Results of a Randomized Controlled Trial Examining the Efficacy of Intranasal Oxytocin to Enhance Alcohol Behavioral Couple Therapy

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Abstract

Objective: This study examined the efficacy of intranasal oxytocin (40 IU), compared to matching placebo (saline), when combined with Alcohol Behavioral Couple Therapy (ABCT) for the treatment of alcohol use disorder (AUD).

Methods: This 12-week clinical trial (2018–2024) utilized a double-blind, randomized, placebo-controlled design. Enrollment occurred from May 2019 to April 2023. Participants were romantic couples (N = 96 dyads; n = 49 oxytocin, n = 47 placebo) consisting of an identified patient (IP) with current AUD per *DSM-5* and their partner. Dyads in which both partners had AUD were eligible, and both partners in each dyad were randomized to the same drug condition (ie, placebo or oxytocin). Participants were observed in their medication self-administration 30 minutes prior to ABCT therapy sessions. Primary outcome measures were alcohol consumption (percent days drinking and percent days heavy drinking; Time Line Follow-Back) and relationship functioning (Dyadic Adjustment Scale-Short Form).

Results: All IPs and 50% of partners met diagnostic criteria for AUD; 62 IPs (64.5%) met criteria for severe AUD. Findings from the intent-to-treat analyses indicate that IPs and partners in both conditions evidenced substantial improvements in alcohol consumption and alcohol problem severity but not relationship functioning. No group differences emerged in alcohol consumption, alcohol problem severity, or relationship functioning at end of treatment. Participants completed an average of 10.2 ABCT sessions (SD = 3.5). There were no group differences in the number of medication doses administered or adverse events.

Conclusions: Oxytocin was safe and tolerable but did not provide additional benefit beyond ABCT at the end of treatment. Alternative strategies are necessary to understand oxytocin's potential to facilitate different domains of AUD recovery.

Trial Registration: ClinicalTrials.gov identifier: NCT03046836.

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Despite persistent efforts, identifying new medications for alcohol use disorder (AUD) continues to challenge the field. Oxytocin is a neuropeptide approved by the US Food and Drug Administration (FDA) to facilitate childbirth and lactation via intravenous administration. In the field of psychiatry, intranasal oxytocin is best known for its anxiolytic effects and positive effects on social cognition and behavior, which have primarily been examined in normative samples. For example, oxytocin has been shown to exert prosocial properties such as trust, empathy, social memory, affect recognition, and generosity in some studies.[1,2] A smaller literature has examined oxytocin's effects on social cognition and behavior among romantic couples; however, this literature has yielded mixed findings.[3–6] Recent literature also suggests that oxytocin is a promising candidate to treat AUD through both behavioral and neurobiological pathways[7]; preclinical and preliminary clinical studies indicate that alcohol misuse disrupts the oxytocinergic system, and conversely, exogenous administration has the potential to reduce alcohol withdrawal, tolerance, craving and self-administration.[8–12]

Despite much enthusiasm, intranasal oxytocin's effects on both social and addictive behaviors in clinical

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We encourage authors to submit papers for consideration as part of our Focus on Psychotherapy section. Please contact John C. Markowitz, MD, at psychiatrist.com/contact/markowitz, or Rachel C. Vanderkruik, PhD, at psychiatrist.com/contact/vanderkruik.

Clinical Points

- Oxytocin has garnered much interest in the addictions and mental health fields as a potential avenue to enhance behavioral treatment outcomes.
- It may be particularly well suited to augment dyadic interventions due to its prosocial effects.
- When paired with 12 sessions of Alcohol Behavioral Couple Therapy, oxytocin did not outperform placebo in alcohol consumption, problem severity, or relationship functioning outcomes.

studies are inconsistent and impacted by various methodological differences emerging in this rapidly proliferating literature. An appealing but perplexing aspect of this investigational medication, which has a brief half-life of 2–4 hours and very few safety contraindications, is that it lends itself to a wide variety of clinical applications, dosing strategies, and experimental designs. Factors such as small sample sizes, underpowered and exploratory designs, measurement inconsistencies in laboratory versus naturalistic trials, and wide variability in dosing potency and strategy have all shaped the complexity of the clinical oxytocin literature to date.[13–15]

In addition to methodological differences, individual and contextual differences influence oxytocin's effects on social cognition and behavior. These nuanced and occasionally iatrogenic findings are often explained by the social salience hypothesis,[16] which proposes that oxytocin is more likely to amplify one's existing social tendencies rather than selectively enhancing prosocial or adaptive cognition and behavior. Romantic relationship functioning is closely related to AUD etiology, course, and treatment,[17] and dyadic interventions that engage both partners concurrently have demonstrated outstanding efficacy, including when rigorously compared to individual treatment modalities.[18] Thus, anchoring oxytocin administration within a behavioral treatment modality that incorporates the relational system in which AUD occurs (ie, an evidence-based couple therapy) and teaches adaptive relationship skills might help overcome these persistent confounds. Although other trials examining the ability of oxytocin to enhance behavioral treatment outcomes are underway, no prior trials have examined the efficacy of oxytocin versus placebo in combination with any behavioral AUD treatment, and none have done so with couples. To our knowledge, this is also the first trial examining a medication to both partners within a couple in order to treat AUD. Only 3 published studies to our knowledge have examined a simultaneous treatment approach: 1 for the treatment of adults with schizophrenia with null findings[19] and 2 preliminary pilot studies for the treatment of PTSD with positive findings.[20,21]

