Archival Report

Biological Psychiatry: GOS

Oxytocin Reduces Noradrenergic-Induced Opioid-Like Withdrawal Symptoms in Individuals on Opioid Agonist Therapy

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ABSTRACT

BACKGROUND: Intranasal administration of the neuropeptide oxytocin has been explored as a potential therapeutic agent for substance use disorder including opioid use disorder (OUD).

METHODS: This phase 1, crossover, randomized, double-blind, placebo-controlled trial tested the safety, tolerability, and efficacy of intranasal oxytocin (80 IU) twice a day for 7 days in participants (N = 20) with OUD who were taking an opioid agonist therapy. In the laboratory, participants underwent opioid cue exposure paired with noradrenergic activation produced by yohimbine (32.4 mg) or placebo. Assessments included, 1) subjective response: craving, withdrawal, anxiety, and stress; 2) biomedical markers: hypothalamic-pituitary-adrenal axis response (cortisol) and noradrenergic activation (α-amylase); and 3) safety measures: hemodynamics and adverse event evaluation. Generalized linear model with model-based estimator in the covariance matrix was used, with medication (oxytocin/placebo) and noradrenergic activation (yohimbine/placebo) as within-subject factors.

RESULTS: Oxytocin significantly reduced opioid-like withdrawal, anxiety symptoms, and cortisol levels elicited by cue exposure under noradrenergic activation produced by yohimbine. This effect was specific because oxytocin did not reduce craving, hemodynamics, or α-amylase levels increased by yohimbine administration. A single dose of yohimbine elicited the noradrenergic stimulation, and 7-day oxytocin administration was safe and well tolerated among individuals diagnosed with OUD and taking opioid agonist therapy.

CONCLUSIONS: The findings of this study suggest that oxytocin alleviates opioid-like withdrawal symptoms and anxiety by modulating the hypothalamic-pituitary-adrenal axis.

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Opioid use disorder (OUD) is characterized by continuous use of opioid-class drugs despite adverse effects on physical, mental, and/or social health (1). In 2017, the opioid crisis was declared a public health emergency in the United States (2). In 2018, the National Institutes of Health established the Helping End Addiction Long-term initiative to support research on the prevention and treatment of OUD (3). Addiction researchers have called for a course of action beyond what is currently underway, denoting that federal legislation and allocation of resources have not yet aligned with the urgency of the opioid public health crisis (4). The present study is focused on a novel adjunct pharmacological intervention for OUD and its associated withdrawal syndrome. There are 3 Food and Drug Administration (FDA)–approved pharmacological treatments for OUD: methadone, buprenorphine or buprenorphine/naloxone (transmucosal and subcutaneous depot administration), and naltrexone (oral and intramuscular) (5,6). In addition, opioid antagonists such as naloxone are used acutely to reverse the effects of an opioid overdose (7). The FDA has also recently approved nalmefene as a longer-acting opioid antagonist used to reverse overdose (8). These medications have been recognized for their key role in treating OUD or reversing the effects of an opioid overdose, but expansion of pharmacological strategies has been called for to further enhance treatment options and improve outcomes, specifically for stress-induced triggers (9).

Oxytocin has drawn recent attention for its potential to modulate prosocial cognition and behavior (10). Oxytocin has been linked to stress-induced substance use behaviors, suggesting that it may have efficacy in OUD (11). In clinical research, intranasal (IN) administration of oxytocin is attractive for its ability to deliver substances to the brain and cerebrospinal fluid by circumventing the blood-brain barrier, which would typically block neuropeptides (12). Research also suggests that much of the neural influence of IN oxytocin occurs through its presence in peripheral blood flow, a finding that is elucidated by its effects being diminished when that peripheral channel is blocked (13). Clinical areas of interest for the use of IN oxytocin include schizophrenia (14) and autism spectrum disorder (15), although with only modest improvement in total symptoms for each (16,17). Recent evidence suggests that pairing IN oxytocin with

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mindfulness-based group therapy yields significant improvement of negative symptoms of schizophrenia (diminished emotional range) (18). In substance use disorder (SUD) research, oxytocin has garnered interest for its potential as a therapeutic agent (19,20). Preclinical and clinical models suggest that oxytocin is involved in inhibiting brain regions responsible for the reward signals in addiction (21). It is hypothesized that many SUDs may stem from, and perpetuate, dysregulation of the endogenous oxytocin system and that supplemental doses of oxytocin may help to remedy this (22,23). A randomized controlled trial that examined the administration of oxytocin in patients with alcohol use disorder found a reduction in alcohol cue-related cravings among individuals with anxiety (24). An ongoing randomized controlled trial is testing IN oxytocin in U.S. veterans with alcohol use disorder and posttraumatic stress disorder comorbidity (25).

The noradrenergic system has been identified as crucial in the rewarding effects and stress activation of SUD (26,27). The α_2-antagonist yohimbine stimulates the noradrenergic and sympathetic nervous systems, thereby releasing noradrenaline and inducing stress and anxiety (28). Yohimbine has been used in both preclinical and clinical models to test drug reinstatement and stress-induced craving (29). Its presence also leads to an increase in excretion of α-amylase in saliva, an indirect biomarker of peripheral noradrenergic activation, and coincides with anxiogenic effects (30). Yohimbine (21.6 mg) has a physiological effect on the circulatory system by increasing blood pressure; however, this effect has been reported as moderate (5 mm Hg) when tested in patients with hypertension (31,32). Yohimbine has also been administered orally (32.4 mg) and intravenously (0.4 mg/kg) in patients with OUD taking buprenorphine (33) and methadone (34,35), respectively, with no serious adverse events (AEs) reported. Furthermore, in clinical research, yohimbine has been co-administered with other medications, as well as alcohol, with no clinically relevant AEs being reported (36).

