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## A two-week pilot study of intranasal oxytocin for cocaine-dependent individuals receiving methadone maintenance treatment for opioid use disorder

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### Abstract

30–60% of patients receiving methadone for opioid use disorder (OUD) actively use cocaine. Cocaine use disorder (CUD) has no FDA-approved pharmacological treatment; existing psychosocial treatments are inadequate. Oxytocin, a social neuropeptide, has preclinical promise as an adjunctive treatment for both OUD and CUD. Twenty-two individuals receiving methadone for OUD with co-occurring CUD were randomized to receive oxytocin or placebo intranasally 40 IU twice daily for two weeks. *A priori* aims were feasibility and safety. Exploratory effectiveness aims included laboratory-based measures of drug craving, drug-related implicit cognition, and drug use. High retention rates (93.5%), the absence of study-related adverse events, and the fact that oxytocin was well tolerated in this population support the feasibility of larger trials. Two weeks of oxytocin (but not placebo) significantly reduced cocaine craving at day 15 compared to baseline (mean change $\pm$ SD: OT= $-0.23\pm 0.19$ ,  $p=0.004$ ; PL= $-0.16\pm 0.29$ ,  $p=0.114$ ). For heroin craving, the placebo group reported a trend-level increase over time while the oxytocin group remained unchanged - with medium to large effect sizes between the groups (Cohen's  $d=0.71-0.90$ ). Oxytocin led to a significant switch from implicit self-association with drugs to implicitly associating drugs with others (mean change $\pm$ SD:  $0.25\pm 0.35$ ,  $p=0.037$ ) and a trend-level reduction in self-reported cocaine use over time ( $Z=-1.78$ ,  $p=0.075$ ). Furthermore, oxytocin significantly increased the accuracy of self-reported cocaine use when correlated with quantitative urine levels of cocaine metabolite. This proof-of-concept study provides promising early evidence

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#### DECLARATION OF INTEREST STATEMENT

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that oxytocin may be an effective adjunct to the treatment of co-occurring CUD and OUD. Further investigation with larger trials is warranted.

### Keywords

cocaine; social; addiction; methadone; oxytocin

## INTRODUCTION

Opioid agonist treatment, including methadone maintenance therapy (MMT), is the mainstay for the treatment of opioid use disorder (OUD). MMT is associated with positive treatment outcomes, including reductions in illicit opioid craving and use and improved social functioning (Bart, 2012). Despite its effectiveness, roughly 30-60% of patients receiving MMT actively use cocaine (Weinstock J, 2010), which is associated with worse treatment outcomes (e.g., more than double the rate of relapse to heroin) (White *et al*, 2014). Those using both cocaine and heroin have mortality rates 14.3 times higher than the general population (de la Fuente, 2014). Moreover, patients often initiate or increase cocaine use after enrolling in MMT clinics (Chaisson RE, 1989). Aside from the influence of behavioral contagion within a clinic setting, increased cocaine use upon starting MMT may result from a synergistic effect of opioids and stimulants on striatal dopamine release (Lan, 2009). In fact, MMT patients report a subjective enhancement in the positive effects of cocaine use compared to non-MMT controls (Preston KL, 1996). No medications are currently FDA-approved for the treatment of cocaine use disorder (CUD); thus, psychosocial interventions remain the predominant treatment modality. Unfortunately, psychosocial treatments have low retention rates (e.g., 30%) (Siqueland *et al*, 2002). In sum, co-occurring OUD and CUD is a highly meaningful clinical problem in patients receiving MMT, and current treatment options do not adequately address the complex needs of this population.

Oxytocin (OT) is a hypothalamo-pituitary neuropeptide well known for its role in social cognition and behavior (Lieberwirth and Wang, 2014; Meyer-Lindenberg A, 2011). Endogenous OT levels are lower in cocaine using individuals (Light, 2004), and lower OT levels in patients receiving MMT are correlated with greater novelty seeking, which is a predictor of addiction-related behavior (Lin, 2015). OT administration has demonstrated myriad anti-addiction effects in animal models of substance dependence (Sarnyai Z, 2014; Carson *et al*, 2013). For example, OT dose-dependently attenuates opioid and cocaine tolerance and opioid withdrawal reactions. This is important because tolerance and withdrawal are key drivers of physiological drug dependence. Behaviorally, OT administration reduces stress-induced opioid seeking (Zanos *et al*, 2014), cue-induced cocaine seeking (Bentzley BS, 2014; Morales-Rivera *et al*, 2014), cocaine-induced stereotyped behavior (Carson *et al*, 2013), and opioid and cocaine self-administration (Sarnyai Z, 2014) in rodents. Thus, OT functions at multiple levels to diminish the effects of both opioids and psychostimulants and, ultimately, reduce their consumption, making it a prime candidate for the treatment of co-occurring OUD and CUD.