Alcohol Behavioral Couple Therapy (ABCT)[22] is a conjoint evidence-based cognitive behavioral treatment. Because ABCT concurrently addresses AUD and relationship functioning, it is an ideal platform with which to rigorously examine whether oxytocin can enhance the positive gains typically made during treatment. Thus, the objective of this clinical trial was to compare the efficacy of ABCT combined with intranasal oxytocin (40 IU) vs matching placebo (saline) self-administered by both members of a couple prior to each therapy session. A priori hypotheses were that identified patients (IPs) in the ABCT + oxytocin group would demonstrate greater reduction in alcohol consumption and greater improvement in relationship functioning at the end of the treatment phase compared to the ABCT + placebo group.

METHODS

Procedures

This clinical trial was pre-registered (NCT03046836; https://clinicaltrials.gov/study/NCT03046836). All study procedures were IRB-approved, and oxytocin was FDA-approved for investigational use in this project. Enrollment occurred from May 2019 to April 2023. A randomized, double-blind, placebo-controlled, and repeated measures design was used. All participants enrolled after March 17, 2020 (n = 74 couples), completed the project via telehealth because of the global COVID-19 pandemic. Participants were recruited through internet advertisements, clinician referrals, and flyers. Following preliminary eligibility screening, IPs and partners completed private written informed consent and a baseline assessment separately for privacy. The baseline assessment included a history and physical (H&P) exam and a battery of standardized self-report and interview measures. Telehealth participants who had no other exclusions based upon their health history did not complete an in-person H&P examination but were required to submit blood pressure and pulse values as a prerequisite to qualifying for the study. For participants of childbearing potential, confirmation of negative pregnancy test was required at baseline and prior to every medication administration. Participants were remunerated for each study visit for a total possible $1,125 paid by Greenphire ClinCard. Additional details were described previously.[23]

Participants

Participants were 96 adult romantic couples (total N = 192 unique participants, 51% women) in which at least 1 partner met diagnostic criteria for AUD in the past 6 months (assessed by the QuickSCID[24]). Participants of any gender identity or sexual orientation were included. Couples were required to have been in their current relationship for at least 6 months.

Participants who were taking psychotropic medications were required to be on a stable dose for 4 weeks before enrolling. Participants were excluded if they met diagnostic criteria for psychotic or bipolar disorder; reported suicidal or homicidal ideation that would prevent them from participating safely; reported severe and unilateral intimate partner violence as defined by the Revised Conflict Tactics Scale (CTS-2[25]); were pregnant or breastfeeding; reported acute alcohol withdrawal determined by a score of ≥10 on the revised Clinician Institute Withdrawal Assessment of Alcohol[26]; or reported any unstable or serious medical condition preventing safe participation as determined by the study medical clinician (eg, seizures and/or a seizure disorder, cardiac arrhythmia, congestive heart failure, diabetes insipidus, significant head trauma or traumatic brain injury, or recent or current cancer diagnosis). See Figure 1 for the CONSORT diagram.

Measures

Both partners in each dyad completed identical assessments at every study time point. This study used a single-reporter approach wherein each individual participant reported on their own behavior. The primary outcome measures were alcohol consumption (percent drinking days and percent heavy drinking days) assessed by the Time Line Follow-Back (TLFB[27]) and relationship functioning assessed by the Dyadic Adjustment Scale-Short Form (DAS-7[28]). Heavy drinking was defined in a sex-specific manner (ie, ≥4 standard drinks for women or ≥5 for men). The TLFB is a semistructured clinical interview that uses calendar prompts to stimulate recall. The DAS-7 assesses 4 domains of relationship functioning (satisfaction, intimacy, affective expression, agreement on matters of importance) and has demonstrated strong psychometric properties.[28] Higher scores are indicative of better relationship functioning. Both the TLFB and DAS-7 were administered at baseline (TLFB covered 60 days prior to study entry), weekly during the treatment phase, and at follow-up visits. Additionally, the Alcohol Use Disorder Identification Test (AUDIT[29]) was administered to assess alcohol problem severity and to stratify randomization. The AUDIT is a 10 item self-report survey, with total scores of 15 or higher indicating moderate to severe AUD. Secondary measures used to characterize the sample include sociodemographic characteristics, the quality of the therapist-participant relationship using the Helping Alliance Questionnaire,[30] intimate partner violence (CTS-2[25]), Penn Alcohol Craving Scale,[31] and the Stages of Change Readiness and Treatment Eagerness Scale.[32]

Study Medication, Dosage, and Administration

Couples were randomized in a 1:1 manner to the oxytocin or placebo condition, stratified by sex and alcohol problem severity of the IP (assessed by the AUDIT[29]). All investigators, participants, and study staff were blind to drug condition. A 40 IU dose of intranasal oxytocin or matching placebo (saline) was self-administered 30 minutes prior to the start of each ABCT therapy session. Medication and placebo were compounded and dispensed by a local research pharmacy. Research staff instructed participants on the correct method of administration and observed participants' self-administration in person or via videoconference for sessions conducted by telehealth. Randomization was carried out by a research pharmacist not involved in clinical management of participants to preserve the double-blind design.

