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Effects of Oxytocin Administration on Cue-Induced Craving in Co-occurring Alcohol Use Disorder and PTSD: A Within-Participant Randomized Clinical Trial

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Abstract

Background: Individuals with alcohol use disorder (AUD) are much more likely to meet criteria for posttraumatic stress disorder (PTSD) than the general population. Compared to AUD alone,

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CONFLICT OF INTEREST
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those with comorbid AUD-PTSD experience worse outcomes. Prior literature suggests that oxytocin, a hypothalamic neuropeptide, may be effective in the treatment of both AUD and PTSD when administered intranasally, although specific mechanisms remain elusive.

Methods: Forty-seven male patients with comorbid AUD-PTSD were administered intranasal oxytocin in a randomized, double-blind, dose-ranging (20 IU, 40 IU, and matched placebo), within-participant design with study visits at least 1 week apart. A cue-induced craving paradigm was conducted using each participant's preferred alcoholic beverage versus a neutral water cue. Self-reported alcohol craving and heart rate (HR) were recorded and analyzed using linear mixed-effect models.

Results: While alcohol cues significantly induced self-reported craving and increased HR compared to neutral water cues, neither dosage of oxytocin compared to placebo reduced self-reported cue-induced alcohol craving nor cue-induced changes in HR in patients with PTSD-AUD.

Conclusions: These preliminary findings suggest that oxytocin does not affect cue-induced craving. Our results contribute to an ever-growing field of research investigating the effects of intranasal oxytocin on the symptoms of substance use disorders and will help further refine methodology and streamline future inquiries in this area.

Keywords

Oxytocin; Craving; PTSD; Alcohol Use Disorder; Comorbidity

EXCESSIVE ALCOHOL CONSUMPTION is a leading cause of preventable death (CDC, 2013) and cost the United States almost $250 billion in 2010 (Sacks et al., 2015). An estimated 14.5 million individuals aged 12 and older had an alcohol use disorder (AUD) in the United States in 2017 (SAMHSA, 2018). Individuals with AUD are much more likely than the general population to meet criteria for posttraumatic stress disorder (PTSD), with odds ratios ranging from 2.00 to 4.87 (Debell et al., 2014). In some high-risk populations, such as military Veterans, comorbid PTSD occurs in up to 63% of those with AUD (Seal et al., 2011). Compared to those with AUD alone, individuals with a dual diagnosis of AUD and PTSD experience greater alcohol craving, higher AUD severity, poorer AUD treatment outcomes, and higher rates of relapse (Blanco et al., 2013; Coffey et al., 2010; Drapkin et al., 2011; Ouimette et al., 1998). Additionally, those with comorbid AUD and PTSD suffer from lower overall functioning and quality of life, higher rates of healthcare utilization, and increased risk of suicide and mortality (Blanco et al., 2013; Heinz et al., 2016; McCarthy and Petrakis, 2010; Ouimette et al., 2006; Simpson et al., 2012). Despite recent literature emphasizing the importance of treating the specific symptom profile of individuals with both disorders (Petrakis and Simpson, 2017; Taylor et al., 2017), AUD treatment research has predominantly excluded patients with comorbid PTSD. Given that the dual diagnosis of AUD and PTSD is common and impactful, innovative treatments specifically addressing this comorbidity are gravely needed (Petrakis and Simpson, 2017; Taylor et al., 2017).

Oxytocin, a hypothalamic neuropeptide, is a crucial component of a complex central and peripheral system that manages mammalian social behavior (Ebert and Brüne, 2018). Emerging evidence suggests that oxytocin administration dose-dependently reduces alcohol consumption and reverses tolerance in animal models (King et al., 2017; Lee et al., 2016;

MacFadyen et al., 2016; Stevenson et al., 2017a). Recent human clinical trials have begun to explore the potential for oxytocin administration to address the symptoms of AUD. The first of these was a small randomized trial of intranasal oxytocin 24 international units (IU; $n = 7$) versus placebo ($n = 4$) given twice daily for 3 days, which demonstrated that oxytocin significantly reduced alcohol withdrawal symptoms, self-reported alcohol craving, and anxiety in patients with AUD undergoing acute alcohol detoxification (Pedersen et al., 2013). The same research group subsequently conducted a 12-week study of outpatients with AUD who self-administered intranasal oxytocin 40 IU ($n = 10$) versus placebo ($n = 5$) 2 to 3 times daily (Pedersen, 2017). Those who received oxytocin demonstrated a significant reduction in heavy drinking days and drinks per drinking day compared to those who received placebo, but there was no significant difference in self-reported alcohol craving or anxiety between treatment groups. Results from 2 additional laboratory-based studies of intranasal oxytocin's effects on alcohol-related behavior in nonclinical samples are mixed (Mitchell et al., 2016; Vena et al., 2018). In sum, animal work suggests that oxytocin administration may be useful in treating the symptoms of AUD, though we are in the early stages of translating this work to humans.

Oxytocin may be a particularly good candidate for the concomitant treatment of both AUD and PTSD. Childhood maltreatment is thought to negatively impact development of the oxytocinergic system, which may in turn lead to an increased susceptibility to stress and risk of developing a substance use disorder (Johnson and Buisman-Pijlman, 2016). Moreover, alcohol (Gibbens and Chard, 1976; Lee et al., 2017; Silva et al., 2002; Stevenson et al., 2017b; Subramanian, 1999) and adult-onset trauma (Donadon et al., 2018) can further dysregulate the oxytocin system. Importantly, Flanagan and colleagues (2019a) conducted a study of U.S. military Veterans with both AUD and PTSD examining the effects of oxytocin 40 IU ($n = 32$) versus placebo ($n = 35$) in response to a Trier Social Stress Test. The study found that oxytocin attenuated cortisol reactivity but did not reduce stress-induced alcohol craving. Because oxytocin has shown promise as an intervention for both disorders, and symptoms of AUD and PTSD are so intertwined, it is worth furthering our understanding of the potential benefits of intranasal oxytocin for individuals with a dual diagnosis of AUD and PTSD.

