STIMULANT OXYTOCIN STUDY

NCT03016598

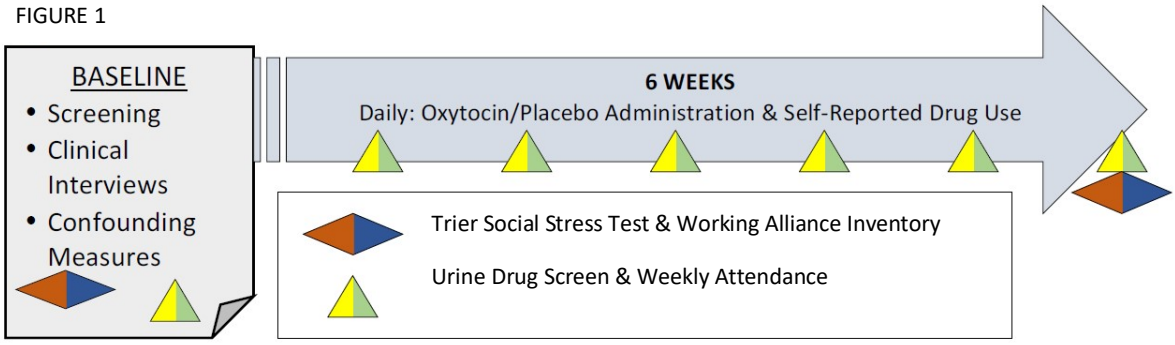
12/18/2017

Study Protocol

RESEARCH DESIGN

We conducted a randomized, double-blind, placebo-controlled study to examine the effects of oxytocin administration on stimulant use, psychosocial treatment engagement, and stress-reactivity in a sample of 40 individuals with stimulant use disorder receiving opioid agonist therapy within an opioid treatment program at the San Francisco and Oakland VA. Following successful screening and an initial baseline visit, participants were randomized to receive either oxytocin 40 IU or placebo intranasally twice daily for six weeks.

FIGURE 1



Research Participants:

We enrolled 40 male research participants with active stimulant use disorder and stabilized on opioid agonist therapy in an opioid treatment program (OTP). OTP clinics operate under strict state and federal guidelines for treatment structure and monitoring. Each patient receiving opioid agonist therapy from the OTP who is actively using stimulants is in "Phase 0" within the OTPs at the San Francisco and Oakland VA. Phase 0 patients must report to the clinic every day the clinic is open for observed opioid agonist dosing (i.e., no take-home doses), must submit urine for random toxicology screening approximately once every two weeks, and are required to attend weekly psychoeducation/therapy groups within the clinic. All patients in the OTP are assigned an individual counselor who meets with them at least monthly to support the lifestyle changes necessary to progress in recovery. Phase 0 patients typically meet with their counselors more frequently.

Recruitment: Participants were recruited from the OTP through the use of flyers posted visibly in clinic common areas and referrals from clinic counselors who were made familiar with inclusion/exclusion criteria through presentations at staff meetings and "Dear Provider" letters.

Adherence Monitoring: Study staff trained in proper spray application (Guastella, Hickie, et al. 2013) intranasally administered participants' morning study drug doses. Each participant was given a nasal spray bottle and trained in proper spray application by study staff. Participants were to administer their evening dose 8-10 hours following their morning dose. Each week, participants will be incentivized to bring their nasal spray bottle from the previous week, whether full or empty, for adherence monitoring via weighing. We successfully used similar contingent management strategies in our previous study of

repeated oxytocin administration in patients with co-occurring cocaine and opioid use disorders. Our participants brought their nasal spray devices in for weighing 98% of the time (no participant forgot more than once) and collectively self-administered >78% of their evening doses.

Randomization: Participants were randomized 1:1 to receive either oxytocin or placebo. A randomization plan was created using www.randomization.com. Randomization was managed by the Investigational Drug Pharmacist at the San Francisco VA, who also managed the double blind.

Inclusion Criteria: Participants must be at least 18 years old, enrolled as a patient at the San Francisco or Oakland VA OTP, be on a stable dose of methadone or buprenorphine for at least two consecutive weeks, and have at least one documented routine urine toxicology screen positive for cocaine or methamphetamine in the past month.

Exclusion Criteria: Urine toxicology screen positive for heroin in the past month; meeting *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V) criteria for previous or current psychotic disorder, severe neuropsychological disorder, premenstrual dysphoric disorder, or current moderate severe alcohol use disorder; active suicidal or homicidal ideation; hemodialysis; sensitivity to E 216, E 218, and chlorbutanol hemihydrate (preservatives used in nasal spray); using hormone supplementation; positive urine pregnancy test or women of child-bearing age not practicing an effective means of non-hormonal birth control; or nasal obstruction, discharge, or bleeding.

METHODS

All measures are listed in detail below. In sum, our primary outcome measure will be **(1)** Stimulant positive urine drug screen collected at baseline and weekly throughout the study. To assess psychosocial measures, participants and their clinic assigned counselor will complete **(2a)** the Working Alliance Inventory – Short Revised (WAI-SR) (Hatcher & Gillaspy 2006), client and therapist forms, respectively, at baseline and after six weeks as well as (**2b**) OTP attendance rates. Additionally, in response to a Trier Social Stress Test, we will measure, **(3a)** self-reported stimulant craving by completing the Cocaine Craving Questionnaire (CCQ-Brief) modified to include methamphetamine in addition to cocaine, **(3b)** psychophysiological measures, including heart rate and heart rate variability, **(3c)** stress biomarker measurements, including salivary cortisol and DHEA, and **(3d)** self-reported anxiety.

