABOUT YOU MAY BE USED AND DISCLOSED AND HOW YOU CAN GET ACCESSS TO THIS INFORMATION. PLEASE REVIEW IT CAREFULLY.

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The Medical University of South Carolina and its affiliates (including but not limited to the Medical University Hospital Authority, MUSC Physicians, MUSC Physicians Primary Care, MUSC Health Partners, MUSC Health Alliance, MUSC Strategic Ventures, LLC, and MUSC Strategic Ventures (MSV) Health, Inc.) participate in a clinically integrated health care setting. As a result of this clinical integration, these organizations function as an Organized Health Care Arrangement (OHCA) as defined by the Health Insurance Portability and Accountability Act (HIPAA). For purposes of this notice, the members of the MUSC OHCA are collectively referred to in this document as "MUSC." **We collect, receive, or share this information about your past, present or future health condition to provide health care to you, to receive payment for this health care, or to operate the hospital and/or clinics.**

OUR PLEDGE REGARDING YOUR HEALTH INFORMATION

MUSC is committed to protecting the privacy of health information we create and obtain about you. This Notice tells you about the ways in which we may use and disclose health information about you. It also describes your rights and certain obligations we have regarding the use and disclosure of your health information. We are required by law to: (i) make sure your health information is protected; (ii) give you this Notice describing our legal duties and privacy practices with respect to your health information; and (iii) follow the terms of the Notice that is currently in effect.

HOW WE MAY USE AND RELEASE YOUR PROTECTED HEALTH INFORMATION (PHI) –

A. The following uses do NOT require your authorization, except where required by SC law:

1. For treatment. Your PHI may be discussed by caregivers to determine your plan of care. For example, the physicians, nurses, medical students and other health care personnel may share PHI in order to coordinate the services you may need.

2. To obtain payment. We may use and disclose PHI to obtain payment for our services from you, an insurance company or a third party. For example, we may use the information to send a claim to your insurance company.

3. For health care operations. We may use and disclose PHI for hospital and/or clinic operations. For example, we may use the information to review our treatment and services and to evaluate the performance of our staff in caring for you.

4. Business Associates. Your medical information could be disclosed to people or companies outside our Health System who provide services. These companies typically are required to sign special confidentiality agreements before accessing your information. They are also subject to fines by the federal government if they use/disclosure your information in a way that is not allowed by law.

5. For public health activities. We report to public health authorities, as required by law, information regarding births, deaths, various diseases, reactions to medications and medical products.

6. Victims of abuse, neglect, domestic violence. Your PHI may be released, as required by law, to the South Carolina Department of Social Services when cases of abuse and neglect are suspected.

7. Health oversight activities. We will release information for federal or state audits, civil, administrative or criminal investigations, inspections, licensure or disciplinary actions, as required by law.

8. Judicial and administrative proceedings. Your PHI may be released in response to a subpoena or court order.

9. Law enforcement or national security purposes. Your PHI may be released as part of an investigation by law enforcement or for continuum of care when in the custody of law enforcement.

10. Military and Veterans. If you are a member of the U.S. or foreign armed forces, we may release your medical information as required by military command authorities.

11. Uses and disclosures about patients who have died. We may provide medical information to coroners, medical examiners and funeral directors so they may carry out their duties.

12. For purposes of organ donation. As required by law, we will notify organ procurement organizations to assist them in organ, eye or tissue donation and transplants.

13. Research. We may use and disclosure your medical information for research purposes. Most research projects are subject to Institutional Review Board (IRB) approval. The law allows some research to be done using your medical information without requiring your written approval.

14. To avoid harm. In order to avoid a serious threat to the health or safety of a person or the public, we may release limited information to law enforcement personnel or persons able to prevent or lessen such harm.

15. For workers compensation purposes. We may release your PHI to comply with workers compensation laws.
16. Marketing. We may send you information on the latest treatment, support groups, reunions, and other resources affecting your health.
17. Fundraising activities. We may use your PHI to communicate with you to raise funds to support health care services and educational programs we provide to the community. You have the right to opt out of receiving fundraising communications with each solicitation.
18. Appointment reminders and health-related benefits and services. We may contact you with a reminder that you have an appointment.
19. Disaster Relief Efforts. We may disclose your medical information to an entity assisting in disaster relief efforts so that your family can be notified about your condition.
Note: incidental uses and disclosures of PHI sometimes occur and are not considered to be a violation of your rights. Incidental uses or disclosures are by-products of otherwise permitted uses or disclosures which are limited in nature and cannot be reasonably prevented.

B. You may object to the following uses of PHI:

1. Inpatient hospital directories. Unless you tell us not to, we may include your name, location, general condition and religious affiliation in our patient directory so your family, friends and clergy can visit you and know how you are doing. **2. Information shared with family, friends or others.** Unless you tell us not to, we may release your PHI to a family member, friend, or other person involved with your care or the payment for your care.
3. Health plan. You have the right to request that we not disclose certain PHI to your health plan for health services or items when you pay for those services or items in full.

