

Investigation of intranasal oxytocin on relapse risk in cocaine-dependent patients

- 1) Data Analysis Plan as part of R01 application submitted on 3/15/2013.
- 2) Description of data analysis conducted 10/31/2018

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

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7. * TYPE OF APPLICANT: M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)
Other (Specify):
Small Business Organization Type Women Owned Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION: New Resubmission Renewal Continuation Revision
If Revision, mark appropriate box(es).
 A. Increase Award B. Decrease Award C. Increase Duration D. Decrease Duration
 E. Other (specify):

* Is this application being submitted to other agencies? Yes No What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Neuropeptide Modulation of Stress: A Novel Approach to Cocaine Relapse

12. PROPOSED PROJECT:
* Start Date 09/01/2013 * Ending Date 08/31/2015

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT** NY-015

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2) Cocaine Craving Scale (CCS, Weiss et al., 1997); 3) Subjective ratings of cocaine craving, depression, anxiety, stress during stress testing (Likert scale 0 to 10, 10 = worse) Physiological tests: 1) Nine drug urine toxicology (Iscreen™ 9 drugs); 2) Stress Sensitivity Testing: serum ACTH, HR, BP for Day 1 and Day 2 (see table 2.)

Phase 2 Measures: The goal of phase 2 is to test if IN OT can reduce relapse risk. Measures collected may inform *Primary Aim 2, Secondary Hypotheses, and Exploratory Aims a, b* (section 3.4). **Compliance monitoring:** a) Witnessed, and recorded insufflations of IN OT vs. Pbo, 3x/wk from a bottle kept refrigerated at STARS; b) Patients will be instructed on storing and using the nasal spray bottle before At-home insufflation begins. They will be told to bring this bottle with them at every visit. [*Monitoring: unbeknownst* to the patient, the at-home bottle will be weighed before being given, and will be weighed at every visit. The metered bottle delivers 5 IU/0.1cc or per puff. Each daily dose requires 4 puffs or 0.4 cc. The weight of each puff or 0.1cc is approximately 0.1g, hence for each at-home insufflation, the bottle weight is expected to change by 400 mg. The expected weight change will be compared to the actual recorded weight.] **Medical monitoring:** a) electrolyte: (Na, K, Cl), spot cortisol, urine pregnancy test for women at week 2, 4, 6; b) weekly medical review for signs and symptoms of hyponatremia and side effects. **Clinician Interviews:** 1) TLFB 3x/wk; 2) CGI-O 1x/wk; 3) Adverse event form 3x/wk; 4) HamD 1x/wk. **Self reports:** 1) PSS 1x/week, 2) CCS 3x/week. 3) subjective ratings of depression, anxiety, stress and cocaine craving (Likert scale 0 to 10) and BAS (table 2). **Physiological tests:** *Stress sensitivity testing:* repeat of Day 1 IN DDAVP 80 IU challenge, ACTH, HR, BP; 2) *Nine drug urine toxicology, 3x/wk.*

Study Assessments: (Table 1). **Physiological tests:** 1) *urine toxicology:* this will be estimated qualitatively at every visit by dipstick (Iscreen™, 9 drugs) which indicates the presence of cocaine, amphetamine, metamphetamine, cannabis, methadone, morphine, oxycodone, barbiturate, benzodiazepine. 2) *stress sensitivity testing:* as outlined in table 2, it is performed on two separate days, [in counterbalanced order.] Day 1: an endocrine challenge with IN DDAVP 80IU (de Goeij et al., 1991). After establishing baseline ACTH secretion, serum samples are taken at time points extending to 90 minutes. The DDAVP challenge is also repeated at the end of phase 2, to see if ACTH secretion is affected by 6 weeks of IN OT administration. Day 2 tests if pretreatment with IN OT treatment can acutely dampen the effect of DDAVP on ACTH secretion. After baseline is measured before and after IN OT, serum samples for ACTH are taken at time points extending to 90 minutes. Serum samples are spun, frozen at -20 Celsius, packed in dry ice, and shipped to the Nathan Kline Laboratory in Orangeburg, NY. 3) Medical monitoring: week 2,4,6: Na, K, Cl, CO3, spot cortisol, β-HCG for women. **Clinician Interviews:** 1) TLFB (Litten and Allan, 1992; baseline, each visit in phase 2). This is an adaptation of the alcohol TLFB, which estimates cocaine use in the past 30 days at baseline, and is then repeated at every visit with the aid of a calendar to obtain a day-by-day registry of cocaine use during phase 2. 2) CGI-O, (Guy, 1976; baseline, weekly during phase 2) the severity and improvement scales measure the overall clinical status of the subject and change from baseline. 3) BAS (Chaplin et al., 2010). This scale is used during stress sensitivity testing. Research staff rate participants on 13 items of behavior relating to arousal during the stress challenge. 4) Adverse event form is a check-list of side effects experienced by participants; 5) HamD, (Williams, 1988; baseline, each wk in phase 2). Estimates 25 depression symptoms. **Self reports:** 1) PSS (Cohen et al., 1983; baseline, weekly during phase 2) measures monthly situations in a subject's lives deemed stressful. Ten questions are scored between 0 (never) to 4 (very often). Modified, it will be administered weekly during phase 2, [and will include a open-ended question inquiring about any adverse life event in the past week.] 2) *Subjective ratings of cocaine craving, depression, anxiety, stress during stress testing (Likert scale 0 to 10, 10 = worse), performed during stress sensitivity testing.* 3) CCS (Weiss et al., 1997) 3-item questionnaire rating cravings for cocaine on a scale of 0 (none) to 9 (Strong).