Yohimbine has also been utilized in preclinical models to trigger alcohol reinstatement in ethanol-seeking female rodents, an effect that was attenuated by administering oxytocin both directly to the brain and peripherally to the circulatory system (37). These findings further support the direct brain/peripheral circulatory routes of oxytocin administration. The current study has a concept that is similar to this preclinical model, despite its differences in target substance and species.

The goal of this study was to examine the potential safety, tolerability, and efficacy of oxytocin in reducing yohimbine-induced opioid craving and withdrawal in human subjects with OUD who were taking either buprenorphine or methadone as an opioid agonist therapy (OAT). We hypothesized that under noradrenergic activation by yohimbine, opioid craving and withdrawal symptoms would be reduced in the oxytocin condition compared with the oxytocin-matched placebo condition. The overarching goal of this study was to evaluate a potential adjunct pharmacotherapy to help individuals with OUD maintain their current abstinence, specifically during stressful events that may precipitate opioid craving or withdrawal and induce drug use recurrence.

METHODS AND MATERIALS

Study Design, Setting, and Approval

This was a phase 1, outpatient, randomized, double-blind, crossover (2 × 2 design with oxytocin and yohimbine), placebo-controlled, human laboratory study (Figure 1). The trial took place at the Center for Alcohol and Addiction Studies at Brown University from 2019 to 2023. The clinical protocol was approved by the Brown University Institutional Review Board, received an FDA Investigational New Drug (IND135570 [holder: CLH-K]), and was registered on clinicaltrials.gov (NCT04051619). The study was initiated as a between-subjects design. However, following the COVID-19 pandemic, to speed up recruitment, the study was changed to a within-subjects crossover design. This modification in the clinical protocol was executed following the FDA Guidance Document on Changes or Modification during conduct of Clinical Investigations (38). After receiving approval from the Brown University Institutional Review Board in November 2021, the FDA was notified in an annual progress report and the study design was updated on clinicaltrials.gov in February 2022.

Participants

Inclusion Criteria. Men and women ages 18 to 70 years who met DSM-5 criteria for current OUD and had been taking methadone or buprenorphine/naloxone for at least 3 months were included in the study. Buprenorphine or methadone use was confirmed via urine testing. Individuals also had to be in good physical health as confirmed by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory analysis. Participants were required to have a breath alcohol content = 0.00 g/dL and a negative drug toxicology screen at each session and be willing to take study medications.

Exclusion Criteria. Persons who tested positive for pregnancy or who were unwilling to use medically approved birth control or were breastfeeding were excluded. Individuals who reported a suicide attempt during the last 3 months were excluded, as well as those with another current SUD other than cannabis, nicotine, and caffeine as assessed by urine toxicology and the Mini-International Neuropsychiatric Interview (39). Additional exclusion criteria included the current use of medications that may interact with oxytocin, history of hypersensitivity to study medications, clinically significant electrolyte abnormalities, current rhinitis, or use of vasoconstricting medications or prostaglandins.

Study Drugs, Dose Justification, and Adherence

Intranasal oxytocin in this study was administered as adjunct therapy to the OAT. Studies on schizophrenia (40,41) have suggested that 40 IU and higher of oxytocin could be more efficacious in the treatment of both negative and positive symptoms (42). Oxytocin was administered as 40 IU/0.12 mL nasal spray in each nostril once in the morning and once in the afternoon for 7 days. Placebo consisted of a combination of purified water, sodium chloride 0.065%, disodium phosphate, phenylcarbinol, monosodium phosphate, and benzalkonium