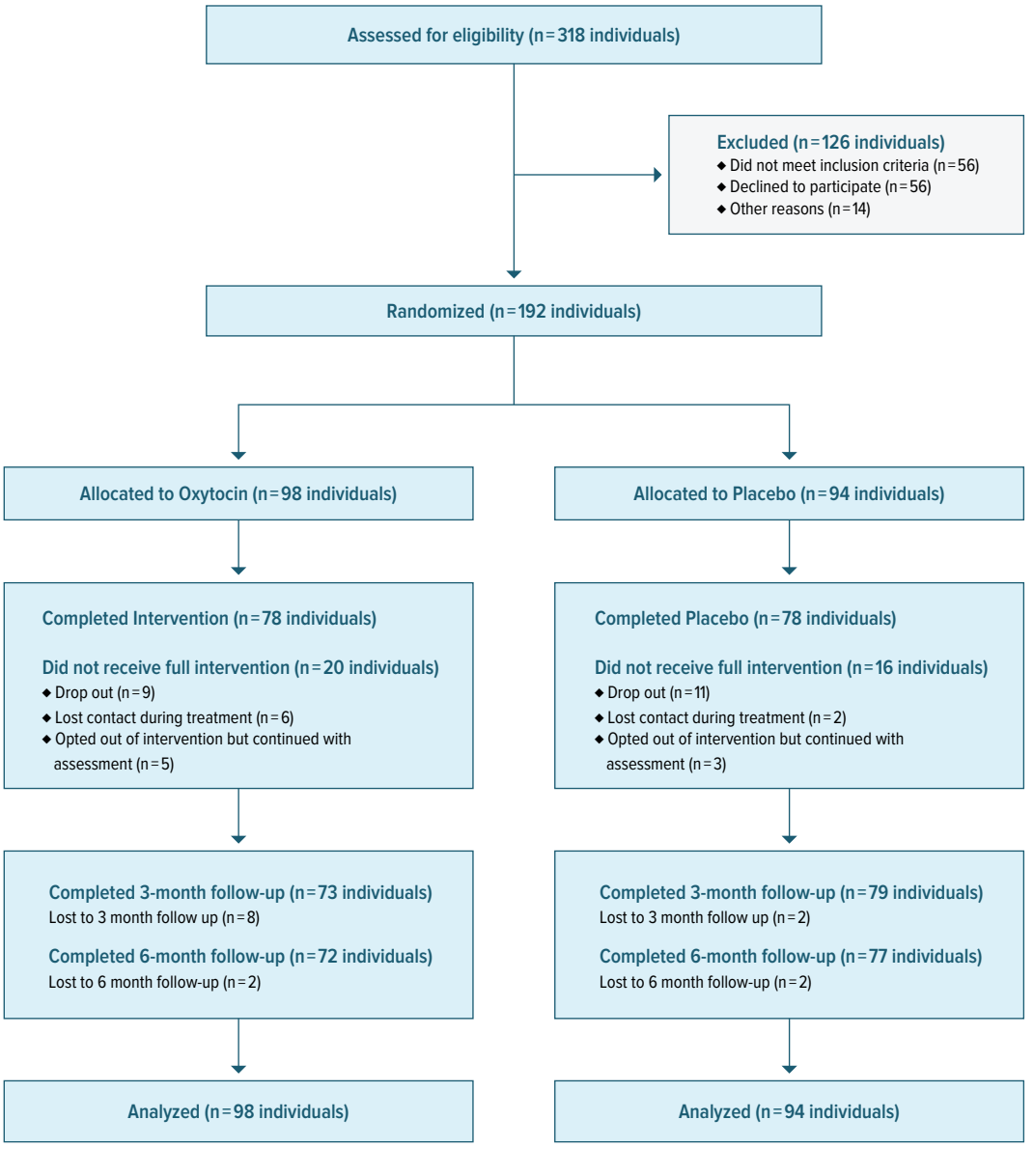
Alcohol Behavioral Couple Therapy (ABCT)

ABCT therapy sessions were delivered by trained doctoral-level clinicians consistent with the published manual.[22] Sessions were video-recorded (provided both partners gave informed consent to do so) and were available to the study therapy supervisor to review on an as-needed basis. Study supervision was conducted weekly, and therapists completed a compliance checklist at every session. ABCT begins with psychoeducation regarding the interconnectedness of AUD and relationship functioning. Subsequent sessions focus on helping participants identify and manage cravings and urges to drink; improving individual problem solving and decision-making abilities related to drinking; identify and plan for "high-risk" situations; learn drink refusal skills; and cope with a potential lapse or relapse. ABCT also helps partners learn to identify and change behaviors that may be high-risk for the IPs drinking and develop more effective skills to respond to negative drinking behaviors. ABCT also helps couples enhance reciprocity and adaptive communication skills, increase positive rewards for initiating and maintaining drinking reductions, help each other prevent and manage drinking triggers, and work together to develop drink refusal skills.