There is a growing interest in the investigation of OT's effects on substance use disorders in humans (Carson *et al*, 2013; Sarnyai Z, 2014; Stauffer and Woolley, 2014; Tops *et al*, 2014). OT administration has been shown to reduce alcohol withdrawal and craving in patients experiencing acute detoxification (Pedersen *et al*, 2013) and to decrease stress-induced marijuana craving in dependent individuals (McRae-Clark *et al*, 2013). The only published study of OT administration in human subjects with CUD (n=23) recruited cocaine-abstinent participants from a mandatory inpatient treatment program (Lee *et al*, 2014) and employed a single dose, double blind, placebo-controlled, crossover design to measure cue-reactivity to cocaine-related video clips. The authors found that OT removed the effect of state anger on several measures of cue-reactivity. They also found a seemingly paradoxical *increase* in baseline self-reported urge to use cocaine after administration of OT compared to placebo; however, there was no effect of OT on cue-induced urge to use.

No studies to our knowledge have investigated OT's effects on patients *actively* using cocaine, a population notoriously challenging to retain in treatment and research (Siqueland *et al*, 2002), particularly crack cocaine users (Rowan-Szal *et al*, 2000). We recruited active cocaine users engaged voluntarily in a harm reduction treatment model in the setting of an MMT clinic, where they were being treated for concomitant OUD. Intranasal OT administration has been found to be extremely safe and well-tolerated in healthy (MacDonald *et al*, 2011) and multiple patient populations (Hofmann *et al*, 2015). However, the dramatic OT-induced loss of opioid tolerance seen in animal studies presents safety concerns for those receiving a steady daily dose of MMT, which could theoretically lead to fatal overdose if a similar reduction in opioid tolerance were to occur in humans. Prior to the current study, our research group conducted a preliminary, single-dose, placebo-controlled, crossover study of intranasal OT 40 International Units (IU) in patients receiving MMT (Woolley, personal communication) and determined that this dosage was safe with no obvious acute effects on opioid tolerance.

The current study is a proof-of-concept, randomized, double-blind, placebo-controlled trial of OT administered intranasally twice daily for two weeks to male and female patients with CUD receiving MMT for OUD. The *a priori* goals of this pilot study were to: 1) determine the feasibility of our novel protocol, which utilizes the structure of an MMT clinic to recruit active crack cocaine users and retain them in a longitudinal clinical trial, and 2) to assess the safety of repeated intranasal OT dosing in patients receiving a steady daily dose of opioid agonist (i.e., MMT) (Clinicaltrials.gov #NCT02028533). Moreover, laboratory-based measures of drug craving (Everitt, 2014) and drug-related implicit cognitions (Marhe *et al*, 2013) predict real-world addictive behavior. Therefore, in addition to our primary outcomes of feasibility and safety, we also aimed to gather preliminary effect size data for OT's influence on measures of 3a) cue-induced drug craving, 3b) drug-related implicit cognitions, and 3c) drug use.

## METHOD

### Recruitment and Participants

The Committee on Human Research at the University of California, San Francisco approved all study protocols. Participants were recruited from the San Francisco General Hospital

Opiate Treatment Outpatient Program (OTOP). All participants had a history of intravenous heroin use, were on a stable dose of methadone for at least two weeks, had at least one routine clinic-administered urine toxicology screen positive for cocaine in the past month, reported to clinic daily for their methadone dose (i.e., no take-home doses), and had no more than three clinic absences in the previous month. We excluded participants with cardiovascular disease, a history of traumatic brain injury, renal dialysis, observable pathology of the nasal mucosa, or urine toxicology screens positive for heroin or methamphetamine in the prior thirty days. No participants were taking hormones or 5HT1a agonists/antagonists, as these agents could hypothetically alter OT levels (Thompson *et al*, 2007). Female participants with a positive pregnancy test or a history of premenstrual dysphoric disorder were excluded. All female participants used a non-hormone-based form of birth control or reported sexual abstinence. Given the comorbidity of substance use disorders and other psychiatric symptoms, taking psychotropic medications was not an exclusion criteria provided the patient did not have a primary Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I diagnosis other than OUD or CUD upon enrollment in the study.

## Overview

During a 90-minute initial evaluation, informed written consent was obtained followed by administration of the Structured Clinical Interview for DSM-IV Disorders – Clinical Trials Version (SCID-4-CT), adapted to our study criteria, and a brief physical exam that included an assessment of the nasal mucosa. The severity of addiction to heroin and cocaine was estimated by determining the number of days of use in the past thirty days and the number of years the substance was used at least three times per week in the participant's lifetime (Cacciola, 2007). Participants were randomized, using gender as a stratum, to receive either OT or placebo.