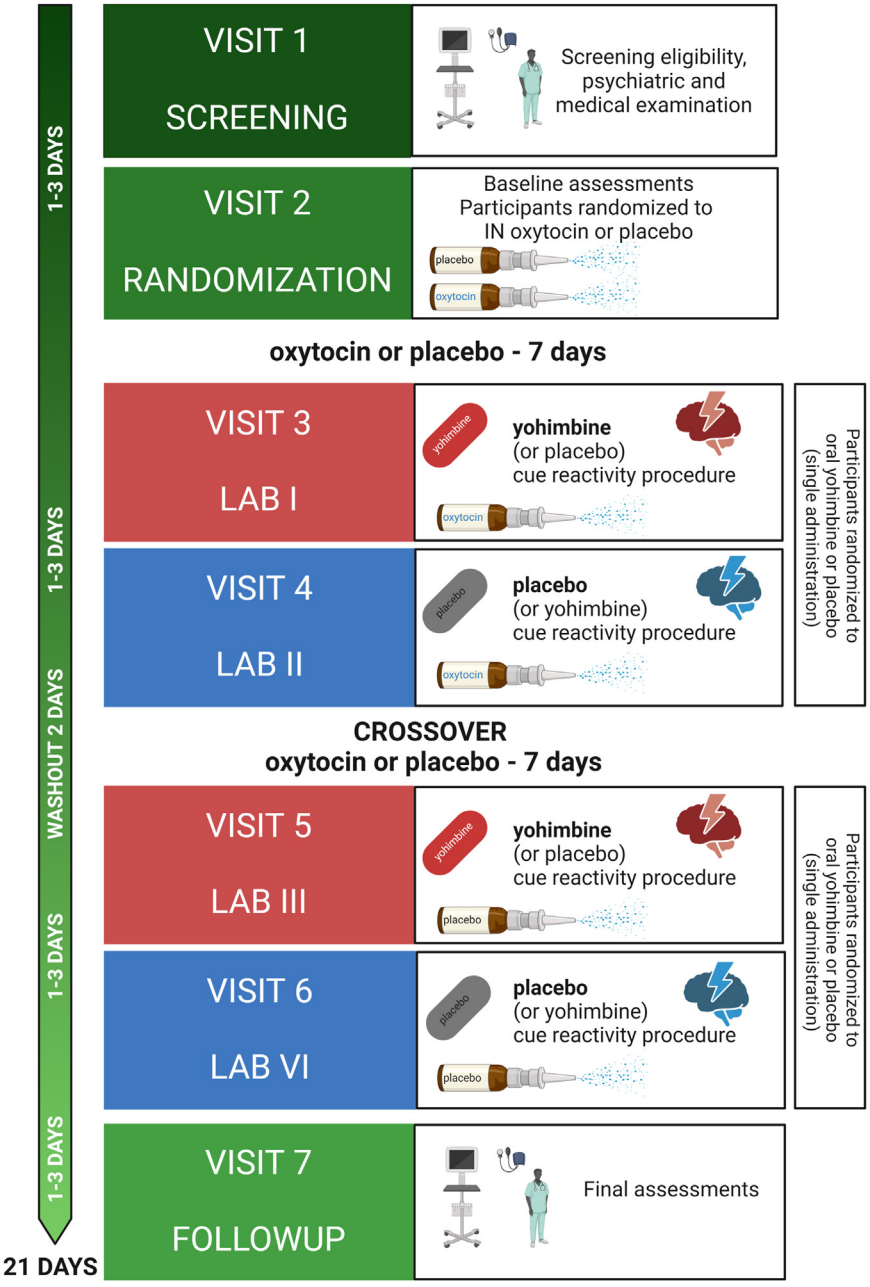

Figure 1. Study design. The figure was created with BioRender. IN, intranasal.

chloride. Participants received a single oral dose of 32.4 mg yohimbine or yohimbine-matched placebo in the laboratory ~45 minutes prior to the cue-exposure procedure, which corresponds to the time it takes yohimbine to reach maximum concentration (t_{max} = 1 hour) (29,43) (Supplemental Methods).

Adherence. Oxytocin and matching placebo bottles were weighed before being distributed at each visit and then reweighed at the subsequent appointments after 5 to 7 days of administration. Yohimbine was administered as a single dose in the laboratory by the research staff (Supplemental Methods).

Study Procedures

Eligible participants were randomized to self-administer IN oxytocin or oxytocin-matched placebo twice a day under double-blinded conditions for 7 days. Between days 5 and 7, participants completed 2 laboratory sessions in which they were randomized to yohimbine or yohimbine-matched placebo (visit 3) and a second laboratory session in which they received the opposite yohimbine condition (visit 4). After a 1-week washout period, participants received the opposite IN oxytocin condition (oxytocin or oxytocin-matched placebo) for another 7 days. Between days 14 and 16, participants

completed 2 additional laboratory sessions where they received yohimbine and yohimbine-matched placebo (randomized, visits 5 and 6). Laboratory sessions were all completed in the mornings or early afternoons to control for fluctuations in cortisol levels. A follow-up (visit 7) was conducted to obtain final assessments. See Figure 1 for study design and Supplemental Methods for a detailed description of each visit.

Statistical Analysis

For all outcomes, we utilized an intention-to-treat approach in which participants were examined based on their a priori randomized protocol and received at least 1 dose of the study medication (oxytocin or oxytocin-matched placebo) (44) (Supplemental Methods).

Outcomes. Primary (craving) and secondary (safety and tolerability) outcomes were assessed in real time in the laboratory. Seven-day oxytocin administration was compared with the oxytocin-matched placebo condition during the cue-exposure procedure, in which noradrenergic activation produced by yohimbine or the yohimbine-matched placebo condition (2×2 design) was measured. We used a generalized linear model with a model-based estimator in the covariance matrix, with medication (oxytocin/placebo) and noradrenergic activation (yohimbine/placebo) as within-subject factors. The model was specified to evaluate the effect of drug (oxytocin/placebo) by noradrenergic (yohimbine/placebo) interaction, the main effect of the drug, and the main effect of noradrenergic activation. Craving was assessed using the Desires for Drug Questionnaire, with time coded as t_0 = relaxation, t_1 = interaction with drug paraphernalia/opioid auditory cues, and t_2 = opioid use video. Safety and tolerability were assessed using systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (vital signs), the Hamilton Anxiety Rating Scale (HAMA), and the State-Trait Anxiety Inventory (STAI) (anxiety). The STAI y1 (state) was included as an additional safety measure for anxiety to ensure that participants were not experiencing acute symptoms of anxiety in the laboratory. The STAI y2 (trait) was inserted as a covariate in the model to control for baseline anxiety level together with stress (Perceived Stress Scale [PSS]), hypothalamic-pituitary-adrenal (HPA) axis activity (cortisol), and noradrenergic response (α-amylase). Time at laboratory sessions was coded as t_0 = baseline, t_{45min} = 45 minutes after yohimbine administration, and t_{90min} = after cue exposure to specifically evaluate the contribution of each laboratory procedure (yohimbine and cue-exposure). Withdrawal symptoms (Clinical Opiate Withdrawal Scale) and AEs were assessed at specific time points: t_0 = prelaboratory and t_1 = postlaboratory procedures.

RESULTS

Participant Characteristics, Retention, and Integrity of the Blinding Measures

The CONSORT (Consolidated Standards of Reporting Trials) diagram is depicted in Figure 2, and participants' sociodemographic and clinical characteristics at screening are reported in Table 1. Seventy-eight participants were screened