The question remains whether oxytocin administration specifically mitigates alcohol-related cue-induced craving, rather than stress-induced craving (Flanagan et al., 2019a), in individuals with AUD. In order to further elucidate specific mechanisms and guide future clinical research involving oxytocin administration for the symptoms of AUD, we implemented a standard cue-induced craving paradigm using each participant's preferred alcoholic beverage versus neutral water as cues. Cue-induced craving paradigms using exposure to actual alcohol have been utilized widely in the investigation of new interventions for AUD (Carter and Tiffany, 1999; Reynolds and Monti, 2013), including studies of individuals with comorbid AUD and PTSD (Coffey et al., 2010; Nosen et al., 2014).

Heart rate (HR) response to interventions known to stimulate sympathetic activity can distinguish individuals with AUD (Irwin and Michael, 2005) and PTSD (Blanchard et al., 1996, 1986; Castro-Chapman et al., 2018; Orr et al., 1997) from healthy controls. However,

HR data for individuals with comorbid AUD and PTSD are lacking. HR has been shown to respond to alcohol cue presentation (Carter and Tiffany, 1999). Previous relevant studies examining intranasal oxytocin's effect on HR have been mixed. While oxytocin had no effect on alcohol-induced HR response in one study (Vena et al., 2018), it has been shown to affect HR response to specific emotionally laden stimuli in individuals with (Sack et al., 2017) and without PTSD (Gamer and Büchel, 2012). The current study measured self-reported alcohol craving in response to cue exposure, and HR was examined as an objective response to our cue-induced craving paradigm.

Furthermore, severity of alcohol use and PTSD symptoms have been shown to impact self-reported alcohol craving (Day et al., 2014; Kaczkurkin et al., 2016) and subjective alcohol cue–induced responses (Jasinska et al., 2014). While there is an emerging literature demonstrating a moderating effect of childhood trauma severity on oxytocin-induced outcomes (Flanagan et al., 2019b), the moderating effects of alcohol use and classic PTSD symptom severity on oxytocin response have not been explored. Therefore, we will test alcohol use and PTSD symptom severity scores as moderating predictors.

Information on the most effective dosage of oxytocin for any indication or clinical population in human trials is lacking (Wynn et al., 2019). Dosages of intranasal oxytocin typically used in research have not been guided by dose–response data, which confounds the field's ability to adequately interpret complex findings in existing trials. Therefore, we employed a dose-ranging study design. Finally, psychological research in general, and oxytocin research in particular, has suffered from low statistical power and failure to replicate. Therefore, we used a within-participant design to increase analytic power and preregistered our aims: to test whether intranasal oxytocin (20 IU and 40 IU) is superior to placebo in reducing cue-induced alcohol craving and HR response in male patients with comorbid AUD and PTSD (see NCT02469259 and https://aspredicted.org; #8732).

MATERIALS AND METHODS

Study Design

This is a randomized, double-blind, placebo-controlled, within-participant study of the effects of oxytocin administration on alcohol cue–induced subjective and psychophysiological responses in individuals with comorbid AUD and PTSD (patients). In order to validate our measures and patient sample, we also recruited age- and education-matched controls.

Participants

A total of 56 patients and 45 controls were enrolled between 5/24/2016 and 12/8/2017. Participants were recruited from the San Francisco Veterans Affairs Health Care System through mental health clinics and via advertisements posted around campus, at several community mental health programs throughout San Francisco, and on Craigslist. A brief, structured telephone interview was used to screen individuals for preliminary eligibility. All participants were 18 to 75 years old. Those in the patient arm met criteria for current PTSD and AUD in the past 12 months, as defined by the *Diagnostic and Statistical Manual of*

Mental Disorders, fifth edition (DSM-5). Due to early challenges recruiting women for our study, we opted to focus subsequent recruitment efforts on male participants only in order to decrease heterogeneity given known sexual dimorphisms in endogenous oxytocin system functioning and response to intranasal oxytocin in both preclinical and clinical studies. A total of 47 male patients and 36 male controls completed at least 2 experimental visits and were included in analyses.

Excluded from this study were individuals with: dementia or other neuropsychiatric disorders impairing ability to complete study-related tasks, clinically significant unstable medical conditions, acute alcohol withdrawal evidenced by a score of ≥12 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar; Sullivan et al., 1989), current participation in a legally mandated alcohol treatment program, suicidal ideation with intent or plan in the past 30 days, suicide attempt in the past 6 months, a seizure disorder requiring anticonvulsant medication, sensitivity to preservatives used in study drug nasal spray (i.e., potassium sorbate or mannitol), pathology of the nasal parenchyma preventing intranasal drug administration or absorption, or hormone supplementation (which may affect the endogenous oxytocin system). Controls could not have a history of PTSD (full or partial), moderate to severe AUD, or a substance use disorder as determined by DSM-5 criteria.

The University of California, San Francisco Institutional Review Board provided ethics review and safety monitoring for this study. All study procedures took place at the San Francisco Veterans Affairs Medical Center.