Study participation included brief daily visits with study staff for twenty-one consecutive days. Participants received OT 40 IU, or matched placebo, (Abbotts Compounding Pharmacy, Berkeley) intranasally twice daily for the first two weeks. This was followed by a washout week of daily safety assessments without any study drug. Study staff trained on proper spray application (Guastella *et al*, 2013) administered each AM dose of the study drug immediately after participants received their daily observed methadone dose from OTOP clinic staff. After being trained on proper self-administration, participants were given a PM dose of OT or placebo to self-administer 8-10 hours following their AM dose. Each PM dose was individually bottled, and participants were incentivized to return each bottle the following day for weighing (adherence monitoring). Participants received \$5 for daily assessments if the PM bottle from the previous day was returned – empty or full – but were only given \$3 for daily assessments if no bottle was returned. Participants received \$5 for each daily visit during the final washout week. Participants were paid \$15 for the initial evaluation; an extra \$10 for completing additional tasks (see below) on days 1, 15, and 21; and a \$20 completion bonus. All compensation was in the form of cash.

## Measures

**1) Feasibility**—Of the 369 patients receiving MMT at the OTOP clinic at the beginning of our six-week recruitment period, 107 (29%) had a documented routine urine toxicology screen positive for cocaine in the previous 30 days. To measure the feasibility of conducting larger longitudinal studies within this population, we recorded the number of patients recruited and screened for study participation. We also tracked study retention and adherence to daily participation within the three-week study protocol.

**2) Safety**—Participants were assessed daily for safety of the intervention. Clinical measures monitoring for acute reduction in opioid tolerance were collected, including: respiratory rate (a sensitive sign of opioid toxicity), pupil size, heart rate, blood pressure, and temperature. We also asked participants to report any adverse events.

**Visual Analog Scale – Effects of Drug (VAS-ED)**—Participants completed a daily computerized questionnaire assessing subjective drug effects. “Drug” was defined as any substance recently used, including: illicit drugs, MMT, or the study drug. The following questions were asked: 1) “Do you feel any drug effects?”, 2) “Does the drug have any good effects?”, 3) “Does the drug have any bad effects?”, 4) “Do you like the drug?”, 5) “Does the drug make you feel sick?”, 6) “How high are you?”. Answers were marked on a 10-cm visual analog scale (VAS) and recorded as a proportion of the full line (range = 0-1). In our preliminary study, we found that a single dose of OT given to participants receiving MMT for OUD (but not actively using any illicit substances) led to a significant increase in ratings of “bad effects” and feeling “high” (Woolley, personal communication).

**3) Effectiveness Measures**—Computerized measures, created on PsychoPy v1.80.03, of drug craving/urge to use and drug-related implicit cognition were conducted on day 1, prior to any study drug administration (baseline), and repeated on day 15, after two weeks of study drug administration, and day 21, after the washout week.

**3a) Craving & Urge Paradigm**—To measure cue-induced craving we employed the following paradigm, which was performed separately using both cocaine and heroin-related cues. Participants were asked “How much are you currently craving [drug]?” and “How high is your urge to use [drug] currently?” and marked their response on a 10-cm VAS, which was recorded as a proportion of the full line (range = 0-1). We collected VAS measurements (in the following order): 1) prior to any drug cue exposure, 2) immediately following exposure to a 1-minute video of publically-available documentary footage depicting [drug] use, and 3) following a 3-minute video of neutral footage. A 3-minute period of neutral stimuli was chosen to allow time for cue-induced craving to subside between tasks (Garavan *et al*, 2000).

**3b) Implicit Association Test (IAT)**—Positive drug-related implicit cognitions are linked to relapse (Marhe, 2013), and there is a growing interest in the development of treatment options that target drug-related implicit cognitions (Rooke, 2008). To measure drug-related implicit cognitions, we used a modified IAT aimed to assess implicit self-identification with drugs. Recent theories suggest that identity change in recovery is socially

negotiated (Best, 2016), thus OT may enhance this process. Images of [drug] paraphernalia versus neutral hardware tools were used as concept discriminations, and words implying “self” (e.g., mine, myself) versus “other” (e.g., theirs, others) were used as attribute discriminations. The IAT was administered separately using both cocaine and heroin-related images. Participants were instructed to categorize images and words as quickly as possible while making as few mistakes as possible. IAT scores are derived from response latencies – assuming that participants respond more rapidly and make fewer mistakes when the concept and attribute sharing the same key are more strongly implicitly associated (Greenwald *et al*, 2003).

### 3c) Drug Use

**Self-Reported:** Participants reported daily on quantity and route of administration of any illicit drug use in the past 24 hours. Crack cocaine use was reported in dollar amounts. Study staff were trained to conduct all interviews using an adapted supportive clinical management approach (Carroll *et al*, 1994). This approach emphasizes confidentiality, rapport-building, and using empathy and non-judgment without providing any active ingredients of drug counseling.