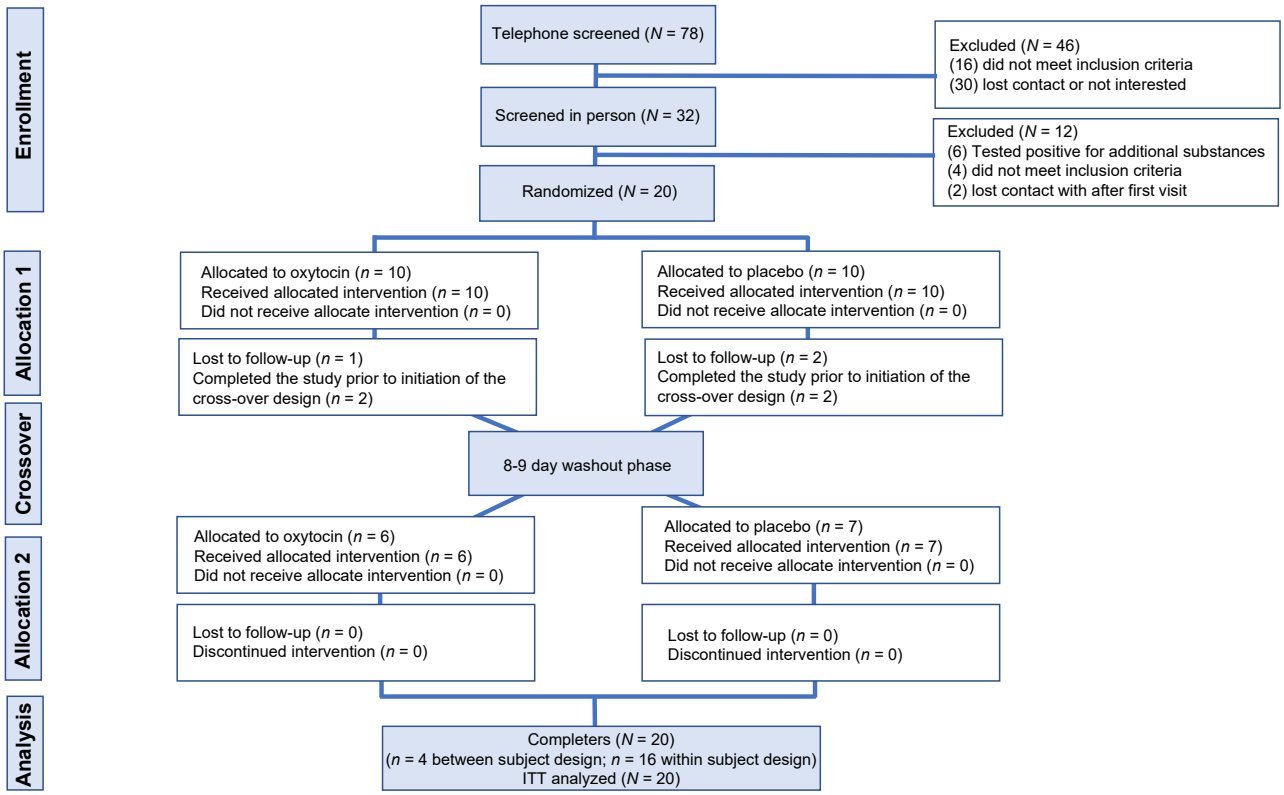

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram. ITT, intention to treat.

Table 1. Sociodemographic and Clinical Characteristics of Study Participants at Screening (*n* = 20)

Variable	Mean (SD) or *n* (%)
Sociodemographic	
Sex, Male	14 (70%)
Age, Years	49.60 (11.65)
Race	
Black or multiracial	4 (20%)
Caucasian	16 (80%)
Ethnicity, Hispanic/Latino	1 (5%)
Education	
Some high school	1 (5%)
High school graduate	8 (40%)
Some college/2-year degree	11 (55%)
Marital Status	
In a relationship (married, partnered, etc.)	6 (30%)
Not in a relationship (single, never married, etc.)	14 (70%)
Employment Status	
Working (full or part time)	5 (25%)
Not working (retired, disabled, unemployed)	15 (75%)
Healthcare Coverage, Yes	20 (100%)
Medical	
Systolic Blood Pressure, mm Hg	124.61 (14.76)
Diastolic Blood Pressure, mm Hg	77.50 (8.91)
Heart Rate, Beats/Minute	75.28 (15.08)
Alanine Transaminase	27.30 (20.98)
Aspartate Transaminase	29.50 (19.79)
Blood Urea Nitrogen	11.45 (2.96)
Bilirubin	0.445 (0.320)
Creatinine	0.767 (0.197)
Estimated Glomerular Filtration Rate	109.9 (12.77)
Substance Use	
ORT	
Methadone (dose: 70–110 mg/mL)	6 (30%)
Buprenorphine/naloxone (dose: 8 mg/2 mg–24 mg/6 mg)	14 (70%)
COWS	0.90 (1.4)
OCS	5.1 (5.48)
Other Substance Use in the Past Month	
Alcohol	4 (20%)
Cannabis	6 (30%)
Tobacco	15 (75%)
Psychiatric	
HAMA	4.10 (4.2)
HAMD	1.84 (2.27)
STAI-State	37.33 (11.23)
STAI-Trait	40.63 (10.59)
PSS	5.70 (3.33)
BTQ	19 (95%)
Diagnosed Comorbidities	
Mood disorder	16 (80%)
Anxiety disorder	15 (75%)
Schizophrenia	1 (5%)
ADHD	4 (20%)

on the telephone, 32 were screened in person, 20 were randomized, and 20 completed the study and were included in the intention-to-treat analysis. Four participants completed the study as a between-subject design with the administration of oxytocin (n = 2) or placebo (n = 2) condition. Sixteen participants completed the study in a crossover design with the administration of both oxytocin and the matching placebo condition. Yohimbine has been shown to increase blood pressure (29,36); therefore, for safety reasons, after consulting with the study physician, we did not administer yohimbine to 4 participants who had a history of cardiovascular events (current hypertension [n = 3] and stroke [n = 1]). Those participants received both oxytocin and oxytocin-placebo conditions and underwent the cue exposure. Data from those 4 single-blinded participants were pooled in the yohimbine-placebo condition. Results were evaluated with and without individuals who did not receive the placebo-controlled yohimbine condition.