3.3 Compensation and data management.

For phase 1, control participants will receive \$150 for their participation; cocaine-dependent patients will receive \$20/day, or will receive \$150 if they complete the whole week. [During phase 2, cocaine-dependent patients accumulate vouchers for completing all study procedures (Bringing home bottle, assessments, study visits).] Each visit with all study procedures completed will earn them \$5. They can also earn \$20 for each week of consecutive and complete participation. Transportation costs are covered (\$5/visit). Total earnings can reach \$450. StudyTrack, a software system for clinical trials will be used for data management.

3.4 Statistical Analysis:

3.4.1. Outcome measures: PHASE 1: **Primary outcomes:** 1) secretion of ACTH (continuous measure of area from the concentration-time curve (AUC) using trapezoid method, pg/mL/min). 2) subjective rating of cocaine craving, stress, depression, anxiety (continuous) 3) difference in ACTH secretion between IN DDAVP (day 1) and IN OT prior to IN DDAVP (day 2) (continuous measure); 4) difference in subjective rating of cocaine

craving, stress, depression, anxiety between IN VP (day 1) and IN OT prior to IN DDAVP (day 2; continuous, controlled for last day of use before entering Phase 1); **PHASE 2: Primary outcome:** 1) maximum number of consecutive abstinent days (continuous measure) ; **Secondary outcome:** 1) cocaine using days (continuous). **Covariates/Predictor Variables:** demographics, age, gender; cocaine data (TLFB, 30 days; IN vs. smoked).

3.4.2. Sample size: In PHASE 1, we will enroll a total of 100 participants: 1) Cocaine group (COC): Cocaine-dependent patients seeking treatment (n=50); 2) Control group (CON): Healthy matched controls (n=50), each matched demographically (see 3.1.1). In PHASE 2, we will randomize the 50 COC patients into two groups: 1) Oxytocin group (OT), n=25; 2) Placebo group (PBO), n=25. An independent statistician will perform, and an independent pharmacist will implement the randomization. Individuals will be stratified by route of cocaine use. The randomization will be balanced in blocks of random size 2 and 4 to prevent compromise of the blind.

3.4.3. Intent to Treat/ Dropouts and missing data: All primary analysis will be on Intent-to-Treat (ITT) sample, i.e. all subjects from COC and CON groups in Phase 1 (50 per arm) and all subjects randomized to OT and PBO groups in Phase 2 (25 per arm). [In Phase 1, we expect little attrition. Measures as described (3.4.1) will provide usable data after 2 days of measurements. For phase 2, we anticipate an attrition rate of 30%, leaving approximately 18 completers per arm.] If a patient drops out during Phase 2, the maximum number of consecutive abstinent days achieved in the trial will be considered as primary outcome. The inferences from analyses with missing data are considered valid provided that they are "missing at random" (Little and Rubin 1987). One can assume either parametric or semi-parametric models for missingness (Diggle and Kenward 1994; Kenward 1998; Liu et al 1999; Rotnitzky et al 1998). Inferences from various models of missingness provides a measure of the efficacy estimate from each models.