**Quantitative:** Urine samples were collected at baseline and subsequently every four days. A liquid chromatography tandem mass spectrometry method described previously was used to quantitate the level of benzoylecgonine, the primary cocaine metabolite, in each urine sample (Lynch *et al*, 2011). This level was then normalized to the concentration of creatinine. Creatinine was measured on a Siemens ADVIA 1800 system using an FDA-approved enzymatic creatininase method according to manufacturer's instructions. The calibration for this method is traceable to SRM967 and correlated with the NIST liquid chromatography isotope-dilution mass spectrometry method. The half-life of benzoylecgonine is 6.6 hours; therefore, the minimum window of detection in urine is approximately 2 days (7 half-lives). It is generally accepted that this window of detection for benzoylecgonine is longer in chronic crack cocaine users.

**Analysis Plan:** Standard descriptive statistics were used to summarize the demographic and clinical data at baseline and to assess feasibility and basic safety aims. Student's t-tests were used to compare the two groups regarding adherence and safety measures. Normality was assessed using the Shapiro-Wilk test. A mixed-effects ANOVA model was estimated and tested using the within-subjects factor of time (baseline, day 15, day 21) and the between-subjects factor of drug (OT, placebo) as independent variables and, separately, measures of cocaine/heroin craving, urge, and implicit association as dependent variables. Similarly, mixed-effects ANOVA was estimated and tested for VAS-ED and urine BE, although the within-subject factor of time was defined as (baseline, day 5, day 9, day 13, day 17, and day 21) and (daily measurements for days 1-7 and 8-14), respectively. Within-subject differences were further explored separately for each study drug group (OT versus placebo) using a repeated measures ANOVA. Within-group differences for self-reported drug use, which was not normally distributed, were calculated using a Wilcoxon signed-rank test. Mean daily self-reported cocaine use was collapsed for days 2-14 and days 15-21, and differences from baseline (day 1) were calculated for each. Due to the exploratory nature of our effectiveness

aims and our small sample size, we also report Cohen's *d* effect sizes for between-group differences of all measures to aid in power analyses of future studies. Figure values are shown as group means and standard error of the mean, and significant or trend-level within-subject changes are marked. Pearson's correlation coefficients were calculated for urine BE levels and mean self-reported use from the four days prior to each BE level. A Fisher *r*-to-*z* transformation was used to assess the significance of the difference in correlation coefficients between the oxytocin and placebo groups at each timepoint, and two-tailed *p*-values were determined.

## RESULTS

### Participants

Participants were predominantly African American with a mean age of 49.5 years. They received a mean daily methadone dose of 101.4mg and used an average of \$28 worth of crack cocaine daily. Eight of the 22 participants were taking one or more psychoactive medications. Participants were prescribed these medications by their regular clinicians prior to study entry and were on a stable dose that did not change through the course of the study. For a summary of demographics and baseline measurements see **Table 1**.

**1) Feasibility**—A total of 78 patients were recruited and screened for participation (**Figure 1**). 23 participants (12 men) were enrolled. One male participant was unable to adequately complete tasks due to neurocognitive deficits; he was removed from the study on day five and not included in analysis. 22 participants completed full study participation for a retention rate of 95.7%. The 22 participants completing the study collectively demonstrated 93.5% daily attendance over the twenty-one day study period with no difference between study groups (mean±SD: OT 19.73±1.27, Placebo 19.55±1.57, *p*=0.77). The daily rate of incentivized return of nasal spray bottles from the previous day's PM dose was 98.05% with no difference between study groups (mean±SD: OT 13.64±0.50, Placebo 13.82±0.41, *p*=0.36).

**2) Safety**—There were no study-related adverse events reported. There were no significant differences in safety measures between the two groups, including respiratory rate (mean ±SD: OT 14.63±0.75, Placebo 14.58±0.92, *p*=0.93). One participant's (female, OT group) methadone dose was increased during study participation in order to address the emergence of opioid withdrawal symptoms triggered by the initiation of rifampin prescribed for a surgery-related skin infection. All other participants' methadone dose remained stable throughout study participation. There was a trend-level between-group effect for the VAS-ED rating "Do you feel any drug effects?" ( $F_{1,3}=8.26$ , *p*=0.06), with the OT group reporting less overall "drug effects" (between-group Cohen's *d* effect size=0.60). There were no significant effects for the other VAS-ED ratings.