Medication Profile. Of the 20 participants, 14 were receiving sublingual buprenorphine (or buprenorphine/naloxone), and 6 were receiving oral methadone treatment for OUD. A list of participants' prescription medications is reported in Supplemental Results (Table S1). Participants (n = 1) who were taking clonidine were asked to hold their dose prior to the laboratory procedures to avoid reducing the yohimbine effect. Participants who were taking stimulants (n = 2) were asked to hold their dose prior to the laboratory procedures to avoid overactivation by yohimbine.

Integrity of the Blinding Measures. Overall, the clinical staff, research staff, and participants were unable to differentiate the oxytocin from the oxytocin matching–placebo condition. However, they were able to correctly differentiate the yohimbine condition from the yohimbine matching–placebo condition in 90% of cases, mostly due to increases in blood pressure, sweating, and nervousness (Supplemental Results).

Outcomes Measured in Real Time in the Laboratory

All outcomes were measured in the laboratory in real time, testing oxytocin, compared with the oxytocin-matched placebo condition, during the cue-exposure procedure under the noradrenergic activation produced by yohimbine or the yohimbine-matched placebo condition (Figure 3). Effect sizes reported as Cohen's d are included in Supplemental Results (Table S2A).

Primary Outcome: Opioid Craving. For opioid craving, there was no interaction or main effect for either oxytocin or yohimbine ($ps > .05$) (Figure 3A). There was also no interaction or main effect for oxytocin or yohimbine ($ps > .05$) on the Desires for Drug Questionnaire subscale, which measures

ADHD, attention-deficit/hyperactivity disorder; BTQ, Brief Traumatic Questionnaire; COWS, Clinical Opiate Withdrawal Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; OCS, Opioid Craving Scale; ORT, opioid replacement therapy; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.