Procedures

To determine full eligibility, participants attended an in-person screening assessment where written informed consent was obtained prior to any study procedures. During screening, participants completed baseline assessments (see Table 1), including the Alcohol Use Disorders Identification Test (AUDIT; Bohn et al., 1995)—a 10-item screening tool that assesses alcohol consumption, drinking behavior, and alcohol-related problems. Trained clinical interviewers with at least Masters' level training in clinical psychology conducted diagnostic interviews, including pertinent sections of the Structured Clinical Interview for *DSM-5* (SCID-5), Research Version (First et al., 2015), and the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5). An examination of the nasal parenchyma was conducted by a study physician.

Further study participation consisted of 3 experimental sessions each separated by at least 1 week. Research assistants were trained to conduct the protocol with a neutral demeanor and wore white laboratory coats in order to standardize social context (Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016). Each participant was assigned the same primary research assistant across the 3 experimental sessions (Chapman et al., 2018). Additional study tasks not described in this manuscript will be published separately. Participants were compensated at each visit for their time and travel.

At all sessions, participants provided a urine sample to screen for illicit substances using a CLIA-waived, 10-panel, Discover Urine Drug Test Cup (American Screening Corp.,

Shreveport, LA). Participants were also screened for acute alcohol consumption using the BACtrack S80 Breathalyzer (BACtrack, San Francisco, CA). If any participant had a breath alcohol concentration of more than 0.00%, or a control had a positive urine drug screen other than for tetrahydrocannabinol (THC), their session was rescheduled for another day. Participants were asked to refrain from using nicotine products starting at the beginning of each experimental session until after the tasks described below.

Participants completed all self-assessment measures using Research Electronic Data Capture, an online data capture tool hosted by the Department of Veterans Affairs, using an iPad (Apple; Cupertino, CA; iOS version 5.1.1). For timing of assessments, see Table 1.

Study Drug.—Study drug consisted of oxytocin 20 IU, oxytocin 40 IU, and matched placebo. Study drug was purchased from Well-spring Compounding Pharmacy (Berkeley, CA). Trained study staff administered study drug intranasally according to standardized techniques (Guastella et al., 2013) using a mucosal atomization device (MAD300 Teleflex; Morrisville, NC) affixed to a Luer lock syringe. A research pharmacist loaded the appropriate study drug and concentration into two 1-milliliter (ml) syringes. The first syringe contained 0.56 ml to accommodate the 0.06 ml dead space in the MAD300, and the second syringe contained 0.50 ml and was administered into the opposite nostril. Previous work has shown that intranasal oxytocin administration increases plasma levels of oxytocin within 30 minutes and lasts for at least 90 minutes (Gossen et al., 2012). Therefore, immediately following study drug administration and prior to any study-related tasks, participants watched 1 of 3 30-minute neutral videos (e.g., documentary about a historical event) presented in a randomized order across experimental sessions.

Randomization and Blinding.—Each participant received all 3 study drugs across the 3 experimental sessions in a randomized order. Patients and controls were allocated separately, and each randomization plan used balanced permutations in blocks of 20, assuming 120 participants. A research pharmacist maintained the blind and oversaw randomization using the second generator from www.randomization.com (reproduction can be viewed using seeds 4,243 and 564 for patients and 19,293 for controls). Study staff remained blinded to study drug until data collection was complete for all participants.

Cue-Induced Craving.—Approximately 65 minutes after study drug administration, a cue-induced craving paradigm, adapted from previous research (MacKillop and Lisman, 2005; Papachristou et al., 2012), was used to elicit alcohol craving. Research assistant #1, the same person handling all face-to-face interactions throughout study participation, presented the participant with a wooden tray containing only a large silver cover with a handle attached. The participant was then left alone with the tray and asked not to act outside of verbal instructions they would receive. Research assistant #2 monitored the participant via live video feed from a nearby room and provided the following scripted instructions through an intercom. Each instruction was followed by 1 minute of physiological recording. If the participant did not properly follow the instructions or strayed from their task within the 1-minute time frame, the prompt was repeated.

1. "After I finish speaking, please remove the lid and place it on the table. Then look at what is presented. Please proceed."
2. "After I finish speaking, uncap the bottle of water/alcohol and pour it into the cup, but DO NOT pick up the cup or drink the water/alcohol. Please proceed."
3. "After I finish speaking, pick up the cup of water/alcohol and swirl it around, smell it, and look at it, but DO NOT drink it. Please proceed."
4. "After I finish speaking, please dip your pointer and middle fingers into the water/alcohol and then touch your fingers to your tongue and lips just to get a taste of the water/alcohol. Again, do not drink the water/alcohol. Please proceed."

In order to prevent transfer effects (Monti et al., 1987), cue-induced craving was always completed using the water cue first; then, a new covered tray was presented to the participant and the same set of instructions was repeated for the alcohol cue. Water cue exposure consisted of an 8-oz plastic water bottle and a 10-oz drinking glass. During the baseline assessment, participants were asked to identify their preferred type—and brand, if specific—of alcoholic beverage, which was then used for alcohol cue exposure in order to ensure maximal craving induction (Staiger and White, 1991). For beer, a standard 12-oz bottle was used (or can, if a bottle was unavailable for their specified brand); for malt liquor, a 40-oz can was used; for wine or sparkling wine, a 187.5-ml bottle was used; and for liquor, a standard 50-ml minibottle was used. Alcohol cues were matched with a corresponding glass (i.e., beer was matched with a pint glass, wine was matched with a standard wine glass, sparkling wine was matched with a flute glass, and liquors were matched with a 1.5-oz shot glass). Empty glasses were standardized to appear on the patient's left and the water/alcohol appeared on the patient's right.

Dependent Variables From Cue-Induced Craving Paradigm.