Data Analytic Plan

The a priori power analysis and statistical power estimations for this project were published previously.[23] We estimated that a sample of n = 70 couples would yield 80% power to detect between-group differences in percent days drinking (PDD) and percent days heavy drinking (PHDD) with effect sizes of 0.6 (ie, 9% or greater change in PDD and 6% or greater change in PHDD). These estimates assumed 30% attrition during the treatment phase, resulting in our final target sample of N = 100 couples. This sample size would also yield 80% power to detect between-group differences of 4 points in DAS-7 scores. Hypothesis testing focused on end-of-treatment outcomes among IPs using an intent-to-treat framework. A general linear mixed model (GLMM) framework was used to test the primary and exploratory post hoc analyses. The outcomes served as dependent variables in the GLMMs, which included

Figure 1.
CONSORT Flowchart



fixed effects for time, treatment group, and time-by–treatment group interaction as independent variables. The models also included sex, baseline AUDIT score, and baseline DAS-7 score as covariates, along with random subject effects with an autoregressive covariance structure to account for within-subject clustering among the assessments over time. Model-based estimates of the means over time (within and between groups) were calculated, along with their 95% confidence intervals. Cohen *d* effect sizes were determined for each outcome. Sensitivity analyses were also conducted in which the TLFB outcomes were transformed via an arcsine square root transformation prior to model fitting, but they are not presented since these findings were not substantively different from the untransformed analyses.

RESULTS

Sociodemographic and clinical characteristics are displayed in Table 1. Most IPs were men (72.9%), met diagnostic criteria for severe AUD (64.5%), and reported drinking on approximately two thirds of days at baseline (mean = 65.7%, 95% CI, 58.2% to 73.1%) and heavy drinking on nearly half the days at baseline (mean = 46.5%, 95% CI, 40.4% to 52.7%). Exactly half of

Table 1.

Baseline Characteristics of Study Participants, Stratified by Role (Identified Patient [IP] vs Partner) and Treatment Group (Oxytocin vs Placebo)

	Role = identified patient		Role = partner		
Characteristic	Oxytocin (n = 49)	Placebo (n = 47)	Oxytocin (n = 49)	Placebo (n = 47)	All participants, range
Sociodemographic					
Age, mean ± SD, y	38.9 ± 11.8	43.3 ± 12.6	38.6 ± 13.5	42.1 ± 12.0	19–73
Sex, % male	75.5	70.2	22.4	27.7	
Race, %					
White	89.8	91.5	91.8	87.2	
Black	6.1	4.3	2.0	4.3	
PI/NH	0.0	0.0	0.0	2.1	
Native American/Alaskan	0.0	2.1	2.0	0.0	
More than 1 race	4.1	2.1	4.1	6.4	
Hispanic, %	2.0	4.3	2.0	10.6	
Education, median [IQR], y	15.5 [13.0–16.0]	16.0* [14.0–18.0]	16.0 [14.0–18.0]	16.0 [14.0–18.0]	11–24
Relationship status, %					
Living with partner	30.6	19.1	30.6	19.1	
Dating, not living with partner	10.2	10.6	10.2	10.6	
Married	59.2	70.2	59.2	70.2	
Employment status, %					
Part-time	10.2	8.5	18.4	21.7	
Full-time	73.5	68.1	67.3	58.7	
Unemployed	10.2	4.3	6.1	8.7	
Retired	2.0	8.5	6.1	4.3	
Student	4.1	4.3	2.0	4.3	
Disabled	0.0	6.4	0.0	2.2	
Clinical					
AUD diagnostic severity, %					
No AUD	0.0	0.0	44.9	55.3	
Mild	10.2	23.4	18.4	21.3	
Moderate	20.4	17.0	16.3	10.6	
Severe	69.4	59.6	20.4	12.8	
AUDIT-C, median [IQR]	19.0 [13.0–25.0]	19.0 [12.0–26.0]	6.0 [3.0–11.0]	5.0 [3.0–9.0]	0–35
DAS-7, mean ± SD	24.6 ± 4.9	24.6 ± 6.3	23.4 ± 5.5	22.7 ± 6.5	9–36
HAQ, median [IQR]	5.2 [4.8–5.7]	5.1 [4.9–5.5]	5.3 [4.9–5.8]	5.2 [4.9–5.8]	2.3–6.0
CTS-2 Perpetration, median [IQR]	9.5 [5.5–30.5]	10.5 [4.0–29.0]	14.0 [6.0–31.0]	11.0 [4.0–32.0]	0–104
CTS-2 Victimization, median [IQR]	8.0 [2.0–24.0]	11.5 [6.0–31.0]	17.5 [5.5–32.0]	10.0 [4.0–39.0]	0–156
PACS, median [IQR]	15.0 [8.0–19.0]	13.5 [7.0–20.0]	4.5 [2.0–11.5]	6.0 [3.0–11.0]	0–28
SOCRATES, median [IQR]					
Ambivalence	14.0 [12.0–16.0]	15.0 [12.0–18.0]	7.5 [4.0–12.5]	7.0 [4.0–11.0]	4–20
Recognition	24.0 [18.0–28.0]	23.0 [16.0–32.0]	11.0 [8.0–17.5]	11.0 [8.0–17.0]	7–35
Steps	27.0 [20.0–31.0]	27.0 [20.0–33.0]	20.5 [9.5–31.0]	20.0 [10.0–28.0]	8–40
Safety and compliance					
Adverse events, median [IQR]	1.0 [0.0–1.0]	1.0 [0.0–1.0]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0–9
Medication doses administered, median [IQR]	12.0 [11.0–12.0]	12.0 [12.0–12.0]	12.0 [11.0–12.0]	12.0 [11.0–12.0]	1–12
Sessions attended, median [IQR]	12.0 [11.0–12.0]	12.0 [12.0–12.0]	12.0 [10.0–12.0]	12.0 [11.0–12.0]	1–12