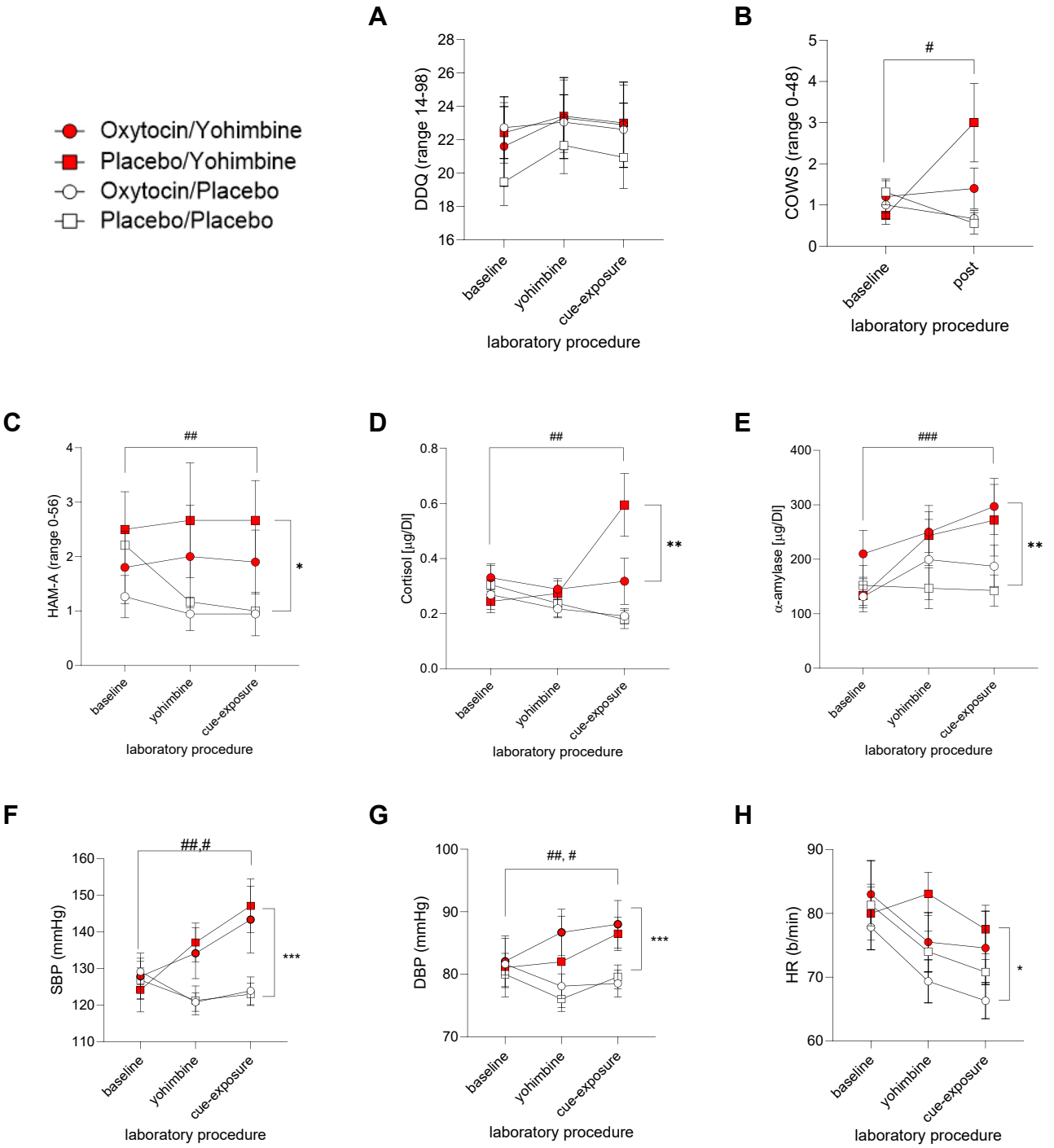

Figure 3. Effect of oxytocin and yohimbine during the laboratory procedures. **(A)** Desires for Drug Questionnaire (DDQ): There was no interaction or main effect for either oxytocin or yohimbine (*p*s $>$ .05). **(B)** Clinical Opiate Withdrawal Scale (COWS): There was an oxytocin $\times$ yohimbine interaction (B_1 = 0.929, p = .035), no main effect of oxytocin (p $>$ .05), but a significant main effect of yohimbine (B_1 = 0.813, p = .011). **(C)** Hamilton Anxiety Rating Scale (HAMA): There was an oxytocin $\times$ yohimbine interaction (B_1 = 0.945, p = .038). There was no main effect of oxytocin (p $>$ .05), but there was a main effect of yohimbine (B_1 = 0.846, p = .011). **(D)** Cortisol: There was an oxytocin $\times$ yohimbine interaction in which cortisol was significantly increased (B_1 = 0.131, p = .005) when paired with an oxytocin-matching placebo. There was also a main effect of yohimbine (B_1 = 0.106, p = .002), but no main effect of oxytocin (p $>$ .05). **(E)** α-amylase: There was an oxytocin $\times$ yohimbine interaction (oxytocin: B_1 = 96.093, p = .003; placebo: B_1 = 69.169, p = .021). There was a main effect of yohimbine (p $<$ .001), but no main effect of oxytocin (p $>$ .05). **(F)** Systolic blood pressure (SBP): There was an oxytocin $\times$ yohimbine interaction (oxytocin: B_1 = 10.928, p = .011; placebo: B_1 = 12.328, p = .003). There was no main effect of oxytocin (p $>$ .05), but there was a main effect of yohimbine (B_1 = 10.948, p $<$ .001). **(G)** Diastolic blood pressure (DBP): There was an oxytocin $\times$ yohimbine interaction (oxytocin: B_1 = 6.967, p = .006). There was no main effect of oxytocin (p $>$ .05), but there was a main effect of yohimbine (B_1 = 5.260, p = .003). **(H)** Heart rate (HR): There was no oxytocin $\times$ yohimbine interaction (p $>$ .05). There was no main effect of oxytocin (p $>$ .05), but there was a main effect of yohimbine (B_1 = 4.762, p = .035). All data presented as mean $\pm$ SEM. $^{*}p$ (main effect), $^{\#}p$ (interaction). All Cohen's *d*s are reported in Table S2A.

desire and intention, negative reinforcement, and control ($ps > .05$).

Secondary Outcome: Opioid Withdrawal. For opioid withdrawal as measured by the Clinical Opiate Withdrawal Scale, there was an oxytocin by yohimbine interaction (B_1 = 0.929, p = .035), with a significant increase of withdrawal symptoms only in the oxytocin-matched placebo with yohimbine condition, suggesting that under the adrenergic stimulation conditions produced by yohimbine, oxytocin was able to reduce opioid-like withdrawal symptoms. There was no main effect of oxytocin ($p > .05$), but there was a significant main effect of yohimbine (B_1 = 0.813, p = .011), with a significant increase of withdrawal symptoms only in the yohimbine condition (Figure 3B).

Secondary Outcome: Anxiety, Stress, and AEs. For the HAMA, there was an oxytocin × yohimbine interaction (B_1 = 0.946, p = .038) suggesting that under adrenergic activation, there was an increase in HAMA scores only in the oxytocin-matched placebo condition. There was no main effect of oxytocin ($ps > .05$), but there was a main effect for yohimbine (B_1 = 0.846; p = .011), with an increase in HAMA scores only in the yohimbine condition (Figure 3C). For the STAI y2 (with STAI y1 inserted as a covariate) and PSS, there were no interactions or main effects for oxytocin or yohimbine ($ps > .05$).

Due to noradrenergic stimulation produced by yohimbine, nonserious AEs occurred in the yohimbine condition at the expected frequency and severity (Supplemental Results and Table S3). The most common nonserious AEs experienced were trembling and nervousness (n = 11) and sweating (n = 10) ($ps < .001$).

Secondary Outcome: Salivary Cortisol and α-Amylase. For cortisol, there was an oxytocin × yohimbine interaction (B_1 = 0.131, p = .005) showing that under adrenergic activation, there was a significant increase of cortisol level only in the oxytocin-matched placebo condition. There was no main effect of oxytocin ($p > .05$), but there was a main effect of yohimbine (B_1 = 0.106, p = .002), with a significant increase in cortisol level only in the yohimbine condition (Figure 3D).

For α-amylase, there was an oxytocin × yohimbine interaction (oxytocin: B_1 = 96.093, p = .003; placebo: B_1 = 69.169, p = .021). There was no main effect of oxytocin ($p > .05$); however, there was a main effect for yohimbine (B_1 = 87.750, $p < .001$) wherein, as expected, α-amylase level was significantly increased only in the yohimbine condition (Figure 3E).

Secondary Outcome: Hemodynamics. For SBP, there was an oxytocin × yohimbine interaction (oxytocin: B_1 = 10.928, p = .011; placebo: B_1 = 12.328, p = .003) showing that under adrenergic activation, there was a significant increase in SBP in both the oxytocin and the oxytocin-matched placebo condition. There was no main effect of oxytocin ($p > .05$), but there was a main effect of yohimbine (B_1 = 10.948, $p < .001$), with a significant increase of SBP only in the yohimbine condition (Figure 3F).

For DBP, there was an oxytocin × yohimbine interaction (oxytocin: B_1 = 6.967, p = .006) suggesting that under adrenergic activation, there was a significant increase in DBP in the oxytocin condition. There was no main effect of oxytocin ($p > .05$), but there was a main effect of yohimbine (B_1 = 5.260, p = .003), with a significant increase of DBP only in the yohimbine condition (Figure 3G).

For heart rate, there was no oxytocin × yohimbine interaction ($p > .05$) and no main effect of oxytocin ($p > .05$), but there was a main effect of yohimbine (B_1 = 4.762, p = .035), with a significant decrease of heart rate only in the placebo condition (Figure 3H).