C. Your prior written authorization is required (to release your PHI) in the following situations:

You may revoke your authorization by submitting a written notice to the privacy contact identified below. If we have a written authorization to release your PHI, it may occur before we receive your revocation.
1. Any uses or disclosures beyond treatment, payment or healthcare operations and not specified in parts A & B above.
2. Mental Health Records unless permitted under an exception in section A.
3. Substance Use Disorder Treatment records unless permitted under an exception in section A.
4. Any circumstance where we seek to sell your information.

WHAT RIGHTS YOU HAVE REGARDING YOUR PHI

Although your health record is the physical property of MUSC, the information belongs to you, and you have the following rights with respect to your PHI:
A. The Right to Request Limits on How We Use and Release Your PHI. You have the right to ask that we limit how we use and release your PHI. We will consider your request, but we are not always legally required to accept it. If we accept your request, we will put any limits in writing and abide by them except in emergency situations. Your request must be in writing and state (1) the information you want to limit; (2) whether you want to limit our use, disclosure or both; (3) to whom you want the limits to apply, for example, disclosures to your spouse; and (4) an expiration date**.**
B. The Right to Choose How We Communicate PHI with You. You have the right to request that we communicate with you about PHI and/or appointment reminders in a certain way or at a certain location (for example, sending information to your work address rather than your home address). You must make your request in writing and specify how and where you wish to be contacted. We will accommodate reasonable requests.
C. The Right to See and Get Copies of Your PHI. You have the right to inspect and/or receive a copy (an electronic or paper copy) of your medical and billing records or any other of our records used to make decisions about your care. You must submit your request in writing. If you request a copy of this information, we may charge a cost-based fee. MUSC will act on a request for access or provide a copy usually within 30 days of receipt of the request. We may deny your request in limited circumstances. If you are denied access to your records, you may request that the denial be reviewed by a licensed health care professional. Additionally, we may use and disclose information through our secure patient portal which may allow you to view and communicate with certain health care providers in a secure manner. For more information see our https://mychart.musc.edu/mychart/
D. The Right to Get a List of Instances of When and to Whom We Have Disclosed Your PHI. This list may not include uses such as those made for treatment, payment, or health care operations, directly to you, to your family, or in our facility directory as described above in this Notice of Privacy Practices. This list also may not include uses for which a signed authorization has been received or disclosures made more than six years prior to the date of your request.
E. The Right to Amend Your PHI. If you believe there is a mistake in your PHI or that a piece of important information is missing, you have the right to request that we amend the existing information or add the missing information. You must provide the request and your reason for the request in writing. We may deny your request in writing if the PHI is correct and complete or if it originated in another facility's record. Notification will be provided within 60 days.
F. The Right to Receive a Paper or Electronic Copy of This Notice: You may ask us to give you a copy of this Notice at any time. For the above requests (and to receive forms) please contact: Health Information Services (Medical Records), Attention: Release of Information / 169 Ashley Avenue / MSC 349 / Charleston, SC 29425. The phone number is (843) 792-3881.
G. The Right to Revoke an Authorization. If you choose to sign an authorization to release your PHI, you can later revoke that authorization in writing. This revocation will stop any future release of your health information except as allowed or required by law.
H. The Right to be Notified of a Breach. If there is a breach of your unsecured PHI, we will notify you of the breach in writing.

HEALTH INFORMATION EXCHANGES

MUSC, along with other health care providers, belongs to health information exchanges. These information exchanges are used in the diagnosis and treatment of patients. As a member of these exchanges, MUSC shares certain patient health information with other health care providers. Should you require treatment at another location that is a part of one of these exchanges, that provider may gather historical health information to assist with your treatment. You have the option of saying that this cannot be done. If you choose not to take part in these alliances, please contact the MUSC Privacy Office at 792-4037.

HOW TO COMPLAIN ABOUT OUR PRIVACY PRACTICES

If you think your privacy rights may have been violated, or you disagree with a decision we made about access to your PHI, you may file a complaint with the office listed in the next section of this Notice. **Please be assured that you will not be penalized and there will be no retaliation for voicing a concern or filing a complaint. We are committed to the delivery of quality health care in a confidential and private environment.**

PERSON TO CONTACT FOR INFORMATION ABOUT THIS NOTICE OR TO COMPLAIN ABOUT OUR PRIVACY PRACTICES

If you have any questions about this Notice or any complaints about our privacy practices please call the Privacy Officer (843) 792-4037, the Privacy Hotline (800) 296-0269, or contact in writing: HIPAA Privacy Officer / 169 Ashley Avenue / MSC 332 / Charleston SC 29425. You also may send a written complaint to the U.S. Dept. of Health and Human Services, Office for Civil Rights. The address will be provided at your request or by visiting www.hhs.gov/ocr/privacy/hipaa/complaints/.

CHANGES TO THIS NOTICE

We reserve the right to change the terms of this Notice at any time. The changes will apply to all existing PHI we have about you.. This Notice will always contain the effective date and may be reviewed at http://academicdepartments.musc.edu/musc/about/compliance/privacy.html

EFFECTIVE DATE OF THIS NOTICE

This Notice went into effect on April 14, 2003 and was last revised on August 2018.

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