Self-Reported Craving: Following the written prompt, "How much are you currently craving alcohol?" participants recorded their response using a numberless, sliding visual analog scale on a tablet screen corresponding to values 0 to 100. Alcohol craving was assessed during each experimental visit at the following time points: (t_1) baseline, prior to any study drug (0 minutes), (t_2) poststudy drug, after intranasal administration and neutral video (~30 minutes), (t_3) after water cue exposure (~75 minutes), and (t_4) after alcohol cue exposure (~85 minutes). Alcohol craving was also assessed at the conclusion of each experimental session (~150 minutes) to ensure craving had safely returned toward baseline, but was not included in analysis. Our dependent variables consisted of t_3 and t_4 separately subtracted from t_1 (i.e., change in alcohol craving from baseline to after water and alcohol cue exposure, respectively; a positive number indicates cue-induced alcohol craving).

Heart Rate (HR): We calculated the mean HR for each 1-minute segment of the 4-minute water and subsequent 4-minute alcohol cue exposures. To remain consistent with methodology for self-reported alcohol craving, the dependent variables for HR consisted of the 60-second mean HR recorded after each prompt subtracted from the mean HR of a 5-minute baseline recorded prior to drug administration (i.e., the change in HR from baseline

to each of the 4 minutes the participants were presented with water cues and each of the corresponding 4 minutes they were presented with alcohol cues). A second 5-minute resting baseline was recorded immediately prior to beginning the cue-induced craving paradigm (~65 minutes).

Electrocardiogram (ECG) was recorded using EL503 electrodes, 7% Ag/AgCl concentration, in a 3-lead configuration (an electrode was placed underneath both the right clavicle and left clavicle, and a third electrode was placed beneath the bottom rib on the left side). Each measurement was sampled at 1,000 Hertz (Hz) using hardware from BIOPAC Systems, Inc, Goleta, CA, USA. and Acqknowledge software (version 4.3.1., Goleta, CA, USA). The signal was amplified using ECG100C set to a gain of 2,000, a 1.0-Hz high-pass filter, and a 35-Hz low-pass notch filter. The ECG signal was digitally filtered for noise using a finite impulse response low-pass filter of 35 Hz, and down to 15 Hz if necessary, with Acqknowledge software (version 5.0.0). R peaks, automatically identified by Acqknowledge and individually confirmed by trained study staff, were used to determine HR.

Statistical Analysis Plan

Data were examined for outliers (>3 standard deviation [SD] from the mean) on dependent measures (alcohol craving and HR). Outliers were replaced with the next highest value based on the Winsor method (Guttman, 1973).

We applied a linear mixed-effect model to our dependent variables (craving and HR separately) at each oxytocin treatment level (20 IU and 40 IU) using R (version 3.5.0., Boston, MA, USA) and select packages (Bates et al., 2014; Gelman, 2018; Gelman and Hill, 2007; Kuznetsova et al., 2017; R Core Team, 2018). Placebo was used as a reference group in all models. Observations were grouped by participant to ascertain changes within participant and between participants across treatment levels. Linear mixed-effect models include participants with missing data and use all available data to estimate the model (Hedeker and Gibbons, 2006). For both models, we assume that random effects are drawn from a bivariate, normal distribution with mean (0,0), with free parameters random slope variance, random intercept variance, and intercept/slope covariance.

Control Variables and Study Effects.—In the models described below, using a maximal approach, we included demographic covariates of age, race, smoking status, Veteran status, alcohol of choice (type of alcohol presented to participant in the cue-induced craving paradigm), proportion of drinking days out of past 30 days, THC use at baseline, cocaine use at baseline, relationship status (primary relationship or not), gender of research assistants #1 and #2 (Chapman et al., 2018), and study drug order as fixed effects. Categorical variables were entered as factors.

Self-Reported Craving.—We developed a baseline model using the maximal approach advocated by Barr and colleagues (2013) and used a likelihood ratio test to measure model fit (Barr et al., 2013). Beginning with a null model, we included a random intercept for participant, to account for clustering in the data among participants. Adding a random slope for participant produced a significantly better fit, so this term was included. Treatment was

tested as a fixed effect and included as a random effect, varying within participant. Additionally, we added a fixed and random effect of alcohol to account for clustering in observation time points where participants were presented with alcohol cues (versus water). Including this variable and allowing its effect to vary across participants produced a significantly better model fit (p-value < 0.001) and reduced model variance.

The equation for the self-reported craving model is as follows:

$$\begin{gathered} Y_{pi} = \beta_0 + P_{0p} + (\beta_1 + P_{1p})X_i + (\beta_2 + P_{2p})\mathrm{ALC}_i + e_{pi} \\ (P_{0p}, P_{1p}, P_{2p}) \sim N\left(0, \begin{bmatrix} \tau_{00}^2 & \rho\tau_{00}\tau_{11} \\ \rho\tau_{00}\tau_{11} & \tau_{00}^2 \end{bmatrix}\right) \\ e_{pi} \sim N(0, \sigma^2) \end{gathered} \tag{1}$$

This model (1) relates response Y for participant p to fixed effect of baseline β, random effects of participant P, and effects of treatment level X and presence of alcohol cue ALC as they vary between and within participants. Y is the change from baseline for self-reported craving at the water and alcohol exposure time points, separately.

Heart Rate.—We again used a linear mixed-effect model to measure the fixed effects of Treatment on HR. To account for clustering, Treatment was included as a random effect and allowed to vary within participant and cue-induced craving paradigm section (minute 1, minute 2, etc.). Adding alcohol cue exposure as a random effect did not contribute to a better model fit; therefore, it was retained as a fixed effect only.