Outcomes Measured Retrospectively in the Ecological Environment

During the 7-day administration of IN oxytocin or oxytocin-matched placebo in an outpatient setting, there was a significant reduction in depression scores (Hamilton Depression Rating Scale) in the IN oxytocin condition compared with the oxytocin-matched placebo condition ($F_{1,58}$ = 5.955, p = .018) (Figure 4). Effect sizes are reported as Cohen's d in Supplemental Results (Table S2B).

We did not observe serious AEs related to the study drugs. Nonserious AEs occurred in both conditions ($p > .05$) at an expected frequency and severity (Supplemental Results and Table S4).

DISCUSSION

Contrary to our hypothesis, oxytocin did not reduce opioid craving under noradrenergic stimulation produced by yohimbine paired with a cue-exposure procedure in the laboratory. Necessary context to this result lies in a 2-fold failure to manipulate craving in the first place. First, the opioid cue-exposure, in the yohimbine and placebo conditions, was ineffective at increasing craving and therefore not a sensitive enough mechanism to evaluate its potential reduction. Second, the yohimbine adrenergic effects may have been more imitative of opioid-like withdrawal symptoms than of stress-related craving.

In this study, we found that under noradrenergic stimulation produced by yohimbine and paired with a cue-exposure procedure in the laboratory, oxytocin reduced opioid-like withdrawal symptoms among individuals with OUD who were on OAT. However, this finding must be considered together with Desires for Drug Questionnaire data, which indicates that the cue exposure did not significantly increase opioid craving in any condition. Throughout, oxytocin's effect remained very low and should be interpreted as the absence of withdrawal (not clinically meaningful) because the mean score fell below the standard threshold for mild withdrawal (45). Oxytocin's effect in these findings was associated with reduction of salivary cortisol levels, but not α-amylase levels, suggesting that this effect in the oxytocin condition, when co-administered with yohimbine, may be a result of regulation of the HPA axis. It should be noted that the lack of α-amylase response may be induced by salivary dysfunction (e.g., xerostomia) created by opioid medications (46). Our data showed that abnormalities of the HPA axis (35) and of

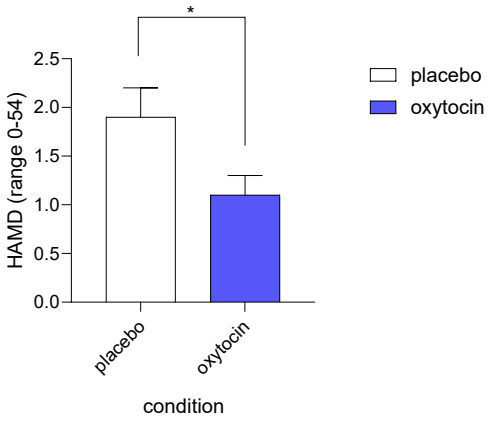

Figure 4. Hamilton Depression Rating Scale (HAMD) score after 5 to 7 days of oxytocin administration. There was a significant reduction in the depression score (HAMD) between intranasal oxytocin compared with oxytocin-matched placebo ($F_{1,58} = 5.955$, $p = .018$). Cohen's *d*s are reported in Table S2B. *$p < .05$.

noradrenergic mediated stress responses, induced by yohimbine, persist in opioid agonist maintenance (47). However, oxytocin was able to regulate this response created by the yohimbine noradrenergic activation.

Yohimbine was utilized to probe the feed-forward loop between projections connecting the noradrenergic/corticotropin-releasing factor–containing neurons, the locus coeruleus, and the paraventricular nucleus of the hypothalamus (Figure 5). In the paraventricular nucleus of the hypothalamus, oxytocin-synthesizing neurons project to amygdala-modulated emotional functions at the limbic level (48). Therefore, oxytocin may replace avoidance or fear with positive emotional states in settings that help to promote this replacement, similar to its attenuation of negative symptoms of schizophrenia when paired with mindfulness-based interventions (18,49).

Oxytocin was also able to significantly reduce anxiety scores (HAMA), supporting the hypothesis that craving and anxiety may have a common mechanism in individuals with OUD (50). However, this effect did not extend to other anxiety (STAI) or stress (PSS) measures. This specificity resulted because there are more autonomic symptom questions in the HAMA than in the STAI or PSS.

Despite the wide range of topics being explored with IN oxytocin intervention (51), the exact mechanisms by which the effects occur are not fully understood (52). Differing theoretical formulations have been put forward that suggest that oxytocin is a prosocial stimulator, a reducer of stress, and/or a conflict resolution–oriented peptide, which together suggest the hypothesis that oxytocin is context dependent depending on social salience (53). In accordance with this gap in understanding, the surge of oxytocin research has been criticized as somewhat premature (54). Taken together, criticisms of oxytocin research have led to more rigorous methodological practices, an evolution that includes the curbing of publication biases so that null or contrary findings are reported and explored (51).

Extensive review of pharmacodynamic evidence suggests that of the large amounts of oxytocin administered in experimental trials, very little actually reaches the brain and cerebrospinal fluid (55). Whether that breakthrough amount is clinically significant is still in question. The current study is limited by its lack of use of differing methods to alter monitor concentrations of oxytocin levels between the central and peripheral nervous systems, which is a method being adopted in other studies (56). A greater understanding of the mechanism by which the effects of oxytocin observed in the current study occurred and whether it was via the brain and cerebrospinal fluid would be garnered by considering the role of these peripheral channels. Dose implementation and sex differences are additional emerging avenues under exploration for their confounding effects (57,58). Furthermore, following recent