See **Figure 1** for Study Design Outline.

PROCEDURES

Screening/Baseline: Potential participants were screened by study staff on site and, if preliminarily eligible, signed a brief clinic-specific consent in order for us to confirm eligibility via OTP medical records. Eligible participants were invited for a baseline interview, which included: 1) written informed consent, 2) a medical history and brief physical exam conducted by a study physician, 3) a structured mental health interview conducted by an advanced psychology trainee, 4) baseline measurements, and 5) a urine pregnancy test (for female participants).

Daily: We asked participants to report daily on their illicit drug use from the previous 24-hours, including specific drug, amount, and route of administration. We also monitored daily OTP clinic attendance.

Weekly: Participants provides a weekly urine sample, which was analyzed for various drugs of abuse.

MEASURES

Screening Measures:

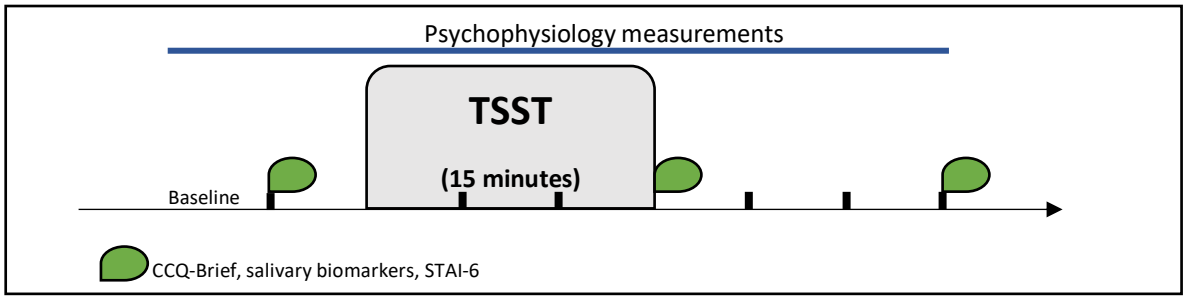
1) **Structured Clinical Interview for DSM-5 Disorders – Clinical Trials Version (SCID-5-CT)**: a structured psychiatric interview based on current diagnostic standards, customized to the inclusion and exclusion criteria of our clinical trial.

Outcome Measures:

1) **Stimulant positive urine drug screen**: (Jufer, Wstadik et al. 2000, Preston, Epstein et al. 2002) was measured from baseline and weekly urine samples. Urine samples were screened for a variety of drugs of abuse.
2) **a. Working Alliance Inventory – Short Revised (WAI-SR):** (Hatcher & Gillaspy, 2006): is a well-validated 12-item measure of therapeutic alliance. Participants completed individual "client forms" for their clinic-assigned individual counselor at baseline and after six weeks. Likewise, the counselor completed the "therapist form" for each participant at baseline and after six weeks of study participation. Time required for administration per form: <5 minutes.

   b. Attendance in OTP clinic: Daily attendance at OTP clinic was tracked for each participant.

FIGURE 2



Psychophysiology measurementsBaselineCCQ-Brief, salivary biomarkers, Likert scalesFigure 6: Social Stress-Induced Cocaine Craving Paradigm. TSST = Trier Social Stress Test, CCQ-Brief –Cocaine Craving Questionnaire-Brief, salivary biomarkers = cortisol and dehydroepiandrosterone, Likert scales = subjective stress and anxiety.

3) **Trier Social Stress Test (TSST**) (see **Figure 2**): in order to evaluate response to social stress, participants engaged in the TSST paradigm at study baseline and after six weeks of intranasal oxytocin or placebo. The TSST is a standardized and well-validated psychological stress challenge which has shown utility for evoking a strong cardiovascular and HPA axis stress response (including salivary cortisol) in a laboratory setting (Dickerson & Kemeny 2004). After a 5-minute preparation period, participants are instructed to give a speech and perform serial subtractions, for five minutes each, in front of a panel of stone-faced adjudicators.

   a. **Cocaine Craving Questionnaire-Brief (CCQ-Brief)**: (Sussner, Smelson et al. 2006) is a valid and reliable 10-item self-report instrument, with each item scored on a scale 1-7, used to measure the respondent's general cocaine craving. We amended this to also include methamphetamine and asked for participants' stimulant of choice. Participants

completed the amended CCQ-Brief at baseline, immediately after the TSST, and 20 minutes after the TSST.

b. **Psychophysiological Stress Measures**: consisted of two main outcome variables: *heart rate* and *heart rate variability*. We recorded continuous physiology during the TSST, we will include the 5-min averages for: baseline, speech prep, speech, mental arithmetic, and 15-20 mins post-TSST.

c. **Salivary cortisol and dehydroepiandrosterone (DHEA)**: are biological markers of HPA-axis stress reactivity. We will collect salivary cortisol and DHEA at baseline, immediately after the TSST, and 20 minutes after the TSST.

d. **State-Trait Anxiety Inventory, 6-item version (STAI-6)**: participants will rate their levels subjective anxiety using the STAI-6 at baseline, immediately after the TSST, and 20 minutes after the TSST.