3.4.4. Significance testing and preliminary analyses: All tests for main effects will be performed at two-tailed significance $\alpha=5\%$. Before performing specific analyses (described below), we will examine all variables for outliers and normality. Demographic variables (ethnicity, gender, age) and baseline measures in the groups will be described in terms of means, standard deviations, proportions and 95% confidence intervals. The covariates (Section 3.4.1) will be included if they are found to affect outcome measures.

Hypotheses:

Primary Aim 1 [Phase 1]: The goal of primary aim 1 is to investigate the effect that both IN DDAVP and OT have on stress sensitivity. **Primary Aim 1a, hypothesis 1:** IN DDAVP will be associated with greater secretion of ACTH and subjective ratings in cocaine dependent patients compared to control patients. **Primary Aim 1b, hypothesis 2:** IN OT treatment will significantly reduce the secretion of ACTH and subjective ratings associated with IN DDAVP in cocaine dependent patients compared to control patients. The differences based on the outcomes specified in hypotheses 1 and 2 between the subjects in COC and CON groups will be examined using parametric or non-parametric matched sample test.

Primary Aim 2 [Phase 2]: The goal of primary aim 2 is to investigate the effect of OT on cocaine use after abstinence induction. **Primary Aim 2, hypothesis 1:** Cocaine-dependent patients receiving IN OT will display significantly more days of consecutive abstinence after abstinence induction compared with IN placebo at the end of the study. The effect of IN OT treatment (based on groups) on the primary outcome (maximum number of consecutive abstinence days for each patient) will be analyzed using generalized linear models (PROC GLIMMIX in SAS®) with main effect of randomization assignment (OT vs. PBO).

Secondary Hypotheses: We will examine the feasibility, safety, tolerability, and potential efficacy of IN OT for relapse prevention in cocaine dependence. 2.1): Cocaine-dependent patients receiving IN OT who complete all 6 weeks of phase 2 will tally fewer cocaine using days than placebo patients who complete all 6 weeks. 2.2): Cocaine-dependent patients receiving OT who relapse will tally fewer cocaine using days than patients receiving placebo who relapse. Regression analysis will be implemented using those who complete (2.1) and those who relapse (2.2) to test the effect of OT on the secondary outcome (cocaine using days).

Exploratory Aims: We will investigate a) if the acute reduction in stress sensitivity with IN OT in Phase 1 or at the end of Phase 2 (repeat IN DDAVP challenge) is associated with a greater number of days of continued abstinence from cocaine in Phase 2; b) if there are gender effects on the primary outcomes.

Power Analysis: **Primary aim 1:** With 50 cocaine dependent subjects and 50 matched controls, we have 50 matched pairs which give us at least 80% power to detect a significant difference between groups using 2-sided hypothesis test at a 5% level of significance for an effect size $\geq .41$. This is considered a small/medium effect size (Araya et al., 2006; Simeon et al., 2011), which are reasonable to expect based on the existing literature. **Primary aim 2:** In Phase 2, we randomize 50 participants into 2 groups (25 in PBO and 25 in OT). The comparison will achieve at least 80% power (testing 2-sided hypothesis of difference at 5% significance) when detecting an effect size ≥ 0.8 . This is a medium effect size that we based on existing relapse studies in cocaine dependence (Back et al., 2010).

Primary outcome:

The primary outcome was maximum number of consecutive cocaine abstinent weeks. Cocaine use was determined using urine toxicology and TLFB self-report. In a given week, cocaine use was defined as positive if any urine toxicology tests or TLFB self-report was positive (regardless if urine toxicology was negative or missing). Cocaine use was defined as negative if both urine toxicology and self-report were negative or if urine toxicology was missing, the self-report was negative. Cocaine use status was defined as missing if both urine toxicology and self-report were missing. Wilcoxon rank-sum tests were used to examine differences in maximum number of consecutive cocaine abstinent weeks by medication group.

Twenty-six cocaine patients were randomized to 6 weeks of Oxytocin (n=15) or Placebo (n=11). The median (IQR) of the maximum number of consecutive abstinent weeks was 1.0 (1.0 to 1.0) for the OT group and 1.0 (1.0 to 2.0) for the PBO group. The Wilcoxon rank-sum test was not significant, there was no effect of treatment arm on the maximum number of consecutive abstinent weeks ($W = 144.5, p = .67$).