The equation for the HR model is as follows:

$$\begin{gathered} Y_{pi} = \beta_0 + P_{0p} + \mathrm{ALC}_{pi} + I_{oi} + (\beta_1 + P_{1p})X_i + e_{pi} \\ (P_{0p}, P_{1p}) \sim N\left(0, \begin{bmatrix} \tau_{00}^2 & \rho\tau_{00}\tau_{11} \\ \rho\tau_{00}\tau_{11} & \tau_{11}^2 \end{bmatrix}\right) \\ I_{0i} \sim N(0, w_{00}^2) \\ e_{pi} \sim N(0, \sigma^2) \end{gathered} \tag{2}$$

This model (2) relates HR Y for participant p as it responds to Treatment X at 1-minute recording corresponding to each prompt.

Moderating Predictors.—We tested AUDIT and CAPS-5 severity scores as moderating predictors. We treated each predictor as a fixed effect and tested for any interaction with the fixed effect of Treatment. Values were rescaled and centered using Gellman's rescaling function in R in order to standardize comparison of effect sizes (Gelman and Hill, 2007). p-values are reported using the Kenward–Rogers approximation method.

RESULTS

Demographics and Baseline Characteristics

For a visualization of participant flow from prescreening to analysis, see Fig. 1. See Table 2 for demographic information and baseline characteristics.

Construct Validity and Study Sample

Nine outliers were identified for self-reported alcohol craving in the control group and were replaced with the next highest values. Using Student's *t*-tests on alcohol craving levels during the placebo condition, we explored the construct validity of our cue-induced craving paradigm (i.e., whether our test was measuring what it purports to be measuring). As expected, self-reported alcohol craving after alcohol cue exposure increased significantly above baseline, $t_{(4\text{-}1)}$, but alcohol craving did not significantly change from baseline after water cue exposure, $t_{(3\text{-}1)}$ (see Fig. 2). This demonstrates that our cue-induced craving paradigm adequately produced alcohol cue–induced craving and was specific for alcohol versus water cue exposure, for both patients and controls.

We also tested whether our patient sample was significantly different from our control group in regard to their alcohol craving. Looking again at the placebo condition for reference, mean self-reported alcohol craving at baseline was significantly higher for patients than for the control group (see Fig. 2), as expected. Moreover, patients experienced a significantly greater increase in craving from baseline to after alcohol cue exposure, $t_{(4\text{-}1)}$, compared to controls ($p < 0.001$); but there was no significant difference from baseline to after water cue exposure, $t_{(3\text{-}1)}$, between patients and controls ($p = 0.67$). While resting baseline HR and HR during both water and alcohol cue exposure did not differ significantly between patients and controls (see Fig. 3), patients did experience a significantly greater change in HR from water to alcohol cue exposure compared to controls. Given the significant differences observed in alcohol cue reactivity between patients and controls, we determined that an adequate AUD patient sample was recruited. Therefore, because our cue-induced craving paradigm and related hypotheses were not designed for individuals without AUD, controls were excluded from further analyses.

Control Variables and Study Effects

Two patients were removed from HR analyses due to missing baseline HR for 2 of 3 sessions. Our model for alcohol craving included a total number of 279 observations, and our model for cue-induced changes in HR included a total number of 995 observations, taking into account missing data.

There was no significant effect of age, race, relationship status, smoking status, Veteran status, alcohol of choice, proportion of drinking days in past 30 days, THC, cocaine, or study drug order on either of our dependent variables. Gender of research assistant #1 was a significant covariate for self-reported craving ($\beta = 16.9$, $SE = 6.02$, 95% CI = [5.11, 28.70], $p = 0.02$), such that the presence of a female research assistant was associated with higher alcohol craving (see Table 3). This significant covariate was controlled for in subsequent analyses.

The presence of the alcohol cue, compared to the water cue, prior to self-reported craving and during HR recording had a significant effect on our dependent variables (see Table 3).

Primary Outcomes

Effect of Oxytocin on Self-Reported Craving.—There was no significant main effect of Treatment on alcohol craving at either dosage of oxytocin and no significant interaction effect of Treatment with alcohol cue exposure (see Table 3).

Effect of Oxytocin on HR.—There was no significant main effect of Treatment on HR at either dosage of oxytocin and no significant interaction effect of Treatment with alcohol cue exposure (see Table 3).

Moderating Predictors

There were no significant main moderating effects of AUDIT or CAPS-5 severity scores on self-reported craving or HR and no significant interaction effect of Treatment and AUDIT or CAPS-5 (see Table 3).

DISCUSSION

Alcohol cue exposure during our laboratory cue-induced craving paradigm sufficiently induced alcohol craving and increased HR compared to neutral water cues, which supports the validity of our task. However, neither 20 IU nor 40 IU of intranasal oxytocin had a significant effect on self-reported alcohol craving or HR. These findings demonstrate that a single administration of oxytocin at these doses does not attenuate real-time alcohol cue–induced craving in men with AUD and PTSD.

Although no previous studies investigated oxytocin's effects on alcohol cue–induced craving in individuals with AUD, our findings are in line with previous research looking at oxytocin's effects on alcohol-related behavior in individuals without an explicit diagnosis of AUD. For example, there was no significant main effect of oxytocin 40 IU on alcohol cue-induced craving or alcohol approach bias in "non–treatment-seeking heavy drinkers" (n = 32) (Mitchell et al., 2016) and no effect of oxytocin 40 IU (with a 20 IU booster) on the enjoyment of or desire for more alcohol ingestion in a laboratory setting with "healthy social drinkers" (Vena et al., 2018). Our data extend these previous null findings to individuals with a diagnosis of AUD. Pedersen (2017) study of individuals with AUD, which demonstrated significant reduction in alcohol use in real-world settings over time with repeated oxytocin dosing, also did not find an effect of oxytocin on self-reported craving, but Pedersen and colleagues' (2013) study did report reduced alcohol craving with repeated oxytocin doses in individuals undergoing acute alcohol detoxification. Our laboratory-based, single-dose study failed to show an effect of oxytocin on alcohol cue–induced craving in men with AUD who were not experiencing acute alcohol withdrawal. Despite animal studies demonstrating reduction in alcohol self-administration in response to oxytocin administration, intranasal oxytocin does not seem to significantly affect alcohol cue–induced craving in humans.