### 3) Effectiveness Measures

**3a) Craving & Urge to Use**—Participants did not report a significant change in craving or urge to use cocaine or heroin in response to our drug-cue videos on any of the testing days. Therefore, measures from the testing paradigm were collapsed into mean ratings for

both craving and urge for each of the three testing days. There was a significant mean effect of time for cocaine craving ( $F_{2,36}=15.32$ ,  $p<0.001$ ), but no significant effect of drug ( $F_{1,18}<0.001$ ,  $p=0.98$ ) or a time\*drug interaction ( $F_{2,36}=0.23$ ,  $p=0.80$ ). Cohen's  $d$  effect sizes measuring between-group differences for change in cocaine craving from baseline were 0.29 and 0.09 between the two groups at days 15 and 21, respectively. There was a significant mean effect of time for urge to use cocaine ( $F_{2,36}=20.16$ ,  $p<0.001$ ), but no significant effects of drug ( $F_{1,18}=0.10$ ,  $p=0.75$ ) or time\*drug interactions ( $F_{2,36}=0.09$ ,  $p=0.92$ ). Cohen's  $d$  effect sizes measuring between-group differences for change in urge to use cocaine from baseline were 0.13 and 0.04 between the two groups at days 15 and 21, respectively. Both groups demonstrated significant within-group changes in cocaine craving (OT:  $F_{2,18}=10.37$ ,  $p=0.001$ ; Placebo:  $F_{2,18}=5.94$ ,  $p=0.01$ ) and urge to use (OT:  $F_{2,18}=9.98$ ,  $p=0.001$ ; Placebo:  $F_{2,18}=10.28$ ,  $p=0.001$ ) (**Figure 2a,b**).

For heroin craving, there were no significant mean effects of time ( $F_{2,38}=0.62$ ,  $p=0.55$ ) or drug ( $F_{1,19}=2.12$ ,  $p=0.16$ ) nor a significant time\*drug interaction ( $F_{2,38}=1.64$ ,  $p=0.21$ ). Cohen's  $d$  effect sizes measuring between-group differences for change in heroin craving from baseline were 0.71 and 0.77 at days 15 and 21, respectively (**Figure 2c**). For urge to use heroin, there were no significant mean effects of time ( $F_{2,38}=1.31$ ,  $p=0.28$ ) or drug ( $F_{1,19}=0.03$ ,  $p=0.87$ ) nor a significant time\*drug interaction ( $F_{2,38}=2.11$ ,  $p=0.14$ ). Cohen's  $d$  effect sizes measuring between-group differences for change in urge to use heroin from baseline were 0.90 and 0.73 at days 15 and 21, respectively. There were trend-level within-group increases in urge to use heroin in the placebo group ( $F_{2,20}=2.70$ ,  $p=0.09$ ), but no significant changes in the OT group ( $F_{2,18}=0.08$ ,  $p=0.92$ ) (**Figure 2d**).

**3b) IAT**—There were no significant mean effects of time ( $F_{2,34}=1.17$ ,  $p=.32$ ) or drug ( $F_{1,17}=2.00$ ,  $p=.18$ ), nor a significant time\*drug interaction ( $F_{2,34}=.80$ ,  $p=.46$ ) on implicit associations of cocaine images with “self” versus “other” words. In the OT group, there was a significant switch from associating cocaine images with “self” words to associating cocaine images with “other” words at day 21 compared to baseline ( $F_{1,10}=5.77$ ,  $p=.04$ ). The placebo group did not change significantly in self-association with cocaine at this time point ( $F_{1,8}=.25$ ,  $p=.63$ ). Cohen's  $d$  effect size measuring between-group differences for change in IAT from baseline was .58 at day 21. Due to a computer error, baseline IAT scores for heroin were only collected for four participants; thus, IAT change scores for heroin were not analyzed.

**3c) Cocaine Use**—The OT group showed a trend-level reduction in self-reported cocaine use for both the Study Drug Days (SDD, days 1-14) and the Washout Week (WW, days 15-21) compared to baseline (SDD:  $Z=-1.78$ ,  $p=0.08$ ; WW:  $Z=-1.68$ ,  $p=0.09$ ), while the placebo group reported no significant change (SDD:  $Z=-1.17$ ,  $p=0.24$ ; WW:  $Z=-1.48$ ,  $p=0.14$ ). Cohen's  $d$  effect sizes measuring change in self-reported cocaine use between the two groups were 0.31 and 0.28 for SDD and WW, respectively (**Figure 3a**). There were no significant mean effects for time ( $F_{5,90}=1.09$ ,  $p=0.37$ ) or drug ( $F_{1,18}=.001$ ,  $p=0.97$ ) nor a significant time\*drug interaction ( $F_{5,90}=1.03$ ,  $p=0.41$ ) for urine BE levels. Cohen's  $d$  effect sizes measuring between-group differences in BE changes from baseline were .19 and .23 at days 15 and 21, respectively (**Figure 3b**). Self-reported cocaine use significantly correlated



with subsequent urine BE levels in the OT group for urine sample timepoints 3, 4, and 5. The placebo group did not demonstrate any significant correlations. There was a trend-level difference in correlation coefficients between the two groups at urine sample timepoint 3 ( $z=1.82$ ,  $p=0.07$ ) and a significant difference at urine sample timepoint 4 ( $z=2.11$ ,  $p=0.03$ ). Between-group differences in correlation coefficients at the other urine sample timepoints were not significant (**Figure 3c**).