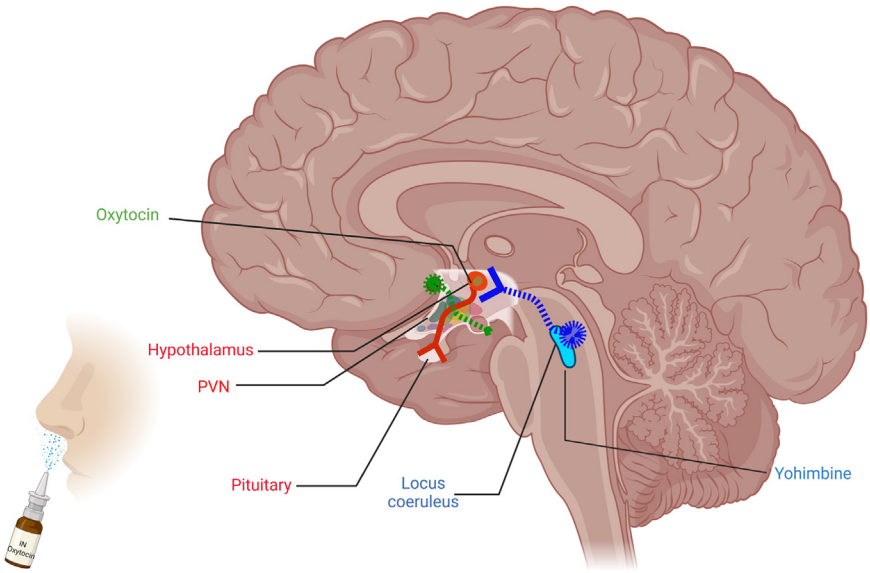

Figure 5. Schematic representation of the effects of intranasal (IN) oxytocin administration during noradrenergic activation produced by yohimbine. Yohimbine was utilized to probe the feed-forward loop between projections connecting the noradrenergic/corticotropin-releasing factor (CRF)–containing neurons, the locus coeruleus, and the paraventricular nucleus of the hypothalamus (PVN) (blue dotted line) that release CRF in the pituitary (orange solid line). Similar to CRF, oxytocin is in part synthesized in the PVN and may be coreleased with CRF as an adaptive response to a variety of challenges or stressors. In the PVN, oxytocin-synthesizing neurons project to amygdala-modulated emotional functions at the limbic level (green dotted line).

findings on the role of peripheral blood channels for oxytocin's effects, an oromucosal avenue of administration for oxytocin is under consideration via the use of oxytocin-based lollipops (59). This form of administration has been touted for its comparable efficacy to IN administration but with greater appeal in pediatric or geriatric populations.

The dose of yohimbine (32.4 mg) used in the current study elicited a noticeable adrenergic response that was nonetheless moderate and consistent with other studies in which yohimbine was administered at 10 mg (60) and 21.6 mg (31,32) doses. Consistent with previous research, additional effects reported by participants included nervousness, tremors, and cold sweats (61). We did not observe serious AEs. Nonserious AEs were encountered at similar frequencies in both the oxytocin and oxytocin-matched placebo conditions. Together, the results of this study support the safety of oxytocin when co-administered with yohimbine in individuals with OUD.

Anxiety and depressive disorders have rarely been investigated in the oxytocin literature (62). In the naturalistic condition of our study, 7-day administration of IN oxytocin led to a reduction in overall depression symptoms. Our results are consistent with the few studies that have explored the effects of oxytocin on depression symptoms in mothers with postpartum depression (63) and in patients with posttraumatic stress disorder (64). In those studies, no overall effect of repeated oxytocin administration was observed, but exploratory analyses revealed some oxytocin intervention differences in their samples' subgroups depending on mood levels and posttraumatic stress disorder severity (63,64).

There are strengths and limitations of measuring opioid craving in a laboratory setting (65,66). The biggest strength of our laboratory setting was environmental control. In the laboratory, we were able to ensure the safety of participants while they underwent procedures that may elicit craving or stress. Despite the ability to control the laboratory environment, there are limitations inherent to attempting to probe and measure opioid craving in this setting. This study utilized a guided opioid visualization technique, the presence of drug paraphernalia, and an opioid-related video cue. These cues were broad, and different aspects of them may have proved significant to participants at different times. However, this method did not personalize opioid cues for each participant to increase their salience, which should be done in future studies. As stated above, even when cues were paired to the noradrenergic effect produced by yohimbine administration, the opioid cue exposure was ineffective at increasing craving. While this is a laboratory procedure limitation, it may also further support the use of OAT for craving management.

Another limitation is this study's small sample size. The effect of oxytocin on craving, withdrawal, anxiety, HPA axis, noradrenergic activation, and hemodynamics resulted in Cohen's *d* values in the low to medium range. There were also limitations in the consideration of sex as a biological variable. This limitation was in part due to the lack of balance between male and female participants, and the few women enrolled in the study were not tested for estrogen levels. Neural and behavioral responses have been shown to differ between sexes due in part to hormonal differences, and future research should take this into consideration through hormone testing (67). Future studies may also benefit by comparing OAT type (methadone vs. buprenorphine/naloxone) and doses. Another limitation of this study is that OAT dose was not measured. However, participants were confirmed to be taking an OAT using urine testing for methadone or buprenorphine.

Conclusions

Intranasal oxytocin, administered after yohimbine-induced noradrenergic stimulation paired to a cue-exposure, effectively reduced opioid-like withdrawal symptoms in individuals with OUD undergoing OAT. This reduction was linked to a decrease in salivary cortisol levels, but not α-amylase levels, suggesting a regulatory effect on the HPA axis. Despite not significantly affecting opioid craving, IN oxytocin demonstrated efficacy in reducing anxiety and opioid-like withdrawal symptoms, thus supporting its potential as an adjunct therapy for OUD.

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The data that support the findings of this study are available from the corresponding author upon request.

CLH-K received mifepristone and matching placebo for another trial and travel support to present the data at the Corcept Therapeutic Conference (September 2022), and she holds 2 patents for the development of negative allosteric modulators that target the stress system. CLH-K and EFM-K hold one patent application on the development of a compound for noradrenergic blockade. All are unrelated to this work. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Oxytocin to Reduce Stress-induced Craving in Individuals With Opioid Use Disorder; https://clinicaltrials.gov/study/NCT04051619?cond=NCT04051619&rank=1; NCT04051619.

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