Oxytocin administration may still prove beneficial by affecting other aspects of AUD in this study population. For example, given oxytocin's involvement with the hypothalamic–pituitary–adrenal axis (Cardoso et al., 2014), oxytocin administration may affect stress-induced alcohol relapse rather than cue-induced craving. This theory would support Flanagan and colleagues' (2019a) finding that oxytocin attenuated cortisol reactivity in individuals with AUD and PTSD after a Trier Social Stress Test, even though they also failed to demonstrate acute changes in self-reported alcohol craving. Moreover, Bowen and colleagues' (2015) finding that oxytocin blocks the effect of alcohol on critical GABA (A) receptor subtypes in rats may be reflected in clinical trial results showing beneficial effects of oxytocin on acute alcohol withdrawal, including self-reported craving (Pedersen et al., 2013), and limiting alcohol ingestion over time (Pedersen, 2017) in individuals with AUD. Another potential role for intranasal oxytocin is as an in-session adjunct to psychotherapy, which has been piloted in patients with PTSD (Flanagan et al., 2018) and substance use disorders (Stauffer et al., 2019). Therefore, further translational work is warranted to examine oxytocin's potential role in alleviating acute alcohol withdrawal, reducing tolerance over time, and preventing stress-induced relapse or other facets of excessive alcohol use in humans.

This study has several additional limitations. Although it is important to explore innovative treatments for individuals with comorbid AUD and PTSD, this limits generalizability to individuals with either disorder on its own. Our results also fail to generalize to women given oxytocin's varying effects based on gender (Hoge et al., 2014). We did not know the treatment-seeking status of our sample; future studies should include this important variable. Furthermore, in our study of male participants, the effect of research assistant #1's gender on participants' craving highlights the importance of carefully controlling the social environment in addiction research, particularly research involving oxytocin —a social peptide—as an intervention (Chapman et al., 2018). Previous studies in healthy and other clinical populations have noted the moderating effects of social contextual aspects or the "social salience hypothesis" (Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016), as well as individual characteristics, including gender, early life adverse experiences, and attachment insecurity (MacDonald, 2013; MacDonald and Feifel, 2014), on response to intranasal oxytocin. For example, attachment anxiety moderated oxytocin's effect on alcohol cue-induced craving in heavy drinkers (Mitchell et al., 2016). Future analyses should factor in potential moderators. Although our study design included 2 different dosages of oxytocin, the optimal dose and frequency of dosing remains a complicated topic for oxytocin research at large, let alone in this specific patient population and outcome. Additionally, our study was limited by use of single administrations of study drug, whereas some prior oxytocin studies in individuals with AUD utilized repeated administrations over multiple days (Pedersen, 2017; Pedersen et al., 2013).

In conclusion, single-administration intranasal oxytocin at 2 standard dosages demonstrated no beneficial effect on alcohol cue–induced craving for individuals with AUD and PTSD, despite our study being carried out in a well-controlled laboratory setting using a within-participant design to improve analytic power. Given the volume of preclinical data supporting our hypotheses (for a review, see Lee et al., 2016), as well as ongoing clinical exploration of oxytocin's effects for the treatment of myriad substance use disorders across

multiple laboratories, it is important that null results be published to avoid the “file drawer problem” (Rosenthal, 1979)—particularly with oxytocin treatment research (Lane et al., 2016). Overall, potential benefits of oxytocin administration in the clinical treatment of AUD, and which AUD symptoms to target, remain largely unclear. Future studies should assess the effects of oxytocin administration in both men and women with comorbid AUD and PTSD using a combination of trauma and alcohol cues (see Coffey et al., 2010; Nosen et al., 2014) with careful attention to social environment and stressors both acutely and longitudinally. Publication of the null results from the current study will allow oxytocin researchers to further refine methodology and streamline inquiries in this area.