*P = .03 when compared to IPs assigned to the oxytocin group by Wilcoxon rank sum test.

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CTS-2 = Conflict Tactics Scale, DAS-7 = Dyadic Adjustment Scale Short Form, HAQ = Helping Alliance Questionnaire, IP = identified patient, IQR = interquartile range, PACS = Penn Alcohol Craving Scale, PI/NH = Pacific Islander/Native Hawaiian, SOCRATES = Stages of Change Readiness and Treatment Eagerness Scale.

partners (50%) also met diagnostic criteria for AUD. At baseline, partners reported drinking on more than one third of days (mean = 42.5%, 95% CI, 36.5% to 48.6%), but heavy drinking was less frequent (mean = 13.6%, 95% CI, 10.2% to 17.1%). Most participants were married (64.5%), identified as white (90.1%), and did not endorse Hispanic ethnicity (95.4%). Most participants reported some college education, although IPs in the placebo group reported having slightly more years of education than IPs in the oxytocin group (median = 16.0 vs 15.5, P = .03).

Primary Outcomes: Alcohol Consumption and Relationship Functioning

Results of a priori hypothesis testing using linear mixed models are presented in Table 2. Although

hypotheses focused only the IPs, the outcomes among IP partners are also presented. Among the IPs, there were significant declines from baseline to week 12 in PDD and PDH for both groups (oxytocin PDD: from 65.2% to 36.8%, $P < .0001$; oxytocin PDH: from 41.5% to 11.8%, $P < .0001$; placebo PDD: from 66.2% to 35.9%, $P < .0001$; placebo PDH: from 51.6% to 9.9%, $P < .0001$). For both PDD (Cohen $d = -0.01$) and PDH (Cohen $d = -0.28$), the declines were not statistically significantly different between the oxytocin and placebo IP groups. For relationship functioning, there were no significant main effects of time or experimental condition. DAS-7 scores increased 0.3 points for both the oxytocin and placebo IPs, but these increases (from 24.7 to 25.0, Cohen $d = 0.0$) were not statistically significant.

Post Hoc Exploratory Outcomes

Two post hoc analyses were conducted. The first examined whether IP groups (ie oxytocin vs placebo) differed on alcohol problem severity. We expected that, similar to the a priori analyses that focused on alcohol consumption, IPs randomized to the oxytocin condition would have greater reduction in AUDIT total scores. Results indicate that, similar to alcohol consumption outcomes, there was a significant main effect of time on alcohol problem severity, with IPs in both groups evidencing substantial and similar improvement from baseline to week 12 (oxytocin: from 18.8 to 14.6, $P < .001$; placebo: from 18.9 to 13.1, $P < .0001$). However, there were no interactive effects of time-by–medication condition. Since a greater proportion of partners than expected also presented with current AUD, the second post hoc analysis examined whether IP outcomes differed when stratified by partner AUD status. We expected that potential drug effects would be dampened among IPs who had partners with AUD. Results indicated that IP outcomes did not differ according to whether their partner had AUD (Table 3).