## DISCUSSION

Our recruitment, retention, and adherence rates support the feasibility of conducting a larger randomized controlled trial of intranasal OT's effects on OUD and CUD in the setting of an MMT clinic. We are the first to demonstrate that OT administration is safe and tolerable for patients receiving MMT; specifically, we found no evidence of reduction in opioid tolerance as a result of OT 40 IU administered intranasally twice daily for two weeks. In fact, we found that participants reported feeling less overall “drug effects” when receiving OT versus placebo, while we would expect the opposite if patients were losing opioid tolerance in the setting of a stable daily dose of MMT. Furthermore, the exploratory measures included in our proof-of-concept study uncovered promising preliminary support for OT's effects on the symptoms of OUD and CUD. While most differences did not reach statistical significance, and much larger trials would be needed to validate the effect sizes found, there is a consistent pattern of more positive outcomes in the OT group compared to the placebo group (see **Figures 2 & 3**). With a strong preclinical evidence base and growing clinical interest, continued early-stage human studies of intranasal OT's effects on the symptoms of OUD and CUD are warranted.

OT has been found to reduce opioid and cocaine-related cue-reactivity in numerous animal studies (Bentzley BS, 2014; Morales-Rivera *et al*, 2014); however, we were unable to assess acute cue-reactivity because our paradigm failed to elicit self-reported increases in cue-induced craving or urge to use cocaine or heroin. Given OT's known role in ameliorating stress reactivity (Cardoso, 2014), future studies of this population should include stress-induced craving paradigms, which likely involve more robust physiological responses than video cues of drugs (Mantsch *et al*, 2015) and may more effectively highlight OT's effects on drug craving in humans (e.g., McRae *et al.*'s, 2013). Additionally, the Cocaine Craving Questionnaire may be a more effective self-report measure of cocaine craving than VAS ratings (Heinz *et al*, 2006). Both groups in our study reported significant reductions in overall cocaine craving and urge to use over the course of the study (**Figure 2a,b**), while measures of heroin craving and urge to use *increased* over time in the placebo group and remained stable in the OT group (**Figure 2c,d**) with large between-group effect sizes. Despite not reaching statistical significance, the directionality of the signals detected in response to OT versus placebo on both cocaine and heroin measures is promising.

Thomas Insel (2003) hypothesized that drugs of abuse hijack a motivational reward system evolved for social interaction, and social context has been deemed highly relevant to addiction treatment outcomes (Alexander and Hadaway, 1982; Robins *et al*, 2010). Sarnyai (2014) hypothesized that OT administration may help shift attentional bias toward adaptive social reward at the expense of conditioned drug-related reward. However, the availability of

adaptive social reward in populations with substance use disorders may be highly limited, leaving substances of abuse as the most salient coping strategy when faced with stressors (Stauffer and Woolley, 2014). This may help explain why participants reported an increased urge to use cocaine in response to OT administration in Lee *et al's* (2014) study of inpatients with CUD. The social context of this study was court-mandated treatment following incarceration and forced abstinence from cocaine for an average of 28 months. Our study, on the other hand, is the first to examine OT's effects in active cocaine users engaged in voluntary addiction treatment. Aside from routine engagement with clinical providers, participants had daily contact with study staff who explicitly emphasized a supportive approach and focused on individual rapport with participants. This positive social context may have facilitated OT's trust- and cooperation-boosting effects (Lieberwirth *et al*, 2014; Meyer-Lindenberg A, 2011) and led to our finding of more honest cocaine use self-reporting in the OT group (**Figure 3(c)**), although this hypothesis requires further exploration to rule out a direct OT-induced reduction in participant defensiveness or enhancement of cognition leading to more accurate reporting. In further support of the hypothesis that OT shifts attentional bias, participants receiving OT switched implicit association of drugs with “self” to drugs with “others” by the end of our study period. To our knowledge, this is the first evidence implying a pharmacological change in any implicit association. Despite the disparity in social context, direct comparison of our study with Lee *et al's* (2014) study is limited due to differences in our study designs (e.g., repeated versus single OT dosing, between-subjects versus crossover design, use of slightly different paradigms and measures). Nonetheless, our results may not generalize beyond patients engaged in the structure of existing psychosocial treatment and frequent supportive contact with staff. Social context has repeatedly been shown to be an important moderating influence on the effects of OT administration (Bartz *et al*, 2011; Declerck *et al*, 2010; Grillon *et al*, 2013), and future studies of substance use disorder populations should factor this into their design.