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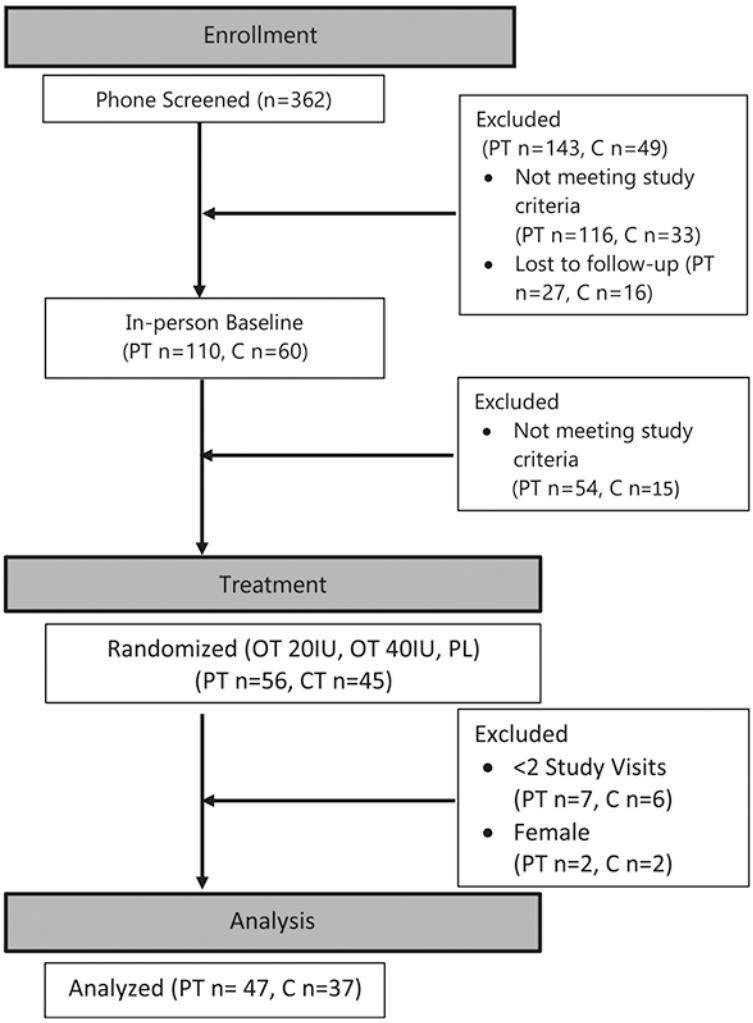

Fig. 1.
Summary flow of participant enrollment. C, controls; PT, patients.

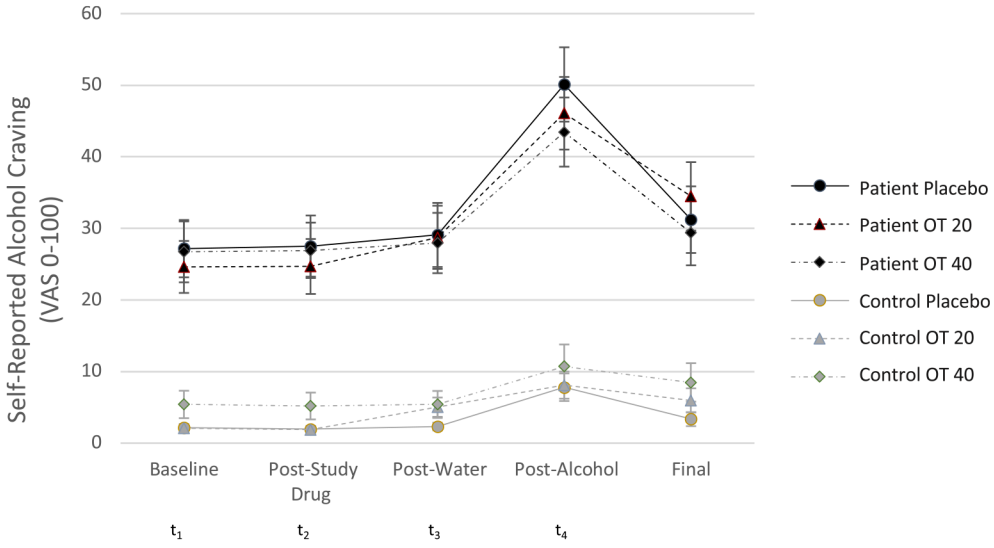

Fig. 2.

Mean self-reported alcohol craving at each time point for patients and controls separated by Treatment condition (placebo, OT 20, OT 40). *Construct validity*: mean change (SEM), placebo condition, patient $t_{(4\text{-}1)}$ = 22.94 (4.13), p-value < 0.001; control $t_{(4\text{-}1)}$ = 5.68 (1.86), p-value = 0.004. Patient $t_{(3\text{-}1)}$ = 1.91 (3.93), p-value = 0.63; control $t_{(3\text{-}1)}$ = 0.19 (0.48), p-value = 0.70. *Patient versus control*: mean (SEM), placebo condition, patient t_1 = 27.17 (4.01) versus control t_1 = 2.14 (0.54); p-value < 0.001. OT, oxytocin; $t_{1\text{-}4}$, cue-induced craving paradigm time points; VAS, visual analog scale. *Error bars* = standard error of the mean (SEM).

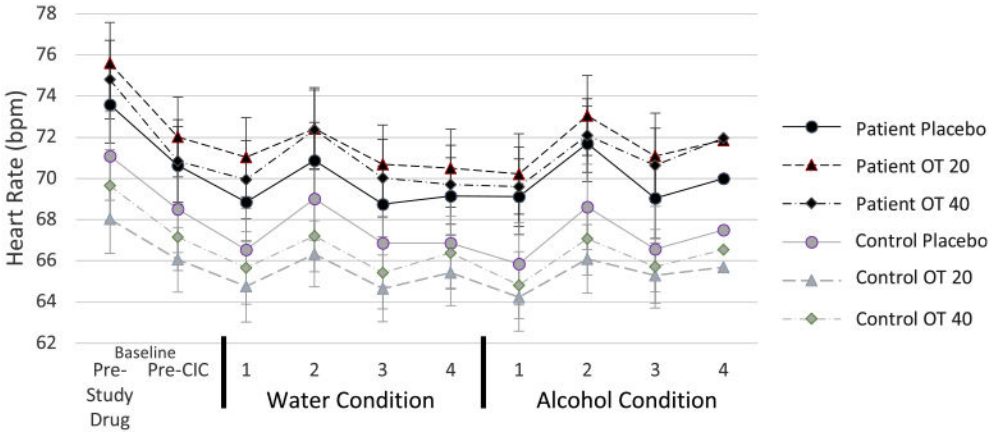

Fig. 3.