Attrition, Safety, and Tolerability

The a priori power analysis assumed that 30% of participants would complete fewer than 9 (eg, 75%) ABCT sessions.[23] Attrition was substantially lower than expected in this study. Participants completed an average of 10.2 ABCT sessions (SD = 3.5). A total of 73.5% of couples in the oxytocin group and 76.6% of couples in the placebo group completed all 12 ABCT sessions. Oxytocin also evidenced strong tolerability in this trial. Groups did not differ in terms of number of medication doses administered (median = 12 for both groups, see Table 1). The most common adverse events (AEs) were upper respiratory tract infections (35), gastrointestinal symptoms (30), and sinusitis (16). No group differences were observed in the total frequency of AEs (median = 1 for both groups, see Table 1). In total, 9 serious AEs (SAEs; 8 medical, 1 psychiatric) occurred during the trial. SAEs were reviewed by the principal investigator, study medical clinician, and Data Safety Monitoring Board, who were in agreement that all SAEs were unrelated to study procedures.

DISCUSSION

This is the first randomized, placebo-controlled trial to examine the efficacy of intranasal oxytocin versus matching placebo administered simultaneously with an evidence-based behavioral treatment for AUD. It is also the first randomized clinical trial to examine simultaneous oxytocin and behavioral treatment among couples for any condition, and we are not aware of any prior trials in the AUD field that have administered medication to a romantic partner to mobilize alcohol consumption or problem severity improvements. Participants in both groups evidenced substantial improvements in percent days drinking, percent days heavy drinking, and alcohol problem severity during the treatment phase. Contrary to hypotheses, no group differences emerged in alcohol consumption or alcohol problem severity, and neither group evidenced substantial improvements in relationship functioning. Retention was substantially higher than anticipated throughout the trial, and AEs were minimal, suggesting that intranasal oxytocin was safe, tolerable, and feasible in this population, including in the context of home-based telehealth administration.

The current study is the first to address several crucial methodological factors obscuring the interpretation of results in some prior clinical oxytocin trials. One particularly important advancement is that this study enjoyed very strong retention, allowing for the detection of even subtler drug effects on the hypothesized outcomes had they been present. Strong retention also ensured that a more than adequate proportion of participants received the intended treatment dose, eliminating concerns about possible confounds related to implementation of the behavioral platform, medication adherence, or missing data. While retention and subsequent statistical power confer confidence in the interpretation this study's results, it is also worth noting that ABCT alone typically yields substantial improvements in alcohol consumption for IPs,[33] making it a challenging modality to improve upon. Although participants in this trial completed 1–2 more sessions, on average, than prior ABCT-only trials, alcohol consumption outcomes were similar, and relationship adjustment findings were lower in magnitude, suggesting that a higher ABCT treatment dose in the absence of drug effects did not result in better drinking or relationship functioning outcomes. Room to improve ABCT outcomes remains, and stakeholders' (ie, patients, partners, clinicians) enthusiasm for the modality suggests that alternative strategies to optimize outcomes are worthy of

Table 2.

Results of the Linear Mixed Models[a]: Primary Outcomes Over Time, Stratified by Role (Identified Patient [IP] vs Partner) and Treatment Group (Oxytocin vs Placebo)

	Role = IP		Role = partner	
Outcomes	Oxytocin (n = 49)	Placebo (n = 47)	Oxytocin (n = 49)	Placebo (n = 47)
Primary (a priori)				
Percent of days drinking				
Baseline: mean (95% CI)	65.2 (54.9 to 75.4)	66.2 (55.9 to 76.5)	41.7 (33.3 to 50.0)	43.4 (35.1 to 51.8)
Week 12: mean (95% CI)	36.8 (25.5 to 48.1)	35.9 (24.7 to 47.1)	33.2 (24.0 to 42.4)	25.1 (16.1 to 34.1)
Change: mean (95% CI)	−28.4 (−42.4 to −14.4)****	−30.3 (−44.4 to −16.2)****	−8.5 (−20.1 to 3.2)	−18.3 (−30.1 to −6.6)**
Cohen *d*	−0.01		−0.24	
Percent of all days involving heavy drinking				
Baseline: mean (95% CI)	41.5 (33.1 to 50.0)	51.6 (43.1 to 60.1)	13.4 (8.7 to 18.2)	13.8 (9.0 to 18.6)
Week 12: mean (95% CI)	11.8 (2.3 to 21.2)	9.9 (0.6 to 19.3)	5.9 (0.5 to 11.2)	5.2 (0.0 to 10.4)
Change: mean (95% CI)	−29.8 (−41.8 to −17.8)****	−41.6 (−53.7 to −29.6)****	−7.6 (−14.5 to −0.6)*	−8.6 (−15.6 to −1.7)*
Cohen *d*	−0.28		−0.04	
DAS-7				
Baseline: mean (95% CI)	24.7 (23.5 to 25.8)	24.7 (23.5 to 25.8)	23.4 (22.2 to 24.5)	23.1 (22.0 to 24.3)
Week 12: mean (95% CI)	25.0 (23.8 to 26.2)	25.0 (23.7 to 26.2)	23.5 (22.2 to 24.8)	23.3 (22.0 to 24.6)
Change: mean (95% CI)	0.3 (−1.3 to 2.0)	0.3 (−1.3 to 2.0)	0.1 (−1.6 to 1.8)	0.2 (−1.5 to 1.9)
Cohen *d*	0.00		−0.01	
Secondary (post hoc)				
AUDIT				
Baseline: mean (95% CI)	18.8 (17.2 to 20.4)	18.9 (17.3 to 20.5)	8.4 (7.5 to 9.2)	8.1 (7.2 to 9.0)
Week 12: mean (95% CI)	14.6 (12.9 to 16.4)	13.1 (11.2 to 14.9)	6.4 (5.5 to 7.4)	6.4 (5.4 to 7.3)
Change: mean (95% CI)	−4.2 (−6.5 to −1.9)***	−5.8 (−8.2 to −3.4)****	−1.9 (−3.2 to −0.7)**	−1.7 (−3.0 to −0.5)**
Cohen *d*	−0.20		0.04	