Like the extant studies of OT's effects in substance use disorders in humans, analyses were limited by our small sample size. For example, it is likely that moderating factors exist for the effectiveness of OT in ameliorating the symptoms of substance use disorders (e.g., gender, OT receptor variation, exposure to early life stress) (Bisagno, 2014; Myers, 2014); however, our sample was too small for such subanalyses. Additionally, animal studies of OT and addiction often demonstrate inverted U-shaped dose response curves. Currently, the most effective dosage of intranasal OT in humans is unknown. Our study utilized a standard dosage from the field, but tiered dosing studies should begin to target the most effective dose range. Lastly, our results may not be generalizable to patients with either OUD or CUD in isolation. However, there is an alarming prevalence of cocaine use in real-world populations of patients receiving MMT, and concomitant OUD and CUD leads to poorer treatment outcomes and higher mortality rates. Furthermore, this challenging clinical problem is often overlooked due to a lack of viable treatment options. Therefore, we feel this is a worthwhile target population, particularly given the evidence of OT's non-specific effects on a wide variety of substances of abuse.

In conclusion, OT is a safe and feasible candidate to address the dire need for innovative treatment options for substance use disorders. Much larger trials will be needed to determine

the efficacy of intranasal OT administration as an adjunctive treatment for co-occurring OUD and CUD prevalent in MMT clinics.

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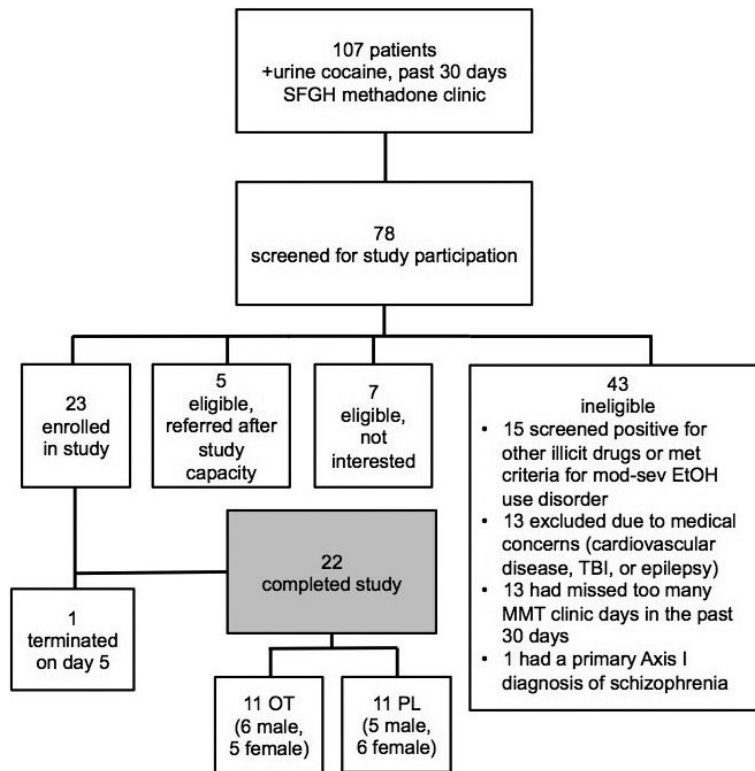
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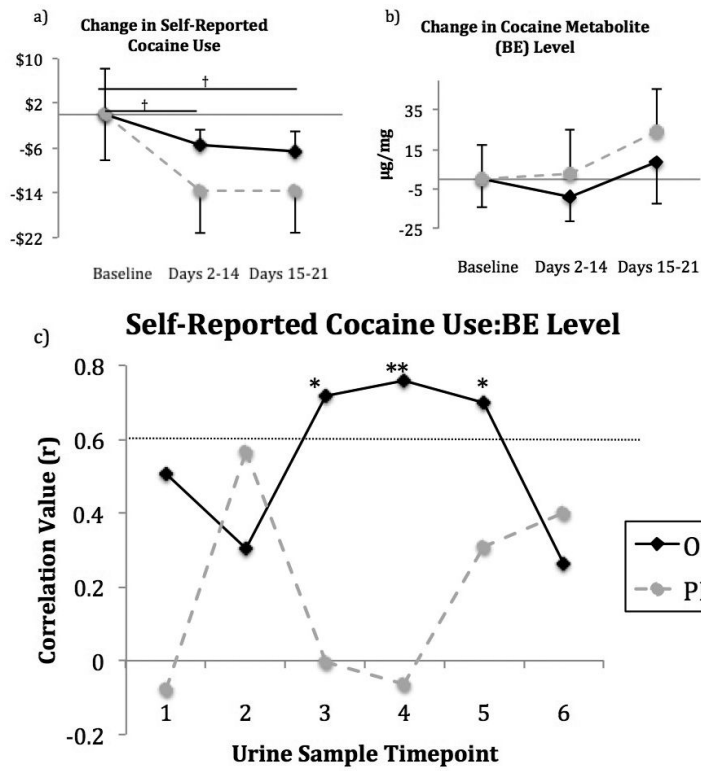
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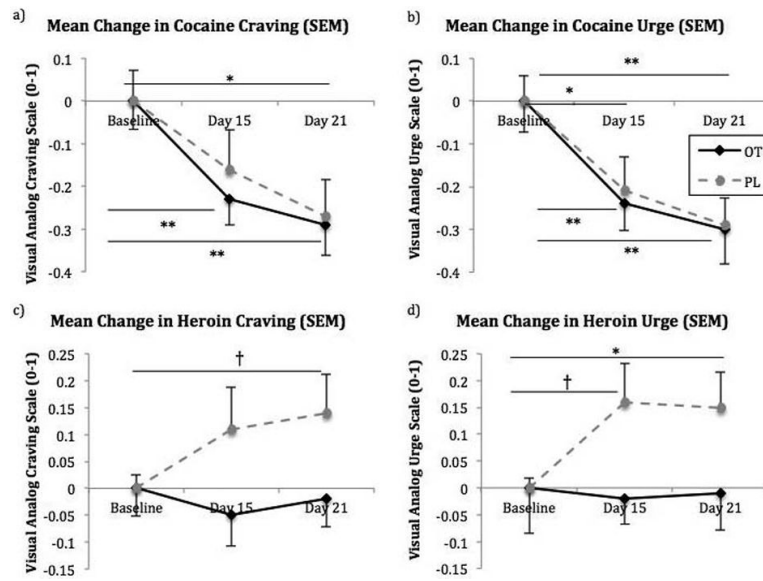
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**Figure 1.** Enrollment flow-chart. SFGH = San Francisco General Hospital, EtOH = alcohol, TBI = traumatic brain injury, MMT = methadone maintenance treatment, OT = oxytocin, PL = placebo.