Mean HR for patients and controls separated by Treatment condition (placebo, OT 20, OT 40). Baseline (prestudy drug and pre-CIC) is 5-minute resting mean HR. 1 to 4 on the x-axis for the water and alcohol cue exposure correspond to the mean HR for the 1-minute periods recorded immediately after each prompt in the CIC paradigm. *Patient versus control*: prestudy drug baseline, mean (SEM), placebo condition, patient = 73.58 (1.97), control = 71.10 (2.15), *p*-value = 0.43. Mean water cue exposure, patient = 69.41 (1.86), control = 67.32 (1.99), *p*-value = 0.45. Mean alcohol cue exposure, patient = 69.96 (1.86), control = 67.14 (2.03), *p*-value = 0.31. (mean alcohol cue exposure) – (mean water cue exposure), patient = 0.56 (0.26), control = −0.18(0.23), *p*-value = 0.04. bpm, beats per minute; CIC, cue-induced craving; HR, heart rate; OT, oxytocin. *Error bars* = standard error of the mean (SEM).

Table 1.

Timing of Measurements

	Study Period					
			Experimental Sessions (1, 2, 3)			
	Screening	**Allocation**	**Prestudy Drug**	**Pre-CIC**	**Post-CIC Water**	**Post-CIC Alcohol**
Enrollment		X				
Eligibility screen	X					
Informed consent	X					
Drug order allocation		X				
Assessments						
Sociodemographic	X					
AUDIT	X					
SCID-5	X					
CAPS-5	X					
CIWA-Ar	X		X			
Urine toxicology	X		X			
Breath alcohol concentration	X		X			
Cue-induced craving task						
Self-reported craving			X	X	X	X
ECG recording			X	X	X	X

AUDIT, Alcohol Use Disorders Identification Test; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CIC, cue-induced craving; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; ECG, electrocardiogram; SCID-5, Structured Clinical Interview for *DSM-5*.

Table 2.

Demographics and Baseline Characteristics

		Patients (*N* = 47)		Controls (*N* = 37)
Age, years (mean ± SD)		50.6 ± 13.0		48.9 ± 13.9
Education, years (mean ± SD)		14.70 ± 2.51		16.24 ± 2.26
AUDIT (mean ± SD)		17.36 ± 8.15		2.25 ± 2.34
No. of days used alcohol/past 30 days (mean ± SD)		0.55 ± 0.37		0.13 ± 0.23
CAPS-5 severity score (mean ± SD)		34.00 ± 12.31		–
	n	**%**	***n***	**%**
Gender, male	47	100	37	100
Race				
Asian	2	4.3	7	18.9
Black	18	38.3	6	16.2
Hispanic	1	2.1	0	0.0
Native American/Pacific Islander	0	0.0	3	8.1
White	17	36.2	17	46.0
Other	9	19.1	4	10.8
In a relationship	19	40.4	18	48.7
Tobacco smoker	21	44.7	6	16.2
Veteran	33	70.2	6	16.2
Alcohol of choice				
Beer	15	31.9	19	51.4
Malt liquor	9	19.2	2	5.4
Wine	2	4.3	7	19.9
Wine cooler	0	0	2	5.4
Liquor	21	44.7	7	19.9
Urine toxicology, baseline				
THC	17	36.2	7	19.9
Cocaine	12	25.5	0	0.0

AUDIT, Alcohol Use Disorders Identification Test; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; SD, standard deviation; THC, tetrahydrocannabinol.

Table 3.

Linear Mixed-Effect Model Results Table

	Self-Reported Craving				Heart Rate			
	β	**SE**	**95% CI**	***p*-Value**	***β***	**SE**	**95% CI**	***p*-Value**
OT20 IU	0.96	4.06	[−6.99, 8.92]	0.812	−0.46	0.70	[−1.84,0.92]	0.516
OT40 IU	−1.22	4.34	[−9.72, 7.29]	0.779	0.10	0.81	[−1.49,1.68]	0.905
ALC	18.86	2.68	[13.61,24.11]	**<0.001**	0.36	0.14	[0.08, 0.65]	**0.012**
ALC:OT 20 IU	−4.21	4.87	[−13.76,5.35]	0.390	−0.11	0.34	[−0.77, 0.56]	0.755
ALC:OT 40 IU	−5.50	4.85	[−15.01, 4.01]	0.259	−0.44	0.34	[−1.11, 0.24]	0.202
AUDIT	6.34	8.95	[−11.21, 23.88]	0.493	−0.66	0.84	[−2.32, 0.99]	0.436
AUDIT:OT 20	−5.29	10.02	[−24.92, 14.35]	0.609	−0.28	0.95	[−2.15, 1.59]	0.767
AUDIT:OT 40	−1.90	10.76	[−22.99, 19.20]	0.860	0.38	1.13	[−1.83, 2.59]	0.735
CAPS-5	−14.19	10.57	[−34.92, 6.53]	0.196	0.04	0.85	[−1.63, 1.70]	0.966
CAPS-5:OT 20	−5.79	11.65	[−28.62, 17.05]	0.629	−1.45	0.91	[−3.23, 0.34]	0.116
CAPS-5:OT 40	18.94	12.47	[−5.50, 43.37]	0.144	−0.74	1.11	[−2.92, 1.44]	0.509
RA female	16.9	6.02	[5.11,28.70]	**0.005**	−2.36	1.47	[−5.25, 0.52]	0.116

ALC, alcohol cue exposure; AUDIT, Alcohol Use Disorders Identification Test; *β*, fixed-effects estimates; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; *CI*, confidence interval; OT, oxytocin; RA, research assistant; *SE*, standard error; IU, international units.

[a]The bold values indicate $p < 0.05$.