[a]Model-based means and CIs are presented. The models were all adjusted for sex, baseline AUDIT score, and baseline DAS-7 score. Positive Cohen *d* values indicate that greater improvement was observed in the oxytocin group, while negative values indicate that greater improvement was observed in the placebo group. There were no statistically significant between-group differences (ie, all $P > .05$).

*$P < .05$ (within-group change), **$P < .01$ (within-group change), ***$P < .001$ (within-group change), ****$P < .0001$ (within-group change).

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, DAS-7 = Dyadic Adjustment Scale Short Form.

exploration. Additional alcohol and relationship outcomes, including abstinence, intimate partner violence, and partners' coping/accommodation in relation to AUD, are potential targets for secondary analysis.

Another consideration is that while ABCT aptly accommodates AUD-concordant couples, only 1 prior ABCT trial presented partner reports of their own drinking, and these reports were limited to baseline.[33] Other prior ABCT trials did not report such information,[34] while others have screened out dyads in which both partners had AUD.[35–37] A much larger proportion of partners than expected (50%) presented with AUD, and although diagnostic severity was most often mild and heavy drinking days were less frequent, partners reported a high frequency of total drinking days at baseline. Considering abundant data demonstrating that romantic partners influence one another's drinking behavior (and changes therein),[38,39] we explored whether partner AUD status impacted drug condition effects among IPs. However, our exploratory post hoc hypothesis was not supported. An important follow-up question for this sample is to examine whether the magnitude of drinking changes is associated between partners within a dyad, and whether within-dyad associations result in differential between-group outcomes. Put another way, it is possible that oxytocin might differentially impact couples who experienced greater shared improvements vs those couples in which one partner improved more than the other. We did not conduct additional post hoc analyses, however, considering that couples in this sample presented with a wide variety of relationship functioning, one such analysis that is warranted in the future is to examine outcomes when stratified by severity of relationship distress because including DAS-7 scores as a covariate may not sufficiently capture potential interactive effects between drug condition and relationship functioning. It may also be important to examine potential interactive effects of relationship functioning with treatment condition on primary alcohol outcomes.

LIMITATIONS

Despite rigorous conduct, this study also has limitations that must be considered. First, while the sample was highly generalizable in terms of variability in AUD severity among IPs and inclusion of partners with AUD, the sample was severely limited in sociodemographic diversity. Most IPs were men, no

Table 3.

Results of the Linear Mixed Models for Post Hoc Analyses[a]: Outcomes Over Time Among Identified Patients, Stratified by Partner AUD Status and Treatment Group (Oxytocin vs Placebo)