**Figure 2.** Changes in a) cocaine craving, b) urge to use cocaine, c) heroin craving, and d) urge to use heroin as measured by a visual-analog scale recorded as a number between 0 and 1. Baseline measures for each group were set to zero. SEM = standard error of the mean, OT = oxytocin, PL = placebo. † $p < 0.10$ , \* $p < 0.05$ , and \*\* $p < 0.01$ .



**Figure 3.** Changes in a) self-reported cocaine use and b) urine cocaine metabolite levels. BE = benzoylecgonine. c) Correlation values (y-axis) for urine BE levels collected every four days (x-axis) and average self-reported cocaine use for the four days prior to each urine collection. Significant correlations existed for the third ( $r = 0.72$ ), fourth ( $r = 0.76$ ), and fifth ( $r = 0.70$ ) urine samples in the oxytocin group. OT = oxytocin, PL = placebo. † $p < 0.10$ , \* $p < 0.05$  (also represented by the dotted line in c), and \*\* $p < 0.01$ .



**Table 1**

Demographic and baseline characteristics for completed subjects.

	Oxytocin (n = 11)		Placebo (n = 11)	
	n	%	n	%
Male	6	55	5	45
Caucasian	4	36	1	9
African American	5	45	7	64
Hispanic	0	0	2	18
Other	2	18	1	9
<b>Psychoactive Medications:</b>				
SSRI	2	18	1	9
Trazodone	1	9	1	9
Mirtazapine	0	0	1	9
Misc. Prescribed Opioid	1	9	3	27

	Mean	SD	Mean	SD
Age (years)	49.3	9.67	49.6	9.63
Education (years)	12.6	2.4	11.1	1.8
Methadone (mg/day)	105.5	27.7	97.3	23.6
Heroin, 30-day <sup>*</sup>	0.02	0.05	0.01	0.02
Heroin, lifetime <sup>†</sup>	0.27	0.17	0.31	0.16
Cocaine, 30-day <sup>*</sup>	0.81	0.28	0.92	0.19
Cocaine, lifetime <sup>†</sup>	0.25	0.17	0.49	0.23

Baseline Measures	Mean	SD	Mean	SD
Cocaine Use, Self-Report (\$)	24.5	28.2	31.5	25.9
Cocaine Use, BE (ng/mg)	70.66	49.12	68.44	61.8
Cocaine Craving	0.49	0.22	0.46	0.23
Cocaine Urge to Use	0.48	0.24	0.50	0.20
Heroin Craving	0.11	0.17	0.08	0.08
Heroin Urge to Use	0.15	0.28	0.06	0.06
IAT score	-0.16	0.46	-0.28	0.23

SSRI = selective serotonin reuptake inhibitor, SD = standard deviation, BE = benzoyllecgonine.

<sup>\*</sup> number of days of drug use/past 30 days<sup>†</sup> number of years using at least three times per week/patient's age.