	Partner has AUD		Partner does not have AUD	
Outcomes	Oxytocin (n = 27)	Placebo (n = 21)	Oxytocin (n = 22)	Placebo (n = 26)
Percent of days drinking				
Baseline: mean (95% CI)	72.9 (60.6 to 85.1)	65.2 (51.3 to 79.0)	54.3 (38.6 to 70.1)	67.7 (53.7 to 81.7)
Week 12: mean (95% CI)	46.6 (32.9 to 60.2)	37.3 (21.8 to 52.7)	24.5 (7.1 to 41.9)	37.8 (22.7 to 52.8)
Change: mean (95% CI)	−26.3 (−43.9 to −8.7)**	−27.9 (−47.8 to −8.0)**	−29.8 (−50.5 to −9.2)**	−29.9 (−48.5 to −11.3)**
Cohen *d*	−0.03		0.00	
Percent of all days involving heavy drinking				
Baseline: mean (95% CI)	47.2 (36.4 to 57.9)	53.3 (41.2 to 65.5)	31.9 (18.6 to 45.3)	49.1 (37.2 to 61.0)
Week 12: mean (95% CI)	15.6 (3.6 to 27.7)	16.5 (2.9 to 30.1)	4.7 (−10.2 to 19.6)	5.3 (−7.5 to 18.2)
Change: mean (95% CI)	−31.5 (−47.3 to −15.8)****	−36.8 (−54.6 to −19.0)****	−27.2 (−45.3 to −9.2)**	−43.8 (−59.9 to −27.6)****
Cohen *d*	−0.13		−0.39	
DAS-7				
Baseline: mean (95% CI)	24.7 (23.3 to 26.1)	24.8 (23.2 to 26.4)	24.6 (22.3 to 26.4)	24.5 (22.9 to 26.1)
Week 12: mean (95% CI)	25.6 (24.1 to 27.2)	25.9 (24.2 to 27.7)	24.3 (22.9 to 26.3)	24.2 (22.4 to 25.9)
Change: mean (95% CI)	0.9 (−1.2 to 3.0)	1.1 (−1.3 to 3.5)	−0.4 (−2.9 to 2.2)	−0.3 (−2.6 to 2.0)
Cohen *d*	−0.04		0.01	
AUDIT				
Baseline: mean (95% CI)	18.0 (12.2 to 19.9)	17.9 (15.7 to 20.0)	19.3 (16.6 to 22.1)	19.8 (17.3 to 22.2)
Week 12: mean (95% CI)	14.3 (15.7 to 16.3)	14.1 (11.7 to 16.6)	14.5 (11.4 to 17.5)	12.6 (9.9 to 15.2)
Change: mean (95% CI)	−3.7 (−6.5 to −1.0)**	−4.6 (−8.0 to −1.3)**	−4.9 (−8.8 to −1.0)*	−7.2 (−10.7 to −3.7)****
Cohen *d*	−0.12		−0.26	

[a]Model-based means and CIs are presented. The models were all adjusted for sex, baseline AUDIT score, and baseline DAS-7 score. Positive Cohen *d* values indicate that greater improvement was observed in the oxytocin group, while negative values indicate that greater improvement was observed in the placebo group. There were no statistically significant between-group differences (ie all $P > .05$).

*$P < .05$ (within-group change), **$P < .01$ (within-group change), ***$P < .001$ (within-group change), ****$P < .0001$ (within-group change).

Abbreviations: AUD = alcohol use disorder, AUDIT = Alcohol Use Disorders Identification Test, DAS-7 = Dyadic Adjustment Scale Short Form.

participants reported a gender identity different than their sex identified at birth, and few same-sex couples enrolled. Further, few participants identified as a member of a race or ethnic minority group, all of which limit generalizability of the sample. Considering that individuals of color and people with sexual and gender minority identities incur substantial barriers to AUD treatment and access to AUD medications in particular, this project failed to achieve a meaningfully diverse enrollment. Another limitation is that this study did not use a dual reporter approach because a single-reporter approach was better aligned with the data analysis plan. However, it is possible that corroborating reports of partner drinking might have differed from self-reports. The fact that ABCT organically incorporates transparency with regard to drinking self-reports within session offsets this concern somewhat and lends additional confidence to the integrity of self-reports in this study. We did not examine abstinence at the end of treatment phase as a dichotomous outcome, diagnostic remission, or rate of drinking improvements for IPs or partners as an outcome. Further, ABCT does not require abstinence from alcohol, and participants with harm-reduction goals were welcome to enroll. Future studies might examine these variables as well as alcohol treatment goals as alternative outcomes. Although we collected 3- and 6-month follow-up assessment data and had a high rate of retention for follow-ups (see Figure 1), we did not examine these data. This is primarily because the a priori hypotheses focused on end of treatment effects. In addition, oxytocin is a short-acting medication, and there is no precedent to expect delayed drug effects long after medication administration stopped. Thus, the lack of drug effects at end of treatment suggests that such an analysis can be treated as exploratory in a possible secondary analysis. Because AUD is a heterogeneous condition with regard to etiology, course, and treatment, secondary analyses are also warranted to examine whether there are treatment condition effects on longer term outcomes. It is possible that medication might impact larger, more sustained reductions in consumption, or achievement of sustained abstinence in different ways compared to shorter-term consumption reductions. Finally, this study was powered to detect moderate differences between treatment groups. If the effects of oxytocin are, in reality, much more subtle, a larger sample size would be warranted.

CONCLUSIONS

The current AUD literature suggests that combining pharmacologic interventions with evidence-based behavioral treatments may help maximize and sustain

AUD treatment outcomes.[40–42] Fewer medications are suited for, or have been examined using simultaneous administration with, the purpose of optimizing within- or between-session gains. While feasible, safe, and tolerable, oxytocin did not confer additional benefit beyond that of ABCT combined with placebo in this trial. Indeed, AUD is a heterogeneous condition with complex etiology and course, and this trial examined 1 promising but highly specific approach to testing oxytocin's efficacy. This medication did not work as hypothesized, but it did not confer harm; thus, we cannot conclude that oxytocin is unhelpful for those with AUD. Other experimental strategies to examine oxytocin to treat AUD are worthy of examination, such as studies enrolling more diverse and less severe patient populations, those using briefer but more frequent dosing designs, and examining oxytocin to mitigate different domains of AUD apart from alcohol consumption.

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